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Number xx

Systematic Review – ADHD Diagnosis and Treatment in Children and Adolescents

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. The Patient-Centered Outcomes Research Institute (PCORI) requested this report from the EPC Program at AHRQ. AHRQ assigned this report to the EPC (to be added for the final version) (Contract Number: to be added for the final version).

AHRQ EPC reviews provide comprehensive, science-based information on common, costly medical conditions, and new healthcare technologies and strategies.

The Patient-Centered Outcomes Research Institute (PCORI) was established to fund research that helps patients and caregivers make better informed health care choices. To fulfill its authorizing mandate, PCORI partners with AHRQ to generate evidence synthesis products and make comparative effectiveness research more available to patients and providers.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, go to www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that the EPC evidence reports and technology assessments, when appropriate, will inform individual health plans, providers, and purchasers as well as the healthcare system as a whole by providing important information to help improve healthcare quality. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the website (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this evidence report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

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Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers. AHRQ may also seek comments from other federal agencies when appropriate.

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Systematic Review – ADHD Diagnosis and Treatment in Children and Adolescents

Abstract

Objective. The systematic review assessed evidence on the diagnosis, treatment, and monitoring of Attention-Deficit/Hyperactivity Disorder (ADHD) in children and adolescents to inform a planned update of the American Academy of Pediatrics (AAP) guidelines.

Data sources. We searched PubMed, EMBASE, PsycINFO, ERIC, and clinicaltrials.gov and prior reviews for primary studies published since 1980. The draft report includes studies published to 2021, and an ongoing update search will capture 2022 and 2023 studies.

Review methods. The review followed a detailed protocol and was supported by a Technical Expert Panel (TEP). Citation screening was facilitated by machine learning; two independent reviewers screened full text citations for eligibility. We abstracted data using software designed for systematic reviews. Risk of bias assessments focused on key sources of bias for diagnostic and intervention studies. We conducted strength of evidence (SoE) and applicability assessments for key outcomes.

Results. Searches identified 22,091 citations, and 6,900 were obtained as full text. We included 533 studies reported in 1,058 publications (223 studies addressed diagnosis, 304 studies addressed treatment, and 9 studies addressed monitoring). Diagnostic studies reported on the diagnostic performance of numerous parental ratings, teacher rating scales, teen/child self-reports, clinician tools, neuropsychological tests, EEG approaches, imaging, biomarkers, activity monitoring, and observation. Multiple approaches showed promising diagnostic performance but estimates of performance varied considerably across studies and the SoE was generally low. Few studies report estimates for children under the age of 7 years. Treatment studies evaluated FDA-approved and newer, non-FDA-approved pharmacological agents, psychological/behavioral approaches, combined pharmacological and behavior approaches, cognitive training, physical exercise, nutrition and supplements, integrative medicine, parent support, school interventions, and provider or model-of-care interventions. Pharmacological treatment was associated with improved broadband scale scores and ADHD symptoms (high SoE) as well as function (moderate SoE), but also appetite suppression and adverse events (high SoE). Psychosocial interventions, neurofeedback, and school interventions showed improvement in ADHD symptoms (moderate SoE). Few studies have evaluated combinations of pharmacological and behavioral interventions and we did not find combination treatments superior to monotherapy. Monitoring approaches for ADHD were limited to nine evaluations of ADHD monitoring strategies, and the SoE is insufficient.

Conclusion. Many diagnostic tools are available to diagnose ADHD, but few monitoring strategies have been studied. Medication therapies remain important treatment options, even as other non-drug treatment approaches emerge.
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Executive Summary

Main Points

Diagnosis
- Diagnostic test performance likely depends on whether youth with ADHD are being differentiated from typically developing children or from clinically referred children who had some kind of mental health or behavioral problem.
- Rating scales for parent, teacher, or self assessment as a diagnostic tool for ADHD have high internal consistency but poor to moderate reliability between raters, indicating that obtaining ratings from multiple informants (the youth, both parents, and teachers) may be valuable to inform clinical judgement.
- Studies evaluating neuropsychological tests of executive functioning (e.g., Continuous Performance Test) used unique combinations of individual cognitive measures, making it difficult to compare performance across studies.
- Diagnostic performance of biomarkers, EEG, and MRI scans show great variability across studies and their ability to aid clinical diagnosis for ADHD remains unclear. Studies have rarely assessed test-retest reliability, no findings have been replicated prospectively using the same measure in independent samples, and real-world effectiveness studies of diagnostic performance have not been conducted.
- Very few studies have assessed performance of diagnostic tools for ADHD in children under the age of 7 years and more research is needed.
- The identified studies did not assess the adverse effects of being labeled correctly or incorrectly as having a diagnosis of ADHD.

Treatment
- We found moderate strength of evidence that several treatment modalities improve core ADHD symptoms with a moderate effect size compared to control groups (e.g., placebo). These include FDA-approved medications, psychosocial interventions, neurofeedback, and school interventions.
- FDA-approved stimulant (e.g., methylphenidate) and non-stimulant (e.g., atomoxetine) medications had the strongest evidence across interventions for significantly improving ADHD symptoms and additional outcomes, including broadband measures and functional impairment.
- Although indirect comparisons across studies suggest that the studies evaluating stimulants report larger effect sizes than studies evaluating non-stimulants for improving ADHD symptoms, head-to-head comparisons did not detect significant differences. Stimulant and non-stimulant medications yielded comparable effects on most effectiveness outcomes and adverse events, including appetite suppression.
- We did not find that combination therapies of medication plus psychosocial therapies produce better results than medication alone, but existing research evaluated unique combinations of intervention components.
- Despite the large body of research, comparative effectiveness and safety information is limited and more research is needed to help choose between treatments.
- Data were insufficient to assess the effect of co-occurring disorders on treatment effects.
• We found too few studies reporting on diversion to quantify the risk of diversion of pharmacological treatment.

Monitoring
• Very few monitoring studies have been reported and more research is needed on how youth with ADHD should be monitored over time.
• Different assessment modalities may provide valid but different perspectives and more than a single assessment modality may be required for comprehensive and effective monitoring of ADHD outcomes over time.

Background and Purpose
ADHD is the single most prevalent behavioral and mental health problem in youth. Approximately 10 percent of US children have received a clinical diagnosis of ADHD, and clinical diagnoses have increased steadily over time.

Commissioned by the Patient-Centered Outcomes Research Institute (PCORI), this review assesses evidence on important gaps in knowledge related to the diagnosis of ADHD; concerns about treatment strategies, including over- and under-treatment; and how to best monitor ADHD patients over time.

This review updates prior AHRQ reviews on ADHD,1-3 and is meant to inform a planned update of the American Academy of Pediatrics (AAP) guidelines.

Methods
The methods for this evidence review follow the Methods Guide for the Evidence-based Practice Center (EPC) Program.4 The evidence report is based on a systematic review protocol. The evidence review team was supported by a technical expert panel (TEP), a diverse panel of relevant stakeholders. The key questions (KQs) and the protocol were posted on the AHRQ Effective Health Care website (https://effectivehealthcare.ahrq.gov/) to allow additional public input. KQs addressed the diagnosis, treatment, and monitoring strategies for ADHD in children and adolescents.

We abstracted diagnostic performance measures as reported by the individual study authors. We converted to scale-independent standardized mean differences (SMD) and relative risks (RR) together with the 95 percent confidence interval (CI) for treatment studies. For monitoring studies, we reported all information on the success and impact of the monitoring strategy. We reported the range of reported diagnostic performance for diagnostic studies; treatment studies were summarized in random effects meta-analyses; monitoring studies were summarized narratively. We differentiated high, moderate, low, and insufficient strength of evidence (SoE).

The draft report includes studies published Through 2021; an ongoing update search will capture 2022 and 2023 studies.

Results
The searches identified 22,091 citations. Of these, we obtained 6,900 as full text. In total, 533 studies reported in 1,058 publications met the eligibility criteria. This included 223 studies addressing diagnosis (KQ1), 304 studies addressing treatment (KQ2), and 9 studies addressing monitoring (KQ3). The risk of bias in included studies varied considerably. The median minimum age in included studies was six years old and the median number of girls included in the studies was 25 percent.
We identified a large number of diagnostic approaches. Studies reported on the diagnostic performance for parental ratings, teacher ratings, teen/child self-reports, clinician tools, neuropsychological tests, EEG approaches, imaging, biomarkers, activity measures, and observation. Diagnostic test performance likely depends on whether youth with ADHD are being differentiated from typically developing children (i.e., a discrimination of little clinical relevance) or from clinically referred children who have some kind of mental health or behavioral problem.

Rating scales for parent, teacher, or self assessment as a diagnostic tool for ADHD have high internal consistency but poor to moderate reliability between raters, indicating that obtaining ratings from multiple informants (the youth, both parents, and teachers) may be valuable to inform clinical judgement. Studies evaluating neuropsychological tests of executive functioning (e.g., Continuous Performance Test) used unique combinations of individual cognitive measures, making it difficult to compare performance across studies.

Diagnostic performance of biomarkers, EEG, and MRI scans show great variability across studies and their ability to aid clinical diagnosis for ADHD remains unclear. Studies have rarely assessed test-retest reliability, no findings have been replicated prospectively using the same measure in independent samples, and real-world effectiveness studies of diagnostic performance have not been conducted.

Very few studies have assessed performance of each of the diagnostic tools for ADHD in children under the age of 7 years and more research is needed. Furthermore, the identified studies did not assess the adverse effects of being labeled correctly or incorrectly as having a diagnosis of ADHD.

Treatment studies evaluated FDA-approved pharmacological and new agents, psychological or behavioral approaches, combined pharmacological and behavior, cognitive training, physical exercise, nutrition and supplements, integrative medicine, parent support, school interventions, and provider or model of care interventions aiming to treat or manage ADHD.

We found moderate to high strength of evidence that several treatment modalities improve core ADHD symptoms with a moderate effect size compared to control groups (e.g., placebo). These include FDA-approved medications (SMD -0.58; CI -0.67, -0.50; 46 studies, n=7237; RR 1.85, CI 1.38, 2.48; 11 studies, n=1751, high SoE), psychosocial interventions (SMD -0.34, CI -0.53, -0.14; 12 studies, n=1450; moderate SoE), neurofeedback (SMD -0.45; CI -0.83, -0.08; 8 studies, n=736; moderate SoE); and school interventions (SMD -0.50; CI -0.92, -0.07; 6 studies, n=898; moderate SoE).

FDA-approved medications had the strongest evidence for significantly improving additional outcomes, including measures describing child behavior more broadly (RR 0.53; CI 0.42, 0.64; 24 studies, n=4044; high SoE) and functional impairment (SMD 0.49; CI 0.12, 0.86; 12 studies, n=2152; moderate SoE). Effect sizes on ADHD symptoms in studies evaluating stimulants versus control (SMD -0.88; CI -1.13, -0.062; 12 studies, n=1471) were larger than those in studies evaluating non-stimulant medications versus control (SMD -0.50; CI -0.57, -0.43; 33 studies, n=5684), though head-to-head comparisons did not detect significant differences between these medication classes on ADHD symptoms (SMD 0.23; CI -0.03, 0.49; 7 studies, n=1611). Medication studies typically did not include children under 6 years of age. Identified combination therapies of medication plus psychosocial interventions did not produce better results than medication alone (e.g., ADHD symptoms SMD -0.02; CI -0.20, 0.15; 4 studies, n=630; moderate SoE), although existing research evaluated unique intervention component combinations, and the evidence base is limited.
Despite the large body of research, comparative effectiveness and safety information is limited. Stimulant and non-stimulant medications yielded comparable effects on most effectiveness outcomes and assessed adverse events. Across studies, medication therapy evaluations reported more adverse events than non-medication interventions.

Data were insufficient to assess the effect of co-occurring disorders on treatment effects. We found too few studies reporting on diversion to quantify the risk of diversion of pharmacological treatment.

We identified only a very small number of evaluations of strategies monitoring ADHD over time. Studies did not provide information on key comparative effectiveness and safety outcomes, and SoE is insufficient.

Strengths and Limitations
Our comprehensive review addresses numerous important diagnostic and treatment questions relevant to clinical practice. Despite the large number of identified studies, some areas remain the subject of future research, including identifying key effect modifiers explaining variation in diagnostic performance and comparative effects of ADHD treatments. In addition, the evidence base for ADHD monitoring strategies is very limited.

Implications and Conclusions
A large number of diagnostic tools are available to inform the clinical diagnosis of ADHD, but few monitoring strategies have been studied. Medication therapy remains a central treatment modality even as evidence for other non-pharmacological therapies strengthen and as novel treatment approaches emerge.

References
1. Introduction

1.1 Background

Attention-Deficit/Hyperactivity Disorder (ADHD) is the single most prevalent behavioral and mental health problem in youth. Approximately 10 percent of US children have received a clinical diagnosis of ADHD. Clinical diagnoses have increased steadily over time, though the higher rates seem attributable to changing clinical practices (including changes in diagnostic criteria, awareness, clinical practice guidelines, and educational policies that motivated clinical assessment and diagnosis), rather than to an increase in true population rates. The prevalence of ADHD based on rigorous diagnostic procedures is approximately 5.3 percent, a rate that is similar across geographic regions worldwide and that has remained constant over more than 20 years when diagnostic criteria have remained constant. This rate, when compared with the much higher rates of clinical diagnoses, suggests that a large number of youth may be receiving a diagnosis when they should not be. The increasing rates of diagnosis could in part represent the clinical recognition of youth who have clinically significant and functionally impairing ADHD symptoms but who may not meet full, formal diagnostic criteria, since increasing evidence suggests that ADHD symptoms are continuously distributed quantitative traits and therefore lie on a continuum of severity in the general population. Some youth, however, are misdiagnosed as having ADHD when they in fact have symptoms of other disorders that are similar to, or overlap with, the symptoms of ADHD -- difficulty concentrating, for example, is a symptom that occurs in many other conditions. ADHD is more than twice as likely to be diagnosed in boys than in girls, though this sex-specific difference in prevalence is thought to derive at least in part from diagnostic biases and cultural influences, in addition to true underlying biological determinants. ADHD is a more prevalent diagnosis in youth from low-income families and in Caucasian compared to Black, Hispanic, and Asian youth, although diagnostic bias and cultural influences may again contribute to these socioeconomic, ethnic, and racial disparities in diagnostic rates.

The first question patients, parents, teachers, and clinicians ask when considering ADHD is, “Does this child truly have ADHD?” Unfortunately, clinician judgement, especially by non-specialist clinicians in primary care, is poor in diagnosing ADHD. Accurately identifying youth who have ADHD has proved difficult at a population level, in part because diagnoses are often made using subjective clinical impressions and limited diagnostic tools. These tools include structured and semi-structured parent, youth, and teacher questionnaires. They represent an improvement over unsupported clinician judgement, but they are nevertheless highly subjective, prone to disagreement across reporters, and likely overestimate the prevalence of ADHD. More objective diagnostic tools have been proposed, including activity monitors, neuropsychological test measures, biomarkers such as genotyping, electrophysiological indices, and MRI measures, though they are not yet established diagnostic tools.

It is essential to know how the comparative accuracy of these diagnostic tools varies by clinical setting, including primary care or specialty clinic, and/or patient subgroup, including age, sex, socioeconomic status, racial or ethnic group, co-occurring mental, emotional, or developmental disorders, or other risk factors associated with ADHD. The accuracy of an ADHD diagnosis is especially poor in preschool-aged children, for whom
1. Introduction

Hyperactivity, general rambunctiousness, and difficulties with impulse control are often relatively normative and difficult to distinguish from ADHD-related behaviors. Preschool youth also typically do not have the same classroom expectations for behavioral self-regulation that children in elementary school are expected to have, further obscuring the distinction between ADHD and neurotypical early childhood behaviors.

ADHD diagnosis is normally based on an assessment to determine whether the patient meets the criteria described in the DSM-5-TR. Rating scales, which can be completed by parents, teachers, and/or patients, are used to evaluate the frequency and severity of each of the 18 symptoms in DSM-5-TR (9 symptoms related to inattention, and 9 symptoms related to hyperactivity/impulsivity), as well as the degree of symptom-related impairment across settings (e.g., home, school, work). Rating scale data are integrated with a clinical interview to determine the onset, course, duration, and impairment associated with symptoms. In addition, screening and clinical evaluation of potential co-occurring psychiatric conditions is a key part of the diagnostic process. Important questions remain about the accuracy of this approach in primary care settings. A particular challenge is separating ADHD from other conditions that may appear similar (e.g., anxiety, conduct disorders, speech or language delay, other developmental disorders) and determining whether another condition may better explain ADHD symptoms or is present as a co-occurring diagnosis.

Inaccurate diagnoses of ADHD can lead either to the administration of treatments, usually stimulant medications, in children who do not need them, or to the withholding of treatment and services for those who would benefit from such treatments. Prescription of stimulant medications across the US population has doubled in the last decade, with a prevalence in 2019 of approximately 6 percent, and as high as 14 percent regionally. These rates are higher than the 5.3 percent population prevalence of rigorously diagnosed ADHD, suggesting that many youth may be receiving stimulants when they do not have ADHD. These trends have created alarm in the lay public, policy makers, and health care providers. Adding to their concern is that diversion and abuse of stimulants is common, particularly in college students. Little is known or understood about how the risk for diversion and abuse of stimulant medications approved for ADHD varies with patient characteristics (e.g., as a function of age, race/ethnicity, or socioeconomic status). Conversely, only about half of US children who receive a clinical diagnosis of ADHD are treated with stimulants, suggesting a large number of children are not receiving medication when perhaps they should be. Additional important clinical consequences of an incorrect diagnosis include stigmatizing youth unnecessarily with a diagnosis of ADHD (i.e., “labeling harms,” which can impair self-esteem or reduce future educational attainment or career opportunities). Misdiagnosis of ADHD not only leads to its overdiagnosis or underdiagnosis, but it can also lead to incorrectly diagnosing as ADHD other conditions that share symptoms with ADHD (e.g., anxiety, conduct disorders, speech or language delay, complex trauma, difficult home environments, attachment problems or other medical disorders/diseases or developmental disorders). Thus, treating disorders misconstrued as ADHD may withhold appropriate psychosocial and psychological therapies for those conditions and instead inappropriately treat them with stimulants and other ADHD therapies that may have little or no effectiveness in treating those conditions.
Once a diagnosis of ADHD is made, patients and their parents ask, “What treatment should be undertaken?” The answer to this question is challenging for most clinicians and requires a detailed and accurate understanding of the comparative safety and effectiveness of pharmacologic and behavioral treatments for improving not only the immediate symptoms of ADHD, but also the long-term impact that ADHD has on academic and occupational success, mental health, substance abuse, and conduct or antisocial behaviors. This answer, however, is always conditioned on characteristics of the individual child or the child’s environment that are known to modify response to treatment. These “tailoring variables” can include patient age, ADHD presentation (primarily inattentive, hyperactive/impulsive, or combined), socioeconomic status, race and ethnicity, prior trauma history, co-occurring conditions (e.g., depression or anxiety), family conflict, and biomarker status (e.g., genotype, cognitive testing profile). Possible benefits of medication must be weighed against risks and side effects. Many parents and clinicians do not have ready access to information that can help them identify and assess these potential risks and whether their child is likely to respond better or worse to any specific possible treatment they might undertake.

Treatment strategies for ADHD are diverse and can be divided into pharmacologic and nonpharmacologic therapies. The main categories of pharmacologic therapies include stimulants (either methylphenidate or amphetamine derivatives) or non-stimulants (selective norepinephrine reuptake inhibitors, alpha-2 agonists, and antidepressants). The current frontline treatment for ADHD is stimulant medication, with or without combined psychological and behavioral therapies. Nonpharmacologic therapies include psychosocial interventions (e.g., homework, organizational, and social skills training, sleep-focused interventions, dialectical behavior therapy, cognitive behavior therapy, and mindfulness training), school-based interventions (e.g., psychoeducation and expert consultation for class-room based interventions by teachers), cognitive training therapies (e.g., training of working memory, executive function, and motor skills using interactive games and tasks), parent support (e.g., behavioral training for parents, in-home nurse visits, group psychotherapy, telephone-assisted self-help, psychoeducation, and parental friendship coaching), provider interventions (e.g., psychoeducation and training of providers, support for monitoring therapeutic response, and expert consultation) neurofeedback (e.g., learning to modulate EEG activity), nutritional or dietary supplements (e.g., Omega-3, vitamins, herbs), complementary, alternative, or integrative medicine (acupuncture, homeopathy, physical therapy, and chiropractic treatment).

In children over the age of 5, the American Academy of Pediatrics (AAP) recommends stimulants as the first line of therapy. Whether combining behavioral therapy with stimulant medication confers a significant benefit over stimulants alone, or whether nonpharmacologic therapy alone may be effective, is at present unclear. Adverse effects of pharmacologic treatment depend on the specific intervention and may include gastrointestinal symptoms, changes in appetite, slowed somatic growth, and sleep disturbance. Treatment can also lead to personality changes or perceived loss of spontaneity. Individuals who are initially misdiagnosed or who have inadequate monitoring may be overtreated with stimulant medications. Overtreatment leads to the risk of treatment with little or no benefit or to unnecessary side effects. Long-term adherence to medication regimens is often poor in youth who have ADHD and can limit the long-term, real-world effectiveness of medication.
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Reported effect sizes on short-term outcomes for either class of stimulant medication (methylphenidate or amphetamine) have been large, whereas effect sizes for psychological and behavioral therapies on short-term outcomes generally have been small or moderate in magnitude. Long-term outcomes for both medication and non-medications therapies have been less well studied, and little is known about which treatment to begin first and for whom, or how best to sequence treatments for ADHD when the first intervention proves ineffective or insufficient. SMART (Sequential Multiple Assignment Randomized Trial) study designs have begun to emerge to help identify the best sequences of treatment and they have begun to call into question the dominant practice of beginning treatment with medication rather than behavioral therapy. Emerging SMART designs also help identify which treatment sequences work best for which type of patient – young or old, in which ethnic group, with which co-occurring illnesses, and with which specific genotypes. Recent advances in the development and testing of novel therapies for ADHD warrant a systematic review of their efficacy and effectiveness that will provide information eagerly awaited by clinicians and stakeholders. These novel therapeutics include cognitive training, game-based digital devices such as the FDA-approved EndeavorRx, and neuromodulation techniques such as repetitive Transcranial Magnetic Stimulation and the FDA-approved external Trigeminal Nerve Stimulator.

Once treatment is begun, the central question is, “Is the treatment working?” The answer to this question is not as straightforward as it may at first appear, as ADHD symptoms and the capacity to compensate for them may vary over time and with circumstance (e.g., school day or weekend, the presence of psychosocial stress), by symptom presentation (e.g., hyperactivity, inattention, impulsivity), and by functional domain (academics, risk-taking behaviors, socialization). Thus, valid and reliable methods are needed to monitor treatment response easily and accurately. If the current treatment is not producing the desired response, or if side effects are limiting the dose of medication prescribed, the final question is what to do next to improve short- and long-term outcomes. For example, is it better to optimize dosing of the current medication, switch to another first-line medication, switch to a second-line medication, add an additional medication, or add an adjunctive psychological or behavioral therapy? And how does a clinician or parent prevent the complete abandonment of treatment, which is exceedingly common, when the first line treatment is ineffective or produces troubling side effects?

After a child is diagnosed with ADHD and an initial treatment strategy is determined, a monitoring strategy is applied to ensure that outcomes are evaluated over time, and modification of treatments are made when needed. Repeat monitoring should provide the opportunity to intervene (e.g., modify the treatment) before the undesirable or adverse outcomes associated with ADHD occur or determine whether and which treatment for remains clinically indicated. Several instruments are available to assess treatment response and adverse effects over time, including the Vanderbilt, Conners, ADHD Rating Scale-5, and SNAP-IV rating scales. Monitoring may also include assessment of any adverse treatment effects. The frequency of monitoring may depend on the age of the child, the specific treatment, duration of treatment, previous symptoms, co-occurring conditions, and family and health care provider preferences. One-third to one-half of patients with ADHD will have clinically significant symptoms that persist into adulthood.
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Co-occurring problems are the rule, as approximately half are diagnosed with an oppositional defiant or conduct disorder diagnosis, one-third have an anxiety disorder, and 20 percent have depression.\(^2\) Youth with ADHD are at increased risk for future problems associated with risk-taking, such as substance abuse, motor vehicle accidents, unprotected sexual intercourse, and criminal behavior. They are at considerable risk as adults for chronic health problems, including diabetes, heart disease, and poor oral health, in part because they engage in behaviors that increase risk for these conditions, and they often fail to adhere to health-protective behaviors. They are also at risk for future depression, anxiety, suicide attempts, and problematic peer and family relationships.\(^4\) In addition, the long-term effectiveness of standard and novel interventions for ADHD, and their potential long-term adverse effects, are not well known\(^7\) and are difficult to detect and document\(^6\) even though they are critically important considerations for patients, parents, and clinicians as they make treatment decisions. Knowledge of the ways in which unique patient characteristics modify these short- and long-term treatment outcomes is essential to tailor and personalize care for individual patients.\(^7\)

1.2 Purpose and Scope of the Systematic Review

This review updates prior AHRQ reviews on ADHD.\(^1\) It builds on the previous reports and will address important gaps in knowledge related to the diagnosis of ADHD, concerns about overtreatment and undertreatment, and conflicting literature about the effectiveness of long-term treatment. The review is especially intended to be a resource for clinicians, researchers, and policymakers, although through them, we hope the review will benefit the many youth who have ADHD, as well as their families and teachers. We anticipate that the analyses and results will be difficult for most parents, educators, and lay persons to understand, although the executive summary, key points, and discussion are intentionally crafted to be accessible to a much wider audience. Finally, this systematic review aims to inform a planned update of the current American Academy of Pediatrics (AAP) clinical guidelines for the diagnosis, evaluation, and treatment of ADHD.

Since the last AHRQ report was published, further diagnostic and treatment strategies have been suggested, warranting an update of the literature. Identified references address predominantly diagnostic questions such as the diagnostic validity of specific tests and suggested diagnostic tools.\(^1\) Furthermore, key studies that provide important information on the diagnosis of ADHD predate the most recent ADHD report. Hence, the current systematic review will include older studies. Searches for studies of diagnostic tools will extend back to 1980, when the diagnosis of ADHD and its diagnostic criteria were first introduced in the DSM as Attention Deficit Disorder with or without hyperactivity (DSM-III).\(^2\)

In addition, since the last AHRQ review, several studies have been published that explore novel interventions, such as game-based cognitive therapy or computer training.\(^5\) Furthermore, key studies that predate the most recent ADHD report provide important information on the treatment of ADHD. Hence, the current systematic review also includes older treatment studies. Searches for studies of ADHD interventions will therefore extend back to 1980, when long-acting stimulants were introduced, heralding the modern era of ADHD pharmacotherapy.
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Given that the 2018 AHRQ report on ADHD identified no monitoring study, we removed limits on the search date for this question and will aim for a comprehensive review that considers older studies (the 2018 report included only studies published to 2009). Based on discussions and preliminary literature searches, we still do not expect to identify many studies for monitoring strategies and long-term outcomes, although we anticipated that some data may be available from the educational and school psychology literature, such as Response to Intervention – Behavioral (RTI-B) strategies to monitor behavioral and psychosocial interventions in the classroom that aim to improve ADHD outcomes.

To our knowledge, no prior reviews of ADHD have been as comprehensive as the current review in the range of diagnostic tools, treatments, clinical outcomes, participant ages, and year of publication for the included studies. We hope that it will be a valuable resource for patients, families, clinicians, educators, policymakers, and researchers for years to come.
2. Methods

2.1 Review Approach

The methods for this evidence review follow the Methods Guide for Evidence-based Practice Center (EPC) Program (available at https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview).

The topic of this report was developed by the Patient-Centered Outcomes Research Institute (PCORI) in consultation with AHRQ. KQs were posted on AHRQ’s Effective Health Care (EHC) website for public comment in August 2021 for three weeks. PCORI conducted an online townhall meeting of stakeholder to discuss the comments in November 2021 (Appendix E). The protocol was refined following stakeholder input through public posting of the KQs, the townhall meeting, and input from key informants. The final protocol is posted on the EHC website at https://effectivehealthcare.ahrq.gov/products/attention-deficit-hyperactivity-disorder/protocol. A panel of technical experts provided high-level content and methodological expertise throughout development of the review protocol.

2.1.1 Key Questions (KQs)

The KQs proposed for the systematic review, addressing diagnosis (KQ1), treatment (KQ2), and monitoring (KQ3) of ADHD, were refined following input from Key Informants, stakeholder input through public posting, and a townhall organized by the Patient-Centered Outcomes Research Institute (PCORI).

We obtained input from eight key informants. Key informants included a parent of an underserved, ethnic minority youth with ADHD, an advocate from the national advocacy group CHADD (Children and Adults with ADHD), an expert in medical safety, an expert in testing and assessment, a representative from the Association for Child and Adolescent Counseling (ACAC), a family medicine representative, and members of the guideline group who will use the review to update the guidelines. The key informants showed strong support for the importance and relevance of the KQs. They suggested relevant references and provided important input on terminology relevant to the literature searches. There were discussions about developments since the last report and about where the field is now from the perspective of each participant.

Additional input on the project was received through public posting of the review questions on the AHRQ website. The posting aimed to elicit responses from stakeholders to ensure that the review is addressing the right questions, and all aspects have been considered. A submission from the American Psychological Association (APA) and a submission from a researcher at Immaculata University addressed all review questions. For KQ1, input stressed the importance of minimizing false positive diagnoses from the presence of co-occurring conditions; costs and reliability of EEG diagnostic information; that a developmental lens should be adopted (e.g., does a child’s relative age and developmental maturity in comparison to classmates influence the odds of receiving a diagnosis of ADHD?); that the role of sleep, trauma, and language development should be considered; and that annual reassessments of behaviors and impairment are important. For KQ2, input addressed the importance of reviewing the effects of medications and the risk of diversion of pharmacological treatment; of treatment fidelity; of adherence to and persistence of medication use; of behavioral treatment, including use of different modalities (in person, video, online); and of the Multimodal Treatment of ADHD study, specifically. For KQ3, the input targeted the conduct of routine assessments, including reports from parents, teachers,
2. Methods

and the children/adolescents, that should be accessible to all parties; and that routine monitoring should be part of the child/adolescent’s record.\textsuperscript{70}

Finally, at the online townhall meeting in November 2021 hosted by PCORI, there were passionate discussions and advocacy for changes in ADHD policy and research. Some participants felt strongly that both important policies and data were lacking across the board. Specific areas identified by this group included lumping ADHD-Inattentive with the Combined presentation, the lack of empirical data on executive function training and executive function coaches, the general lack of specific and feasible non-pharmacological interventions that parents can use easily and have access to, as well as the lack of availability of parent training programs being offered before initiating stimulant medication.

Following key informant and stakeholder input, the KQs are as follows:

KQ1. For the diagnosis of ADHD:
   a. What is the comparative diagnostic accuracy of approaches that can be used in the primary care practice setting or by specialists to diagnose ADHD among individuals younger than 7 years of age?
   b. What is the comparative diagnostic accuracy of EEG, imaging, or approaches assessing executive function that can be used in the primary care practice setting or by specialists to diagnose ADHD among individuals aged 7 through 17?
   c. For both populations, how does the comparative diagnostic accuracy of these approaches vary by clinical setting, including primary care or specialty clinic, or patient subgroup, including, age, sex, or other risk factors associated with ADHD?
   d. What are the adverse effects associated with being labeled correctly or incorrectly as having ADHD?

KQ2. What are the comparative safety and effectiveness of pharmacologic and/or nonpharmacologic treatments of ADHD in improving outcomes associated with ADHD?
   a. How do these outcomes vary by presentation (inattentive, hyperactive/impulsive, and combined) or other co-occurring conditions?
   b. What is the risk of diversion of pharmacologic treatment?

KQ3. What are the comparative safety and effectiveness of different empirical monitoring strategies to evaluate the effectiveness of treatment in improving ADHD symptoms or other long-term outcomes?

While the diagnosis and treatment KQs are unchanged from the 2018 AHRQ EPC report on the topic, the KQ regarding monitoring ADHD over time was rephrased for clarity. Of note, the restricted age range for sub-question 1b is based on recognition that most of these specialized technologies require the child to remain very still, which is difficult for children younger than seven. Neuropsychological tests as well as genetic markers are included in 1a and 1b. In question 1d, we will assess whether the literature suggests whether these adverse effects differ for those youth who are on the threshold of clinical or subclinical diagnoses. Co-morbidities may include co-occurring conditions such as conduct disorder, mood disorders, autism spectrum disorders,
Williams syndrome, Down syndrome, learning and language disabilities, and developmental coordination disorder. Questions 2 and 3 address effectiveness as well as adverse outcomes.

### 2.1.2 Analytic Framework

The analytic framework (Figure 1) depicts the KQs and outcomes to evaluate the diagnosis, treatment, and monitoring strategies for ADHD.

**Figure 1. Analytic Framework**

- **Adverse Effects of Diagnosis:**
  - Labelled correctly or incorrectly

- **Intermediate Outcomes:**
  - Standardized symptom scores
  - Progress toward patient-identified goals
  - Executive functioning measures
  - Acceptability of treatment
  - Functional impairment
  - Changes in treatment or dose

- **Final Outcomes:**
  - Academic performance
  - Workforce participation
  - Quality of peer relationships
  - Divorce/relationship status
  - Motor vehicle collisions or other accidents
  - Motor vehicle violations
  - Risk-taking behaviors
  - Incarceration or other legal system involvement
  - Obesity
  - Tobacco use
  - Substance abuse
  - Mood disorders
  - Depression and anxiety
  - Self-injurious behavior
  - Suicide (attempted/completed)
  - Suicidal ideation
  - Mortality

### 2.2 Study Selection

The **eligibility criteria** are organized in a PICOTS (population, intervention, comparator, outcome, timing, setting, study design, and other limiters) framework. The draft report includes studies published from 1980 to 2021, an ongoing update search will capture 2022 and 2023 studies.

#### 2.2.1 Search Strategy

For primary research studies, we searched the database PubMed (biomedical literature), EMBASE (pharmacology emphasis), PsycINFO (psychological research), and ERIC (education research). We also searched the U.S. trial database – ClinicalTrials.gov – to capture all relevant data regardless of the publication status. Increasingly trial registries include data and a complete record of adverse events, making them an important evidence review tool to identify all relevant data and to reduce publication bias.
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We used existing reviews for reference-mining; these were identified through the same databases used for primary research plus searching the Cochrane Database of Systematic Reviews, Campbell Collaboration, What Works in Education, and PROSPERO. Scoping searches identified several published reviews. These often address medication treatment with an increased focus on safety.86-90 Given that many practice guidelines are now based on systematic reviews, we also searched the ECRI Guidelines Trust, G-I-N, and ClinicalKey. Using external systematic reviews in addition to building on prior AHRQ reports increases the certainty that all relevant studies have been captured.

The literature searches for this project were built on prior ADHD reports published by AHRQ. KQ1 searches covered 1980 to 2011, and 2016 to present. Since research published between 2011 and 2016 was thoroughly screened by the 2018 review, we used the identified studies listed in the 2018 AHRQ report to cover 2011 to 2016. KQ2 searches covered 1980 to 2011 and 2016 to date, omitting search terms covered in the 2011 AHRQ report, and adding the adolescent population, which was not previously fully covered. We used the identified studies in the AHRQ report and reference-mining of pertinent reviews to identify relevant studies. KQ3 searches were not limited by date. We simplified the search strategies and removed filters for specific interventions for key databases to ensure that no existing test or intervention evaluation would be missed. Searches were designed, executed, and documented by the evidence review center librarian. The search strategy underwent peer review to ensure high quality searches. The search strategies for the databases are shown in the methods appendix (Appendix A).

Furthermore, we used information provided by content experts,91 and the technical expert panel reviewed the list of included studies to ensure that all relevant literature has been captured.

We used detailed pre-established criteria to determine eligibility for inclusion and exclusion of publications in accordance with the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews. To reduce reviewer errors and bias, all citations were reviewed by a human reviewer and screened by a machine learning algorithm. Citations deemed potentially relevant were obtained as full text. Each full-text article was reviewed for eligibility by two literature reviewers, including any articles suggested by peer reviewers or that arose from the public posting process, submission through the SEADS (Supplemental Evidence And Data for Systematic reviews) portal, or response to Federal Register notice. Any disagreements were resolved by consensus. We maintain a record of studies excluded at the full-text level with reasons for exclusion (see Appendix B).

The SEADS portal was open from July 1st through August 15th 2022. We received two submissions, including one from the American Academy of Child and Adolescent Psychiatry. Submissions include comments on the need for an evidence review of ADHD research, the usefulness of the review as outlined in the posted protocol, and in total four published studies were submitted to be considered for the systematic review.

While the draft report is under peer review and open for public comment, we will update the search and include any eligible studies identified either during that search or through peer or public reviews in the final report.

2.2.2 Eligibility Criteria

The detailed inclusion and exclusion criteria are listed in Table 1.
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<table>
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<td><strong>PICOTS Element</strong></td>
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<td><strong>Population</strong></td>
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<td><strong>Study Design</strong></td>
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<th>PICOTS Element</th>
<th>KQ1 (Diagnosis)</th>
<th>KQ2 (Treatments)</th>
<th>KQ3 (Monitoring)</th>
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<tr>
<td>• For diagnostic accuracy, observational studies, are eligible if they include patients with diagnostic uncertainty and direct comparison of diagnosis in primary care to diagnosis by a specialist</td>
<td>• Controlled clinical trials and prospective and retrospective observational studies with comparator for non-drug treatments</td>
<td>• No study size restriction</td>
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<tr>
<td>• Controlled clinical trials and prospective and retrospective observational studies with comparator for non-drug treatments</td>
<td><strong>Exclusion:</strong> Editorials, nonsystematic reviews, letters, case series, case reports, pre-post studies. Systematic reviews are not eligible for inclusion but will be retained.</td>
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<td><strong>Other limiters</strong></td>
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<td></td>
<td>• Published after 1980</td>
<td>• Published after 1980</td>
<td>• Monitoring strategies and long-term effects have no publication year restriction</td>
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<td><strong>Exclusion:</strong> Non-English language and abbreviated publications (abstracts, letters)</td>
<td><strong>Exclusion:</strong> Non-English language and abbreviated publications (abstracts, letters)</td>
<td>• Journal manuscripts and trial record data with results</td>
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<td><strong>Exclusion:</strong> Non-English language and abbreviated publications (abstracts, letters)</td>
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Note: FDA: Food and Drug Administration, KQ: Key Question

Compared to the prior 2018 report on ADHD, the eligibility criteria were simplified and now includes all tests used to diagnose ADHD and all treatments for ADHD treatments. In addition, randomized controlled trials (RCTs) are no longer limited by sample size given that RCTs allow strong evidence statements; however, treatment studies with fewer than 100 participants had to report a power calculation indicating sufficient power for at least one patient outcome to ensure that the studies were designed to detect a difference between the intervention and comparison group. Not all studies can be combined in meta-analyses to aggregate data, because the intervention, comparator, and reported outcome combinations are often unique to the study; hence we required individual studies to show sufficient power to detect effects. We specified that intervention studies had to have a treatment duration of four weeks; we excluded experiments of shorter duration (e.g., proof of concept studies) and focused on treatment for ADHD. Finally, no comparator is needed anymore for monitoring studies, and these are not restricted by publication date, given the small evidence base (the 2018 report found no relevant study).

Relevant systematic reviews and meta-analyses were retained as background or for reference-mining but will not be included as evidence. Publications reporting on the same participants were consolidated into one study record. Studies exclusively published in non-English language publications remain excluded given the high volume of literature, the focus on the review on populations in the U.S., the scope of the KQs, and the aim to support a U.S. clinical practice guideline.
2. Methods

2.3 Data Extraction

We abstracted detailed information regarding study characteristics, participants, methods, and results. The review team created data abstraction forms for the KQs in DistillerSR, an online program for systematic reviews. Forms included extensive guidance to support reviewers, both to aid reproducibility and standardization of data collection. One literature reviewer abstracted the data, and a second reviewer checked for accuracy and completeness. Further data checks were conducted while synthesizing results across studies. Disagreements were resolved by consensus.

We designed the data abstraction forms to collect the data required to evaluate the study, as well as demographic and other data needed for determining outcomes, informed by existing research.92-95 We paid particular attention to describing the details of the treatment (e.g., pharmacotherapy dosing, methods of behavioral interventions), patient characteristics (e.g., ADHD presentation, co-occurring disorders, age), and study design (e.g., RCT versus observational), which may influence the reported outcome results. In addition, we carefully described comparators, as treatment standards may have changed during the period covered by the review. In addition, data necessary for assessing quality and applicability as described in the EPC Methods Guide were abstracted. Forms were pilot-tested with a sample of included articles to ensure that all relevant data elements are captured and that ambiguity is avoided.

The abstracted information was used for analyses as well as to populate the evidence tables showing characteristics for each included study. Final abstracted data will be uploaded to SRDR per EPC requirements and will be publicly available.

2.4 Risk of Bias Assessment

The critical appraisal for individual studies applied criteria consistent with QUADAS 2 for diagnostic studies and the RoB 2 guidance for common sources of bias in intervention studies adapted for the eligible study designs.96, 97

QUADAS 2 evaluates four domains: patient selection, index test characteristics, reference standard quality, as well as flow and timing:97

- **Patient selection:** The domain patient selection addresses whether the selection of patients could have introduced bias, taking into account whether the study enrolled a consecutive or random sample, whether the data are not based on a retrospective case-control design, and whether the study avoided inappropriate or problematic exclusions from the patient pool.

- **Index test:** The index test domain evaluates whether the conduct or interpretation of the test could have introduced bias, taking into account whether the results of the test were interpreted without knowledge of the results of the reference standard and whether any thresholds or cut-offs were pre-specified (e.g., instead of determined during the study to maximize diagnostic performance).

- **Reference standard:** The domain reference standard evaluates whether the reference standard, its conduct, or its interpretation may have introduced bias, taking into account the quality of the reference standard in correctly classifying the condition and whether the reference standard test results were interpreted without knowledge of the results of the index test.

- **Flow and timing:** The last domain, flow and timing, evaluates whether the conduct of the study may have introduced bias. The assessment takes into account whether the interval between the test and the reference standard was appropriate, whether all patients received
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the reference standard and whether they received the same reference standard, and whether all patients were included in the analysis. For each domain, we assessed the potential risk of bias in the study in order to identify high risk of bias and low risk of bias studies. We evaluated for each study and appraisal domain whether there are concerns regarding the applicability of the study results to the review question (Appendix D). This encompassed whether the patients included in the studies match the review question; whether the test, its conduct, or interpretation differ from the review question; or whether the target condition as defined by the reference standard fully matches the review question.

For treatment and monitoring studies, we assessed the six domains selection, detection, performance, attrition, reporting, and study-specific sources of bias:

- **Selection bias**: For selection bias, we assessed the randomization sequence and allocation concealment in RCTs as well as baseline differences and potential confounders in all studies.

- **Performance bias**: Performance bias evaluated whether patient- or caregiver knowledge of the intervention allocation or circumstances such as the trial context may have affected the outcome, and whether any deviations from intended interventions were balanced between groups.

- **Attrition bias**: Attrition bias considered the number of dropouts, any imbalances across study arms, and whether missing values may have affected the reported outcomes.

- **Detection bias**: Detection bias assessed whether outcome assessors were aware of the intervention allocation, whether this knowledge could have influenced the outcome measurement, and whether the outcome ascertainment could differ between arms.

- **Reporting bias**: Reporting bias assessment includes an evaluation of whether a pre-specified analysis plan exists (e.g., a published protocol), whether the numerical results likely have been selected on the basis of the results, and whether key outcomes were not reported (e.g., an obvious effectiveness indicator is missing) or inadequately reported (e.g., anecdotal adverse event reporting).

- **Other potential sources of bias**: In addition to the types of bias listed above, we assessed other potential sources of bias such as inadequate reporting of intervention details.

Each study was initially appraised by the data abstractor for the study. In a second step, we reviewed risk of bias results across studies to ensure consistency of ratings. Risk of bias results informed the study limitation assessment in the quality of evidence assessment across studies.

2.5 Data Synthesis and Analysis

We summarized key features of the included studies, including study design; participant characteristics; diagnostic, treatment, and monitoring strategies; and frequent outcomes in a narrative overview. We answered each KQ with the available evidence using quantitative syntheses across studies where possible to increase statistical power, to increase precision, and to objectively summarize results across all available evidence. We ordered our findings by diagnostic, treatment, and monitoring strategy, i.e., the KQs.

We broadly characterized tests (KQ1), interventions (KQ2), and monitoring strategies (KQ3). For diagnostic studies, we reported the range of reported diagnostic performance. For KQ2, we differentiated effectiveness and comparative effectiveness results (i.e., comparing to a passive comparison in the form of a control group, or an active comparator in the form of an alternative intervention). We documented results by the pre-specified key outcomes.
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consistently abstracted the longest follow up for each study. We converted reported standard errors and confidence intervals to standard deviations to compute effect sizes. We reversed originally reported outcomes where necessary to facilitate comparisons across studies. For statistical pooling, we used random-effects models corrected for small numbers of studies where necessary to synthesize the available evidence quantitatively.\textsuperscript{98} We computed standardized mean differences (SMD) for continuous outcomes and relative risks (RR) for categorical outcomes to document results across studies. We present summary estimates and 95 percent confidence intervals (CI) for all summary estimates. We tested for heterogeneity using graphical displays and the I-squared statistics. The statistic ranges from zero to 100 percent and we noted in particular results where heterogeneity exceeded 70 percent or above. We anticipated that intervention effects may be heterogeneous across studies. We explored potential sources of heterogeneity, while recognizing that the ability of statistical methods to detect individual sources of heterogeneity may be limited in the presence of multiple sources of heterogeneity.\textsuperscript{99} We hypothesized that the methodological rigor of individual studies and patients’ underlying clinical presentations are potentially associated with the intervention effects. We performed meta-regression analyses to examine these hypotheses and reported sensitivity analyses where necessary. For KQ3, we documented outcomes as reported by the original authors.

Pre-defined subgroups for KQ1 included children younger than 7 years of age and children and adolescents, 7 through 17. We assessed whether diagnostic performance is associated with the age of participants using reported sensitivity and specificity estimates in a regression analysis across studies. In addition, we assessed the effect of treatment and diagnosis in participants with concomitant morbidities; the racial and ethnic composition of study samples; and the potential effect of the diagnostic, treatment, and monitoring setting in meta-regressions across studies and KQs. We assessed the potential for publication bias for all key outcomes using the Begg and the Egger test.\textsuperscript{100, 101} The trim and fill method provides alternative estimates where evidence of publication bias was detected.\textsuperscript{102}

Applicability was assessed in accordance with the AHRQ’s Methods Guide. Factors that may affect applicability, which we have identified a priori, include patient, intervention, comparisons, outcomes, settings, and study design features. We used this information to assess the situations in which the evidence is most relevant and to evaluate applicability to real-world clinical practice in typical U.S. settings, summarizing applicability assessments qualitatively.

2.6 Grading the Body of Evidence

The strength of evidence assessment documents uncertainty, outlines the reasons for insufficient evidence where appropriate, and communicates our confidence in the findings.

The strength of evidence for each body of evidence (based on the KQ, diagnostic and treatment approach, comparator, and outcome) was initially assessed by one researcher with experience in determining strength of evidence for each primary clinical outcome by following the principles for adapting GRADE (Grading of Recommendations Assessment, Development and Evaluation), outlined in the AHRQ methods guide.\textsuperscript{103} The initial assessment was then discussed in the team.

2.6.1 Key Outcomes

We prioritized outcomes with the help of the TEP in combination with team expertise. The panelists reviewed a large number of possible outcomes. We considered outcomes most
2. Methods

clinically relevant and important to patients and clinicians to guide clinical practice. The following outcomes were selected for the strength of evidence assessment:

- **Key Question 1:**
  - Sensitivity
  - Specificity
  - Costs
  - Inter-rater reliability
  - Internal consistency
  - Test-retest reliability
  - Misdiagnosis

- **Key Question 2:**
  - Behavior changes
  - Broadband scale scores
  - Standardized symptom scores
  - Functional impairment
  - Acceptability of treatment
  - Academic rating scale scores
  - Appetite changes and growth suppression
  - Number of participants with adverse events

- **Key Question 3:**
  - Functional impairment
  - Broadband scale scores
  - Standardized symptom scores
  - Progress toward patient-identified goals
  - Acceptability of treatment
  - Academic rating scale scores
  - Any long-term effects
  - Growth suppression
  - Quality of peer relationships

For diagnostic studies in KQ1, we abstracted the number of true positive and true negatives in order to compute diagnostic performance measures, but we also abstracted all values as reported by the authors. We added information on the specific cut-off and model used to achieve the diagnostic performance where reported. The impact of misdiagnosis included the risk of missed conditions that can appear as ADHD as well as being incorrectly labeled as having or not having ADHD.

For treatment studies in KQ2, we abstracted numerical values for all key outcomes to facilitate meta-analysis. We also abstracted a brief narrative for the evidence table for each outcome focusing on the comparison to a control or a comparator group (rather than pre-post data). In addition, we summarized study-specific health outcomes and reported adverse events to complete the evidence table for all included studies. For the behavior change domain, we abstracted individual behaviors such as aggression or conduct problems, either from direct observations or behavior ratings, where studies reported these in addition to global impression or symptom scales. We used global psychological, mental health, and child development assessments, such as the CGI (Clinical Global Impression)\(^{104}\) and total scores of the Conners rating scales, that go beyond assessing individual ADHD symptoms as broadband scale scores. For standardized symptom scores, we included summary measures for ADHD symptoms, such
2. Methods

as ADHD-RS-IV (ADHD Rating Scale Version IV),105,106 or, when unavailable, subclasses of individual symptoms for ADHD, such as inattention. For functional impairment, we abstracted functional measures such as the Weiss Functional Impairment Rating Scale.107,108 For acceptability of treatment we abstracted child, parent, or teacher satisfaction with intervention, depending on what was reported. We abstracted academic rating scale scores where reported, in the absence of these, we used broad academic performance measures such as GPA (grade point average). Other, narrower performance measures, such as specific cognitive skills, were summarized in the free text field in the evidence table. For appetite changes and growth suppression, we abstracted indicators such as decreased appetite or growth during the study period. The number of participants with adverse events was restricted to documenting the number of patients reporting at least one adverse event; all other measures (including the number of adverse events across participants) were summarized in the free adverse event text field in the evidence table.

For monitoring studies eligible for KQ 3, we abstracted all information provided by the authors on the suitability of the applied monitoring strategy in addition to all pre-specified outcomes.

The synthesis documented the presence and the absence of evidence for the key outcomes for all included diagnostic tests, treatment interventions, and monitoring strategies in the respective sections.

2.6.2 Strength of Evidence Assessments

In determining the quality of the body of evidence, the following domains were evaluated:

- **Study limitations**: The extent to which studies reporting on a particular outcome are likely to be protected from bias. The aggregate risk of bias across individual studies reporting an outcome is considered; graded as low, medium, or high level of study limitations.
- **Inconsistency**: The extent to which studies report the same direction or magnitude of effect for a particular outcome; graded as consistent, inconsistent, or unknown (in the case of a single study).
- **Indirectness**: Describes whether the intervention (test, treatment, or strategy) and the comparator were directly compared (i.e., in head-to-head trials) or indirectly (e.g., through meta-regressions across studies). In addition, indirectness reflects whether the outcome is directly or indirectly related to health outcomes of interest. The domain is graded as direct or indirect.
- **Imprecision**: Describes the level of certainty of the estimate of effect for a particular outcome, where a precise estimate is one that allows a clinically useful conclusion. Graded as precise or imprecise. When quantitative synthesis is not possible, sample size and assessment of variance within individual studies will be considered.
- **Reporting bias**: Occurs when publication or reporting of findings is based on their direction or magnitude of effect. Publication bias, selective outcome reporting, and selective analysis reporting are types of reporting bias. Reporting bias is difficult to assess as systematic identification of unpublished evidence is challenging. If sufficient numbers of RCTs are available, we reviewed Begg and Egger tests and used trim and fill methods to assess the robustness of effect estimates.

Bodies of evidence consisting of RCTs were initially considered as high strength, while bodies of comparative observational studies began as low-strength evidence. The strength of the
2. Methods

evidence could be downgraded based on the limitations described above. There are also situations where evidence may be upgraded (e.g., large magnitude of effect, presence of dose-response relationship, or plausible unmeasured confounders could potentially increase the magnitude of effect) as described in the AHRQ Methods guides. A final strength of evidence grade for each evidence statement was assigned by evaluating and weighing the combined results of the above domains. We differentiated an overall grade of high, moderate, low, or insufficient according to a four-level scale outlined in Table 2.

Table 2. Definitions of the grades of overall strength of evidence

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable (i.e., another study would not change the conclusions).</td>
</tr>
<tr>
<td>Moderate</td>
<td>We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.</td>
</tr>
<tr>
<td>Low</td>
<td>We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.</td>
</tr>
<tr>
<td>Insufficient</td>
<td>We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available, or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.</td>
</tr>
</tbody>
</table>

Summary tables include reasons for downgrading or upgrading the strength of evidence. We will summarize updated evidence and describe what it adds to the previous review and highlight changes to the key findings.

2.7 Peer Review and Public Commentary

The report will be updated after having undergone peer review and public commentary.
3. Results

3. Results: Description of Included Evidence

Below we provide the report results, including the Key Points for each KQ, and describe the included evidence, as well as the data synthesis and a summary of the strength of evidence. Details on results of literature searches, included studies, and the strength of evidence can be found in the Appendix.

The searches identified 22,091 citations. Of these, we obtained 6,900 as full text. The flow diagram (Figure 2) describes the study flow through the literature review.

**Figure 2. Flow Diagram**

In total, 533 studies reported in 1,058 publications met the eligibility criteria.17, 20, 23, 26, 27, 52, 59, 83, 110-1159 This included 223 studies addressing KQ1, 304 studies addressing KQ2, and 9 studies addressing KQ3. The flow diagram summarizes the main reason for exclusion from the review. In addition, it shows that we retained a large number of papers as Background. The list of excluded studies and background studies is listed in Appendix B. In most cases, these were
3. Results

existing systematic reviews addressing an individual aspect of ADHD research that were then reference-mined to ensure that all eligible studies had been included in the report. The median minimum age in included studies was six years old and the median number of girls included in the studies was 25 percent.

The following subchapters address each KQ.
4. Results: Diagnosis of ADHD

The KQ is divided into four subquestions:

- **KQ1a.** What is the comparative diagnostic accuracy of approaches that can be used in the primary care practice setting or by specialists to diagnose ADHD among individuals younger than 7 years of age?
- **KQ1b.** What is the comparative diagnostic accuracy of EEG, imaging, or approaches assessing executive function that can be used in the primary care practice setting or by specialists to diagnose ADHD among individuals aged 7 through 17?
- **KQ1c.** For both populations, how does the comparative diagnostic accuracy of these approaches vary by clinical setting, including primary care or specialty clinic, or patient subgroup, including, age, sex, or other risk factors associated with ADHD?
- **KQ1d.** What are the adverse effects associated with being labeled correctly or incorrectly as having ADHD?

The gold standard or reference standard against which diagnostic tools were compared was diagnosis by a mental health specialist, such as a psychologist, psychiatrist or other care provider, using a well-validated and reliable process of confirming the diagnosis of ADHD according to the DSM. Many identified studies included a broader age range rather than differentiating clearly between younger (KQ1a) or older (KQ1b) than 7 years of age. Hence we added a section describing the results for parental ratings, teacher ratings, clinician tools, and biomarkers before addressing the key questions. The section summarizes results by test and most studies evaluated a combined sample of children and adolescents. The KQ1a section describes all diagnostic approaches for children younger than 7 years of age regardless of the applied test. The KQ1b section describes teen/child self reports, EEG, imaging, and neuropsychological tests.

### 4.1 KQ1 ADHD Diagnosis Key Points

Key points pertaining to the diagnosis of ADHD are as follows.

- Diagnostic test performance likely depend on whether youth with ADHD are being differentiated from typically developing children or from clinically referred children who had some kind of mental health or behavioral issue.
- Rating scales for parent, teacher, or self assessment as a diagnostic tool for ADHD have high internal consistency but poor to moderate reliability between raters, indicating that obtaining ratings from multiple informants (the youth, both parents, and teachers) may be valuable to inform clinical judgement.
- Studies evaluating neuropsychological tests of executive functioning (e.g., Continuous Performance Test) used unique combinations of individual cognitive measures, making it difficult to compare performance across studies.
- Diagnostic performance of biomarkers, EEG, and MRI scans show great variability across studies and their ability to aid clinical diagnosis for ADHD remains unclear. Studies have rarely assessed test-retest reliability, no findings have been replicated prospectively using the same measure in independent samples, and real-world effectiveness studies of diagnostic performance have not been conducted.
- Very few studies have assessed performance of diagnostic tools for ADHD in children under the age of 7 years and more research is needed.
- The identified studies did not assess the adverse effects of being labeled correctly or incorrectly as having a diagnosis of ADHD.
4. Results: Diagnosis of ADHD

4.2 KQ1 ADHD Diagnosis Summary of Findings


Table 3. KQ1 Summary of Findings and Strength of Evidence for the Diagnosis of ADHD

<table>
<thead>
<tr>
<th>Tests to diagnose ADHD</th>
<th>Outcome</th>
<th>Number of Studies; Study Design; IDs</th>
<th>Findings</th>
<th>SoE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ1a Diagnostic tests for under 7 year olds</td>
<td>Sensitivity</td>
<td>6 studies170, 175, 193, 326, 406, 458</td>
<td>Sensitivity ranged from 66% combining teacher and parent ratings (no corresponding specificity reported)193 to 97% (corresponding specificity 84%) for an activity measure190 differentiating ADHD and neurotypical development Sensitivity ranged from 64% (corresponding specificity 75%) for a neuropsychological test170 to 76% (corresponding specificity 70%) for a different neuropsychological test158 in clinical samples</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1a Diagnostic tests for under 7 year olds</td>
<td>Specificity</td>
<td>6 studies170, 175, 193, 326, 406, 458</td>
<td>Specificity ranged from 38% (corresponding sensitivity 95) using EEG data193 to 84% (corresponding sensitivity 97% and 87%)193, 406 for an activity measure and an EEG algorithm differentiating ADHD and neurotypical development Specificity ranged from 70% (corresponding sensitivity 76%) for a neuropsychological test158 to 91% (corresponding sensitivity 71%) for the Child Behavior Checklist for ages 1.5 to 5 Attention-Deficit/Hyperactivity Problems scale26 in clinical samples</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1a Diagnostic tests for under 7 year olds</td>
<td>Accuracy</td>
<td>5 studies170, 193, 326, 406, 455</td>
<td>Accuracy ranged from 64%155 combining different executive function tasks to 93%155 combining teacher and parent ratings, both in a model supported by machine learning differentiating ADHD and neurotypical development Accuracy ranged from 70%170 for a neuropsychological test to 80%126 for parent rating of the Child Behavior Checklist for ages 1.5 to 5 Attention-Deficit/Hyperactivity Problems scale in clinical samples</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1a Diagnostic tests for under 7 year olds</td>
<td>AUC</td>
<td>6 studies175, 193, 326, 402, 406, 455</td>
<td>AUC ranged from 0.68150 using EEG data to 0.98155 for combined teacher and parent ratings differentiating ADHD and neurotypical development AUC was 0.83 in a clinical sample126 using the Child Behavior Checklist for ages 1.5 to 5 Attention-Deficit/Hyperactivity Problems scale</td>
<td>Low</td>
</tr>
</tbody>
</table>
### 4. Results: Diagnosis of ADHD

<table>
<thead>
<tr>
<th>Tests to diagnose ADHD</th>
<th>Outcome</th>
<th>Number of Studies; Study Design; IDs</th>
<th>Findings</th>
<th>SoE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ1a Diagnostic tests for under 7 year olds</td>
<td>Inter-rater reliability</td>
<td>1 study&lt;sup&gt;473&lt;/sup&gt;</td>
<td>ICC 0.92 between researchers administering the <em>Disruptive Behavior Diagnostic Observation Schedule</em>&lt;sup&gt;173&lt;/sup&gt; differentiating ADHD and neurotypical development</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1a Diagnostic tests for under 7 year olds</td>
<td>Internal consistency</td>
<td>2 studies&lt;sup&gt;455, 504&lt;/sup&gt;</td>
<td>Neurotypical samples: Cronbach’s alpha 0.92 for parent ratings on the <em>Diagnostic Infant and Preschool Assessment Likert version (DIPA-L)</em>&lt;sup&gt;504&lt;/sup&gt; Cronbach’s alpha <em>Behavior Rating Inventory of Executive Function</em> preschool version 0.976 for teacher ratings and 0.970 for parent ratings; child version 0.724 for teacher ratings and 0.978 for parent ratings&lt;sup&gt;455&lt;/sup&gt;</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1a Diagnostic tests for under 7 year olds</td>
<td>Test-retest reliability</td>
<td>1 study&lt;sup&gt;504&lt;/sup&gt;</td>
<td>ICC 0.91 and Kappa 0.84 for parent ratings on the <em>Diagnostic Infant and Preschool Assessment Likert version (DIPA-L)</em>, 30 days or less between interviews&lt;sup&gt;504&lt;/sup&gt; differentiating ADHD and neurotypical development</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1a Diagnostic tests for under 7 year olds</td>
<td>Misdiagnosis consequences</td>
<td>0 studies</td>
<td>No data</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ1a Diagnostic tests for under 7 year olds</td>
<td>Costs</td>
<td>0 studies</td>
<td>No data</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ1b Diagnostic tests for 7-18 year olds</td>
<td>Sensitivity</td>
<td>See test-specific results</td>
<td>See test-specific results</td>
<td>See test-specific results</td>
</tr>
<tr>
<td>KQ1b Diagnostic tests for 7-18 year olds</td>
<td>Specificity</td>
<td>See test-specific results</td>
<td>See test-specific results</td>
<td>See test-specific results</td>
</tr>
<tr>
<td>KQ1b Diagnostic tests for 7-18 year olds</td>
<td>Accuracy</td>
<td>See test-specific results</td>
<td>See test-specific results</td>
<td>See test-specific results</td>
</tr>
<tr>
<td>KQ1b Diagnostic tests for 7-18 year olds</td>
<td>AUC</td>
<td>See test-specific results</td>
<td>See test-specific results</td>
<td>See test-specific results</td>
</tr>
<tr>
<td>KQ1b Diagnostic tests for 7-18 year olds</td>
<td>Inter-rater reliability</td>
<td>See test-specific results</td>
<td>See test-specific results</td>
<td>See test-specific results</td>
</tr>
<tr>
<td>KQ1b Diagnostic tests for 7-18 year olds</td>
<td>Internal consistency</td>
<td>See test-specific results</td>
<td>See test-specific results</td>
<td>See test-specific results</td>
</tr>
<tr>
<td>KQ1b Diagnostic tests for 7-18 year olds</td>
<td>Test-retest reliability</td>
<td>See test-specific results</td>
<td>See test-specific results</td>
<td>See test-specific results</td>
</tr>
<tr>
<td>KQ1b Diagnostic tests for 7-18 year olds</td>
<td>Misdiagnosis consequences</td>
<td>See test-specific results</td>
<td>See test-specific results</td>
<td>See test-specific results</td>
</tr>
</tbody>
</table>
4. Results: Diagnosis of ADHD

<table>
<thead>
<tr>
<th>Tests to diagnose ADHD</th>
<th>Outcome</th>
<th>Number of Studies; Study Design; IDs</th>
<th>Findings</th>
<th>SoE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ1b</td>
<td>Costs</td>
<td>See test-specific results</td>
<td>See test-specific results</td>
<td>See test-specific results</td>
</tr>
<tr>
<td>KQ1c (effect modifier)</td>
<td>Sensitivity</td>
<td>N/A</td>
<td>Indirect analyses indicated that the setting may be associated with reported results (p&lt;0.001)</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1c (effect modifier)</td>
<td>Specificity</td>
<td>N/A</td>
<td>Indirect analyses indicated that the setting may be associated with reported results (p&lt;0.001)</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1c (effect modifier)</td>
<td>Sensitivity</td>
<td>N/A</td>
<td>Indirect analyses did not detect a systematic effect (p 0.21)</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1c (effect modifier)</td>
<td>Specificity</td>
<td>N/A</td>
<td>Indirect analyses indicated that the population may be associated with reported results (p 0.04)</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1c (effect modifier)</td>
<td>Sensitivity</td>
<td>N/A</td>
<td>Indirect analyses did not detect a systematic effect (p 0.90, p 0.58)</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1c (effect modifier)</td>
<td>Specificity</td>
<td>N/A</td>
<td>Indirect analyses did not detect a systematic effect (p 0.35, 0.45)</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1c (effect modifier)</td>
<td>Sensitivity and specificity</td>
<td>N/A</td>
<td>Indirect analyses did not detect a systematic effect (p 0.80) but the number of female participants was small</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ1d (labeling)</td>
<td>Any outcome</td>
<td>0 studies</td>
<td>No data</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

Notes: KQ key question, N/A not applicable, SoE strength of evidence

As documented in the summary of findings table, tests to diagnose ADHD were very diverse, and studies reported a large range of diagnostic and psychometric performance. Few studies were available to diagnose ADHD in young children. Effect modifier analyses were hindered by the lack of reported detail, although indirect analyses indicated that the diagnostic setting (primary care or specialty care) may influence sensitivity and specificity estimates and population characteristics (comparison to neurotypical developing or clinical samples) may affect specificity estimates. Given that both aspects may be associated (e.g., clinical samples are seen in specialty care), we stratified the remainder of the result presentation by neurotypical or clinical sample. We did not identify studies reporting on the impact of correctly or incorrectly labeling youth as having ADHD.

**Strength of evidence** assessments for this group were low or insufficient for all outcomes. We downgraded results for study limitation (lack of details on the selected tests and employed machine learning algorithm), imprecision (large variation in reported diagnostic performance across studies), and/or lack of replication in more than one study assessing the same test (i.e., consistency could not be assessed).

The methodological rigor and the reporting varied substantially in the identified studies. The potential for risk of bias in the studies is documented in Figure 3. The critical appraisal for the individual studies is in Appendix D.
Selection bias was likely present in two thirds of studies. Often samples were restricted and did not necessarily represent the full range of children with ADHD. For example, in Robles et al., 2011, a convenience sampling strategy was used. Index test issues were present in ten percent of studies. Although the review was restricted to studies reporting a clinical diagnosis of ADHD for participants, reference standard issues were also present in a small number of studies, in particular due to lack of details on procedures and/or diagnosticians. Flow and timing was rated as high risk of bias in several studies. Typically this was due to an unclear participant flow (e.g., it was unclear whether the diagnosis was known before the results of the index test was known).

We also assessed possible applicability issues that could influence the generalizability of the reported data. Figure 4 shows the summary of rated applicability. The applicability for the individual studies is in Appendix D.
4. Results: Diagnosis of ADHD

In several studies, samples were employed that do not represent the general population of children with ADHD, usually because children with co-morbidities were excluded. In addition, several papers took place in specialty care settings with diagnostic and treatment options that go beyond the standard course of action for children with ADHD.

4.3 Summary ADHD Diagnosis By Tests for All Age Groups

We broadly differentiated between parental ratings, teacher ratings, tools for clinicians, teen self-reports, neuropsychological tests, imaging, EEG, biomarker, activity markers, and other (e.g., EKG indicators). This section describes diagnostic tools relevant to all age groups.

4.3.1 Parental Ratings

We identified 35 studies using Parental ratings to diagnose ADHD. The earliest study meeting inclusion criteria was published in 1994. Evaluations of parental rating tools came from five different English-language speaking countries, but most studies were from the US. The populations studied were predominately males between the ages of five and 18. Three studies exclusively included children younger than seven years old. For studies that distinguished between ADHD presentations, most of the participants were diagnosed with the combined or inattentive presentations. In one study focusing on preschool age children who presented with disruptive behavior disorders, 57 percent of participants were diagnosed with the hyperactive/impulsive presentation. While ADHD participants with co-occurring disorders were not excluded from most studies, only a few purposely included children with specific co-occurring disorders such as disruptive behavior disorders or autism. However, about half of identified studies came from clinical samples, rather than general neurotypically developing
4. Results: Diagnosis of ADHD

children -- i.e., they identified children undergoing a diagnostic workup for a potential diagnosis of ADHD, conduct disorders, autism, or depression.

In 13 studies, White participants made up more than 70 percent of the sample. Two studies evaluated samples in which over 50 percent of participants were Black/African American, and one study was identified in which 85 percent of participants were Hispanic or Latino.

Studies reported predominantly on sensitivity, specificity, and area under the curve (AUC). Table 4 shows the findings for the outcomes of interest together with the number of studies and study identifiers. We report findings from population samples that differentiated ADHD from neurotypical developing children separately from results obtained in clinical samples, given that the population was identified as one of the sources of heterogeneity in reported results (see KQ1c).

<table>
<thead>
<tr>
<th>KQ1 Diagnostic Test</th>
<th>Outcome</th>
<th>Number of Studies and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ1 Parental Ratings</td>
<td>Sensitivity</td>
<td>13 studies 176, 300, 311, 326, 335, 352, 414, 437, 450, 515, 542, 569, 629</td>
<td>Sensitivity ranged from 61% (corresponding specificity 73%) to 94% (corresponding specificity 51%) differentiating ADHD and neurotypical development. Sensitivity showed more variation and ranged from 38% (corresponding specificity 96%) to 87% (corresponding specificity 41%) differentiating ADHD in clinical samples.</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Parental Ratings</td>
<td>Specificity</td>
<td>13 studies 176, 300, 311, 326, 335, 352, 414, 437, 450, 515, 542, 569, 629</td>
<td>Specificity ranged from 50% (corresponding sensitivity 82%) to 94% (corresponding sensitivity 73%) differentiating ADHD and neurotypical development. Specificity ranged from 22% (corresponding sensitivity 81%) to 96% (corresponding sensitivity 38%) differentiating ADHD in clinical samples.</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Parental Ratings</td>
<td>Accuracy</td>
<td>6 studies 326, 335, 417, 450, 524, 620</td>
<td>Accuracy ranged from 67% to 86% differentiating ADHD and neurotypical development. Accuracy ranged from 60% to 84% differentiating ADHD in clinical samples.</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Parental Ratings</td>
<td>AUC</td>
<td>13 studies 176, 238, 239, 266, 300, 326, 335, 338, 352, 480, 542, 569</td>
<td>AUC ranged from 0.70 to 0.91 differentiating ADHD and neurotypical development. AUC ranged from 0.65 to 0.97 differentiating ADHD in clinical samples.</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Parental Ratings</td>
<td>Inter-rater reliability</td>
<td>1 study 413</td>
<td>ICC 0.51 for inattention, 0.56 for hyperactivity, and 0.58 for impulsivity between mother and father subscale ratings on the DSM-ADHD-Symptom Rating Scale in a sample of children with ADHD.</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Parental Ratings</td>
<td>Internal consistency</td>
<td>6 studies 176, 335, 338, 352, 413, 414, 515</td>
<td>In neurotypical samples: Cronbach’s alpha Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scale (SWAN) 0.95; Cronbach’s alpha Behavior Assessment System for Children, Second Edition (BASC-2), Executive Function Screener parent rating global sum score 0.91.</td>
<td>Low</td>
</tr>
</tbody>
</table>

Table 4. KQ1 Summary of Findings and Strength of Evidence for Parental Ratings
### 4. Results: Diagnosis of ADHD

<table>
<thead>
<tr>
<th>KQ1 Diagnostic Test</th>
<th>Outcome</th>
<th>Number of Studies and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cronbach’s alpha Parent Disruptive Behavior Disorder Ratings Scale (DBDRS) Inattention 0.94, hyperactivity / impulsivity 0.91&lt;sup&gt;515&lt;/sup&gt; In clinical samples: Cronbach’s alpha Child Behavior Checklist (CBCL) Attention Problems 0.76&lt;sup&gt;316&lt;/sup&gt;; Cronbach’s alpha Behavior Rating Inventory of Executive Function, Second Edition (BRIEF2) global executive composite summary score 0.97&lt;sup&gt;315&lt;/sup&gt;; Cronbach’s alpha DSM-ADHD-Symptom Rating Scale total 0.90 for mother’s rating, 0.91 for father’s rating&lt;sup&gt;413&lt;/sup&gt;; Cronbach’s alpha The Pediatric Symptom Checklist (PSC) attention subscale 0.90&lt;sup&gt;414&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>KQ1 Parental Ratings</th>
<th>Test-retest reliability</th>
<th>0 studies</th>
<th>N/A</th>
<th>Insufficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ1 Parental Ratings</td>
<td>Misdiagnosis</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ1 Parental Ratings</td>
<td>Costs</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

Notes: AUC area under the curve, KQ key question, N/A not applicable, SoE strength of evidence

Parental ratings reported mainly on the sensitivity, specificity, accuracy, and area under the curve. A few studies reported perfect diagnostic performance for parental ratings for either sensitivity or specificity, but not both together. Little information was provided in these diagnostic studies regarding the reliability of the measures. We downgraded the strength of evidence for imprecision (large variation in reported diagnostic performance) and for inconsistency (when consistency could not be assessed because only one study was identified reporting on the test and outcome of interest, and results had not been replicated by another author group). None of the included studies provided information on the effect of misdiagnosis. None of the identified studies reported the costs associated with obtaining parental ratings.

### 4.3.2 Teacher Ratings

We identified 13 studies using Teacher ratings to diagnose ADHD<sup>17, 222, 300, 311, 338, 352, 355, 382, 480, 507, 515, 516, 629</sup>. The earliest study meeting eligibility criteria was published 2008<sup>222</sup> from five different English-speaking countries, primarily the US.<sup>338, 352, 382, 480, 507, 515, 516, 629</sup> The populations studied were predominately males between the ages of five and 18. One study exclusively included children younger than seven years old<sup>507</sup> and one exclusively in children eight years or older.<sup>352</sup> For studies that distinguished between ADHD presentations, most of the participants were diagnosed with the combined or inattentive presentations. Almost all of the studies mention race and ethnicity demographics, with seven studies where White participants made up greater than 70 percent of the sample;<sup>311, 338, 352, 355, 382, 507, 629</sup> and one study where over 85 percent of the participants were Black/African American.<sup>480</sup>

ADHD participants with co-occurring disorders were not excluded from most of the studies. Studies were divided into clinical samples and those recruited from a less selective population. None of the included studies includes children where all had a dual diagnosis, such as ADHD and conduct disorder.
4. Results: Diagnosis of ADHD

Studies reported a variety of outcomes, with sensitivity, specificity, and area under the curve (AUC) being the most frequently reported outcomes. Table 5 shows the findings for the outcomes of interest together with the number of studies and study identifiers.

**Table 5. KQ1 Summary of Findings and Strength of Evidence for Teacher Ratings**

<table>
<thead>
<tr>
<th>KQ1 Diagnostic Test</th>
<th>Outcome</th>
<th>Number of Studies and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ1 Teacher Ratings</td>
<td>Sensitivity</td>
<td>6 studies [300, 311, 352, 515, 516, 629]</td>
<td>Sensitivity ranged from 48% in a long-term predictive validity study (corresponding specificity 70%) to 82% (corresponding specificity 55%) differentiating ADHD and neurotypical development. Sensitivity ranged from 72% (corresponding specificity 75%) to 97% (corresponding specificity 26%) in clinical sample.</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Teacher Ratings</td>
<td>Specificity</td>
<td>6 studies [300, 311, 352, 515, 516, 629]</td>
<td>Specificity ranged from 55% (corresponding sensitivity 82%) to 73% (corresponding sensitivity 70%) differentiating ADHD and neurotypical development. Specificity ranged from 26% (corresponding sensitivity 97%) to 91% (corresponding sensitivity 48%) in clinical samples.</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Teacher Ratings</td>
<td>Accuracy</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ1 Teacher Ratings</td>
<td>AUC</td>
<td>4 studies [300, 338, 352, 480]</td>
<td>AUC was 0.83 differentiating ADHD and neurotypical development. AUC was 0.56 in a clinical sample.</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Teacher Ratings</td>
<td>Inter-rater reliability</td>
<td>2 studies [355, 382]</td>
<td>In clinical samples: Pearson correlations between teacher and parent ratings ranged from 0.17 to 0.41 over four subscales on the Conduct-Hyperactive-Attention Problem- Oppositional Symptom (CHAOS) scale; Kappa 0.29 between teacher and parent ratings on the Attention-Deficit/Hyperactivity Disorder Rating Scale, 4th edition.</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Teacher Ratings</td>
<td>Internal consistency</td>
<td>5 studies [338, 352, 382, 515, 516]</td>
<td>In neurotypical samples: Cronbach’s alpha 0.94 for both teacher-rated inattention and hyperactivity symptom counts on the Disruptive Behavior Disorder Rating Scale (DBDRS); Cronbach’s alpha was 0.95 for the Behavior Assessment System for Children, 2nd edition (BASC-2), executive function screener; Cronbach’s alpha was 0.94 for the Teacher Disruptive Behavior Disorder Scale (DBDRS) in clinical samples; Cronbach’s alpha 0.95 for the Teacher Report Form (TRF) Attention Problems; Cronbach’s alpha ranged from 0.64 to 0.91 over four subscales on the Conduct-Hyperactive-Attention Problem- Oppositional Symptom (CHAOS) scale.</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Teacher Ratings</td>
<td>Test-retest reliability</td>
<td>1 study [382]</td>
<td>Pearson correlations ranged from 0.74 to 0.87 over four subscales on the Conduct-Hyperactive-Attention Problem- Oppositional Symptom (CHAOS) scale, retest between 1 and 829 days in a clinical sample.</td>
<td>Low</td>
</tr>
</tbody>
</table>
4. Results: Diagnosis of ADHD

<table>
<thead>
<tr>
<th>KQ1 Diagnostic Test</th>
<th>Outcome</th>
<th>Number of Studies and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ1 Teacher Ratings</td>
<td>Misdiagnosis</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ1 Teacher Ratings</td>
<td>Costs</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

Notes: AUC area under the curve, KQ key question, N/A not applicable, SoE strength of evidence

Across all teacher rating studies, reported sensitivity in individual studies were up to 97 percent in a clinical sample, but the corresponding specificity was only 26 percent.\(^{311}\) We downgraded the strength of evidence for imprecision (large variation in reported diagnostic performance) and for inconsistency (when consistency could not be assessed because only one study was identified reporting on the test and outcome of interest and results had not been replicated by another author group). Identified diagnostic accuracy studies did not report on several of the other key outcomes.

4.3.3 Teen/Child Self Reports

We identified three studies using teen/child self-reports to diagnose ADHD.\(^{176, 297, 480}\) The earliest study was published in 2017\(^{480}\) and data came from two different countries, the US\(^{297, 480}\) and Canada.\(^{176}\) Self-reports were primarily completed by adolescents ages 12 to 18, however one study provided a research assistant to help read the questions for participants under 11 years old.\(^{297}\) Only one study documented the ADHD presentation: 10 percent inattentive presentation, four percent hyperactive/impulsive presentation, and 25 percent combined presentation.\(^{480}\) Two studies mentioned race and ethnicity demographics. In one study, White participants made up 61 percent of the sample\(^{297}\) and one study reported 89 percent of the participants were Black/African American.\(^{480}\)

Studies reported a limited number of outcomes, with area under the curve (AUC) being the most frequently reported outcome. Table 6 shows the findings for the outcomes of interest together with the number of studies and study identifiers.

Table 6. KQ1 Summary of Findings and Strength of Evidence for Self Reports

<table>
<thead>
<tr>
<th>KQ1 Diagnostic Test</th>
<th>Outcome</th>
<th>Number of Studies and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ1 Self Reports</td>
<td>Sensitivity</td>
<td>1 study^176</td>
<td>Sensitivity 57% (corresponding specificity 81%) using the Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scale (SWAN) Self report,(^{176}) differentiating ADHD and neurotypical development</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Self Reports</td>
<td>Specificity</td>
<td>1 study^176</td>
<td>Specificity 81% (corresponding sensitivity 57%) using the Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scale (SWAN) Self report,(^{176}) differentiating ADHD and neurotypical development</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Self Reports</td>
<td>Accuracy</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>
## 4. Results: Diagnosis of ADHD

<table>
<thead>
<tr>
<th>KQ1 Diagnostic Test</th>
<th>Outcome</th>
<th>Number of Studies and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ1 Self Reports</td>
<td>AUC</td>
<td>3 studies(^{176, 297, 480})</td>
<td>AUC was 0.71 for the <em>Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scale</em> (SWAN) Self report,(^{176}) and the Kiddie-Computerized adaptive test (K-CAT)(^{297}) differentiating ADHD and neurotypical development. AUC was 0.56(^{480}) for the <em>Youth Self Report of the Achenbach System of Empirically Based Assessment</em> (ASEBA) in a clinical sample.</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Inter-rater reliability</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td>Internal consistency</td>
<td>1 study(^{176})</td>
<td>Cronbach’s alpha was 0.88 for the <em>Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scale</em> (SWAN) Self Report(^{176}) differentiating ADHD and neurotypical development.</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Test-retest reliability</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td>Misdiagnosis</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td></td>
<td>Costs</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

Notes: AUC area under the curve, KQ key question, N/A not applicable, SoE strength of evidence

The reported diagnostic performance of teen self-reports was limited. We downgraded for inconsistency (inability to judge the consistency across studies because only one study was identified reporting on the test and outcome of interest). In several cases, our searches identified no studies and the strength of evidence is insufficient for the outcome.

### 4.3.4.1 Combined Ratings

We identified only four studies that assessed the diagnostic performance of ratings combined across informants.\(^{17, 279, 297, 455}\) Only one of these studies compared performance when combining data from multiple informants vs single informants: it found negligible improvement when combining youth self-report to the parent report alone using an adaptive testing questionnaire (AUC youth only 0.71 parent only 0.85; combined 0.86) in a treatment-seeking population.\(^{297}\) A second study combined parent and teacher ratings on the Conners scales by requiring youth to meet diagnostic cutoffs (T-score ≥65) in one setting and substantial symptoms in the other setting (T-score ≥60). It reported a diagnostic sensitivity of 83.5 percent and specificity of 35.7 percent for the combined rating when distinguishing ADHD from other clinically referred youth.\(^{17}\) The study did not report diagnostic performance using either parent or teacher rating alone. A third study reported findings from a discriminant function analysis of mother, father, and teacher ratings on the Conners scale when distinguishing ADHD youth who were considered either intellectually gifted or not from typically developing, intellectually gifted youth. It found that the discriminant function using all three informants distinguished the typically developing youth from the two ADHD groups but did not distinguish the two ADHD groups from one another.\(^{279}\) A fourth study of 4 to 7 year old children used machine learning to combine parent and teacher ratings on the BRIEF in distinguishing youth with ADHD from typically developing controls. It reported an average diagnostic accuracy of 0.93, with teacher ratings being the most...
informative in the machine learning algorithm, though it did not formally compare accuracy for combined informants with accuracy for either informant alone. The study also found that the addition of neuropsychological test measures and cortical thickness measures to the machine learning algorithm did not meaningfully improved diagnostic performance over use of the BRIEF alone.\(^\text{455}\)

### 4.3.4 Clinicians Tools

We identified a small number of studies evaluating additional clinician tools (beyond neuropsychological tests; parent, teacher, or self report ratings; biomarkers; or imaging) to aid the diagnosis of ADHD.\(^\text{26, 128, 175, 298, 355, 406, 487, 530}\) One study assessed an insurance claim-based algorithm\(^\text{553}\) and another an electronic health record phenotype algorithm.\(^\text{530}\) One study focused on the clinical utility of ICD-11 diagnostic guidelines\(^\text{487}\) and a clinician diagnosis combined with an assessment aid that involved integrating EEG and theta/beta ratio data.\(^\text{26}\) The earliest identified study was published in 2015.\(^\text{26}\) Evaluations were published in three different countries, including one from the US.\(^\text{26}\) Three studies measured child activity levels,\(^\text{128, 298, 406}\) and two evaluated direct observation as a diagnostic tool.\(^\text{175, 355}\)

The populations studied were predominately males between the ages of five and 17. None of the studies distinguished between ADHD presentations. Two studies mentioned race and ethnicity demographics; for both, the majority of participants were White (69%).\(^\text{26}\)

Studies are difficult to compare since they assess different tools and approaches. Studies reported a variety of outcomes, with sensitivity, specificity, and inter-rater reliability being the most frequently reported outcomes. Table 7 shows the findings for the key outcomes of interest together with the number of studies and study identifiers. Where all identified studies evaluated the same tool, the first column of the study indicates the tool, otherwise estimates are reported across all tools.

<table>
<thead>
<tr>
<th>KQ1 Diagnostic Test</th>
<th>Outcome</th>
<th>Number of Studies and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ1 Clinician tool – activity measurement</td>
<td>Sensitivity</td>
<td>3 studies</td>
<td>Activity measures ranged from 80% (corresponding specificity 90%)(^\text{298}) to 98% (corresponding specificity 100%)(^\text{128}) differentiating ADHD and neurotypical development</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Clinician tool – activity measurement</td>
<td>Specificity</td>
<td>3 studies</td>
<td>Activity measures ranged from 84% (corresponding sensitivity 97%)(^\text{298}) to 100% (corresponding sensitivity 98%)(^\text{128}) differentiating ADHD and neurotypical development</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Clinician tool – activity measurement</td>
<td>Accuracy</td>
<td>2 studies</td>
<td>Activity measures ranged from 0.82(^\text{298}) to 0.99(^\text{26}) differentiating ADHD and neurotypical development</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Clinician tool – activity measurement</td>
<td>AUC</td>
<td>2 studies</td>
<td>Activity measures ranged from 0.94(^\text{406}) to 0.999(^\text{128}) differentiating ADHD and neurotypical development</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Clinician tools</td>
<td>Inter-rater reliability</td>
<td>2 studies(^\text{26, 487})</td>
<td>Kappa was 0.46(^\text{487}) and ICC was 0.83(^\text{26}) in clinical samples</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Clinician tools</td>
<td>Internal consistency</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ1 Clinician tools</td>
<td>Test-retest reliability</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>
4. Results: Diagnosis of ADHD

We downgraded the strength of evidence for imprecision (very large variation in reported diagnostic performance) and for inconsistency (when consistency could not be assessed because only one study was identified reporting on the test, and outcome of interest and results had not been replicated by another author group). The tools were difficult to compare and answered study-specific questions.

4.3.5 Biomarkers

We identified six studies using proposed biomarkers to diagnose ADHD that were not based on EEG or imaging. EEG and imaging approaches are reported in the next section. Four studies used blood measures, including membrane potential ratio, miRNA, and erythropoietin/erythropoietin receptor. The other two studies evaluated pupillometrics (pupil-size dynamics) and urine tetrahydroisoquinoline levels. The earliest identified study was published in 2007. Evaluations were published in five different countries, including two from the US.

The populations studied were predominately males between the ages of six and 17. Most studies required participants to not be taking stimulant medication. For studies that distinguished between ADHD presentations, most of the participants were diagnosed with the combined presentation. Only two studies mentioned race and ethnicity demographics, one where 100 percent of the participants were Han Chinese and the other where the majority of participants (71%) were Black/African American. None of the studies used a clinical sample or children with a consistent co-morbidity.

Table 8 shows the findings for the outcomes of interest together with the number of studies and study identifiers.

<table>
<thead>
<tr>
<th>KQ1 Diagnostic Test</th>
<th>Outcome</th>
<th>Number of Studies and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ1 Biomarkers</td>
<td>Sensitivity</td>
<td>6 studies: 218, 307, 489, 551, 592, 623</td>
<td>Sensitivity ranged from 56% (corresponding specificity 95%) to 100% (corresponding specificity 100%) differentiating ADHD and neurotypical development</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Biomarkers</td>
<td>Specificity</td>
<td>6 studies: 218, 307, 489, 551, 592, 623</td>
<td>Specificity ranged from 25% (corresponding sensitivity 79%) to 100% (corresponding sensitivity 100%) differentiating ADHD and neurotypical development</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Biomarkers</td>
<td>Accuracy</td>
<td>3 studies: 218, 551, 592</td>
<td>Accuracy ranged from 55% to 85% differentiating ADHD and neurotypical development</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Biomarkers</td>
<td>AUC</td>
<td>4 studies: 218, 307, 592, 623</td>
<td>AUC ranged from 0.68 to 1.00 differentiating ADHD and neurotypical development</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Biomarkers</td>
<td>Inter-rater reliability</td>
<td>0 studies</td>
<td>No data</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>
4. Results: Diagnosis of ADHD

<table>
<thead>
<tr>
<th>KQ1 Diagnostic Test</th>
<th>Outcome</th>
<th>Number of Studies and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ1 Biomarkers</td>
<td>Internal consistency</td>
<td>0 studies</td>
<td>No data</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ1 Biomarkers</td>
<td>Test-retest reliability</td>
<td>0 studies</td>
<td>No data</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ1 Biomarkers</td>
<td>Misdiagnosis</td>
<td>0 studies</td>
<td>No data</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ1 Biomarkers</td>
<td>Costs</td>
<td>0 studies</td>
<td>No data</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ1 Blood Biomarkers</td>
<td>Sensitivity</td>
<td>4 studies</td>
<td>Sensitivity ranged from 68% (corresponding specificity 71%) to 100% (corresponding specificities 97% and 100%) differentiating ADHD and neurotypical development</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Blood Biomarkers</td>
<td>Specificity</td>
<td>4 studies</td>
<td>Specificity ranged from 25% (corresponding sensitivity 79%) to 100% (corresponding sensitivity 100%) differentiating ADHD and neurotypical development</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Blood Biomarkers</td>
<td>Accuracy</td>
<td>4 studies</td>
<td>Accuracy ranged from 55% to 85% differentiating ADHD and neurotypical development</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Blood Biomarkers</td>
<td>AUC</td>
<td>4 studies</td>
<td>AUC ranged from 0.68 to 1.00 differentiating ADHD and neurotypical development</td>
<td>Low</td>
</tr>
</tbody>
</table>

Notes: AUC area under the curve, KQ key question, N/A not applicable, SoE strength of evidence

Biomarker studies reported mainly on the sensitivity and specificity. Individual studies achieved very high sensitivity. Little information was provided in the studies regarding the reliability of the markers or combinations of markers. None of the included studies provided information on the effect of misdiagnosis. None of the identified studies reported the costs associated with analyzing biomarkers. We identified four studies that reported on blood biomarkers specifically.

4.3.6 Diagnosis Supported by Machine Learning

We identified 44 studies in total using machine learning algorithms to diagnose ADHD using different measurement modalities and came from 20 different countries, but primarily the US and China. A third of identified studies used electroencephalogram (EEG) markers as the data source with another third of the studies using functional magnetic resonance imaging (MRI) or multimodal MRI (using some combination of structural, functional, or diffusion tensor imaging). A wide variety of machine learning algorithms were used for classification, with the most popular being support vector machine followed by neural network classification. Studies reported a variety of outcomes, with sensitivity, specificity, and accuracy being the most frequently reported outcomes.

The majority of studies reported on sensitivity. Reported sensitivity ranged from 59 percent (corresponding specificity 83%) to 100 percent (corresponding specificity 100%). Specificity estimates ranged from 55 percent (corresponding sensitivity 95%) to 100 percent.
4. Results: Diagnosis of ADHD

(corresponding sensitivities 100, 97, 75, 98, and 100% respectively).\textsuperscript{128, 150, 160, 364, 439} Accuracy was reported in 40 studies \textsuperscript{122, 127, 128, 150, 160, 165, 180, 191, 192, 215, 218, 256, 283, 318, 336, 359, 364, 385, 426, 438, 439, 455, 456, 461, 482, 483, 506, 532, 558, 567, 580, 586, 592, 618-621, 1153 and ranged from 61 percent\textsuperscript{283} to 100 percent.\textsuperscript{150, 160, 456} Area under the curve estimates were reported in some of the included studies\textsuperscript{127, 128, 187, 191, 215, 218, 238, 239, 402, 455, 506, 567, 586, 592, 619, 621, 1153 and performance ranged from 0.698\textsuperscript{1153} to 0.9993\textsuperscript{128} Studies rarely reported on reliability measures, and the impact of misdiagnosis or costs were not mentioned.

In studies using EEG data only, sensitivity ranged from 80 percent (corresponding specificity 80%)\textsuperscript{187} to 98 percent (corresponding specificity 92% and 99%).\textsuperscript{165, 180} One study combining EEG data and demographics reported a sensitivity of 100% (corresponding specificity 100%).\textsuperscript{150} In the studies using neuroimaging datasets, sensitivity ranged from 61 percent (corresponding specificity 68%)\textsuperscript{1153} to 99 percent (corresponding specificity 99%).\textsuperscript{567} Several studies combined neuroimaging data with demographic data; sensitivity ranged from 70 percent (corresponding specificity 65%)\textsuperscript{506} to 89 percent (corresponding specificity 84%)\textsuperscript{619} including two near-infrared spectroscopy studies that reported 73 percent sensitivity (corresponding specificity 87%)\textsuperscript{215} and 89 percent sensitivity (corresponding specificity 84%).\textsuperscript{619}

4.4.1 KQ1a. What is the comparative diagnostic accuracy of approaches that can be used in the primary care practice setting or by specialists to diagnose ADHD among individuals younger than 7 years of age?

We identified three studies that explicitly reported on diagnostic performance data collected in primary care.\textsuperscript{170, 433, 595} The earliest identified study was published in 2004\textsuperscript{595} with data from the US and Portugal. The percent female ranged from 24 to 39 percent, where reported. One study was restricted to young children,\textsuperscript{170} whereas the others had a broader age range. One study reported on race and ethnicity and included 23 percent Hispanic and 10 percent African American children.\textsuperscript{1160}

Studies evaluated parent ratings and neuropsychological tests. Sensitivity and specificity was reported in all three studies. Sensitivity ranged widely, with estimates from 28 percent (corresponding specificity 95%)\textsuperscript{433} using a neuropsychological test battery, to 84 percent (corresponding specificity 84%) for the attention problems subscale of the Child Behavior Checklist.\textsuperscript{595}

We identified 10 studies focused on the diagnosis of ADHD in children under seven years old.\textsuperscript{170, 175, 193, 326, 402, 406, 455, 458, 504, 507} The earliest study was published in 2012\textsuperscript{406} and data came from six different countries, primarily the US.\textsuperscript{170, 326, 402, 455, 504, 507} The populations studied were predominately males between the ages of one and seven. Half of the studies mentioned race and ethnicity demographics with five studies where White participants made up over 50 percent of the sample,\textsuperscript{170, 175, 326, 504, 507} and one study that was 83 percent Hispanic or Latino.\textsuperscript{455} Several studies used clinic populations of children referred for diagnostic purposes and children often presented with multiple co-occurring disorders.

The most common tests used for diagnosis in these studies were parent rating, teacher rating, and neuropsychological testing. Two studies used electroencephalography (EEG),\textsuperscript{193, 402} one study used imaging,\textsuperscript{455} one used 24-hour long actigraphic registries,\textsuperscript{406} and one used observation of behavior.\textsuperscript{175}
4. Results: Diagnosis of ADHD

Studies reported a variety of outcomes, with sensitivity, specificity, and area under the curve (AUC) being the most frequently reported outcomes. The KQ1a section of the Summary of Findings Table 3 shows the findings for the outcomes of interest together with the number of studies and study identifiers for children under seven years old. The table shows that six studies\textsuperscript{170, 175, 193, 326, 406, 458} reported on sensitivity, with the results depending highly on the test used for diagnosis and the sample characteristic (e.g., clinical samples or general samples differentiating ADHD from neurotypical development). Sensitivity ranged from 66 percent combining teacher and parent ratings\textsuperscript{193} to 97 percent for an activity measure\textsuperscript{406} in samples differentiating ADHD and neurotypical development. Sensitivity ranged from 64 percent for a neuropsychological test\textsuperscript{170} to 76 percent for a different neuropsychological test\textsuperscript{458} in clinical samples. Specificity also varied substantially and ranged from 38 percent using EEG data in this age group\textsuperscript{193} to 84 percent\textsuperscript{193, 406} for an activity measure and an EEG algorithm differentiating ADHD and neurotypical development. Specificity ranged from 70 percent for a neuropsychological test\textsuperscript{458} to 91 percent for a rating scale\textsuperscript{326} in clinical samples. Similar variation was seen in other diagnostic measures.

Few of these diagnostic studies reported reliability measures. Most commonly reported was the internal consistency of rating scales. Cronbach’s alpha was 0.92 for parent ratings on the Diagnostic Infant and Preschool Assessment Likert version (DIPA-L)\textsuperscript{504} Cronbach’s alpha for the Behavior Rating Inventory of Executive Function preschool version was 0.976 for teacher ratings and 0.970 for parent ratings and 0.724 for teacher ratings and 0.978 for parent ratings for the child version.\textsuperscript{455}

We did not identify any study reporting on the adverse effect following a misdiagnosis (not being diagnosed or incorrectly diagnosed) in this age group. In addition, none of the diagnostic studies mentioned costs of tests in this subsample.

4.4.2 KQ1b. What is the comparative diagnostic accuracy of EEG, imaging, or approaches assessing executive function that can be used in the primary care practice setting or by specialists to diagnose ADHD among individuals aged 7 through 17?

This section documents the evidence for diagnostic approaches using EEG and various imaging technologies. In addition, the section summarizes the diagnostic utility of neuropsychological tests. The neuropsychological tests included multiple measures of executive function. Questionnaires assessing executive function through parent or teacher report are documented in the beginning of the chapter.

We identified 34 EEG, imaging, or executive function studies restricting to children between the ages of seven and 17.\textsuperscript{118, 127, 147, 161, 180, 195, 218, 256, 283, 297-299, 309, 345, 346, 352, 359, 364, 373, 385, 388, 426, 434, 438, 452, 453, 455, 482, 506, 558, 567, 586, 597, 1153 However, we identified a large number of studies that included younger as well as older children, suggesting a broader applicability of the evaluated tests. Most of the identified samples did not include very young children, but the large majority included five and six year old children. In addition, meta-regressions (see KQ1) did not detect a systematic effect of the proportion of young children in the sample on the reported effect sizes. Hence, the following sections report on the results for the individual tests across all identified
4. Results: Diagnosis of ADHD

diagnostic studies, and we did not restrict to studies that exclusively targeted individuals aged 7 and above.

**presentation**

4.4.2.1 EEG

We identified 35 studies using EEG markers to diagnose ADHD.26, 118, 122, 127, 150, 165, 180, 187, 191-193, 196, 201, 309, 318, 336, 345, 359, 361, 362, 364, 385, 386, 388, 402, 403, 405, 426, 438, 453, 456, 461, 476, 482, 580. The earliest identified study was published in 2005.386 EEG evaluations were published in 17 different countries, primarily Iran,122, 165, 359, 426, 482 China,191, 192, 385, 386 and Taiwan.187, 193, 201 The populations studied were predominately males between the ages of six and 17, with only three studies including children as young as four years old.165, 193, 336 One study included only female participants,201 and seven studies included only males.118, 187, 402, 403, 438, 456, 461 In several studies, participants were required to demonstrate an IQ of 80 or higher.118, 187, 191, 192, 336, 385, 388 Almost half of the studies required that participants not take stimulant medication or stop medication several days before testing. For studies that distinguished between ADHD presentations, most focused on the combined and inattentive presentations. Only two studies included individuals solely with the hyperactive/impulsive presentation.318, 361 Race and ethnicity demographics were not mentioned in most studies.

While ADHD participants with co-occurring disorders were not excluded from most studies, only a few studies purposely included specific co-occurring disorders to evaluate the diagnostic test performance in children with co-occurring conduct disorder364 or other behavioral disorders.150 The large majority of studies had unselected samples, i.e., comparing children with ADHD to neurotypical developing children.

Two thirds of studies used machine learning algorithms for classification. Table 9 shows findings for the outcomes of interest together with the number of studies and study identifiers.

**Table 9. KQ1 Summary of Findings and Strength of Evidence for EEG**

<table>
<thead>
<tr>
<th>KQ1 Diagnostic Test</th>
<th>Outcome</th>
<th>Number of Studies and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ1 EEG Sensitivity</td>
<td>18 studies26, 118, 122, 127, 150, 165, 180, 187, 193, 201, 336, 345, 364, 386, 388, 403, 461, 476, 580</td>
<td>Sensitivity ranged from 46% (corresponding specificity 74%)201 to 100% (corresponding specificities 71% or 100%)150, 403 differentiating ADHD and neurotypical development</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>KQ1 EEG Sensitivity</td>
<td>18 studies26, 118, 122, 127, 150, 165, 180, 187, 193, 201, 336, 345, 364, 386, 388, 403, 461, 476, 580</td>
<td>Sensitivity ranged from 46% (corresponding specificity 74%)201 to 100% (corresponding specificities 71% or 100%)150, 403 differentiating ADHD and neurotypical development</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>KQ1 EEG Accuracy</td>
<td>26 studies26, 118, 122, 127, 148, 150, 165, 180, 191-193, 201, 318, 336, 345, 359, 362, 364, 385, 388, 426, 438, 456, 461, 482, 580</td>
<td>Accuracy ranged from 58%201 to 100%150, 456 differentiating ADHD and neurotypical development</td>
<td>Low</td>
<td></td>
</tr>
</tbody>
</table>
4. Results: Diagnosis of ADHD

<table>
<thead>
<tr>
<th>KQ1 Diagnostic Test</th>
<th>Outcome</th>
<th>Number of Studies and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ1 EEG</td>
<td>AUC</td>
<td>9 studies 127, 187, 191, 193, 201, 336, 402, 403, 405</td>
<td>AUC ranged from 0.63 201 to 0.92 191 differentiating ADHD from neurotypical development AUC was 0.91 127 in a study with children 7 and above</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 EEG</td>
<td>Inter-rater reliability</td>
<td>3 studies 118, 122, 127</td>
<td>Kappa between the DSM and behavioral/psychological/neurophysiological data was 0.75 118 (all children were 7 and above) Kappa for classifiers ranged from 0.73 127 to 0.99 122 differentiating ADHD and neurotypical development Kappa was reported as 0.75 118 and 0.82 127 in children 7 and above</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 EEG</td>
<td>Internal consistency</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ1 EEG</td>
<td>Test-retest reliability</td>
<td>1 study 26</td>
<td>ICC was 0.83 for Theta/Beta ratio; repeated measures collected on two different visits in a clinical sample 26 (all children were 7 and above)</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 EEG</td>
<td>Misdiagnosis</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ1 EEG</td>
<td>Costs</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ1 EEG plus ratings or demographics combined</td>
<td>Sensitivity</td>
<td>4 studies 26, 150, 193, 345</td>
<td>Sensitivity ranged from 87% (corresponding specificity 84%) 193 to 100% (corresponding specificity 100%) 150 differentiating ADHD and neurotypical development Sensitivity was 82% (corresponding specificity 94%) 26 in clinical samples</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 EEG plus ratings or demographics combined</td>
<td>Specificity</td>
<td>4 studies 26, 150, 193, 345</td>
<td>Specificity ranged from 84% (corresponding sensitivity 87%) 193 to 100% (corresponding sensitivity 100%) 150 differentiating ADHD and neurotypical development Specificity was 82% (corresponding sensitivity 94%) 26 in a clinical sample</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 EEG plus ratings or demographics combined</td>
<td>Accuracy</td>
<td>5 studies 26, 150, 193, 318, 345</td>
<td>Accuracy ranged from 76% 118 to 100% 150 differentiating ADHD and neurotypical development Accuracy was 88% 26 in a clinical sample</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 EEG plus ratings or demographics combined</td>
<td>AUC</td>
<td>1 study 193</td>
<td>AUC was 0.92 203 differentiating ADHD and neurotypical development</td>
<td>Low</td>
</tr>
</tbody>
</table>

Notes: AUC area under the curve, KQ key question, N/A not applicable, SoE strength of evidence

EEG studies predominantly reported accuracy estimates. Sensitivity in individual studies ranged widely from 46 percent 201 to perfect sensitivity (corresponding specificities 71%); 150, 403 the range was reduced in studies restricting to older children. Studies in clinical samples reported a reduced range of sensitivity and specificity compared to studies differentiating children with ADHD from neurotypically developing children, but the identified samples were small or they augmented EEG predictions with demographic variables. Some studies combined EEG data with
4. Results: Diagnosis of ADHD

demographics; the achieved sensitivity was reported as 100 percent (corresponding specificity 100%) in one study.\textsuperscript{150} We downgraded the strength of evidence for imprecision (large variation in performance across studies). In addition, we downgraded for study limitations as diagnostic approaches were often not well described. For some outcomes, no study was identified, and it was not possible to determine the effects associated with the test.

4.4.2.2 Imaging

We identified 17 studies using neuroimaging, mainly magnetic resonance imaging (MRI), to diagnose ADHD.\textsuperscript{27, 195, 215, 283, 315, 452, 455, 483, 506, 512, 538, 558, 567, 618, 619, 621, 1153} A publicly available dataset (ADHD-200) produced numerous analyses.\textsuperscript{195, 283, 483, 567} The populations studied were predominately males between the ages of six and 17, with three studies including only male participants.\textsuperscript{215, 483, 618} In several studies, participants were required to demonstrate an IQ of 80 or higher to be included in the sample.\textsuperscript{215, 483, 538, 558, 618, 619} A quarter of the studies required participants not take stimulant medication or stop medication several days before testing.\textsuperscript{215, 558, 618, 621} Approximately a third of the studies included only right-handed participants.\textsuperscript{483, 558, 618, 1153} For studies that distinguished between ADHD presentations, most focused on the combined and inattentive presentations. Only three studies specified including individuals with the hyperactive/impulsive presentation.\textsuperscript{215, 538, 621} Nearly all studies did not include race and ethnicity demographics.

While ADHD participants with co-occurring disorders were not excluded from most of the studies, no studies specifically assessed test performance in children with specific co-occurring disorders. One study differentiated children with ADHD from those with dyslexia.\textsuperscript{512} One evaluated the diagnostic performance of an algorithm differentiating ADHD from autism.\textsuperscript{283} All studies used unselected, general samples, rather than clinical samples referred for further diagnostic workup (where a large proportion of children will either be diagnosed with ADHD, conduct disorders, autism, or depression).

Most imaging studies used a large number of imaging indicators and utilized machine learning algorithms to detect markers and to optimize the classifications. Reported diagnostic accuracy estimates varied widely. Table 10 shows the findings for the outcomes of interest, together with the number of studies and study identifiers.

<table>
<thead>
<tr>
<th>KQ1 Diagnostic Test</th>
<th>Outcome</th>
<th>Number of Studies and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ1 Imaging to diagnose ADHD</td>
<td>Sensitivity</td>
<td>13 studies\textsuperscript{27, 215, 283, 315, 483, 506, 538, 558, 567, 618, 619, 621, 1153}</td>
<td>Sensitivity ranged from 61% (corresponding specificity 64%) combining structural and functional MRI\textsuperscript{1153} to 100% (corresponding specificity 100%) utilizing resting state functional MRI in a complex machine learning procedure\textsuperscript{195} differentiating ADHD and neurotypical development (both studies restricted to children 7 and above)</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Imaging to diagnose ADHD</td>
<td>Specificity</td>
<td>13 studies\textsuperscript{27, 215, 283, 315, 483, 506, 538, 558, 567, 618, 619, 621, 1153}</td>
<td>Specificity ranged from 55% (corresponding sensitivity 95%) in a model using resting state functional MRI\textsuperscript{106} to 100% (corresponding sensitivity 100%) utilizing resting state functional MRI in a complex machine learning procedure\textsuperscript{195} differentiating ADHD and neurotypical development (both studies restricted to children 7 and above)</td>
<td>Low</td>
</tr>
</tbody>
</table>
## 4. Results: Diagnosis of ADHD

<table>
<thead>
<tr>
<th>KQ1 Diagnostic Test</th>
<th>Outcome</th>
<th>Number of Studies and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ1 Imaging to diagnose ADHD</td>
<td>Accuracy</td>
<td>11 studies&lt;sup&gt;215, 283, 315, 483, 506, 558, 618, 619, 621, 1153&lt;/sup&gt;</td>
<td>Accuracy ranged from 64% combining functional and structural MRI&lt;sup&gt;153&lt;/sup&gt; to 99.6% in a model based on resting state functional MRI&lt;sup&gt;195&lt;/sup&gt; differentiating ADHD and neurotypical development (both studies restricted to children 7 and above)</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Imaging to diagnose ADHD</td>
<td>AUC</td>
<td>8 studies&lt;sup&gt;215, 215, 283, 306, 538, 567, 619, 621, 1153&lt;/sup&gt;</td>
<td>AUC ranged from 0.72&lt;sup&gt;206&lt;/sup&gt; in a complex machine learning approach to 0.996 in a model based on resting state functional MRI&lt;sup&gt;109&lt;/sup&gt; differentiating ADHD and neurotypical development (the same range was also seen in studies restricting to children 7 and above)</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Imaging to diagnose ADHD</td>
<td>Inter-rater reliability</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ1 Imaging to diagnose ADHD</td>
<td>Internal consistency</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ1 Imaging to diagnose ADHD</td>
<td>Test-retest reliability</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ1 Imaging to diagnose ADHD</td>
<td>Misdiagnosis</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ1 Imaging to diagnose ADHD</td>
<td>Costs</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ1 Imaging and phenotypic or demographic variables</td>
<td>Sensitivity</td>
<td>5 studies&lt;sup&gt;215, 283, 506, 619, 621&lt;/sup&gt;</td>
<td>Sensitivity ranged from 70% (corresponding specificity 65%)&lt;sup&gt;206&lt;/sup&gt; to 89% (corresponding specificity 84%) in a complex machine learning approach to 0.996 in a model based on resting state functional MRI&lt;sup&gt;195&lt;/sup&gt; differentiating ADHD and neurotypical development</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Imaging and phenotypic or demographic variables</td>
<td>Specificity</td>
<td>5 studies&lt;sup&gt;215, 283, 506, 619, 621&lt;/sup&gt;</td>
<td>Specificity ranged from 55% (corresponding sensitivity 95%) in a complex machine learning approach&lt;sup&gt;206&lt;/sup&gt; to 100% (corresponding sensitivity 100%) in a model based on resting state functional MRI&lt;sup&gt;195&lt;/sup&gt; differentiating ADHD and neurotypical development</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Imaging and phenotypic or demographic variables</td>
<td>Accuracy</td>
<td>6 studies&lt;sup&gt;215, 283, 483, 506, 619&lt;/sup&gt;</td>
<td>Accuracy ranged from 68% in a complex machine learning approach&lt;sup&gt;206&lt;/sup&gt; to 86% in a model based on resting state functional MRI&lt;sup&gt;195&lt;/sup&gt; differentiating ADHD and neurotypical development</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 Imaging and phenotypic or demographic variables</td>
<td>AUC</td>
<td>4 studies&lt;sup&gt;215, 506, 619, 621&lt;/sup&gt;</td>
<td>AUC ranged from 0.70 using structural, functional, and diffusion-tensor MRI plus age, sex, and IQ&lt;sup&gt;621&lt;/sup&gt; to 0.898 in a model based on resting state functional MRI&lt;sup&gt;195&lt;/sup&gt; differentiating ADHD and neurotypical development</td>
<td>Low</td>
</tr>
</tbody>
</table>

Notes: AUC area under the curve, KQ key question, N/A not applicable, SoE strength of evidence

Studies reported primarily on sensitivity, specificity, and accuracy. Across all neuroimaging studies, reported sensitivity varied widely. We downgraded the strength of evidence for imprecision (large variation in performance reported across studies). In addition, we downgraded for study limitations as the individual diagnostic models were often not well described and the number and type of predictor variables feeding into the model was unclear. For some outcomes, no study was identified, and it was not possible to determine the effects associated with the
4. Results: Diagnosis of ADHD

diagnostic modality. Some studies combined neuroimaging data and demographics, though the relevance is unclear, since the only demographic characteristic that is likely associated with a diagnosis of ADHD is sex, with a higher prevalence in males.

4.4.2.3 Neuropsychological Tests

We identified a large number of studies using neuropsychological tests, assessing executive function and/or encompassing a variety of cognitive assessments, including continuous performance tests, to diagnose ADHD.20, 23, 147, 148, 160, 161, 170, 178, 194, 202, 250, 256, 266, 270, 298, 312, 341, 346, 373, 384, 412, 433, 434, 439, 450, 455, 457-459, 475, 488, 525, 532, 597, 603, 620, 627, 634 Rating scales of executive function are described in the parent and teacher rating section in the beginning of the chapter.

Studies evaluating neuropsychological tests were published between 2000597 and 2021193, 373, 455, 458, 525 from 18 different countries, primarily the US.147, 160, 170, 178, 266, 338, 450, 455, 597 The populations studied were predominately males between the ages of six and 18. Four studies exclusively included children seven years old or younger.170, 193, 455, 458 in several studies, participants were required to demonstrate an IQ of 70 or higher23, 341, 346, 361, 453, 455, 457, 488 with some studies requiring IQ to be at least 8020, 160, 256, 458, 634 or 85373, 434, 475 Almost 60 percent of the studies required participants not take stimulant medication or stop medication several days before testing. For studies that distinguished between ADHD presentations, most of the participants were diagnosed with the combined or inattentive presentations. About a third of the studies mentioned race and ethnicity demographics, with seven studies where White participants made up half or more of the sample,20, 170, 178, 266, 338, 450, 455, 597 one study where all of the participants were Asian384 one study where over 50% were Black/African American,450 and one study where 83 percent of the participants were Hispanic or Latino.455

ADHD participants with co-occurring disorders were not excluded from most of the studies. Some studies used clinical samples with participants who were referred for diagnostic work-up where all children presented with attention issues or other symptoms indicative of ADHD or a different clinical diagnosis.23, 161, 170, 266, 312, 338, 458 One study specifically looked at distinguishing between children with ADHD, developmental dyslexia, and those who had both disorders.434 The remaining studies used samples of neurotypically developing children as controls rather than clinical samples.

Studies described a wide range of test batteries but 25 studies used continuous performance testing (CPT) to diagnose children and adolescents.20, 23, 147, 148, 160, 161, 170, 194, 202, 256, 266, 298, 312, 341, 364, 439, 450, 457, 459, 488, 525, 532, 620, 627, 634 CPTs provide multiple behavioral outputs relevant to ADHD, including omission errors (reflecting inattention), commission errors (reflecting impulsivity), and reaction time standard deviation (RTSD; reflecting moment-to-moment response variability). Studies varied in their use of traditional visual CPTs, such as the TOVA, or more novel, multifaceted CPT approaches. These latter “hybrid” CPT paradigms included CPTs that combined auditory and visual attentional processing demands together in the same task, those that monitored physical movements during task administration, and virtual reality CPTs built upon environments designed to emulate real-world distractibility in a classroom setting. The included studies often used idiosyncratic combinations of individual cognitive measures. Multiple studies reported on attention and impulsivity measures included in the continuous performance tests.

Studies reported a variety of statistical parameters to determine the accuracy of the diagnostic approach. Sensitivity, specificity, and accuracy were the most frequently reported diagnostic
4. Results: Diagnosis of ADHD

measures. Table 11 shows the findings for the outcomes of interest together with the number of studies and study identifiers for key outcomes that were assessed in more than one study.

<table>
<thead>
<tr>
<th>KQ1 Diagnostic Test</th>
<th>Outcome</th>
<th>Number of Studies and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KQ1 Neuropsychological tests</strong></td>
<td>Sensitivity</td>
<td>26 studies^{28, 23, 160, 161, 170, 178, 193, 202, 256, 270, 341, 346, 373, 384, 433, 434, 439, 450, 457-459, 475, 525, 532, 627, 634}</td>
<td>Sensitivity ranged from 28% (corresponding specificity 95%)^{111} to 100% (corresponding specificity 100%)^{160} differentiating ADHD and neurotypical development. Sensitivity ranged from 59% (corresponding specificity 77%)^{411} to 91% (corresponding specificity 22%)^{627} in clinical samples. Sensitivity ranged from 63%^{161} to 83%^{256} in studies restricting to children 7 and above.</td>
<td>Low</td>
</tr>
<tr>
<td><strong>KQ1 Neuropsychological tests</strong></td>
<td>Specificity</td>
<td>26 studies^{28, 23, 160, 161, 170, 178, 193, 202, 256, 270, 341, 346, 373, 384, 433, 434, 439, 450, 457-459, 475, 525, 532, 627, 634}</td>
<td>Specificity ranged from 46% (corresponding sensitivity 85%)^{457} to 100% (corresponding sensitivity 100% and 75% respectively)^{160, 439} differentiating ADHD and neurotypical development. Specificity ranged from 22% (corresponding sensitivity 91%)^{627} to 85% (corresponding sensitivity 63%)^{161} in clinical samples. Specificity ranged from 70%^{603} to 94%^{603} in studies restricting to children 7 and above.</td>
<td>Low</td>
</tr>
<tr>
<td><strong>KQ1 Neuropsychological tests</strong></td>
<td>Accuracy</td>
<td>18 studies^{160, 170, 178, 193, 202, 256, 341, 439, 450, 453, 455, 457, 459, 488, 525, 532, 597, 620}</td>
<td>Accuracy ranged from 57%^{458} to 100%^{160} differentiating ADHD and neurotypical development. Accuracy ranged from 64%^{170} to 84%^{597} in children with co-occurring oppositional defiance disorder. Accuracy ranged from 70%^{147} to 87%^{256} restricting to children 7 and above.</td>
<td>Low</td>
</tr>
<tr>
<td><strong>KQ1 Neuropsychological tests</strong></td>
<td>AUC</td>
<td>14 studies^{23, 147, 178, 193, 202, 266, 270, 341, 346, 433, 434, 435, 457, 475}</td>
<td>AUC ranged from 0.65%^{457} to 0.93 for individual Go/No-Go task measures^{384} differentiating ADHD and neurotypical development. AUC ranged from 0.62%^{147} to 0.87%^{256} in clinical samples. AUC ranged from 0.80%^{146} to 0.92%^{147} in studies restricting to children 7 and above.</td>
<td>Low</td>
</tr>
<tr>
<td><strong>KQ1 Neuropsychological tests</strong></td>
<td>Inter-rater reliability</td>
<td>3 studies^{178, 256, 627}</td>
<td>Neurotypical samples: Kappa was 0.55 between Cognitive Assessment System discriminant function analysis classifications and a priori diagnosis^{178}. Clinical samples: Kappa 0.15 between Groundskeeper game and Conners subscales, 0.18 between Groundskeeper game and Conners Continuous Performance Test (CPT), and 0.3 between Conners subscales and Conners CPT^{256}. Kappa 0.15 between Test of Variables of Attention and diagnosis by clinical assessment^{627}.</td>
<td>Low</td>
</tr>
<tr>
<td><strong>KQ1 Neuropsychological tests</strong></td>
<td>Internal consistency</td>
<td>1 study^{202}</td>
<td>Cronbach’s alpha ranged from 0.906 to 0.987 across 15 variables in the diagnosis-supported decision support system (DS-ADHD) across all children^{202}.</td>
<td>Low</td>
</tr>
<tr>
<td><strong>KQ1 Neuropsychological tests</strong></td>
<td>Test-retest reliability</td>
<td>1 study^{457}</td>
<td>ICC less than 0.5 for the ADHD group on all visual and auditory test variables on The Advanced Test of Attention repeated after 2 weeks^{457}.</td>
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</table>
## 4. Results: Diagnosis of ADHD

<table>
<thead>
<tr>
<th>KQ1 Diagnostic Test</th>
<th>Outcome</th>
<th>Number of Studies and IDs</th>
<th>Findings</th>
<th>SoE</th>
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<tr>
<td>KQ1 Neuropsychological tests</td>
<td>Misdiagnoses</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
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<tr>
<td>KQ1 Neuropsychological tests</td>
<td>Costs</td>
<td>1 study&lt;sup&gt;12&lt;/sup&gt;</td>
<td>£31 (~$42) for QbTest including 30-minute appointment, £108 a consultation within the UK Medway NHS Trust at the time of audit&lt;sup&gt;112&lt;/sup&gt; in a clinical sample</td>
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<tr>
<td>KQ1 CPT</td>
<td>Sensitivity</td>
<td>19 studies&lt;sup&gt;20, 23, 147, 160, 170, 202, 256, 266, 298, 312, 341, 439, 459, 457, 488, 525, 532, 620, 634&lt;/sup&gt;</td>
<td>Sensitivity ranged from 84% (corresponding specificity 94%) combining two commercial test software scores&lt;sup&gt;20&lt;/sup&gt; to 100% (corresponding specificity 75%) for a virtual reality based test differentiating ADHD from neurotypical development</td>
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<tr>
<td>KQ1 CPT</td>
<td>Sensitivity</td>
<td>10 studies&lt;sup&gt;23, 161, 170, 341, 384, 450, 457, 459, 525, 627&lt;/sup&gt;</td>
<td>Specificity ranged from 46% (corresponding sensitivity 85%) using the Advanced Test of Attention&lt;sup&gt;457&lt;/sup&gt; to 100% (corresponding sensitivity 89%) using the PANDAS&lt;sup&gt;439&lt;/sup&gt; differentiating ADHD from neurotypical development</td>
<td>Low</td>
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<tr>
<td>KQ1 CPT</td>
<td>Specificity</td>
<td>8 studies&lt;sup&gt;148, 341, 439, 457, 459, 488, 525, 620&lt;/sup&gt;</td>
<td>Accuracy ranged from 57% using a virtual reality CPT&lt;sup&gt;488&lt;/sup&gt; to 95% using TOVA&lt;sup&gt;148&lt;/sup&gt; differentiating ADHD from neurotypical development</td>
<td>Low</td>
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<tr>
<td>KQ1 CPT</td>
<td>AUC</td>
<td>5 studies&lt;sup&gt;147, 206, 341, 384, 457&lt;/sup&gt;</td>
<td>AUC ranged from 0.65 using the Advanced Test of Attention&lt;sup&gt;457&lt;/sup&gt; to 0.92 using the MOXO CPT&lt;sup&gt;147&lt;/sup&gt; differentiating ADHD from neurotypical development</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 CPT Attention</td>
<td>Sensitivity</td>
<td>3 studies&lt;sup&gt;20, 23, 170&lt;/sup&gt;</td>
<td>Sensitivity ranged from 48% (corresponding specificity 83%)&lt;sup&gt;23&lt;/sup&gt; to 68% (corresponding specificity 76%),&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Low</td>
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<tr>
<td>KQ1 CPT Attention</td>
<td>Specificity</td>
<td>3 studies&lt;sup&gt;20, 23, 170&lt;/sup&gt;</td>
<td>Specificity ranged from 64% (corresponding sensitivity 55%)&lt;sup&gt;170&lt;/sup&gt; to 83% (corresponding sensitivity 48%)&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 CPT Impulsivity</td>
<td>Sensitivity</td>
<td>2 studies&lt;sup&gt;23, 170&lt;/sup&gt;</td>
<td>Sensitivity ranged from 48% (corresponding specificity 83%)&lt;sup&gt;23&lt;/sup&gt; to 55% (corresponding specificity 64%)&lt;sup&gt;170&lt;/sup&gt;</td>
<td>Low</td>
</tr>
<tr>
<td>KQ1 CPT Impulsivity</td>
<td>Specificity</td>
<td>2 studies&lt;sup&gt;23, 170&lt;/sup&gt;</td>
<td>Specificity ranged from 64% (corresponding sensitivity 55%)&lt;sup&gt;170&lt;/sup&gt; to 83% (corresponding sensitivity 48%)&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Low</td>
</tr>
</tbody>
</table>

Notes: AUC area under the curve, KQ key question, N/A not applicable, SoE strength of evidence; CPT continuous performance test, TOVA test of variable attention

Studies evaluating neuropsychological tests reported predominantly on sensitivity and specificity. Selected studies reported perfect diagnostic performance for neuropsychological tests.<sup>160</sup> However, those studies reported the diagnostic performance for composite measures (unique combinations of individual cognitive measures), making it difficult to compare test performance across studies. The wide range in performance was narrower in studies restricting to children 7 and above. Reliability measures were rarely reported in the identified studies. No study addressed the effects of misdiagnosis. Costs were reported in only one study. We
4. Results: Diagnosis of ADHD

downgraded the strength of evidence for imprecision (large variation in performance reported across studies). For some outcomes, no study was identified, and it was not possible to determine the effects associated with the test.
4. Results: Diagnosis of ADHD

4.4.3 KQ1c. For both populations, how does the comparative diagnostic accuracy of these approaches vary by clinical setting or patient subgroup, or other risk factors associated with ADHD?

We did not identify studies comparing the accuracy in different settings in direct, head-to-head comparisons. Hence, we had to address this KQ in indirect analyses across studies. Our analyses were further limited by studies providing insufficient details on the accuracy of performance (e.g., reporting clearly on the false positives and false negatives) and could not be based on a meta-analytic model. Instead, we used the reported summary performance measures of sensitivity and specificity as reported by the study authors to explore potential effect modifiers. The most common reported diagnostic performance measures were sensitivity and specificity. Figure 5 plots reported sensitivity by setting.

Figure 5. Sensitivity by Setting

The figure shows the large number of community settings that, when reporting on sensitivity, reported homogenous values around 80 percent. Studies specifying the context as healthcare settings primary care or specialty care reported a larger range of achieved sensitivity. Comparing the reported sensitivities, a simple regression analysis indicated that setting is associated with reported sensitivity (p<0.001). However, the result should be interpreted with caution, as it does not take study size or quality into account, and it was not established within a meta-analytic model. The corresponding reported specificities are shown in Figure 6.
4. Results: Diagnosis of ADHD

Figure 6. Specificity by Setting

Reported specificity values ranged considerably in all settings. Comparing the reported specificities, a simple regression analysis indicated that setting is associated with reported specificity ($p<0.001$). However, the result should be interpreted with caution, as it does not take study size or quality into account, and it was not established within a meta-analytic model.

We also evaluated whether the studies in clinical samples (i.e., referred for a clinical diagnosis of ADHD, oppositional defiance disorder, or autism) and those with primarily neurotypical developing children reported different diagnostic performance values. The figure plots the sensitivity results for the two populations (Figure 7).
4. Results: Diagnosis of ADHD

Figure 7. Sensitivity by Clinical Population

Across studies, we did not detect a statistically significant difference in reported sensitivity results (p 0.21). The next figure plots the specificity stratified by population (Figure 8).

Figure 8. Specificity by Clinical Population

The analysis indicated that the reported specificity was associated with the population that was used to establish diagnostic accuracy (p 0.04). On average, clinical samples reported lower specificities than studies in neurotypical samples (mean 71.3, SD 26.4 vs mean 82.0, SD 14.4). The result suggests that the clinical population appears to be a source of heterogeneity seen in the
4. Results: Diagnosis of ADHD

studies. However, the result should be interpreted with caution as the data were not analyzed in a meta-analytical model, but used the diagnostic performance data as reported by the original authors.

We further investigated whether age of the participants is associated with the achieved diagnostic performance. Figure 9 plots sensitivity by minimum age in the sample.

Figure 9. Sensitivity by Minimum Age

Across studies, we did not detect a statistically significant linear association between samples including younger children versus not on sensitivity (p 0.90). However, it should be noted that the number of studies that included smaller children was low and thus hindered statistical power to detect differences. The equivalent figure for the specificity is shown in Figure 10.

Figure 10. Specificity by Minimum Age

Across studies, there was no statistically significant linear association between samples including younger children or not on specificity (p 0.35). We also categorized studies as younger versus older children and results are shown in the next sample. Using a dichotomous indicator
4. Results: Diagnosis of ADHD

differentiating between young (under 7) and older children (7 and over) also did not indicate a systematic effect for sensitivity (p 0.58) or specificity (p 0.45).

We also analyzed the gender distribution in the identified studies, as the accuracy of a diagnosis may be associated with the reported gender of the participants. Figure 11 plots the percent female participants and sensitivity.

**Figure 11. Sensitivity and Specificity by Proportion of Female Participants**

Across samples, the proportion of girls was not associated with reported sensitivity or specificity (p 0.80). However, the number of female participants was small across studies, which lowers the statistical power to detect an effect.

There were insufficient numbers of studies to evaluate any other risk factors or participant variables.

**4.4.4 KQ1d. What are the adverse effects associated with being labeled correctly or incorrectly as having ADHD?**

Identified studies did not address consequence for patients correctly or not correctly receiving a diagnosis of ADHD or adverse effects associated with being labeled correctly or incorrectly as having ADHD. One study highlighted that a missed diagnosis has implications for accessing funding in the Australian healthcare system (e.g., national Disability Insurance Scheme) but provided no further empirical data.435 None of the included studies reported on stigma associated with being diagnosed or labeled with ADHD.
5. Results: Treatment of ADHD

This section describes studies reporting on a treatment of ADHD. Key points are listed first, followed by a summary of findings section before going into the effects and comparative effects of specific interventions.

5.1 KQ2 ADHD Treatment Key Points

- We found moderate strength of evidence that several treatment modalities improve core ADHD symptoms with a moderate effect size compared to control groups (e.g., placebo). These include FDA-approved medications, psychosocial interventions, school interventions, and neurofeedback.
- FDA-approved stimulant (e.g., methylphenidate) and non-stimulant (e.g., atomoxetine) medications had the strongest evidence for significantly improving ADHD symptoms and additional outcomes, including broadband measures and functional impairment.
- Although indirect comparisons across studies suggest that studies evaluating stimulants report larger effect sizes than studies evaluating non-stimulants for improving ADHD symptoms, head-to-head comparisons did not detect significant differences. Stimulant and non-stimulant medications yielded comparable effects on most effectiveness outcomes and adverse events, including appetite suppression.
- We did not find that combination therapies of medication plus psychosocial therapies produce better results than medication alone, but existing research evaluated unique combinations of intervention components.
- Despite the large body of research, comparative effectiveness and safety information is limited and more research is needed to help choose between treatments.
- Data were insufficient to assess the effect of co-occurring disorders on treatment effects.
- We found too few studies reporting on diversion to quantify the risk of diversion of pharmacological treatment.

5.2 KQ2 ADHD Treatment Summary of Findings

We identified 304 studies evaluating a treatment for ADHD. Although studies from 1980 were eligible, the earliest treatment studies meeting inclusion criteria were published in 1995. Studies were published in 30 different countries, although about 40 percent were US studies (contributing 120 included studies). The summary of findings table broadly summarizes the available evidence for the key outcomes across identified treatment studies. The potential for risk of bias in KQ2 studies is documented in Figure 12. The critical appraisal for the individual studies is in Appendix D.
5. Results: Treatment of ADHD

Figure 12. Risk of Bias in KQ2 ADHD Treatment Studies

Across studies, selection bias was likely present in multiple identified studies. This was predominantly attributable to highly selected samples and exclusions, or a biased allocation into groups because of study logistics. The review was open to all studies evaluating intervention in youth with a ADHD without further limitations, but some included studies reported a number of additional inclusion and exclusion criteria. Performance bias was noted in half of the included studies. An example of this kind of bias is that participants deviated from protocol medication administration (e.g., parents frequently reduced weekend medication use on their own). Attrition bias was also often noted, with large numbers of participants being unavailable for follow-up assessments. Detection bias was detected in many studies where blinding was not possible or would be very difficult and the outcome assessors (often the parents of the participants) were aware of the participants’ intervention assignment. Reporting bias was also suspected in some of the studies, usually indicating that the study did not report on key ADHD outcomes, and no study protocol was published specifying that prospectively. Other sources of bias were identified in a third of studies, concerning small samples or inadequate descriptions of either the interventions or study flow.

Figure 13 shows the distribution of KQ2 studies with applicability issues. The applicability for the individual studies is documented in Appendix D.
5. Results: Treatment of ADHD

Applicability issues primarily concerned the participant samples in the identified studies. Some of the samples were less diverse than the typical population seen in clinical practice, often because of very strict inclusion criteria for the study (e.g., excluding children with co-occurring disorders). A large number of studies did not report any characteristics that flagged the comparator or the setting as different from the level of care in the community.

The populations studied were predominately males, and some studies (2%) were restricted to boys; samples included on average a quarter female participants. The youngest children in individual studies were three years old. Race and ethnicity demographics were not mentioned in over half of the studies. For studies that distinguished between ADHD presentations, the most prevalent type was the combined type.

The following sections summarize the effects of interventions on the key outcomes. Additional information on study-specific primary outcomes are documented in the evidence table.

5.2.1 Effects of ADHD Treatment on Behavior

The results for any achieved changes in behavior (e.g., conduct problems) across the diverse ADHD interventions evaluating a continuous outcome (and reporting sufficient information to allow effect size calculations) showed a positive effect compared to passive control groups (SMD 0.33; CI 0.10, 0.56; 27 studies, n=2989). There was evidence of heterogeneity (I-squared 87%). We tested whether the intervention was the key source of heterogeneity to explain differences in effects, but we did not detect a systematic effect (p 0.78). There was evidence of publication bias (Begg p 0.04, Egger, p 0.03). However, the alternative effect estimate using the trim and fill method was unchanged. We also estimate in a sensitivity analysis whether the result was mainly driven by high risk-of-bias studies; after removing high risk-of-bias studies, the estimate was similar (SMD 0.30; CI 0.02, 0.58). Across studies, only three studies were
5. Results: Treatment of ADHD

identified reporting on categorical outcomes (e.g., assessing whether or not behavior had improved). Results indicated reductions in problematic behavior associated with ADHD treatment (RR 0.46; CI 0.24, 0.87; 3 studies, n=154). In this small set of studies, there was no evidence of heterogeneity or publication bias (Begg p 0.33, Egger p 0.58). None of the studies was classified as high risk.

5.2.2 Effects of ADHD Treatment on Broadband Measures

The results for broadband scales describing a child’s behavior more generally showed positive effects of ADHD interventions (SMD 0.43, CI 0.33, 0.54; 52 studies, n=6997). There was some evidence of heterogeneity (I-squared 74%). We tested whether the intervention was the key source of heterogeneity to explain differences in effects and the analysis suggested that the type of intervention is systematically associated with the effect size seen in the study (p 0.03). There was no evidence of publication bias (Begg p 0.77, Egger p 0.45). We removed high risk-of-bias studies in a sensitivity analysis, but the effect estimate remained similar (SMD 0.48, CI 0.35, 0.61). Multiple studies also reported on these global impressions as categorical variables and the effect was similar for the categorical broadband measures, indicating improvement associated with ADHD treatment (RR 0.56; CI 0.48, 0.65; 36 studies, n=5515). There was evidence of heterogeneity (I-squared 77%). We tested whether the intervention was the key source of heterogeneity to explain differences in effects, but we did not detect a systematic effect (p 0.71). There was evidence of publication bias (Begg 0.01, Egger 0.001) and an alternative estimate using the trim and fill method showed a somewhat smaller effect (RR 0.63; CI 0.54, 0.74). We also conducted a sensitivity analysis to determine whether results are robust when removing six high risk-of-bias studies; the estimate was very similar to the original results (RR 0.56; CI 0.46, 0.68).

5.2.3 Effects of ADHD Treatment on ADHD Symptoms

A large number of studies reported on standardized symptom assessment tools. Standardized mean difference results across studies using continuous data found a positive effect of interventions successfully reducing ADHD symptom severity (SMD -0.46, CI -0.55, -0.38; 126 studies, n=16743). There was evidence of heterogeneity (I-squared 85%). We tested whether the intervention was the key source of heterogeneity to explain differences in effects and found that the reported effect size is systematically associated with the type of intervention evaluated (p 0.04). There was no statistically significant evidence of publication bias (Begg p 0.28, Egger, p 0.06). Excluding 40 high-risk-of-bias studies in a sensitivity analysis resulted in a similar estimate (SMD -0.45, CI -0.55, -0.35) and heterogeneity was not reduced. A smaller number of studies reported on a dichotomous outcome for ADHD symptoms (e.g., meeting or not meeting an improvement target). Across studies, we found a positive effect of ADHD interventions (RR 1.58, CI 1.28, 1.95; 21 studies, n=3041). We detected heterogeneity (I-squared 76%) but a moderator analysis did not detect the intervention as a source of heterogeneity (p 0.46). There was evidence of publication bias (Begg p 0.04, Egger p<0.001). A more appropriate estimate of the true effect on symptom reduction may be somewhat smaller (RR 1.31, CI 1.02, 1.70). We also removed four high risk of bias studies in a sensitivity analysis which showed the treatment effect to be robust (RR 1.52, CI 1.23, 1.95) but heterogeneity was not reduced.
5. Results: Treatment of ADHD

5.2.4 Effects of ADHD Treatment on Functional Impairment

The results for functional impairment measures across the diverse interventions in studies reporting on a continuous outcome found a positive effect of ADHD interventions on functional impairment (SMD 0.39; CI 0.23, 0.54; 33 studies, n=4293). There was evidence of heterogeneity (I-squared 81%). We tested whether the intervention was the key source of heterogeneity to explain differences in effects, but we did not detect a systematic effect (p 0.86). There was no significant publication bias (Begg p 0.09, Egger p 0.08). When removing ten high risk of bias studies in a sensitivity analysis, the estimate remained similar (SMD 0.35; CI 0.16, 0.53) and heterogeneity was not reduced. Very few studies reported on functional impairment as a categorical variable, and only one study reported sufficient information to compute effect sizes. The study indicated improvement but the confidence interval was wide (RR 1.29; CI 1.00, 1.66; 1 study, n=332).

5.2.5 Effects of ADHD Treatment on Acceptability of Treatment

Only one study assessed treatment acceptability formally in a rating scale for all groups and reported sufficient detail to compute effect sizes; the study did not find a statistically significant difference between groups (SMD 0.22; CI -0.09, 0.53; 1 study, n=164). One study reported categorical data to express satisfaction with the treatment; the study favored the intervention (RR 0.47; CI 0.32, 0.68; 1 study, n=198). There were insufficient data for further analyses.

5.2.6 Effects of ADHD Treatment on Academic Performance

The results for academic performance changes reported in sufficient detail across the diverse interventions favored ADHD treatment arms, but we did not detect a statistically significant difference between ADHD treatment and passive control groups on academic performance (SMD -0.26; CI -0.62, 0.09; 9 studies, n=1549). There was evidence of heterogeneity (I-squared 88%). We tested whether the intervention was the key source of heterogeneity to explain differences in effects and the intervention contributed to the heterogeneity of effects (p 0.04). Publication bias tests did not indicate potential bias (Begg p 0.12, Egger 0.62). Removing high risk-of-bias studies in a sensitivity analysis showed a smaller effect, and the difference between groups remained not statistically significant (-0.052; CI -0.23, 0.13). None of the studies comparing to a control group reported on a categorical outcome in sufficient detail to allow effect size calculation.

5.2.7 Effects of ADHD Treatment on Appetite Changes

We identified several studies that reported on a continuous measure to capture appetite changes or growth suppression. Across ADHD interventions, analyses indicated an effect on significantly reducing appetite in studies reporting continuous outcomes (SMD 0.44; CI 0.04, 0.84; 12 studies, n=2016). Heterogeneity was high (I-squared 92%). The type of intervention was one source of heterogeneity, as indicated in a meta-regression (p 0.01). There was no evidence of publication bias (Begg p 1.00, Egger 0.34). Removing two high-risk-of-bias studies in a sensitivity analysis found a similar point estimate, but the effect was not statistically significant (SMD 0.48; CI -0.01, 0.97); heterogeneity was not reduced. Across all ADHD interventions, ADHD treatment was associated with decreased appetite compared to control group participants (RR 2.66; CI 2.10, 3.42; 56 studies, n=8070). A large number of studies and participants...
5. Results: Treatment of ADHD

contributed to the results, and while many individual interventions did not detect statistically significant effects for this rare event, the data aggregation across studies shows a statistically significant effect. Heterogeneity was not remarkable (I-squared 60%). We tested whether the intervention was the key source of heterogeneity to explain some of the heterogeneity, but we did not detect a systematic effect (p 0.61). It should be noted that adverse events generally were more systematically reported in drug studies, and this outcome in particular was usually only reported in studies evaluating a pharmacological component; hence the analysis of the source of heterogeneity should be interpreted with caution. There was some evidence of publication bias (Egger p 0.08, Begg p<0.04). The alternative estimate of the effect using the trim and fill method to account for unpublished studies was somewhat smaller (RR 2.22; CI 1.70, 2.90). We also conducted a sensitivity analysis removing high risk-of-bias studies; the resulting estimate suggested an even stronger effect (RR 2.88; CI 2.20, 3.77) and heterogeneity was reduced further.

5.2.8 Effects of ADHD Treatment on Number of Participants with Adverse Events

Several identified studies reported on the number of participants experiencing an adverse event. Across ADHD interventions, participants undergoing active ADHD treatment were more likely to report adverse events than control group participants (RR 1.25; CI 1.17, 1.32; 55 studies, n=8191). We did not detect noticeable heterogeneity in this analysis (I-squared 58%). An analysis of the intervention as a potential source of heterogeneity indicated borderline results (p 0.5). There was no evidence of publication bias (Begg p 0.84, Egger p 0.25). Removing 11 high risk-of-bias studies in a sensitivity analysis did result in a similar point estimate (RR 1.25; CI 1.17, 1.34) and heterogeneity estimates were unchanged.

5.3 Effects by Intervention

The identified interventions were highly diverse and addressed ADHD treatment in very different ways. In addition, exploring heterogeneity across studies indicated that for several key outcomes the type of intervention that was evaluated is a key source explaining variation in effect estimates. Hence, we broadly differentiated different types of interventions:

- Combined pharmacological and behavioral treatment
- FDA-approved pharmacological agents
- New pharmaceutical agents
- Psychosocial treatment
- Cognitive training
- Neurofeedback
- Physical exercise
- Nutrition and supplements
- Complementary, alternative, and integrative medicine (CAM)
- Parent support
- School interventions
- Provider intervention

The scope of each intervention category is described in detail in each intervention section. In addition to categorizing the type of intervention, we noted whether the intervention was tested as
augmentation, i.e., it was given in addition to and concurrently with stimulant medication. In these studies, the intervention as well as the control group received stimulants while the intervention group was given an additional intervention component. The following provides an overview of the available studies for each intervention category, together with a summary of the effects of the interventions on outcomes.

5.3.1 Combined Pharmacological and Behavioral Treatment

We identified nine eligible treatment studies that evaluated a combination of pharmacological intervention and nonpharmacological behavioral therapy. The behavioral or psychological treatment had to be directed at the participating children in order to be included here. Studies assessing the effect of parental training in combination with medication are reported in the parent intervention section. The earliest identified set of studies were those published from the NIMH Multimodal Treatment Study of Children with ADHD (MTA), which dates to 1999. For the current review, we used the Jensen et al. 3-year follow-up as the key outcome data publication, but we reviewed information from the MTA that has been aggregated thus far in 73 articles, as shown in the evidence table. Half of the identified combined pharmacological and behavioral studies were conducted in the US. The populations studied were predominately males (girls/females comprised a quarter of the target ADHD cohorts across studies) between the ages of five and 18. Evidence of intellectual disability (i.e., full-scale IQ < 70) was exclusionary in all studies, and most studies required full-scale IQ scores of 80 or higher. Half of the studies allowed participants to be included if they had prior exposure to stimulant treatment for ADHD, whereas the remaining studies required participants to be stimulant naïve, or else it was unclear what their inclusion criteria were regarding prior treatment with stimulant medication. For studies that distinguished between ADHD presentations (i.e., ADHD-combined type, ADHD-inattentive type, and ADHD-hyperactive/impulsive type), the most prevalent type (ranging from 54% to 88% of the ADHD participants) was the ADHD-combined presentation. In most studies, children were allowed to have common co-occurring conditions such as oppositional defiant disorder, conduct disorder, or dyslexia/learning disorder, but more severe neurodevelopmental conditions such as autism were exclusionary in this subarea of studies. One study159 specifically required ADHD plus a co-occurring disruptive disorder and significant aggressive behavior, as it examined the usefulness of adjunctive risperidone and/or divalproex sodium in addition to optimal stimulant dosing and behavior therapy. Most studies reported at least some general information regarding the racial/ethnic makeup of their sample; on average, children of Caucasian/European ancestry comprised two thirds of sample makeup, a third were Hispanic or Latino, and a smaller percentage were African American.

The pharmacological treatment components employed in this area were predominantly short- or long-acting stimulants (such as methylphenidate and amphetamine) or else the non-stimulant medication atomoxetine, which is an SNRI (Serotonin and Norepinephrine Reuptake Inhibitor). Behavioral treatment components varied in approach and complexity and included cognitive behavioral therapy, multi-modal psychosocial treatment, a solution-focused approach, behavioral therapy, and a humanistic intervention. Studies compared most frequently combinations of pharmacological and psychosocial treatment to pharmacology or psychosocial treatment alone rather than no treatment or placebo.
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Studies reported a variety of often study-specific outcomes, such as improvement in core ADHD symptoms or co-occurring symptoms. In terms of pre-specified key outcomes, symptom scores were most frequently reported.

Three studies reported on changes in a specific behavior, but they used different metrics and reported different effect estimates and could not be combined; none detected statistically significant difference between the intervention and a control group (SMD -0.04; CI -2.26, 2.18; 2 studies, n=311; RR 0.47; CI 0.18, 1.25; 1 study, n=26).114, 159, 339 Studies reporting on broadband measures are shown in Figure 14.

Figure 14. Effects of Combined Pharmacological and Psychological Treatment on Broadband Measures (SMD)

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect Size (SMD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abikoff, 2004</td>
<td>0.26 [-0.21, 0.74]</td>
</tr>
<tr>
<td>Coelho, 2017</td>
<td>0.10 [-0.41, 0.60]</td>
</tr>
<tr>
<td>Sprich, 2016</td>
<td>1.03 [0.40, 1.66]</td>
</tr>
</tbody>
</table>

Across studies, we found no systematic difference between intervention and control groups (SMD 0.43; CI -0.76, 1.63; 3 studies, n=171), but it should be noted that all studies included in this analysis compared to the medication component of the combined intervention (i.e., control participants received one of the two intervention components). The included studies evaluated different interventions (multimodal psychosocial treatment plus methylphenidate;114 CBT plus methylphenidate;205 and CBT plus FDA-approved medication471) and compared to medication alone.114, 205, 548 The analysis detected some heterogeneity (I-squared 66%). There was no indication of publication bias. All three studies were judged to be high risk of bias. A study reporting on a categorical outcome also found no difference between studies (RR 0.85; CI 0.54, 1.36; 1 study, n=227).485

Studies reporting on ADHD symptom scales are shown in the next forest plot (Figure 15).
Studies did not identify a systematic treatment effect to indicate superiority of the combined pharmacological and psychological treatment versus control (SMD -0.21; CI -0.80, 0.38; 4 studies, n=630). However, the control groups consisted of groups that received the pharmacological intervention component alone rather than no intervention, i.e., the analysis was typically a comparative effectiveness analysis rather than a pure effectiveness analysis. There was some indication of statistical heterogeneity (I-squared 71%). The analysis did not detect publication bias. Removing two high risk of bias studies in a sensitivity analysis did not result in a different effect (SMD -0.02; CI -0.89, 0.85). The forest plot (Figure 16) shows studies reporting on a categorical symptom assessment.
5. Results: Treatment of ADHD

Figure 16. Effects of Combined Pharmacological and Psychological Treatment on Symptoms (RR)

<table>
<thead>
<tr>
<th>Study</th>
<th>RR [CI]</th>
</tr>
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<tbody>
<tr>
<td>Abikoff, 2004 (#14875)</td>
<td>5.00 [0.63, 39.79]</td>
</tr>
<tr>
<td>David, 2021 (#7107)</td>
<td>1.28 [0.68, 2.42]</td>
</tr>
<tr>
<td>Perez-Alvarez, 2009 (#17336)</td>
<td>1.29 [0.78, 2.11]</td>
</tr>
<tr>
<td>RE Model</td>
<td>1.35 [0.92, 1.98]</td>
</tr>
</tbody>
</table>

Studies did not identify a statistically significant treatment effect in the categorical outcome either (RR 1.35; CI 0.92, 1.98; 3 studies, n=155) that would suggest superiority of the combined treatment compared to medication alone. There was no indication of heterogeneity in this small set of studies and further analyses were not possible due to the small number of studies.

The MTA follow up reporting on functional impairment (SMD 0.11; CI -0.15, 0.37; 1 study, n=243) and an academic performance measure (SMD -0.12; CI -0.37, 0.14; 1 study, n=243) also did not find statistically significant differences. We did not identify studies reporting on treatment satisfaction. One study reporting on appetite suppression found no difference between groups (RR 0.93; CI 0.29, 3.03; 1 study, n=29). None of the identified studies reported on the number of participants experiencing adverse events.

5.3.1.1 Combined Pharmacological and Psychological Treatment Comparative Effectiveness

In addition to comparing combined pharmacologic and psychological interventions to pharmacologic treatments alone, one study also compared one pharmacologic and psychological intervention to an alternative pharmacologic and psychological intervention. The study compared combined behavioral therapy and stimulant treatment plus risperidone versus behavioral therapy and stimulants plus divalproex sodium in children with aggressive behavior and ADHD. The study reported on aggressive behavior and concluded that both adjuvants were efficacious (RR 0.61; CI 0.31, 1.20; 1 study, n=175) but also noted that rigorous titration of stimulant medication and concurrent behavior therapy may avert the need for additional medication.

5.3.1.2 Combined Pharmacological and Psychological Treatment Summary of Findings

Table 12 shows the findings for all key outcomes of interest, together with the number of studies and study identifiers.
5. Results: Treatment of ADHD

Table 12. KQ2 Summary of Findings and Strength of Combined Pharmacological and Psychological Treatment

<table>
<thead>
<tr>
<th>Intervention and Comparison</th>
<th>Outcome</th>
<th>Number of Studies; Study Design and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ2 combined treatment vs control (individual component or usual care)</td>
<td>Behavior</td>
<td>3 RCTs\textsuperscript{114, 159, 339}</td>
<td>No systematic difference (SMD -0.04; CI -2.26, 2.18; 2 studies, n=311; RR 0.47; CI 0.18, 1.25; 1 study, n=26)</td>
<td>Low for no difference</td>
</tr>
<tr>
<td>KQ2 combined treatment vs control (individual component, wait list)</td>
<td>Broadband measures</td>
<td>4 studies\textsuperscript{114, 205, 485, 548}</td>
<td>Studies favored the combination intervention but there was no statistically significant difference and effect estimates varied (SMD 0.43; CI -0.76, 1.63; 3 studies, n=171; RR 0.85; CI 0.54, 1.36; 1 study, n=227)</td>
<td>Low for no difference</td>
</tr>
<tr>
<td>KQ2 combined treatment vs control (individual component, usual care, wait list)</td>
<td>ADHD symptoms</td>
<td>6 studies, 5 RCTs, \textsuperscript{114, 229, 339, 462, 485} and one crossover trial\textsuperscript{548}</td>
<td>Analyses did not detect a difference between groups across two analyses (SMD -0.02; CI -0.20, 0.15; 4 studies, n=630; RR 1.17; CI 0.91, 1.51; 3 studies, n=155)</td>
<td>Moderate for no difference</td>
</tr>
<tr>
<td>KQ2 combined treatment vs control (individual component, usual care)</td>
<td>Functional impairment</td>
<td>2 RCTs\textsuperscript{114, 339}</td>
<td>No systematic differences between groups detected (SMD 0.11; CI -0.15, 0.37; 1 study, n=243)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 combined treatment vs control</td>
<td>Acceptability of treatment</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 combined treatment vs usual care</td>
<td>Academic performance</td>
<td>1 RCT\textsuperscript{339}</td>
<td>No systematic differences between groups (SMD -0.12; CI -0.37, 0.14; 1 study, n=243)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 combined treatment vs control (individual component, usual care)</td>
<td>Appetite suppression</td>
<td>2 RCTs\textsuperscript{220, 339}</td>
<td>No systematic differences (RR 0.93; CI 0.29, 3.03; 1 study, n=29)</td>
<td>Low for no difference</td>
</tr>
</tbody>
</table>

Notes: CI 95% confidence interval, KQ key question, N/A not applicable, RR relative risk, RCT randomized controlled trial, SMD standardized mean differences, SoE strength of evidence

The summary of findings table above generally shows little support that a treatment modality comprising combined medication and behavior treatment as superior to control groups where control groups typically provided medication alone. For multiple outcomes we found very few or no studies to determine intervention effects. We downgraded the strength of evidence for functional impairment, academic performance, and adverse events to insufficient due to study limitation and inconsistency (downgraded by 2 given that consistency could not be determined as only one study has reported on the outcome to date).

5.3.2 FDA-approved Pharmacological Treatment

We identified 103 studies evaluating an FDA-approved pharmacological intervention.\textsuperscript{115, 116, 125, 133, 137, 138, 144, 153, 162, 166, 169, 172, 182, 183, 197, 198, 200, 206, 209, 211, 212, 221, 224, 230, 231, 251-253, 273-276, 282, 288, 289, 292, 303, 304, 317, 321, 333, 337, 342, 367, 368, 370, 372, 374, 375, 379, 404, 408, 409, 415, 421, 422, 430, 432, 441-444, 447-449, 470, 492, 499, 500, 513, 514, 526-528, 544, 545, 549, 555, 555, 562, 578, 585, 593, 598-601, 605-608, 610-612, 615, 622, 632, 892, 1088, 1161} Although studies from 1980 were eligible, the earliest studies meeting inclusion criteria were published in 1995.\textsuperscript{142, 528} Evaluations were published in 15 different countries, but 60 percent
5. Results: Treatment of ADHD

was US-based. Although the percent of female participants ranged from seven to 56 percent, samples were predominantly male. The age minimum varied, but across all identified studies, only five studies included children three to five years old.\textsuperscript{116, 198, 237, 274, 372} Studies varied in whether they required participants to be drug naïve at study beginning, while others allowed concomitant medication even during the study. The identified studies included some that explicitly tested adjunctive medication to augment stimulant treatment.\textsuperscript{111, 114, 260, 367, 477, 585, 611}

Studies included different presentations of ADHD. Where reported, the combined presentation was most common in studies, on average representing two thirds of the sample. While ADHD participants with co-occurring disorders were not excluded from most of the studies, only a few studies purposely included specific co-occurring disorders, including oppositional defiant disorder or conduct disorder,\textsuperscript{182, 211, 224, 231, 260, 422, 612} Tourette syndrome or tic disorder,\textsuperscript{125, 374, 528, 544} or learning disabilities.\textsuperscript{514, 526} Demographics were often not reported, but where studies reported a breakdown by race or ethnicity, on average, 75 percent of children were white.

Of the identified studies, the majority reported on the comparison to a control group not receiving pharmacological treatment, most frequently placebo. Half of identified studies reported alternatively or in addition on the effects of an alternative intervention, for example a different dose of the same medication or a different medication. Studies most frequently reported on symptom scale scores. Studies that reported on a control group with sufficient detail to allow effect size calculations for individual behavior changes (not already captured in broadband or symptom score measures) are shown in Figure 17.

Figure 17. Effects of FDA-Approved Pharmacological ADHD Treatment on Behavior (SMD)

<table>
<thead>
<tr>
<th>Study and Year</th>
<th>Medication</th>
<th>SMD and CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eli Lilly, 2006 (#13928) ATX</td>
<td>0.48 [0.12, 0.84]</td>
<td></td>
</tr>
<tr>
<td>Hazell, 2003 (#14216) HCl stim</td>
<td>0.31 [-0.17, 0.80]</td>
<td></td>
</tr>
<tr>
<td>Michelson, 2001 (#17979) ATX</td>
<td>0.92 [0.60, 1.24]</td>
<td></td>
</tr>
<tr>
<td>Newcorn, 2008 (#17455) ATX, MPH</td>
<td>0.80 [0.43, 1.17]</td>
<td></td>
</tr>
<tr>
<td>RE Model</td>
<td>0.66 [0.22, 1.10]</td>
<td></td>
</tr>
</tbody>
</table>

Figure notes: ATX atomoxetine, HCl clonidine hydrochloride, MPH methylphenidate, stim stimulants (not further defined)

Across studies, pharmacological intervention (all non-stimulants) were associated with significant improvements in individual problem behaviors (SMD 0.66; CI 0.22, 1.10; 4 studies, n=523). The minimum age in the included studies was six years old. There was little evidence of heterogeneity (49%). There was no indication of publication bias. Excluding a high risk of bias
study in a sensitivity analysis increased the CI and the effect was not statistically significant (SMD 0.64; CI -0.22, 1.51), but did not reduce heterogeneity. Stratifying the non-stimulants further, the norepinephrine reuptake inhibitor (SNRI) atomoxetine showed improved problem behaviors (SMD 0.74; CI 0.17, 1.32; 3 studies), while alpha agonist study detected no difference (SMD 0.31; CI -0.17, 0.80; 1 study). We identified one study reporting on a categorical variable based on a behavior measure and providing sufficient detail to allow effect size computation. The identified study evaluated the alpha-agonist clonidine adjunctive to psychostimulant medication\textsuperscript{317}; the study did not detect a statistically significant difference between arms (RR 0.31; CI -0.17, 0.80; 1 study, n=66).

Multiple studies reported on a broadband measure as shown in Figure 18.

Figure 18. Effects of FDA-Approved Pharmacological ADHD Treatment on Broadband Measures (SMD)

Across studies, pharmacological treatment was associated with a systematic benefit on broadband scale assessments compared to control (SMD 0.73; CI 0.40, 1.06; 27 studies, n=4618). Only one study included children younger than six years old.\textsuperscript{116} Studies assessed different medication regimes but analyses detected little heterogeneity (I-squared 58%). Largest effects were reported in studies evaluating lisdexamfetamine dimesylate,\textsuperscript{137} atomoxetine,\textsuperscript{251} methylphenidate,\textsuperscript{116} and extended-release guanfacine added to usual care stimulant therapy,\textsuperscript{585} respectively. There was no evidence of publication bias. Removing six high-risk-of-bias studies in a sensitivity analysis found a smaller but also significant effect estimate (SMD 0.53; CI 0.38, 0.69), indicating that the documented treatment effect is not mainly based on biased studies.
5. Results: Treatment of ADHD

Several studies included in the pharmacological analysis assessed stimulants and when restricting to stimulants alone, we also found statistically significantly improved broadband scale scores, but heterogeneity in this intervention subgroup was not reduced but increased (SMD 0.67; CI 0.16, 1.18; 6 studies; I-squared 87%). Stratifying the stimulants into methylphenidate and amphetamine medication, we found that methylphenidate studies showed a similar point estimate, but the result was not statistically significant in this small subset and heterogeneity was negligible (SMD 0.58; CI -0.03, 1.19; 3 studies; I-squared 25%). Similarly, results across amphetamine versus placebo were not statistically significant in this equally small subset and heterogeneity was high and not reduced (SMD 0.76; CI -0.96, 2.46; 3 studies; I-squared 94%). A large intervention subgroup included in the pharmacological medications reporting on broadband measures were non-stimulants. Across studies, non-stimulants improved broadband scale scores with reduced, negligible heterogeneity (SMD 0.52; CI 0.41, 0.64; 18 studies; I-squared 32%). Results restricting to SNRIs only were similar to the combined non-stimulant analysis and indicated a clear effect on broadband measure scores, with heterogeneity reduced further (SMD 0.54; CI 0.42, 0.65; 15 studies; I-squared 25%). Most of the non-stimulant studies evaluated atomoxetine and excluding three viloxazine studies did not change the estimate (SMD 0.58; 0.43, 0.73; 12 studies; I-squared 38%). The alpha agonist studies that contributed to the non-stimulant estimate reported a similar effect to the main analysis and there was no heterogeneity in this subset (SMD 0.47; CI 0.10, 0.85; 3 studies; I-squared 0).

Multiple studies reported on broadband scale as a categorical outcome (e.g., criteria for improvement met or not) as shown in Figure 19.

**Figure 19. Effects of FDA-Approved Pharmacological ADHD Treatment on Broadband Measures (RR)**

Notes: DEX dexamphetamine, GXR guanfacine, LDX lisdexamfetamine dimesylate, MPH methylphenidate, stim stimulants (not further defined)
5. Results: Treatment of ADHD

Across studies, results also indicated that pharmacological ADHD treatment was associated with a systematic benefit compared to control (RR 0.50; CI 0.43, 0.59; 25 studies, n=3959). Only two studies included children younger than six years old.\textsuperscript{116, 372} Analyses detected some heterogeneity (I-squared 74\%). There was evidence of publication bias (Begg p 0.003, Egger p<0.001) and an alternative estimate using the trim and fill method suggested a somewhat smaller effect (RR 0.60; CI 0.50, 0.72). When excluding six high-risk-of-bias studies in a sensitivity analysis, effect estimates were similar to the original effect (RR 0.53; CI 0.42, 0.69) and heterogeneity was not reduced. This analysis included a substantial number of studies evaluating different stimulants and restricting to stimulants alone, we also found improved broadband scale scores with reduced heterogeneity (RR 0.39; CI 0.31, 0.49; 13 studies; I-squared 46\%). Restricting to methylphenidate alone reduced heterogeneity further and the effect was also statistically significant in this smaller subset (RR 0.39; CI 0.30, 0.49; 9 studies; I-squared 33\%). In the subset of amphetamine, results were similar but there was evidence of heterogeneity (RR 0.39; CI 0.26, 0.60; 3 studies; I-squared 65\%). Across studies, non-stimulants compared to placebo improved broadband scale score evaluations and heterogeneity was low (RR 0.66; CI 0.57, 0.76; 11 studies; I-squared 36\%). Results of restricting analyses to SNRIs to identify sources of heterogeneity also showed an improvement in broadband scale scores (RR 0.58; CI 0.46, 0.73; 4 studies),\textsuperscript{162, 372, 430, 470} and the analysis did not detect any heterogeneity. The equivalent analysis for alpha agonists versus placebo was also statistically significant with little heterogeneity (RR 0.69; CI 0.58, 0.82; 7 studies; I-squared 49\%).\textsuperscript{153, 321, 368, 447, 499, 612} A large number of studies reported on symptom improvements. Standardized mean differences are shown in Figure 20.
5. Results: Treatment of ADHD

Figure 200. Effects of FDA-Approved Pharmacological ADHD Treatment on ADHD Symptoms (SMD)

Across studies, pharmacological interventions for ADHD were associated with a systematic reduction in symptom scale scores compared to control (SMD -0.59; CI -0.68, -0.51; 47 studies, n=7358). Only two studies included children younger than six years old. There was some evidence of heterogeneity (I-squared 67%). Tests for publication bias were not statistically significant. Excluding nine high-risk-of-bias studies in a sensitivity analysis estimated similar symptom reductions, indicating that the result is not primarily driven by high risk studies (SMD -0.60; CI -0.71, -0.49). Restricting medications to stimulants also showed improved ADHD symptoms but heterogeneity remained (SMD -0.88; CI -1.13, -0.06; 12 studies; I-squared 77%). When restricting to methylphenidate evaluations only to explore heterogeneity, we found that methylphenidate showed improvement in ADHD symptom scores and heterogeneity was considerably reduced (SMD -0.61; CI -0.84, -0.39; 6 studies; I-squared 29%). The equivalent analysis for amphetamine studies also showed improvement in symptom scores but heterogeneity was not reduced (SMD -1.13; CI -1.62, -0.54; 5 studies; I-squared 79%).

Non-stimulants also improved ADHD symptom scores and heterogeneity was not remarkable (SMD -0.51; CI -0.58, -0.44; 35 studies; I-squared 47%). Results of restricting to SNRIs were similar to the overall non-stimulant analysis with heterogeneity further reduced (SMD -0.52; -0.60, -0.43; 24 studies; I-squared 34%). Most of these studies evaluated
atomoxetine specifically, and excluding other studies (assessing guanfacine or viloxanzine) found a similar treatment effect (SMD -0.57; CI -0.68, -0.46; 18 studies; I-squared 40%). Effects for alpha agonists versus placebo were also statistically significant (SMD -0.49; CI -0.64, -0.34; 11 studies).

Results for symptom measures used as categorical data are shown in Figure 21.

5. Results: Treatment of ADHD

Results across studies also indicated a significant benefit (RR 1.75, CI 1.32, 2.31; 12 studies, n=1850). None of the studies included children under six years of age. There was some evidence of heterogeneity (I-squared 71%). There was also some evidence of publication bias (Begg p 0.07, Egger p 0.02). Applying the trim and fill method for an alternative estimate, results were similar (RR 1.76; CI 1.36, 2.27). When removing high risk of bias studies in a sensitivity analysis, the treatment effect was even higher than the main analysis (RR 1.92, CI 1.42, 2.59) and heterogeneity was further reduced, indicating that methodological rigor of the studies was one source of heterogeneity. Stratifying studies further found that stimulants improved ADHD symptoms (RR 2.61; CI 1.00, 6.77; 3 studies) and the small subset did not detect heterogeneity. Results for methylphenidate alone showed the same point estimate but results were not statistically significant due to wide confidence intervals (RR 1.72; CI 0.52, 5.12; 2 studies). The only amphetamine study reported a statistically significant effect (RR 4.28; CI 2.49, 7.35; 1 study). Across studies, non-stimulants improved ADHD symptoms with negligible heterogeneity (RR 1.49; CI 1.21, 1.83; 10 studies; I-squared 46%). Most of the non-stimulant studies evaluated atomoxetine and excluding all other studies showed a very similar effect estimate (RR 1.49; CI 1.13, 1.95; 6 studies; I-squared 69%). One study assessing an alpha agonist did not find a systematic difference between groups due to wide confidence intervals (RR 2.04; CI 0.82, 5.06; 1 study).
5. Results: Treatment of ADHD

Some of the identified studies reported on functional outcomes as shown in Figure 22.

Figure 22. Effects of FDA-Approved Pharmacological ADHD Treatment on Functional Impairment (SMD)

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abikoff, 2007 (#18292) MPH</td>
<td>0.14 [-0.32, 0.60]</td>
</tr>
<tr>
<td>Banaschewski, 2013 (#14417) LDX, MPH</td>
<td>0.58 [0.30, 0.85]</td>
</tr>
<tr>
<td>Buiterlaar, 2007 (#17592) ATX</td>
<td>0.02 [-0.29, 0.33]</td>
</tr>
<tr>
<td>Childress, 2019 (#487) amph</td>
<td>0.60 [-0.07, 1.27]</td>
</tr>
<tr>
<td>Concordia Pharmaceuticals, 201 (#13782) HCl</td>
<td>-0.00 [-0.34, 0.34]</td>
</tr>
<tr>
<td>Michelson, 2001 (#17979) ATX</td>
<td>0.51 [0.20, 0.82]</td>
</tr>
<tr>
<td>Nasser, 2020 (#259) SPN</td>
<td>0.42 [0.19, 0.64]</td>
</tr>
<tr>
<td>Nasser, 2021 (#2978) SPN</td>
<td>-0.04 [-0.33, 0.24]</td>
</tr>
<tr>
<td>Nasser, 2021 (#3004) SPN</td>
<td>0.21 [-0.07, 0.50]</td>
</tr>
<tr>
<td>Tris Pharma, 2014 (#13784) amph</td>
<td>1.90 [1.43, 2.37]</td>
</tr>
<tr>
<td>Wigal, 2011 (#17070) MPH</td>
<td>1.41 [1.06, 1.76]</td>
</tr>
</tbody>
</table>

Notes: amph amphetamines (not further defined), ATX atomoxetine, LDX lisdexamfetamine dimesylate, MPH methylphenidate, SPN SPN-812, stim stimulants (not further defined)

Across studies, treatment was associated with a decrease in functional impairment (SMD 0.51; CI 0.10, 0.92; 11 studies, n=1739). Only one study included children younger than six years old.116 There was evidence of substantial heterogeneity (I-squared 92%). There was no evidence of publication bias. Excluding three high-risk-of-bias studies in a sensitivity analysis did not change the treatment estimate (SMD 0.50; CI 0.08, 0.92) and heterogeneity was not reduced. Across studies, stimulants specifically improved functional impairment; however, estimates varied substantially, and heterogeneity was high (SMD 0.93; CI 0.05, 1.81; 5 studies; I-squared 91%). Restricting to methylphenidate to explore the source of heterogeneity left two studies reporting different effect estimates for functional impairment that could not be meaningfully combined and the effect was not statistically significant (SMD 0.78; CI -7.36, 8.92; 2 studies, I-squared 94%). The results of the equivalent analysis for amphetamines showed a significant effect but there remained heterogeneity (SMD -1.16; CI -1.20, -0.67; 5 studies; I-squared 79%).137, 197, 575 Across studies, non-stimulants also improved functional impairment but there remained evidence of heterogeneity (SMD 0.22; CI 0.02, 0.41; 7 studies; I-squared 56%). Removing the one alpha agonist study (SMD 0.00; CI -0.34, 0.34; 1 study)209 and restricting to SNRIs alone did not change the effect estimate substantially and heterogeneity was not reduced (SMD 0.27; CI 0.00, 0.55; 6 studies; I-squared 71%). Restricting to atomoxetine studies, evaluated in three of the included studies, did not detect a systematic effect between intervention versus control and also did not reduce heterogeneity (SMD 0.34; CI -0.48, 1.17; 3 studies; I-squared 80%).

We only identified one study formally assessing treatment satisfaction for all study arms; the study reported significant satisfaction with the alpha agonist treatment compared to placebo.
5. Results: Treatment of ADHD

treatment (RR 0.47; CI 0.32, 0.68; 1 study, n=198). Only one study reported on academic performance; the study reported improvements in the methylphenidate compared to control group (SMD -1.37; CI -1.72, -1.03; 1 study, n=156) in the correct answers on the Permanent Product Measure of Performance (PERMP).

All studies reporting in sufficient detail on a continuous measure for appetite, weight or growth suppression are shown in the Figure 23.

**Figure 23. Effects of FDA-Approved Pharmacological ADHD Treatment on Appetite Suppression (SMD)**

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buitelaar, 2007(#17592) ATX</td>
<td>1.05</td>
</tr>
<tr>
<td>Coghill, 2014(#14575) LDX</td>
<td>0.17</td>
</tr>
<tr>
<td>Daviss, 2008(#15335) HCl MPH</td>
<td>-0.13</td>
</tr>
<tr>
<td>Hazell, 2003(#14216) HCl stim</td>
<td>0.38</td>
</tr>
<tr>
<td>Kurowski, 2019(#415) MPH</td>
<td>0.22</td>
</tr>
<tr>
<td>Spencer, 2008(#18353) ATX</td>
<td>1.06</td>
</tr>
</tbody>
</table>

RE Model: 0.48 [-0.04, 1.00]

Notes: ATX atomoxetine, HCl clonidine hydrochloride, LDX lisdexamfetamine dimesylate, MPH methylphenidate, stim stimulants (not further defined)

Across studies, pharmacological treatment indicated reduced appetite but the effect was not statistically significant (SMD 0.48; CI -0.04, 1.00; 6 studies, n=605). There was evidence of heterogeneity (I-squared 82%). We did not detect publication bias. Removing one high-risk-of-bias study in a sensitivity analysis did not change the effect (SMD 0.46; CI 0.08, 0.83) and heterogeneity was not reduced. Across studies in this analysis, we found no statistically significant effect of stimulants on appetite suppression (SMD 0.12; CI -0.30, 0.54; 3 studies; I-squared 0) and no heterogeneity was detected in this subset of studies. A study evaluating methylphenidate found a smaller and not significant effect (SMD 0.22; CI -0.41, 0.84; 1 study). The single amphetamine study also did not show a statistically significant effect (SMD 0.13, 0.50; 1 study). Across non-stimulant studies, we found a statistically significant effect of non-stimulants on increasing appetite suppression but heterogeneity remained high (SMD 0.64; CI 0.04, 1.25; 4 studies; I-squared 84%). The alpha agonist studies reported conflicting results and did not detect a systematic effect across studies (SMD 0.13; CI -3.12, 3.39; 2 studies; I-squared 51%).

A much larger number of studies reported on appetite suppression as a categorical measure (e.g., reported incidences per sample) indicating the number of patients reporting this adverse event as shown in Figure 24.
5. Results: Treatment of ADHD

Figure 244. Effects of FDA-Approved Pharmacological ADHD Treatment on Appetite Suppression (RR)

Across studies, pharmacological treatment was associated with a suppression in appetite compared to control groups (RR 3.24; CI 2.49, 4.20; 46 studies, n=7389). Only two studies included children under the age of six. Heterogeneity was negligible (I-squared 45%). There was evidence of publication bias (Begg p 0.03, Egger p<0.005). An alternative treatment estimate using the trim and fill method suggested a somewhat smaller effect on appetite suppression (RR 2.41; CI 1.79; 3.25). When removing six high-risk-of-bias studies in a sensitivity analysis, effect estimates were similar to the main effect (RR 3.18; CI 2.35, 4.32). Across studies, stimulants specifically were associated with suppressed appetite compared to placebo, but there was some heterogeneity (RR 3.85; CI 2.33, 6.36; 19 studies; I-squared 64%). Restricting to methylphenidate only to explore heterogeneity found a somewhat reduced, but still clear and statistically significant effect (RR 3.02; CI 1.11, 8.25; 6 studies; I-squared 64%) and heterogeneity was not reduced when restricting to this subset. Amphetamine were also associated with appetite suppression compared to placebo and heterogeneity was not remarkable (RR 6.23; CI 2.48, 15.66; 7 studies; I-squared 55%). The non-stimulants were also associated with suppressed appetite compared to placebo with negligible heterogeneity (RR 2.86; CI 2.09, 3.91; 25 studies; I-squared 24%). Results restricting to SNRIs also showed an association with suppressed appetite compared to placebo with no heterogeneity (RR 3.29; CI
5. Results: Treatment of ADHD

2.42, 4.47; 22 studies; I-squared 2%). Most studies evaluated atomoxetine and excluding all other studies did not change the estimate substantially and heterogeneity was essentially nonexistent (RR 3.21; CI 2.34, 4.39; 17 studies; I-squared 4%). Although the small set did also not detect heterogeneity, the alpha agonist studies reported conflicting results and did not indicate a systematic effect (RR 1.25; CI 0.58, 2.70; 4 studies; I-squared ).

The number of participants experiencing any adverse event is documented in Figure 25.

Figure 255. Effects of FDA-Approved Pharmacological ADHD Treatment on Number of Participants with Adverse Events (RR)

Pharmacological interventions were associated with a higher risk of experiencing adverse events compared to control groups (RR 1.29; CI 1.23, 1.36; 42 studies, n=7130). None of the studies included children under the age of six. We detected only negligible heterogeneity (I-squared 45%). There was evidence of publication bias (Begg p 0.12, Egger p<0.001) and an alternative effect estimate using the trim and fill method suggested a smaller effect (RR 1.23; CI 1.16, 1.30). We also assessed in a sensitivity analysis whether results were mainly driven by high-risk-of-bias studies; estimates remained stable (RR 1.28; CI 1.22, 1.35) after excluding eight high-risk of bias studies and heterogeneity was reduced further. Across studies, we found that stimulants were associated with an increased reporting of adverse events compared to control and heterogeneity remained the same as in the main analysis (RR 1.29; CI 1.14, 1.46; 14...
5. Results: Treatment of ADHD

Studies; I-squared 51%). Stratifying medications further, we did not find a statistically significant effect of methylphenidate on the number of participants reporting on adverse events but heterogeneity estimates were higher than in the overall stimulant analysis (RR 1.22; CI 0.95, 1.55; 7 studies) (I-squared 72%). Amphetamine treatment was associated with an increased risk of experiencing adverse events compared to placebo and the analysis detected no heterogeneity in this stimulant medication subset (RR 1.34; CI 1.20, 1.50; 7 studies). Non-stimulants were equally associated with increased reported adverse events (RR 1.29; CI 1.20, 1.38; 21 studies; I-squared 40%). Results restricting to SNRIs also showed increased reporting of adverse events in this subgroup and heterogeneity was further reduced (RR 1.36; CI 1.24, 1.50; 11 studies; I-squared 28%). Most of these studies evaluated atomoxetine and excluding all other studies found a similar effect estimate (RR 1.32; CI 1.18, 1.49; 8 studies; I-squared 34%). Similarly, alpha agonists were associated with the number of participants experiencing adverse events compared to placebo with some heterogeneity (RR 1.21; CI 1.10, 1.32; 13 studies; I-squared 61%).

5.3.2 FDA-Approved ADHD Pharmacological Treatment Comparative Effects

We identified over 60 studies comparing pharmacological agents to an alternative treatment; however, comparators varied. Comparators were often different doses of the same medication and some found a dose-response effect. For example, one study compared 200mg with 100mg of SPN-812 (extended release viloxazine, an SNRI) and reported improvement in both symptoms and functional impairment in both dosage groups, while the rate of children reporting decreased appetite was 7.5 in the 200mg group compared to 4.5 in the 100mg group.\(^{442}\) The evidence table in the appendix shows results for dose comparisons in detail.

The following documents results of direct comparisons within head-to-head trials, followed by indirect comparisons across studies where possible.

5.3.2.1 Non-Stimulants versus Stimulants

Non-stimulants versus stimulants in direct, head-to-head comparisons within identified studies for individual problem behaviors are shown in Figure 26.
Across studies, non-stimulants (all SNRIs) were slightly but statistically significantly associated with more reductions in individual problem behavior compared to stimulants (SMD -0.08; CI -0.14, -0.03; 4 studies, n=608); all studies compared atomoxetine versus methylphenidate. None of the studies included children under the age of 6. The analysis did not detect heterogeneity or evidence of publication bias. However, removing all high risk of bias studies left only one study, which individually did not detect a difference between atomoxetine versus methylphenidate (SMD -0.13; CI -0.43, 0.17). There were insufficient studies reporting on the outcome for indirect comparisons between non-stimulant and stimulant studies. Given the difference between medications, the next figure (Figure 27) reports a subgroup analysis for non-stimulants on problem behavior.
5. Results: Treatment of ADHD

Figure 277. Subgroup Analysis: Non-Stimulants versus Control on Problem Behavior (SMD)

In the subgroup of non-stimulant studies, treatment was associated with a reduction in problem behavior compared to placebo (SMD 0.66; CI 0.22, 1.10; 4 studies, n=523). We identified only one study that compared stimulants alone to a control group, the study did not detect a systematic difference between methylphenidate and placebo (SMD 0.31; CI -0.33, 0.95; n=91).²²⁸

Results for broadband measures are shown in Figure 28; all studies compared atomoxetine with methylphenidate.
5. Results: Treatment of ADHD

Figure 28. Comparison Non-stimulants (All SNRIs, all Atomoxetine) versus Stimulants (All Methylphenidate) on Broadband Measures (SMD)

Across studies, we did not detect a systematic difference between stimulants and non-stimulants for continuous broadband measure outcomes (SMD -0.16; CI -0.36, 0.04; 4 studies, n=1080); all studies compared the SNRI atomoxetine versus methylphenidate. We did not detect heterogeneity or evidence of publication bias. Removing all high risk of bias studies left only one study that reported a similar effect estimate (SMD -0.15; CI -0.37, 0.06). We also assessed in indirect comparisons whether the subgroup of studies evaluating non-stimulants versus studies evaluating stimulants reported different effect sizes (both compare the intervention against a control group, rather than comparing the two drug classes directly). We did not detect differences for continuous outcomes in this analysis (p 0.17).

We identified only one study that reported on a categorical assessment of a broadband impression; the study found no difference between non-stimulants and stimulants (RR 1.01; CI 0.75, 1.37; 1 study, n=237); the study compared the SNRI atomoxetine versus methylphenidate specifically. However, a meta-regression for categorical broadband measures indicated a statistically significant difference between results reported in non-stimulant versus stimulant studies (p 0.0004). The next figure (Figure 29) shows the subgroup analysis results.
5. Results: Treatment of ADHD

Figure 29. Subgroup Analysis: Non-Stimulants versus Control on Broadband Measures (RR)

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biederman, 2008 (#17495)</td>
<td>0.48 [0.29, 0.80]</td>
</tr>
<tr>
<td>Block, 2009 (#19273)</td>
<td>0.66 [0.46, 0.94]</td>
</tr>
<tr>
<td>Hervas, 2014 (#19229)</td>
<td>0.84 [0.68, 1.04]</td>
</tr>
<tr>
<td>Kollins, 2011 (#17124)</td>
<td>0.62 [0.42, 0.90]</td>
</tr>
<tr>
<td>Kratochvil, 2011 (#19239)</td>
<td>0.55 [0.29, 1.03]</td>
</tr>
<tr>
<td>Montoya, 2009 (#17348)</td>
<td>0.64 [0.42, 0.99]</td>
</tr>
<tr>
<td>Newcorn, 2016 (#13247)</td>
<td>0.65 [0.49, 0.86]</td>
</tr>
<tr>
<td>Prasad, 2007 (#17526)</td>
<td>0.40 [0.24, 0.66]</td>
</tr>
<tr>
<td>Sallee, 2009 (#17319)</td>
<td>0.54 [0.40, 0.71]</td>
</tr>
<tr>
<td>Wilens, 2012 (#19257)</td>
<td>0.80 [0.68, 0.96]</td>
</tr>
<tr>
<td>Wilens, 2015 (#19233)</td>
<td>0.72 [0.55, 0.93]</td>
</tr>
<tr>
<td>RE Model</td>
<td>0.66 [0.57, 0.76]</td>
</tr>
</tbody>
</table>

In the subgroup of non-stimulant studies, treatment was associated with a reduction in broadband measures, but the effect was smaller than for stimulants (RR 0.66; CI 0.57, 0.76; 11 studies, n=2174). Only one of the studies included children under the age of six.\textsuperscript{372} The subgroup analysis of stimulant studies is shown in Figure 30.

Figure 30. Subgroup Analysis: Stimulants versus Control on Broadband Measures (RR)

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abikoff, 2007 (#18292)</td>
<td>0.62 [0.27, 1.44]</td>
</tr>
<tr>
<td>Bostic, 2000 (#18016)</td>
<td>0.04 [0.00, 0.63]</td>
</tr>
<tr>
<td>Coghill, 2014 (#14575)</td>
<td>0.25 [0.15, 0.42]</td>
</tr>
<tr>
<td>Findling, 2008 (#19232)</td>
<td>0.34 [0.16, 0.74]</td>
</tr>
<tr>
<td>Findling, 2010 (#17270)</td>
<td>0.47 [0.32, 0.67]</td>
</tr>
<tr>
<td>Findling, 2011 (#17155)</td>
<td>0.52 [0.38, 0.70]</td>
</tr>
<tr>
<td>Greenhill, 2006 (#17665)</td>
<td>0.20 [0.09, 0.43]</td>
</tr>
<tr>
<td>Simonoff, 2013 (#14570)</td>
<td>0.18 [0.07, 0.48]</td>
</tr>
<tr>
<td>Spencer, 2006 (#15089)</td>
<td>0.42 [0.26, 0.68]</td>
</tr>
<tr>
<td>Tourette’s Syndrome Study Group, 2002 (#17966)</td>
<td>0.36 [0.21, 0.60]</td>
</tr>
<tr>
<td>Weiss, 2021 (#13544)</td>
<td>0.60 [0.40, 0.89]</td>
</tr>
<tr>
<td>Wigal, 2004 (#15041)</td>
<td>0.31 [0.17, 0.58]</td>
</tr>
<tr>
<td>Wolraich, 2001 (#15145)</td>
<td>0.36 [0.22, 0.60]</td>
</tr>
<tr>
<td>RE Model</td>
<td>0.39 [0.31, 0.49]</td>
</tr>
</tbody>
</table>
5. Results: Treatment of ADHD

As already indicated in the prior section, the effect estimate for stimulant studies showed a clear effect for individual studies and across studies in this medication subgroup (RR 0.39; CI 0.31, 0.49; 13 studies, n=1569). Only one study included children younger than six years old.116

A large number of studies reported on ADHD symptoms, and we identified a number of head-to-head comparisons. The analysis comparing non-stimulants versus stimulants for ADHD symptoms is shown in Figure 31.

Figure 31. Comparison Non-stimulant (All SNRI) versus Stimulant on ADHD Symptoms (SMD)

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Comparator</th>
<th>SMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedard</td>
<td>2015</td>
<td>MPH</td>
<td>0.26 [-0.02, 0.54]</td>
</tr>
<tr>
<td>Dittmann</td>
<td>2013</td>
<td>MPH</td>
<td>0.50 [0.26, 0.75]</td>
</tr>
<tr>
<td>Kratochvil</td>
<td>2002</td>
<td>MPH</td>
<td>0.01 [-0.32, 0.34]</td>
</tr>
<tr>
<td>Mount Sinai</td>
<td>2012</td>
<td>MPH</td>
<td>-0.26 [-0.85, 0.34]</td>
</tr>
<tr>
<td>Newcorn</td>
<td>2008</td>
<td>MPH</td>
<td>0.19 [0.01, 0.38]</td>
</tr>
<tr>
<td>Wang</td>
<td>2007</td>
<td>MPH</td>
<td>0.05 [-0.17, 0.27]</td>
</tr>
<tr>
<td>Zhu</td>
<td>2017</td>
<td>MPH</td>
<td>0.71 [0.32, 1.11]</td>
</tr>
</tbody>
</table>

Although more studies favored stimulants, across studies, we did not detect a systematic difference between non-stimulants (all SNRI) versus stimulants (methylphenidate in all but one case) in direct comparisons (SMD 0.23; CI -0.03, 0.49; 7 studies, n=1611). We detected some heterogeneity (I-squared 69%) in this analysis. There was no evidence of publication bias. Removing all high risk of bias studies left only two studies that also found no systematic difference between interventions (SMD 0.33; CI -3.53, 4.20). When restricting to the comparator methylphenidate, the difference between stimulants and non-stimulants was not statistically significant either (SMD 0.18; CI -0.18, 0.44; 6 studies); all the studies compared atomoxetine versus methylphenidate in this comparison. Across studies, more evaluations favored methylphenidate, but overall, there was no systematic or statistically significant difference between atomoxetine versus methylphenidate in direct comparisons.144, 370, 448, 527, 593, 632 There was little heterogeneity (I-squared 49%) in this analysis, although the direction of effects varied by study. There was no indication of publication bias. Removing high-risk-of-bias studies did not identify a statistically significant difference between atomoxetine versus methylphenidate for ADHD symptoms either (SMD 0.33; CI -3.53, 4.20) and heterogeneity was not reduced. However, we also analyzed whether indirect comparisons between non-stimulant versus stimulant studies indicate systematic differences, and we found a statistically significant difference (p 0.0001). The effect estimates for the subgroups are documented in the following section. Figure 32 shows the subgroup analysis for non-stimulants reporting on ADHD symptoms.
5. Results: Treatment of ADHD

In the subgroup of non-stimulant studies, results were associated with a reduction in ADHD symptoms measured as a continuous variable (SMD -0.52; CI -0.58, -0.45; 34 studies, n=5593). Only one study included children younger than six years old. Results for the subgroup of stimulant studies on ADHD symptoms are shown in Figure 33.

Figure 333. Subgroup Analysis: Stimulants versus Control on ADHD Symptoms (SMD)
5. Results: Treatment of ADHD

In the subgroup of stimulant studies, treatment was associated with a substantial reduction in ADHD symptoms (SMD -0.88; CI -1.13, -0.62; 12 studies, n=1471). Only one study included children younger than six years old.\textsuperscript{116} None of the direct, head-to-head trials reported on symptom improvement as a categorical measure (e.g., treatment response vs not). An indirect comparison suggested that non-stimulant versus stimulant studies report statistically significantly different results (p= 0.02). The subgroups are shown separately in Figures 34 and 35.

**Figure 34. Subgroup Analysis: Non-Stimulants versus Control on ADHD Symptoms (RR)**

<table>
<thead>
<tr>
<th>Study</th>
<th>RR  [CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block, 2009(#19273) ATX</td>
<td>1.07 [0.84, 1.35]</td>
</tr>
<tr>
<td>Buitelaar, 2007(#17592) ATX</td>
<td>4.94 [1.12, 21.85]</td>
</tr>
<tr>
<td>Dell’Agnello, 2009(#17394) ATX</td>
<td>4.17 [1.38, 12.56]</td>
</tr>
<tr>
<td>Harfterkamp, 2012(#24399) ATX</td>
<td>2.30 [0.76, 6.96]</td>
</tr>
<tr>
<td>Hazell, 2003(#14216) HCl stim</td>
<td>2.04 [0.82, 5.06]</td>
</tr>
<tr>
<td>Kelsey, 2004(#24395) ATX</td>
<td>1.88 [1.28, 2.75]</td>
</tr>
<tr>
<td>Nasser, 2021(#2978) SPN</td>
<td>1.45 [1.03, 2.06]</td>
</tr>
<tr>
<td>Nasser, 2021(#3004) SPN</td>
<td>1.60 [1.06, 2.42]</td>
</tr>
<tr>
<td>Nasser, 2021(#3054) SPN</td>
<td>1.66 [1.13, 2.43]</td>
</tr>
<tr>
<td>Prasad, 2007(#17526) ATX</td>
<td>1.63 [1.27, 2.08]</td>
</tr>
<tr>
<td>Svanborg, 2009(#17314)</td>
<td>1.15 [0.87, 1.52]</td>
</tr>
</tbody>
</table>

In the subgroup of non-stimulant studies, we found a clear treatment effect on ADHD symptoms (RR 1.52; CI 1.24, 1.87; 11 studies, n=1697). None of the studies included children under the age of six. However, the effect was not as pronounced as in the single stimulant study that was identified (evaluating lisdexamfetamine dimesylate), which reported a very large treatment effect (RR 4.28; CI 2.49, 7.35; 1 study, n=153).\textsuperscript{206} We did not identify studies reporting on functional impairment in a head-to-head comparison. Indirect analysis comparing non-stimulant versus stimulant studies showed a statistically significant result (p 0.02). Subgroup analyses are shown in Figure 35.
5. Results: Treatment of ADHD

**Figure 355. Subgroup Analysis: Non-Stimulants versus Control on Functional Impairment (SMD)**

<table>
<thead>
<tr>
<th>Study Description</th>
<th>SMD</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buitelaar, 2007 (#17592) ATX</td>
<td>0.02</td>
<td>[-0.29, 0.33]</td>
</tr>
<tr>
<td>Concordia Pharmaceuticals, 2011 (#13782) HCl</td>
<td>-0.00</td>
<td>[-0.34, 0.34]</td>
</tr>
<tr>
<td>Michelson, 2001 (#17979) ATX</td>
<td>0.51</td>
<td>[0.20, 0.82]</td>
</tr>
<tr>
<td>Nasser, 2020 (#259) SPN</td>
<td>0.42</td>
<td>[0.19, 0.64]</td>
</tr>
<tr>
<td>Nasser, 2021 (#2978) SPN</td>
<td>-0.04</td>
<td>[-0.33, 0.24]</td>
</tr>
<tr>
<td>Nasser, 2021 (#3004) SPN</td>
<td>0.21</td>
<td>[-0.07, 0.50]</td>
</tr>
<tr>
<td>RE Model</td>
<td>0.20</td>
<td>[-0.05, 0.44]</td>
</tr>
</tbody>
</table>

In the subgroup of **non-stimulant studies**, treatment was associated with a small but not statistically significant improvement in functional impairment (SMD 0.20; CI -0.05, 0.44; 6 studies, n=1163). None of the studies included children under the age of six. The equivalent analysis for stimulant studies is shown in Figure 36.

**Figure 366. Subgroup Analysis: Stimulants versus Control on Functional Impairment (SMD)**

<table>
<thead>
<tr>
<th>Study Description</th>
<th>SMD</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abikoff, 2007 (#18292) MPH</td>
<td>0.14</td>
<td>[-0.32, 0.60]</td>
</tr>
<tr>
<td>Banaschewski, 2013 (#14417) LDX, MPH</td>
<td>0.58</td>
<td>[0.30, 0.85]</td>
</tr>
<tr>
<td>Childress, 2019 (#487) amph</td>
<td>0.60</td>
<td>[-0.07, 1.27]</td>
</tr>
<tr>
<td>Tris Pharma, 2014 (#13784) amph</td>
<td>1.90</td>
<td>[1.43, 2.37]</td>
</tr>
<tr>
<td>Wigal, 2011 (#17070) MPH</td>
<td>1.41</td>
<td>[1.06, 1.76]</td>
</tr>
<tr>
<td>RE Model</td>
<td>0.93</td>
<td>[0.05, 1.81]</td>
</tr>
</tbody>
</table>

In the subgroup of **stimulant studies**, treatment was associated with large improvement in functional impairment (SMD 0.93; CI 0.05, 1.81; 5 studies, n=576). Only one study included children younger than six years old.¹¹⁶
5. Results: Treatment of ADHD

There were insufficient studies for analyses regarding treatment satisfaction as well as academic performance. Both direct and indirect comparisons could not be analyzed due to the small number of identified studies. Results for appetite suppression are shown in Figure 37.

Figure 37. Comparison Non-stimulant (all SNRIs) versus Stimulant on Appetite Suppression (RR)

Across studies, we found no systematic difference between non-stimulant (all identified studies evaluated SNRIs) versus stimulants (RR 0.82; CI 0.53, 1.26; 8 studies, n=1463). There continued to be heterogeneity (I-squared 78%). There was no evidence of publication bias. Removing high risk of bias studies in a sensitivity analysis left only two studies; results remained not statistically significantly different between interventions (RR 1.34: CI 0.51, 3.52). When restricting the comparator to methylphenidate, we found no systematic difference between SNRI and methylphenidate interventions either and heterogeneity was reduced, but in this subset, all studies compared atomoxetine versus methylphenidate (RR 0.98; CI 0.67, 1.44; 7 studies; I-squared 58%). Results varied, sometimes favoring atomoxetine, sometimes methylphenidate and across studies, no systematic difference was detected. Publication bias was not detected. An indirect comparison did not detect systematic differences between non-stimulant and stimulant studies for appetite suppression (p 0.34).

The comparative studies reporting sufficient detail to compute effect sizes for the number of participants with adverse events is shown in Figure 38.
5. Results: Treatment of ADHD

Across studies, we found no systematic difference between non-stimulant (all identified studies were SNRIs) versus stimulant interventions (RR 1.11; CI 0.90, 1.37; 4 studies, n=756). There was some indication of heterogeneity (I-squared 63%). There was no evidence of publication bias. Removing high risk of bias studies left one study; the study favored stimulants (RR 1.28; CI 1.14, 1.45). When restricting to methylphenidate as the stimulant comparator, there was a trend towards favoring methylphenidate, but the comparison between interventions was not statistically significant (RR 1.23; CI 0.99, 1.52; 3 studies); studies in this analysis all compared atomoxetine versus methylphenidate. In this small set of studies, no heterogeneity was detected and there were insufficient studies for further analyses. We also evaluated in indirect comparisons across studies whether non-stimulant and stimulant studies vary systematically in effect size reporting. However, we did not detect an effect (p 0.94).

Stimulant Comparisons: Amphetamine versus Methylphenidate

A small number of included studies compared amphetamine and methylphenidate in direct, head-to-head comparisons.

We did not identify any studies reporting on individual behaviors for a direct comparison of amphetamine and methylphenidate and indirect comparisons across studies also had insufficient number of studies for comparisons.

A single study reported on a broadband measure and found more positive change in lisdexamfetamine dimesylate (an amphetamine) versus osmotic-release oral system methylphenidate (SMD 0.29; CI 0.02, 0.56; 1 study, n=211). Indirect comparisons across studies did not detect a systematic difference between amphetamine and methylphenidate studies (continuous outcomes p 0.97, categorical outcomes 0.89).

The single study also reported better symptom control with the amphetamine lisdexamfetamine dimesylate versus osmotic-release oral system methylphenidate (SMD -0.46; CI -0.73, -0.19; 1 study, n=221). Indirect comparisons detected a statistically significant
5. Results: Treatment of ADHD

difference across studies for the continuous outcome analysis (p 0.02). The figure shows the results separately for the stimulant subgroups (see Figure 39 below).

Figure 399. Subgroup Analysis: Amphetamine versus Control on ADHD Symptoms (SMD)

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banaschewski, 2013(#14417), MPH</td>
<td>-1.53</td>
</tr>
<tr>
<td>Brams, 2018(#514)</td>
<td>-0.76</td>
</tr>
<tr>
<td>Coghill, 2014(#14575)</td>
<td>-1.46</td>
</tr>
<tr>
<td>Ichikawa, 2020(#330)</td>
<td>-1.34</td>
</tr>
<tr>
<td>Mattingly, 2020(#3060)</td>
<td>-0.77</td>
</tr>
<tr>
<td>RE Model</td>
<td>-1.16</td>
</tr>
</tbody>
</table>

In the subgroup of amphetamine studies, we found a significant effect of treatment (SMD -1.16; CI -1.20, -0.67; 5 studies, n=757). None of the studies included children under the age of six. The subgroup analysis results for methylphenidate studies are shown in Figure 40.

Figure 40. Subgroup Analysis: Methylphenidate versus Control on ADHD Symptoms (SMD)

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abikoff, 2007(#18292)</td>
<td>-0.43</td>
</tr>
<tr>
<td>Abikoff, 2009(#17420)</td>
<td>-0.68</td>
</tr>
<tr>
<td>Corkum, 2020(#3716)</td>
<td>-0.47</td>
</tr>
<tr>
<td>Findling, 2010(#17270)</td>
<td>-0.80</td>
</tr>
<tr>
<td>Simonoff, 2013(#14570)</td>
<td>-0.33</td>
</tr>
<tr>
<td>Wolraich, 2001(#15145), MPH</td>
<td>-0.77</td>
</tr>
<tr>
<td>RE Model</td>
<td>-0.61</td>
</tr>
</tbody>
</table>

In the subgroup of methylphenidate studies, we found a significant treatment effect but effect estimates were smaller (SMD -0.61; CI -0.84, -0.39; 5 studies, n=757). Only one study
5. Results: Treatment of ADHD

included children younger than six years old. Indirect comparisons between amphetamine and methylphenidate using categorical data were not statistically significant (p 0.58).

There was no statistically significant differences in functional impairment in a head-to-head comparison (SMD 0.16; CI -0.11, 0.43; 1 study, n=211). The indirect comparison across studies did also not detect a systematic difference (p 0.76). We identified no studies report on treatment satisfaction or academic performance in direct head-to-head comparisons and there were insufficient data for indirect analyses.

Results for direct comparisons on the outcome appetite suppression are shown in Figure 41.

**Figure 41. Comparison Amphetamine versus Methylphenidate on Participants with Adverse Events (RR)**

<table>
<thead>
<tr>
<th>Study Description</th>
<th>RR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banaschewski, 2013(#14417)</td>
<td>1.06</td>
<td>[0.58, 1.95]</td>
</tr>
<tr>
<td>Duke University, 2009(#13823)</td>
<td>0.85</td>
<td>[0.33, 2.17]</td>
</tr>
<tr>
<td>RE Model</td>
<td>0.99</td>
<td>[0.27, 3.64]</td>
</tr>
</tbody>
</table>

The two studies reporting on appetite suppression did not find a systematic difference between the amphetamine lisdexamfetamine dimesylate versus osmotic-release oral system methylphenidate (RR 0.99; CI 0.27, 3.64; 2 studies, n=294). Similarly, indirect comparisons across studies did also not detect a significant difference between the two stimulant classes (p 0.29).

One study reporting on a number of participants reporting adverse event found no statistically significant difference between intervention (RR 1.11; CI 0.93, 1.33). Similarly, indirect comparisons did also not detect a difference between amphetamines and methylphenidate regarding the number of participants reporting adverse events (p 0.18).

**Non-Stimulant Comparisons: SNRIs versus Alpha Agonists**

We identified one study comparing an alpha agonist (guanfacine) with an SNRI (atomoxetine) directly. The study detected no difference for a broadband measure (number of improved patients per CGI). However, ADHD symptom improvement (ADHD-RS-IV) favored guanfacine over atomoxetine (SMD -0.47; CI -0.73, -0.2; 1 study). The study did not report on other effectiveness measures but found fewer instances of decreased appetite for guanfacine versus atomoxetine (RR 0.48; CI 0.27, 0.83; 1 study). There were no differences in the number of patients experiencing adverse events (RR 1.14; CI 0.97, 1.34) between the interventions.

In indirect comparisons, there were no differences for problem behaviors (p 0.31), broadband measures (p 0.75), ADHD symptoms (p 0.94), or functional impairment (p 0.38).
5. Results: Treatment of ADHD

Effects for treatment satisfaction and academic performance could not be evaluated. However, indirect comparisons for the outcome appetite suppression indicated a significant difference between SNRIs and alpha agonists (p = 0.003). The following shows the subgroup results for SNRI studies versus control separately for ADHD symptoms (Figure 42).

Figure 42. Subgroup Analysis: SNRIs versus Control on ADHD Symptoms (SMD)

In the subgroup of SNRI studies, we found a clear effect on ADHD symptoms (SMD = -0.52; CI: -0.60, -0.43; 24 studies, n=4111). Only one study included children younger than six years old. The equivalent analysis for the subgroup of alpha agonist studies is shown in Figure 43.
5. Results: Treatment of ADHD

Figure 433. Subgroup Analysis: Alpha Agonists versus Control on ADHD Symptoms (SMD)

In the smaller subgroup of alpha agonist studies, we also found a clear effect on ADHD symptoms (SMD -0.52; CI -0.67, -0.37; 11 studies, n=1885). None of the studies reported on children younger than six years of age. Results for appetite suppression are shown in Figure 44.

Figure 444. Subgroup Analysis: SNRIs versus Control on Appetite Suppression (SMD)

In the subgroup of SNRI studies, we found a substantially increased risk of appetite suppression (RR 3.08; CI 2.22, 4.27; 23 studies, n=3520). Only one study included children
5. Results: Treatment of ADHD

younger than six years old. The equivalent analysis for the subgroup of alpha agonist studies is shown in Figure 45.

**Figure 45. Subgroup Analysis: Alpha Agonists versus Control on Appetite Suppression (SMD)**

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biederman, 2008 (#17495)</td>
<td>0.40 [0.08, 2.01]</td>
</tr>
<tr>
<td>Hervas, 2014 (#19229)</td>
<td>1.22 [0.60, 2.48]</td>
</tr>
<tr>
<td>Wilens, 2012 (#19257)</td>
<td>1.53 [0.56, 4.19]</td>
</tr>
<tr>
<td>Young, 2014 (#15140)</td>
<td>2.09 [0.54, 8.16]</td>
</tr>
<tr>
<td>RE Model</td>
<td>1.25 [0.58, 2.70]</td>
</tr>
</tbody>
</table>

Unlike in the SNRI studies, in the subgroup of alpha agonist studies, no systematic effect of appetite suppression was detected (RR 1.25; CI 0.58, 2.70; 4 studies; n=919). Potential differential effects for the number of participants reporting adverse events could not be evaluated.

5.3.3 FDA-Approved Medication Summary of Findings

Table 13 shows the findings for the outcomes of interest together with the number of studies and study identifiers. The table only shows unique comparison for the individual outcome, i.e., for some outcomes, we did not identify non-stimulant versus stimulant studies that were not atomoxetine versus methylphenidate.

**Table 13. KQ2 Summary of Findings and Strength of Evidence for Pharmacological Interventions**

<table>
<thead>
<tr>
<th>Intervention and Comparison</th>
<th>Outcome</th>
<th>Number of Studies and Study Design</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ2 pharmacological vs control</td>
<td>Behavior</td>
<td>9 RCTs162, 231, 251, 317, 374, 422, 448, 598, 599</td>
<td>Results favored intervention (SMD 0.66; CI -0.22, 1.10; 4 studies, n=523); RR 0.45; CI 0.25, 0.81; 2 studies, n=128)</td>
<td>Low for benefit</td>
</tr>
<tr>
<td>KQ2 pharmacological vs control</td>
<td>Broadband measures</td>
<td>57 RCTs116, 137, 153, 162, 166, 169, 198, 206, 209, 211, 224, 231, 251, 273, 275, 276, 288, 292, 303, 321, 337, 342, 367, 368, 372, 374, 404, 409, 415, 421, 422, 430, 441-444, 447-449, 470, 499, 526, 544, 545, 585, 598-601, 606, 608, 611, 612, 615, 622, 892</td>
<td>Results favored intervention (SMD 0.73; CI 0.40, 1.06; 27 studies, n=4618; RR 0.50; CI 0.43, 0.59; 25 studies, n=3959)</td>
<td>High for benefit</td>
</tr>
<tr>
<td>KQ2 pharmacological vs control</td>
<td>ADHD symptoms</td>
<td>69115, 136, 125, 137, 138, 153, 162, 166, 169, 172, 198, 206, 209, 211, 212, 221, 224, 251, 273-276, 288, 292, 303, 304, 317, 321, 333, 463, 466, 512, 526, 527, 528, 544, 545, 555, 585, 598-601, 606, 608, 611, 612, 615, 622, 892</td>
<td>Results favor intervention (SMD -0.58; CI -0.67, -0.50; 46 studies, n=7237; RR 1.85, CI 1.38, 2.48; 11 studies, n=1751)</td>
<td>High for benefit</td>
</tr>
</tbody>
</table>
## 5. Results: Treatment of ADHD

<table>
<thead>
<tr>
<th>Intervention and Comparison</th>
<th>Outcome</th>
<th>Number of Studies and Study Design</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ2 non-stimulants vs control</td>
<td>ADHD symptoms</td>
<td>34 studies</td>
<td>Results favor intervention (SMD -0.36, 0.04; 4 studies, n=1080)</td>
<td>High for benefit</td>
</tr>
<tr>
<td>KQ2 stimulants vs control</td>
<td>ADHD symptoms</td>
<td>12 studies</td>
<td>Results favor intervention (SMD -0.88; CI -1.13, -0.62; 12 studies, n=1471; RR 4.26; CI 2.49, 7.36; 1 study, n=153)</td>
<td>High for benefit</td>
</tr>
<tr>
<td>KQ2 pharmacological vs control</td>
<td>Functional impairment</td>
<td>19 RCTs</td>
<td>Results favor intervention (SMD 0.51; CI 0.10, 0.92; 11 studies, n=1739)</td>
<td>Moderate for benefit</td>
</tr>
<tr>
<td>KQ2 non-stimulants vs control</td>
<td>Functional impairment</td>
<td>6 RCTs</td>
<td>No systematic effect (SMD 0.20; CI -0.05, 0.44; 6 studies, n=1163)</td>
<td>Low for no benefit</td>
</tr>
<tr>
<td>KQ2 stimulants vs control</td>
<td>Functional impairment</td>
<td>5 RCTs</td>
<td>Results favor intervention (SMD 0.93; CI 0.05, 1.81; 5 studies, n=576)</td>
<td>Moderate for benefit</td>
</tr>
<tr>
<td>KQ2 pharmacological vs control</td>
<td>Acceptability of treatment</td>
<td>2 RCTs</td>
<td>Results favor alpha agonist intervention (RR 0.47; CI 0.32, 0.68; 1 study, n=198)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 pharmacological vs control</td>
<td>Academic performances</td>
<td>4 RCTs</td>
<td>Results favor intervention (SMD -1.37; -1.72, -1.03; 1 study, n=156)</td>
<td>Low for benefit</td>
</tr>
<tr>
<td>KQ2 pharmacological vs control</td>
<td>Appetite suppression</td>
<td>52 RCTs</td>
<td>Intervention is associated with appetite suppression (SMD 0.48; CI -0.04, 1.00; 6 studies, n=605; RR 3.24; CI 2.49, 4.20; 46 studies, n=7389)</td>
<td>High for increased risk</td>
</tr>
<tr>
<td>KQ2 pharmacological vs control</td>
<td>Participants with adverse events</td>
<td>37 RCTs</td>
<td>Pharmacological treatment is associated with a higher risk of reported adverse events (RR 1.30; CI 1.23, 1.36; 41 studies, n=6972)</td>
<td>High for increased risk</td>
</tr>
<tr>
<td>KQ2 Atomoxetine vs Methylphenidate</td>
<td>Behavior</td>
<td>4 studies</td>
<td>SNRIs showed more improvement than stimulants (SMD -0.08; CI -0.14, -0.03; 4 studies, n=608)</td>
<td>Low for larger effects in SNRI</td>
</tr>
<tr>
<td>KQ2 Non-Stimulants vs Stimulants</td>
<td>Broadband measures</td>
<td>N/A (indirect comparison)</td>
<td>Non-stimulant studies reported smaller effects than stimulant studies (RR 0.66; CI 0.57, 0.76; 11 studies, n=2174 vs RR 0.39; CI 0.31, 0.49; 13 studies, n=1569; p 0.0004)</td>
<td>Low for larger effects in stimulants</td>
</tr>
<tr>
<td>KQ2 Atomoxetine vs Methylphenidate</td>
<td>Broadband measures</td>
<td>4 studies</td>
<td>No difference detected (SMD -0.16; CI -0.36, 0.04; 4 studies, n=1080)</td>
<td>Low for no difference</td>
</tr>
<tr>
<td>KQ2 Non-stimulants vs stimulants</td>
<td>ADHD symptoms</td>
<td>N/A (indirect comparison)</td>
<td>Non-stimulant studies reported smaller effects than stimulant studies (SMD -0.49; CI -0.56, -0.42; 33 studies, n=5861 vs SMD -0.88; CI)</td>
<td>Low for larger effects in stimulants</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Intervention and Comparison</th>
<th>Outcome</th>
<th>Number of Studies and Study Design</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ2 SNRIs vs stimulants</td>
<td>ADHD symptoms</td>
<td>7 studies 144, 230, 370, 448, 527, 593, 632</td>
<td>No difference detected (SMD 0.24; CI -0.02, 0.50; 7 studies)</td>
<td>Low for no difference</td>
</tr>
<tr>
<td>KQ2 Atomoxetine vs Methylphenidate</td>
<td>ADHD symptoms</td>
<td>6 studies 144, 370, 448, 527, 593, 632</td>
<td>No difference detected (SMD -0.16; CI -0.36, 0.04)</td>
<td>Low for no difference</td>
</tr>
<tr>
<td>KQ2 Non-stimulants vs stimulants</td>
<td>Functional impairment</td>
<td>N/A (indirect comparison)</td>
<td>Non-stimulant studies reported small effects than stimulant studies (SMD 0.22; CI 0.02, 0.41; 7 studies, n=1576 vs SMD 0.93; CI 0.05, 1.81; 5 studies, n=576; p 0.02)</td>
<td>Low for larger effects in stimulants</td>
</tr>
<tr>
<td>KQ2 Non-stimulants vs stimulants</td>
<td>Appetite suppression</td>
<td>8 studies 183, 230, 370, 508, 527, 555, 632</td>
<td>No difference detected (RR 0.82; CI 0.53, 1.26; 8 studies, n=1463)</td>
<td>Low for no difference</td>
</tr>
<tr>
<td>KQ2 Atomoxetine vs Methylphenidate</td>
<td>Appetite suppression</td>
<td>7 studies 183, 230, 370, 508, 527, 555, 632</td>
<td>No difference detected (RR 0.89; CI 0.71, 1.35; 7 studies, n=1201)</td>
<td>Low for no difference</td>
</tr>
<tr>
<td>KQ2 SNRIs vs stimulants</td>
<td>Participants with adverse events</td>
<td>4 studies 183, 230, 370, 593</td>
<td>No difference detected (RR 1.11; CI 0.90, 1.37; 4 studies, n=756)</td>
<td>Low for no difference</td>
</tr>
<tr>
<td>KQ2 Atomoxetine vs Methylphenidate</td>
<td>Participants with adverse events</td>
<td>3 studies 183, 527, 593</td>
<td>No difference detected (RR 1.23; CI 0.99, 1.52; 3 studies, n=494)</td>
<td>Low for no difference</td>
</tr>
<tr>
<td>KQ2 Amphetamine vs Methylphenidate</td>
<td>ADHD symptoms</td>
<td>N/A (indirect comparison)</td>
<td>Amphetamine studies reported larger effects than methylphenidate studies for continuous outcomes (SMD -1.16; CI -1.64, -0.67; n=757; SMD -0.61; CI -0.84, -0.39; 6 studies, n=672; p 0.02) but there was no systematic difference for categorical outcomes (p 0.58)</td>
<td>Insufficient for determining differences</td>
</tr>
<tr>
<td>KQ2 Amphetamine vs Methylphenidate</td>
<td>Appetite suppression</td>
<td>2 studies 137, 578</td>
<td>No difference detected (RR 0.99; CI 0.27, 3.64; 2 studies, n=294)</td>
<td>Low for no difference</td>
</tr>
<tr>
<td>KQ2 SNRI vs Alpha agonists</td>
<td>Appetite suppression</td>
<td>N/A (indirect comparison)</td>
<td>SNRI studies reported larger effects than alpha agonist studies (RR 3.29; CI 2.42, 4.47; 22 studies, n=3295 vs RR 1.25; CI 0.58, 2.70; 4 studies; n=919; p 0.003)</td>
<td>Low for favoring alpha agonist studies</td>
</tr>
</tbody>
</table>

Notes: CI 95% confidence interval, KQ key question, N/A not applicable, RR relative risk, RCT randomized controlled trial, SMD standardized mean differences, SoE strength of evidence

Across studies, we found high strength of evidence that ADHD medication had beneficial effects on broadband measures and ADHD symptom scores when comparing to passive control groups. Results were consistent when excluding high risk of bias studies or using an alternative estimate to account for possible publication bias. However, it should be noted that only few studies included children under six years of age in the evaluated interventions. We also found moderate strength of evidence that pharmacological treatment reduces impairment but we downgraded the strength of evidence due to heterogeneity. Across studies, there was high strength of evidence that ADHD medication is associated with appetite suppression and that ADHD medication increases the risk of experiencing an adverse event compared to passive control groups.
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The analyses comparing two alternative interventions and the corresponding strength of evidence were more limited. While SNRIs had more favorable results than stimulants on problem behaviors, the number of studies and the effect was small, and the strength was downgraded due to study limitations. For the direct comparisons, we downgraded the strength of evidence for broadband measures and ADHD symptoms due to differences in direction of effects and study limitation. We downgraded the strength of evidence for appetite suppression for all comparisons due to differences in direction of effects, and some were further downgraded due to the small number of studies leading to imprecision, though alpha agonist studies did not reduce appetite significantly. Comparing atomoxetine versus methylphenidate did not identify systematic differences for any of the key outcomes, but strength of evidence was low or insufficient. The comparison between amphetamine versus methylphenidate was downgraded to low due to imprecision in the small number of identified studies. All indirect comparisons were downgraded to low due to indirectness and insufficient where there were conflicting results between continuous and categorical variables.

5.3.3 New Pharmaceutical Agents

We also identified a small number of studies evaluating a pharmaceutical agent not FDA-approved for ADHD.112, 120, 121, 129, 142, 154, 155, 163, 173, 210, 223, 267, 272, 302, 348, 371, 391, 427, 495, 496, 501, 561, 609, 624, 625 This included new formulations, off-label use of existing medication approved for other conditions such as modafinil,129, 154, 155, 302, 348, 561 amantadine,527 or venlafaxine,624 and agents no longer available in the US such as agomelatine.496 Identified studies were published between 2005 and 2020, with some only available as a trial record. Agents were evaluated in five different countries; with the majority of studies originating in the United States272, 371 and Iran.223, 348, 427, 496 All studies used a randomized control trial design. Nearly all children within the studies received a confirmatory diagnosis by a specialist and/or clinician; exceptions495, 625 required only a preliminary clinical diagnosis. The populations were predominantly males between the ages of six and eighteen. Female population proportions ranged from 15 percent495 to 29 percent301 where reported. In nearly all studies, participants were required to demonstrate an IQ of 70 or higher. For studies that distinguished between ADHD presentations, the most prevalent (ranging from 58%649 to 100%348) was the combined presentation. Approximately half of studies did not report data regarding ADHD presentation type.120, 267, 272, 317 The only study that addressed co-occurring disorders in the form of a dual diagnosis evaluated children with ADHD and mood disorders.371 Race and ethnicity demographics were described only in a portion of studies.120, 272, 371, 391

A variety of new pharmaceutical agents were tested for their efficacy in treating ADHD symptoms. Several studies evaluated the use of modafinil for youth with ADHD.120, 154, 155, 302, 348, 561 Modafinil is a stimulant medication that has been FDA-approved for the treatment of narcolepsy and sleep apnea. Two studies evaluated ABT-089, a neuronal nicotinic receptor partial agonist.112, 121 Two studies tested an inhibitor of G protein-coupled inward-rectifying potassium channels (GIRKs, tipepidine).223, 495 All of the studies of new pharmaceutical agents reported on a control group, typically placebo.223, 272, 348, 371, 391, 495, 625 The most common adjunctive treatment was methylphenidate. In addition to controls, several studies reported efficacy results for comparator groups, usually composed of participants who received a reduced dose of the pharmaceutical agent being tested.272, 371, 391, 495
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Studies reported a variety of study-specific outcomes, such as treatment-related adverse effects. In terms of pre-specified outcomes, broadband scale scores, standardized symptom scores, and appetite changes were the most frequently reported outcomes.

Only some of the identified studies reported sufficient detail to compute effect sizes for our key outcomes. The identified new agents are difficult to compare, particularly as they are chemically very diverse, and it is unclear whether any represent promising approaches for ADHD treatment. However, three agents were assessed in multiple studies.

5.3.3.1 Modafinil

The identified studies that reported on a broadband measure are shown in Figure 46.

Figure 46. Effects of Modafinil on Broadband Measures (RR)

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biederman, 2005(#17782)</td>
<td>0.36 [0.22, 0.60]</td>
</tr>
<tr>
<td>Biederman, 2006(#17689)</td>
<td>0.98 [0.54, 1.79]</td>
</tr>
<tr>
<td>Greenhill, 2006(#17666)</td>
<td>0.35 [0.20, 0.59]</td>
</tr>
<tr>
<td>RE Model</td>
<td>0.49 [0.12, 2.07]</td>
</tr>
</tbody>
</table>

Across studies, we did not detect a systematic effect of modafinil on broadband scores (RR 0.49; CI -1.2, 2.07; 3 studies, n=539). Two out of three studies were positive and there was heterogeneity (I-squared 76%). There was no indication of publication bias. None of the studies was considered high risk of bias, hence methodological rigor was not a likely source of the heterogeneity. Studies reporting on symptoms are shown in Figure 47.
5. Results: Treatment of ADHD

Figure 47. Effects of Modafinil on ADHD Symptoms (SMD)

<table>
<thead>
<tr>
<th>Study</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biederman, 2005 (#17782)</td>
<td>-0.54 [-0.81, -0.27]</td>
</tr>
<tr>
<td>Greenhill, 2006 (#17666)</td>
<td>-0.52 [-0.82, -0.22]</td>
</tr>
<tr>
<td>Kahbazi, 2009 (#17364)</td>
<td>-1.83 [-2.52, -1.14]</td>
</tr>
<tr>
<td>Swanson, 2006 (#14341)</td>
<td>-0.42 [-0.72, -0.11]</td>
</tr>
</tbody>
</table>

Although all studies reported a positive effect, estimates varied and we did not find a statistically significant effect due to wide confidence intervals (SMD -0.76; CI -1.75, 0.23; 4 studies, n=667). Heterogeneity was high (I-squared 91%). Results for publication bias were borderline (Begg p 1.00, Egger p 0.05) but the alternative estimate using the trim and fill method showed the same effect estimate. One study reported on the number of responders and found a large effect size given that most of the intervention participants showed at least a 40 percent decrease in the ADHD rating scores but none of the placebo participants did (RR 37.00; CI 2.36, 578.24; 1 study, n=46).348 Studies did not report on other outcomes other than appetite suppression (see Figure 48).
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5.3.3.2 Tipepidine

Although two studies assessed tipepidine, the studies did not report on the same outcome measures. One study each found no difference in a broadband measure (SMD 0.38; CI -0.17, 0.93; 1 study, n=51)\textsuperscript{223} or appetite suppression (RR 0.30; CI 0.01, 6.98; 1 study, n=105).\textsuperscript{495} One of the studies reported on symptoms and found a significant effect on ADHD symptoms (SMD -0.58, CI -1.14, -0.02; 1 study, n=51).\textsuperscript{223}

5.3.3.3 ABT-089

Two studies by the same author group reported on α4β2 neuronal nicotinic receptor partial agonist for use in ADHD.\textsuperscript{112,609} Both studies reported on a broadband measure but reported conflicting results and no meaningful summary measure could be derived (SMD 0.02, -2.58, 2.53; 2 studies, n=168). One of the studies reported on ADHD symptoms and found improvement (SMD -1.02; -1.46, -0.57; 1 study, n=88). Results for the number of participants reporting an adverse event are documented in Figure 49.
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Across studies, we found no statistically significant effect for an increased risk of adverse events (RR 0.90; CI 0.64, 1.25; 2 studies, n=171). We detected no heterogeneity, there was no effect of publication bias, and none of the studies was considered high risk.

5.3.3.4 Summary of Findings New Pharmacological Agents

Given the diversity of agents that cannot be combined easily, no summary of findings across all studies could be established. Results of the individual studies are shown in the evidence table in the appendix. The summary of findings table is limited to the agents assessed in multiple studies and Table 14 only shows results where effect size calculation was possible.

Table 14. KQ2 Summary of Findings and Strength of Evidence for New Pharmacological Agents

<table>
<thead>
<tr>
<th>Intervention and Comparison</th>
<th>Outcome</th>
<th>Number of Studies; Study Design and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ2 modafinil vs control</td>
<td>Broadband measures</td>
<td>3 RCTs154, 155, 302</td>
<td>No systematic effect detected (RR 0.49; CI -0.12, 2.07; 3 studies, n=539).</td>
<td>Low for no effect</td>
</tr>
<tr>
<td>KQ2 modafinil vs control</td>
<td>ADHD symptoms</td>
<td>4 RCTs155, 302, 348, 561</td>
<td>All individual studies were positive (SMD -0.76; CI -1.75, 0.23; 4 studies, n=667; RR 37.00; CI 2.36, 578.24; 1 study, n=46)</td>
<td>Low for benefit</td>
</tr>
<tr>
<td>KQ2 modafinil vs control</td>
<td>Appetite suppression</td>
<td>5 RCTs154, 155, 302, 348, 561</td>
<td>Intervention was associated with an effect (RR 4.44; CI 2.27, 8.69; 5 studies; n=780)</td>
<td>Moderate for effect</td>
</tr>
<tr>
<td>KQ2 ABT-089 vs control</td>
<td>Broadband measure</td>
<td>2 studies112, 609</td>
<td>No meaningful summary estimate could be derived (SMD 0.02, -2.58, 2.53; 2 studies, n=168)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 ABT-089 vs control</td>
<td>Number of participants reporting on the event</td>
<td>2 RCTs112, 609</td>
<td>No systematic effect (RR 0.90; CI 0.64, 1.25; 2 studies, n=171)</td>
<td>Low for no effect</td>
</tr>
</tbody>
</table>

Notes: CI 95% confidence interval, KQ key question, N/A not applicable, RR relative risk, RCT randomized controlled trial, SMD standardized mean differences, SoE strength of evidence

Modafinil was associated with positive effects on ADHD symptoms (low SoE, downgraded due to imprecision by 2). Modafinil was also associated with appetite suppression (moderate for
5. Results: Treatment of ADHD

We did not find a positive effect on broadband measure scores, but the strength of evidence was limited (downgraded for study limitations).

The research benefit of ABT-089 is limited. We could not establish a meaningful effect estimate on broadband measures (downgraded to insufficient due to heterogeneity and imprecision). There was low strength of evidence (study limitation, imprecision) indicating that the intervention is associated with adverse events.

5.3.4 Psychosocial Treatment

We identified 24 studies evaluating psychological, psychosocial, or behavioral interventions for children and adolescents with ADHD. We included studies in this section that evaluated psychosocial interventions targeting children or adolescents with ADHD, either alone or combined with components for the children's parents or their teachers. The intervention category did not include combinations of psychosocial treatments plus medication unless the control group received the same medication.

The earliest identified eligible study was first published in 2009. Evaluations were conducted in ten different countries, primarily the US. The populations studied were children and adolescents with ADHD between the ages of “preschool” and 18, with half of the studies including teenagers. In studies that distinguished between ADHD presentations, the most prevalent type (ranging from 23.4% to 100% of the ADHD participants) was the combined presentation. While ADHD participants with co-occurring disorders were not excluded from most of the studies, three studies purposely included patients with language difficulties, homework problems, and organizational deficits. Race and ethnicity demographics were not mentioned in most studies.

Interventions studied included skills training (e.g., homework and organizational skills), problem-solving coach and/or mentoring, social skills training, sleep-focused intervention, dialectical behavior therapy, cognitive behavior therapy, and mindfulness training. Many interventions had multiple components involving patients, parents, teachers, therapists, and counselors in addition to direct interventions for the participating children (interventions addressing parents exclusively are documented in the parent education and support section).

Of the identified studies, 19 reported on a control group, including attention-matched groups, no intervention (i.e., wait list), or treatment as usual where it varied what treatment individual children received. One of those studies included an alternative psychological or behavioral intervention to test the comparative effectiveness of the intervention in addition to a control group comparison. Four studies had no control group, only an alternative intervention in the form of another psychological approach or a combined medication and behavioral support program.

The most frequently reported outcomes in the included studies were the Conners Parent Rating Scales (CPRS), Clinical Global Impression (CGI) scores, and the ADHD Rating Scale, Version IV.

Figure 50 shows the effect of the intervention on individual problem behaviors such as tardiness, delinquency, and conduct problems, assessed in the individual studies.
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Figure 50. Effects of Psychosocial Interventions on Behavior (SMD)

Across studies, we did not detect a systematic effect of the interventions on problematic behaviors (SMD 0.10; CI -0.12, 0.32; 7 studies, n=897). The analysis did not detect substantial heterogeneity (I-squared 50%). We did not detect publication bias. Removing high risk of bias studies in a sensitivity analysis left only three studies and showed a different estimate with wide confidence intervals, but the effect was still not statistically significant (RR -0.06; CI -0.64, 5.2).

Studies reporting on broadband measure score changes are documented in Figure 51.

Figure 51. Effects of Psychosocial Interventions on Broadband Measures (SMD)

The small number of studies reported different estimates and, although both positive, the pooled effect was not statistically significant (SMD 0.50; -0.18, 1.17; 2 studies, n=170). In this
5. Results: Treatment of ADHD

small set of studies, no heterogeneity was detected, there was no indications of publication bias, and no sensitivity analyses could be conducted. Removing high risk of bias studies in a sensitivity analysis left only one study; the study indicated a beneficial treatment effect.\textsuperscript{464}

All studies reporting sufficient detail for changes on a continuous symptom scale are shown in Figure 52.

Figure 52. Effects of Psychosocial Interventions on ADHD Symptoms (SMD)

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coles, 2020#4155</td>
<td>-0.27 [-0.70, 0.17]</td>
<td></td>
</tr>
<tr>
<td>Huang, 2015#17030</td>
<td>-0.02 [-0.41, 0.36]</td>
<td></td>
</tr>
<tr>
<td>Huang, 2021#7795</td>
<td>-0.54 [-0.83, -0.25]</td>
<td></td>
</tr>
<tr>
<td>Pfiffner, 2014#17038</td>
<td>-0.69 [-1.10, -0.27]</td>
<td></td>
</tr>
<tr>
<td>Qian, 2021#369</td>
<td>-0.57 [-1.10, -0.05]</td>
<td></td>
</tr>
<tr>
<td>Schuck, 2018#19228</td>
<td>-0.19 [-0.62, 0.25]</td>
<td></td>
</tr>
<tr>
<td>Sciberras, 2020#419</td>
<td>-0.43 [-0.73, -0.13]</td>
<td></td>
</tr>
<tr>
<td>Sibley, 2016#12327</td>
<td>-0.68 [-1.05, -0.32]</td>
<td></td>
</tr>
<tr>
<td>Sibley, 2021#313</td>
<td>0.03 [-0.21, 0.26]</td>
<td></td>
</tr>
<tr>
<td>Siebelink, 2021#3333</td>
<td>-0.23 [-0.63, 0.18]</td>
<td></td>
</tr>
<tr>
<td>Storebo, 2012#17044</td>
<td>0.15 [-0.38, 0.69]</td>
<td></td>
</tr>
<tr>
<td>Valero, 2021#3676</td>
<td>-0.90 [-1.65, -0.15]</td>
<td></td>
</tr>
</tbody>
</table>

Analyses indicated a symptom reduction associated with the psychological or behavioral intervention (SMD -0.34; CI -0.53, -0.14; 12 studies, n=1450). Interventions were diverse and often included multiple components. Particularly successful interventions included social skills plus parent skills training (compared to no intervention),\textsuperscript{331} a multi-component child life and attention skills program (compared to treatment as usual and a diagnostic report),\textsuperscript{464} ecological executive skills training with parent components (compared to waitlist),\textsuperscript{474} a family intervention focused on sleep (compared to usual care without focus on sleep management),\textsuperscript{511} family therapy focused on teens’ academic needs (compared to usual care without family therapy),\textsuperscript{521} and mindfulness training for children and parents (compared to waitlist).\textsuperscript{581} The youngest children included in the studies were five years old, and several studies targeted pre-teens and teenagers. Statistical heterogeneity was not remarkable, highlighting the diversity of the approaches. Statistical heterogeneity was not remarkable (I-squared 57%). There was some indication of publication bias (Begg p 0.31, Egger p 0.02) but an alternative effect estimate using the trim and fill method came to similar results (SMD -0.56; CI -1.02, -0.09). Removing high risk of bias studies in a sensitivity analysis indicated a stronger treatment effect, but the confidence interval was wide and the effect was not statistically significant anymore (SMD -0.33; CI -0.71, 0.05).

One study reported on symptom improvement as a categorical variable; the study favored a multi-component, behavioral psychosocial treatment integrated across home and school (Child
5. Results: Treatment of ADHD

Life and Attention Skills) for youth with ADHD compared to families receiving a diagnostic report and a resource list (RR 0.69; CI 0.54, 0.88; 1 study, n=125).

Very few studies reported on functional outcomes and two studies reporting on functional impairment as a categorical outcome could not be combined to a meaningful estimate (SMD 0.40; CI -1.16, 1.97; 2 studies, n=245).464, 511

Only one study reported sufficient detail to compute an effect size for treatment satisfaction, indicating no statistically significant difference between a parent-teen intervention focusing on safe driving and an attention-matched control group (SMD 0.19; CI -0.12, 0.49; 1 study; n=164).264

Studies reporting on academic outcomes and reporting sufficient detail to compute effect sizes are shown in Figure 53.

Figure 53. Effects of Psychosocial Interventions on Academic Performance (SMD)

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect Size (SMD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sibley, 2016[12327]</td>
<td>-0.14 [-0.50, 0.22]</td>
</tr>
<tr>
<td>Sibley, 2021[313]</td>
<td>0.28 [ 0.05, 0.52]</td>
</tr>
<tr>
<td>Storebo, 2012[17044]</td>
<td>-0.04 [-0.57, 0.50]</td>
</tr>
<tr>
<td>RE Model</td>
<td>0.07 [-0.52, 0.66]</td>
</tr>
</tbody>
</table>

Across studies, we did not detect a systematic effect of the intervention on academic performance compared to control groups (SMD -0.07; CI -0.52, 0.66; 3 studies, n=459). The analysis detected little heterogeneity (I-squared 52%). There was no indication of publication bias. None of the studies included in this analysis was judged to be high risk of bias, suggesting that the lack of effect is not primarily driven by high risk of bias studies.

Only one study formally reported on the number of participants with adverse events; the study found no increased risk associated with the social skills training intervention compared to treatment as usual (RR 0.97; CI 0.02, 47.1; 1 study, n=55).552

5.3.4.1 Psychosocial Treatment Comparative Effects

We identified a small number of studies that compared diverse psychological and behavioral interventions to an alternative therapeutic approach.52, 168, 325, 464, 469, 522

One study compared a group parent and adolescent skills training versus a dyadic skills training blended with motivational interviewing and reported similar results across assessed outcomes, including ADHD symptoms (SMD -0.23; CI -0.61, 0.16; 1 study, n=123).522 A study comparing two cognitive behavioral therapy programs (planning skills CBT versus solution-
5. Results: Treatment of ADHD

focused therapy (CBT) reported initially more favorable results for the planning skills program, but the effect was not maintained, including for ADHD symptoms (SMD -0.14; CI -0.45, 0.17; 1 study, n=159).168

A study comparing a multi-component program (Child Life and Attention Skills, CLAS) versus a parent-focused treatment with fewer school interactions, found the intensive program to have more positive effects, but there was no difference in broadband measures (SMD 0.20; CI -0.13, 0.52 and RR 1.23; CI 0.89, 1.71; 1 study, n=199).464 A family-school intervention versus an intervention about coping with ADHD through relationships and education (CARE) favored the family-school interventions for ADHD symptoms (SMD -0.34; CI -0.61, -0.06; 1 study, n=199) but other outcomes assessed in the study did not show differences between interventions.469 One study (n=145) compared a multi-component intervention of motivational components, homework management and schoolwork organization training, as well as family-school partnership building versus a complex medication integration protocol that included psychoeducation, medication decision-making, and integrated medication management. There were insufficient details reported to allow effect size calculations, but the authors concluded that both interventions showed positive effects.325

One study addressed sequencing of interventions.52 Children assigned to a multi-component behavioral intervention consisting of social skills training for children, parent training to establish a daily reward system, teacher consultations, and a case manager versus medication first reported significantly fewer classroom rule violations per hour than the medication first intervention. The study found no difference in the disruptive behavior disorder rating scales across groups (SMD -0.02; CI -0.34, 0.31; 1 study, n=152) or functional impairment (SMD -0.01; CI -0.33, 0.31; 1 study, n=153).

5.3.4.2 Psychosocial Treatment Summary of Findings

Table 15 shows the findings for the outcomes of interest together with the number of studies and study identifiers. Only findings are shown for which effect sizes could be computed.

<table>
<thead>
<tr>
<th>Intervention and Comparison</th>
<th>Outcome</th>
<th>Number of Studies; Study Design and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ2 psychosocial treatment vs control</td>
<td>Behavior</td>
<td>7 RCTs 331, 510, 511, 520, 521, 523, 581</td>
<td>No systematic effect (SMD 0.10, CI -0.12, 0.32; 7 studies, n=897)</td>
<td>Low for no effect</td>
</tr>
<tr>
<td>KQ2 psychosocial treatment vs control</td>
<td>Broadband measures</td>
<td>3 RCTs 113, 351, 464</td>
<td>Pooled result was not statistically significant (SMD 0.50, CI -0.18, 1.17; 2 studies, n=170)</td>
<td>Low for no effect</td>
</tr>
<tr>
<td>KQ2 psychosocial treatment vs control</td>
<td>ADHD symptoms</td>
<td>13 RCTs 208, 330, 331, 416, 464, 474, 510, 511, 520, 521, 523, 552, 581</td>
<td>Results favored intervention (SMD -0.34, CI -0.53, -0.14; 12 studies, n=1450; RR 0.69; CI 0.54, 0.88; 1 study, n=125)</td>
<td>Moderate for benefit</td>
</tr>
<tr>
<td>KQ2 psychosocial treatment vs control</td>
<td>Functional impairment</td>
<td>4 RCTs 113, 464, 474, 511</td>
<td>Pooled result was not statistically significant (SMD 0.40, CI -1.16, 1.97; 2 studies, n=245)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 psychosocial treatment vs control</td>
<td>Acceptability of treatment</td>
<td>4 RCTs 113, 264, 464, 520</td>
<td>No systematic effect (SMD 0.22, CI -0.09, 0.53; 1 study, n=164)</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>
## 5. Results: Treatment of ADHD

<table>
<thead>
<tr>
<th>Intervention and Comparison</th>
<th>Outcome</th>
<th>Number of Studies; Study Design and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ2 psychosocial treatment vs control</td>
<td>Academic performance</td>
<td>4 RCTs\textsuperscript{320, 321, 352}</td>
<td>No systematic effect (SMD 0.07, CI -0.52, 0.66; 3 studies, n=459)</td>
<td>Low for no effect</td>
</tr>
<tr>
<td>KQ2 psychosocial treatment vs control</td>
<td>Appetite suppression</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 psychosocial treatment vs control</td>
<td>Participants with adverse events</td>
<td>1 RCT\textsuperscript{352}</td>
<td>No effect (RR 0.97; CI 0.02, 47.01; 1 study, n=55)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 intensive family-school intervention vs coping intervention</td>
<td>ADHD symptoms</td>
<td>1 RCT\textsuperscript{469}</td>
<td>Results favored family-school success intervention (SMD -0.34; -.061, -0.06; 1 study, n=199)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 intensive family-school intervention vs coping intervention</td>
<td>Acceptability of treatment</td>
<td>1 RCT\textsuperscript{469}</td>
<td>Results favored family-school success intervention (SMD -0.34; -.061, -0.06; 1 study, n=199)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 intensive family-school intervention vs coping intervention</td>
<td>Academic performance</td>
<td>1 RCT\textsuperscript{469}</td>
<td>No difference detected (SMD -0.21; -0.49, 0.07; 1 study, n=199)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 intensive child life and attention skills intervention vs less intense intervention</td>
<td>Broadband measures</td>
<td>1 RCT\textsuperscript{464}</td>
<td>No difference detected (SMD 0.20; CI -0.13, 0.52; 1 study, n=199)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 intensive child life and attention skills intervention vs less intense intervention</td>
<td>ADHD symptoms</td>
<td>1 RCT\textsuperscript{464}</td>
<td>No difference detected (SMD -0.27; CI -0.60, 0.05 and RR 1.23; CI 0.89, 1.71; 1 study, n=199)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 planning CBT vs solution-focused CBT</td>
<td>ADHD symptoms</td>
<td>1 RCT\textsuperscript{168}</td>
<td>No difference detected (SMD -0.14; CI -0.45, 0.17; 1 study, n=159)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 group parent and adolescent skills training vs dyadic skills training with motivational interviewing</td>
<td>ADHD symptoms</td>
<td>1 RCT\textsuperscript{322}</td>
<td>No difference detected (SMD -0.23; CI -0.61, 0.16; 1 study, n=159)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 multi-component</td>
<td>Behavior</td>
<td>1 RCT\textsuperscript{32}</td>
<td>Behavioral management intervention associated with fewer classroom rule</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>
5. Results: Treatment of ADHD

<table>
<thead>
<tr>
<th>Intervention and Comparison</th>
<th>Outcome</th>
<th>Number of Studies; Study Design and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>behavior management intervention vs methylphenidate</td>
<td>Violations (incidence rate ratio 0.66, p&lt;0.01; 1 study, n=152)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KQ2 multi-component behavior management intervention vs methylphenidate</td>
<td>Symptoms</td>
<td>1 RCT 52</td>
<td>No systematic difference (SMD -0.02; CI -0.34, 0.31; 1 study, n=152)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 multi-component behavior management intervention vs methylphenidate</td>
<td>Functional impairment</td>
<td>1 RCT 52</td>
<td>No systematic difference (SMD -0.01; CI -0.33, 0.31; 1 study, n=152)</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

Notes: CI 95% confidence interval, KQ key question, N/A not applicable, RR relative risk, RCT randomized controlled trial, SMD standardized mean differences, SoE strength of evidence

The majority of psychological and behavioral interventions were multicomponent interventions and we found favorable effects of these on ADHD symptoms with a moderate strength of evidence. We downgraded all outcomes for study limitation as studies were at high or moderate risk of bias, often because studies of behavioral interventions versus no intervention cannot be blinded, and unblinded parents provided most outcome data. We found low strength of evidence that psychological interventions do not improve problem behaviors across studies and we also found no effect on broadband measure scores. These findings were also downgraded for inconsistency (direction of effects varied). There was insufficient evidence for functional outcomes due to additional imprecision as it was not clear whether or not psychological interventions influence functional impairment. Meta-analysis across studies found no difference in academic outcomes; strength of evidence is insufficient due to inconsistency of direction, lack of precision, and risk of bias. Only one study reported sufficient detail to compute effect sizes for treatment acceptability; the strength of evidence was rated insufficient. No studies reported on appetite changes or growth suppression, and only one study reported on the number of participants with adverse events; strength of evidence was determined to be insufficient.

The comparative effectiveness results were downgraded due to study limitation and the lack of replication (downgraded by two for inconsistency) and strength of evidence was determined to be insufficient.

5.3.5 Cognitive Training

We identified 19 studies evaluating cognitive training to treat ADHD. The earliest identified study was from 2013. Evaluations were published in 16 different countries, including the USA, China, Netherlands, and Spain.
5. Results: Treatment of ADHD

The populations studied were predominately males aged six to 17 years, with only one study including children as young as three years old. Evidence of intellectual disability (i.e., full-scale IQ < 70) was exclusionary in all studies, and eight studies required full-scale IQ scores of 80 or higher. Over 70 percent of studies included participants with a history of stimulant medication treatment, and of those, two thirds of their ADHD cohorts had prior or ongoing stimulant treatment. Five of the studies required stimulant treatment to be discontinued at least 24-hours before undergoing cognitive training, and several required an even longer washout period. For studies that distinguished between ADHD presentations (combined, inattentive, hyperactive/impulsive), the most prevalent (ranging from 26% to 100% of the ADHD participants) was ADHD-combined type. While ADHD participants with typical co-occurring disorders such as conduct disorder were not excluded from most studies, a few studies purposefully included children with concomitant learning disorders (e.g., dyslexia, language disorder). Race and ethnicity demographics were not mentioned in almost all studies.

Cognitive training interventions were delivered across different settings, including home-based and hospital/clinic-based programs. More than half of the studies used a computerized video game format such as the Cogmed digital working memory training program. The other studies used other non-computerized cognitive training modalities including structured, interactive games (e.g., Training Executive, Attention, and Motor Skills) and paper-and-pencil neuropsychological tasks, or they employed functional cognitive rehabilitation paradigms used in occupational therapy settings to improve ADHD. Some studies included a control group comprising demographically similar children and adolescents with ADHD. ADHD-matched control groups received treatment as usual, treatment as usual but then the targeted intervention during a crossover trial, non-adaptive/non-calibrated versions of the targeted cognitive intervention, cognitive training of a separate domain (e.g., training of working memory vs. training of inhibitory control), or else they were randomized to a waitlist and received no extra intervention during the trial. Other studies reported on the comparative effects for two alternative interventions, such as a different modality (e.g., behavioral parent training); or cognitive training using a different intervention.

Studies reported a variety of study-specific outcomes, such as improvement in individual cognitive tasks. In terms of pre-specified key outcomes for this review, symptom rating scale scores were most frequently reported.

Across identified studies, only two reported on a passive control group and reported on a problematic behavior, but the studies (although both favoring the intervention) reported very different treatment effects and could not be combined to a meaningful summary estimate (SMD 0.24; CI -0.31, 0.78; 2 studies, n=101).

Studies reporting on broadband measure scores as a continuous variable are documented in figure 54.
5. Results: Treatment of ADHD

Figure 54. Effects of Cognitive Training on Broadband Measures (SMD)

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect Size (SMD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzing, 2019(#258)</td>
<td>0.38 [-0.18, 0.94]</td>
</tr>
<tr>
<td>Hahn-Markowitz, 2020(#5578)</td>
<td>0.66 [0.24, 1.08]</td>
</tr>
<tr>
<td>Nejati, 2022(#23876)</td>
<td>0.54 [-0.19, 1.27]</td>
</tr>
<tr>
<td>RE Model</td>
<td>0.56 [0.18, 0.93]</td>
</tr>
</tbody>
</table>

The interventions were associated with an improvement in broadband measures (SMD 0.56; CI -0.18, 0.93; 3 studies, n=173). Children included in the studies were between six and seven, and seven and ten, where reported. The analysis did not detect statistical heterogeneity and there were too few studies for further analyses. Only one study reported sufficient detail for a categorical analysis indicating no difference between groups (RR 0.96; CI 0.59, 1.55; 1 study, n=339).

The studies reporting on the effect of cognitive training on ADHD symptoms are shown in Figure 55.

Figure 55. Effects of Cognitive Training on Symptoms (SMD)

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect Size (SMD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bigorra, 2016(#12758)</td>
<td>-0.29 [-0.85, 0.27]</td>
</tr>
<tr>
<td>Bikic, 2018(#40)</td>
<td>0.44 [-0.03, 0.92]</td>
</tr>
<tr>
<td>Chu, 2021(#18891)</td>
<td>-0.34 [-0.66, -0.01]</td>
</tr>
<tr>
<td>Dentz, 2020(#7159)</td>
<td>0.19 [-0.36, 0.73]</td>
</tr>
<tr>
<td>Egeland, 2013(#17026)</td>
<td>-0.10 [-0.55, 0.36]</td>
</tr>
<tr>
<td>Estrada-Plana, 2019(#422)</td>
<td>-0.88 [-1.67, -0.09]</td>
</tr>
<tr>
<td>Nejati, 2021(#4746)</td>
<td>-0.00 [-0.72, 0.72]</td>
</tr>
<tr>
<td>Nejati, 2022(#23876)</td>
<td>-0.85 [-1.60, -0.10]</td>
</tr>
<tr>
<td>Shuai, 2020(#3265)</td>
<td>-0.22 [-0.63, 0.18]</td>
</tr>
<tr>
<td>RE Model</td>
<td>-0.18 [-0.48, 0.12]</td>
</tr>
</tbody>
</table>

Standardized Mean Difference
5. Results: Treatment of ADHD

Across studies, we did not identify a systematic improvement of ADHD symptoms associated with cognitive training compared to control groups not receiving cognitive training (SMD -0.18; CI -0.48, 0.12; 9 studies, n=574). The analysis did not detect substantial heterogeneity (I-squared 49%). There was no evidence of publication bias. Removing studies with high risk of bias indicated a similar lack of systematic effect (SMD -0.08; CI -0.65, 0.49). An additional study reporting on a categorical symptom outcome (number with at least 30% improvement) did not detect differences between groups (RR 1.28; CI 0.85, 1.94; 1 study, n=337).366

Studies reporting on effects of cognitive training on functional impairment are shown in Figure 56.

**Figure 56. Effects of Cognitive Training on Functional Impairment (SMD)**

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bigorra, 2016(#12758)</td>
<td>0.44</td>
<td>[-0.10, 0.98]</td>
</tr>
<tr>
<td>Bikic, 2018(#40)</td>
<td>0.20</td>
<td>[-0.13, 0.53]</td>
</tr>
<tr>
<td>Chu, 2021(#18891)</td>
<td>0.32</td>
<td>[-0.01, 0.64]</td>
</tr>
<tr>
<td>Egeland, 2013(#17026)</td>
<td>0.23</td>
<td>[-0.23, 0.69]</td>
</tr>
<tr>
<td>Estrada-Plana, 2019(#422)</td>
<td>1.32</td>
<td>[0.70, 1.95]</td>
</tr>
<tr>
<td>RE Model</td>
<td>0.44</td>
<td>[-0.08, 0.97]</td>
</tr>
</tbody>
</table>

Studies indicated an improvement in functional impairment, but the effect was not statistically significant (SMD 0.44; CI -0.08, 0.97; 5 studies, n=462). There was some heterogeneity and effect estimates varied somewhat (I-squared 67%). There was no indication of publication bias. Excluding high risk of bias studies in a sensitivity analysis (and thereby removing an outlier) did result in a smaller effect estimate (number of participants improved by 1 point on rating scale) but the effect was statistically significant (SMD 0.29; CI 0.03, 0.55). An additional study reporting on impairment as a categorical variable did not detect differences between groups (RR 1.29; CI 1.00, 1.66, n=348).366

We could not compute effect estimates for treatment satisfaction or academic performance ratings in this intervention subset. Appetite suppression was not assessed but the number of participants experiencing an adverse event is shown in Figure 57.
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5.3.5.1 Cognitive Training Comparative Effects

A small number of individual studies had active comparators. One study compared structured games versus parent training. The study did not report on key outcomes but it concluded that working memory training is effective.

Three studies compared different cognitive training approaches. A study comparing central executive training versus inhibitory control training did not report on outcomes of interest in sufficient detail to allow us to compute effect sizes, but the study concluded that the finding supported the use of central executive training. Another study compared Cogmed working memory training versus a new active working memory and executive function compensatory training (paying attention in class). The study found no difference in a broadband measure but reported insufficient details to compute effect sizes. An additional study compared executive function training with multiple targets versus working memory training or inhibition and cognitive flexibility. The study did not report on key outcomes addressed in this review but concluded that there was no significant difference on any executive function measures.

5.3.5.1 Cognitive Training Summary of Findings

Table 16 shows the findings for the outcomes of interest together with the number of studies and study identifiers. Comparative effectiveness and safety results are not shown as none of the identified studies reported on the key outcomes in sufficient detail.
## 5. Results: Treatment of ADHD

### Table 16. KQ2 Summary of Findings and Strength of Evidence for Cognitive Training

<table>
<thead>
<tr>
<th>Intervention and Comparison</th>
<th>Outcome</th>
<th>Number of Studies; Study Design and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ2 cognitive training vs control</td>
<td>Behavior</td>
<td>3 RCTs&lt;sup&gt;156, 261, 446&lt;/sup&gt;</td>
<td>Two studies favored the intervention, but estimates varied and could not be combined to a meaningful estimate (SMD 0.59; CI -3.75, 4.92; 2 studies, n=101)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 cognitive training vs control</td>
<td>Broadband measures</td>
<td>3 studies, 2 RCTs&lt;sup&gt;146, 366&lt;/sup&gt; 1 CT&lt;sup&gt;310&lt;/sup&gt;</td>
<td>Cognitive training was associated with positive effects in some studies (SMD 0.56; CI -0.18, 0.93; 3 studies, n=173; RR 0.96; CI 0.59, 1.55; 1 study, n=339)</td>
<td>Low for benefit</td>
</tr>
<tr>
<td>KQ2 cognitive training vs control</td>
<td>Symptoms</td>
<td>12 RCTs&lt;sup&gt;146, 156, 225, 226, 261, 363, 366, 518&lt;/sup&gt;</td>
<td>No systematic effect (SMD -0.13; CI -0.41, 0.16; 8 studies, n=544; RR 1.28; CI 0.85, 1.93; 1 study, n=337)</td>
<td>Low for no effect</td>
</tr>
<tr>
<td>KQ2 cognitive training vs control</td>
<td>Functional impairment</td>
<td>6 RCTs&lt;sup&gt;99, 156, 203, 247, 361, 366&lt;/sup&gt;</td>
<td>No systematic effect (SMD 0.44; CI -0.08, 0.97; 5 studies, n=462)</td>
<td>Low for no effect</td>
</tr>
<tr>
<td>KQ2 cognitive training vs control</td>
<td>Acceptability of treatment</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 cognitive training vs control</td>
<td>Academic performance</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 cognitive training vs control</td>
<td>Appetite suppression</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 cognitive training vs control</td>
<td>Participants with adverse events</td>
<td>2 RCTs&lt;sup&gt;261, 366&lt;/sup&gt;</td>
<td>No systematic effect (RR 3.30; CI 1.01, 10.83; 2 studies, n=402)</td>
<td>Low for no effect</td>
</tr>
</tbody>
</table>

Notes: CI 95% confidence interval, KQ key question, N/A not applicable, RR relative risk, RCT randomized controlled trial, SMD standardized mean differences, SoE strength of evidence

The summary of findings table above generally shows an emerging evidence base. Studies predominantly reported on specific measures rather than generally important outcomes such as ADHD symptoms. Strength of evidence was downgraded due to heterogeneity and imprecision. The evidence for multiple outcomes of interest is insufficient to date.

While different cognitive trainings have been compared in comparative effectiveness and safety evaluations, studies reported on study-specific intermediate outcomes and it is unclear whether and which cognitive training is superior to others.

### 5.3.6 Neurofeedback

We identified 15 studies using neurofeedback.<sup>83, 110, 136, 219, 244, 291, 294, 301, 316, 390, 424, 472, 473, 550, 554</sup> The earliest identified study was published in 2010 and studies came from ten different countries. Almost all studies used a randomized control trial study design, except for one<sup>301</sup> a non-randomized clinical trial. All children received a confirmatory ADHD diagnosis by a specialist and/or clinician. The populations studied were between the ages of six and 18 years. Female population proportions ranged from 15<sup>390</sup> to 37<sup>301</sup> percent; only two studies did not include females.<sup>83, 219</sup> In nearly all studies, participants were required to demonstrate an IQ of 80 or higher. For studies that distinguished between ADHD presentations, the most prevalent type, ranging from 15<sup>83</sup> to 100<sup>554</sup> percent of ADHD participants, was the combined type. There were no reported systemic co-occurring disorders within the included study populations, though many...
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did not exclude commonly associated co-occurring disorders within their study population. Race and ethnicity demographics were described in few of the identified studies.110, 550

A variety of neurofeedback protocols were tested for their efficacy in treating ADHD symptoms. Two thirds of the neurofeedback protocols that were investigated involved theta/beta EEG marker modulation.83, 110, 136, 180, 219, 244, 291, 294, 301, 390, 550 One third of protocols centered around modulation of slow cortical potentials.294, 316, 424, 554 Among the neurofeedback studies, three quarters reported on a passive control group, including attention-matched task,219, 291 waitlisted for intervention,83, 390 and no intervention groups.301, 550 Several studies reported efficacy results compared to an alternative intervention; methylphenidate244, 291, 472 and cognitive trainings294, 316, 424, 550 were the most common comparators.

Studies reported a variety of often study-specific outcomes, such as improvement in individual cognitive tasks as documented in the evidence table. In terms of pre-specified outcomes, broadband scale scores and standardized symptom scores were the most frequently reported outcomes.

Studies reporting on reductions in problematic behaviors, such as aggression and off-task behavior at school, are shown in Figure 58.

Figure 58. Effects of Neurofeedback on Behavior (SMD)

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect Size (SMD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dashbozorgi, 2021(#18905)</td>
<td>1.29 [0.61, 1.98]</td>
</tr>
<tr>
<td>Neurofeedback Collaborative Group, 2014(#307)</td>
<td>0.12 [-0.22, 0.45]</td>
</tr>
<tr>
<td>Steiner, 2014(#17053)</td>
<td>-0.25 [-0.72, 0.22]</td>
</tr>
</tbody>
</table>

RE Model 0.35 [-1.61, 2.31]

Study results varied considerably and no systematic effect was seen across studies (SMD 0.35; CI -1.61, 2.31; 3 studies, n=252). Despite the small number of studies, the analysis detected heterogeneity (I-squared 90%). There was no indication of publication bias. Removing one high risk of bias study did reduce heterogeneity but there was still no systematic positive effect on the intervention (SMD -0.03; CI -2.33, 2.27).

Two studies reported on broadband measure scores, but effect estimates varied so that the pooled estimate had very large confidence intervals (SMD 0.67; CI -2.65, 3.99; 2 studies, n=195). One of the studies also reported on a categorical broadband scale outcome (improvement of more than 2 on the CGI); the study did not find a statistically significant difference between groups (RR 0.88; CI 0.66, 1.19; 1 study, n=142).110

Results for ADHD symptoms are reported in Figure 59.
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Across studies, neurofeedback was associated with a statistically significant ADHD symptom reduction compared to different passive control groups (SMD -0.47; CI -0.83, -0.11; 8 studies, n=736). The youngest children included in the studies were six years old. The analysis detected some heterogeneity (I-squared 69%). Excluding three high risk of bias studies found smaller but more precise and still statistically significant estimate (SMD -0.27; CI -0.35, -0.17) and there was no indication of heterogeneity anymore, suggesting that risk of bias was a key source of heterogeneity. We detected no evidence for publication bias.

Two studies reported on functional impairment outcomes but effect estimates varied considerably and no meaningful summary effect could be derived due to wide confidence intervals (SMD 0.19; CI -1.74, 2.13; 2 studies, n=212). We did not identify treatment satisfaction or academic performance estimates.

Appetite suppression was reported in one study; the Neurofeedback Collaborative group found no statistically significant difference between intervention and control group participants (RR 1.64; CI 0.77, 3.49; 1 study, n=142). We could not determine the presence or absence of participants experiencing adverse events as none of the identified studies reported on the outcome.

### 5.3.6.1 Neurofeedback Comparative Effects

Seven studies reported on active comparators, including cognitive training, medication with methylphenidate, and electromyographic biofeedback as documented in the next subsections.

#### 5.3.6.1.1 Neurofeedback Versus Cognitive Training

Two studies reported on individual behaviors as documented in Figure 60.
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Figure 60. Neurofeedback versus Cognitive Training on Behaviors (SMD)

- Gevensleben, 2010 (#17058) 0.17 [-0.35, 0.69]
- Steiner, 2014 (#17053) 0.10 [-0.37, 0.58]

Across studies, we found no statistically significant difference between neurofeedback and cognitive training, but the number of identified studies contributing to the comparison was small (SMD 0.13; CI -0.31, 0.57; 2 studies, n=129). The set did not identify heterogeneity. The identified studies did not report on broadband measures. Results for ADHD symptoms are shown in Figure 61.

Figure 61. Neurofeedback versus Cognitive Training on Symptoms (SMD)

- Gevensleben, 2010 (#17058) -0.24 [-0.82, 0.34]
- Minder, 2018 (#4689) 0.24 [-0.40, 0.88]
- Steiner, 2014 (#17053) 0.19 [-0.28, 0.67]

Across studies, we found no systematic difference between interventions (SMD 0.07; CI -0.55, 0.70; 3 studies, n=167) and in the small set of studies, no heterogeneity was detected. Two of the studies were judged to be high risk of bias, leaving only one study for a sensitivity analysis. The study also detected no statistically significant difference between neurofeedback and cognitive training (SMD 0.19; CI -0.28, 0.67)
Two studies reported on a functional impairment measure. Both reported no statistically significant difference between interventions, but estimates varied and the studies could not be combined to a meaningful effect estimate (SMD 0.08; CI -1.27, 1.44; 2 studies, n=133) given the wide confidence intervals.\textsuperscript{294, 550} We did not identify studies that evaluated neurofeedback versus cognitive training that reported on other outcomes of interest for the review.

### 5.3.6.1.2 Neurofeedback Versus Stimulants

Two studies were identified that made comparisons to medication and each one reported on some of the outcomes of interest. One study compared personalized at-home neurofeedback training versus methylphenidate.\textsuperscript{472} The study found more improvement in broadband measures in the medication group compared to neurofeedback (RR 3.61; 2.36, 5.52; 1 study, n=149). Both studies reported on ADHD symptom measures comparing neurofeedback versus methylphenidate.\textsuperscript{291, 472} Both studies found more improvement associated with methylphenidate but effect estimates differed and resulted in wide confidence intervals, precluding a meaningful effect estimate (SMD 0.57; CI -1.68, 2.81; 2 studies, n=209).

One of the studies reported adverse events; the study found significantly fewer participants experienced adverse events in the neurofeedback versus the methylphenidate group (RR 0.23; CI 0.15, 0.35; 1 study, n=149).\textsuperscript{472}

### 5.3.6.1.3 Neurofeedback Versus Other Active Comparators

One study compared neurofeedback and electromyographic biofeedback.\textsuperscript{136} The authors reported that for ADHD symptoms, results favored neurofeedback in parent reports but no effect estimate could be derived.

### 5.3.6.2 Neurofeedback Summary of Findings

Table 17 shows the findings for the outcomes of interest, together with the number of studies and study identifiers.

<table>
<thead>
<tr>
<th>KQ2 Intervention and Comparison</th>
<th>Outcome</th>
<th>Number of Studies; Study Design and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ2 neurofeedback vs control</td>
<td>Behavior</td>
<td>3 RCTs\textsuperscript{110, 219, 550}</td>
<td>No systematic effect (SMD 0.35; CI -1.61, 2.31; 3 studies, n=252)</td>
<td>Low for no effect</td>
</tr>
<tr>
<td>KQ2 neurofeedback vs control</td>
<td>Broadband measures</td>
<td>4 RCTs\textsuperscript{83, 110, 390, 473}</td>
<td>The studies indicated improvements, but estimates varied or could not be computed and no meaningful summary estimate could be derived (SMD 0.77; CI -4.16, 5.7; 2 studies, n=195; RR 0.88; CI 0.66, 1.19; 1 study, n=142)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 neurofeedback vs control</td>
<td>ADHD symptoms</td>
<td>9 studies, 8 RCTs\textsuperscript{219, 244, 291, 316, 390, 473, 550, 554, 1 CT\textsuperscript{501}}</td>
<td>Results favor intervention (SMD -0.45; CI -0.83, -0.08; 8 studies, n=736)</td>
<td>Moderate for benefit</td>
</tr>
<tr>
<td>KQ2 neurofeedback vs control</td>
<td>Functional impairment</td>
<td>2 RCTs\textsuperscript{110, 550}</td>
<td>1 study reported an improvement, 1 no difference and no summary estimate could be derived (SMD 0.2; -1.61, 2.00; 2 studies; n=212)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 neurofeedback vs control</td>
<td>Acceptability of treatment</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>
### 5. Results: Treatment of ADHD

<table>
<thead>
<tr>
<th>KQ2 neurofeedback vs</th>
<th>Academic</th>
<th>0 studies</th>
<th>N/A</th>
<th>Insufficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>performance</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| KQ2 neurofeedback vs | Appetite | 1 study\(^{110}\) | No systematic effect (RR 1.45; CI 0.68, 3.10; 1 study, n=142) | Insufficient |
| control              | suppression |           |     |              |

| KQ2 neurofeedback vs | Participants | 0 studies | N/A | Insufficient |
| control              | with adverse events |           |     |              |

| KQ2 neurofeedback vs | Behavior | 2 studies\(^{294, 550}\) | No systematic difference (SMD 0.13; CI -0.31, 0.57; 2 studies, n=129) | Low for no difference |
| cognitive training   |           |           |     |              |

| KQ2 neurofeedback vs | Symptoms | 3 studies\(^{294, 424, 550}\) | No systematic difference (SMD 0.07; CI -0.55, 0.70; 3 studies, n=167) | Low for no difference |
| cognitive training   |           |           |     |              |

| KQ2 neurofeedback vs | Broadband measures | 1 study\(^{472}\) | Results favored methylphenidate (RR 3.61; CI 2.36, 5.52; 1 study, n=149) | Low for favoring methylphenidate |
| methylphenidate      |           |           |     |              |

| KQ2 neurofeedback vs | ADHD symptoms | 2 studies\(^{291, 472}\) | Both studies favored methylphenidate but no statistically significant difference between groups (SMD 0.57; CI -1.68, 2.81; 2 studies, n=209) | Insufficient |
| methylphenidate      |           |           |     |              |

| KQ2 neurofeedback vs | Participants with adverse events | 1 study\(^{472}\) | Results favored neurofeedback (RR 0.23; CI 0.15, 0.35; 1 study, n=149) | Insufficient |
| methylphenidate      |           |           |     |              |

Notes: CI 95% confidence interval, KQ key question, N/A not applicable, RR relative risk, RCT randomized controlled trial, SMD standardized mean differences, SoE strength of evidence

The summary of finding table shows an improvement for ADHD symptom scores compared to passive control (moderate strength of evidence, downgraded for study limitation). Results for other outcomes were less favorable or unclear. For all outcomes, we downgraded for imprecision where no summary estimate could be derived. We downgraded the strength of evidence for appetite suppression due to imprecision. It should be noted that the included neurofeedback approaches varied by study and results of individual studies are shown in the evidence table in more detail.

We detected no systematic difference between neurofeedback and cognitive training in the small number of studies that reported on this comparison for the outcomes of interest. We upgraded the evidence for broadband measure scores comparing neurofeedback versus methylphenidate due to the large effect. All other comparisons were downgraded for inconsistency by two (results were based on a single study and it was not possible to determine whether another study by another author group would report an effect) and study limitation (unclear whether the study was statistically powered to detect an effect for the outcome).

### 5.3.7 Physical Exercise

We identified two studies reporting on physical exercise that met eligibility criteria.\(^{243, 347}\) One RCT published in 2020\(^{243}\) compared treadmill training plus whole body vibration training, versus treadmill training alone, in children with ADHD. Training took place three days per week for eight weeks. The study was conducted in Turkey; children ranged in age from 7 to 11 years and were treatment naïve. Eighty percent of participants had combined type ADHD and the same percentage were male. The study reported no difference between groups (SMD 0.16; -0.55, 0.88; 1 study, n=30) for a broadband measure. A 2019 RCT (n=40) conducted in Tunisia evaluated the effect of Taekwondo exercises. The study reported on attentional inhibitory control and visual...
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attention and concluded that Taekwondo improved performance on measures of selective attention using the Stroop test in adolescents with ADHD.347

5.3.7.1 Exercise Comparative Effectiveness
We did not detect exercise studies comparing to different active treatments.

5.3.7.2 Exercise Summary of Findings
Table 18 below shows the results for the outcomes of interest.

Table 18. KQ2 Summary of Findings and Strength of Evidence for Physical Exercise

<table>
<thead>
<tr>
<th>KQ2 Intervention and Comparison</th>
<th>Outcome</th>
<th>Number of Studies; Study Design and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ2 exercise vs control</td>
<td>Behavior</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 exercise vs control</td>
<td>Broadband measures</td>
<td>1 RCT1243</td>
<td>1 RCT1243 reported whole body vibration training plus treadmill training group improved more on Conners Parent Rating Scale-Revised/Long Form total score than the treadmill training alone group, but the difference did not reach statistical significance (p 0.055), the Intervention group had significantly more improvement in the teacher version of same instrument.</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 exercise vs control</td>
<td>Symptoms</td>
<td>0 RCT</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 exercise vs control</td>
<td>Functional impairment</td>
<td>0 RCT</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 exercise vs control</td>
<td>Acceptability of treatment</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 exercise vs control</td>
<td>Academic performance</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 exercise vs control</td>
<td>Appetite suppression</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 exercise vs control</td>
<td>Participants with adverse events</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

Notes: CI 95% confidence interval, KQ key question, N/A not applicable, RR relative risk, RCT randomized controlled trial, SMD standardized mean differences, SoE strength of evidence

Given the lack of studies or lack of replication of effects in more than one study, we determined evidence for all outcomes of interest to be insufficient.

5.3.8 Nutrition and Supplements
We identified 32 studies of nutrition or supplement interventions.111, 123, 143, 157, 186, 214, 216, 265, 295, 308, 314, 320, 323, 343, 344, 353, 356, 358, 401, 428, 429, 431, 460, 466, 477, 493, 497, 498, 573, 577, 583, 596 The vast majority were placebo-controlled studies of dietary supplements; one of those was a crossover trial.1 Two studies evaluated diets.358, 460 Several evaluated nutritional supplements as augmentation to stimulant medication. The earliest eligible study was published in 2004. Only two of the identified studies were conducted in the US.344, 596 Most others were conducted in the Middle
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All studies but one (which included children as young as four) enrolled children at least six years of age. Race and ethnicity were rarely reported, perhaps due to the racial homogeneity of the trial locations. Two studies had no females, one did not report sex, and the rest were majority male. ADHD presentations were rarely reported. Children with psychological and psychiatric co-occurring disorders were excluded from at least half of the studies. One studied children with co-occurring epilepsy.

The studies assessed a wide range of dietary and supplement approaches. However, Omega 3 fatty acid (DHA and/or EPA) was evaluated in more than one study.

Other nutritional supplements included saffron, zinc sulfate, Vitamin D, a multivitamin containing essential minerals, amino acids and antioxidants, a different multivitamin, a herbal preparation including spirulina, pycnogenol (an extract from the bark of the French maritime pine), and St. John’s wort. The DASH (Dietary Approaches to Stop Hypertension) diet and an individually designed restricted elimination diet were also studied. And one study each of saffron, melatonin, Ma’aljobon powder, or iron.

The most common categories of outcomes were broadband and ADHD symptom scores. In terms of instruments, Conners Parent Rating Scale (CPRS) and the ADHD Rating Scale, 4th Version (ADHD RS-IV) were the most frequently reported outcome measures. Figure 62 shows results for individual problem behavior such as teacher-reported conduct problems evaluated in individual studies.

### Figure 62. Effects of Nutrition or Supplements on Behavior (SMD)

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD [CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crippa, 2019</td>
<td>0.18 [-0.38, 0.75]</td>
</tr>
<tr>
<td>Hirayama, 2014</td>
<td>0.33 [-0.33, 0.99]</td>
</tr>
<tr>
<td>Rucklidge, 2018</td>
<td>0.23 [-0.18, 0.63]</td>
</tr>
<tr>
<td>Tzang, 2016</td>
<td>0.27 [-0.09, 0.64]</td>
</tr>
<tr>
<td><strong>RE Model</strong></td>
<td><strong>0.25 [ 0.17, 0.33]</strong></td>
</tr>
</tbody>
</table>

Across studies, nutritional approaches (docosahexaenoic acid, phosphatidylserine, vitamins and minerals, sarcosine), were associated with improvement in problem behavior compared to control (SMD 0.25; CI 0.17, 0.33; 4 studies, n=294). None of the studies included children under six years of age. There was no evidence of heterogeneity and publication bias was not detected. None of the included studies was considered high risk of bias. The included Omega 3 study reported no statistically significant differences (SMD 0.15; CI -0.41, 0.72; 1 study, n=55). Results of nutrition and supplements on broadband measures are shown in Figure 63.
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Figure 63. Effects of Nutrition or Supplements on Broadband Measures (SMD)

Across studies, we did not detect a consistent effect of the intervention compared to control (SMD 0.03; CI -0.29, 0.34; 8 studies, n=818). There was evidence of heterogeneity (I-squared 70%). Heterogeneity was not explained by risk of bias. There was no evidence of publication bias. A few studies assessed the number of participants that improved according to a broadband measure as shown in Figure 64.
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Figure 64. Effects of Nutrition or Supplements on Broadband Measures (RR)

Similar effects are shown for broadband measures used as a categorical variable and the analysis did not detect a systematic treatment effect (RR 0.65; CI 0.35, 1.21; 3 studies, n=273). The three studies assessed different interventions, including micronutrients, vitamin-mineral treatment, and St. John’s Wort and there was some evidence of heterogeneity (I-squared 73%). None of the studies was judged to be high risk of bias. There was some evidence of publication bias for the categorical outcome but the alternative estimate based on the trim and fill method was unchanged from the original effect.

The most common supplement assessed in this category was Omega 3. Restricting to Omega 3 studies, results for broadband measures were similar to the overall analyses in that they did not show a systematic benefit compared to control groups (SMD 0.07; CI -0.39, 0.53; 6 studies, n=620).

All studies reporting on ADHD symptoms are shown in Figure 65.
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Figure 65. Effects of Nutrition or Supplements on ADHD Symptoms (SMD)

Across studies, analyses for the nutritional approaches and supplements showed a positive effect on ADHD symptoms compared to control (SMD -0.49; CI -0.80, -0.17; 19 studies, n=1854). The youngest children included in the studies were four years old. There was considerable heterogeneity (I-squared 89%) in results across studies. The largest effects were reported by a study evaluating a zinc sulfate supplement\(^{157}\) and a restricted elimination diet.\(^{450}\) Excluding three high risk of bias studies suggested a smaller treatment effect and the result was not statistically significant anymore (SMD -0.65; CI -0.79, 0.10), but heterogeneity was still not reduced. There was no evidence of publication bias. An omega 3 supplement was the only intervention that was studied in more than one of the otherwise very diverse studies. Restricting to Omega 3 studies did not find any benefits of the supplement (SMD -0.09; CI -0.53, 0.35; 6 studies, n=559).\(^{186, 214, 216, 314, 343, 429}\) In this subset, heterogeneity was reduced, but still present (I-squared 75%). Two nutrition studies reported on symptom improvement as a categorical variable (i.e., number of participants showing a treatment response) but estimates varied and no meaningful effect estimate could be derived due to the large confidence interval (RR 1.88; CI 0.01, 678.58; 2 studies, n=256). Despite the small number of studies, some heterogeneity was detected (I-squared 43%). There was no evidence of publication bias either. One of the studies with a categorical ADHD symptom measure evaluated Omega 3; the study found no statistically significant effect (RR 3.93; 0.93, 16.95; 1 study, n=75)\(^{343}\) and the estimate was imprecise.

Effects of nutrition and supplements on functional outcomes are shown in Figure 66.
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Figure 66. Effects of Nutrition or Supplements on Functional Impairment (SMD)

<table>
<thead>
<tr>
<th>Study</th>
<th>Standardized Mean Difference</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemamy, 2021 (#511)</td>
<td>0.66</td>
<td>[0.16, 1.15]</td>
</tr>
<tr>
<td>Johnstone, 2022 (#18993)</td>
<td>0.00</td>
<td>[-0.37, 0.37]</td>
</tr>
<tr>
<td>Khoshbakht, 2021 (#3097)</td>
<td>0.54</td>
<td>[0.09, 0.98]</td>
</tr>
<tr>
<td>RE Model</td>
<td>0.37</td>
<td>[-0.51, 1.26]</td>
</tr>
</tbody>
</table>

Across available studies reporting sufficient detail for effect size calculations, no systematic benefit was found on functional impairment (SMD 0.37; CI -0.51, 1.26; 3 studies, n=272). Studies evaluated different interventions, including vitamin D plus magnesium, micronutrients, and the DASH (dietary approach to stop hypertension) diet. Despite the small number of studies, the analysis detected heterogeneity (I-squared 65%). There were no data for treatment satisfaction or academic performance. None of the omega 3 studies reported on these outcomes. A few studies addressed height, BMI, and weight changes as shown in Figure 67.

Figure 67. Effects of Nutrition or Supplements on Appetite Suppression (SMD)

<table>
<thead>
<tr>
<th>Study</th>
<th>Standardized Mean Difference</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnstone, 2022 (#18993)</td>
<td>-0.22</td>
<td>[-0.60, 0.15]</td>
</tr>
<tr>
<td>Manor, 2012 (#14854)</td>
<td>0.20</td>
<td>[-0.18, 0.59]</td>
</tr>
<tr>
<td>Rucklidge, 2018 (#4909)</td>
<td>-0.14</td>
<td>[-0.58, 0.29]</td>
</tr>
<tr>
<td>RE Model</td>
<td>-0.05</td>
<td>[-0.63, 0.52]</td>
</tr>
</tbody>
</table>
5. Results: Treatment of ADHD

There were no differences between treatment arms (SMD -0.05; CI -0.63, 0.52; 3 studies, n=373) for appetite suppression. Heterogeneity was negligible (I-squared 26%). There was no indication of publication bias. Removing one high risk of bias study showed no effect either (SMD -0.19; CI -0.67, 0.29). One of the studies assessed omega 3 specifically; the study did not detect a statistically significant effect (SMD 0.20; CI -0.18, 0.59; 1 study, n=200). The equivalent analysis for a categorical outcome (number of participants reporting appetite suppression) is shown in Figure 68.

**Figure 68. Effects of Nutrition or Supplements on Appetite Suppression (RR)**

<table>
<thead>
<tr>
<th>Study</th>
<th>RR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbasi, 2011#17191</td>
<td>0.87</td>
<td>[0.39, 1.95]</td>
</tr>
<tr>
<td>Akhondzadeh, 2004#24386</td>
<td>1.14</td>
<td>[0.50, 2.61]</td>
</tr>
<tr>
<td>Katz, 2010#17032</td>
<td>0.46</td>
<td>[0.04, 4.93]</td>
</tr>
<tr>
<td>Mohammadi, 2012#17034</td>
<td>1.17</td>
<td>[0.67, 2.06]</td>
</tr>
<tr>
<td>Rafei-Torghabeh, 2021#318</td>
<td>0.75</td>
<td>[0.30, 1.90]</td>
</tr>
<tr>
<td>Tzang, 2016#13495</td>
<td>1.25</td>
<td>[0.82, 1.92]</td>
</tr>
</tbody>
</table>

The equivalent analyses for a categorical outcome came to similar conclusions and did not detect an effect on appetite suppression (RR 1.10; CI 0.88, 1.38; 6 studies, n=439). The analysis did not detect heterogeneity. There was some indication of publication bias (Begg p 0.08, Egger p 0.02). An alternative estimate using the trim and fill method also showed no systematic benefit (RR 1.16; CI 0.88, 1.54). Removing a high-risk of bias study in a sensitivity analysis found a similar effect (RR 1.14; CI 0.79, 1.64) suggesting that the result was not primarily driven by poor methodology.

Studies evaluating the effects on nutrition or supplements on adverse events are shown in Figure 69.
5. Results: Treatment of ADHD

Figure 69. Effects of Nutrition or Supplements on Participants with Adverse Events (RR)

<table>
<thead>
<tr>
<th>Study</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cornu, 2018(#283)</td>
<td>0.70</td>
<td>[0.30, 1.65]</td>
</tr>
<tr>
<td>Crippa, 2019(#455)</td>
<td>1.00</td>
<td>[0.02, 48.52]</td>
</tr>
<tr>
<td>Fallah, 2018(#4252)</td>
<td>1.40</td>
<td>[0.44, 4.42]</td>
</tr>
<tr>
<td>Johnstone, 2022(#18993)</td>
<td>0.55</td>
<td>[0.41, 0.73]</td>
</tr>
<tr>
<td>Pongpitakdamrong, 2021(#4839)</td>
<td>1.00</td>
<td>[0.02, 48.59]</td>
</tr>
<tr>
<td>Van der Heijden, 2007(#24345)</td>
<td>20.61</td>
<td>[1.24, 342.90]</td>
</tr>
<tr>
<td>Weber, 2008(#17429)</td>
<td>0.92</td>
<td>[0.49, 1.70]</td>
</tr>
</tbody>
</table>

Across studies, there was no indication that the interventions were associated with a higher risk of experiencing an adverse event (RR 0.80; CI 0.44, 1.43; 7 studies, n=600). Heterogeneity was negligible (I-squared 33%), there was no evidence of publication bias, and none of the studies contributing to the effect estimate were considered high risk of bias. This analysis included three omega 3 studies.\textsuperscript{214, 216, 265} The result for this subset was similar to the overall analysis and omega 3 was also not associated with an increased risk of experiencing adverse events (RR 0.90; CI 0.46, 1.77; 3 studies, n=263).

5.3.8.1 Nutrition and Supplements Comparative Effects

Few of the nutrition and supplement studies used active comparators comparing the nutrition or supplement to a different intervention.

Two studies compared to methylphenidate while the intervention group received saffron\textsuperscript{143} or ginkgo biloba\textsuperscript{497} Both studies reported on symptoms but they found conflicting results. One reported no difference between saffron versus methylphenidate groups, while one favored methylphenidate over ginkgo biloba and the studies could not be combined to a meaningful summary estimate (SMD 0.40; CI -4.79, 5.58; 2 studies, n=104). However, both studies reported also appetite suppression and found more events in the methylphenidate groups (RR 0.29; CI 0.14, 0.59; 2 studies, n=104).

One study compared omega 3 versus zinc supplements and found no difference in a broadband measure (SMD 0.02; CI -0.37, 0.41; 1 study, n=150).\textsuperscript{498}

5.3.8.2 Nutrition and Supplements Summary of Findings

Table 19 displays the findings for each outcome category along with the number of studies and study identifiers. All outcomes displayed are for the longest follow-up reported. The summary of findings table displays data for all outcomes of interest across nutrition/supplements and for specific supplements where more than one study reported on the particular agent for the outcome. Results of individual studies are documented in the evidence table in the appendix.
### 5. Results: Treatment of ADHD

#### Table 19. KQ2 Summary of Findings and Strength of Evidence for Nutrition and Supplements

<table>
<thead>
<tr>
<th>KQ2 Intervention and Comparison</th>
<th>Outcome</th>
<th>Number of Studies; Study Design and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ2 nutrition/supplements vs control</td>
<td>Behavior</td>
<td>4 RCTs(216, 493, 573, 577)</td>
<td>Results favored intervention (SMD 0.25; CI 0.17, 0.33; 4 studies, n=294)</td>
<td>Low for benefit</td>
</tr>
<tr>
<td>KQ2 nutrition/supplements vs control</td>
<td>Broadband measures</td>
<td>10 RCTs(214, 216, 308, 343, 344, 401, 493, 498, 573, 596)</td>
<td>No systematic effect (SMD 0.03; CI -0.29, 0.34; 8 studies, n=818; RR 0.65; CI 0.35, 1.21; 3 studies, n=273)</td>
<td>Moderate for no effect</td>
</tr>
<tr>
<td>KQ2 nutrition/supplements vs control</td>
<td>ADHD symptoms</td>
<td>18 RCTs(295, 314, 356, 428, 429, 431, 466)</td>
<td>Positive effect (SMD -0.49; CI -0.80, -0.17; 19 studies, n=1854; RR 1.88; CI 0.01, 677.13; 2 studies)</td>
<td>Low for benefit</td>
</tr>
<tr>
<td>KQ2 nutrition/supplements vs control</td>
<td>Functional impairment</td>
<td>4 RCTs(350, 343, 358, 401)</td>
<td>No systematic effect (SMD 0.37; CI 0.05, 1.26; 3 studies, n=272)</td>
<td>Low for no effect</td>
</tr>
<tr>
<td>KQ2 nutrition/supplements vs control</td>
<td>Acceptability of treatment</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 nutrition/supplements vs control</td>
<td>Academic performance</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 nutrition/supplements vs control</td>
<td>Appetite changes and growth suppression</td>
<td>6 RCTs(334, 353, 401, 493, 577)</td>
<td>No systematic effect (SMD -0.05; CI -0.63, 0.52; 3 studies, n=373; RR 1.10; CI 0.88, 1.38; 6 studies, n=439)</td>
<td>Low for no effect</td>
</tr>
<tr>
<td>KQ2 nutrition/supplements vs control</td>
<td>Number of participants with adverse events</td>
<td>9 RCTs(214, 216, 265, 314, 344, 401, 428, 466, 596)</td>
<td>No systematic effect (RR 0.80; CI 0.44, 1.43; 7 studies, n=600)</td>
<td>Moderate for no effect</td>
</tr>
<tr>
<td>KQ2 Omega 3 vs control</td>
<td>Broadband measures</td>
<td>6 RCTs(214, 216, 308, 343, 401, 498)</td>
<td>No systematic effect (SMD 0.03; CI -0.33, 0.38; 6 studies, n=620)</td>
<td>Moderate for no effect</td>
</tr>
<tr>
<td>KQ2 Omega 3 vs control</td>
<td>ADHD symptoms</td>
<td>6 RCTs(186, 214, 216, 314, 343, 429)</td>
<td>No systematic effect (SMD -0.08; CI -0.51, 0.34; 6 studies, n=559; RR 3.97; CI 0.93, 16.95; 1 study, n=64)</td>
<td>Low for no effect</td>
</tr>
<tr>
<td>KQ2 Omega 3 vs control</td>
<td>Number of participants with adverse events</td>
<td>3 RCTs(214, 216, 265)</td>
<td>No systematic effect (RR 0.90; CI 0.46, 1.77; 3 studies, n=263)</td>
<td>Low for no effect</td>
</tr>
<tr>
<td>KQ2 Supplement vs methylphenidate</td>
<td>ADHD symptom</td>
<td>2 RCTs(143, 497)</td>
<td>No systematic difference (SMD 0.40; CI -4.79, 5.58; 2 studies, n=104)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 Supplement vs methylphenidate</td>
<td>Appetite changes and growth suppression</td>
<td>2 RCTs(143, 497)</td>
<td>Supplements reported fewer events (RR 0.29; CI 0.14, 0.59; 2 studies, n=104)</td>
<td>Low for favoring supplements</td>
</tr>
</tbody>
</table>

Notes: CI 95% confidence interval, KQ key question, N/A not applicable, RR relative risk, RCT randomized controlled trial, SMD standardized mean differences, SoE strength of evidence
5. Results: Treatment of ADHD

The majority of studies reported on ADHD symptoms and we found low strength of evidence that nutrition and supplements can show benefits. We downgraded by two for inconsistency since we only found effects for one outcome type (continuous, not categorical data) and the continuous data showed considerable heterogeneity. In addition, the evaluated supplements and dietary approaches were very diverse and it was not possible to identify an effect of a specific intervention that has shown positive effects in more than one study. There was also a positive effect shown for individual problem behaviors but the number of studies and samples were small, none of the individual studies reported statistically significant effects, and an additional study may change the statistical significance of the pooled effect (downgraded by two for imprecision). We found no systematic effect on broadband measures or functional impairment but we downgraded the strength of evidence due to heterogeneity (inconsistency). There was insufficient evidence to estimate the effect on acceptability of treatment and academic performance due to the lack of research studies. There was moderate strength evidence that nutrition and supplement interventions are just as safe as a placebo but we downgraded for study limitation as some studies had reported adverse events but did not report on the number of participants experiencing adverse events.

The evaluated supplements and dietary approaches were very diverse but the effect of omega 3 has been assessed in multiple studies. We found no evidence that omega 3 improves behavior, broadband measure scores, or ADHD symptoms, and it was not associated with appetite suppression or experiencing adverse events. We downgraded the omega 3 evidence due to study limitations.

We found two studies that reported the comparative effectiveness of supplements versus methylphenidate. While both reported on ADHD symptoms, we determined the strength of evidence to be insufficient because of the small number of studies reporting on two different supplements (inconsistency), studies reported conflicting results (inconsistency) and no meaningful summary estimate could be derived (imprecision). There was low strength of evidence that supplements reported fewer appetite suppression events than methylphenidate (downgraded for inconsistency and imprecision).

We downgraded the strength of evidence for no difference between omega 3 and zinc in broadband measures to insufficient (study limitation, downgraded by two as the single study did not let us assess inconsistency).

5.3.9 CAM

We identified four studies that evaluated complementary, alternative, or integrative medicine (CAM) interventions.\(^{158, 280, 281, 327}\) Studies were published between 2001 and 2019; they were conducted in Switzerland,\(^{280, 281}\) Iran,\(^{158}\) and Korea.\(^{327}\) All studies included both children and adolescents and participants were predominately male. Race or ethnicity was not reported, presumably because populations of these countries are fairly homogenous. ADHD presentations and presentations were not reported. Studies evaluated acupuncture and homeopathy. Three studies compared to a passive control group (waitlist, placebo, attention-matched control).

None of the studies reported on individual problem behaviors. One of the identified studies reported on a broadband measure in sufficient detail to calculate an effect size; the study found no systematic improvement associated with acupuncture compared to waitlist (SMD: -0.19; CI: -0.60, 0.22; 1 study, n=93).\(^{327}\) One homeopathy study reported insufficient detail for effect size calculations but concluded that the intervention had improved the Conners Global Index compared to placebo.\(^{280}\)
5. Results: Treatment of ADHD

Two studies reported on ADHD symptoms, but the effects varied somewhat and no meaningful summary estimate could be derived (SMD 0.18; CI -1.66, 2.01; 2 studies, n=190).\textsuperscript{158, 327} The studies evaluated traditional acupuncture and auricular acupuncture. One of the studies reported on symptom improvement as a categorical variable and found auricular acupuncture improved symptoms (RR 4.26; CI 1.42, 12.77; 1 study, n=50).\textsuperscript{158}

None of the identified studies reported sufficient detail to calculate effect estimates for the other outcomes of interest, including functional impairment, treatment satisfaction, academic performance, appetite suppression, or participants experiencing adverse events.

5.3.9.1 CAM Comparative Effects

One of the identified studies (n=115) compared homeopathy and methylphenidate.\textsuperscript{281} The high risk of bias study used the Clinical Global Impression (CGI) scale but did not provide sufficient detail to allow computation of effect sizes. The authors concluded that homeopathic treatment appears to be similar to the effect of methylphenidate.

5.3.9.2 CAM Summary of Findings

Table 20 shows the findings for the outcomes of interest together with the number of studies and study identifiers.

<table>
<thead>
<tr>
<th>Intervention and Comparison</th>
<th>Outcome</th>
<th>Number of Studies: Study Design and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ2 CAM vs control</td>
<td>Behavior</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 CAM vs control</td>
<td>Broadband measures</td>
<td>2 RCTs\textsuperscript{280, 327}</td>
<td>No systematic effect (SMD -0.19; -0.60, 0.22; 1 study, n=140)</td>
<td>Low for no effect</td>
</tr>
<tr>
<td>KQ2 CAM vs control</td>
<td>ADHD symptoms</td>
<td>2 RCTs\textsuperscript{158, 327}</td>
<td>Conflicting results (SMD 0.19; CI 1.72, 2.11; 2 studies, n=190; RR 4.26; CI 1.42, 12.77; 1 study, n=44)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 CAM vs control</td>
<td>Functional impairment</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 CAM vs control</td>
<td>Acceptability of treatment</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 CAM vs control</td>
<td>Academic performance</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 CAM vs control</td>
<td>Appetite suppression</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 CAM vs control</td>
<td>Participants with adverse events</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

Notes: CI 95% confidence interval, KQ key question, N/A not applicable, RR relative risk, RCT randomized controlled trial, SMD standardized mean differences, SoE strength of evidence

Very few studies reported on the key outcomes selected for the review and the conclusion for several outcomes was that the evidence base is insufficient because of lack of research. The strength of evidence was downgraded for broadband measure scores due to inconsistency and imprecision (both studies reported a positive effect but estimates varied). The strength of evidence was determined to be insufficient for symptoms because of conflicting results and it is unclear whether CAM interventions have an effect on ADHD symptoms.
5. Results: Treatment of ADHD

Only one comparative effectiveness study was identified and the study reported insufficient details to compute effect sizes for the outcomes of interest.

5.3.10 Parent Support

We identified 18 studies evaluating an intervention primarily targeting parents. Of note, some psychosocial studies presented earlier in the chapter also included a parent component, but in addition to targeting the children and adolescents directly. The earliest identified parent support study was published in 2001. Evaluations were published in ten different countries, primarily the US and the UK. The populations studied were parents of children with ADHD between the ages of three and up to 18 years, but only three studies included teenagers. For studies that distinguished between ADHD presentations, the most prevalent type (ranging from 33.5% to 63% of the ADHD participants) was the combined type. While ADHD participants with co-occurring disorders were not excluded from most of the studies, no studies purposely included specific co-occurring disorders such as oppositional defiant disorder or conduct disorder, i.e., where the children had a dual diagnosis. Two studies included children with sleep problems. Race and ethnicity demographics for the parents or children were not mentioned in most studies.

Interventions were diverse in terms of intervention approach as well as intensity and included behavioral training for parents, in-home nurse visits, group psychotherapy, telephone-assisted self help, psychoeducation, and parental friendship coaching. One intervention each targeted sleep or reading, several evaluated the New Forest Parenting Program. Of the identified studies, most reported on a control group, including attention-matched groups, no intervention, waitlist, or treatment as usual. Some studies included both a control group and an alternative psychological or behavioral intervention. Three studies had no control group, only an alternative intervention. Two studies compared parent training as stimulant augmentation to medication alone.

We only included studies that reported data on the effects on the children with ADHD; studies reporting only on parental outcomes were excluded (see eligibility criteria). Studies reported a variety of often study-specific outcomes, such as family dynamics and parental stress. In terms of pre-specified outcomes, broadband scales and symptom scores were the most frequently reported outcomes. Figure 70 shows the effects on individual behaviors assessed in the studies, including showing physical aggression, externalizing problem behavior in the family, and observed ADHD behavior in a play situation.
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Figure 70. Effects of Parent Support on Behavior (SMD)

Across studies, we did not detect a systematic effect of the parent-oriented interventions (SMD 0.35; CI -0.70, 1.40; 3 studies, n=252). The analysis did detect statistical heterogeneity (I-squared 70%). None of the studies was considered high risk. There was no evidence of publication bias.

Results for broadband measures are shown in Figure 71.

Figure 71. Effects of Parent Support on Broadband Measures (SMD)

Analyses found positive effects of parent support interventions but the effect was only borderline statistically significant (SMD 0.42; CI 0.01, 0.83; 4 studies, n=379). The youngest children included in the studies were three years old, the oldest were 18. The included
5. Results: Treatment of ADHD

treatments were all multi-component interventions targeting parents, but the content varied considerably. Interventions included the New Forest Parenting Package for parents of preschoolers versus wait list, a combination of methylphenidate plus parental training and support versus medication alone, a psychoeducation interventions versus treatment as usual, and parent training for mothers versus waitlist, in the individual studies. Heterogeneity was unremarkable (I-squared 28%). There was no evidence of publications bias and none of the studies was considered high risk of bias.

A number of studies reported on ADHD symptom measures (Figure 72).

Figure 72. Effects of Parent Support on Symptoms (SMD)

Analyses indicated a benefit of the parent interventions on ADHD symptoms compared to control groups not receiving the intervention, but the effect was small and the statistical significance was borderline (SMD -0.23; CI -0.45, -0.00; 10 studies; n=1053). The youngest children included in the studies were three years old, the oldest were 18. There was little statistical heterogeneity (I-squared 51%) in results, but the multi-component interventions varied in content and complexity. Strongest effects were shown for an education and behavior strategy program for parents of preschoolers, psychoeducation for families, and the New Forest Parenting Package for parents of preschoolers, specifically. Removing high risk of bias studies suggested a smaller, not statistically significant effect (SMD -0.20; CI -1.00, 0.60) but heterogeneity increased in this sensitivity analysis. There was no evidence of publication bias. One study evaluating an education and behavior strategy program for parents of preschoolers reported on a categorical symptom outcome; the study found no statistically significant effect (RR 0.47; CI 0.20, 1.07; 1 study, n=50).

Functional impairment outcomes were also frequently reported in identified studies as shown in Figure 73.
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Figure 73. Effects of Parent Support on Functional Impairment (SMD)

Pooled effect estimates showed no systematic effect of the intervention on functional impairment (SMD 0.29; CI -0.29, 0.86; 4 studies, n=344). There was some heterogeneity (I-squared 61%). Removing two high risk of bias studies reported also a non-significant effect with wide confidence intervals (SMD 0.47; CI -4.18, 5.11). There was no evidence of publication bias. There were insufficient data to calculate effects on treatment satisfaction or academic outcomes.

One study reported on appetite suppression and found no systematic effect (RR 7.14; CI 0.38, 134.71; 1 study, n=99) but the estimate was very imprecise. The study also reported on the number of participants with adverse events, but results were likely driven by the pharmacological component of the intervention: the study found more events in psychoeducation for parents plus atomoxetine versus psychoeducation for parents plus placebo (RR 1.21; CI 1.00, 1.47; 1 study, n=92).

5.3.10.1 Parent Support Comparative Effectiveness

Multiple studies compared two different parenting approaches.

Two studies assessed the New Forest Parenting program compared to an alternative approach. One study compared the New Forest Parenting versus an alternative comprehensive program (helping the noncompliant child) and found no difference in aggressive behaviors (SMD 0.05; CI -0.29, 0.40; 1 study, n=164) but the CPRS ratings were lower in the helping the noncompliant child group (SMD -0.41; CI 0.76, -0.07; 1 study, n=164). There was no difference in treatment satisfaction (SMD -0.13; CI -0.48, 0.21; 1 study, n=164). One study compared the New Forest Parenting program with the Incredible Years alternative parenting program. The study found no difference in ADHD symptom scores (SMD -0.09; CI -0.33, 0.15; 1 study, n=307). A study by the same author group compared a parent training focusing on education about ADHD and behavior management strategies versus a parent counseling and support intervention. The study found no differences in behavior in direct observations (SMD 0.36; CI -0.36, 0.88; 1 study, n=307) or broadband measure scores (RR 0.74; 0.42, 1.30; 1 study, n=307) but results favored
5. Results: Treatment of ADHD

the parent training when comparing the parental account of childhood symptom score to assess ADHD (SMD -0.69; CI -1.22, -0.16; 1 study, n=307).

A study comparing parent psychoeducation to parent counseling found no statistically significant differences in ADHD symptom assessments (SMD -0.32; -0.77, 0.13; 1 study, n=81) or functional impairment (SMD 0.07; CI -0.38, 0.52; 1 study, n=81) and concluded that psychoeducation is a complementary rather than a substitute treatment.268

A study comparing parent psychoeducation to parent counseling found no statistically significant differences in ADHD symptom assessments (SMD -0.32; -0.77, 0.13; 1 study, n=81) or functional impairment (SMD 0.07; CI -0.38, 0.52; 1 study, n=81) and concluded that psychoeducation is a complementary rather than a substitute treatment.268

A study (n=92) evaluating a behavioral parent training for children with ADHD targeting executive function versus a consequence-based program did not report sufficient detail on our key outcomes to calculate effect sizes, but the study concluded positive effects on daily rated problem behaviors and hyperactivity-impulsivity symptoms for both interventions. Results favored the targeted behavioral training for inattention.328 A nursing case-management intervention working with families versus receiving a parenting book and newsletter did not report sufficient detail to assess effect sizes but the study (n=174) indicated that for broadband measures there were no significant differences between groups (while the overall evaluation was considered positive).304 A study (n=172) comparing a parental friendship coaching intervention versus psychoeducation and social support found no significant differences in aggressive behaviors in the children with ADHD and did not report sufficient detail for effect size calculations, but the study concluded that the coaching intervention showed parents providing more emotion strategies and praise.533

Authors comparing the STEPP (Strategies To Enhance Positive Parenting) program to a traditional parent training program found no differences in ADHD symptoms (SMD 0.16; CI -0.28, 0.60; 1 study, 120) but found lower functional impairment scores favoring STEPP (SMD 0.51; CI 0.07, 0.96; 1 study, n=120).184

5.3.10.2 Parent Support Summary of Findings

Table 21 shows the findings for the outcomes of interest together with the number of studies and study identifiers.

<table>
<thead>
<tr>
<th>Intervention and Comparison</th>
<th>Outcome</th>
<th>Number of Studies; Study Design and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ2 parent support vs control</td>
<td>Behavior</td>
<td>5 RCTs117, 290, 328, 316, 539</td>
<td>No systematic effect (SMD 0.35; CI -0.70, 1.40; 3 studies, n=252)</td>
<td>Low for no effect</td>
</tr>
<tr>
<td>KQ2 parent support vs control</td>
<td>Broadband measures</td>
<td>6 RCTs117, 266, 269, 539, 540, 560</td>
<td>Results favor intervention (SMD 0.42; CI 0.01, 0.83; 4 studies, n=379)</td>
<td>Low for benefit</td>
</tr>
<tr>
<td>KQ2 parent support vs control</td>
<td>ADHD symptoms</td>
<td>14 RCTs184, 233, 269, 290, 316, 539, 541, 560, 572</td>
<td>Results favor intervention (SMD -0.23; CI -0.45, -0.00; 10 studies, n=1053; RR 0.47, CI 0.20, 1.07; 1 study, n=50)</td>
<td>Low for benefit</td>
</tr>
<tr>
<td>KQ2 parent support vs control</td>
<td>Functional impairment</td>
<td>4 RCTs184, 233, 269, 290</td>
<td>No systematic effect (SMD 0.29; CI -0.29, 0.86; 4 studies, n=344)</td>
<td>Low for no effect</td>
</tr>
<tr>
<td>KQ2 parent support vs control</td>
<td>Acceptability of treatment</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 parent support vs control</td>
<td>Academic performance</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 parent support vs control</td>
<td>Appetite suppression</td>
<td>1 RCT560</td>
<td>No systematic effect (RR 7.14; CI 0.38, 134.71; 1 study, n=99)</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>
## 5. Results: Treatment of ADHD

<table>
<thead>
<tr>
<th>Intervention and Comparison</th>
<th>Outcome</th>
<th>Number of Studies; Study Design and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ2 parent support vs control</td>
<td>Participants with adverse events</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 New Forest Parenting program vs Helping the Noncompliant Child</td>
<td>Behavior</td>
<td>1 RCT</td>
<td>No systematic difference (SMD 0.05; CI -0.29, 0.40; 1 study, n=164)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 New Forest Parenting program vs Helping the Noncompliant Child</td>
<td>Broadband measures</td>
<td>1 RCT</td>
<td>Results favored the helping-the-noncompliant-child intervention (SMD -0.41; CI 0.76, -0.07; 1 study, n=164)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 New Forest Parenting program vs Helping the Noncompliant Child</td>
<td>Functional impairment</td>
<td>1 RCT</td>
<td>No systematic difference (SMD -0.13; CI -0.48, 0.21; 1 study)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 New Forest Parenting program vs The Incredible Years</td>
<td>ADHD symptoms</td>
<td>1 RCT</td>
<td>No systematic difference (SMD 0.09; CI -0.33, 0.15; 1 study, n=307)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 Parent training vs parent counseling</td>
<td>Behavior</td>
<td>1 RCT</td>
<td>No systematic difference (SMD 0.36; CI -0.16, 0.88; 1 study, n=78)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 Parent training vs parent counseling</td>
<td>Broadband measures</td>
<td>1 RCT</td>
<td>No systematic difference (SMD 0.74; CI 0.42, 1.30; 1 study, n=78)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 Parent training vs parent counseling</td>
<td>ADHD symptoms</td>
<td>1 RCT</td>
<td>Results favored the parent training intervention (SMD -0.69; CI -1.22, -0.16; 1 study, n=78)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 Parent friendship coaching vs psychoeducation</td>
<td>Behavior</td>
<td>1 RCT</td>
<td>No systematic difference (SMD 0.14; CI -0.16, 0.43; 1 study, n=172)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 Parent psychoeducation vs parent counseling</td>
<td>ADHD symptoms</td>
<td>1 RCT</td>
<td>No systematic difference (SMD -0.32; CI -0.77, 0.13; 1 study, n=81)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 Parent psychoeducation vs parent counseling</td>
<td>Functional impairment</td>
<td>1 RCT</td>
<td>No systematic difference (SMD 0.07; CI -0.38, 0.52; 1 study, n=81)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 Strategies to Enhance Positive Parenting Program vs traditional parent behavior training</td>
<td>ADHD symptoms</td>
<td>1 RCT</td>
<td>No systematic difference (SMD -0.16; CI -0.28, 0.60; 1 study, n=120)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 Strategies to Enhance Positive Parenting Program vs traditional parent behavior training</td>
<td>Functional impairment</td>
<td>1 RCT</td>
<td>Results favored the positive parenting program (SMD 0.51; CI 0.07, 0.96; 1 study, n=120)</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

Notes: CI 95% confidence interval, KQ key question, N/A not applicable, RR relative risk, RCT randomized controlled trial, SMD standardized mean differences, SoE strength of evidence
5. Results: Treatment of ADHD

Across studies, parent training interventions were associated with improvements in broadband measure scores (low strength of evidence, downgraded for inconsistency given the variation and small number of studies and imprecision) and standardized symptom scores (moderate strength of evidence, downgraded for inconsistency and imprecision) as well as. There was no systematic effect on individual behaviors assessed in the studies, but the existing evidence is limited (inconsistency). We found no systematic effect on functional impairment (inconsistency). Evidence was insufficient to determine acceptability of treatment, academic performance, and participants with adverse events due to lack of research reporting on the outcome. Although one study reported on appetite suppression, the estimate was so imprecise and the study did not assess parent interventions per se (it assessed the combinations parent training plus atomoxetine versus parent training plus placebo) that we also determined the evidence base as insufficient for that outcome (downgraded due to study limitation, inconsistency as no replication could be evaluated, and imprecision due to the wide confidence intervals).

The comparative studies were downgraded to insufficient as studies had not been replicated yet and all results were unique to the reported study and the robustness of results could not be further evaluated; in addition it was unclear whether the study was sufficiently powered to detect a difference for the outcome examined (downgraded for inconsistency, study limitation).

5.3.11 School Interventions

We identified ten studies reporting on teacher or school environment interventions. The earliest study was published in 2009. Interventions were evaluated in four different countries, predominantly the US. The populations studied were most often children attending elementary through middle school between the ages of six and 14, with only one study including adolescents up to 17 years old. In two studies, participants were required to demonstrate an IQ of 80 or higher. Only one study required participants to not be taking stimulant medication or to be on a stable dose with no plans of change during the study duration. The majority of participants used ADHD medication at baseline. For studies that provided information on ADHD presentations, the combined type was the most prevalent presentation, followed by inattentive type. While ADHD participants with co-occurring disorders were not excluded from most of the studies, one study purposely required participants to have word-reading difficulties or reading disabilities in addition to ADHD. Several studies also report on participant co-occurring disorders, with the most common conditions reported being oppositional defiant disorder, conduct disorder, and anxiety and mood disorders.

Approximately half of the studies used a multimodal intervention strategy comprising both teacher training and parent training, with some studies also including intervention components targeting children with ADHD. Two studies examined teacher-specific interventions. One tested a web-based online learning modules for elementary-school teachers, while the other tested two different types of ADHD consultation services for teachers to help them plan and execute classroom-based ADHD interventions for students. Most studies reported on a control group, including waitlist control, no intervention, and ADHD medication only (compared to other modes of active treatment). Some studies reported on an alternative intervention, such a lower intensity intervention or a modified version of an original intervention, or multimodal intervention packets targeted at both parents and teachers and evaluated the comparative effectiveness of these interventions.
5. Results: Treatment of ADHD

Studies reported a variety of often study-specific outcomes, such as improvement in individual cognitive tasks. In terms of pre-specified outcomes, symptom scores, functional impairment, and academic scores were the most frequently reported outcomes. Two studies reported on individual problem behaviors, but results were conflicting and could not be combined to a meaningful summary estimate (SMD 0.01; CI -1.36, 1.38; 2 studies, n=395).\textsuperscript{242, 519} We did not identify studies reporting on broadband measure scores. Studies reporting on ADHD symptoms are shown in Figure 74.

Figure 74. Effects of School Interventions on ADHD Symptoms (SMD)

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corkum, 2019 (#377)</td>
<td>-0.87 [-1.40, -0.33]</td>
</tr>
<tr>
<td>Schramm, 2016 (#10874)</td>
<td>-0.49 [-0.95, -0.03]</td>
</tr>
<tr>
<td>Shen, 2021 (#19124)</td>
<td>-0.38 [-0.65, -0.10]</td>
</tr>
<tr>
<td>Sibley, 2018 (#4979)</td>
<td>0.06 [-0.22, 0.33]</td>
</tr>
<tr>
<td>Tamm, 2017 (#5052)</td>
<td>-0.35 [-0.68, -0.02]</td>
</tr>
<tr>
<td>Zheng, 2020 (#3326)</td>
<td>-1.04 [-1.33, -0.75]</td>
</tr>
</tbody>
</table>

RE Model: -0.50 [-0.92, -0.07]

Across studies, school interventions were associated with a reduction in ADHD symptoms (SMD -0.50; CI -0.92, -0.07; 6 studies, n=898). The age of the children in the included studies ranged from six to 17. There was evidence of heterogeneity (I-squared 82%). We found no indication of publication bias. Removing high risk of bias studies in a sensitivity analysis left only three studies; the effect estimate was smaller and was not statistically significant anymore (SMD -0.24; CI -1.00, 0.48). Heterogeneity was reduced, suggesting that the methodological rigor of the study is one source of heterogeneity.

Two studies reported on functional outcomes, however, they reported conflicting results and could not be combined to a meaningful estimate (SMD 0.22; CI -4.39, 4.82; 2 studies; n=274).\textsuperscript{213, 262} There was heterogeneity (I-squared 83%) but no further analyses could be performed due to the small number of studies. One study evaluated a web-based intervention for teachers of elementary students with ADHD\textsuperscript{213} and reported improvements. The other assessed a school-based training intervention program for adolescents but found no differences compared to community care in the relation with peer scale domain of the IRS (Impairment Rating Scale).\textsuperscript{262}

A small number of studies reported on academic performance measures as shown in Figure 75.
5. Results: Treatment of ADHD

Figure 75. Effects of School Interventions on Academic Performance (SMD)

Although all individual studies reported a reduction, across studies, the effect was not statistically significant (SMD -0.25; CI -0.59, 0.08; 4 studies, n=691). There was little heterogeneity (I-squared 47%). We did not detect potential publication bias. Removing one high-risk of bias study found a smaller effect that was not statistically significant (SMD -0.15; CI 0.44, 0.14) and the analysis detected no heterogeneity, suggesting that methodological rigor of the studies was a source of heterogeneity. Identified studies did not report on other prespecified outcomes for the review.

5.3.11.1 School Interventions Comparative Effects

One study assessed a dose-response question and compared a high versus a low intensity summer program. The study is shown in more detail in the appendix; the authors found no differences in school disciplinary incidents (SMD 0.01; CI -0.26, 0.28; 1 study, n=325), ADHD symptom assessments (SMD 0.01; CI -0.26, 0.29; 1 study, n=325), functional impairment (SMD -0.14; CI -0.42, 0.13; 1 study, n=325), or academic performance (SMD -0.25; -0.64, 0.14; 1 study, n=325) but concluded that the high intensity intervention was superior in engagement and uptake of selected skills.519

Other school interventions reported on the comparison to alternative, school-based or teacher-led interventions. This included a study comparing two homework management programs, one focused on contingency management-based treatment versus a planning skill program.171 The study found no statistically significant differences in GPA (grade point average) scores (SMD 0.12; CI -0.14, 0.39; 1 study, n=222) and concluded that developing a strong
working alliance and engaging parents and students are key elements for school-based programs. Comparing the after-school version of the program Challenging Horizons versus the mentoring version of the program found no differences in functional impairment (SMD 0.02; CI -0.24, 0.28; 1 study, n=326) or academic performance as measured by GPA (SMD -0.19; CI -0.46, 0.07; 1 study, n=326), but the study concluded that the after school version offers more benefits for adolescents.262 Another study compared approach of ongoing feedback for teachers that selected interventions for students on the basis of functional and academic assessment data versus a traditional data-based approach chosen by the teacher. The difference between interventions for academic performance was not statistically significant (SMD -0.26; CI -0.56, 0.05; 1 study, n=167).590

One study compared an academic problem solving and organization skill intervention versus progressive muscle relaxation and found no statistically significant difference in ADHD symptoms (SMD -0.29; CI -0.74, 0.16; 1 study, n=113).509

5.3.11.2 School Interventions Summary of Findings

Table 22 shows the findings for the outcomes of interest together with the number of studies and study identifiers.

<table>
<thead>
<tr>
<th>Intervention and Comparison</th>
<th>Outcome</th>
<th>Number of Studies; Study Design and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ2 school intervention vs control</td>
<td>Behavior</td>
<td>2 RCTs242, 519</td>
<td>Conflicting results (SMD 0.01; CI -1.36, 1.38; 2 studies, n=395)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 school intervention vs control</td>
<td>Broadband measures</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 school intervention vs control</td>
<td>ADHD symptoms</td>
<td>7 RCTs213, 262, 509, 517, 519, 564, 628</td>
<td>Results favor interventions (SMD -0.50; CI -0.92, -0.07; 6 studies, n=898)</td>
<td>Moderate for benefit</td>
</tr>
<tr>
<td>KQ2 school intervention vs control</td>
<td>Functional impairment</td>
<td>2 RCTs213, 262</td>
<td>Conflicting results (SMD 0.22; CI -4.39, 4.82; 2 studies, n=274)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 school intervention vs control</td>
<td>Acceptability of treatment</td>
<td>3 RCTs213, 517, 519</td>
<td>Studies reported favorable results but effect could not be estimated</td>
<td>Low for benefit</td>
</tr>
<tr>
<td>KQ2 school intervention vs control</td>
<td>Academic performance</td>
<td>4 RCTs171, 262, 517, 519</td>
<td>No statistically significant difference but all studies positive (SMD -0.25; CI -0.59, 0.08; 4 studies, n=691)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 school intervention vs control</td>
<td>Appetite suppression</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 school intervention vs control</td>
<td>Participants with adverse events</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 contingency-management based vs planning skills homework program</td>
<td>Academic performance</td>
<td>1 RCT171</td>
<td>No systematic difference (SMD 0.12; CI -0.14, 0.39; 1 study, n=222)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 After school program vs mentoring program</td>
<td>Functional impairment</td>
<td>1 RCT262</td>
<td>No systematic difference (SMD 0.02; CI -0.24, 0.28; 1 study, n=326)</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Intervention and Comparison</th>
<th>Outcome</th>
<th>Number of Studies; Study Design and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ2 After school program vs mentoring program</td>
<td>Academic performance</td>
<td>1 RCT&lt;sup&gt;262&lt;/sup&gt;</td>
<td>No systematic difference SMD -19; CI -0.46, 0.07; 1 study, n=376)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 Consultant and data-driven interventions vs teacher selected interventions</td>
<td>Academic performance</td>
<td>1 RCT&lt;sup&gt;390&lt;/sup&gt;</td>
<td>No systematic difference SMD -0.26; CI -0.56, 0.05; 1 study, n=326)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 School skills training vs progressive muscle relaxation</td>
<td>ADHD symptoms</td>
<td>1 RCT&lt;sup&gt;309&lt;/sup&gt;</td>
<td>No systematic difference (SMD -0.29; CI -0.74, 0.16; 1 study, n=113)</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

Notes: CI 95% confidence interval, KQ key question, N/A not applicable, RR relative risk, RCT randomized controlled trial, SMD standardized mean differences, SoE strength of evidence

School interventions showed favorable results for ADHD symptoms (moderate strength of evidence) but we downgraded the effect for study limitations (effects were lower and not statistically significant when removing high risk of bias studies). Identified studies showed conflicting results for behavior and functional impairment, and given the small number of studies, we were not able to determine whether school interventions improve these outcomes and judged the evidence base to be insufficient. Treatment acceptability (low strength of evidence) was favorable across multiple studies, but no effect estimate could be determined (downgraded by two for imprecision). We did not identify studies reporting on appetite suppression or participants with adverse events and no evidence statement could be derived.

The comparative studies were downgraded to insufficient as evaluations had not been replicated yet and all results were unique to the reported study, the specific intervention and the specific comparator, and the robustness of results could not be further evaluated(downgraded for inconsistency, study limitation).

### 5.3.12 Provider Interventions

We identified eight studies<sup>257-259, 306, 365, 378, 440, 454</sup> evaluating provider interventions or interventions changing how ADHD care is delivered. The earliest study was published in 2007.<sup>259</sup> All evaluations were conducted in the US. The populations studied were children with ADHD; no studies included teenagers. Only one study<sup>378</sup> reported ADHD presentation type; 41 percent of children were classified as inattentive, ten percent as hyperactive and 49 percent as combined presentation. No studies purposely included patients with specific co-occurring disorders. A study conducted in Philadelphia<sup>306</sup> reported that 46 percent of patients were African American. The majority of patients in the other studies were White.

Of the identified studies, five reported on a control group that underwent treatment as usual.<sup>258, 259, 306, 378, 454</sup> In one of these trials, pediatricians used titration trials to determine optimal medication dosages; doses were standardized by week, but doctors were blinded to exact dosage.<sup>259</sup> Another study<sup>258</sup> held four training sessions for providers and installed a web portal to assist with treatment monitoring. Another combined a web portal with an ADHD care manager.<sup>306</sup> One study provided office-based training in using stimulant medications to physicians and one hour of training to office staff in the use of new software.<sup>378</sup> Another created a web-based platform that enabled clinicians to administer online clinical questionnaires to
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Parents and teachers to monitor patients remotely between visits. Finally, one head to head study compared collaborative care, where a care manager delivered three or four content modules to parents and children, to “enhanced usual care” from a provider known to the care manager.

The studies are difficult to compare and assessed unique interventions. In addition, many used study-specific evaluation measures and rarely reported on key outcomes for this review or did not report sufficient detail to compute effect sizes. One study reported on a broadband measure and indicated children under the care of providers that used a trigger algorithm and alert resolution process to facilitate online clinical questionnaires to monitor patients remotely between visits, reported less improvement in global functioning (SMD -0.36; CI -0.65, -0.07; 1 study, n=263) than control group participants.

Parent-reported outcomes were the only outcomes reported in more than one study. Studies reported conflicting results and no meaningful summary estimate could be derived (SMD 0.26; CI -4.79, 5.31; 2 studies, n=537). This included the trigger algorithm study which did not find positive effects and a study evaluating a care manager combined with an online electronic health record portal to enhance communication and shared decision making which favored the intervention.

5.3.12.1 Provider Interventions Comparative Effects

Two studies also compared provider interventions to an alternative model. One assessed a collaborative care model versus a referral to mental health providers in an enhanced usual care condition. The study (n=411) did not report sufficient detail to compute effect sizes but concluded that the collaborative care model improved symptoms more than the referred group.

A telehealth service delivery model combining pharmacotherapy and caregiver behavior training versus children remaining under the care of their primary care provider who received only a single consultation with a tele-psychiatrist who shared treatment recommendations were compared in the second study. The study reported improvement in symptom measures in the telehealth intervention (SMD -0.54; CI -0.81, -0.27; RR 1.64; CI 1.09, 2.47; 1 study, n=223) and functional impairment (SMD 0.27; CI 0.01, 0.54; 1 study, n=223).

5.3.12.2 Provider Interventions Summary of Findings

Table 23 displays the findings for the outcomes of interest together with the number of studies and study identifiers. Comparative effectiveness results are only shown for outcomes where effect sizes could be calculated.

<table>
<thead>
<tr>
<th>Intervention and Comparison</th>
<th>Outcome</th>
<th>Number of Studies; Study Design and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ2 provider interventions vs control</td>
<td>Behavior</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 provider interventions vs control</td>
<td>Broadband measures</td>
<td>1 RCT454</td>
<td>Results favored intervention (SMD -0.36; CI -0.65, -0.07; 1 study, n=263)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 provider interventions vs control</td>
<td>ADHD symptoms</td>
<td>5 RCTs258, 259, 306, 378, 454</td>
<td>Conflicting results (SMD 0.26; CI -4.79, 5.31; 2 studies; n=537)</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>
5. Results: Treatment of ADHD

<table>
<thead>
<tr>
<th>Intervention and Comparison</th>
<th>Outcome</th>
<th>Number of Studies; Study Design and IDs</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ2 provider interventions vs control</td>
<td>Functional impairment</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 provider interventions vs control</td>
<td>Acceptability of treatment</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 provider interventions vs control</td>
<td>Academic performance</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 provider interventions vs control</td>
<td>Appetite suppression</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 Tele-psychiatry program vs single consultation</td>
<td>Participants with adverse events</td>
<td>0 studies</td>
<td>N/A</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 Tele-psychiatry program vs single consultation</td>
<td>ADHD symptoms</td>
<td>1 RCT&lt;sup&gt;440&lt;/sup&gt;</td>
<td>Results favored the tele-psychiatry program (SMD -0.54; CI -0.81, -0.27; RR 1.64; CI 1.09, 2.47; 1 study, n=223)</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2 Tele-psychiatry program vs single consultation</td>
<td>Functional impairment</td>
<td>1 RCT&lt;sup&gt;440&lt;/sup&gt;</td>
<td>Results favored the tele-psychiatry program (SMD 0.27; CI 0.01, 0.54; 1 study, n=223)</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

Notes: CI 95% confidence interval, KQ key question, N/A not applicable, RR relative risk, RCT randomized controlled trial, SMD standardized mean differences, SoE strength of evidence

Studies reported on very different intervention approaches and studies were difficult to compare and many did not report in sufficient detail (or not at all) on the outcomes of interest for this review. All studies had moderate or high risk of bias, as randomization at the provider level led to some imbalances in patient characteristics between groups. Attrition and detection bias also affected most studies. Strength of evidence was determined to be insufficient either for lack of research (behavior, functional impairment, treatment acceptability, academic performance, appetite suppression, participants with adverse events), study limitations and lack of replication (broadband measure scores), or studies reporting conflicting results making it difficult to determine whether interventions do affect the outcomes of interest (ADHD symptoms).
5. Results: Treatment of ADHD

5.4 KQ2a. How do these outcomes vary by presentation (inattentive, hyperactive/impulsive, and combined) or other co-occurring conditions?

5.4.1 Key Points KQ2a Effect of Presentation

- We did not detect differential treatment effects associated with ADHD presentation, but analyses were based on indirect comparisons and should be interpreted with caution.
- We identified only a small number of studies systematically addressing co-occurring disorders, and evidence is insufficient for concrete evidence statements.

Table 24 documents the results across studies.

Table 24. KQ2a Summary of Findings and Strength of Evidence for ADHD Interventions

<table>
<thead>
<tr>
<th>Intervention and Comparison</th>
<th>Outcome</th>
<th>Number of Studies; Study</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ2a effect modifier ADHD presentation</td>
<td>Behavior changes</td>
<td>N/A</td>
<td>Indirect comparisons did not suggest an effect</td>
<td>Low for no effect</td>
</tr>
<tr>
<td>KQ2a effect modifier ADHD presentation</td>
<td>Broad-band scale score</td>
<td>N/A</td>
<td>Indirect comparisons did not suggest an effect</td>
<td>Low for no effect</td>
</tr>
<tr>
<td>KQ2a effect modifier ADHD presentation</td>
<td>Standardized symptom scores</td>
<td>N/A</td>
<td>Indirect comparisons did not suggest an effect</td>
<td>Low for no effect</td>
</tr>
<tr>
<td>KQ2a effect modifier ADHD presentation</td>
<td>Functional impairment</td>
<td>N/A</td>
<td>Indirect comparisons did not suggest an effect</td>
<td>Low for no effect</td>
</tr>
<tr>
<td>KQ2a effect modifier ADHD presentation</td>
<td>Acceptability of treatment</td>
<td>N/A</td>
<td>Indirect comparisons did not suggest an effect</td>
<td>Low for no effect</td>
</tr>
<tr>
<td>KQ2a effect modifier ADHD presentation</td>
<td>Academic performance</td>
<td>N/A</td>
<td>Indirect comparisons did not suggest an effect</td>
<td>Low for no effect</td>
</tr>
<tr>
<td>KQ2a effect modifier ADHD presentation</td>
<td>Appetite suppression</td>
<td>N/A</td>
<td>Indirect comparisons did not suggest an effect</td>
<td>Low for no effect</td>
</tr>
<tr>
<td>KQ2a effect modifier ADHD presentation</td>
<td>Participants with adverse events</td>
<td>N/A</td>
<td>Indirect comparisons did not suggest an effect</td>
<td>Low for no effect</td>
</tr>
<tr>
<td>KQ2a effect modifiers co-occurring disorders</td>
<td>Behavior changes</td>
<td>N/A</td>
<td>Indirect comparisons did not detect effects, but few studies addressed co-occurring disorders systematically</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2a effect modifiers presentation and co-occurring disorders</td>
<td>Broad-band scale score</td>
<td>N/A</td>
<td>Indirect comparisons did not detect effects, but few studies addressed co-occurring disorders systematically</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2a effect modifiers presentation and co-occurring disorders</td>
<td>Standardized symptom scores</td>
<td>N/A</td>
<td>Indirect comparisons did not detect effects, but few studies addressed co-occurring disorders systematically</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>
### 5. Results: Treatment of ADHD

<table>
<thead>
<tr>
<th>Intervention and Comparison</th>
<th>Outcome</th>
<th>Number of Studies; Study</th>
<th>Findings</th>
<th>SoE</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ2a effect modifiers presentation and co-occurring disorders</td>
<td>Functional impairment</td>
<td>N/A</td>
<td>Indirect comparisons did not detect effects, but few studies addressed co-occurring disorders systematically</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2a effect modifiers presentation and co-occurring disorders</td>
<td>Acceptability of treatment</td>
<td>N/A</td>
<td>Indirect comparisons did not detect effects, but few studies addressed co-occurring disorders systematically</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2a effect modifiers presentation and co-occurring disorders</td>
<td>Academic performance</td>
<td>N/A</td>
<td>Indirect comparisons did not detect effects, but few studies addressed co-occurring disorders systematically</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2a effect modifiers presentation and co-occurring disorders</td>
<td>Appetite suppression</td>
<td>N/A</td>
<td>Indirect comparisons did not detect effects, but few studies addressed co-occurring disorders systematically</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2a effect modifiers presentation and co-occurring disorders</td>
<td>Participants with adverse events</td>
<td>N/A</td>
<td>Indirect comparisons did not detect effects, but few studies addressed co-occurring disorders systematically</td>
<td>Insufficient</td>
</tr>
<tr>
<td>KQ2b diversion</td>
<td>Misuse</td>
<td>2 studies^444, 485</td>
<td>Did not indicate any issues</td>
<td>Insufficient</td>
</tr>
</tbody>
</table>

Notes: CI 95% confidence interval, KQ key question, N/A not applicable, RR relative risk, RCT randomized controlled trial, SMD standardized mean differences, SoE strength of evidence

Across identified studies, we either detected no evidence of effect modifiers or the research base was insufficient for any evidence statements.

### 5.5 KQ2a. How do outcomes vary by presentation or other co-occurring conditions?

We assessed for all key outcomes whether the impact of interventions was associated with the ADHD presentation and whether co-occurring conditions were associated with the treatment effect. Studies varied in what proportion of children with inattentive, hyperactive/impulsive, and combined presentation of ADHD were included. Some studies targeted specific presentations, e.g., evaluated an intervention in a sample with exclusively combined presentation. And while most identified studies did not exclude children with co-occurring disorders, we identified a few studies that purposefully addressed interventions for children with specific co-occurring disorders. In these studies, all children had a dual diagnosis.

#### 5.5.1 ADHD Presentation

Most studies included a range of ADHD presentations. However, we identified one study that only included participants with inattentive ADHD presentation.\(^{464}\) The study evaluated an integrated psychosocial treatment approach; results are documented in the evidence table in the appendix. A number of studies included only children with combined presentation.\(^{111, 156, 234, 264, 295, 348, 427, 432, 496, 497, 510, 554, 624}\) The studies evaluated diverse interventions. Half of the studies
5. Results: Treatment of ADHD

restricting to the combined presentation evaluated FDA-approved pharmacological treatments, and individual studies assessed the effects of a behavior intervention, nutrition intervention, psychosocial interventions, neurofeedback, cognitive training, and a new pharmacological agent. We assessed the effect of the presentation in indirect comparisons across studies and we documented results of subgroup analyses as reported by the individual authors.

5.5.1.1 Indirect analyses

We first conducted indirect analyses across the large number of studies included in the review. For individual behavior measures, we did not find an effect of the proportion of children with inattentive (p 0.09), hyperactive (p 0.23), or combined (p 0.32) presentation on the reported effect size across all included interventions. For broadband assessments, we did not find an effect on the reported effect size for the proportion of children with inattentive presentation (continuous data p 0.74, categorical data p 0.90), hyperactive (continuous data p 0.67, categorical data p 0.92), or combined (continuous data p 0.34, categorical data p 0.96) across all included interventions.

For ADHD symptom scores in studies reporting a continuous outcome, we did not find an effect on the reported effect size for the proportion of children with inattentive presentation (p 0.55), hyperactive (p 0.70), or combined (p 0.52) across all included interventions. However, the equivalent analysis for categorical outcomes was statistically significant for inattentive presentation (p 0.03). The analysis indicated that treatment effects were lower in samples with a higher proportion of inattentive children, but the effect was very small (1 percentage point increase in the inattentive proportion was associated with a 1.3% reduction in the relative risk for symptom improvement). Results for hyperactive (p 0.17) and combined (p 0.41) presentation were not statistically significant.

None of the analysis for the outcome functional impairment were significant; results were borderline for the proportion of children with inattentive presentation (p 0.12), hyperactive (p 0.31), or combined (p 0.10), indicating a systematic effect across all included interventions. Results could not be confirmed in the analyses for categorical data as too few studies were available for the analysis.

There were insufficient data to test the effect for treatment satisfaction. For academic performance outcomes, results were borderline for the proportion of children with inattentive presentation (p 0.06), but results for hyperactive presentation (p 0.59) and combined presentation (p 0.25) were not statistically significant. Findings could not be confirmed or refuted with categorical data due to lack of studies.

For the outcome appetite suppression, we did not find an effect of the presentation on the reported effect size in the continuous data analyses, i.e., results for inattentive (p 0.39), hyperactive (p 0.24), or combined presentation (p 0.52) were not significant across all included interventions. However, for the equivalent analyses for the more commonly reported outcome analyzing appetite suppression as categorical data, effects for the combined presentation was borderline (p 0.05). Results for inattentive (p 0.18) or hyperactive (p 0.31) presentation did not indicate a systematic effect. Similarly, across studies, we did not identify an effect of the likelihood of experiencing an adverse event based on the ADHD presentation as results for inattentive presentation (p 0.34), hyperactive presentation (p 0.42), and combined presentation (p 0.50) were not statistically significant.
5. Results: Treatment of ADHD

5.5.1.2 Reported Analyses for Subgroups in ADHD Presentation

Some of the identified studies reported results stratified by ADHD presentation or reported results of a moderator analysis that evaluated the effects of the ADHD presentation on treatment effects. The studies reported on different intervention types including: FDA-approved pharmacological interventions, a new pharmaceutical agent, psychosocial interventions, cognitive training, nutritional supplements, and provider training respectively. The reported subgroup results were primarily for ADHD symptoms and broadband assessments.

A cognitive training intervention identified a subgroup of boys who had both a lower hyperactivity and a higher conduct disorder symptom score with significantly better planning/organizing skills than the total group of participants. A study evaluating an omega-3 supplement reported that improvements were significantly more frequent in the inattentive ADHD presentation (p 0.03) than in the combined ADHD presentation (no statistically significant treatment effect). One omega 3 and zinc study reported the superior effect of zinc over omega-3 was only seen in the inattentive, not in the combined presentation of ADHD children (p 0.21).

All other studies did not detect systematic effects of ADHD presentation. One study evaluating long-acting methylphenidate reported that inattentive and combined ADHD subgroups did not differ significantly in their improvements in the parent (p 0.61) or teacher (p 0.85) SNAP-IV ratings. A further study reported no significant treatment interaction between relapse and the ADHD presentation. A study evaluating atomoxetine reported that baseline ADHD severity did not moderate treatment efficacy on response inhibition (p 0.54), sustained attention (p 0.96), or fear identification (p 0.66). A study assessing the effects of omega 3 found a higher percentage of children who ranked below the median in hyperactivity/impulsivity on a continuous performance test improved more in ADHD symptom severity, but the difference was not statistically significant (p 0.177). Reported results for the effects of a provider intervention on ADHD Rating Scale-IV Scores and SNAP-IV Scores showed no treatment effects specific to combined ADHD presentation or ADHD inattentive presentation. A study of atomoxetine assessed changes from baseline of ADHD-RS-IV-Parent Total Score and did not find any interaction.

Some studies stratified by clinical severity. A study evaluating mixed amphetamine salts stratified participants by low or high baseline severity on ADHD-RS-IV Scale and CGI scores. The mean reduction in ADHD severity was greater for low baseline severity in all dose groups relative to placebo (p<.01) on the ADHD-RS-IV scale and for doses above 10mg on CGI Impression Scores (p<.01). One study evaluating pantogam indicated that treatment effects were maximized in patients with the ADHD combined presentation group but between-group differences were not statistically significant. Stratified analyses of an omega 3 intervention evaluating ADHD Rating Scale-IV Scores explored whether children rated with abnormal scores in at least two of the Conners’ subscales showed a different treatment response. The interaction was statistically significant (p < 0.15) in four out of the eight CRS-P subscales. A behavioral sleep intervention for children with ADHD reported that children with ADHD symptom severity scores above the 75th percentile were more likely to have moderate/severe sleep problems over time. ADHD symptom severity was a moderator for ADHD symptoms (p 0.04) and quality of life (p 0.04) over time, suggesting the intervention is less effective for youth who have sleep problems.
5. Results: Treatment of ADHD

All other studies did not detect an effect. Evaluated efficacy and adverse effects of methylphenidate treatment for baseline ADHD severity as reported by teachers and parents found no significant effect on parent- or teacher-rated Conners ADHD index at 16 weeks (p values >0.1).526

5.5.2 Effect of Co-Occurring Disorders

We abstracted the results of study-reported effects (subgroup analyses or moderator analyses) as well as indirect comparisons across studies using a meta-regression approach.

A small number of studies addressed co-occurring disorders presenting with ADHD overall. Identified studies targeting specific populations included participants with ADHD as well as oppositional defiance disorder or conduct disorder, learning disabilities, sleep conditions, mood disorders such as depression and anxiety, tic disorders, traumatic brain injury, epilepsy, substance use disorder, iron deficiency, genetic disorders, or organizational deficits, respectively. Few of the studies reported statistically significant, systematic effects of co-occurring conditions and only selected studies reported effects on the key outcomes for this report.

In the MTA study, children with ADHD-only or ADHD with ODD or conduct disorder (but without anxiety disorders) responded best to MTA medication treatments (with or without behavioral treatments), while children with multiple comorbid disorders (anxiety and ODD/conduct disorder) responded optimally to combined (medication and behavioral) treatments.339 Children with comorbid anxiety, particularly those with overlapping disruptive disorder comorbidities, showed preferential benefits to the intervention;835 no detrimental effect of anxiety on medication response for core ADHD or other outcomes in anxious or non-anxious ADHD children was demonstrated;576; comorbid anxiety disorder did moderate outcome, in participants without anxiety, results paralleled intent-to-treat findings, for those with anxiety disorders, behavioral treatment yielded significantly better outcomes than community care (and was no longer statistically different from medication management and combined treatment) regarding ADHD symptoms;908; comorbidity with oppositional defiant disorder or conduct disorder (54% of the sample yielded such preintervention comorbidity) significantly moderated findings, initial comorbidity with anxiety disorder served as a clear moderator of treatment response. Whereas the 66% of the MTA sample without anxiety at baseline displayed a response to treatment that was close to that of the overall sample, the 34% with comorbid anxiety showed a relatively better response to the behavioral aspects of the MTA treatments.802 Parent-reported anxiety and ODD/CD status were noted on response to treatment, indicating that children with ADHD and anxiety disorders (but no ODD/CD) were likely to respond equally well to the MTA behavioral and medication treatments, children with ADHD-only or ADHD with ODD/CD (but without anxiety disorders) responded best to MTA medication treatments (with or without behavioral treatments), while children with multiple comorbid disorders (anxiety and ODD/CD) responded optimally to combined (medication and behavioral) treatments.834 For other functioning domains (social skills, academics, parent-child relations, oppositional behavior, anxiety/depression), results suggested slight advantages of combined over single treatments (medical management, behavior) and community care, children with parent-defined comorbid anxiety disorders, particularly those with overlapping disruptive disorder comorbidities, showed preferential benefits to the behavioral and combined interventions.835 A further study449 reported that youths with ADHD and comorbid ODD showed statistically significant improvement in
ADHD, ODD, and quality-of-life measures following atomoxetine treatment; treatment response was similar in youths with and without ODD, except that the comorbid group showed improvement compared with placebo at 1.8 mg/kg/day but not 1.2 mg/kg/day. In contrast, youths without ODD showed improvement at 1.2 mg/kg/day and no incremental benefit at 1.8 mg/kg/day. A third study reported that children with ODD did not benefit as much from the atomoxetine than other children. All other studies did not detect treatment effect differences associated with co-occurring conditions or reported on other outcomes such as ODD scores as documented in the evidence table.

We assessed whether the subgroup influences the impact of the interventions for the key outcomes in indirect comparisons. For the outcome behavior, we did not find a systematic effect across any of the evaluated subgroups that provided sufficient data for the analysis (sleep p 0.93, ODD p 0.32). For broadband scale scores, we also found no systematic effect (sleep p 0.85, ODD p 0.68, learning disability p 0.11). Symptom scores provided the most data for the comparisons; however, the analysis did not detect systematic effects (sleep p 0.61, ODD p 0.66, learning disability p 0.83, coordination disorder p 0.77). For functional outcomes also, results were not statistically significant (sleep p 0.93, ODD p 0.57). Treatment satisfaction could not be evaluated due to the small number of studies. Appetite suppression was not significant (ODD p 0.69, learning disability p 0.24), nor was adverse events (sleep p 0.94, ODD p 0.87).

We did not detect evidence indicating a differential effect associated with co-occurring disorders. However, based on the small number of studies and the indirect nature of effect analysis, the results have to be interpreted with caution.
5.6 KQ2b. What is the risk of diversion of pharmacologic treatment?

5.6.1 Key Points KQ2b

Only two studies reported on diversion and it was not possible to quantify the risk of diversion of pharmacological treatment.

Only two studies met inclusion criteria for KQ2b. One was an RCT evaluating either 200 or 400 mg viloxazine vs placebo and found no evidence for misuse. Viloxazine, however, is a non-stimulant (SNRI) medication with low abuse potential.

The other study was a double-blind RCT of OROS (Osmotic-Release Oral System) methylphenidate plus cognitive behavioral therapy (CBT) versus placebo plus CBT in adolescents with ADHD and a co-occurring substance use disorder. Rates of misuse or diversion in the stimulant group (2.1%-4.8%) were approximately double the rates in the placebo group, though the differences did not reach statistical significance. Findings are difficult to generalize to non-substance-use ADHD populations, as misuse and diversion rates may be higher in this subpopulation than in ADHD adolescents without substance use disorder. On the other hand, nearly doubled rates of misuse may be clinically relevant, given that participants were blinded to treatment assignment, and rates were systematically higher in the stimulant group.
6. Results: Monitoring of ADHD

6.1 KQ3 ADHD Monitoring Key Points

- Very few monitoring studies have been reported and more research is needed on how youth with ADHD should be monitored over time.
- Different assessment modalities may provide valid but different perspectives and more than a single assessment modality may be required for comprehensive and effective monitoring of ADHD outcomes over time.

6.2 KQ 3 ADHD Monitoring Summary of Findings

We identified a small number of studies addressing a monitoring strategy. Results of the individual studies are shown in the evidence table in the appendix. However, studies did not provide information on the predefined key outcomes.

The potential for risk of bias in the KQ3 studies is documented in Figure 76. The critical appraisal for the individual studies is in Appendix D.

Figure 76. Risk of Bias in KQ3 Studies

Across studies, selection bias was likely present in two studies. Performance bias was present in two studies. Attrition bias was also present in two of the identified studies. Detection bias was determined to be present in three studies. Reporting bias was likely in one study. In the small set of studies, a third were rated as high risk of bias for other sources.

Figure 77 shows the distribution of applicability issues in KQ3 studies. The applicability for the individual studies is in Appendix D.
### 6. Results: Monitoring of ADHD

**Figure 777. KQ3 Applicability Rating**

![Figure 777. KQ3 Applicability Rating](image)

Given the small number of available studies, results of the different monitoring strategies are documented in Table 25.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population: Target</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cedergren, Göteborg University, 2021</td>
<td>Participants between the ages of 6-18; ADHD diagnosis meets DSM-V criteria; IQ &gt; 70; excluded if participant physically/psychologically unable to complete monitoring test, has cardiovascular disease, seizures, other unstable medical conditions, bipolar disorder, conduct disorder, psychosis, severe autism, or other severe psychiatric conditions, taking psychoactive</td>
<td>Open-label monitoring consisting of 5 follow-up visits in 12 months using a continuous performance test (QbTest) and investigator rating on the ADHD-RS. Qualitative comparison of change in ADHD-RS and QbTest scores over 12 months Naturalistic follow up, with medication administered according to clinician judgement of need.</td>
<td>Bonferroni-adjusted pairwise comparisons showed significant reductions in QbTest and ADHD-RS scores over the 12-month study. Both measures appear to capture symptom change over time, but weak correlations between the measures suggest that their role in medical follow-up might be complementary rather than interchangeable.</td>
</tr>
</tbody>
</table>
6. Results: Monitoring of ADHD

<table>
<thead>
<tr>
<th>Study: Author, year; Multiple publications; Design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Co-occurring disorders; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen, 1989&lt;sup&gt;397&lt;/sup&gt;</td>
<td>Randomized, double-blind, placebo-controlled crossover study of the use of monitoring ADHD symptoms – before and during treatment with methylphenidate – using the ADD-H Comprehensive Teacher Rating Scale, Conners parent rating scale, and the Gordon Diagnostic System (a computerized continuous performance task assessing vigilance and impulse control).</td>
<td>Both rating scales demonstrated significant change in symptoms (inattention and hyperactivity on the ADD-H scale; hyperactivity on the Conners scale) during treatment with methylphenidate compared with placebo, whereas the Gordon task did not demonstrate change. Rating scales, but not this continuous performance task, appear helpful in monitoring the short-term effects of stimulant treatment.</td>
<td></td>
</tr>
</tbody>
</table>
### 6. Results: Monitoring of ADHD

<table>
<thead>
<tr>
<th>Study: Author, year; Multiple publications; Design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Co-occurring disorders; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein, 2007&lt;sup&gt;259&lt;/sup&gt; ID: NA Cluster RCT Multicenter N = 377 US Setting: Primary Care</td>
<td>Target: 377 children from participating practices who met DSM-IV criteria for ADHD, stimulant-I, attending 1&lt;sup&gt;st&lt;/sup&gt; – 5&lt;sup&gt;th&lt;/sup&gt; grade 52 pediatricians (27 men, 25 women) from 12 practices; 146 randomly selected for follow-up assessments ADHD presentation: N/A Diagnosis: Confirmation by specialist Comorbidity: N/A Female: 36.3 % Age mean: 7.8 (1.5) Minimum age: 6 Maximum age: 10 Ethnicity: % Hispanic or Latino: .68 % Black/African American: 16.4 % White: 79.5 Other info on race or ethnicity:</td>
<td>12 pediatric practices were randomly assigned to receive access to collaborative consultative services or a control group. In the collaborative consultation services, pediatricians were encouraged and assisted to use rating scales for symptom monitoring and titration trials to determine optimal medication dosages. Physicians were taught to prescribe 4 different doses of methylphenidate during a titration trial (placebo, 18 mg, 36 mg, 54 mg); the order of week-long dosing was blinded but standardized across patients (week 1, 18 mg; week 2, placebo; week 3, 36 mg; week 4, 54 mg) to determine optimal dosing for each patient. Parents and teachers completed weekly behavioral ratings (Conners Global Index) &amp; side effect rating scales. Data were returned to Duke Univ psychiatrist to determine the best starting medication dose; a report describing the titration results was faxed back to pediatricians. Patients in control group practices received treatment as usual, without access to consultative services. Assessed Conners Global Index &amp; side effect rating scales.</td>
<td>Use of symptom ratings did not differ significantly by group, nor did the change in symptoms over time. Pediatrician compliance with the collaborative consultation service was poor (pediatricians for 29 of 59 patients in the consultation group received a titration trial and 13/59 participated in monthly medication monitoring). Preliminary secondary analyses indicated that those children whose pediatricians complied with titration had significantly better outcomes compared with those who did not and TAU controls (group x time P&lt;.01) Children in the collaborative consultation service–complier group had a 27% reduction in symptom scores compared with 18% reduction in the TAU controls and 13% reduction in consultation non-compliers.</td>
</tr>
</tbody>
</table>
## 6. Results: Monitoring of ADHD

<table>
<thead>
<tr>
<th>Study: Author, year; Multiple publications; Design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Co-occurring disorders; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein, 2016&lt;sup&gt;238&lt;/sup&gt; Childrens Hospital Medical Center, Cincinnati, 2010&lt;sup&gt;692&lt;/sup&gt; ID: NCT01143701 Cluster RCT Multicenter N = 577 US Setting: Primary Care</td>
<td>Target: 577 patients in grades 1 through 5, presenting for ADHD evaluation, and were ADHD medicalnaive 50 community-based pediatric primary care practices with ≥2 physicians (213 providers), uses an electronic billing system, office has Internet access, must not have co-located mental health care ADHD presentation: N/A Diagnosis: Confirmation by specialist DSM-IV by research staff Co-occurring disorders: N/A Female: 29.5 % Age mean: 7.8 (1.4) Minimum age: Maximum age: Ethnicity: Other info on race or ethnicity: Other: 36.7% were --on-white --unspecified</td>
<td>Monthly follow up with Conners and side effect rating scales for 12 months, sent to Duke U psychiatrists for interpretatin, with recommendations returned to the pediatrician</td>
<td>Cluster randomized controlled trial of either a technology-assisted quality improvement (QI) intervention or TAU control. QI intervention consisted of 4 training sessions, office flow modification, guided QI, and an ADHD Internet portal to assist with treatment monitoring versus TAU control practices Assessed intervention effects on parent- and teacher-rated ADHD severity using the Vanderbilt ADHD total symptom score. 12 months follow up</td>
</tr>
<tr>
<td>Fiks, 2017&lt;sup&gt;271&lt;/sup&gt; Childrens Hospital of Philadelphia, 2014&lt;sup&gt;693&lt;/sup&gt; ID: NCT02271386</td>
<td>Target: Children aged 5-12 years with ADHD diagnosis; children with autism spectrum disorder excluded. 105 clinicians practicing at 19 sites within a</td>
<td>Cluster-randomized open label trial at the practice level (9 intervention, 10 control sites) for 3-component quality-improvement program that employs distance learning: (1) 3 15-minute web-based</td>
<td>Differences between intervention arms were not statistically significant, though clinicians in both study arms were significantly more likely to administer and receive parent and teacher rating scales compared to an 8-</td>
</tr>
</tbody>
</table>
## 6. Results: Monitoring of ADHD

<table>
<thead>
<tr>
<th>Study: Cluster RCT</th>
<th>Population: hospital-owned primary care research network</th>
<th>Intervention: presentations on evidence-based practices for managing ADHD in primary care; (2) optional collaborative consultation with ADHD experts via a health system online networking site or private email/telephone conversation; (3) and performance feedback reports or calls every 2 months informing them of their rates of sending and receiving ADHD rating scales from parents and teachers and allowed them to compare their results to results of the entire group; feedback reports were discussed during four, 1-hour conference calls). Participation qualified for Maintenance of Certification credit from the American Board of Pediatrics. Collection of rating scales was facilitated via an electronic application linked to the electronic health record versus waitlist control</th>
<th>Results: month baseline period. Intervention clinicians who participated in at least one performance feedback call were more likely to send out parent rating scales than intervention clinicians who did not participate (relative difference of 14.2 percentage points, 95% CI: 0.6, 27.7. For all study outcomes, practices with the highest rates of clinician participation in the study (≥ 80%), were not superior to practices with lower rates of involvement (&lt; 80%). Participation was low (105 of 166 invited); 42 of 53 in the intervention group completed all 3 education presentations; 30 (57%) participated in at least one feedback call, and 19 (36%) participated in all 3 components of the intervention.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autor, year; Multiple publications; Design; Sites; Study size; Location Setting</td>
<td>Study size: N = 790</td>
<td>Minimum age: 2</td>
<td>Maximum age: 12</td>
</tr>
<tr>
<td>hospital-owned primary care research network</td>
<td>ADHD presentation: N/A</td>
<td>Diagnosis: Confirmation by specialist Diagnosis made by clinicians</td>
<td>Co-occurring disorders: N/A</td>
</tr>
<tr>
<td>Florida International University, 2010</td>
<td>Target: 23 children with ADHD with no history of chronic stimulant use</td>
<td>ADHD presentation: N/A</td>
<td>Diagnosis: Confirmation by specialist Comorbidity: N/A</td>
</tr>
</tbody>
</table>
## 6. Results: Monitoring of ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
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</thead>
<tbody>
<tr>
<td><strong>Study:</strong> Author, year; Multiple publications; Design; Sites; Study size; Location Setting</td>
<td><strong>Population:</strong> Setting; Study target; ADHD presentation; Diagnosis; Co-occurring disorders; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td><strong>Intervention:</strong> Minimum age; Maximum age; Ethnicity: Other info on race or ethnicity: N/A</td>
<td>supplementation (p&lt;0.01) and drug holidays (p&lt;0.05) increased weight velocity more than monitoring of height and weight. Over the entire study, participants declined in standardized weight (-0.44 z-units) and height (-0.20 z-units).</td>
</tr>
<tr>
<td><strong>Oppenheimer, 2019</strong>&lt;sup&gt;54&lt;/sup&gt; Boston Childrens Hospital, 2014&lt;sup&gt;678&lt;/sup&gt; ID: NCT02097355 Cluster RCT Multicenter N = 518 US Setting: Specialty care</td>
<td><strong>Target:</strong> 98 children receiving ongoing treatment for ADHD, prescribed ADHD medication, parents and children proficient in English. 88 clinicians providing ADHD care <strong>ADHD presentation:</strong> N/A <strong>Diagnosis:</strong> Confirmation by specialist Neurology department clinician at 1 of 5 locations <strong>Comorbidity:</strong> N/A <strong>Female:</strong> 24.3 % <strong>Age mean:</strong> 11 <strong>Intervention:</strong> 9.85 (3.21), control 11.09 (3.24) <strong>Minimum age:</strong> 8 <strong>Maximum age:</strong> 15 <strong>Ethnicity:</strong> % Hispanic or Latino: 5.8 % White: 78.4, Other: 406 Other info on race or ethnicity:</td>
<td><strong>Intervention:</strong> Naturalistic study of a web-based platform enabling clinicians to administer online monthly clinical questionnaires to parents and teachers for monitoring of patients remotely between visits. Trigger algorithm alerts clinicians to clinically actionable events that are documented in the medical record versus non-alert group. Patients were the unit of analysis. Parent and teacher reports of current medication, medication side effects inventory, Vanderbilt ADHD Parent Rating Scale, Clinical Global Impression-Severity (CGI-S) scale, and Clinical Global Impression-Improvement (CGI-I) scale</td>
<td>Trigger algorithms produced alerts requiring immediate review in 8% of the parent reports. Clinicians perceived 74% of alerts to be significant enough to prompt urgent follow-up with parents, suggesting a low rate of false positive alerts. Patients who generated alerts compared to those who did not had more severe ADHD symptoms (beta = 5.8, 95% CI: 3.5–8.1 [p &lt; 0.001] in the 90 days prior to an alert, further supporting validity of the alerts.</td>
</tr>
<tr>
<td><strong>Smith, 2000</strong>&lt;sup&gt;534&lt;/sup&gt; ID: N/A Cohort study Single center N = 36</td>
<td><strong>Target:</strong> 36 adolescents who completed a summer treatment program; 12 years and older; diagnosis meets DSM-III criteria; verbal IQ higher</td>
<td><strong>Intervention:</strong> assessed the reliability, validity, and unique contributions of self-reports by adolescents receiving treatment for ADHD in a summer treatment program that</td>
<td>Average reliability for the adolescent self-report across all measures was .78 (range .74-.83), similar to the reliability of .82 for counselors (range .78-.85), and significantly better than the</td>
</tr>
</tbody>
</table>
### 6. Results: Monitoring of ADHD

<table>
<thead>
<tr>
<th>Study:</th>
<th>Population:</th>
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<tbody>
<tr>
<td>Author, year; Multiple publications; Design; Sites; Study size; Location Setting</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Co-occurring disorders; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>included self-monitoring as a treatment component.</td>
<td>teacher reliability of .60 (range .51-.68). Teacher and counselor ratings on the Conners changed significantly during stimulant treatment whereas adolescent self-ratings did not. The findings suggest that adolescents can provide reliable information on their symptoms, but not beyond what parents can provide. Adolescents may also be poor sources of information about the change in ADHD symptoms, but a good source of information about improved interactions with others in response to treatment.</td>
</tr>
</tbody>
</table>

#### US

**Setting:** Specialty care

than 80; no medical conditions that precluded stimulant medication or full participation in study’s academic and physical activities

**ADHD presentation:** N/A

**Diagnosis:** Confirmation by specialist Psychologist confirmed

**Comorbidity:** N/A

**Female:** 19 %

**Age mean:** 13.4 (0.8)

1994 cohort; 14.1 (1.5) for 1995 cohort

**Minimum age:** 12

**Maximum age:**

**Ethnicity:**

Other: 6

% White: 85

Other info on race or ethnicity:

Self-reported IOWA Conners Inattention/Overactivity and Oppositional/Defiant subscales, ratings of interactions with peers and staff. Assessed changes in reliability during a placebo-controlled, cross-over study of 30 mg of methylphenidate.

Observed frequencies of negative behavior, rating from parents and teachers

#### Yang, 2012

**ID:** N/A

**Crossover trial**

**Single center**

N = 39

**Korea**

**Setting:** Other

Target: 39 children ages between ages 7-13; diagnosis meets DSM-IV criteria; capacity to communicate with investigators; current use of fixed dose osmotic-controlled release oral delivery system methylphenidate medication; exclusion of children with developmental disorders, severe medical conditions, seizure disorder; children excluded if medication was adjusted during study period

**ADHD presentation:**

inattentive : 15.4, hyperactive : 2.6, combined : 76.9

Naturalistic study of medication adherence assessed using the Medication Event Monitoring System (MEMS), a bottle cap with a microprocessor that records all instances and times that the bottle is opened

Patient self-report, clinician rating, pill count assessed; measure of adherence 8 weeks follow up

The rate of non-adherence measured by the MEMS was 46.2%, higher than patient self-report of 17.9%, clinician rating of 31.7%, and pill count of 12.8%. Pill count and MEMS concordance was 0.249 (95% CI: 0.102-0.386). Self-report and MEMS concordance was 0.237 (95% CI: -0.024-0.468). Non-adherent patients (based on the MEMS) had more severe symptoms at baseline and inferior improvement compared with adherent patients.
6. Results: Monitoring of ADHD

<table>
<thead>
<tr>
<th>Study: Author, year; Multiple publications; Design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Co-occurring disorders; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diagnosis: Confirmation by specialist Child-adolescent psychiatrists</td>
<td>Comorbidity: N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female: 10.3 %</td>
<td>Age mean: 10.44 (2.22)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minimum age: 7</td>
<td>Maximum age: 13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ethnicity: Other info on race or ethnicity: N/A</td>
<td></td>
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</tr>
</tbody>
</table>

We identified 9 studies addressing some type of monitoring strategy for ADHD. Three studies of ADHD rating scales and/or a computerized continuous performance task assessed their reliability and sensitivity to detect symptom change over time. The studies reported a relatively poor correlation between these measures over time, whether the correlations were between different raters on the same rating scale or between assessment modalities (e.g., rating scale vs computerized performance test). Both subjective assessment modalities (e.g., self-report, parent, teacher, and clinician rating scales) and more objective measurement modalities (e.g., continuous performance task) may be sensitive to clinical change in response to treatment, but one study suggested that subjective measures may be more sensitive to detecting treatment-associated changes in ADHD symptom severity and other functional outcomes.

Three studies assessed the impact on ADHD symptoms of interventions that target medication prescriber training to improve either symptom monitoring or adherence to treatment guidelines. One study assessed the impact of collaborative consultative services, and two assessed the impact of a quality improvement intervention on outcome monitoring or ADHD symptoms. Collectively, the studies showed that medication prescribers (mostly pediatricians) exhibited poor compliance in attending training programs for quality improvement in treating ADHD. Even when they did participate in those trainings, pediatrician compliance with treatment guidelines was poor, as the pediatricians rarely acquired ratings of symptom severity from either parents or, even less often, from teachers, even when the intervention increased the collection of ratings compared with waitlist controls. Moreover, pediatricians often did not prescribe stimulant medication for youth who met diagnostic criteria for ADHD, and when they did prescribe, the doses were sub-optimal, even when provided intensive advice and support services from mental health specialists. Youth whose prescribers participated in the consultative services from specialists, however, had greater reductions in ADHD symptom severity. One study assessed the validity of alerts generated by a computer algorithm based on ratings from monthly monitoring of ADHD symptom severity.
6. Results: Monitoring of ADHD

Alerts were then sent to prescribers notifying them of putatively actionable clinical events.\textsuperscript{454} Prescribers deemed the alerts to be generally valid, suggesting that computerized algorithms applied to symptom ratings combined with automated clinician alerts may have clinical utility.

One study of youth who had stimulant-induced weight loss compared the effects of (1) height and weight monitoring alone, with (2) caloric supplementation plus monitoring, and (3) medication holidays plus monitoring on the trajectory of weight gain.\textsuperscript{277} All three interventions increased weight significantly, suggesting that monitoring of height and weight during medication administration may be efficacious in attenuating stimulant-induced weight loss, though the study did not include the no-intervention control that would have been needed to prove this. Intent-to-treat analyses showed that the addition of caloric supplementation or medication holidays did not provide significant incremental benefit on attenuating weight loss when compared with monitoring alone, though per-protocol analyses suggested that the use of these additional interventions yielded significant additional benefits.

One study assessed the use of an electronic bottle cap (the Medication Event Monitoring System) for stimulant medication to monitor treatment adherence.\textsuperscript{617} Non-adherence was shown to be higher when monitored with this bottle cap compared with patient report, clinician rating, and pill count. The methods used to assess adherence correlated weakly with one another. Non-adherent patients had more severe symptoms at baseline and inferior improvement compared with adherent patients, providing evidence for the validity of the bottle cap method for monitoring adherence. If the bottle cap is considered the gold-standard, then self-reports, clinician impressions, and even pill counts would be deemed unreliable measures of medication adherence.
7. Discussion

We identified a large body of evidence contributing to the knowledge base on ADHD diagnostic tools, treatment outcomes, and monitoring strategies. We included studies dating back to 1980, marking the advent of modern diagnostic criteria for ADHD and the introduction of long-acting forms of stimulant medication. The questions addressed in our review were informed by key informants and supported by a technical expert panel. A dedicated systematic review team with content experts conducted a detailed synthesis of existing research, including over 400 studies in this systematic review.

Despite the large number of publications included, our review has limitations in its scope due, in part, to decisions about which studies to include in the review. For example, we required intervention studies to treat participants for at least four weeks to ensure that the studies assessed sustained, and not merely temporary, effects on outcomes. This decision excluded some early studies of ADHD treatment that have contributed to the development of the field. We also required studies to be either large or to report a power analysis to ensure that they were sufficiently powered to detect effects. This criterion ensured the reader would not be left guessing whether a study was either underpowered to show effects or genuinely showed the absence of evidence of an effect. This criterion, however, also excluded studies that have contributed historically to the evidence base. We furthermore limited treatment studies to youth with a clinical diagnosis of ADHD, which excluded studies that evaluated interventions in broader populations. Finally, we restricted publications to the English language, which may have excluded other important studies that have contributed to the evidence base.

Findings in Relation to the Decisional Dilemma(s)

The following text discusses findings in the context of the decisional dilemmas the review set out to address.

Diagnostic Approaches for ADHD

Studies of diagnostic approaches most commonly report sensitivity (true positive rate) and specificity (true negative rate) for a given diagnostic threshold applied to the measure being assessed. Sensitivity and specificity, however, depend on the diagnostic threshold selected, and their values are inherently a trade-off, such that varying the diagnostic threshold to increase either sensitivity or specificity reduces the other. Interpreting diagnostic performance in terms of sensitivity and specificity is therefore difficult. Investigators instead often report performance for sensitivity and specificity in terms of Receiver Operating Characteristics (ROC) curves because the Area Under the Curve (AUC) provides an overall, single index of performance that does not depend on the diagnostic threshold for the tool being assessed. AUC values range from 0.5 (corresponding to the y=x diagonal of the ROC curve, and indicating that the tool provides no information above chance for classification) to 1.0 (corresponding to the x=0 vertical line, which indicates that the test can correctly classify all participants as having ADHD, and all non-ADHD participants as not having it – a perfect test). AUC values are commonly interpreted as follows: 90 to 100 represents excellent performance; 80 to 90 is good; 70 to 80 fair; 60 to 70 poor; and 50 to 60 indicates failed performance.

Many diagnostic studies in this review aimed to distinguish ADHD youth from neurotypical controls, which is of limited clinical relevance: in clinically referred youth, most parents, teachers, and clinicians are reasonably confident that something is wrong, but they are unsure
whether the cause of their concern is ADHD. The more clinically relevant and difficult question, therefore, is how well the measures distinguish ADHD youth from youth who have other emotional and behavioral problems. Moreover, studies that simply discriminate ADHD youth from neurotypical controls cannot discern whether diagnostic performance is determined by the presence of ADHD or by the presence of any other characteristics that accompany clinical “caseness”, such as the presence of comorbid illnesses or effects of chronic stress or current or past treatment.

AUCs for parent rating scales ranged widely from “poor”\(^{335}\) to excellent,\(^{620}\) with a low strength of evidence (SoE) due to imprecision and inconsistency. Only one study reported inter-rater reliability (between mothers and fathers), with an intraclass correlation coefficient of 0.51 for inattention, 0.56 for hyperactivity, and 0.58 for impulsivity, indicating moderate inter-rater reliability. Internal consistency for rating scale items was generally high across most rating scales.

AUCs for teacher rating scales ranged from “failed performance” (distinguishing ADHD from other patients\(^{480}\)) to “good” (distinguishing ADHD from healthy controls or from patients with reading disability\(^{352}\)) to “excellent” (distinguishing ADHD from typically developing controls),\(^{455}\) again with a low SoE due to imprecision and consistency. The internal consistency for scale items was generally high. Teacher ratings demonstrated very low inter-rater reliability with the corresponding parent rating scales, suggesting either a problem with the instruments or a large variability in symptom presentation that depended on environmental context (home or school). Clinicians likely need ratings from both parents and teachers to yield a more complete representation of symptom expression across informants or settings. We found only two studies, however, that formally combined ratings from parents and teachers to diagnose ADHD, with one study reporting poor specificity (35.7 per cent with associated sensitivity of 83.5 per cent) when using the Conners to distinguish ADHD from other clinically referred youth,\(^{17}\) and a machine learning study reporting a diagnostic accuracy of 0.93 when using the BRIEF to distinguish ADHD youth from typically developing controls.\(^{455}\)

Though data are limited, self-reports from youth seem to perform less well than corresponding parent and teacher reports, with AUCs ranging from 0.56 (“fail” for CBCL/ASEBA distinguishing ADHD from other patients\(^{480}\)) to 0.71 (“fair” for the SWAN distinguishing ADHD from community controls).\(^{176, 297}\)

Studies employing combined approaches, such as integrating diagnostic aids with clinician impressions, were limited. One study reported increased sensitivity and specificity when an initial clinician diagnosis was combined with an EEG biomarker for that patient (the reference standard was a consensus diagnosis from a panel of ADHD experts).\(^{26}\) These findings were not independently replicated, and no test-retest reliability was reported.

AUCs for all biomarkers ranged from 0.68 (serum miRNAs)\(^{623}\) to 1.00 (erythropoietin and erythropoietin receptors levels)\(^{307}\) but with a low SoE. None have been independently replicated, and no test-retest reliability was reported.

**Diagnostic Accuracy for Youth Younger than 7 Years of Age**

We found only a small number of studies in youth younger than 7 year of age (Table 3).\(^{175, 193, 326, 402, 406, 455}\) Only three of the studies assessed the performance of rating scales: the CBCL ADHD Problems Scale to distinguish ADHD (co-occurring with a disruptive behavior disorder) from a disruptive behavior disorder alone (“good” AUC 0.83);\(^{175}\) or the total score for the Disruptive Behavior Diagnostic Observation Schedule to distinguish ADHD (with or without a
comorbid disruptive behavior disorder) from typically developing youth ("good" AUC 0.81); or the BRIEF to distinguish ADHD from typically developing controls (average diagnostic accuracy of 0.93). The other studies assessed imaging or EEG measures, with AUCs ranging from fair to excellent. The findings provide very little evidence for the utility of any diagnostic approach in youth younger than age 7, though the two studies of rating scales suggest that performance may be comparable to performance of similar scales in youth older than 7.

**Comparative diagnostic accuracy of EEG, imaging, or executive function measures for youth aged 7 through 17**

Most studies used machine learning for classification based on EEG measures. AUCs ranged from 0.63 to 0.97. SoE is low due to large variations in diagnostic performance across studies, and often the methods for classification were not well described. The ICC for the Theta/Beta ratio, based on repeated measures on two different visits, was 0.83.

AUCs ranged from “poor” for distinguishing ADHD youth without co-occurring disorders from healthy controls to “excellent” for distinguishing ADHD youth from healthy controls in the neuroimaging studies. Most studies relied on machine learning to develop the diagnostic algorithms, and none assessed test-retest reliability or the independent reproducibility of findings.

Many machine learning studies have been reported to date. Machine learning has usually been applied retrospectively to pre-existing datasets or repositories. AUCs generally were not reported for machine learning studies. Using EEG data, sensitivity ranged from 80 percent (with a corresponding specificity of 80%) to 98 percent (with a corresponding specificity of 92% or 99%). Using MRI data, sensitivity ranged from 61 percent (with a corresponding specificity of 68%) to 99 percent (with a corresponding specificity of 99%). Most studies attempted to discriminate ADHD youth from healthy controls retrospectively in pre-existing datasets, not from other clinical populations and not prospectively. In addition, reporting of final mathematical models or algorithms differentiating the diagnostic groups was limited. The overall SoE is low.

Most of the EEG and imaging studies have employed leave-one-out cross validation and have rarely assessed performance in independent samples not contributing to generation of the diagnostic algorithm -- a serious overall weakness. No independent replication studies using the same marker/measure have been conducted, and very few have assessed test-retest or inter-rater reliability. No clinical effectiveness studies have been performed using these measures or diagnostic algorithms in the real world. Thus, biomarker, EEG, imaging, and machine learning algorithms do not seem remotely close to being ready for clinical application.

Studies evaluating neuropsychological tests yielded AUCs ranging from “poor” to “excellent”, with a low SoE due to imprecision and inconsistency. Many studies used idiosyncratic combinations of cognitive measures, including various measures from continuous performance tests (e.g. errors of omission, errors of commission, response time, response time variability, and detectability) to differentiate ADHD from control participants. These idiosyncratic measures make the results of meta-analyses difficult to interpret. Extracting specific, comparable measures of inattention and impulsivity from CPTs yielded only fair diagnostic performance. Only one diagnostic study assessed test-retest reliability, which was poor. No studies provided an independent replication of diagnosis using the same measure. SoE for CPT measures is low due to imprecision. Thus, despite the widespread use of neuropsychological testing in the evaluation of youth suspected as having ADHD, often at
considerable expense, the performance of neuropsychological test measures in the diagnosis of ADHD is comparable to the diagnostic performance of ADHD rating scales from a single informant, and the overall SOE for estimates of that diagnostic performance is low. Moreover, in head-to-head comparisons, the diagnostic accuracy of parent rating scales is typically better than neuropsychological test measures.\textsuperscript{455, 712}

**Variation in Diagnostic Accuracy by Clinical Setting or Patient Subgroup**

We did not identify studies that directly compared diagnostic accuracy in head-to-head comparisons across different clinical settings. Instead, we had to compare performance indirectly, across studies. In addition, the reporting of diagnostic accuracy data was limited, and therefore analyses had to be performed on estimates as reported by the original authors, precluding meta-analytic modeling. Indirect comparisons nevertheless indicated that the setting is an effect modifier for diagnostic performance. The range of reported diagnostic sensitivities (with a mode at 80\%) was much narrower in community settings, indicating that the detection of true positive cases was more consistent across studies in the community when compared to clinical settings, perhaps because ADHD youth identified in community samples are much less complex in their presentations than those presenting in clinical settings. We also found that the population appeared to modify diagnostic performance, in that specificity (the rate of identifying true negatives) was significantly lower when discriminating ADHD youth from neurotypical developing youth. A lower true negative rate indicated that clinically identified youth who did not have ADHD were mistakenly diagnosed as having ADHD, likely because they had symptoms or other non-specific aspects of clinical “caseness” that were confused with those of ADHD. Thus, the diagnostic group being differentiated from ADHD – whether it is a neurotypical “healthy” control, or youth who have a different emotional/behavioral/psychiatric disorder -- has a critical role in diagnostic performance. We found some indication that diagnostic performance was better for youth who were older compared with younger than 7 years of age (Figure 9), but effects were not statistically significant. Hence we analyzed studies of mixed samples together and reported on the diagnostic performance by diagnostic test modality, rather than by age group, and reported on the diagnostic performance by diagnostic test modality rather than by age group.

**Adverse Effects of Being Labeled Correctly or Incorrectly as Having ADHD**

We did not identify any study that addressed the consequence of correctly or incorrectly receiving a diagnosis of ADHD.

**Safety and Effectiveness of Pharmacologic and Nonpharmacologic Treatments**

Analyses that included studies of all therapeutic interventions, regardless of treatment modality, provided strong evidence for the significant efficacy of treatments in improving ADHD outcomes. We conducted extensive analyses to understand which classes of interventions produced significant therapeutic responses in various clinical outcome domains. We can compare the magnitude of those therapeutic responses (effect sizes) across interventions, as well as within and across outcome measures, using the Standardized Mean Difference (SMD) for the active
compared with control intervention. SMD values of 0.2 to 0.5 are considered small, 0.5 to 0.8 medium, and above 0.8 are large. We will use the descriptive terms in summarizing the magnitude of treatment responses here, but the precise numerical values can be found in the Results section.

Numerous classes of intervention yielded significant effects on measures of ADHD symptom severity. These included: FDA-approved medications collectively; psychosocial treatment; neurofeedback; nutrition or supplements; school interventions; and parent support. All had medium effect sizes, except small effects were observed for psychosocial interventions, parent support, neurofeedback, and nutrition and supplements. The SoE for effects on ADHD symptoms is high for FDA-approved medications; moderate for psychosocial interventions, neurofeedback, parent support, and school interventions; and low for nutritional interventions. We note that many of the studies for psychosocial interventions and parent support compared the active intervention against either wait list controls, treatment as usual, or another passive intervention group, and therefore they did not adequately control for the effects of parent or therapist attention and other non-specific effects of therapy. Other studies compared the active intervention against one that did not adequately blind either participants or study assessors to the treatments and hypotheses. These limitations in study design considerably undermines the SOE for psychosocial and parent interventions. Similar considerations limit the SOE for studies of neurofeedback and nutrition and supplements.

For broadband measures, FDA-approved medications collectively yielded significant, medium-sized effects, parent support had significant small effects across four studies (low SOE), and cognitive training had medium effects across three studies (low SOE). For disruptive behaviors, only nutrition or supplements yielded significant but small effects across four different supplements (low SOE). For functional impairments, only FDA-approved medications collectively yielded significant effects that were medium-sized. No treatment modality yielded significant effects on academic performance, though only nine studies (3 psychological, 1 stimulant, 1 combined psychological plus stimulant, and 4 school interventions) assessed this as a treatment outcome, with all individual studies yielding nonsignificant improvements of small effect size. We found only two studies for the effects of exercise, and two for the effects of complementary and alternative medicines, that met our inclusion criteria, and they did not yield significant improvement in any ADHD outcome domain. Thus, the large number of studies combined with their medium-to-large effect sizes allow us to conclude with a high SOE that FDA-approved medications collectively improve ADHD clinical outcomes in all domains we assessed – in ADHD symptom severity, broadband measures, disruptive problem behaviors, and functional impairment. Only one study assessed the effectiveness of an FDA-approved medication in improving academic performance, and it reported large, significant, and positive effects.

We also found benefits from more specific medication classes. Stimulant medications, for example, significantly improved broadband scale scores with medium effect sizes, with comparable effects for amphetamine and methylphenidate derivatives, though amphetamines yielded much more variable effects across studies. Only one study included children younger than six years of age. Similarly, stimulants significantly improved ADHD symptoms, with modest but homogeneous effects across methylphenidate studies and large but highly variable effects across amphetamine studies. Stimulants significantly improved functional impairment, with large effect sizes. A newer stimulant medication, modafinil, produced significant
improvement in ADHD symptoms in each of four studies, though in aggregate the improvement was not statistically significant, due to effect size heterogeneity.

*Non-stimulant medications* collectively yielded significant improvements in ADHD symptom scores with a medium effect size; similar effect sizes were observed separately for the SNRIs and alpha agonists compared with placebo. Non-stimulants also improved broadband scale scores, with similar effects observed for the SNRI subclass. Only one study included children younger than six years old. Non-stimulants reduced functional impairment with a significant but small effect size, and comparable effects observed for SNRIs alone (the effects of alpha agonists could not be assessed).

Medication therapies reported substantially more adverse events than did the other interventions, including appetite suppression, with a high SoE. Stimulants were associated with an increased reporting of adverse events compared with placebo, with a similar but nonsignificant effect of methylphenidate and a similar though significant effect of amphetamines on adverse events. Stimulants were associated with appetite suppression compared to placebo, with somewhat smaller effects for methylphenidate than for amphetamines. Modafinil significantly suppressed appetite, with very large effect sizes. Non-stimulants compared with placebo were associated with an increased number of participants reporting adverse events, with comparable rates in SNRI studies and alpha agonists. Non-stimulants were also associated with suppressed appetite compared to placebo, with significant appetite suppression from SNRIs but much weaker and non-significant effects from alpha agonists.

The most common head-to-head comparison between two alternative medication treatments was atomoxetine vs methylphenidate, which did not detect significant differences in effects on ADHD symptoms, broadband measures, behavioral problems, functional impairment, appetite suppression, or the number of patients experiencing adverse events, though the direction of effects consistently favored methylphenidate. Indirect comparison of studies evaluating stimulants and non-stimulants compared to control groups, however, showed larger reported effect sizes for stimulants providing much greater improvement for ADHD symptoms and functional impairment, while effect sizes for broadband measures and appetite suppression were comparable. We did not identify head-to-head comparisons of SNRIs versus alpha agonists that met eligibility criteria.

We found no evidence that interventions are better when delivered in combination than as monotherapies. Furthermore, our findings suggest that combined medication and behavioral therapies do not improve ADHD symptoms better than either medication or behavioral therapy alone. We note, however, that these analyses do not consider the possibility that exact sequencing of psychological and medication therapies may produce differential effects on outcomes.

### Variation in Outcomes by Clinical Presentation

We found little evidence that treatment outcomes varied by ADHD presentation.

### Risk of Medication Diversion

We found only one study that assessed the risk of medication diversion in the treatment of ADHD. It was a double-blind RCT comparing stimulant plus CBT vs placebo plus CBT in treating adolescents who had ADHD with comorbid substance use disorder (SUD). The stimulant arm had twice the self-reported rate of diversion than the placebo arm which, though
7. Discussion

not statistically significant, suggests that further studies of diversion and stimulant misuse is warranted, particularly in ADHD youth with SUD. Caution is indicated when prescribing stimulants to ADHD youth who have comorbid SUD.

ADHD Monitoring

We identified only nine studies pertaining to the assessment of monitoring strategies for ADHD outcomes.

Several of the studies indicated that monitoring measures correlated poorly over time, whether the correlations were between different raters using the same rating scale or between different assessment modalities (e.g., rating scale with computerized performance test). These findings suggest that assessment modalities may be more complementary than interchangeable, and that more than a single assessment modality may be required for comprehensive and effective monitoring of ADHD outcomes. One study suggested that subjective outcome measures, such as rating scales, may be more sensitive than more objective measures, such as the continuous performance task, for detecting treatment-induced changes in ADHD.

Three studies assessed the effects on ADHD symptoms of interventions that train pediatricians to improve either their symptom monitoring or their adherence to treatment guidelines. Despite very extensive training efforts, and even when expert support and consultation was available, pediatricians exhibited poor compliance in attending training programs for treating ADHD, and even when they did attend, pediatrician compliance with treatment guidelines was poor, both in terms of monitoring treatment response and in following dosing guidelines. Use of expert consultative services and compliance with recommendations was poor.

One study suggested that monitoring height and weight, combined with either medication holidays or caloric supplementation, may be helpful for attenuating stimulant-associated weight loss but not slowing of height velocity. Another study suggested that use of an electronic bottle cap may be more accurate and valid than patient reports, clinician impression, or pill counts for monitoring of medication adherence.

Findings in Relation to Existing Research Syntheses and Practice Guidelines

The conclusions and clinical recommendations of this review are generally consistent with those of the two prior AHRQ reviews on ADHD. The key questions of the 2011 review focused primarily on long-term (> 1 year) treatment effectiveness and adverse effects, whereas the three key questions of the 2018 review were nearly identical to ours. The 2018 review served as an important resource for development of the 2019 clinical practice guidelines for the evaluation and treatment of ADHD from the American Academy of Pediatrics (AAP), which in turn was the primary source for the recommendations from the US Center for Disease Control for the diagnosis and treatment of ADHD.

Our findings for diagnostic tools suggest that the clinical diagnosis of ADHD likely benefits from ratings of ADHD symptoms from multiple informants, which is consistent with the AAP guidelines that advise documentation of symptoms and impairment in more than one setting (such as home and school), with information obtained from parents, school personnel, and mental health clinicians. To these informants we would add that inquiring about symptoms from
7. Discussion

both parents, and directly from the youth, can also be helpful. The 2018 review did not assess the
diagnostic performance of ADHD rating scales. That review concluded, however, that brain
imaging and EEG had insufficient evidence to support their use as diagnostic tools, consistent
with our conclusions, and despite the FDA approval of one EEG measure as a purported
diagnostic aid.25, 26 To those conclusions we add that neuropsychological tests (including
measures from continuous performance tests) and blood biomarkers also do not yet have
sufficient evidence to serve as diagnostic tools.

Our treatment findings concluded that FDA-approved stimulant and non-stimulant
medications had the greatest strength of evidence across all interventions for significantly
improving ADHD symptoms and other outcomes. Thirty-five papers that met criteria for
inclusion in the current review assessed treatment effectiveness for more than a year, which was
the focus of the 2011 review. That 2011 review concluded with a low SOE that methylphenidate
and atomoxetine were both effective long-term, though the average effect sizes after a year were
somewhat lower than those for the short-term studies included in the present review. The 2018
review did not restrict the time frame for treatment, but nevertheless found insufficient evidence
to modify conclusions for the effectiveness of FDA-approved medications. The present review
adds to these prior reviews by providing mean effect sizes for comparisons of FDA-approved
medication with placebo on improving not only ADHD symptoms, but a range of other
important outcomes as well, at least for short-term outcomes. The current review also provided
showed that stimulant and non-stimulant medications yielded comparable effects on most
effectiveness outcomes when these medications were compared head-to-head, though the overall
direction of effects across all outcomes tended to favor stimulant medications. Clinical
guidelines advise starting treatment for youth older than 6 years of age with FDA-approved
medications, which the findings of this review support.

The current review did not find that combination therapies of medication plus psychosocial
therapies produce better results than medication alone. Moreover, we found that the effect sizes
for parent therapies tended to be smaller than those for other interventions in improving ADHD
outcomes. The 2011 review found larger effect sizes than we found for parent training for
preschool youth with ADHD or disruptive behavioral disorders, but the prior review included
many studies that did not meet criteria for inclusion in our review. The 2018 review also found
that parent training improved ADHD symptoms, though did not provide a mean effect size.
Neither of the prior reviews assessed the effectiveness of combination treatment. The AAP
clinical guidelines for preschool children advise treatment with parent training and/or classroom
behavioral interventions as the first line of treatment, if available. These recommendations
remain supported by the present review, particularly given the paucity of prior medication
studies for preschool children. The guidelines also recommend the combination of parent
training, classroom interventions, or behavioral interventions with medication therapy for older
youth with ADHD, though no evidence suggests that this combination of therapies is better than
monotherapy, and some evidence from head-to-head comparison studies suggests that the
combination is not better than monotherapy.

The 2018 review found some evidence that cognitive training, and insufficient evidence that
neurofeedback, improve ADHD symptoms. We found low SoE that cognitive training does not
improve ADHD symptoms, and moderate SOE that neurofeedback does. Clinical guidelines do
not currently recommend neurofeedback as a second line treatment, but should consider doing
so. We also found, with low SOE, that nutritional supplements and dietary interventions improve
ADHD symptoms and problem behaviors. The SOE for nutritional interventions is still too low to recommend their routine use.

The 2018 review found no papers pertaining to the assessment of monitoring strategies for youth with ADHD, whereas our current review identified 9 such papers. The APA and CDC clinical guidelines do not include recommendations for monitoring strategies.

Implications

ADHD treatment guidelines should educate clinicians on the complementary nature of rating scales from multiple informants – from both parents if possible and from teachers, and even from the youth as well – since the scores tend to correlate poorly with one another and because ADHD symptom in the same child can vary across settings. No single informant is a gold-standard. Multiple informants will provide a more complete clinical picture for how symptoms are expressed and perceived in different settings, and they will accordingly inform clinical judgement when making a diagnosis. Similarly, neuropsychological test measures of executive functioning, such as the CPT, may help inform a clinical diagnosis, but they are not definitive either in ruling in or ruling out a diagnosis of ADHD. Rating scales and neuropsychological tests are more helpful in diagnosis when the clinical question is whether a youth has ADHD or is healthy, rather than when the clinical question is whether a youth had ADHD or another mental health or behavioral problem, which tends to incorrectly identify youth with other clinical conditions as having ADHD. Biomarkers, EEG, and MRI are not yet close to being ready to aid clinical diagnosis. Ultimately, a valid and reliable diagnosis of ADHD requires the judgement of a clinician who is experienced in the evaluation of youth with and without ADHD, with the aid of standardized rating scales and input from multiple informants across multiple settings, including parents, teachers, and the youth themselves.

An increasing number of treatment modalities have been shown to significantly improve ADHD symptoms, and with comparable effect sizes when delivered as monotherapies. These include stimulant medications (methylphenidate and amphetamine), non-stimulant medications (particularly the SNRIs atomoxetine and viloxazine, as well as the alpha agonists clonidine and guanfacine), individual psychosocial treatments, neurofeedback, nutritional interventions, and school interventions (often combined with parent training). Psychosocial interventions, parent support, neurofeedback, and nutrition and supplements may exert considerably weaker effects on ADHD symptoms than the other interventions. Strength of evidence is high for medications and moderate for the other treatment modalities. The absence of head-to-head studies comparing the effectiveness of these monotherapies precludes recommendations regarding which is most likely to be helpful and should be tried first. Stimulant and SNRI medications, separately and in head-to-head comparisons, have shown effectiveness and similar rates of side effects, including appetite suppression. The combination of treatment modalities, including combined medication plus psychosocial therapy, has minimal evidence for improving ADHD outcomes, and in fact a moderate strength of evidence indicates that combined therapy is no better than monotherapy. Treatment guidelines that recommend combination therapy should consider that successful combinations showing clear superiority still need to be explored and identified. A further finding of this review with clinical implications is that only FDA-approved medications have been shown to significantly improve broadband symptoms and functional impairment.

Findings from studies that attempted to train pediatricians in better adherence to ADHD monitoring and treatment guidelines suggest that training established pediatricians to adhere more closely to the guidelines does not work and that either much stronger incentives are needed
7. Discussion

for established pediatricians (such as including training and demonstrated compliance in criteria for maintenance of board certification), or else demonstrable guideline adherence should be included in pediatric residency training programs.

Strengths and Limitations

A major strength of this review is its inclusiveness, incorporating publications from 1980 and yielding more than 400 separate studies that informed our findings. Other strengths include: a review of evidence for the utility of biomarkers, EEG, and neuroimaging measures in the diagnosis of ADHD; parsing of non-pharmacological therapies by the target of the therapy (the youth, parent, or school); and the parsing of ADHD outcome measures to provide more clarity on the functional domains that treatments affect.

Space limitations precluded a more detailed parsing of putative diagnostic tools (such as similar rating scales or specific domains of cognitive functioning) and medication classes across the large number of available treatments. Those finer-grained analyses will be the subject of future publications. Moreover, despite the large number of included studies, we restricted this review to studies that reported on children with a clinically confirmed diagnosis of ADHD, excluding studies with broader samples (such as evaluations of psychosocial programs that were not specific to youth with a clinical diagnosis). In addition, although studies of children of all ages were eligible for inclusion in the report, the number of studies exclusively addressing younger children with ADHD were relatively few. The median minimum age in included studies was six years old. Samples were predominantly male, and the median number of girls included in the studies was only 25 percent. Furthermore, smaller studies were not included unless they demonstrated a power analysis, which may have excluded more smaller studies of more intensive treatments. We also excluded studies documenting very short-term treatment effects by requiring studies to report on a minimum treatment duration of four weeks. This requirement may have excluded relevant brief interventions, or very intense psychosocial interventions delivered in a short time period. Furthermore, this synthesis was focused on outcomes selected with the help of an expert panel, and it should be noted that individual interventions may show effects on other outcomes. Finally, despite a very comprehensive search, few monitoring studies were available to inform this report.

Future Research

One of the most important potential uses of this systematic review would be the identification of effect modifiers for both the performance of diagnostic tools and therapeutic interventions – for example, determining whether a diagnostic tool performs better or worse, or a treatment is more or less effective, in one patient subgroup than another (KQ1c and KQ2a), such as in younger or older patients, in ethnic minorities, in those experiencing material hardship, in patients with a comorbid illness, or in those with a specific ADHD presentation. These analyses are essential for improving clinical assessments and treatment planning. Because studies did not compare effects in direct, head-to-head comparisons, we had to explore modifiers indirectly, across studies. Future studies of ADHD should more systematically address the modifier effects of these patient characteristics. Much more research is needed in the use of diagnostic tools, effectiveness of medication and other therapies, and monitoring strategies in preschool youth who have ADHD.
Future Research on ADHD Diagnosis

Future studies of diagnostic tools should include assessment of how well the tools distinguish ADHD youth not simply from typically developing youth, but especially from youth who have other emotional and behavioral problems. They should also assess the potential adverse consequences of youth being incorrectly diagnosed with or without ADHD. Research is needed to identify consensus algorithms that combine rating scale data from multiple informants to improve the clinical diagnosis of ADHD, which at present is unguided, ad hoc, and suboptimal.

Despite the theoretical promise and a large number of prior studies of the use of continuous performance tests, EEG, or imaging to diagnose ADHD, conclusions about these potential diagnostic tools was severely limited by the use of different diagnostic measures within each test modality, differing diagnostic thresholds applied to those measures across studies, and differing algorithms that combine those variables to reach a diagnostic decision, and the frequent failure to clearly report those study elements in the publication. Therefore, to support future efforts at synthetic analyses, diagnostic studies should report sufficient detail of their measures and diagnostic algorithms -- precise operational definitions and measurements of the variable(s) used for diagnosis, any diagnostic algorithm employed, the chosen statistical cut-offs, and the number of false positives and false negatives the diagnostic tool yields.

Studies of diagnostic tools should include ROC analyses to support comparison of test performance across studies that are independent of diagnostic threshold for the tool. Studies should also include assessment of test-retest reliability to help discern whether variability in measures and test performance across settings is a function of setting or is a consequence of measurement variability across time. Future studies should address the role of co-occurring disorders in the diagnostic process and their influences on their performance of the diagnostic tools. In addition, more studies are needed that compare the diagnostic accuracy of different test modalities head-to-head.

Making available in public repositories the raw, individual-level data, as well as the algorithms or computer code, for diagnostic tools is important to aid future efforts at replication, synthesis, and new discovery. Independent replication of performance measures of diagnostic tools in real-world settings is essential prior to FDA approval and before recommendations for widespread clinical use.

Finally, the "diagnostic tests" that are most often used clinically, usually at considerable financial expense, are neuropsychological measures of "executive functioning". These include, among others, measures of working memory and errors of omission on continuous performance tests (thought to represent the clinical construct of inattention) and measures of impulsive responding on continuous performance tests (thought to represent the clinical construct of impulsivity). These and other objective, quantitative neuropsychological test measures of executive functioning notoriously correlate only weakly with the clinical constructs of inattention, impulsivity, and hyperactivity that are based on observation of real-world behavior and that define ADHD.181 Many youth with ADHD have normal executive functioning profiles on neuropsychological testing, and many who have impaired executive functioning on neuropsychological tests do not have ADHD.1169 A major open question for future research is how these two constructs -- neuropsychological test measures of executive functioning and the real-world functional problems that define ADHD -- map on to one another, and how the correspondence of that mapping can be improved.
Future Research on ADHD Treatment

More trials are needed that compare alternative interventions head-to-head or that compare combination treatments with monotherapy. Future studies of psychosocial and parent interventions should employ study designs that support more valid causal inferences and higher SOE for the effectiveness of the interventions assessed, including active attention comparator conditions and effective blinding of participants and assessors to study interventions and hypotheses. More and higher quality studies with independent replication are needed to assess the effectiveness of individual complementary and alternative therapies, as well as exercise. Much more research is needed to assess long-term treatment compliance, treatment effectiveness across a wide array of interventions and outcomes, medication diversion, and adverse effects associated with treatment.

Studies evaluating ADHD interventions should address the role of patient characteristics as modifiers of treatment effects. This effort will help to identify which treatments are most effective for which patients, to aid in the development of personalized treatments for youth with ADHD. To aid discovery and confirmation of these modifiers, future treatment studies should make publicly available all individual-level demographic, clinical, treatment, and all available outcome data (not only the primary outcomes), together with a detailed data dictionary. Patient-centered outcomes that assess functional domains other than ADHD symptoms, such as functional impairment and academic performance, should be acquired in clinical trials and shared publicly.

Future Research on ADHD Monitoring

Much more research is needed that compares the utility of various strategies for monitoring treatment and outcomes in ADHD youth. The temporal stability of outcome measures and their sensitivity to change in response to treatment should be assessed. Future synthetic studies should consider reviewing studies of long-term outcomes in ADHD youth, even if not in the context of comparing monitoring strategies, as the findings will be of interest to patients, parents, and clinicians and will critically inform treatment decisions.

Applicability

Several included studies reported multiple exclusions for eligible participants, which limited the generalizability of findings. Diagnostic performance, as well as treatment effects in clinical practice, may not translate from the favorable effects shown in the documented research to real world practice.
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References


Abbreviations and Acronyms
### Abbreviations and Acronyms

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<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>AAP</td>
<td>American Academy of Pediatrics</td>
</tr>
<tr>
<td>ACAC</td>
<td>Association for Child and Adolescent Counseling</td>
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<tr>
<td>ADD-H</td>
<td>attention deficit disorder with hyperactivity</td>
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<td>ADHD</td>
<td>Attention-Deficit/Hyperactivity Disorder</td>
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<tr>
<td>ADHD-RS-IV</td>
<td>ADHD Rating Scale Version IV</td>
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<td>AHDD</td>
<td>attention hyperactivity deficit disorder</td>
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<td>AHRQ</td>
<td>Agency for Healthcare Research and Quality</td>
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<td>APA</td>
<td>American Psychological Association</td>
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<td>ASD</td>
<td>autism spectrum disorder</td>
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<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
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<td>BASC-2</td>
<td>Behavior Assessment System for Children, Second Edition</td>
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<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>BRIEF2</td>
<td>Behavior Rating Inventory of Executive Function, Second Edition</td>
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<tr>
<td>CAM</td>
<td>complementary, alternative, or integrative medicine</td>
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<td>CBCL</td>
<td>Child Behavior Checklist</td>
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<td>CBT</td>
<td>Cognitive-behavioral therapy</td>
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<td>CHADD</td>
<td>Children and Adults with ADHD</td>
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<td>CHAOS</td>
<td>Conduct-Hyperactive-Attention Problem-Oppositional Symptom</td>
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<tr>
<td>CGI</td>
<td>Clinical Global Impression</td>
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<td>CGI-I</td>
<td>Clinical Global Impression-Improvement</td>
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<tr>
<td>CGI-S</td>
<td>Clinical Global Impression-Severity</td>
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<td>CI</td>
<td>Confidence Intervals</td>
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<td>CNS</td>
<td>Central nervous system</td>
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<td>CPRS</td>
<td>Conners Parent Rating Scale</td>
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<td>CPT</td>
<td>Continuous Performance Test</td>
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<td>DASH</td>
<td>Dietary Approaches to Stop Hypertension</td>
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<tr>
<td>DBDRS</td>
<td>Disruptive Behavior Disorder Ratings Scale</td>
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<td>DHA</td>
<td>Docosahexaenoic acid</td>
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<td>DIPA-L</td>
<td>Diagnostic Infant and Preschool Assessment, Likert version</td>
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<td>DS-ADHD</td>
<td>diagnosis-supported attention deficit hyperactivity disorder</td>
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<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
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<td>DSM-III</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, Third Edition</td>
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<tr>
<td>DSM-5</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition</td>
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<tr>
<td>EEG</td>
<td>electroencephalogram / electroencephalography</td>
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<td>e.g.</td>
<td>exempli gratia</td>
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<td>EHC</td>
<td>Effective Health Care</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>EKG</td>
<td>electrocardiogram</td>
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<tr>
<td>EPA</td>
<td>Eicosapentaenoic acid</td>
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<tr>
<td>EPC</td>
<td>Evidence-based Practice Center</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GPA</td>
<td>Grade Point Average</td>
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<tr>
<td>GRADE</td>
<td>Grading of Recommendations Assessment, Development and Evaluation</td>
</tr>
<tr>
<td>GIRK</td>
<td>G protein-coupled inward-rectifying potassium channel</td>
</tr>
<tr>
<td>ICC</td>
<td>Intraclass Correlation Coefficient</td>
</tr>
<tr>
<td>ICD-11</td>
<td>International Classification of Diseases, Eleventh Edition</td>
</tr>
<tr>
<td>ID</td>
<td>identification</td>
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<tr>
<td>IQ</td>
<td>Intelligence quotient</td>
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<tr>
<td>KQ1</td>
<td>Key Question 1</td>
</tr>
<tr>
<td>KQ2</td>
<td>Key Question 2</td>
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<tr>
<td>KQ3</td>
<td>Key Question 3</td>
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<tr>
<td>MEMS</td>
<td>Medication Event Monitoring System</td>
</tr>
<tr>
<td>mg</td>
<td>milligram</td>
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<tr>
<td>MPH</td>
<td>Methylphenidate</td>
</tr>
<tr>
<td>MTA</td>
<td>Multimodal Treatment Study of Children with ADHD</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>N</td>
<td>Sample size</td>
</tr>
<tr>
<td>N/A</td>
<td>Not applicable</td>
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<tr>
<td>ODD</td>
<td>oppositional defiant disorder</td>
</tr>
<tr>
<td>OROS</td>
<td>osmotic-release oral system</td>
</tr>
<tr>
<td>p</td>
<td>probability</td>
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<tr>
<td>PCORI</td>
<td>Patient-Centered Outcomes Research Institute</td>
</tr>
<tr>
<td>PICOTSO</td>
<td>Population, Intervention, Comparator, Outcome, Timing, Setting, Study Design, and Other limiters</td>
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<tr>
<td>PSC</td>
<td>The Pediatric Symptom Checklist</td>
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<tr>
<td>QbTest</td>
<td>continuous performance test</td>
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<tr>
<td>QI</td>
<td>quality improvement</td>
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<tr>
<td>QUADAS 2</td>
<td>Quality Assessment of Diagnostic Accuracy Studies</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<td>RoB 2</td>
<td>Risk-of-Bias tool for randomized trials, version 2</td>
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<tr>
<td>RTI-B</td>
<td>Response to Intervention – Behavioral</td>
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<tr>
<td>RR</td>
<td>Relative Risks</td>
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<tr>
<td>SEADS</td>
<td>Submit Supplemental Evidence and Data for Systematic Reviews</td>
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<tr>
<td>SMART</td>
<td>Sequential Multiple Assignment Randomized Trial</td>
</tr>
<tr>
<td>SMD</td>
<td>standardized mean differences</td>
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### Abbreviations and Acronyms

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<th>Description</th>
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<tr>
<td>SNAP-IV</td>
<td>Swanson, Nolan, and Pelham (SNAP) Questionnaire</td>
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<tr>
<td>SNRI</td>
<td>Serotonin and norepinephrine reuptake inhibitor</td>
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<tr>
<td>SoE</td>
<td>strength of evidence</td>
</tr>
<tr>
<td>SPN-812</td>
<td>viloxazine extended release</td>
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<tr>
<td>SRDR</td>
<td>Systematic Review Data Repository</td>
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<tr>
<td>SUD</td>
<td>substance use disorder</td>
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<tr>
<td>SWAN</td>
<td>Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scale</td>
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<tr>
<td>TAU</td>
<td>Treatment-as-usual</td>
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<tr>
<td>TEP</td>
<td>Technical Expert Panel</td>
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<tr>
<td>TOO</td>
<td>Task Order Officer</td>
</tr>
<tr>
<td>TRF</td>
<td>Teacher Report Form</td>
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<tr>
<td>UK</td>
<td>United Kingdom</td>
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<tr>
<td>US</td>
<td>United States</td>
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Appendix A. Methods

Search Strategies

Search Strategy KQ1

PubMed
1 "Attention Deficit Disorder with Hyperactivity"[Mesh] OR "attention deficit hyperactivity disorder"[tiab] OR "ADHD"[tiab] OR "attention deficit disorder"[tiab]
Appendix A. Methods

6 animals[mh]
7 humans[mh]
8 English[la]
9 #1 AND #2 AND #3 AND #4 NOT #5 NOT #6 NOT #7 AND #8
PUBLICATION DATE RANGE: 2016 to Jan 2023

KQ #2

PubMed
1 "Attention Deficit Disorder with Hyperactivity"[Mesh] OR "attention deficit hyperactivity disorder"[tiab] OR "ADHD"[tiab] OR "attention deficit disorder"[tiab]
5.
6 animals[mh]
7 humans[mh]
Appendix A. Methods

English

#1 AND #2 AND #3 NOT #4 NOT #5 NOT #6 AND #7

PUBLICATION DATE RANGE: 1980 to Jan 2023

**PsycInfo**

S1
MAINSUBJECT.EXACT("Attention Deficit Disorder with Hyperactivity") OR SU "Attention Deficit Disorder with Hyperactivity" OR TI ("attention deficit hyperactivity disorder" OR ADHD OR "attention deficit disorder") OR AB ("attention deficit hyperactivity disorder" OR ADHD OR "attention deficit disorder")

S2
AG (adolescence) OR TI (teenager OR teenagers OR teen OR teens OR adolescent OR adolescents OR adolescence OR youth) OR AB (teenager OR teenagers OR teenaged OR teen OR teens OR adolescent OR adolescents OR adolescence OR youth)

S3
(MAINSUBJECT.EXACT("Attention Deficit Disorder with Hyperactivity") OR SU "Attention Deficit Disorder with Hyperactivity" OR TI ("attention deficit hyperactivity disorder" OR ADHD OR "attention deficit disorder") OR AB ("attention deficit hyperactivity disorder" OR ADHD OR "attention deficit disorder")) AND (AG (adolescence) OR TI (teenager OR teenagers OR teen OR teens OR adolescent OR adolescents OR adolescence OR youth) OR AB (teenager OR teenagers OR teenaged OR teen OR teens OR adolescent OR adolescents OR adolescence OR youth))

S4
DE "CNS Stimulating Drugs" OR DE "Methylphenidate" OR DE "Dextroamphetamine" OR DE "Amphetamine" OR DE "Clonidine" OR DE "Serotonin Norepinephrine Reuptake Inhibitors" OR DE "Atomoxetine" OR DE "Tricyclic Antidepressant Drugs" OR DE "Desipramine" OR DE "Nortriptyline" OR DE "Bupropion" OR DE "Serotonin Norepinephrine Reuptake Inhibitors" OR DE "Venlafaxine" OR DE "Monoamine Oxidase Inhibitors" OR DE "Amantadine" OR TI (Azstarys OR Cotempla XR-ODT OR Desoxyn OR "Alpha agonist" OR psychostimulants OR "CNS stimulating" OR "Central Nervous System stimulants" OR methylphenidate OR Dexamethasone OR Dextroamphetamine OR lisdexamfetamine OR Amphetamine OR aptensio OR concerta OR Ritalin OR methyl OR medikinet OR equasym OR quillivant OR metabolite OR daytrana OR focalin OR Dextedrine OR dextrostat OR procentra OR zenzedi OR Adderall OR vyvanse OR elvanse OR tyvense OR dyanavel OR evekeo OR "alpha-2 agonists" OR guanfacine OR intuniv OR tenex OR estulic OR afken OR clonidine OR catapres OR clophelin OR kapvay OR nексїeон OR duraclon OR "Serotonin Norepinephrine Reuptake Inhibitors" OR Strattera OR atomoxetine OR "Tricyclic Antidepressants" OR "Desipramine" OR "Nortriptyline" OR norpramin OR pertofrane OR pamelor OR "dopamine reuptake inhibitors" OR modanifil OR Provigil OR alertec OR modavigil OR modiodal OR modalart OR armodafinil OR nuvigil OR "norepinephrine-dopamine reuptake inhibitors" OR bupropion OR Wellbutrin OR zyban OR forfivo OR "Serotonin Norepinephrine Reuptake Inhibitors" OR duloxetine OR Cymbalta OR "serotonin norepinephrine dopamine reuptake inhibitors" OR "Venlafaxine" OR Effexor OR trevilor OR (Monoamine Oxidase AND Inhibitors) OR selegiline OR eldepryl OR emsam OR selgene OR zelapar OR "n methyl d aspartate receptor agonists" OR "Amantadine" OR symmetrel OR memantine OR Namenda)
OR AB (Azstarys OR Cotempla XR-ODT OR Desoxyn OR "Alpha agonist" OR psychostimulants OR "CNS stimulating" OR "Central Nervous System stimulants" OR methylphenidate OR Dexamethylphenidate OR Dextroamphetamine OR lisdexamfetamine OR Amphetamine OR aptensio OR concerta OR Ritalin OR methylin OR medikinet OR equasym OR quillivant OR metadate OR daytrana OR focalin OR dexedrine OR dextrostat OR procentra OR zenzedi OR Adderall OR vyvanse OR elvanse OR tyvense OR dyanavel OR evekeo OR "alpha-2 agonists" OR guanfacine OR intuniv OR tenex OR estulic OR afken OR clonidine OR catapres OR clophelin OR kapvay OR nexiclon OR duraconl OR "Serotonin Norepinephrine Reuptake Inhibitors" OR Strattera OR atomoxetine OR "Tricyclic Antidepressants" OR "Desipramine" OR "Norlompramine" OR norpramin OR pertofrane OR pamelor OR "dopamine reuptake inhibitors" OR modanifil OR Provigil OR alertec OR modavigil OR mododial OR modalert OR armodafinil OR nuvigil OR "nepinephinedopamine reuptake inhibitors" OR bupropion OR Wellbutrin OR zyban OR forfivo OR "Serotonin Norepinephrine Reuptake Inhibitors" OR duloxetine OR Cymbalta OR "serotonin norepinephrine dopamine reuptake inhibitors" OR "Venlafaxine" OR Effexor OR trevilor OR (Monoamine Oxidase AND Inhibitors) OR selegiline OR eldepryl OR emsam OR selgene OR zelapar OR "n methyl d aspartate receptor agonists" OR "Amantadine" OR symmetrel OR memantine OR Namenda) SS
DE "Psychotherapy" OR DE "Adolescent Psychotherapy" OR DE "Multisystemic Therapy" OR DE "Behavior Therapy" OR DE "Dialectical Behavior Therapy" OR DE "Brief Psychotherapy" OR DE "Child Psychotherapy" OR DE "Play Therapy" OR DE "Cognitive Behavior Therapy" OR DE "Group Psychotherapy" OR DE "Mindfulness" OR DE "School Based Intervention" OR DE "Memory Training" OR DE "Biofeedback Training" OR DE "Biofeedback" OR DE "Computer Assisted Instruction" OR DE "Intelligent Tutoring Systems" OR DE "Dietary Supplements" OR DE "Food Additives" OR DE "Fatty Acids" OR DE "Acupuncture" OR DE "Remedial Education" OR DE "Early Intervention" OR DE "Alternative Medicine" OR TI (Monarch external Trigeminal Nerve Stimulation OR eTNS OR "EndeavorRx" OR ((classroom OR school OR schools) AND (behavior intervention OR behavioral interventions)) OR "peer intervention" OR (("organization skills") AND (training OR intervention)) OR "psychosocial therapy" OR "psychosocial intervention" OR "psychosocial interventions" OR "psychosocial approach" OR "psychosocial approaches" OR "psychosocial treatment" OR "psychosocial support" OR "psychoeducation" OR "nonpharmacologic therapy" OR "non-drug therapy" OR "Play Therapy" OR "cognitive behavioral therapy" OR "cognitive behavior therapy" OR "cognitive behavioural therapy" OR "cognitive behaviour therapy" OR "Mindfulness OR complementary OR "alternative medicine" OR "alternative therapy" OR "alternative therapies" OR "Interpersonal skills training" OR "Parent-Child Interaction Therapy" OR "parent training" OR "parent engagement" OR "parent management" OR "parenting skills" OR "parenting intervention" OR "parenting interventions" OR "Barkley's defiant child" OR "Teacher-Child Interaction Training" OR "Incredible Years" OR "New Forest Parenting" OR "Triple P" OR "Helping the Noncompliant Child" OR "child life and attention skills" OR "clas" OR PCIT OR "parent child interaction therapy" OR "Summer Treatment Program" OR "Daily Report Card" OR "organization skills" OR "organizational skills" OR...
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"time management" OR "homework intervention" OR braintrain OR "memory training" OR "Captain's log mindpower builder" OR "memory gyms" OR "attention gym" OR "smartdriver plus" OR "smartmind pro" OR "RoboMemo" OR "play attention" OR metronome OR brainmaster OR mindmed OR "attention lab" OR (activate AND c8) OR "attention training" OR “CogniPlus” OR cogmed OR "working memory training" OR biofeedback OR neurofeedback OR neuroagility OR neurooptimal OR acupuncture OR "vision training" OR "visual training" OR "vision therapy" OR "education intervention" OR "cognitive remediation" OR neurotherapy OR "elimination diet" OR "diet therapy" OR "low carb" OR "low carbohydrate" OR "low carbohydrates" OR "gluten free") AND diet) OR "feingold diet" OR "red dye" OR ((vitamin OR vitamins) AND (supplement OR supplements)) OR "herbal supplement" OR "herbal supplements" OR probiotics OR "omega 3" OR "slow cortical potentials" OR "few foods diet" OR "oligoantigenic diet" OR "restriction diet" OR "food intolerance" OR "food allergy" OR "food allergies" OR "food sensitivity" OR "food sensitivities" OR “multimodal treatment” OR homeopathy OR homeopathic OR chiropractic OR chiropractor ) OR AB ( Monarch external Trigeminal Nerve Stimulation OR eTNS OR "EndeavorRx" OR ((classroom OR school OR schools) AND (behavior intervention OR behavior interventions)) OR "peer intervention” OR ("organization skills") AND (training OR intervention)) OR "psychosocial therapy" OR "psychosocial intervention" OR "psychosocial interventions" OR "psychosocial approach" OR "psychosocial approaches" OR "psychosocial treatment" OR "psychosocial support" OR "psychoeducation" OR "nonpharmacologic therapy" OR "nondrug therapy" OR "non-drug therapy" OR "Play Therapy" OR "cognitive behavioral therapy" OR "cognitive behavior therapy" OR "cognitive behavioural therapy" OR "cognitive behaviour therapy" OR Mindfulness OR complementary OR "alternative medicine" OR "alternative therapy" OR "alternative therapies" OR "Interpersonal skills training" OR "Parent-Child Interaction Therapy" OR "parent training" OR "parent engagement" OR "parent management" OR "parenting skills" OR "parenting intervention" OR "parenting interventions" OR "Barkley's defiant child" OR "Teacher-Child Interaction Training" OR "Incredible Years" OR "New Forest Parenting" OR "Triple P" OR "Helping the Noncompliant Child" OR "child life and attention skills" OR "clas" OR PCIT OR "parent child interaction therapy" OR "Summer Treatment Program" OR "Daily Report Card" OR "organization skills" OR "organizational skills" OR "time management" OR "homework intervention" OR braintrain OR "memory training" OR "Captain's log mindpower builder" OR "memory gyms" OR "attention gym" OR "smartdriver plus" OR "smartmind pro" OR "RoboMemo" OR "play attention" OR metronome OR brainmaster OR mindmed OR "attention lab" OR (activate AND c8) OR "attention training" OR “CogniPlus” OR cogmed OR "working memory training" OR biofeedback OR neurofeedback OR neuroagility OR neurooptimal OR acupuncture OR "vision training" OR "visual training" OR "vision therapy" OR "education intervention" OR "cognitive remediation" OR neurotherapy OR "elimination diet" OR "diet therapy" OR "low carb" OR "low carbohydrate" OR "low carbohydrates" OR "gluten free") AND diet) OR "feingold diet" OR "red dye" OR ((vitamin OR vitamins) AND (supplement OR supplements)) OR "herbal supplement" OR "herbal supplements" OR probiotics OR "omega 3" OR "slow cortical potentials" OR "few foods diet" OR "oligoantigenic diet" OR "restriction diet" OR "food intolerance" OR "food allergy" OR "food allergies" OR "food sensitivity" OR "food sensitivities" OR “multimodal treatment” OR homeopathy OR homeopathic OR chiropractic OR chiropractor )

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(DE "CNS Stimulating Drugs" OR DE "Methylphenidate" OR DE "Dextroamphetamine" OR DE "Amphetamine" OR DE "Clonidine" OR DE "Serotonin Norepinephrine Reuptake Inhibitors" OR DE "Atomoxetine" OR DE "Tricyclic Antidepressant Drugs" OR DE "Desipramine" OR DE "Nortriptyline" OR DE "Bupropion" OR DE "Serotonin Norepinephrine Reuptake Inhibitors" OR DE "Venlafaxine" OR DE "Monoamine Oxidase Inhibitors" OR DE "Amantadine" OR TI ( Azstarys OR Cotempla XR-ODT OR Desoxyn OR "Alpha agonist" OR psychostimulants OR "CNS stimulating" OR "Central Nervous System stimulants" OR methylphenidate OR Dexmethylphenidate OR Dextroamphetamine OR lisdexamfetamine OR Amphetamine OR aptensio OR concerta OR Ritalin OR methylin OR medikinet OR equasym OR quillivant OR metadata OR daytrana OR focalin OR Dextedrine OR dextrostat OR procentra OR zenzedi OR Adderall OR vyvanse OR elvanse OR tyvense OR dyanavel OR evekeo OR "alpha-2 agonists" OR guanfacine OR intuniv OR tenex OR estulic OR afken OR clonidine OR catapres OR clophelin OR kapvay OR nexitclon OR duracron OR "Serotonin Norepinephrine Reuptake Inhibitors" OR Strattera OR atomoxetine OR "Tricyclic Antidepressants" OR "Desipramine" OR "Nortriptyline" OR norpramin OR pertofrane OR pamelor OR "dopamine reuptake inhibitors" OR modanifil OR Provigil OR alertec OR modavigil OR modiodal OR modalert OR armodafinil OR nuvigil OR "norepinephrine-dopamine reuptake inhibitors" OR bupropion OR Wellbutrin OR zyban OR forfivo OR "Serotonin Norepinephrine Reuptake Inhibitors" OR duloxetine OR Cymbalta OR "serotonin norepinephrine dopamine reuptake inhibitors" OR "Venlafaxine" OR Effexor OR trevilor OR (Monoamine Oxidase AND Inhibitors) OR selegline OR eldepryl OR emsam OR selgene OR zelapar OR "n methyl d aspartate receptor agonists" OR "Amantadine" OR symmetrel OR memantine OR Namenda) OR AB ( Azstarys OR Cotempla XR-ODT OR Desoxyn OR "Alpha agonist" OR psychostimulants OR "CNS stimulating" OR "Central Nervous System stimulants" OR methylphenidate OR Dexmethylphenidate OR Dextroamphetamine OR lisdexamfetamine OR Amphetamine OR aptensio OR concerta OR Ritalin OR methylin OR medikinet OR equasym OR quillivant OR metadata OR daytrana OR focalin OR Dextedrine OR dextrostat OR procentra OR zenzedi OR Adderall OR vyvanse OR elvanse OR tyvense OR dyanavel OR evekeo OR "alpha-2 agonists" OR guanfacine OR intuniv OR tenex OR estulic OR afken OR clonidine OR catapres OR clophelin OR kapvay OR nexitclon OR duracron OR "Serotonin Norepinephrine Reuptake Inhibitors" OR Strattera OR atomoxetine OR "Tricyclic Antidepressants" OR "Desipramine" OR "Nortriptyline" OR norpramin OR pertofrane OR pamelor OR "dopamine reuptake inhibitors" OR modanifil OR Provigil OR alertec OR modavigil OR modiodal OR modalert OR armodafinil OR nuvigil OR "norepinephrine-dopamine reuptake inhibitors" OR bupropion OR Wellbutrin OR zyban OR forfivo OR "Serotonin Norepinephrine Reuptake Inhibitors" OR duloxetine OR Cymbalta OR "serotonin norepinephrine dopamine reuptake inhibitors" OR "Venlafaxine" OR Effexor OR trevilor OR (Monoamine Oxidase AND Inhibitors) OR selegline OR eldepryl OR emsam OR selgene OR zelapar OR "n methyl d aspartate receptor agonists" OR "Amantadine" OR symmetrel OR memantine OR Namenda) ) OR (DE "Psychotherapy" OR DE "Adolescent Psychotherapy" OR DE "Multisystemic Therapy" OR DE "Behavior Therapy" OR DE "Dialectical Behavior Therapy" OR DE "Brief Psychotherapy" OR DE "Child Psychotherapy" OR DE "Play Therapy" OR DE "Client Centered Therapy" OR DE "Cognitive Behavior Therapy" OR DE "Group Psychotherapy" OR DE "Therapeutic Community" OR DE "Integrative Psychotherapy" OR DE "Psychotherapeutic Counseling" OR DE "Family Therapy" OR DE "Supportive Psychotherapy" OR DE "Cognitive Therapy" OR DE "Parent Training" OR DE "Parent Child Relations" OR DE "Time
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Management" OR DE "Mindfulness" OR DE "School Based Intervention" OR DE "Memory Training" OR DE "Biofeedback Training" OR DE "Biofeedback" OR DE "Computer Assisted Instruction" OR DE "Intelligent Tutoring Systems" OR DE "Diets" OR DE "Dietary Supplements" OR DE "Food Additives" OR DE "Fatty Acids" OR DE "Acupuncture" OR DE "Remedial Education" OR DE "Early Intervention" OR DE "Alternative Medicine" OR TI (Monarch external Trigeminal Nerve Stimulation OR eTNS OR "EndeavorRx" OR ((classroom OR school OR schools) AND (behavior intervention OR behavior interventions)) OR "peer intervention" OR ("organization skills") AND (training OR intervention)) OR "psychosocial therapy" OR "psychosocial intervention" OR "psychosocial interventions" OR "psychosocial approach" OR "psychosocial approaches" OR "psychosocial treatment" OR "psychosocial support" OR "psychoeducation" OR "nonpharmacologic therapy" OR "nondrug therapy" OR "non-drug therapy" OR "Play Therapy" OR "cognitive behavioral therapy" OR "cognitive behavior therapy" OR "cognitive behavioural therapy" OR "cognitive behaviour therapy" OR Mindfulness OR complementary OR "alternative medicine" OR "alternative therapy" OR "alternative therapies" OR "Interpersonal skills training" OR "Parent-Child Interaction Therapy" OR "parent training" OR "parent engagement" OR "parent management" OR "parenting skills" OR "parenting interventions" OR "parenting intervention" OR "Barkley's defiant child" OR "Teacher-Child Interaction Training" OR "Incredible Years" OR "New Forest Parenting" OR "Triple P" OR "Helping the Noncompliant Child" OR "child life and attention skills" OR "clas" OR PCIT OR "parent child interaction therapy" OR "Summer Treatment Program" OR "Daily Report Card" OR "organization skills" OR "organizational skills" OR "time management" OR "homework intervention" OR "memory training" OR "Captain's log mindpower builder" OR "memory gyms" OR "attention gym" OR "smartdriver plus" OR "smartmind pro" OR "RoboMemo" OR "play attention" OR "metronome OR brainmaster OR mindmed OR "attention lab" OR (activate AND c8) OR "attention training" OR "CogniPlus" OR cogmed OR "working memory training" OR biofeedback OR neurofeedback OR neuroagility OR neurooptimal OR acupuncture OR "vision training" OR "visual training" OR "vision therapy" OR "education intervention" OR "cognitive remediation" OR neurotherapy OR "elimination diet" OR "diet therapy" OR (("low carb" OR "low carbohydrate" OR "low carbohydrates" OR "gluten free") AND diet) OR "feingold diet" OR "red dye" OR ((vitamin OR vitamins) AND (supplement OR supplements)) OR "herbal supplement" OR "herbal supplements" OR probiotics OR "omega 3" OR "slow cortical potentials" OR "few foods diet" OR "oligoantigenic diet" OR "restriction diet" OR "food intolerance" OR "food allergy" OR "food allergies" OR "food sensitivity" OR "food sensitivities" OR "multimodal treatment" OR homeopathy OR homeopathic OR chiropractic OR chiropractor OR AB (Monarch external Trigeminal Nerve Stimulation OR eTNS OR "EndeavorRx" OR ((classroom OR school OR schools) AND (behavior intervention OR behavior interventions)) OR "peer intervention" OR ("organization skills") AND (training OR intervention)) OR "psychosocial therapy" OR "psychosocial intervention" OR "psychosocial interventions" OR "psychosocial approach" OR "psychosocial approaches" OR "psychosocial treatment" OR "psychosocial support" OR "psychoeducation" OR "nonpharmacologic therapy" OR "nondrug therapy" OR "non-drug therapy" OR "Play Therapy" OR "cognitive behavioral therapy" OR "cognitive behavior therapy" OR "cognitive behavioural therapy" OR "cognitive behaviour therapy" OR Mindfulness OR complementary OR "alternative medicine" OR "alternative therapy" OR "alternative therapies" OR "Interpersonal skills training" OR "Parent-Child Interaction Therapy" OR "parent training" OR "parent engagement" OR "parent management" OR
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((MAINSUBJECT.EXACT("Attention Deficit Disorder with Hyperactivity") OR SU "Attention Deficit Disorder with Hyperactivity" OR TI ("attention deficit hyperactivity disorder" OR ADHD OR "attention deficit disorder") OR AB ("attention deficit hyperactivity disorder" OR ADHD OR "attention deficit disorder")) AND (AG (childhood OR adolescence ) OR DE "Pediatrics" OR TI ( child OR children OR infant OR infants OR preschool OR preschooler OR pediatric OR teenager OR teenagers OR teenaged OR teen OR teens OR adolescent OR adolescents OR adolescence OR youth ) OR AB ( child OR children OR infant OR infants OR preschool OR preschooler OR pediatric OR teenager OR teenagers OR teenaged OR teen OR teens OR adolescent OR adolescents OR adolescence OR youth ) ) ) AND ((DE "CNS Stimulating Drugs" OR DE "Methylphenidate" OR DE "Dextroamphetamine" OR DE "Amphetamine" OR DE "Clonidine" OR DE "Serotonin Norepinephrine Reuptake Inhibitors" OR DE "Atomoxetine" OR DE "Tricyclic Antidepressant Drugs" OR DE "Desipramine" OR DE "Nortriptylne" OR DE "Bupropion" OR DE "Serotonin Norepinephrine Reuptake Inhibitors" OR DE "Venlafaxine" OR DE "Monoamine Oxidase Inhibitors" OR DE "Amantadine" OR TI ( Azstarys OR Cotempla XR-ODT OR Desoxyn OR "alpha agonist" OR psychostimulants OR "CNS stimulating" OR "Central Nervous System stimulants" OR methylphenidate OR Dexamphetamine OR Dextroamphetamine OR lisdexamfetamine OR Amphetamine OR aptensio OR concerta OR Ritalin OR methylphen OR medikinet OR equasym OR quillivant OR metadate OR daytrana OR focalin OR Dexedrine OR dextrostat OR procentra OR zenzedi OR Adderal OR Vyvanse OR elvanse OR tyvense OR dyanavel OR evekeo OR "alpha-2 agonists" OR guanfacine OR intuniv OR tenex OR estulic OR afken OR clonidine OR catapres OR clophelin OR kapvay OR nexiaron OR duracon OR "Serotonin Norepinephrine Reuptake Inhibitors" OR Strattera OR atomoxetine OR "Tricyclic Antidepressants " OR "Desipramine" OR "Nortriptylne" OR norpramin OR pertofrane OR pamelor OR "dopamine reuptake inhibitors" OR modanifil OR Provigil OR alertec OR modavigil OR modiodal OR modalert OR armodafinil OR nuvigil OR "norepinephrine-dopamine reuptake inhibitors" OR...
bupropion OR Wellbutrin OR zyban OR forfivo OR "Serotonin Norepinephrine Reuptake Inhibitors" OR duloxetine OR Cymbalta OR "serotonin norepinephrine dopamine reuptake inhibitors" OR "Venlafaxine" OR Effexor OR trevilor OR (Monoamine Oxidase AND Inhibitors) OR selegiline OR eldepryl OR emsam OR selgene OR zelapar OR "n methyl d aspartate receptor agonists" OR "Amantadine" OR symmetrel OR memantine OR Namenda) OR AB ( Azstarys OR Cotempla XR-ODT OR Desoxyn OR "Alpha agonist" OR psychostimulants OR "CNS stimulating" OR "Central Nervous System stimulants" OR methylphenidate OR Dexmethylphenidate OR Dextroamphetamine OR lisdexamfetamine OR Amphetamine OR aptensio OR concerta OR Ritalin OR methylin OR medikinet OR equasym OR quillivant OR metadata OR daytrana OR focalin OR Dextedrine OR dextrostat OR procentra OR zenzedi OR Adderall OR vyvanse OR elvanse OR tyvense OR dyanavel OR evekeo OR "alpha-2 agonists" OR guanfacine OR intuniv OR tenex OR estulic OR afken OR clonidine OR catapres OR clophelin OR kapvay OR nexioncl OR duraclon OR "Serotonin Norepinephrine Reuptake Inhibitors" OR Strattera OR atomoxetine OR "Tricyclic Antidepressants" OR "Desipramine" OR "Nortriptyline" OR norpramin OR pertofrane OR pamelor OR "dopamine reuptake inhibitors" OR modanifil OR Provigil OR alertec OR modavigil OR modiodal OR modalert OR armodafinil OR nuvigil OR "norepinephrinedopamine reuptake inhibitors" OR bupropion OR Wellbutrin OR zyban OR forfivo OR "Serotonin Norepinephrine Reuptake Inhibitors" OR duloxetine OR Cymbalta OR "serotonin norepinephrine dopamine reuptake inhibitors" OR "Venlafaxine" OR Effexor OR trevilor OR (Monoamine Oxidase AND Inhibitors) OR selegiline OR eldepryl OR emsam OR selgene OR zelapar OR "n methyl d aspartate receptor agonists" OR "Amantadine" OR symmetrel OR memantine OR Namenda) ) OR (DE "Psychotherapy" OR DE "Adolescent Psychotherapy" OR DE "Multisystemic Therapy" OR DE "Behavior Therapy" OR DE "Dialectical Behavior Therapy" OR DE "Brief Psychotherapy" OR DE "Child Psychotherapy" OR DE "Play Therapy" OR DE "Client Centered Therapy" OR DE "Cognitive Behavior Therapy" OR DE "Group Psychotherapy" OR DE "Therapeutic Community" OR DE "Integrative Psychotherapy" OR DE "Psychotherapeutic Counseling" OR DE "Family Therapy" OR DE "Supportive Psychotherapy" OR DE "Cognitive Therapy" OR DE "Parent Training" OR DE "Parent Child Relations" OR DE "Time Management" OR DE "Mindfulness" OR DE "School Based Intervention" OR DE "Memory Training" OR DE "Biofeedback Training" OR DE "Biofeedback" OR DE "Computer Assisted Instruction" OR DE "Intelligent Tutoring Systems" OR DE "Diets" OR DE "Dietary Supplements" OR DE "Food Additives" OR DE "Fatty Acids" OR DE "Acupuncture" OR DE "Remedial Education" OR DE "Early Intervention" OR DE "Alternative Medicine" OR TI (Monarch external Trigeminal Nerve Stimulation OR eTNS OR "EndeavorRx" OR ((classroom OR school OR schools) AND (behavior intervention OR behavior interventions)) OR "peer intervention" OR (("organization skills") AND (training OR intervention)) OR "psychosocial therapy" OR "psychosocial intervention" OR "psychosocial interventions" OR "psychosocial approach" OR "psychosocial approaches" OR "psychosocial treatment" OR "psychosocial support" OR "psychoeducation" OR "nonpharmacologic therapy" OR "nondrug therapy" OR "non-drug therapy" OR "Play Therapy" OR "cognitive behavioral therapy" OR "cognitive behavior therapy" OR "cognitive behavioural therapy" OR "cognitive behaviour therapy" OR Mindfulness OR complementary OR "alternative medicine" OR "alternative therapy" OR "alternative therapies" OR "Interpersonal skills training" OR "Parent-Child Interaction Therapy" OR "parent training" OR "parent engagement" OR "parent management" OR "parenting skills" OR "parenting intervention" OR "parenting interventions" OR "Barkley's
Appendix A. Methods

defiant child" OR "Teacher-Child Interaction Training" OR "Incredible Years" OR "New Forest Parenting" OR "Triple P" OR "Helping the Noncompliant Child" OR "child life and attention skills" OR "clas" OR PCIT OR "parent child interaction therapy" OR "Summer Treatment Program" OR "Daily Report Card" OR "organization skills" OR "organizational skills" OR "time management" OR "homework intervention" OR braintrain OR "memory training" OR "Captain's log mindpower builder" OR "memory gyms" OR "attention gym" OR "smartdriver plus" OR "smartmind pro" OR "RoboMemo" OR "play attention" OR metronome OR brainmaster OR mindmed OR "attention lab" OR (activate AND c8) OR "attention training" OR “CogniPlus” OR cogmed OR "working memory training" OR biofeedback OR neurofeedback OR neuroagility OR neuroptimal OR acupuncture OR "vision training" OR "visual training" OR "vision therapy" OR "education intervention" OR "cognitive remediation" OR neurotherapy OR "elimination diet" OR "diet therapy" OR ("low carb" OR "low carbohydrate" OR "low carbohydrates" OR "gluten free") AND diet) OR "feingold diet" OR "red dye" OR ((vitamin OR vitamins) AND (supplement OR supplements)) OR "herbal supplement" OR "herbal supplements" OR probiotics OR "omega 3" OR "slow cortical potentials" OR "few foods diet" OR "oligoantigenic diet" OR "restriction diet" OR "food intolerance" OR "food allergy" OR "food allergies" OR "food sensitivity" OR "food sensitivities" OR "multimodal treatment" OR homeopathy OR homeopathic OR chiropractic OR chiropractor ) OR AB (Monarch external Trigeminal Nerve Stimulation OR eTNS OR "EndeavorRx" OR ((classroom OR school OR schools) AND (behavior intervention OR behavior interventions)) OR "peer intervention” OR (("organization skills") AND (training OR intervention)) OR "psychosocial therapy" OR "psychosocial intervention" OR "psychosocial interventions" OR "psychosocial approach" OR "psychosocial approaches" OR "psychosocial treatment" OR "psychosocial support" OR "psychoeducation" OR "nonpharmacologic therapy" OR "nondrug therapy" OR "non-drug therapy" OR "Play Therapy" OR "cognitive behavioral therapy" OR "cognitive behavior therapy" OR "cognitive behavioural therapy" OR "cognitive behaviour therapy" OR "Mindfulness OR complementary OR "alternative medicine" OR "alternative therapy" OR "alternative therapies" OR "Interpersonal skills training" OR "Parent-Child Interaction Therapy" OR "parent training" OR "parent engagement" OR "parent management" OR "parenting skills" OR "parenting intervention" OR "parenting interventions" OR "Barkley's defiant child" OR "Teacher-Child Interaction Training" OR "Incredible Years" OR "New Forest Parenting" OR "Triple P" OR "Helping the Noncompliant Child" OR "child life and attention skills" OR "clas" OR PCIT OR "parent child interaction therapy" OR "Summer Treatment Program" OR "Daily Report Card" OR "organization skills" OR "organizational skills" OR "time management" OR "homework intervention" OR braintrain OR "memory training" OR "Captain's log mindpower builder" OR "memory gyms" OR "attention gym" OR "smartdriver plus" OR "smartmind pro" OR "RoboMemo" OR "play attention" OR metronome OR brainmaster OR mindmed OR "attention lab" OR (activate AND c8) OR "attention training" OR “CogniPlus” OR cogmed OR "working memory training" OR biofeedback OR neurofeedback OR neuroagility OR neuroptimal OR acupuncture OR "vision training" OR "visual training" OR "vision therapy" OR "education intervention" OR "cognitive remediation" OR neurotherapy OR "elimination diet" OR "diet therapy" OR ("low carb" OR "low carbohydrate" OR "low carbohydrates" OR "gluten free") AND diet) OR "feingold diet" OR "red dye" OR ((vitamin OR vitamins) AND (supplement OR supplements)) OR "herbal supplement" OR "herbal supplements" OR probiotics OR "omega 3" OR "slow cortical potentials" OR "few foods diet" OR "oligoantigenic diet" OR "restriction diet" OR "food intolerance" OR "food allergy" OR
Appendix A. Methods

"food allergies" OR "food sensitivity" OR "food sensitivities" OR “multimodal treatment” OR homeopathy OR homeopathic OR chiropractic OR chiropractor ))
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ZC "longitudinal study" OR ZC "empirical study" OR ZC "followup study" OR ZC "longitudinal study" OR ZC "meta analysis" OR ZC "prospective study" OR ZC "retrospective study" OR ZC "systematic review" OR ZC "treatment outcome/clinical trial" OR DE "Clinical Trials" OR DE "Cohort Analysis" OR DE "Followup Studies" OR DE "Longitudinal Studies" OR DE "Prospective Studies" OR DE "Meta Analysis" OR TI (randomized OR randomised OR randomization OR randomisation OR randomly OR trial OR groups OR trials OR "evaluation study" OR evaluation studies OR "intervention study" OR "intervention studies" OR "case-control" OR cohort OR longitudinal OR longitudinally OR prospective OR prospectively OR "comparative study" OR "meta-analysis" OR "meta-analyses"") OR AB (randomized OR randomised OR randomization OR randomisation OR randomly OR trial OR groups OR trials OR "evaluation study" OR evaluation studies OR "intervention study" OR "intervention studies" OR "case-control" OR cohort OR longitudinal OR longitudinally OR prospective OR prospectively OR "comparative study" OR "meta-analysis" OR "meta-analyses") AND (ZZ "journal article")
S9
((MAINSUBJECT.EXACT("Attention Deficit Disorder with Hyperactivity") OR SU "Attention Deficit Disorder with Hyperactivity" OR TI ("attention deficit hyperactivity disorder" OR ADHD OR "attention deficit disorder") OR AB ("attention deficit hyperactivity disorder" OR ADHD OR "attention deficit disorder")) AND (AG (childhood OR adolescence ) OR DE "Pediatrics" OR TI (child OR children OR infant OR infants OR preschool OR preschooler OR pediatric OR teenager OR teenagers OR teenaged OR teen OR teens OR adolescent OR adolescents OR adolescence OR youth ) OR AB (child OR children OR infant OR infants OR preschool OR preschooler OR pediatric OR teenager OR teenagers OR teenaged OR teen OR teens OR adolescent OR adolescents OR adolescence OR youth )) AND ((DE "CNS Stimulating Drugs" OR DE "Methylphenidate" OR DE "Dextroamphetamine" OR DE "Amphetamine" OR DE "Clonidine" OR DE "Serotonin Norepinephrine Reuptake Inhibitors" OR DE "Atomoxetine" OR DE "Tricyclic Antidepressant Drugs" OR DE "Desipramine" OR DE "Nortriptyline" OR DE "Bupropion" OR DE "Serotonin Norepinephrine Reuptake Inhibitors" OR DE "Venlafaxine" OR DE "Monoamine Oxidase Inhibitors" OR DE "Amantadine" OR TI (Azstarys OR Cotempla XR-ODT OR Desoxyn OR "Alpha agonist" OR psychostimulants OR "CNS stimulating" OR "Central Nervous System stimulants" OR methylphenidate OR Dexmethylphenidate OR Dextroamphetamine OR lisdexamfetamine OR Amphetamine OR aptensio OR concerta OR Ritalin OR methyl OR medikinet OR equasym OR quillivant OR metadate OR daytrana OR focalin OR Dextedrine OR dextrostat OR procentra OR zenzedi OR Adderall OR vyvanse OR elvanse OR tyvense OR dyanavel OR evokeo OR "alpha-2 agonists" OR guanfacine OR intuniv OR tenex OR estucil OR afken OR clonidine OR catapres OR clophelin OR kavpay OR nexionlon OR duraclon OR "Serotonin Norepinephrine Reuptake Inhibitors" OR Straterra OR atomoxetine OR "Tricyclic Antidepressants" OR "Desipramine" OR "Nortriptyline" OR norpramin OR pertofrane OR pamelar OR "serotonin reuptake inhibitors" OR modanifil OR Provigil OR alertec OR modavigil OR modiodal OR modalert OR armodafinil OR nuvigil OR "norepinephrine-dopamine reuptake inhibitors" OR bupropion OR Wellbutrin OR zyban OR forfivo OR "Serotonin Norepinephrine Reuptake Inhibitors" OR duloxetine OR Cymbalta OR "serotonin norepinephrine dopamine reuptake inhibitors" OR...
inhibitors" OR "Venlafaxine" OR Effexor OR trevilor OR (Monoamine Oxidase AND Inhibitors) OR selegiline OR eldepryl OR emsam OR selgene OR zelapar OR "n methyl d aspartate receptor agonists" OR "Amantadine" OR symmetrel OR memantine OR Namenda) OR AB (Azstarys OR Cotempla XR-ODT OR Desoxyn OR "Alpha agonist" OR psychostimulants OR "CNS stimulating" OR "Central Nervous System stimulants" OR methylphenidate OR Dexamethylphenidate OR Dextroamphetamine OR lisdexamfetamine OR Amphetamine OR aptenisio OR concerta OR Ritalin OR methylin OR medikinet OR equasym OR quillivant OR metadata OR daytrana OR focalin OR Dextedral OR dextrostat OR procentra OR zenedi OR Adderall OR vyvanse OR elvanse OR tyvense OR dyanavel OR evekeo OR "alpha-2 agonists" OR guanfacine OR intuniv OR tenex OR estulic OR afken OR clonidine OR catapres OR clophelin OR kapvay OR nexion OR duraclon OR "Serotonin Norepinephrine Reuptake Inhibitors" OR Strattera OR atomoxetine OR "Triyclic Antidepressants" OR "Desipramine" OR "Nortriptyline" OR norpramin OR pertofran OR pemelor OR "dopamine reuptake inhibitors" OR modanifil OR Provigil OR alertec OR modavigil OR modiodal OR modalert OR armodafinil OR nuvigil OR "norepinephrine-reuptake inhibitors" OR bupropion OR Wellbutrin OR zyban OR forfivo OR "Serotonin Norepinephrine Reuptake Inhibitors" OR duloxetine OR Cymbalta OR "serotonin norepinephrine dopamine reuptake inhibitors" OR "Venlafaxine" OR Effexor OR trevilor OR (Monoamine Oxidase AND Inhibitors) OR selegiline OR eldepryl OR emsam OR selgene OR zelapar OR "n methyl d aspartate receptor agonists" OR "Amantadine" OR symmetrel OR memantine OR Namenda) OR (DE "Psychotherapy" OR DE "Adolescent Psychotherapy" OR DE "Multisystemic Therapy" OR DE "Behavior Therapy" OR DE "Dialectical Behavior Therapy" OR DE "Brief Psychotherapy" OR DE "Child Psychotherapy" OR DE "Play Therapy" OR DE "Client Centered Therapy" OR DE "Cognitive Behavior Therapy" OR DE "Group Psychotherapy" OR DE "Therapeutic Community" OR DE "Integrative Psychotherapy" OR DE "Psychotherapeutic Counseling" OR DE "Family Therapy" OR DE "Supportive Psychotherapy" OR DE "Cognitive Therapy" OR DE "Parent Training" OR DE "Parent Child Relations" OR DE "Time Management" OR DE "Mindfulness" OR DE "School Based Intervention" OR DE "Memory Training" OR DE "Biofeedback Training" OR DE "Biofeedback" OR DE "Computer Assisted Instruction" OR DE "Intelligent Tutoring Systems" OR DE "Diets" OR DE "Dietary Supplements" OR DE "Food Additives" OR DE "Fatty Acids" OR DE "Acupuncture" OR DE "Remedial Education" OR DE "Early Intervention" OR DE "Alternative Medicine" OR TI (Monarch external Trigeminal Nerve Stimulation OR eTNS OR "EndeavorRx" OR ((classroom OR school OR schools) AND (behavior intervention OR behavior interventions)) OR "peer intervention" OR (("organization skills") AND (training OR intervention)) OR "psychosocial therapy" OR "psychosocial intervention" OR "psychosocial interventions" OR "psychosocial approach" OR "psychosocial approaches" OR "psychosocial treatment" OR "psychosocial support" OR "psychoeducation" OR "nonpharmacologic therapy" OR "nondrug therapy" OR "non-drug therapy" OR "Play Therapy" OR "cognitive behavioral therapy" OR "cognitive behavior therapy" OR "cognitive behavioural therapy" OR "cognitive behaviour therapy" OR Mindfulness OR complementary OR "alternative medicine" OR "alternative therapy" OR "alternative therapies" OR "Interpersonal skills training" OR "Parent-Child Interaction Therapy" OR "parent training" OR "parent engagement" OR "parent management" OR "parenting skills" OR "parenting intervention" OR "parenting interventions" OR "Barkley's defiant child" OR "Teacher-Child Interaction Training" OR "Incredible Years" OR "New Forest Parenting" OR "Triple P" OR "Helping the Noncompliant Child" OR "child life and attention
Appendix A. Methods

skills" OR "clas" OR PCIT OR "parent child interaction therapy" OR "Summer Treatment Program" OR "Daily Report Card" OR "organization skills" OR "organizational skills" OR "time management" OR "homework intervention" OR braintrain OR "memory training" OR "Captain's log mindpower builder" OR "memory gyms" OR "attention gym" OR "smartdriver plus" OR "smartmind pro" OR "RoboMemo" OR "play attention" OR metronome OR brainmaster OR mindmed OR "attention lab" OR (activate AND c8) OR "attention training" OR "CogniPlus" OR cogmed OR "working memory training" OR biofeedback OR neurofeedback OR neuroagility OR neuroptimal OR acupuncture OR "vision training" OR "visual training" OR "vision therapy" OR "education intervention" OR "cognitive remediation" OR neurotherapy OR "elimination diet" OR "diet therapy" OR ("low carb" OR "low carbohydrate" OR "low carbohydrates" OR "gluten free") AND diet OR "feingold diet" OR "red dye" OR ((vitamin OR vitamins) AND (supplement OR supplements)) OR "herbal supplement" OR "herbal supplements" OR probiotics OR "omega 3" OR "slow cortical potentials" OR "few foods diet" OR "oligoantigenic diet" OR "restriction diet" OR "food intolerance" OR "food allergy" OR "food allergies" OR "food sensitivity" OR "food sensitivities" OR “multimodal treatment” OR homeopathy OR homeopathic OR chiropractic OR chiropractor ) OR AB ( Monarch external Trigeminal Nerve Stimulation OR eTNS OR "EndeavorRx" OR ((classroom OR school OR schools) AND (behavior intervention OR behavior interventions)) OR “peer intervention” OR (("organization skills") AND (training OR intervention)) OR"psychosocial therapy" OR "psychosocial intervention" OR "psychosocial interventions" OR "psychosocial approach" OR "psychosocial approaches" OR "psychosocial treatment" OR "psychosocial support" OR "psychoeducation" OR "nonpharmacologic therapy" OR "nondrug therapy" OR "non-drug therapy" OR "Play Therapy" OR "cognitive behavioral therapy" OR "cognitive therapy" OR "cognitive behavioural therapy" OR "cognitive behaviour therapy" OR "cognitive behaviour therapy" OR Mindfulness OR complementary OR "alternative medicine" OR "alternative therapy" OR "alternative therapies" OR "Interpersonal skills training" OR "Parent-Child Interaction Therapy" OR "parent training" OR "parent engagement" OR "parent management" OR "parenting skills" OR "parenting intervention" OR "parenting interventions" OR "Barkley's defiant child" OR "Teacher-Child Interaction Training" OR "Incredible Years" OR "New Forest Parenting" OR "Triple P" OR "Helping the Noncompliant Child" OR "child life and attention skills" OR "clas" OR PCIT OR "parent child interaction therapy" OR "Summer Treatment Program" OR "Daily Report Card" OR "organization skills" OR "organizational skills" OR "time management" OR "homework intervention" OR braintrain OR "memory training" OR "Captain's log mindpower builder" OR "memory gyms" OR "attention gym" OR "smartdriver plus" OR "smartmind pro" OR "RoboMemo" OR "play attention" OR metronome OR brainmaster OR mindmed OR "attention lab" OR (activate AND c8) OR "attention training" OR “CogniPlus” OR cogmed OR "working memory training" OR biofeedback OR neurofeedback OR neuroagility OR neuroptimal OR acupuncture OR "vision training" OR "visual training" OR "vision therapy" OR "education intervention" OR "cognitive remediation" OR neurotherapy OR "elimination diet" OR "diet therapy" OR ("low carb" OR "low carbohydrate" OR "low carbohydrates" OR "gluten free") AND diet OR "feingold diet" OR "red dye" OR ((vitamin OR vitamins) AND (supplement OR supplements)) OR "herbal supplement" OR "herbal supplements" OR probiotics OR "omega 3" OR "slow cortical potentials" OR "few foods diet" OR "oligoantigenic diet" OR "restriction diet" OR "food intolerance" OR "food allergy" OR "food allergies" OR "food sensitivity" OR "food sensitivities" OR “multimodal treatment” OR homeopathy OR homeopathic OR chiropractic OR chiropractor )))) AND (ZC "longitudinal
Appendix A. Methods

study" OR ZC "empirical study" OR ZC "followup study" OR ZC "longitudinal study" OR ZC "meta analysis" OR ZC "prospective study" OR ZC "retrospective study" OR ZC "systematic review" OR ZC "treatment outcome/clinical trial" OR DE "Clinical Trials" OR DE "Cohort Analysis" OR DE "Followup Studies" OR DE "Longitudinal Studies" OR DE "Prospective Studies" OR DE "Meta Analysis" OR TI (randomized OR randomised OR randomization OR randomisation OR randomly OR trial OR groups OR trials OR "evaluation study" OR evaluation studies OR "intervention study" OR "intervention studies" OR "case-control" OR cohort OR longitudinal OR longitudinally OR prospective OR prospectively OR retrospective OR "comparative study" OR "meta-analysis" OR "meta-analyses" ) OR AB (randomized OR randomised OR randomization OR randomisation OR randomly OR trial OR groups OR trials OR "evaluation study" OR evaluation studies OR "intervention study" OR "intervention studies" OR "case-control" OR cohort OR longitudinal OR longitudinally OR prospective OR prospectively OR retrospectively OR "comparative study" OR "meta-analysis" OR "meta-analyses") AND (ZZ "journal article")

S10

((MAINSUBJECT.EXACT("Attention Deficit Disorder with Hyperactivity") OR SU "Attention Deficit Disorder with Hyperactivity" OR TI ("attention deficit hyperactivity disorder" OR ADHD OR "attention deficit disorder") OR AB ("attention deficit hyperactivity disorder" OR ADHD OR "attention deficit disorder")(AND (AG (childhood OR adolescence) OR DE "Pediatrics" OR TI (child OR children OR infant OR infants OR preschool OR preschooler OR pediatric OR teenager OR teenagers OR teen OR children OR adolescent OR adolescents OR adolescence OR youth) OR AB (child OR children OR infant OR infants OR preschool OR preschooler OR pediatric OR teenager OR teenagers OR teen OR children OR adolescent OR adolescents OR adolescence OR youth)))) AND ((DE "CNS Stimulating Drugs" OR DE "Methylphenidate" OR DE "Dextroamphetamine" OR DE "Amphetamine" OR DE "Clonidine" OR DE "Serotonin Norepinephrine Reuptake Inhibitors" OR DE "Atomoxetine" OR DE "Tricyclic Antidepressant Drugs" OR DE "Desipramine" OR DE "Nortriptyline" OR DE "Bupropion" OR DE "Serotonin Norepinephrine Reuptake Inhibitors" OR DE "Venlafaxine" OR DE "Monoamine Oxidase Inhibitors" OR DE "Amantadine") OR TI (Azstarys OR Cotempla XR-ODT OR Desoxyn OR "Alpha agonist" OR psychostimulants OR "CNS stimulating" OR "Central Nervous System stimulants" OR methylphenidate OR Dexmethylphenidate OR Dextroamphetamine OR lisdexamfetamine OR Amphetamine OR apensio OR concerta OR Ritalin OR methylphenin OR medicinet OR equasym OR quillivant OR metabolite OR daytrana OR focalin OR Dexamphetamine OR dextrostat OR procentra OR zenzedi OR Adderall OR vyvanse OR elvanse OR tyvanse OR dyvanvel OR evkevo OR "alpha-2 agonists" OR guanfacine OR intuniv OR tenex OR estulic OR afken OR clonidine OR catapres OR clophelin OR kapvy OR nixcilon OR duraclon OR "Serotonin Norepinephrine Reuptake Inhibitors" OR Strattera OR atomoxetine OR "Tricyclic Antidepressants" OR "Desipramine" OR "Nortriptyline" OR norpramin OR pertofrane OR pamelor OR "dopamine reuptake inhibitors" OR modanifil OR Provigil OR alertec OR modavigil OR modiodal OR modalert OR armodafinil OR nuvigil OR "norepinephrine-dopamine reuptake inhibitors" OR bupropion OR Wellbutrin OR zyban OR forfivo OR "Serotonin Norepinephrine Reuptake Inhibitors" OR duloxetine OR Cymbalta OR "serotonin norepinephrine dopamine reuptake inhibitors" OR "Venlafaxine" OR Effexor OR trevilor OR (Monoamine Oxidase AND Inhibitors) OR selegeline OR eldepryl OR emsam OR selgene OR zelapar OR "n methyl d aspartate receptor agonists" OR "Amantadine" OR symmetrel OR memantine OR Namenda)
OR AB (Azstarys OR Cotempla XR-ODT OR Desoxyn OR "Alpha agonist" OR psychostimulants OR "CNS stimulating" OR "Central Nervous System stimulants" OR methylphenidate OR Dexamethylphenidate OR Dextroamphetamine OR lisdexamfetamine OR Amphetamine OR apensio OR concerta OR Ritalin OR methylin OR medikinet OR equasym OR quillivant OR metadate OR daytrana OR focalin OR Dexedrine OR dextrostat OR procentra OR zenzedi OR Adderall OR vyvanse OR elvanse OR tyvense OR dyvan OR evehyo OR "alpha-2 agonists" OR guanfacine OR intuniv OR tenex OR estulic OR afken OR clonidine OR catapers OR clophelin OR kapvay OR nesxilon OR duracon OR "Serotonin Norepinephrine Reuptake Inhibitors" OR Strattera OR atomoxetine OR "Tricyclic Antidepressants " OR "Desipramine" OR "Nortriptyline" OR norpramin OR pertofrane OR pamelor OR "dopamine reuptake inhibitors" OR modanafil OR Provigil OR alertec OR modavigil OR modiodal OR modalert OR armodafinil OR nughil OR "norepinephrinereuptake inhibitors" OR bupropion OR Wellbutrin OR zyban OR forfivo OR "Serotonin Norepinephrine Reuptake Inhibitors" OR duloxetine OR Cymbalta OR "serotonin norepinephrine dopamine reuptake inhibitors" OR "Venlafaxine" OR Effexor OR trevilor OR (Monoamine Oxidase AND Inhibitors OR selegiline OR eldepryl OR ensam OR selgene OR zelapar OR "n methyl d aspartate receptor agonists" OR "Amantadine" OR symmetrel OR memantine OR Namenda) ) OR (DE "Psychotherapy" OR DE "Adolescent Psychotherapy" OR DE "Multisystemic Therapy" OR DE "Behavior Therapy" OR DE "Dialectical Behavior Therapy" OR DE "Brief Psychotherapy" OR DE "Child Psychotherapy" OR DE "Play Therapy" OR DE "Client Centered Therapy" OR DE "Cognitive Behavior Therapy" OR DE "Group Psychotherapy" OR DE "Therapeutic Community" OR DE "Integrative Psychotherapy" OR DE "Psychotherapeutic Counseling" OR DE "Family Therapy" OR DE "Supportive Psychotherapy" OR DE "Cognitive Therapy" OR DE "Parent Training" OR DE "Parent Child Relations" OR DE "Time Management" OR DE "Mindfulness" OR DE "School Based Intervention" OR DE "Memory Training" OR DE "Biofeedback Training" OR DE "Biofeedback" OR DE "Computer Assisted Instruction" OR DE "Intelligent Tutoring Systems" OR DE "Diets" OR DE "Dietary Supplements" OR DE "Food Additives" OR DE "Fatty Acids" OR DE "Acupuncture" OR DE "Remedial Education" OR DE "Early Intervention" OR DE "Alternative Medicine" OR TI (Monarch external Trigeminal Nerve Stimulation OR eTNS OR "EndeavorRx" OR ((classroom OR school OR schools) AND (behavior intervention OR behavior interventions)) OR "peer intervention" OR (("organization skills") AND (training OR intervention)) OR "psychosocial therapy" OR "psychosocial intervention" OR "psychosocial interventions" OR "psychosocial approach" OR "psychosocial approaches" OR "psychosocial treatment" OR "psychosocial support" OR "psychoeducation" OR "nonpharmacologic therapy" OR "nondrug therapy" OR "non-drug therapy" OR "Play Therapy" OR "cognitive behavioral therapy" OR "cognitive behavior therapy" OR "cognitive behaviour therapy" OR "cognitive behavoural therapy" OR "cognitive behaviour therapy" OR Mindfulness OR complementary OR "alternative medicine" OR "alternative therapy" OR "alternative therapies" OR "Interpersonal skills training" OR "Parent-Child Interaction Therapy" OR "parent training" OR "parent engagement" OR "parent management" OR "parenting skills" OR "parenting intervention" OR "parenting interventions" OR "Barkley's defiant child" OR "Teacher-Child Interaction Training" OR "Incredible Years" OR "New Forest Parenting" OR "Triple P" OR "Helping the Noncompliant Child" OR "child life and attention skills" OR "clam" OR PCIT OR "parent child interaction therapy" OR "Summer Treatment Program" OR "Daily Report Card" OR "organization skills" OR "organizational skills" OR "time management" OR "homework intervention" OR braintrain OR "memory training" OR
Appendix A. Methods

"Captain's log mindpower builder" OR "memory gyms" OR "attention gym" OR "smartdriver plus" OR "smartmind pro" OR "RoboMemo" OR "play attention" OR metronome OR brainmaster OR mindmed OR "attention lab" OR (activate AND c8) OR "attention training" OR “CogniPlus” OR cogmed OR "working memory training" OR biofeedback OR neurofeedback OR neuroagility OR neurooptimal OR acupuncture OR "vision training" OR "visual training" OR "vision therapy" OR "education intervention" OR "cognitive remediation" OR neurotherapy OR "elimination diet" OR "diet therapy" OR ("low carb" OR "low carbohydrate" OR "low carbohydrates" OR "gluten free") AND diet OR "feingold diet" OR "red dye" OR ((vitamin OR vitamins) AND (supplement OR supplements)) OR "herbal supplement" OR "herbal supplements" OR probiotics OR "omega 3" OR "slow cortical potentials" OR "few foods diet" OR "oligoantigenic diet" OR "restriction diet" OR "food intolerance" OR "food allergy" OR "food allergies" OR "food sensitivity" OR "food sensitivities" OR “multimodal treatment” OR homeopathy OR homeopathic OR chiropractic OR chiropractor ) OR AB ( Monarch external Trigeminal Nerve Stimulation OR eTNS OR "EndeavorRx" OR ((classroom OR school OR schools) AND (behavior intervention OR behavior interventions)) OR peer intervention) OR (("organization skills") AND (training OR intervention)) OR "psychosocial therapy" OR "psychosocial intervention" OR "psychosocial interventions" OR "psychosocial approach" OR "psychosocial approaches" OR "psychosocial treatment" OR "psychosocial support" OR "psychoeducation" OR "nonpharmacologic therapy" OR "nondrug therapy" OR "non-drug therapy" OR "Play Therapy" OR "cognitive behavioral therapy" OR "cognitive behavior therapy" OR "cognitive behavioural therapy" OR "cognitive behaviour therapy" OR Mindfulness OR complementary OR "alternative medicine" OR "alternative therapy" OR "alternative therapies" OR "Interpersonal skills training" OR "Parent-Child Interaction Therapy" OR "parent training" OR "parent engagement" OR "parent management" OR "parenting skills" OR "parenting intervention" OR "parenting interventions" OR "Barkley's defiant child" OR "Teacher-Child Interaction Training" OR "Incredible Years" OR "New Forest Parenting" OR "Triple P" OR "Helping the Noncompliant Child" OR "child life and attention skills" OR "clas" OR PCIT OR "parent child interaction therapy" OR "Summer Treatment Program" OR "Daily Report Card" OR "organization skills" OR "organizational skills" OR "time management" OR "homework intervention" OR braintrain OR "memory training" OR "Captain's log mindpower builder" OR "memory gyms" OR "attention gym" OR "smartdriver plus" OR "smartmind pro" OR "RoboMemo" OR "play attention" OR metronome OR brainmaster OR mindmed OR "attention lab" OR (activate AND c8) OR "attention training" OR “CogniPlus” OR cogmed OR "working memory training" OR biofeedback OR neurofeedback OR neuroagility OR neurooptimal OR acupuncture OR "vision training" OR "visual training" OR "vision therapy" OR "education intervention" OR "cognitive remediation" OR neurotherapy OR "elimination diet" OR "diet therapy" OR ("low carb" OR "low carbohydrate" OR "low carbohydrates" OR "gluten free") AND diet OR "feingold diet" OR "red dye" OR ((vitamin OR vitamins) AND (supplement OR supplements)) OR "herbal supplement" OR "herbal supplements" OR probiotics OR "omega 3" OR "slow cortical potentials" OR "few foods diet" OR "oligoantigenic diet" OR "restriction diet" OR "food intolerance" OR "food allergy" OR "food allergies" OR "food sensitivity" OR "food sensitivities" OR “multimodal treatment” OR homeopathy OR homeopathic OR chiropractic OR chiropractor ))) AND (ZC "longitudinal study" OR ZC "empirical study" OR ZC "followup study" OR ZC "longitudinal study" OR ZC "meta analysis" OR ZC "prospective study" OR ZC "retrospective study" OR ZC "systematic review" OR ZC "treatment outcome/clinical trial"OR DE "Clinical Trials" OR DE "Cohort
Appendix A. Methods

Analysis" OR DE "Followup Studies" OR DE "Longitudinal Studies" OR DE "Prospective Studies" OR DE "Meta Analysis" OR TI (randomized OR randomised OR randomization OR randomisation OR randomly OR trial OR groups OR trials OR "evaluation study" OR evaluation studies OR "intervention study" OR "intervention studies" OR "case-control" OR cohort OR longitudinal OR longitudinally OR prospective OR prospectively OR retrospective OR "comparative study" OR "meta-analysis" OR "meta-analyses") OR AB (randomized OR randomised OR randomization OR randomisation OR randomly OR trial OR groups OR trials OR "evaluation study" OR evaluation studies OR "intervention study" OR "intervention studies" OR "case-control" OR cohort OR longitudinal OR longitudinally OR prospective OR prospectively OR retrospective OR "comparative study" OR "meta-analysis" OR "meta-analyses") AND (ZZ "journal article") AND yr(1980-2011)

ERIC
S1 DE "Attention Deficit Hyperactivity Disorder" OR SU "Attention Deficit Hyperactivity Disorder" OR ("attention deficit hyperactivity disorder" OR ADHD OR "attention deficit disorder")
S2 adolescence OR teenager OR teenagers OR teenaged OR teen OR teens OR adolescent OR adolescents OR adolescence OR youth
S3 S1 AND S2
S4 ("CNS Stimulating Drugs" OR "Methylphenidate" OR "Dextroamphetamine" OR "Amphetamine" OR "Clonidine" OR "Serotonin Norepinephrine Reuptake Inhibitors" OR "Atomoxetine" OR "Tricyclic Antidepressant Drugs" OR "Desipramine" OR "Nortriptyline" OR "Bupropion" OR "Serotonin Norepinephrine Reuptake Inhibitors" OR "Venlafaxine" OR "Monoamine Oxidase Inhibitors" OR "Amantadine") OR (Azstarys OR Cotempla XR-ODT OR Desoxyn OR "Alpha agonist" OR psychostimulants OR "CNS stimulating" OR "Central Nervous System stimulants" OR methylphenidate OR Dexamethylphenidate OR Dextroamphetamine OR lisdexamfetamine OR Amphetamine OR aptensio OR concerta OR Ritalin OR methylin OR medikinet OR equasym OR quillivant OR metadate OR daytrana OR focalin OR Dexedrine OR dextrostat OR procentra OR zenzedi OR Adderall OR vyvanse OR elvanse OR tyvense OR dyanavel OR evekeo OR "alpha-2 agonists" OR guanfacine OR intuniv OR tenex OR estulic OR afken OR clonidine OR catapres OR clophelin OR kapvay OR nексион OR duraclon OR "Serotonin Norepinephrine Reuptake Inhibitors" OR Strattera OR atomoxetine OR "Tricyclic Antidepressants" OR "Desipramine" OR "Nortriptyline" OR norpramin OR pertofrane OR pamelor OR "dopamine reuptake inhibitors" OR modanifil OR Provigil OR alertec OR modavigil OR modiodal OR modalert OR armodafinil OR nuvigil OR "norepinephrine-dopamine reuptake inhibitors" OR bupropion OR Wellbutrin OR zyban OR forfivo OR "Serotonin Norepinephrine Reuptake Inhibitors" OR duloxetine OR Cymbalta OR "serotonin norepinephrine dopamine reuptake inhibitors" OR "Venlafaxine" OR Effexor OR trevilor OR (Monoamine Oxidase AND Inhibitors) OR selegiline OR eldepryl OR emsam OR selegene OR zelapar OR "n methyl d aspartate receptor agonists" OR "Amantadine" OR symmetrel OR memantine OR Namenda )
S5
Appendix A. Methods

"Psychotherapy" OR "Adolescent Psychotherapy" OR "Multisystemic Therapy" OR "Behavior Therapy" OR "Dialectical Behavior Therapy" OR "Brief Psychotherapy" OR "Child Psychotherapy" OR "Play Therapy" OR "Client Centered Therapy" OR "Cognitive Behavior Therapy" OR "Group Psychotherapy" OR "Therapeutic Community" OR "Integrative Psychotherapy" OR "Psychotherapeutic Counseling" OR "Family Therapy" OR "Supportive Psychotherapy" OR "Cognitive Therapy" OR "Parent Training" OR "Parent Child Relations" OR "Time Management" OR "Mindfulness" OR "School Based Intervention" OR "Memory Training" OR "Biofeedback Training" OR "Biofeedback" OR "Computer Assisted Instruction" OR "Intelligent Tutoring Systems" OR "Diets" OR "Dietary Supplements" OR "Food Additives" OR "Fatty Acids" OR "Acupuncture" OR "Remedial Education" OR "Early Intervention" OR "Alternative Medicine" OR Monarch external Trigeminal Nerve Stimulation OR eTNS OR "EndeavorRx" OR ((classroom OR school OR schools) AND (behavior intervention OR behavior interventions)) OR "peer intervention" OR ("("organization skills") AND (training OR intervention)) OR "psychosocial therapy" OR "psychosocial intervention" OR "psychosocial interventions" OR "psychosocial approach" OR "psychosocial approaches" OR "psychosocial treatment" OR "psychosocial support" OR "psychoeducation" OR "nonpharmacologic therapy" OR "nondrug therapy" OR "non-drug therapy" OR "Play Therapy" OR "cognitive behavioral therapy" OR "cognitive behavior therapy" OR "cognitive behavioural therapy" OR "cognitive behaviour therapy" OR "cognitive behaviour therapy" OR Mindfulness OR complementary OR "alternative medicine" OR "alternative therapy" OR "alternative therapies" OR "Interpersonal skills training" OR "Parent-Child Interaction Therapy" OR "parent training" OR "parent engagement" OR "parent management" OR "parenting skills" OR "parenting intervention" OR "parenting interventions" OR "Barkley's defiant child" OR "Teacher-Child Interaction Training" OR " Incredible Years" OR "New Forest Parenting" OR "Triple P" OR "Helping the Noncompliant Child" OR "child life and attention skills" OR "clas" OR PCIT OR "parent child interaction therapy" OR "Summer Treatment Program" OR "Daily Report Card" OR "organization skills" OR "organizational skills" OR "time management" OR "homework intervention" OR brainstorm OR "memory training" OR "Captain's log mindpower builder" OR "memory gyms" OR "attention gym" OR "smartdriver plus" OR "smartmind pro" OR "RoboMemo" OR "play attention" OR metronome OR brainmaster OR mindmed OR "attention lab" OR (activate AND c8) OR "attention training" OR "CogniPlus" OR cogmed OR "working memory training" OR biofeedback OR neurofeedback OR neuroaqility OR neuroptimal OR acupuncture OR "vision training" OR "visual training" OR "vision therapy" OR "education intervention" OR "cognitive remediation" OR "neurotherapy" OR "elimination diet" OR "diet therapy" OR (("low carb" OR "low carbohydrate" OR "low carbohydrates" OR "gluten free") AND diet) OR "feingold diet" OR "red dye" OR ((vitamin OR vitamins) AND (supplement OR supplements)) OR "herbal supplement" OR "herbal supplements" OR probiotics OR "omega 3" OR "slow cortical potentials" OR "few foods diet" OR "oligoantigenic diet" OR "restriction diet" OR "food intolerance" OR "food allergy" OR "food allergies" OR "food sensitivity" OR "food sensitivities" OR "multimodal treatment" OR homeopathy OR homeopathic OR chiropractic OR chiropractor

S6
S4 OR S5
S7
S3 AND S6
S8
Appendix A. Methods

"longitudinal study" OR "empirical study" OR "followup study" OR "longitudinal study" OR "meta analysis" OR "prospective study" OR "retrospective study" OR "systematic review" OR "treatment outcome/clinical trial" OR "Clinical Trials" OR "Cohort Analysis" OR "Followup Studies" OR "Longitudinal Studies" OR "Prospective Studies" OR "Meta Analysis" OR randomized OR randomised OR randomization OR randomisation OR randomly OR trial OR groups OR trials OR "evaluation study" OR evaluation studies OR "intervention study" OR "intervention studies" OR "case-control" OR cohort OR longitudinal OR longitudinally OR prospective OR prospectively OR retrospective OR "comparative study" OR "meta-analysis" OR "meta-analyses" S9 S7 AND S8

Publication Date Range: 1980-2011; Publication Type: Journal Articles

EMBASE
1 'attention deficit disorder'/exp OR 'attention deficit disorder' OR 'attention deficit hyperactivity disorder':ab,ti OR 'adhd':ab,ti OR 'attention deficit disorder':ab,ti
2 'adolescent'/exp OR teenager:ab,ti OR teenagers:ab,ti OR teenaged:ab,ti OR teen:ab,ti OR teens:ab,ti OR adolescent:ab,ti OR adolescents:ab,ti OR adolescence:ab,ti OR youth:ab,ti
3 #1 AND #2
4 'azstarys':ab,ti OR 'cotempla xr-odt':ab,ti OR 'desoxyn':ab,ti OR 'alpha agonist':ab,ti OR 'attention deficit disorder'/exp OR 'central stimulant agent'/exp OR 'psychostimulant agent'/exp OR 'guanfacine'/exp OR 'adrenergic receptor affecting agent'/exp OR 'atomoxetine'/exp OR 'antidepressant agent'/exp OR 'n methyl dextro aspartic acid receptor' exp OR 'memantine'/exp OR 'amantadine'/exp OR 'dopamine uptake inhibitor'/exp OR 'central nervous system stimulants':ab,ti OR 'psychostimulant':ab,ti OR 'methylphenidate':ab,ti OR 'methylphenidate hydrochloride':ab,ti OR 'aptensio':ab,ti OR 'concerta':ab,ti OR 'ritalin':ab,ti OR 'ritalin la':ab,ti OR 'medikinet':ab,ti OR 'equasym':ab,ti OR 'quillivant':ab,ti OR 'metadate':ab,ti OR 'daytrana':ab,ti OR 'dexamphetamine':ab,ti OR 'dopamine uptake inhibitors':ab,ti OR 'dexamphetamine':ab,ti OR 'dextroamphetamine':ab,ti OR 'dextrostat':ab,ti OR 'procentra':ab,ti OR 'zenzedi':ab,ti OR 'mixed amphetamine salts':ab,ti OR 'adderall':ab,ti OR 'lisdexamfetamine':ab,ti OR 'lisdexamfetamine dimesylate':ab,ti OR 'vyvanse':ab,ti OR 'venvanse':ab,ti OR 'elvanse':ab,ti OR 'tyvense':ab,ti OR 'dyanavel':ab,ti OR 'evekeo':ab,ti OR 'guanfacine':ab,ti OR 'sympatholytics':ab,ti OR 'central alpha-2 adrenergic agonist':ab,ti OR 'clonidine':ab,ti OR 'intuniv':ab,ti OR 'estulic':ab,ti OR 'tenex':ab,ti OR 'catapres':ab,ti OR 'clophealin':ab,ti OR 'kapvay':ab,ti OR 'nexitilon':ab,ti OR 'duraclon':ab,ti OR 'norepinephrine reuptake inhibitors':ab,ti OR 'selective norepinephrine reuptake inhibitors':ab,ti OR 'adrenergic uptake inhibitors':ab,ti OR 'atomoxetine':ab,ti OR 'tricyclic antidepressants':ab,ti OR 'desipramine':ab,ti OR 'norpramin':ab,ti OR 'nortriptyline':ab,ti OR 'pamelor':ab,ti OR 'dopamine reuptake inhibitors':ab,ti OR 'modafinil':ab,ti OR 'provigil':ab,ti OR 'armodafinil':ab,ti OR 'norepinephrine-dopamine reuptake inhibitors':ab,ti OR 'bupropion':ab,ti OR 'wellbutrin':ab,ti OR 'forfivo':ab,ti OR 'venlafaxine':ab,ti OR 'reboxetine':ab,ti OR 'monoamine oxidase type b inhibitors':ab,ti OR 'selegiline':ab,ti OR 'nmda receptors':ab,ti OR 'n-methyl-d-aspartate receptor antagonists':ab,ti OR 'amantadine':ab,ti OR
Appendix A. Methods

'memantine':ab,ti OR 'pertofrane':ab,ti OR 'nuvigil':ab,ti OR 'cymbalta':ab,ti OR 'duloxetine':ab,ti OR 'effexor':ab,ti OR 'eldepryl':ab,ti OR 'emsam':ab,ti OR 'trevilor':ab,ti OR 'symmetryrel':ab,ti OR 'namenda':ab,ti OR 'zelapar':ab,ti
5
'monarch external trigeminal nerve stimulation':ab,ti OR etns:ab,ti OR ((classroom:ab,ti OR school:ab,ti OR schools:ab,ti) AND ('behavior intervention':ab,ti OR 'behavior interventions':ab,ti)) OR 'peer intervention':ab,ti OR ('organization skills':ab,ti AND (training:ab,ti OR intervention:ab,ti)) OR 'attention deficit disorder'/exp/mj/dm_rh,dm_dm OR 'psychotherapy'/exp OR 'child psychiatry'/exp OR 'child parent relation'/exp OR 'time management'/exp OR 'feedback system'/exp OR 'teaching'/exp OR 'adaptive behavior'/exp OR 'diet therapy'/exp OR 'omega 3 fatty acid'/exp OR 'vitamin'/exp/dd_do,dd_dt,dd_ad OR 'food additive'/exp/dd_ae OR 'probiotic agent'/exp OR 'acupuncture'/exp OR 'early childhood intervention'/exp OR 'alternative medicine'/exp OR 'psychosocial therapy':ab,ti OR 'psychosocial intervention':ab,ti OR 'psychosocial interventions':ab,ti OR 'psychosocial approach':ab,ti OR 'psychosocial approaches':ab,ti OR 'psychosocial treatment':ab,ti OR 'psychosocial support':ab,ti OR 'psychoeducation':ab,ti OR 'nonpharmacologic therapy':ab,ti OR 'nondrug therapy':ab,ti OR 'non-drug therapy':ab,ti OR 'play therapy':ab,ti OR 'cognitive behavioral therapy':ab,ti OR 'cognitive behaviour therapy':ab,ti OR 'cognitive behaviour therapy':ab,ti OR 'cognitive behaviour therapy':ab,ti OR 'cognitive behaviour therapy':ab,ti OR 'complementary':ab,ti OR 'alternative medicine':ab,ti OR 'alternative therapy':ab,ti OR 'alternative therapies':ab,ti OR 'interpersonal skills training':ab,ti OR 'parent-child interaction therapy':ab,ti OR 'parent training':ab,ti OR 'parental engagement':ab,ti OR 'parent management':ab,ti OR 'parenting skills':ab,ti OR 'parenting intervention':ab,ti OR 'parenting interventions':ab,ti OR 'barkleys defiant child':ab,ti OR 'teacher-child interaction training':ab,ti OR 'incredible years':ab,ti OR 'new forest parenting':ab,ti OR 'tripple p':ab,ti OR 'helping the noncompliant child':ab,ti OR 'child life and attention skills':ab,ti OR 'clas':ab,ti OR 'pcit':ab,ti OR 'parent child interaction therapy':ab,ti OR 'summer treatment program':ab,ti OR 'daily report card':ab,ti OR 'organization skills':ab,ti OR 'organizational skills':ab,ti OR 'time management':ab,ti OR 'homework intervention':ab,ti OR 'braintrain':ab,ti OR 'memory training':ab,ti OR 'captains log mindpower builder':ab,ti OR 'memory gyms':ab,ti OR 'attention gym':ab,ti OR 'smartdriver plus':ab,ti OR 'smartmind pro':ab,ti OR 'robomemo':ab,ti OR 'play attention':ab,ti OR 'metronome':ab,ti OR 'brainmaster':ab,ti OR 'mindmed':ab,ti OR 'attention lab':ab,ti OR (activate:ab,ti AND c8:ab,ti) OR 'attention training':ab,ti OR 'cogniplus':ab,ti OR 'cognomed':ab,ti OR 'working memory training':ab,ti OR 'biofeedback':ab,ti OR 'neurofeedback':ab,ti OR 'neuroagility':ab,ti OR 'neuroptimal':ab,ti OR 'acupuncture':ab,ti OR 'vision training':ab,ti OR 'visual training':ab,ti OR 'vision therapy':ab,ti OR 'education intervention':ab,ti OR 'cognitive remediation':ab,ti OR 'neurotherapy':ab,ti OR 'elimination diet':ab,ti OR 'diet therapy':ab,ti OR ('low carb' OR 'low carbohydrate' OR 'low carbohydrates':ab,ti OR 'gluten free') AND diet:ab,ti OR 'feingold diet':ab,ti OR 'red dye':ab,ti OR ((vitamin:ab,ti OR vitamins:ab,ti) AND (supplement:ab,ti OR supplements:ab,ti)) OR 'herbal supplement':ab,ti OR 'herbal supplements':ab,ti OR 'probiotics':ab,ti OR 'omega 3':ab,ti OR 'slow cortical potentials':ab,ti OR 'few foods diet':ab,ti OR 'oligoantigenic diet':ab,ti OR 'restriction diet':ab,ti OR 'food intolerance':ab,ti OR 'food allergy':ab,ti OR 'food allergies':ab,ti OR 'food sensitivity':ab,ti OR 'food sensitivities':ab,ti OR 'multimodal treatment':ab,ti OR 'homeopathy':ab,ti OR 'homeopathic':ab,ti OR 'chiropractic':ab,ti OR 'chiropractor':ab,ti
6
Appendix A. Methods

#4 OR #5
7
#3 AND #6
8
(randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind
procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR factorial*:ab,ti OR
crossover*:ab,ti OR ((cross NEAR/1 over*)):ab,ti) OR placebo*:ab,ti OR ((doubl* NEAR/1
blind*):ab,ti) OR ((singl* NEAR/1 blind*):ab,ti) OR assign*:ab,ti OR allocat*:ab,ti OR
volunteer*:ab,ti OR 'clinical study'/exp OR 'clinical trial':ti,ab OR 'clinical trials':ti,ab OR
'controlled study'/exp OR 'evaluation'/exp OR 'evaluation study':ab,ti OR 'evaluation
studies':ab,ti OR 'intervention study':ab,ti OR 'intervention studies':ab,ti OR 'case control':ab,ti
OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR
prospectively:ab,ti OR retrospective:ab,ti OR 'follow up'/exp OR 'follow up':ab,ti OR
'comparative effectiveness'/exp OR 'comparative study'/exp OR 'comparative study':ab,ti OR
'comparative studies':ab,ti OR 'evidence based medicine'/exp OR 'systematic review':ab,ti OR
'meta-analysis':ab,ti OR 'meta-analyses':ab,ti) NOT ('case report'/exp OR 'case study'/exp OR
'editorial'/exp OR 'letter'/exp OR 'note'/exp)
9
#7 AND #8
10
#9 AND [embase]/lim NOT [medline]/lim
11
#10 AND [humans]/lim AND [1980-2011]/py

Cochrane Reviews
#1
[mh "Attention Deficit Disorder with Hyperactivity"]
#2
attention deficit hyperactivity disorder:ab,ti OR "ADHD":ab,ti OR "attention deficit
disorder":ab,ti
#3
#1 OR #2
#4
[mh Adolescent]
#5
teenager:ab,ti OR teenagers:ab,ti OR teenaged:ab,ti OR teen:ab,ti OR teens:ab,ti OR
adolescent:ab,ti OR adolescents:ab,ti OR adolescence:ab,ti OR youth:ab,ti
#6
#4 OR #5
#7
[mh "Attention Deficit Disorder with Hyperactivity"/DT] OR [mh "Central Nervous System
Stimulants"] OR [mh Methylphenidate] OR [mh Dexamethasone] OR [mh
[mh Clonidine] OR [mh "Adrenergic Uptake Inhibitors"] OR [mh "alpha-2 Adrenergic
Receptors"] OR [mh "Adrenergic alpha-Agonists"] OR [mh "Adrenergic alpha-2 Receptor
Agonists"] OR [mh "Tricyclic Antidepressive Agents"] OR [mh Desipramine] OR [mh
Appendix A. Methods

"Dopamine Uptake Inhibitors"] OR [mh Sympathomimetics] OR [mh "Serotonin Uptake Inhibitors"] OR [mh "Monoamine Oxidase Inhibitors"] OR [mh "Monoamine Oxidase"] OR [mh Selegiline] OR [mh Bupropion] OR [mh "N-Methyl-D-Aspartate Receptors"] OR [mh Memantine] OR [mh Amantadine] #8

"Azstarys":ab,ti OR “Cotempla XR-ODT”:ab,ti OR “Desoxyn”:ab,ti OR "Alpha agonist":ab,ti OR “psychostimulants”:ab,ti OR "CNS stimulating":ab,ti OR "Central Nervous System Stimulants":ab,ti OR “psychostimulant”:ab,ti OR “Methylphenidate”:ab,ti OR "Methylphenidate Hydrochloride":ab,ti OR “Aptensio”:ab,ti OR “Concerta”:ab,ti OR “Ritalin”:ab,ti OR “Ritalin LA”:ab,ti OR “Medikinet”:ab,ti OR “Equasym”:ab,ti OR “Quillivant”:ab,ti OR “Metadate”:ab,ti OR “Daytrana”:ab,ti OR "Dexmethylphenidate":ab,ti OR “Dexmethylphenidate Hydrochloride”:ab,ti OR “Focalin”:ab,ti OR “Dextroamphetamine”:ab,ti OR “Dexedrine”:ab,ti OR “Dextrostat”:ab,ti OR “ProCentra”:ab,ti OR “Zensedi”:ab,ti OR “mixed amphetamine salts”:ab,ti OR "Adderall":ab,ti OR “lisdexamfetamine”:ab,ti OR “lisdexamfetamine dimesylate”:ab,ti OR “Vyvanse”:ab,ti OR "Venvanse":ab,ti OR "Elvanse":ab,ti OR "Tyvense":ab,ti OR "Dyanavel":ab,ti OR “Evekeo”:ab,ti OR "Guanfacine":ab,ti OR "Sympatholytics":ab,ti OR "Central alpha-2 Adrenergic Agonist":ab,ti OR “Clonidine”:ab,ti OR "Intuniv":ab,ti OR "Estulic":ab,ti OR “Tenex”:ab,ti OR "Catapres":ab,ti OR “Clophelin”:ab,ti OR "Kapvay":ab,ti OR “Nexclon”:ab,ti OR "Duraclon":ab,ti OR “Norepinephrine Reuptake Inhibitors”:ab,ti OR “Selective Norepinephrine Reuptake Inhibitors”:ab,ti OR Adrenergic Uptake Inhibitors:ab,ti OR "atomoxetine":ab,ti OR "Strattera":ab,ti OR "Tricyclic antidepressants":ab,ti OR "Desipramine":ab,ti OR "Norpramin":ab,ti OR "Nortriptyline":ab,ti OR "Pamelor":ab,ti OR Dopamine Reuptake Inhibitors:ab,ti OR "modafinil":ab,ti OR "Provigil":ab,ti OR Armodafinil:ab,ti OR Norepinephrine-dopamine Reuptake Inhibitors:ab,ti OR "Buproprion":ab,ti OR "Wellbutrin":ab,ti OR “Forfivo”:ab,ti OR "Cymbalta":ab,ti OR "venlafaxine":ab,ti OR "reboxetine":ab,ti OR Monoamine Oxidase Type B inhibitors:ab,ti OR "Selegiline":ab,ti OR “Eldepryl”:ab,ti OR “Zelapar”:ab,ti OR “NMDA receptors”:ab,ti OR N-Methyl-D-aspartate receptor Antagonists:ab,ti OR "Amantadine":ab,ti OR "Memantine":ab,ti OR “Pertofrane”:ab,ti OR “Nuvigil”:ab,ti OR "Cymbalta":ab,ti OR "duloxetine":ab,ti OR "Effexor":ab,ti OR "Eldepryl":ab,ti OR "Emsam":ab,ti OR "Trevilor":ab,ti OR "Symmetrel":ab,ti OR "Namenda":ab,ti OR "Zelapar":ab,ti #9

#8 OR #9


#9 OR #10
psychosocial therapy:ab,ti OR "psychosocial intervention":ab,ti OR "psychosocial interventions":ab,ti OR "psychosocial approach":ab,ti OR "psychosocial approaches":ab,ti OR "psychosocial treatment":ab,ti OR "psychosocial support":ab,ti OR "psychoeducation":ab,ti OR "nonpharmacologic therapy":ab,ti OR "nondrug therapy":ab,ti OR "non-drug therapy":ab,ti OR "Play Therapy":ab,ti OR "cognitive behavioral therapy":ab,ti OR "cognitive behavior therapy":ab,ti OR "cognitive behavioural therapy":ab,ti OR "cognitive behaviour therapy":ab,ti OR "cognitive behaviour therapy":ab,ti OR Mindfulness:ab,ti OR complementary:ab,ti OR "alternative medicine":ab,ti OR "alternative therapy":ab,ti OR "alternative therapies":ab,ti OR "Interpersonal skills training":ab,ti OR "Parent-Child Interaction Therapy":ab,ti OR "parent training":ab,ti OR "parent engagement":ab,ti OR "parent management":ab,ti OR "parenting skills":ab,ti OR "parenting intervention":ab,ti OR "parenting interventions":ab,ti OR "Barkley's defiant child":ab,ti OR "TeacherChild Interaction Training":ab,ti OR "Incredible Years":ab,ti OR "New Forest Parenting":ab,ti OR "Triple P":ab,ti OR "Helping the Noncompliant Child":ab,ti OR "child life and attention skills":ab,ti OR "clas":ab,ti OR PCIT:ab,ti OR "parent child interaction therapy":ab,ti OR "Summer Treatment Program":ab,ti OR "Daily Report Card":ab,ti OR "organization skills":ab,ti OR "organizational skills":ab,ti OR "time management":ab,ti OR "homework intervention":ab,ti OR braintrain:ab,ti OR "memory training":ab,ti OR "Captain's log mindpower builder":ab,ti OR "memory gyms":ab,ti OR "attention gym":ab,ti OR "smartdriver plus":ab,ti OR "smartmind pro":ab,ti OR "RoboMemo":ab,ti OR "play attention":ab,ti OR metronome:ab,ti OR brainmaster:ab,ti OR mindmed:ab,ti OR "attention lab":ab,ti OR (activate:ab,ti AND c8:ab,ti) OR "attention training":ab,ti OR "CogniPlus":ab,ti OR cogmed:ab,ti OR "working memory training":ab,ti OR biofeedback:ab,ti OR neurofeedback:ab,ti OR neuroagility:ab,ti OR neuroptimal:ab,ti OR acupuncture:ab,ti OR "vision training":ab,ti OR "visual training":ab,ti OR "vision therapy":ab,ti OR "education intervention":ab,ti OR "cognitive remediation":ab,ti OR neurotherapy:ab,ti OR "elimination diet":ab,ti OR "diet therapy":ab,ti OR (("low carb" OR "low carbohydrate" OR "low carbohydrates":ab,ti OR "gluten free") AND diet:ab,ti) OR "feingold diet":ab,ti OR "red dye":ab,ti OR ((vitamin:ab,ti OR vitamins:ab,ti) AND (supplement:ab,ti OR supplements:ab,ti)) OR "herbal supplement":ab,ti OR "herbal supplements":ab,ti OR probiotics:ab,ti OR "omega 3":ab,ti OR "slow cortical potentials":ab,ti OR "few foods diet":ab,ti OR "oligoantigenic diet":ab,ti OR "restriction diet":ab,ti OR "food intolerance":ab,ti OR "food allergy":ab,ti OR "food allergies":ab,ti OR "food sensitivity":ab,ti OR "food sensitivities":ab,ti OR "multimodal treatment":ab,ti OR homeopathy:ab,ti OR homeopathic:ab,ti OR chiropractic:ab,ti OR chiropractor:ab,ti #12
#10 OR #11
#13
#12 OR #9
#14
#3 AND #6 AND #13
with Cochrane Library publication date Between Jan 1980 and Dec 2011, in Cochrane Reviews #15
#3 AND #6
in Cochrane Reviews
ADHD KQ3

PubMed
1 "Attention Deficit Disorder with Hyperactivity"[Mesh] OR "attention deficit hyperactivity disorder"[tiab] OR "ADHD"[tiab] OR "attention deficit disorder"[tiab]
6 animals[mh]
7 humans[mh]
8 English[la]
9 #1 AND #2 AND #3 AND #4 NOT #5 NOT #6 NOT #7 AND #8
Publication Date Range: To January 2023

PsycINFO
#1
SU "Attention Deficit Disorder with Hyperactivity" OR TI ( "attention deficit hyperactivity disorder" OR ADHD OR "attention deficit disorder" ) OR AB ( "attention deficit hyperactivity disorder" OR ADHD OR "attention deficit disorder" )
Appendix A. Methods

AGE (childhood OR adolescence ) OR SU "Pediatrics" OR TI ( child OR children OR infant OR infants OR preschool OR preshooler OR pediatric OR teenager OR teenagers OR teenaged OR teen OR teens OR adolescent OR adolescents OR adolescence OR youth ) OR AB ( child OR children OR infant OR infants OR preschool OR preshooler OR pediatric OR teenager OR teenagers OR teenaged OR teen OR teens OR adolescent OR adolescents OR adolescence OR youth )

#3
TI(monitor OR monitored OR monitoring OR (“follow up” OR “followed up” OR visit OR visits OR session OR sessions OR appointment OR appointments) AND (schedule* OR strategy*) OR “longitudinal” OR longitudinally OR “long term”) OR AB(monitor OR monitored OR monitoring OR (“follow up” OR “followed up” OR visit OR visits OR session OR sessions OR appointment OR appointments) AND (schedule* OR strategy*) OR “longitudinal” OR longitudinally OR “long term”)

#4
"longitudinal study" OR "empirical study" OR "followup study" OR "longitudinal study" OR "meta analysis" OR "prospective study" OR "retrospective study" OR "systematic review" OR "treatment outcome/clinical trial"OR "Clinical Trials" OR "Cohort Analysis" OR "Followup Studies" OR "Longitudinal Studies" OR "Prospective Studies" OR "Meta Analysis" OR TI (randomized OR randomised OR randomization OR randomisation OR randomly OR trial OR groups OR trials OR "evaluation study" OR evaluation studies OR "intervention study" OR "intervention studies" OR "case-control" OR cohort OR longitudinal OR longitudinally OR prospective OR prospectively OR retrospective OR "comparative study" OR "meta-analysis" OR "meta-analyses" ) OR AB (randomized OR randomised OR randomization OR randomisation OR randomly OR trial OR groups OR trials OR "evaluation study" OR evaluation studies OR "intervention study" OR "intervention studies" OR "case-control" OR cohort OR longitudinal OR longitudinally OR prospective OR prospectively OR retrospective OR "comparative study" OR "meta-analysis" OR "meta-analyses" ) AND (RTYPE "journal article")

#5
#1 AND #2 AND #3 AND #4
#6
#5, English
Publication Date Range: To 2021

ERIC

#1
"Attention Deficit Disorder with Hyperactivity" OR TI/AB "attention deficit hyperactivity disorder" OR ADHD OR "attention deficit disorder"

#2
childhood OR adolescence OR "Pediatrics" OR TI/AB ( child OR children OR infant OR infants OR preschool OR preshooler OR pediatric OR teenager OR teenagers OR teenaged OR teen OR teens OR adolescent OR adolescents OR adolescence OR youth )

#3
TI/AB monitor OR monitored OR monitoring OR (“follow up” OR “followed up” OR visit OR visits OR session OR sessions OR appointment OR appointments) AND (schedule* OR strategy*) OR longitudinal OR longitudinally OR “long term”

#4
Appendix A. Methods

"longitudinal study" OR "empirical study" OR "followup study" OR "longitudinal study" OR "meta analysis" OR "prospective study" OR "retrospective study" OR "systematic review" OR "treatment outcome/clinical trial" OR "Clinical Trials" OR "Cohort Analysis" OR "Followup Studies" OR "Longitudinal Studies" OR "Prospective Studies" OR "Meta Analysis" OR TI/AB (randomized OR randomised OR randomization OR randomisation OR randomly OR trial OR groups OR trials OR "evaluation study" OR evaluation studies OR "intervention study" OR "intervention studies" OR "case-control" OR cohort OR longitudinal OR longitudinally OR prospective OR prospectively OR retrospective OR "comparative study" OR "meta-analysis" OR "meta-analyses")

#5
#1 AND #2 AND #3 AND #4

EMBASE

#1
‘attention deficit disorder'/exp OR "attention deficit hyperactivity disorder":ab,ti OR "ADHD":ab,ti OR "attention deficit disorder":ab,ti

#2
‘pediatrics'/exp OR 'adolescent'/exp OR 'infant'/exp OR 'child'/exp OR child:ab,ti OR children:ab,ti OR infant:ab,ti OR infants:ab,ti OR preschool:ab,ti OR preschooler:ab,ti OR pediatric:ab,ti OR teenager:ab,ti OR teenagers:ab,ti OR teen:ab,ti OR teens:ab,ti OR adolescent:ab,ti OR adolescents:ab,ti OR youth:ab,ti

#3
monitor:ab,ti OR monitored:ab,ti OR monitoring:ab,ti OR ('follow up':ab,ti OR 'followed up':ab,ti OR visit:ab,ti OR visits:ab,ti OR session:ab,ti OR sessions:ab,ti OR appointment:ab,ti OR appointments:ab,ti) AND (schedule* OR strategy*) OR 'longitudinal':ab,ti OR longitudinally:ab,ti OR 'long term':ab,ti

#4
('randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR (cross NEAR/1 over*):ab,ti OR placebo*:ab,ti OR (doubl* NEAR/1 blind*):ab,ti OR (singl* NEAR/1 blind*):ab,ti OR assign*:ab,ti OR volunteer*:ab,ti OR 'clinical study'/exp OR 'clinical trial':ti,ab OR 'clinical trials':ti,ab OR 'controlled study'/exp OR 'evaluation'/exp OR 'evaluation study':ab,ti OR 'evaluation studies':ab,ti OR 'intervention study':ab,ti OR 'intervention studies':ab,ti OR 'case control':ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR retrospectively:ab,ti OR retrospective:ab,ti OR 'follow up'/exp OR 'follow up':ab,ti OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR 'comparative studies':ab,ti OR 'comparative studies':ab,ti OR 'evidence based medicine'/exp OR 'systematic review':ab,ti OR 'meta-analysis':ab,ti OR 'meta-analyses':ab,ti NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp)

#5
#1 AND #2 AND #3 AND #4

#6
#5 AND [humans]/lim

#7
#6 AND [embase]/lim NOT [medline]/lim
Appendix A. Methods

Publication Date Range: To 2021

**Cochrane Reviews**

#1
[mh "Attention Deficit Disorder with Hyperactivity"]

#2
attention deficit hyperactivity disorder:ab,ti OR ADHD:ab,ti OR attention deficit disorder:ab,ti

#3
#1 OR #2

#4

#5
child:ab,ti OR children:ab,ti OR infant:ab,ti OR infants:ab,ti OR preschool:ab,ti OR preschooler:ab,ti OR pediatric:ab,ti OR teenager:ab,ti OR teenagers:ab,ti OR teenaged:ab,ti OR teen:ab,ti OR teens:ab,ti OR adolescent:ab,ti OR adolescents:ab,ti OR adolescence:ab,ti OR youth:ab,ti

#6
#4 OR #5

#7
monitor:ab,ti OR monitored:ab,ti OR monitoring:ab,ti OR ("follow up":ab,ti OR “followed up”:ab,ti OR visit:ab,ti OR visits:ab,ti OR session:ab,ti OR sessions:ab,ti OR appointment:ab,ti OR appointments:ab,ti) AND (schedule* OR strategy*) OR longitudinally:ab,ti OR longitudinal:ab,ti OR “long term”:ab,ti

#8
#6 OR #7

#9
#3 AND #6 AND #8

#10
Limit to CDSR

**ClinicalTrials.gov**

Conditions: ADHD OR attention deficit
Recruitment: Completed studies
Study Results: All studies
Study type: Interventional studies
Age group: Child
Phase : Phase 2, Phase 3, Phase 4
Appendix B. List of Excluded Studies

This appendix shows the list of excluded studies with reasons for exclusion. We only recorded one reason per publication.

   *Design*


5. The pharmacological treatment of attention-deficit hyperactivity disorder (ADHD) in adolescents is effective and relatively safe. Drugs and Therapy Perspectives. 2007;23(11):9-12. doi: 10.2165/00042310-200723110-00003. *Design*


7. ADHD medications may be linked to sudden unexplained death. Formulary. 2009;44(7):192. *Design*


Appendix B. List of Excluded and Background Studies


Appendix B. List of Excluded and Background Studies


Appendix B. List of Excluded and Background Studies


Appendix B. List of Excluded and Background Studies


90. Akili Interactive Labs I. Software Treatment for Actively Reducing Severity of ADHD as Adjunctive Treatment to Stimulant. 2018. Design


Appendix B. List of Excluded and Background Studies


Appendix B. List of Excluded and Background Studies


112. Alegre HdCdP, Tecnológico CNdD Ce. Cost-Effectiveness Study Of The Treatment Of Attention Deficit/Hyperactivity Disorder In Brazil. 2010. Intervention


121. Alford JL. Inhibition in children with attention/deficit/hyperactivity disorder, combined type (ADHD+C): An examination of Barkley’s hybrid model and Zentall’s optimal stimulation model: Pacific Graduate School of Psychology; 2007. Design

Appendix B. List of Excluded and Background Studies


Appendix B. List of Excluded and Background Studies

148. Alza Corporation D, USA. An Effectiveness and Safety Study Evaluating OROS Methylphenidate Hydrochloride (HCl), Ritalin (Methylphenidate HCl) and Placebo in Children With Attention Deficit Hyperactivity Disorder. 1998. *Intervention*


Appendix B. List of Excluded and Background Studies


167. Amsterdam VUo, Shire. The Effects of Long-acting Methylphenidate on Academic Activity and Related Constructs in Children With ADHD. 2013. Outcome


Appendix B. List of Excluded and Background Studies


Appendix B. List of Excluded and Background Studies


Appendix B. List of Excluded and Background Studies


217. Arbor Pharmaceuticals I. Crossover Study to Evaluate the Efficacy of AR11 in Pediatric Patients With ADHD in a Laboratory Classroom Setting. 2013. *Outcome*

218. Arbor Pharmaceuticals I. AR08 for Treatment of ADHD in Children. 2013. *Outcome*


Appendix B. List of Excluded and Background Studies


234. Arizona Uo, Health NIOH. Methylphenidate Study in Young Children With Developmental Disorders. 2001. *Outcome*

Appendix B. List of Excluded and Background Studies


247. Arnold LE, Jensen PS. MICRONUTRIENTS AS TREATMENT AND PREVENTION: NEW FINDINGS FROM 2 RCTS (MADDY AND NUTRIMUM) FOR ADHD, EMOTIONAL


259. Arria AM, Caldeira KM, O'Grady KE, et al. Nonmedical use of prescription stimulants among college students: associations with attention-deficit-hyperactivity disorder and polydrug
Appendix B. List of Excluded and Background Studies


Appendix B. List of Excluded and Background Studies


Appendix B. List of Excluded and Background Studies


Appendix B. List of Excluded and Background Studies


Appendix B. List of Excluded and Background Studies


Appendix B. List of Excluded and Background Studies


Appendix B. List of Excluded and Background Studies


Appendix B. List of Excluded and Background Studies

   Duplicate

   Design

   Population

   Intervention

   Intervention

   Intervention

   Intervention

   Design

   Intervention

   Intervention

356. Barkley RA, Anastopoulos AD, Guevremont DC, et al. Adolescents with attention deficit hyperactivity disorder: mother-adolescent interactions, family beliefs and conflicts, and maternal
Appendix B. List of Excluded and Background Studies


Appendix B. List of Excluded and Background Studies


Appendix B. List of Excluded and Background Studies


Appendix B. List of Excluded and Background Studies


Appendix B. List of Excluded and Background Studies

Deficit/Hyperactivity Disorder: A Randomized Pilot Study. SAGE Open. 2020 01/01;10(4). PMID: EJ1283372. Power


Appendix B. List of Excluded and Background Studies


Intervention


Timing


Outcome


Intervention


Power


Intervention


Outcome


Outcome


428. Bédard AC SK, Krone B, Pedraza J, Duhoux S, Halperin JM, Newcorn JH. Neural mechanisms underlying the therapeutic actions of guanfacine treatment in youth with ADHD: a
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545. Björnsdotter A, Ghaderi A, Enebrink P. Cluster Analysis of Child Externalizing and Prosocial Behaviors in a Randomized Effectiveness Trial of the Family-Check Up and Internet-
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616. Breaux R, Langberg JM. Development and Refinement of the RELAX Intervention, an Intervention Targeting Emotion Dysregulation and Interpersonal Conflict in Adolescents with
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640. Brown RT, Borden KA, Clingerman SR. Pharmacotherapy in ADD adolescents with special attention to multimodality treatments. Psychopharmacol Bull. 1985;21(2):192-211. PMID: 2860691. Design


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704. Bustamante EE. Physical Activity Intervention for ADHD and DBD: University of Illinois at Chicago; 2013. Design


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743. Cantwell DP. Pharmacotherapy of ADD in adolescents: what do we know, where should we go, how should we do it? Psychopharmacol Bull. 1985;21(2):251-7. PMID: 3889970. Design


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801. Center HUM. Pharmacogenetic Study of Methylphenidate in Attention Deficit/Hyperactivity Disorder (ADHD). 2005. Intervention


803. Center SZM. Virtual Reality a Novel Screening and Treatment Aid in Attention Deficit Disorder. 2006. Intervention

804. Center T-ASM. Supplementation of Phosphatidylserine (PS) and n-3 Long Chain Fatty Acids (EPA, DHA) in Children With ADHD. 2004. Population


808. Cephalon, R TBPP, D I. Evaluate the Safety and Efficacy of Modafinil in Children and Adolescents With ADHD. 2003. Intervention

809. Cephalon, R TBPP, D I. Study to Assess Satisfaction With Modafinil Treatment in Children and Adolescents With ADHD. 2005. Intervention

810. Cephalon, R TBPP, D I. Study to Evaluate the Efficacy of Modafinil Treatment in Patients With Attention Deficit Hyperactivity Disorder (ADHD) Who Are Responders to Modafinil Treatment. 2006. Outcome


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874.  THE EFFECT OF APPLYING CINNAMON AROMATHERAPY FOR CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER. 2008. Power


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910. Children's Hospital Medical Center C. Response Variability in Children With Attention Deficit Hyperactivity Disorder (ADHD). 2006. Timing

911. Children's Hospital Medical Center C. Improving Sleep and Daytime Functioning Among Children Diagnosed With Attention Deficit Hyperactivity Disorder (ADHD). 2010. Power
912. Children's Hospital Medical Center C, Health NIoM. Attention Deficit Disorder Medication Response Study. 2006. *Timing*

913. Children's Hospital Medical Center C, Health NIoM. Comparing School Based Interventions for Adolescents With Attention Deficit Hyperactivity Disorder. 2010. *Outcome*


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971. Cincinnati Uo, DSM Nutritional Products I. Effect of Omega-3 Fatty Acid on Cortical Function in ADHD. 2013. Design


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1004. Coghill DR, Banaschewski T, Nagy P, et al. Long-Term Safety and Efficacy of Lisdexamfetamine Dimesylate in Children and Adolescents with ADHD: A Phase IV, 2-Year,
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1016. Colomer C, Berenguer C, Roselló B, et al. The Impact of Inattention, Hyperactivity/Impulsivity Symptoms, and Executive Functions on Learning Behaviors of
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1364. Eli Lilly Company. Treatment With Atomoxetine Hydrochloride in Children and Adolescents With ADHD. 2003. Intervention


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1574. Freiburg UH, Novartis. Pharmacokinetics of Two Extended-Release Formulations of Methylphenidate in Children With Attention Deficit Hyperactivity Disorder (ADHD). 2008. Outcome


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1592. Frogner L, Andershed AK, Andershed H. Psychopathic Personality Works Better than CU Traits for Predicting Fearlessness and ADHD Symptoms among Children with Conduct...
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1603. Furu K, Karlstad Ø, Zoega H, et al. Utilization of Stimulants and Atomoxetine for Attention-Deficit/Hyperactivity Disorder among 5.4 Million Children Using Population-Based
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1712. Ginsberg Y, Arngrim T, Philipsen A, et al. Long-term (1 year) safety and efficacy of methylphenidate modified-release long-acting formulation (MPH-LA) in adults with attention-deficit hyperactivity disorder: a 26-week, flexible-dose, open-label extension to a 40-week,


1724. Goetz M, Yeh CB, Ondrejka I, et al. A 12-month prospective, observational study of treatment regimen and quality of life associated with ADHD in central and eastern europe and
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1758. Gomez R, Vance A, Stavropoulos V. Correlated Trait-Correlated Method Minus One Analysis of the Convergent and Discriminant Validity of the Conners 3 Short Forms.
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1795. Grazioli S, Mauri M, Rosi E, et al. Use of machine learning on clinical questionnaires data to support the diagnostic classification of Attention Deficit Hyperactivity Disorder: a


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2112. Hospital BC, Center HUM. Genetic Polymorphism and OROS-Methylphenidate Treatment in Attention Deficit Hyperactivity Disorder(ADHD). 2006. Intervention

2113. Hospital BCs, Health NIoM. Methylphenidate for Treating Attention Deficit Hyperactivity Disorder in Children With Both ADHD and Epilepsy. 2003. Outcome

2114. Hospital H, Health NIo. Effect of Working Memory Training on ADHD Brain Function. 2009. Outcome

2115. Hospital MG. Study of Medication Patch to Treat Children Ages 6-12 With ADHD. 2006. Power

2116. Hospital MG. Proton Magnetic Spectroscopy in Children and Adolescents With ADHD Before and After Treatment With OROS Methylphenidate. 2006. Intervention

2117. Hospital MG. Omega-3 Supplementation to ADHD Medication in Children. 2014. Intervention

2118. Hospital MG, Abuse NIoD. Effectiveness of ATMX in Treating Adolescents With ADHD and SUD. 2004. Outcome


2122. Hospital RI. The Effect of a Once Daily Dose of Atomoxetine (ATX) on ADHD-Related Insomnia in Children and Adolescents. 2005. Outcome

2123. Hospital SCs, Novartis. Sleep and Tolerability Study: Comparing the Effects of Adderall XR and Focalin XR. 2006. Power
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2209. Institute NYSP. Long-Duration Stimulant Treatment Study of ADHD in Young Children. 2005. Intervention

2210. Institute NYSP. Pilot Study of Vyvanse™ In ADHD Adolescents at Risk for Substance Abuse. 2008. Intervention


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2244. Jacobs GR, Voineskos AN, Hawco C, et al. Integration of brain and behavior measures for identification of data-driven groups cutting across children with ASD, ADHD, or OCD.


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2304. Johnson, Ltd JT. A Study to Determine Effective and Tolerable Titration Scheme for OROS-Methylphenidate in Children With Attention-deficit Hyperactivity Disorder. 2006. Intervention


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2325. The efficacy of homoeopathic simillimum in the treatment of attention-deficit/hyperactivity disorder (AD/HD) in schoolgoing children aged 6-11 years. 2009. Design

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2431. KemPharm I. KP415 Classroom Study in Children (6-12 Years of Age) With ADHD. 2017. Intervention


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2461. Kids CU. Implementation of Climb Up Program for Children With Attention Deficit Hyperactivity Disorder (ADHD) and Dyslexia in a School in India. 2007. Intervention


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2577. Krone B, Bedard AC, Downes L, et al. 5.9 DOUBLE DISSOCIATION OF NEUROPSYCHOLOGICAL CORRELATES FOR COGNITIVE PHENOTYPES IN ADHD.
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2589. Kumpersek HG, Gricar A, Ülen I, et al. A Pilot Randomized Control Trial With the Probiotic Strain Lactobacillus rhamnosus GG (LGG) in ADHD: Children and Adolescents
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2601. Kutlu A, Akyol Ardic U, Ercan ES. Effect of Methylphenidate on Emotional Dysregulation in Children With Attention-Deficit/Hyperactivity Disorder + Oppositional Defiant
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2606. La Marca JP, O'Connor RE. Neurofeedback as an intervention to improve reading achievement in students with attention-Deficit/hyperactivity disorder, inattentive subtype. NeuroRegulation. 2016;3(2):55-77. doi: 10.15540/nr.3.2.55. Intervention


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2649. Larsson JO, Larsson H, Lichtenstein P. Genetic and environmental contributions to stability and change of ADHD symptoms between 8 and 13 years of age: a longitudinal twin
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2704. Lee V. Balance training for paediatric patients with developmental coordination disorder, attention deficit hyperactivity disorder, or a combination of both. PROSPERO 2017 CRD42017077786. 2017. https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=77786. Design


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2777. Lilly E, Company. Long-Term, Open Label Atomoxetine Study. 2000. Intervention


2779. Lilly E, Company. Comparison Atomoxetine Hydrochloride and Comparator in Pediatric Outpatients With ADHD. 2003. Outcome


2782. Lilly E, Company. Safety and Efficacy of Switching From a Stimulant Medication to Atomoxetine in Children and Adolescents With ADHD. 2004. Intervention


2784. Lilly E, Company. Comparison of Atomoxetine Plus Either Comparator or Placebo in Children With ADHD Who Haven't Responded to Stimulant Therapy. 2004. Intervention


2787. Lilly E, Company. Open-Label Trial of Atomoxetine to Evaluate Academic Outcome in Children Ages 8-11 Years With Attention Deficit/Hyperactivity Disorder. 2004. Intervention


2795. Lilly E, Company. Comparison of Atomoxetine and Placebo in Children With Attention-Deficit/Hyperactivity Disorder (ADHD) and/or Reading Disorder (RD). 2005. Power

2796. Lilly E, Company. Efficacy of Atomoxetine on Psychosocial Function of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder (ADHD). 2006. Intervention


2798. Lilly E, Company. A Study for Patients With Attention-Deficit/Hyperactivity Disorder Treated With Atomoxetine. 2007. Comparator
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2799. Lilly E, Company. Effects of Atomoxetine on Brain Activation During Attention & Reading Tasks in Participants With ADHD & Comorbid Dyslexia. 2008. *Power*


2811. Linden M, Habib T, Radojevic V. A controlled study of the effects of EEG biofeedback on cognition and behavior of children with attention deficit disorder and learning disabilities.
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2862. Lori A. Schweickert M, Shire, Schweickert LA, M.D. Inuniv and Working Memory. 2010. Comparator


2867. Ltd. A. Safety and Tolerability Study of Metadoxine Extended Release (MDX) (Previously Known as MG01CI) in PI-ADHD Adolescent Subjects. 2014. Intervention


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2901. Lyon HCd. Efficacy of Phosphatidylserine Enriched With n-3 PUFA Supplementation on ADHD in Children With Epilepsy. 2015. *Outcome*


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2956. Mannuzza S, Klein RG, Moulton JL, 3rd. Persistence of Attention-Deficit/Hyperactivity Disorder into adulthood: what have we learned from the prospective follow-up studies? J Atten
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2980. Marina Martin-Moratinos MB-FHB-F. Effects of music on ADHD symptomatology and potential application of music in video games: A systematic review. PROSPERO 2021
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2992. Martel MM. Hormonal associations with childhood ADHD and associated trait and neuropsychological mechanisms: Michigan State University; 2009. Intervention

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3030. Mayes SD, Handford HA, Schaefer JH, et al. The relationship of HIV status, type of coagulation disorder, and school absenteeism to cognition, educational performance, mood, and
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3103. Mehrabi-Taleghani S, Taheri H, Mashhadi A, et al. Comparing the effects of consistent and inconsistent physical activities on decreasing the symptoms in students featuring attention
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3138. Mian A, Jansen PW, Nguyen AN, et al. Children's Attention-Deficit/Hyperactivity Disorder Symptoms Predict Lower Diet Quality but Not Vice Versa: Results from Bidirectional
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3152. Miklavcic JJ, Ivity E, MacDonald IM, et al. AA and DHA are decreased in paediatric AD/HD and inattention is ameliorated by increased plasma DHA. Human Nutrition and Metabolism. 2023;31. doi: 10.1016/j.hnm.2022.200183. Outcome


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3426. Northup J, Reitman D, de Back J. The STAR Program: A Description and Analysis of a Multifaceted Early Intervention for Young Children with a Diagnosis of Attention Deficit Hyperactivity Disorder. Child & Family Behavior Therapy. 2009 01/01/;31(2):75-93. PMID: EJ861679. Comparator


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3432. Noven Pharmaceuticals I, Therapeutics N. Study to Evaluate Safety & Efficacy of d-Amphetamine Transdermal System Compared to Placebo in Children & Adolescents With ADHD. 2012. *Intervention*


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3539. Packard SS. EFFECTS OF VIGOROUS BOUTS OF PHYSICAL ACTIVITY IN ELEMENTARY STUDENTS WITH AND WITHOUT A DIAGNOSIS OF ATTENTION DEFICIT DISORDER: AN EXAMINATION OF HOW PHYSICAL ACTIVITY
INFLUENCES THE ATTENTION AND CONCENTRATION OF STUDENTS IN THE SCHOOL ENVIRONMENT: Miami University; 2007. Design


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3657. Peyre H, Galera C, van der Waerden J, et al. Relationship between early language skills and the development of inattention/hyperactivity symptoms during the preschool period: Results


3664. Pfizer. NWP09 in Children With Attention Deficit Hyperactivity Disorder (ADHD). 2012. Intervention


3668. Pharmaceuticals I, Development I. Pharmacokinetics of HLD200 in Children and Adolescents With ADHD. 2013. Intervention

3669. Pharmaceuticals I, Development I. A Trial Evaluating the Efficacy and Safety of HLD200 in Children With ADHD. 2014. Intervention

3670. Pharmaceuticals I, Development I. A Pivotal Efficacy Trial to Evaluate HLD200 in Children With ADHD in a Naturalistic Setting. 2015. Timing
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3671. Pharmaceuticals I, Development I. A Pivotal Efficacy Trial to Evaluate HLD200 in Children With ADHD in a Classroom Setting. 2015. Timing

3672. Pharmaceuticals I, Development I. A Study of Delayed and Extended Release Formulation of Dextroamphetamine Sulfate (HLD100) in Children With ADHD. 2016. Population


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3698. Pittsburgh Uo, Abuse NiOa, Alcoholism. Atomoxetine to Treat Adolescents With Coexisting Alcohol and Other Substance Use Disorder and ADHD. 2006. Intervention


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3725. Porter SS, Omizo MM. The effects of group relaxation training/large muscle exercise, and parental involvement on attention to task, impulsivity, and locus of control among hyperactive boys. The Exceptional Child. 1984 1984/03/01;31(1):54-64. doi: 10.1080/0156655840310107. *Power*


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3786. Queens College TCUoNY. Non-pharmacological Interventions for Preschoolers With Attention Deficit Hyperactivity Disorder (ADHD). 2011. Power


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3804. Ramer JD, Santiago-Rodríguez ME, Davis CL, et al. Exercise and Academic Performance Among Children With Attention-Deficit Hyperactivity Disorder and Disruptive Behavior
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3831. RCSI, Campus UM, Penang Hospital M. Tocotrienols for School-going Children With ADHD. 2012. Outcome


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3856. Rhodes Pharmaceuticals LP. Time Course of Response to Methylphenidate HCl ER Capsules in Children 6 to 12 Years With ADHD in Classroom Setting. 2010. Intervention

3857. Rhodes Pharmaceuticals LP. Efficacy and Safety of Methylphenidate HCl ER Capsules in Children and Adolescents With ADHD. 2010. Intervention

3858. Rhodes Pharmaceuticals LP. Pharmacokinetic Study of Methylphenidate HCl Extended-Release Capsules in Children 4 to Under 6 Years of Age With ADHD. 2016. Intervention

3859. Rhodes Pharmaceuticals LP. A Flexible-Dose Titration Study of Aptensio XR in Children Ages 4 to Under 6 Years Diagnosed With ADHD. 2016. Intervention


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3874. Richardson CC. Self-assessment of regular physical activity and academic achievement in students with attention-deficit/ hyperactivity disorder (Doctoral Dissertation) 2009. Intervention


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3988. Rumsey RK. Executive functioning in boys and girls with attention-deficit/hyperactivity disorder with and without a comorbid reading disability: University of Wisconsin; 2004. Design


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4034. Samuele Cortese JZAD-R. Meditation-based interventions for ADHD in children, adolescents, and adults: a systematic review and meta-analysis. PROSPERO 2018
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4071. Sasser TR, Kalvin CB, Bierman KL. Developmental trajectories of clinically significant attention-deficit/hyperactivity disorder (ADHD) symptoms from grade 3 through 12 in a high-
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4172. Sears D, Sears D, M.D. A Study of Combination Therapy in Children With ADHD. 2014. Outcome


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4263. Shire, Takeda. Analog Classroom Study Comparison of ADDERALL XR With STRATTERA in Children Aged 6-12 With ADHD. 2003. Intervention

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4265. Shire, Takeda. A Classroom Study to Assess the Time of Onset of Vyvanse (Lisdexamfetamine Dimesylate) in Pediatric Subjects Aged 6-12 With Attention Deficit/Hyperactivity Disorder (ADHD). 2007. Intervention


4269. Shire, Takeda. Safety and Tolerability Study of SPD489 in Preschool Children Aged 4-5 Years, Diagnosed With Attention-deficit/Hyperactivity Disorder. 2015. Intervention

4270. Shire, Takeda. Safety, Tolerability, Pharmacokinetic, and Efficacy Study of SPD489 in Preschool Children With Attention-deficit/Hyperactivity Disorder. 2015. Intervention


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4295. Sidhu P. The efficacy of mindfulness meditation in increasing the attention span in children with ADHD [Ph.D.]. United States -- California: Pacifica Graduate Institute; 2013. Design


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4366. So R, Makino K, Hirota T, et al. The 2-Year Course of Internet Addiction Among a Japanese Adolescent Psychiatric Clinic Sample with Autism Spectrum Disorder and/or

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4367. So Y-c. Effectiveness of Methylphenidate and Combined Treatment (Methylphenidate and Psychosocial Treatment) for Chinese Children with Attention-Deficit Hyperactivity Disorder in a Community Mental Health Center. Hong Kong, China: Chinese University of Hong Kong; 2005. Design


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4517. Sul FUoRGd, Tecnológico CNdDCe, Alegre HdCdP. The Role of Adverse Environment Factors, Family Functioning and Parental Psychopathology in the Response to Treatment With Methylphenidate in Children and Adolescents With Attention Deficit/Hyperactivity Disorder. 2006. Intervention


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4533. Sunovion. A Study to Evaluate the Efficacy and Safety of Dasotraline in Children 6 to 12 Years of Age With Attention-Deficit Hyperactivity Disorder (ADHD) in a Simulated Classroom Setting. 2016. Intervention

4534. Sunovion. A Study to Evaluate the Efficacy and Safety of Dasotraline in Children 6 to 12 Years Old With Attention-Deficit Hyperactivity Disorder (ADHD) in a Simulated Classroom Setting. 2017. Intervention


4536. Supernus Pharmaceuticals I. Phase 2a Study of Safety and Tolerability of SPN-810 in Children With ADHD and Persistent Serious Conduct Problems. 2008. Power


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4582. Takeda T, Nissley-Tsiopinis J, Nanda S, et al. Factors Associated With Discrepancy in Parent-Teacher Reporting of Symptoms of ADHD in a Large Clinic-Referred Sample of
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4640. The University of Texas Health Science Center H, Health NIoM. Methylphenidate for Attention Deficit Hyperactivity Disorder and Autism in Children. 2005. Power

4641. Therapeutics N. Classroom Study to Assess Efficacy and Safety of MTS in Pediatric Patients Aged 6-12 With ADHD. 2004. Intervention

4642. Therapeutics N. Characterization of Dermal Reactions in Pediatric Patients With ADHD Using DAYTRAN. 2007. Intervention
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4643. Therapeutics N. Evaluate the Safety and Efficacy of Methylphenidate Transdermal System (MTS) in Adolescents Aged 13-17 Years With ADHD. 2007. Intervention


4645. Therapeutics N, Noven Pharmaceuticals I. Safety & Tolerability of MTS in Children Aged 6-12 Diagnosed With ADHD & Previously Treated With Extended-Release Methylphenidate Therapy. 2005. Intervention


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4722. Trust OH. ERP Based Single-dose Predictions of Stimulants. 2006. Intervention


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4763. University C. Tipepidine in Children With Attention Deficit/Hyperactivity Disorder (AD/HD): a Double-blind, Placebo-controlled Trial. 2015. Outcome

4764. University FI. Examining Tolerance to CNS Stimulants in ADHD. 2013. Timing

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4769. University of North Carolina CH, Health NLoM. Large-scale Brain Organization During Cognitive Control in ADHD. 2016. Intervention


4772. University TE. Effects of Atx and Oros-mph on Executive Functions. 2014. Outcome


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4804. van de Weijer-Bergsma E, Formsma AR, de Bruijn EI, et al. The Effectiveness of Mindfulness Training on Behavioral Problems and Attentional Functioning in Adolescents with
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4874. Vigliano P, Galloni GB, Bagnasco I, et al. Sleep in children with attention-deficit/hyperactivity disorder (ADHD) before and after 6-month treatment with methylphenidate:

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4933. Wang LJ, Huang YH, Chou WJ, et al. Potential disturbance of methylphenidate of gonadal hormones or pubescent development in patients with attention-deficit/hyperactivity...


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5004. Westwood SJ, Bozhilova N, Criaud M, et al. The effect of transcranial direct current stimulation (tDCS) combined with cognitive training on EEG spectral power in adolescent boys
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5120. Wolff Metternich-Kaizman T, Schröder S, Doepfner M. Effectiveness of parent-child inpatient treatment for families with severe parent-child interaction problems: A multilevel
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5167. Yang Q, Pan L, Shen C, et al. Mothers' prenatal tobacco smoke exposure is positively associated with the occurrence of developmental coordination disorder among children aged 3-6
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5179. Yeari M, Avramovich A, Schiff R. Online inferential and textual processing by adolescents with attention-deficit/hyperactivity disorder during reading comprehension:
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5275. Zheng Y, Du Y, Su LY, et al. Reliability and validity of the chinese version of questionnaire – Children with difficulties for chinese children or adolescents with attention-
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Background
3. 6th World Congress on ADHD: From Child to Adult Disorder. ADHD Attention Deficit and Hyperactivity Disorders. 2017;9(1). Background
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58. Bosch A, Bierens M, de Wit AG, et al. A two arm randomized controlled trial comparing the short and long term effects of an elimination diet and a healthy diet in children with ADHD
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70. Canadian Attention Deficit Hyperactivity Disorder Resource Alliance (CADDRA). Canadian ADHD practice guidelines CADDRA. Toronto: 2020. Background

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75. Cha AE. CDC warns that Americans may be overmedicating youngest children with ADHD. The Washington Post. 2016. Background


82. Charach A, Dashti B, Carson P, et al. Attention Deficit Hyperactivity Disorder: Effectiveness of Treatment in At-Risk Preschoolers; Long-Term Effectiveness in All Ages; and Variability in Prevalence, Diagnosis, and Treatment. Comparative Effectiveness Review No. 44 (Prepared by the McMaster University Evidence-based Practice Center under Contract No. MME2202 290-02-0020.) AHRQ Publication No. 12-EHC003-EF Agency for Healthcare Research and Quality Rockville, MD: Oct Preschoolers; Long-Term Effectiveness in All Ages;
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93. Christiansen MS, Labriola M, Kirkeskov L, et al. The impact of childhood diagnosed ADHD versus controls without ADHD diagnoses on later labour market attachment—a systematic review
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197. Hartge J, Toledo P. Attention Deficit Hyperactivity Disorder (ADHD) and its Comorbid Mental Disorders: An Evaluation of their Labor Market Outcomes. J Ment Health Policy Econ. 2018 Sep 1;21(3):105-21. PMID: 30530871. Background


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249. Krogh HB, Storebø OJ, Faltinsen E, et al. Methodological advantages and disadvantages of parallel and crossover randomised clinical trials on methylphenidate for attention deficit
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262. Lee CSC, Chen TT, Gao Q, et al. The Effects of Theta/Beta-based Neurofeedback Training on Attention in Children with Attention Deficit Hyperactivity Disorder: A Systematic Review
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273. Leopold DR, Christopher ME, Olson RK, et al. Invariance of ADHD symptoms across sex and age: A latent analysis of ADHD and impairment ratings from early childhood into

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319. Mohr-Jensen C, Steinhausen H-C. A meta-analysis and systematic review of the risks associated with childhood attention-deficit hyperactivity disorder on long-term outcome of
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Copyright © NICE 2018.; 2018. Background


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423. Shahabuddin ZA, Parikh S. Program Evaluation: Misdiagnosis and Mistreatment of A dhd-like Symptoms Among Youth in Foster Care. Pediatrics. 2022;149. Background
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## Appendix C. Evidence Tables

### Table C.1. KQ1 evidence table

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| Activity: Amado-Caballero, 2020<sup>138</sup> Case series N = 148 Spain Setting: N/A | **Target:** Diagnosed with combined ADHD according to the DSM-5, none have taken medication  
**Other:** Healthy children  
**ADHD presentation:** combined : 100  
**Diagnosed by:** Unclear/NR  
**Comorbidity:** N/A  
**Female:** % N/A  
**Age mean:** N/A  
**Min age:** 6  
**Max age:** 15  
**Ethnicity:** Other info on race or ethnicity: N/A | **Reference standard:** Clinical diagnosis  
Clinicians diagnosis using DSM-5  
**Timing:** Prior diagnosis  
**Index test:** Activity ActiGraph GT3x device placed in wrist of patient, data of physical activity and sedentary activity in a 24 hour period used to develop Convolutional Neural Network (CNN) able to diagnose combined ADHD from actigraphic record. 70/30 train/test split used for validation.  
Sensitivity: 98 70%/30% train/test with 300 second window size  
Specificity: 100 70%/30% train/test with 300 second window size  
PPV: 100 70%/30% train/test with 300 second window size  
NPV: 98 70%/30% train/test with 300 second window size  
LR+: 21  
LR-: 0.0238  
AUC:  
| **Index test 2:**  
**Sensitivity:**  
**Specificity:**  
**PPV:**  
**NPV:**  
**LR+:**  
**Accuracy:**  
**AUC:**  
Rater agreement:  
Kappa:  
Internal consistency:  
Alpha:  
Costs:  
**Index test 3:**  
**Sensitivity:**  
**Specificity:**  
**PPV:**  
**NPV:**  
**LR+:**  
**Accuracy:**  
**AUC:**  
Rater agreement:  
**Index test 4:**  
Sensitivity: |
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<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| Activity   | Lindhiem, 2022<sup>2nd</sup> Case series N = 30 US Setting: N/A | **Target:** Recruited via a web-based research registry through the University of Pittsburgh’s Clinical and Translational Science Institute program; not on medication during the testing period  
**Other:** Recruited via a web-based research registry through the University of Pittsburgh’s Clinical and Translational Science Institute program  
**ADHD presentation:** N/A : ADHD-combined and hyperactive subtypes only  
**Diagnosed by:** Unclear/NR  
**Comorbidity:** N/A  
**Female:** 40% | **Reference standard:** Clinical diagnosis ADHD module of the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (K-SADS-PL) and the hyperactivity items of the Vanderbilt Assessment Scale-Parent report (VAS-P)  
**Timing:** Prior diagnosis  
**Index test:** Activity LemurDx app prototype on Apple smarwatch tracking motion, heart rate, and location of participants paired with activity labels in 30 minute increments reported by the parents; random forest classifier, leave-one-participant-out cross validation; pilot study | **Index test 2:**  
**Sensitivity:**  
**Specificity:**  
**PPV:**  
**NPV:**  
**LR+:**  
**Accuracy:**  
**AUC:**  
**Rater agreement:**  
**Kappa:**  
**Internal consistency:**  
**Alpha:**  
**Costs:**  
**Index text 5:**  
**Specificity:**  
**PPV:**  
**NPV:**  
**AUC:**

Accuracy: 99 70%/30% train/test with 300 second window size  
AUC: 0.9993 70%/30% train/test with 300 second window size  
Rater agreement:  
Kappa:  
ICC:  
Internal consistency:  
Alpha:  
Test-retest:  
Costs:  
Misdiagnosis:  
Labeling:  
Costs:
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
|            | **Age mean:** 9.6 (1.6) for the ADHD group, 10.1 (1.8) for the control group   | **Sensitivity:** 93  
**Specificity:** 86  
**PPV:** 87  
**NPV:** 92  
**LR+:**  
**LR-:**  
**Accuracy:** 89  
**AUC:**  
**Rater agreement:**  
**Kappa:**  
**ICC:**  
**Internal consistency:**  
**Alpha:**  
**Test-retest:**  
**Costs:**  
**Misdiagnosis:**  
**Labeling:**  
**Costs:**  |
|            | **Min age:** 6  
**Max age:** 11  
**Ethnicity:**  
% Black/African American : 7  
% White : 83  
% Multiracial : 3  
Other info on race or ethnicity: Other : 7% race not reported |                                                                                                                      |                                                                 |                       |
|            | **Target:** Children with combined type ADHD and no type of sleep disorder such as restless legs syndrome or periodic limb movement  
**Other:** Children without ADHD from public hospitals and health centers  
**ADHD presentation:** combined : 100  
**Diagnosed by:** Unclear/NR  
**Comorbidity:** N/A  
**Female:** % N/A | **Reference standard:** Clinical diagnosis  
Diagnosed as having the combined kind of ADHD according to the DSM-IV criteria.  
**Timing:** Prior diagnosis  
**Index test:** Activity Nonlinear signal processing of 24 h-long actigraphic registries  
**Sensitivity:** 97  
By means of multidimensional classifiers driven by | **Index test 2:** 
**Sensitivity:**  
**Specificity:**  
**PPV:**  
**NPV:**  
**LR+:**  
**Accuracy:**  
**AUC:**  
**Rater agreement:**  
**Kappa:**  
**Internal consistency:** |
| Activity   | Martin-Martinez, 2012  
Case series  
N = 63  
Spain  
Setting: Mixed |                                                                                                                      |                                                                 |                       |

### Additional index tests

**Index test 3:** 
- Sensitivity:  
- Specificity:  
- PPV:  
- NPV:  
- LR+:  
- Accuracy:  
- AUC:  
- Rater agreement:  

**Index test 4:** 
- Sensitivity:  
- Specificity:  
- PPV:  
- NPV:  
- AUC:  

**Index test 5:** 
- Sensitivity:  
- Specificity:  
- PPV:  
- NPV:  
- AUC:  
- Rater agreement:  
- Kappa:  
- Internal consistency:  

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<table>
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<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
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<tr>
<td>Index Type</td>
<td>Study:</td>
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<tr>
<td></td>
<td>Author, year; Multiple publications; Study design; Study size; Location</td>
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<tr>
<td>Biomarker</td>
<td>Das, 2021&lt;sup&gt;218&lt;/sup&gt; Case series N = 50 Multiple countries Setting: Mixed</td>
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<th>Population:</th>
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<td>Setting;</td>
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<td>Study target;</td>
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<td>ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
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<tr>
<td>Reference standard:</td>
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<tr>
<td>Diagnosis of ADHD and ADHD-C according to DSM-IV criteria Timing: Prior diagnosis</td>
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<table>
<thead>
<tr>
<th>Results:</th>
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<tbody>
<tr>
<td>Reference standard: Clinical diagnosis</td>
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<tr>
<td>Index test: Biomarker Pupillometrics (pupil-size dynamics). Subjects were required to complete a visuospatial working memory task, which consisted of multiple 8 s trials, during which pupil-sizes were measured. Support vector machine (SVM) classifier, nested 10-fold cross validation</td>
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<tr>
<td>Sensitivity: 77 Support vector machine classifier Specificity: 75 Support vector machine classifier</td>
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<tr>
<td>PPV:</td>
</tr>
<tr>
<td>NPV:</td>
</tr>
<tr>
<td>LR+:</td>
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<td>LR-:</td>
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<tr>
<td>Accuracy: 76 Support vector machine classifier AUC: 0.856 Support vector machine classifier</td>
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<td>Rater agreement: Kappa:</td>
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<td>Internal consistency: Alpha:</td>
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<td>Test-retest: Costs:</td>
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<table>
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<th>Additional index tests</th>
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<tr>
<td>Index test 4: Sensitivity: Specificity: PPV: NPV: AUC:</td>
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<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| Biomarker  | Gungor, 2021<sup>107</sup> Case series N = 70 Turkey Setting: N/A | **Target:** Drug-naive, without comorbid psychiatric disorders, genetic syndromes, metabolic disorders, neurological disease and obesity; IQ>80  
**Other:** Age and sex-matched healthy children  
**ADHD presentation:** N/A  
**Diagnosed by:** Unclear/NR  
**Comorbidity:** N/A  
**Female:** 42.85%  
**Age mean:** 8.83 (2.99)  
**Min age:** 6 Max age: 12  
**Ethnicity:** Other info on race or ethnicity: Other | **Reference standard:** Clinical diagnosis  
Clinical diagnosis using DSM-5  
**Timing:** Prior diagnosis  
**Index test:** Biomarker Serum erythropoietin levels  
Sensitivity: 100  
Specificity: 97  
PPV:  
NPV:  
LR+:  
LR-:  
Accuracy:  
AUC: 0.980  
Rater agreement:  
Kappa:  
**Index test 2:** Biomarker Serum erythropoietin receptor levels  
Sensitivity: 100  
Specificity: 100  
PPV:  
NPV:  
LR+:  
Accuracy:  
AUC: 1.00  
Rater agreement:  
Kappa:  
Internal consistency:  
Alpha:  
Costs:  
**Index test 3:**  
Sensitivity:  
Specificity:  
PPV:  
NPV:  | Misdiagnosis:  
Labeling:  
Costs: |

Index text 5:
### Appendix C. Evidence Tables

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<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
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</thead>
<tbody>
<tr>
<td>Biomarker</td>
<td>Roessner, 2007&lt;sup&gt;499&lt;/sup&gt; Case series N = 66 Germany Setting: Specialty care</td>
<td>Target: Children and Adolescents in Germany who were patients of specialty clinics, 18 of the 42 ADHD participants were on stimulant medication at the day of urine sampling; 16 had one or more coexisting psychiatric problems including conduct disorder (n=13), learning disorders (n=4), tic disorders (n=2), and others (n=5) Other: Healthy controls ADHD presentation: N/A Diagnosed by: Unclear/NR Comorbidity: N/A Female: % N/A Age mean: 12.1 (3.2) Min age: Max age: Ethnicity:</td>
<td>Reference standard: Clinical diagnosis All children were referred and fulfilled DSMIV-TR criteria for ADHD. Timing: Prior diagnosis Index test: Biomarker tetrahydroisoquinolines (TIQ) urine levels: Salsolinol (free) Sensitivity: 56 Specificity: 95 PPV: NPV: LR+: LR-: Accuracy: AUC: Rater agreement: Kappa:</td>
<td>Index text 2: Biomarker tetrahydroisoquinolines (TIQ) urine levels: N-methyl-Salsolinol (free) Sensitivity: 93 Specificity: 94 PPV: NPV: LR+: Accuracy: AUC: Rater agreement: Kappa: Internal consistency: Alpha: Costs:</td>
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## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Study: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
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<td>Other info on race or ethnicity: N/A</td>
<td>ICC: Internal consistency: Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
<td><strong>Index text 3</strong>: biomarker tetrahydroisoquinolines (TIQ) urine levels: Norsalsolinol (free)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sensitivity: 88 88 Specificity: 80 PPV: NPV: LR+: Accuracy: AUC: Rater agreement:</td>
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<td><strong>Index text 4</strong>: biomarker tetrahydrosoquinolines (TIQ) urine levels: N-methyl-Norsalsolinol (free)</td>
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<tr>
<td></td>
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<td>Sensitivity: 69 Specificity: 94 PPV: NPV: AUC:</td>
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<td><strong>Index text 5</strong>:</td>
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<td>Study:</td>
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<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
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<tr>
<td>Study: Stepanova, 2021</td>
<td>Target: Recruited from community advertisements and physician referrals; not currently taking psychostimulants. 46% provided another blood draw 30 days after receiving psychostimulants; children with bipolar disorder excluded</td>
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<td></td>
<td>Other: Children without ADHD</td>
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<tr>
<td></td>
<td>ADHD presentation: inattentive: 33.3, hyperactive: 0, combined: 66.7</td>
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<td></td>
<td>Diagnosed by: Provider</td>
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<td></td>
<td>Comorbidity: N/A</td>
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<tr>
<td></td>
<td>Female: 33.3%</td>
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<td></td>
<td>Age mean: 11.61(3.30)</td>
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<td>Min age: 6 Max age: 17</td>
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<td>Ethnicity: % Hispanic or Latino: 12.5</td>
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<td>% Black/African American: 70.8</td>
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<tr>
<td></td>
<td>% Asian: 0</td>
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<td></td>
<td>% White: 8.3</td>
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<td>Results:</td>
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<tr>
<td></td>
<td>Completed Mini-International Neuropsychiatric Interview 7 and was evaluated by a clinical psychiatrist</td>
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<td></td>
<td>Timing: Prior diagnosis</td>
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<td>Index test: Biomarker Membrane potential ratio (MPR). ADHD cutoff score provided by the MPR™ test developers of &gt;0.75 is considered positive for ADHD.</td>
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<td>Sensitivity: 79</td>
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<td>Accuracy: 55</td>
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<td>AUC:</td>
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<td>Rater agreement:</td>
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| Index text 4: |
| Sensitivity: |
| Specificity: |
| PPV: |
| NPV: |
| AUC: |
### Index Type

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<th>Population: Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| Biomarker | Wang, 2018<sup>99</sup> Case series N = 40 Taiwan Setting: Specialty care | **Target:** Medication naive; no major physical illnesses (such as genetic, metabolic, or infectious conditions) or a history of comorbid major neuropsychiatric diseases (such as intellectual disabilities, autism spectrum disorder, bipolar disorders, major depressive disorders, psychotic disorders, substance use disorders, epilepsy, or severe head trauma)  
**Other:** Children without any known major physical illnesses or any of the aforementioned major neuropsychiatric diseases within the same catchment area  
ADHD presentation: N/A  
Diagnosed by: Specialist  
Comorbidity: N/A  
Female: 30%  
In the test group  
Age mean: 8.7 (2.2) for the ADHD test group, 9.2 (2.5) for the control test group  
Min age: 6 Max age: 16 | **Reference standard:** Clinical diagnosis  
Diagnosed with ADHD based off DSM-IV-TR criteria and the Chinese version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children, epidemiologic version (K-SADS-E)  
Timing: Prior diagnosis  
**Index test:** Biomarker miRNA-based diagnostic panel using 13 miRNA candidate biomarkers, SVM classifier  
Sensitivity: 90% For test group  
Specificity: 80% For test group  
PPV:  
NPV:  
LR+:  
LR-:  
Accuracy: 85% For test group  
AUC: 0.91 Test set  
Rater agreement:  
Kappa:  
ICC: | Index test 2: Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy:  
AUC:  
Rater agreement:  
Kappa:  
Internal consistency:  
Alpha:  
Costs:  
Index test 3: Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy:  |
## Appendix C. Evidence Tables

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<td>Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
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<th>Additional index tests</th>
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<tbody>
<tr>
<td></td>
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<td>Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
<td><strong>Index test 3</strong>: biomarker Biomarker miRNA: hsa-miR-138-5p</td>
<td><strong>Sensitivity</strong>: 82 82 <strong>Specificity</strong>: 79 <strong>PPV</strong>: <strong>NPV</strong>: <strong>LR+</strong>: <strong>Accuracy</strong>: AUC: 0.856 Rater agreement:</td>
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<td><strong>Index test 4</strong>: biomarker Combined biomarkers hsa-miR101-3p, hsa-miR-106b-5p, hsa-miR-138-5p, hsa-miR-130a-3p, hsa-miR-195-5p</td>
<td><strong>Sensitivity</strong>: 68 <strong>Specificity</strong>: 71 <strong>PPV</strong>: <strong>NPV</strong>: AUC: 0.68</td>
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<td><strong>Index test 5</strong>:</td>
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<td>Lau, 2018[17]</td>
<td>Author, year;</td>
<td>Setting; 377; Study target; ADHD presentation;</td>
<td>Reference standard;</td>
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<td>Case series</td>
<td>Multiple</td>
<td>Study design; Multiple publications; Study size;</td>
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<tr>
<td>N = 3,464</td>
<td>publications;</td>
<td>Location; Canada;</td>
<td>Ethnicity;</td>
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<tr>
<td>Canada</td>
<td>Study design;</td>
<td></td>
<td>Reference standard;</td>
<td>NPV:</td>
</tr>
<tr>
<td>Setting: Specialty care</td>
<td>Study size; Location</td>
<td></td>
<td>Provisional diagnoses were obtained from the clinical record or completed by the psychiatrist, attending physician, or qualified psychologist at the time of assessment</td>
<td>LR+:</td>
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<td></td>
<td></td>
<td></td>
<td>Timing: Concurrent</td>
<td>Accuracy:</td>
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<td></td>
<td>Index test: Clinician rating scale The interRAI Child and Youth Mental Health Hyperactive/Distraction Scale (HDS), a semi-structured clinician assessment tool; analysis done on subsample that had undergone a diagnostic assessment (n=2849)</td>
<td>AUC:</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Sensitivity: Using a combination of Youden’s index and Pythagorean’s method, optimal sensitivity ranged from 77.6 to 81.8% at a score of 7</td>
<td>Rater agreement:</td>
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<tr>
<td></td>
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<td>Specificity: Using a combination of Youden’s index and Pythagorean’s method, optimal specificity ranged from 60.7 to 65.1% at a score of 7</td>
<td>Kappa:</td>
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<td>PPV:</td>
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<td>Alpha:</td>
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<td>LR+:</td>
<td>Costs:</td>
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<td>Author, year;</td>
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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
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<tr>
<td>Clinician rating scale</td>
<td>Robles, 2021&lt;sup&gt;587&lt;/sup&gt; Case series N = 52 Mexico Setting: Specialty care</td>
<td><strong>Target</strong>: Those without the presence of communication difficulties, cognitive dysfunctions, and disabilities; seeking mental health services at two specialized psychiatric care facilities in Mexico City <strong>Other</strong>: Children seeking mental health services at two specialized psychiatric care facilities in Mexico City not diagnosed with ADHD <strong>ADHD presentation</strong>: N/A <strong>Diagnosed by</strong>: Specialist <strong>Comorbidity</strong>: N/A <strong>Female</strong>: 37% <strong>Age mean</strong>: 11.9 (3.2) <strong>Min age</strong>: 6 <strong>Max age</strong>: 17 <strong>Ethnicity</strong>: Other info on race or ethnicity: N/A</td>
<td><strong>Reference standard</strong>: Clinical diagnosis Two psychiatrists independently established diagnosis, blind to each others evaluation Timing: Concurrent <strong>Index test</strong>: Clinician rating scale Evaluation of interrater reliability of ICD11 diagnostic guidelines for mental and behavioral disorders in children and adolescents to assess clinical utility. Each participant was interviewed by a pair of psychiatrists (interviewer and observer), who independently codified established diagnoses and evaluated the clinical utility of the guidelines. <strong>Sensitivity</strong>: <strong>Specificity</strong>: <strong>PPV</strong>: <strong>NPV</strong>: <strong>LR+</strong>: <strong>LR-</strong>: <strong>Accuracy</strong>:</td>
<td><strong>Index text 5</strong>: Internal consistency: Standardized Cronbach's Alpha (using polychoric correlations) Alpha: 0.86 Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
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### Appendix C. Evidence Tables

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<td>Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
<td>Accuracy: AUC; Rater agreement:</td>
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<tr>
<td>Combined rating</td>
<td>Francois-Sevigny, 2022</td>
<td><strong>Target</strong>: ADHD or ADHD+gifted; IQ&gt;=130 on the Full-Scale Intelligence Quotient or the General Aptitude Index of the Wechsler Intelligence Scale for Children 5th edition to be included in the ADHD+gifted group; all drug naive; children with a mental health disorder such as anxiety and depression were included; children with ASD or intellectual disability were excluded <strong>Other</strong>: Gifted children; IQ&gt;=130 on the Full-Scale Intelligence Quotient or the General Aptitude Index of the Wechsler Intelligence Scale for Children 5th edition ADHD presentation: N/A Diagnosed by: Specialist Comorbidity: N/A</td>
<td><strong>Index text 4</strong>:</td>
<td><strong>Index text 5</strong>:</td>
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<td></td>
<td>Case series N = 92 Canada Setting: Specialty care</td>
<td>Reference standard: Clinical diagnosis Semi-structured K-SADS-PL interview, Conners Continuous Performance Test, the Test of Everyday Attention for Children, the Delis-Kaplan Executive Function System (D-KEFS), the Tower of London test, the Behavior Assessment System for Children (BASC-3) Timing: Concurrent</td>
<td>Sensitivity: Specificity: PPV: NPV: AUC:</td>
<td>Combined rating Conners 3 symptom scales teacher and parent ratings; discriminant function analysis with 3 categories (ADHD+gifted vs ADHD vs gifted) Sensitivity: 70% of the ADHD+gifted children were correctly classified, 66% of the ADHD children were correctly classified Specificity: 100 PPV: NPV: LR+: Accuracy: 76</td>
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<tr>
<td>Index Type</td>
<td>Study: Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
<td>Additional index tests</td>
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<td><strong>Female: 29%</strong>&lt;br&gt;<strong>Age mean:</strong> 9.85 (2.51)&lt;br&gt;<strong>Min age:</strong> 6 <strong>Max age:</strong> 16</td>
<td><strong>Ethnicity:</strong> Other info on race or ethnicity: N/A</td>
<td><strong>Sensitivity:</strong> 72% of the ADHD+gifted children were correctly classified, 68% of the ADHD children were correctly classified&lt;br&gt;<strong>Specificity:</strong> 100&lt;br&gt;<strong>PPV:</strong>&lt;br&gt;<strong>NPV:</strong>&lt;br&gt;<strong>LR+:</strong>&lt;br&gt;<strong>LR-:</strong>&lt;br&gt;<strong>Accuracy:</strong> 78&lt;br&gt;<strong>AUC:</strong>&lt;br&gt;<strong>Rater agreement:</strong>&lt;br&gt;<strong>Kappa:</strong>&lt;br&gt;<strong>ICC:</strong>&lt;br&gt;<strong>Internal consistency:</strong>&lt;br&gt;<strong>Alpha:</strong>&lt;br&gt;<strong>Test-retest:</strong>&lt;br&gt;<strong>Costs:</strong>&lt;br&gt;<strong>Misdiagnosis:</strong> Gifted children may exhibit behaviors that look similar to the characteristics of ADHD, contributing to misdiagnosis. The fact that the only differences between gifted/ADHD children and ADHD children were observed in terms of hyperactive–impulsive symptom&lt;br&gt;<strong>Labeling:</strong>&lt;br&gt;<strong>Costs:</strong></td>
<td><strong>AUC:</strong>&lt;br&gt;<strong>Rater agreement:</strong>&lt;br&gt;<strong>Kappa:</strong>&lt;br&gt;<strong>Internal consistency:</strong>&lt;br&gt;<strong>Alpha:</strong>&lt;br&gt;<strong>Costs:</strong>&lt;br&gt;<strong>Index text 3:</strong>&lt;br&gt;<strong>Sensitivity:</strong>&lt;br&gt;<strong>Specificity:</strong>&lt;br&gt;<strong>PPV:</strong>&lt;br&gt;<strong>NPV:</strong>&lt;br&gt;<strong>LR+:</strong>&lt;br&gt;<strong>LR-:</strong>&lt;br&gt;<strong>Accuracy:</strong>&lt;br&gt;<strong>AUC:</strong>&lt;br&gt;<strong>Rater agreement:</strong>&lt;br&gt;<strong>Index text 4:</strong>&lt;br&gt;<strong>Sensitivity:</strong>&lt;br&gt;<strong>Specificity:</strong>&lt;br&gt;<strong>PPV:</strong>&lt;br&gt;<strong>NPV:</strong>&lt;br&gt;<strong>AUC:</strong>&lt;br&gt;<strong>Index text 5:</strong>&lt;br&gt;<strong>Sensitivity:</strong>&lt;br&gt;<strong>Specificity:</strong>&lt;br&gt;<strong>PPV:</strong>&lt;br&gt;<strong>NPV:</strong>&lt;br&gt;<strong>AUC:</strong></td>
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<tr>
<th>Index Type</th>
<th>Study:</th>
<th>Population:</th>
<th>Results:</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
|            | Gibbons, 2020<sup>297</sup> | Target: English speakers only. Children were excluded if they had autism spectrum, intellectual developmental, or a psychotic disorder that would limit their ability to provide accurate self-reports. Other: Children without evidence of psychiatric disorder ADHD presentation: N/A Diagnosed by: Specialist Comorbidity: Other: Study includes children with primary diagnosis of major depressive disorder, bipolar disorder with manic symptoms, anxiety, ODD, and CD Female: 32.2% Age mean: 11.1 (3.2) for ADHD group, 12.2 (3.1) for control group Min age: 7 Max age: 17 Ethnicity: % Hispanic or Latino: 5.4 % White: 61.2 Other info on race or ethnicity: | Reference standard: Clinical diagnosis K-SADS-PL, Children's Global Assessment Scale (CGAS), review of medical record recruited from psychiatric institute and clinic, local clinics and providers Timing: Prior diagnosis Index test: Combined rating Kiddie-Computerized adaptive test (K-CAT) using combined item response scale scores from parent and child, 3-fold cross validation Sensitivity: 75 with specificity fixed at 80 % Specificity: 80 fixed specificity PPV: NPV: LR+: LR-: Accuracy: 86 AUC: 0.86 Rater agreement: Kappa: ICC: Internal consistency: Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs: | Index test 2: Parental rating scale Kiddie-Computerized adaptive test (K-CAT) using combined item response scale scores from parent. The test was administered using tablet computers. 3-fold cross validation Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: 0.85 Rater agreement: Kappa: Internal consistency: Alpha: Costs: Index test 3: Teen/child self report Kiddie-Computerized adaptive test (K-CAT) using combined item response scale scores from child. The test was administered using tablet computers. Items were tested for readability using the Flesch-
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</tr>
</thead>
</table>
| Combined rating | Longridge, 2019<sup>396</sup>  
Case series  
N = 288  
UK  
Setting: Specialty care | Target: Secondary analysis of a cohort of children attending two child and adolescent mental health services between 2006 and 2009  
Other: Children with no diagnosis of ADHD per Development and Well-Being Assessment, part of the same referral process as ADHD group  
ADHD presentation: N/A  
Diagnosed by: Unclear/NR  
Comorbidity: N/A  
Female: 13.8% | Reference standard: Clinical diagnosis  
Clinicians completed a brief questionnaire in 6 month intervals assessing multiple clinical conditions including ADHD  
Timing: Later diagnosis  
Index test: Combined rating Development and Well-Being Assessment (DAWBA) with parents and teacher ratings, a modular standardised diagnostic assessment with structured questions that are based directly on DSM-IV (APA 2000) and ICD-10 (WHO 2009) diagnostic criteria; If a respondent | Kincaid reading grade level.  
The overall average reading  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy:  
AUC: 0.71  
Rater agreement:  
Index test 4:  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
AUC:  
Index test 5:  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy:  
AUC:  
Rater agreement:  
Kappa:  
Internal consistency:
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<tr>
<td></td>
<td>Age mean: 7.4 (1.6) for ADHD group, 8.0 (1.7) for comparison group&lt;br&gt;Min age: 5 Max age: 11&lt;br&gt;Ethnicity: % White: 69 Other info on race or ethnicity: Other: 31% Black and Minority ethnicity</td>
<td>reports any difficulty in any one module, semistructured questions are used to expand on the details of these reported difficulties; a computerised algorithm generates provisional diagnoses&lt;br&gt;Sensitivity:&lt;br&gt;Specificity:&lt;br&gt;PPV:&lt;br&gt;NPV:&lt;br&gt;LR+:&lt;br&gt;LR-:&lt;br&gt;Accuracy:&lt;br&gt;AUC:&lt;br&gt;Rater agreement: DAWBA provisional diagnosis versus clinician diagnosis during the study period Kappa was 0.40 for those with a definite or possible diagnosis at any time point Kappa: 0.30 ICC:&lt;br&gt;Internal consistency: Alpha:&lt;br&gt;Test-retest: Costs:&lt;br&gt;Misdiagnosis:&lt;br&gt;Labeling: Costs:</td>
<td>Alpha: Costs:</td>
<td>Index test 3:&lt;br&gt;Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement:</td>
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<td>Index test 4:&lt;br&gt;Sensitivity: Specificity: PPV: NPV: AUC:</td>
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<td>Index test 5:</td>
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<td>Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
<td></td>
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<tr>
<td>Oztekin, 2021&lt;sup&gt;555&lt;/sup&gt;</td>
<td>Target: IQ&gt;=70. No confirmed history of Autism Spectrum Disorder. 70% had a comorbid oppositional defiant disorder or conduct disorder diagnosis. Recruited from local schools and mental health agencies via brochures, radio and newspaper ads, and open houses/parent workshops</td>
<td><strong>Reference standard:</strong> Clinical diagnosis Computerized-Diagnostic Interview Schedule for Children and Disruptive Behavior Disorders Rating Scale, Impairment Rating Scale Timing: Prior diagnosis</td>
<td><strong>Index test 2:</strong> neuropsychological, EF Executive function tasks: Flanker task, the Dimensional Change Card Sorting task, and the Head-Toes-Knees-Shoulders task. Support vector machine (SVM) classifier, 5-fold cross validation Sensitivity: 64 Specificity: PPV: 71 NPV: LR+: Accuracy: 67 AUC: 0.738 Rater agreement: Kappa:</td>
</tr>
<tr>
<td>Case series</td>
<td>Other: Typically developing children ADHD presentation: N/A Diagnosed by: Specialist Comorbidity: N/A Female: 26% Age mean: mean 5.55 Min age: 4 Max age: 7 Ethnicity: % Hispanic or Latino: 82.6 Other info on race or ethnicity:</td>
<td><strong>Index test:</strong> Combined rating Emergent Metacognition Index t-score from the Behavior Rating Inventory of Executive Function (Preschool or Child version) parent and teacher ratings combined; support vector machine (SVM) classifier, 5-fold cross validation Sensitivity: 74 Specificity: PPV: 94 NPV: LR+: Accuracy: 93 AUC: 0.962 Rater agreement: Kappa: ICC: Internal consistency: Cronbach’s alpha 0.976 for teacher ratings and 0.970 for parent ratings on the Preschool version; 0.724 for teacher ratings and 0.978 for parent ratings on the Child version. Alpha:</td>
<td></td>
</tr>
<tr>
<td>Combined rating</td>
<td></td>
<td></td>
<td><strong>Index test 3:</strong> Imaging Structural MRI scans assessing neural measures of cortical thickness in target regions that support executive function. Support vector machine (SVM) classifier, 5-fold cross validation Sensitivity: 65 65 Specificity:</td>
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<tr>
<td></td>
<td>Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
<td>PPV: 64 NPV: LR+: Accuracy: 61 AUC: 0.624 Rater agreement:</td>
<td><strong>Index text 4:</strong> Imaging Full model includes demographics, parent/teacher ratings, cognitive measures of executive function, and cortical thickness in the left anterior cingulate, the left intraparietal transverse parietal sulci and the left superior frontal gyrus from structural Sensitivity: Specificity: PPV: NPV: AUC:</td>
<td><strong>Index text 5:</strong></td>
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<tr>
<td>Combined rating</td>
<td>Parker, 2016[1]; McGonnell, 2009[2]; Davidson, 2016[3]; Case series N = 279 Canada Setting: Specialty care</td>
<td>Target: Children of an ADHD clinic which is restricted to children who have no previous diagnosis of ADHD, are psychotropic medication-naive, and have not received a psychoeducational assessment within the past 2 years Other: Children referred to the ADHD clinic who were not diagnosed with ADHD; 66% of these children were diagnosed with another mental disorder or a learning disability, the remaining children were not diagnosed with ADHD, a learning disability, or any other mental disorder ADHD presentation: inattentive: 26.0, hyperactive: 6.8, combined: 66.4, N/A: 0.7 ADHD-not otherwise specified Diagnosed by: Specialist Comorbidity: N/A Female: 30.8% Age mean: 8.49 (1.70) Minimum age: 5.95 Maximum age: 12.67 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Reference standard: Clinical diagnosis Semistructured diagnostic interview based on DSM-IV criteria for use with parents, the child also received a standard psychoeducational assessment battery; ADHD Clinic team made possible diagnoses based on the results of the above measurements Timing: Concurrent Index test: Combined rating Teacher Telephone Interview and Parent Interview for Child Symptoms combined Sensitivity: 92 Specificity: 71 PPV: NPV: LR+: LR-: Accuracy: AUC: Rater agreement: Kappa: Internal consistency: Alpha: Costs:</td>
<td>Index test 2: Combined rating Conners Teacher Rating Scale and Conners Parent Rating Scale combined Sensitivity: 84 Specificity: 36 PPV: NPV: LR+: Accuracy: AUC: Rater agreement: Kappa: Internal consistency: Alpha: Costs:</td>
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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
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<tbody>
<tr>
<td>Combined rating</td>
<td>Sullivan, 2007&lt;sup&gt;55&lt;/sup&gt; Case series N = 92 US Setting: Other</td>
<td>Target: Subset of participants diagnosed with ADHD in a Memory, Attention, and Planning Study recruited with announcements distributed to local physicians, schools, bulletin boards, a counseling center, and the newspaper; IQ&gt;=80 Other: Subset of participants not diagnosed with ADHD in a Memory, Attention, and Planning Study recruited with announcements distributed to local physicians, schools, bulletin boards, a counseling center, and the newspaper; IQ&gt;=80; participants either had no cl ADHD presentation: inattentive : 34,combined : 66 Diagnosed by: Specialist Comorbidity: N/A Female: 15% Age mean: 11.32 (1.99) Min age: 9 Max age: 15</td>
<td>Reference standard: Clinical diagnosis Comprehensive psychological evaluation that included measures of cognitive ability, achievement, language, memory, executive function, attention, behavior, and emotional functioning Timing: Prior diagnosis</td>
<td>Index text 4: Parental rating scale The Behavior Rating Inventory of Executive Functioning parent rating&lt;sup&gt;712&lt;/sup&gt; Sensitivity: Specificity: PPV: NPV: AUC:</td>
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<tr>
<td>Index text 5:</td>
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Index text 2: Combined rating Conners’ Parent Rating Scale-Short Form (CPRS) and Conners’ Teacher Rating Scale- Short Form (CTRS) Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement: Parent ratings on the Conners’ scales were significantly correlated with teacher ratings on the same scales Kappa: Internal consistency:
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</tr>
</thead>
</table>
| EEG        | Abramov, 2019<sup>11</sup>
Case series
N = 39
Brazil
Setting: N/A | **Target:** ADHD boys without a history of chronic diseases, and without suspicion of psychiatric disorders other than ADHD (psychosis, affective, obsessive-compulsive and tic disorders, phobic and post-traumatic stress conditions, anorexia, bulimia, enuresis, or enuresis) as screened by K-SADS-PL; (2) No use of any psychotropic medicines for at least 30 days; (3) estimated Intelligence Quotient (I.Q.) equal or lower than 80; and (4) no less | **Reference standard:** Clinical diagnosis Classified as ADHD in accordance with the DSM-IV-TR Timing: Prior diagnosis **Index test:** EEG Attentional Network Test with recordings of event-related potentials from the mid-frontal, mid-parietal, right frontal, and central scalp areas (C3-C4, F8, F4, Fz, Pz) for a biological classification | Alpha: Costs: **Index test 3:**
Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement: **Index text 4:**
Sensitivity: Specificity: PPV: NPV: AUC: **Index text 5:**

| Ethnicity: | % Hispanic or Latino : 8 % Black/African American : 11 % Asian : 1 % White : 80 Other info on race or ethnicity: | Rater agreement: Behavior Rating Inventory of Executive Function (BRIEF) parent versus teacher ratings Parent ratings on the BRIEF scales were significantly correlated with teacher ratings on the same scales (all <=0.05) Kappa: ICC: Range 0.31 to 0.59 (median 0.48) over 11 subscales Internal consistency: Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs: |

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<sup>11</sup> Abrams, 2019
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<td>than 6 h of regular sleep and (5) no report of somnolence before the ANT testing</td>
<td>using the clustering of variables method. 80/20 train/test split repeated 100 times.</td>
<td>Kappa:</td>
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<td></td>
<td>Other: Typically developing boys</td>
<td>Sensitivity: 89</td>
<td>Internal consistency: Alpha:</td>
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<td></td>
<td>ADHD presentation: N/A</td>
<td>Specificity: 75</td>
<td>Costs:</td>
<td></td>
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<td></td>
<td>Diagnosed by: Researcher</td>
<td>PPV:</td>
<td></td>
<td>Index test 3:</td>
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<tr>
<td></td>
<td>Comorbidity: N/A</td>
<td>NPV:</td>
<td>Sensitivity:</td>
<td></td>
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<tr>
<td></td>
<td>Female: 0%</td>
<td>LR+:</td>
<td>Specificity:</td>
<td></td>
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<tr>
<td></td>
<td>Age mean: 11.52</td>
<td>LR-:</td>
<td>PPV:</td>
<td></td>
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<tr>
<td></td>
<td>Min age: 10 Max age: 13</td>
<td>Accuracy: 82</td>
<td>NPV:</td>
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<td></td>
<td>Ethnicity: Other info on race or ethnicity: N/A</td>
<td>AUC:</td>
<td>LR+:</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Rater agreement: Agreement between DSM and behavioral/psychological/neurophysiological data</td>
<td>Accuracy:</td>
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<td></td>
<td></td>
<td>Kappa: 0.75</td>
<td>AUC:</td>
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<td>Internal consistency: Alpha:</td>
<td>Rater agreement:</td>
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<td>Test-retest:</td>
<td>Index test 4:</td>
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<tbody>
<tr>
<td>EEG</td>
<td>Ahmadi, 2021&lt;sup&gt;22&lt;/sup&gt;</td>
<td><strong>Target:</strong> Right handed children, none had any neuro-feedback or any other neuro-modulation treatment, none had been treated with methylphenidate, 13 with ADHD combined and 12 with ADHD inattention presentation; all selected from Hamrah Child and Adolescent Multidisciplinary Neuropsychiatric Center, Tabriz, Iran&lt;br&gt;&lt;br&gt;<strong>Other:</strong> Healthy children&lt;br&gt;&lt;br&gt;<strong>ADHD presentation:</strong> inattentive : 48, combined : 52&lt;br&gt;&lt;br&gt;<strong>Diagnosed by:</strong> Specialist&lt;br&gt;&lt;br&gt;<strong>Comorbidity:</strong> N/A&lt;br&gt;&lt;br&gt;<strong>Female:</strong> 36%&lt;br&gt;&lt;br&gt;<strong>Age mean:</strong> ADHD-C 8.5 (0.7), ADHD-I 8.75 (0.65), control 8.92 (1.38)&lt;br&gt;&lt;br&gt;<strong>Min age:</strong> 6  <strong>Max age:</strong> 11&lt;br&gt;&lt;br&gt;<strong>Ethnicity:</strong> Other info on race or ethnicity: N/A</td>
<td><strong>Reference standard:</strong> Clinical diagnosis Swanson, Nolan, and Pelham IV questionnaire parent and teacher ratings. The child behavior checklist completed by parents. The final diagnosis of the children was independently performed by a child psychologist and a child psychiatrist who both were blind&lt;br&gt;&lt;br&gt;<strong>Timing:</strong> Prior diagnosis&lt;br&gt;&lt;br&gt;<strong>Index test:</strong> EEG EEG, eyes open resting-state; spatial and frequency band feature extraction and classification done using deep convolutional neural network; combination of beta 1, beta 2, and gamma bands used for classification. 5 times 5-fold cross validation&lt;br&gt;&lt;br&gt;<strong>Sensitivity:</strong> 99&lt;br&gt;&lt;br&gt;<strong>Specificity:</strong> 99&lt;br&gt;&lt;br&gt;<strong>PPV:</strong>&lt;br&gt;&lt;br&gt;<strong>NPV:</strong>&lt;br&gt;&lt;br&gt;<strong>LR+:</strong>&lt;br&gt;&lt;br&gt;<strong>LR-:</strong>&lt;br&gt;&lt;br&gt;<strong>Accuracy:</strong> 99&lt;br&gt;&lt;br&gt;<strong>AUC:</strong></td>
<td><strong>Index test 2:</strong>&lt;br&gt;&lt;br&gt;<strong>Sensitivity:</strong>&lt;br&gt;&lt;br&gt;<strong>Specificity:</strong>&lt;br&gt;&lt;br&gt;<strong>PPV:</strong>&lt;br&gt;&lt;br&gt;<strong>NPV:</strong>&lt;br&gt;&lt;br&gt;<strong>LR+:</strong>&lt;br&gt;&lt;br&gt;<strong>LR-:</strong>&lt;br&gt;&lt;br&gt;<strong>Accuracy:</strong>&lt;br&gt;&lt;br&gt;<strong>AUC:</strong>&lt;br&gt;&lt;br&gt;<strong>Rater agreement:</strong>&lt;br&gt;&lt;br&gt;<strong>Kappa:</strong>&lt;br&gt;&lt;br&gt;<strong>Internal consistency:</strong>&lt;br&gt;&lt;br&gt;<strong>Alpha:</strong>&lt;br&gt;&lt;br&gt;<strong>Costs:</strong></td>
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<tr>
<td>EEG</td>
<td>Altinkaynak, 2020&lt;sup&gt;137&lt;/sup&gt; Case series N = 46 Turkey Setting: Specialty care</td>
<td>Target: ADHD referrals from university hospital psychiatry department, all were drug-naïve, without neurological conditions or hearing problems, all were right-handed Other: Healthy controls with no neurological, endocrine or psychiatric illness, and normal hearing function ADHD presentation: N/A Diagnosed by: Specialist Comorbidity: N/A Female: 30.4% Age mean: 9.09 (1.62) for ADHD group, 9.13 (1.63) for control group Min age: 7 Max age: 12 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Reference standard: Clinical diagnosis Psychiatrists used DSM-IV to diagnose patients with ADHD Timing: Prior diagnosis Index test: EEG Time and frequency analysis of Event Related Potentials (ERP) obtained from EEG signals while participants performed an auditory oddball task; multilayer Perception classifier, leave-one out cross validation Sensitivity: 91 Specificity: 91 PPV: N/A NPV: N/A LR+: N/A LR-: Accuracy: 91 AUC: 0.91 Rater agreement: Inter-rater reliability for the classifier Kappa: 0.82</td>
<td>Index text 5: Index text 2: EEG Time and frequency analysis of Event Related Potentials (ERP) obtained from EEG signals while participants performed an auditory oddball task; support vector machine (SVM) classifier, leave-one out cross validation Sensitivity: 95 Specificity: 82 PPV: N/A NPV: N/A LR+: N/A LR-: Accuracy: 89 AUC: 0.89 Rater agreement: Inter-rater reliability for the classifier Kappa: 0.78 Internal consistency: Alpha:</td>
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<td></td>
<td>ICC: Internal consistency: Alpha: Test-retest: Costs: Misdiagnosis: Labeling:</td>
<td>Costs:</td>
<td><strong>Index test 3:</strong> EEG Time and frequency analysis of Event Related Potentials (ERP) obtained from EEG signals while participants performed an auditory oddball task; naïve Bayes classifier, leave-one out cross validation</td>
<td>Sensitivity: 86 Specificity: 86 PPV: NPV: LR+: Accuracy: 87 AUC: 0.94 Rater agreement: Inter-rater reliability for the classifier</td>
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<td></td>
<td></td>
<td>Costs:</td>
<td><strong>Index test 4:</strong> EEG Time and frequency analysis of Event Related Potentials (ERP) obtained from EEG signals while participants performed an auditory oddball task; k-nearest neighbor classifier, leave-one out cross validation</td>
<td>Sensitivity: 91 Specificity: 82 PPV:</td>
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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
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</table>
| EEG        | Beriha, 2018<sup>[19]</sup> Case series N = 297 India Setting: School | **Target:** Children recruited from 15 elementary schools, 5 of which were particularly for children with disorders, diagnosed with ADHD  
**Other:** Children with anxiety, depression, or conduct disorder, and neurotypical children from same recruitment process as ADHD group  
**ADHD presentation:** N/A  
**Diagnosed by:** Unclear/NR  
**Comorbidity:** N/A  
**Female:** % N/A  
**Age mean:** N/A  
**Min age:** Max age: N/A  
**Ethnicity:** Other info on race or ethnicity: N/A | **Reference standard:** Clinical diagnosis  
Experts used the DSM-V to determine diagnosis ADHD, anxiety, depression, conduct disorder, and control  
**Timing:** Prior diagnosis  
**Index test:** EEG EEG recording during visual attention and mental task, extraction of four non-linear features combined with symptoms important for differentiation of psychiatric disorders, particle swarm optimization tuned back propagation neural network (PSO-BPNN) classifier  
**Sensitivity:** 100  
**Specificity:** 100  
**PPV:** N/A  
**NPV:** 100  
**LR+:**  
**LR-:**  
**Accuracy:** 100  
**AUC:**  
**Rater agreement:** | **Index test 2:** EEG  
EEG recording during visual attention and mental task, extraction of four non-linear features combined with symptoms important for differentiation of psychiatric disorders, particle swarm optimization tuned radial basis function (PSO-RBF) classifier  
**Sensitivity:** 90  
**Specificity:** 89  
**PPV:** N/A  
**NPV:**  
**LR+:**  
**LR-:**  
**Accuracy:** 97  
**AUC:**  
**Rater agreement:**  
**Kappa:**  
**Internal consistency:**  
**Alpha:** | |
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
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<tbody>
<tr>
<td>EEG</td>
<td>Boroujeni, 2019&lt;sup&gt;163&lt;/sup&gt; Case series N = 76 Iran Setting: Specialty care</td>
<td><strong>Target:</strong> Children who had come to doctor Mohammad Behdad (neurologist) clinic for EEG signal recording <strong>Other:</strong> Typically developing children <strong>ADHD presentation:</strong> N/A <strong>Diagnosed by:</strong> Specialist <strong>Comorbidity:</strong> N/A <strong>Female:</strong> 26% <strong>Age mean:</strong></td>
<td><strong>Reference standard:</strong> Clinical diagnosis Diagnosis confirmed by neurologist using DSM-IV criteria <strong>Timing:</strong> Concurrent <strong>Index test:</strong> EEG EEG signals obtained during eyes open, eyes closed, and a Continuous Performance Test (CPT), combination of non-linear features, support vector machine (SVM) classification, 70/30 training/testing split. Best results obtained from combination of correlation dimension</td>
<td><strong>Index test 3:</strong> Costs: <strong>Kappa:</strong> <strong>Index test 4:</strong> Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: <strong>Index test 5:</strong> Costs: <strong>Index test 2:</strong> Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: <strong>Kappa:</strong> <strong>Internal consistency:</strong></td>
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<th>Additional index tests</th>
</tr>
</thead>
</table>
|            | Min age: 4 Max age: 15   
Ethnicity: Other info on race or ethnicity: N/A | and fractal dimension in FP2 channel, and correlation dimension and sample entropy in Fz channel. 
Sensitivity: 98 
Specificity: 92 
PPV:  
NPV:  
LR+:  
LR-:  
Accuracy: 96 
AUC:  
Rater agreement:  
Kappa:  
ICC:  
Internal consistency:  
Alpha:  
Test-retest:  
Costs:  
Misdiagnosis:  
Labeling:  
Costs:  | Alpha:  
Costs:  | Index test 3: 
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
LR-:  
Accuracy:  
AUC:  
Rater agreement: | Index test 4: 
Sensitivity:  
Specificity:  
PPV:  
NPV:  
AUC:  | Index test 5: |
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<tr>
<th>Index Type</th>
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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| EEG        | Chang, 2019 \cite{187} Case series N = 60 Taiwan Setting: Specialty care | **Target:** IQ > 80. All male, did not receive any medication for ADHD testing, no history of epilepsy, mental retardation, drug abuse, head injury, or psychotic disorders  
**Other:** Age-matched controls  
**ADHD presentation** combined : 100  
**Diagnosed by:** Specialist  
**Comorbidity:** N/A  
**Female:** 0%  
**Age mean:** 8.4 (1.9) for ADHD group, 8.4 (1.7) for control group  
**Min age:** Max age:  
**Ethnicity:** Other info on race or ethnicity: N/A | **Reference standard:** Clinical diagnosis Swanson, Nolan, and Pelham (SNAP-IV) Teacher and Parent Rating Scale. Examined by a pediatric neurologist or psychiatrist. Timing: Prior diagnosis  
**Index test:** EEG Quantitative EEG (qEEG), eyes closed, 21 electrodes for 20 minutes at a sampling rate of 256 Hz, electrodes arranged based on the international 10-20 system. Support vector machine (SVM) classification with 8 features, 10 fold cross validation.  
Sensitivity: 80  
Specificity: 80  
PPV:  
NPV:  
LR+:  
LR-:  
Accuracy: AUC: 0.8778 | **Index test 2:**  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy: AUC:  
Rater agreement:  
Kappa:  
Internal consistency:  
Alpha:  
Costs:  
**Index test 3:**  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy: |
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<tbody>
<tr>
<td></td>
<td>AUC: Rater agreement:</td>
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<tr>
<td></td>
<td>Index text 4: Sensitivity: Specificity: PPV: NPV: AUC:</td>
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<td>Index text 5:</td>
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<th>Additional index tests</th>
</tr>
</thead>
</table>
| Chen, 2019<sup>1092</sup>  
Case series  
N = 107  
China  
Setting: Specialty care | Target: Right-handed; no lifetime history of head trauma with loss of consciousness; no history of neurological illness or another severe disease; no history of psychiatric disorders; IQ higher than 80; no history of taking stimulants or other medication to treat inattention problems. Recruited from the outpatient clinic at Beijing Children's Hospital, Capital Medical University  
Other: Handedness and age matched typically developing children recruited from local schools  
ADHD presentation: N/A  
Diagnosed by: Specialist  
Comorbidity: N/A | LR-:  
Accuracy: 85 Classifier model which selected from all tested features  
AUC: 0.9158 Classifier model which selected from all tested features  
Rater agreement:  
Kappa:  
ICC:  
Internal consistency:  
Alpha:  
Test-retest:  
Costs:  
Misdiagnosis:  
Labeling:  
Costs: | NPV:  
LR+:  
Accuracy:  
AUC:  
Rater agreement:  
Index text 4:  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
AUC:  
Index text 5: |

**EEG**

| Study: Author, year;  
Multiple publications;  
Study design;  
Study size;  
Location | Population:  
Setting;  
Study target;  
ADHD presentation;  
Diagnosis;  
Comorbidity;  
% Female;  
Age mean;  
Minimum age;  
Maximum age;  
Ethnicity | Results:  
Reference standard;  
Index test;  
Diagnostic accuracy;  
Rater agreement;  
Other outcomes | Additional index tests |
|------------------|------------------|-----------------|-----------------|
| Chen, 2019<sup>1092</sup>  
Case series  
N = 107  
China  
Setting: Specialty care | 10.44 (0.75) for ADHD group, 10.92 (0.69) for control group  
Min age: Max age:  
Ethnicity:  
Other info on race or ethnicity: N/A | LR-:  
Accuracy: 85 Classifier model which selected from all tested features  
AUC: 0.9158 Classifier model which selected from all tested features  
Rater agreement:  
Kappa:  
ICC:  
Internal consistency:  
Alpha:  
Test-retest:  
Costs:  
Misdiagnosis:  
Labeling:  
Costs: | NPV:  
LR+:  
Accuracy:  
AUC:  
Rater agreement:  
Index text 4:  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
AUC:  
Index text 5: |
<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| EEG        | Chen, 2021<sup>193</sup> Case series N = 70 Taiwan Setting: Specialty care       | Female: 18%  
Age mean: 10.44 (0.75) for ADHD group, 10.92 (0.69) for control group  
Min age: Max age:  
Ethnicity: Other info on race or ethnicity: N/A : Assume Chinese ethnicity | AUC:  
Rater agreement: Kappa: ICC:  
Internal consistency: Alpha: Test-retest: Costs:  
Misdiagnosis: Labeling: N/A Costs: | Index test 3:  
Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement:  
Index test 4:  
Sensitivity: Specificity: PPV: NPV: AUC:  
Index test 5:  
Reference standard: Clinical diagnosis Diagnosis of participants with ADHD was provided or confirmed by the child and adolescent psychiatrists in a clinical setting. Timing: Concurrent |
|            |                                                                                  |                                                                                     | Index test 2: EEG EEG data, independent testing data (n=9) used for cross validation  
Sensitivity: 95 Specificity: 38 PPV: 64 NPV: 86 LR+: Accuracy: 69 |
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
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<tbody>
<tr>
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<td>Author, year; Multiple publications; Study design; Study size; Location</td>
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<tr>
<td></td>
<td>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
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<tr>
<td></td>
<td>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
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<td></td>
<td>Additional index tests</td>
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<tr>
<td></td>
<td>Test, independent testing data (n=9) used for cross validation</td>
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<tr>
<td></td>
<td>AUC: 0.677 0.55 in independent cross validation test sample n=9</td>
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<tr>
<td></td>
<td>Rater agreement: Kappa:</td>
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<tr>
<td></td>
<td>Internal consistency: Alpha:</td>
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<td></td>
<td>Costs:</td>
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<tr>
<td></td>
<td>Index test 3: Combined rating Disruptive Behavior Disorder Rating Scale parent and teacher versions, independent testing data (n=9) used for cross validation</td>
</tr>
<tr>
<td></td>
<td>Sensitivity: 66 66</td>
</tr>
<tr>
<td></td>
<td>Specificity: 84</td>
</tr>
<tr>
<td></td>
<td>PPV: 83</td>
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<tr>
<td></td>
<td>NPV: 68</td>
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<td></td>
<td>LR+:</td>
</tr>
<tr>
<td></td>
<td>Accuracy: 74</td>
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<tr>
<td></td>
<td>AUC: 0.812</td>
</tr>
<tr>
<td></td>
<td>Rater agreement:</td>
</tr>
<tr>
<td></td>
<td>Index test 4: CPT Conners Kiddie Continuous Performance Test, independent testing data (n=9) used for cross validation</td>
</tr>
<tr>
<td></td>
<td>Sensitivity: 42</td>
</tr>
<tr>
<td></td>
<td>Specificity: 97</td>
</tr>
</tbody>
</table>

### Additional Index Tests

**Test:** 5.68 (0.52) for ADHD group, 5.72 (0.46) for control group

**Min age:** 5  **Max age:** 7

**Ethnicity:** Other info on race or ethnicity: N/A
### Appendix C. Evidence Tables

<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>EEG</td>
<td>Chiarenza, 2018&lt;sup&gt;796&lt;/sup&gt; Case series N = 50 Italy Setting: Specialty care</td>
<td><strong>Target:</strong> Children diagnosed with ADHD combined subtype or ADHD combined subtype+ODD <strong>Other:</strong> No non-ADHD participants <strong>ADHD presentation:</strong> combined : 100 <strong>Diagnosed by:</strong> Specialist <strong>Comorbidity:</strong> N/A <strong>Female:</strong> 8% <strong>Age mean:</strong> 10.1 (3.1) for ADHD only group, 10.3 (2.2) for ADHD plus oppositional defiant disorder group <strong>Min age:</strong> 6 <strong>Max age:</strong> 15 <strong>Ethnicity:</strong> Other info on race or ethnicity: N/A</td>
<td><strong>Reference standard:</strong> Clinical diagnosis Diagnoses were based on a DSM-V criteria <strong>Timing:</strong> Prior diagnosis <strong>Index test:</strong> EEG Quantitative EEG, Quantitative EEG Tomographic Analysis, and the Junior Temperament Character Inventory to classify ADHD only from ADHD+ODD <strong>Sensitivity:</strong> <strong>Specificity:</strong> <strong>PPV:</strong> <strong>NPV:</strong> <strong>LR+:</strong> <strong>LR-:</strong> <strong>Accuracy:</strong> <strong>AUC:</strong> 0.95 for the Junior Temperament Character Inventory Z-scores plus Z-spectra at the electrodes (quantitative EEG) and 0.91 for the Junior Temperament Character Inventory Z-scores plus Z-spectra at the</td>
<td>PPV: 94 NPV: 58 AUC: 0.737 <strong>Index text 5:</strong></td>
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</table>

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<th>Additional index tests</th>
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<tbody>
<tr>
<td>EEG</td>
<td>Chow, 2019&lt;sup&gt;311&lt;/sup&gt; Chow, 2019&lt;sup&gt;299&lt;/sup&gt; Case series N = 60 Taiwan Setting: N/A</td>
<td>Target: Female children; not taking medications at time of testing; no history of epilepsy, mental retardation, drug abuse, head injury, or psychotic disorders; diagnosis meets DSM-V criteria Other: Age-matched controls ADHD presentation: inattentive : 100 Diagnosed by: Specialist Comorbidity: N/A Female: 100% Age mean: 7.8 (2.2) for ADHD group, 8.1 (2.0) for control group Min age: Max age: Ethnicity:</td>
<td>Reference standard: Clinical diagnosis Clinical diagnosis from a pediatric neurologist or psychiatrist using DSM-V criteria Timing: Prior diagnosis Index test: EEG 20 minutes, eyes closed, Hjorth Mobility analysis of EEG, dataset randomly split into a training set and a test set in a size ratio of 9:1 and repeated 20 times. Logistic regression classifier with principle component analysis-based feature reduction, 10 fold cross validation. Sensitivity: 80 Specificity: 80 PPV: NPV:</td>
<td>AUC: Rater agreement: Index text 4: Sensitivity: Specificity: PPV: NPV: AUC: Index text 5: Index text 2: EEG 20 minutes, eyes closed, Theta/Beta ratio (TBR) of the EEG band, dataset randomly split into a training set and a test set in a size ratio of 9:1 and repeated 20 times. Logistic regression classifier with principle component analysis-based feature reduction Sensitivity: 46 Specificity: 74 PPV: NPV: LR+: Accuracy: 57.5 AUC: 0.633</td>
</tr>
</tbody>
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<td>Additional index tests</td>
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<tr>
<td></td>
<td></td>
<td>Other info on race or ethnicity: N/A</td>
<td>LR+: Accuracy: 79.2 AUC: 0.885 Rater agreement: Kappa: ICC: Internal consistency: Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
<td>Rater agreement: Kappa: Internal consistency: Alpha: Costs:</td>
</tr>
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<td>Index test 3: EEG 20 minutes, eyes closed, approximate entropy analysis of EEG, dataset randomly split into a training set and a test set in a size ratio of 9:1 and repeated 20 times. Logistic regression classifier with principle component analysis-based feature reduction, Sensitivity: 85 85 Specificity: 82 PPV: NPV: LR+: Accuracy: 82 AUC: 0.862 Rater agreement:</td>
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</thead>
<tbody>
<tr>
<td>EEG</td>
<td>Ekhlasi, 2022&lt;sup&gt;239&lt;/sup&gt; Case series N = 121 Iran Setting: Specialty care</td>
<td>Target: Children with ADHD symptoms Other: Neurotypical developing children ADHD presentation: N/A Diagnosed by: Specialist Comorbidity: N/A Female: % N/A Age mean: 9.73 (1.76) Min age: Max age: Ethnicity: Other info on race or ethnicity: N/A</td>
<td><strong>Reference standard:</strong> Clinical diagnosis Diagnosed by an experienced psychiatrist Timing: Prior diagnosis <strong>Index test:</strong> EEG EEG recorded during a visual attention task; weighted directed graphs constructed using the Phase Transfer Entropy measure; Naive Bayes classifier, 10-fold cross validation; Local graph measures in-degree and strength in the theta band Sensitivity: Specificity: PPV: NPV: LR+: LR-: Accuracy: 89 AUC: Rater agreement: Kappa: Internal consistency: Alpha:</td>
<td>Index text 5: EEG EEG recorded during a visual attention task; weighted directed graphs constructed using the Phase Transfer Entropy measure; Naive Bayes classifier, 10-fold cross validation; Feature matrix of all local graph measures (local efficiency, clustering coefficient) Sensitivity: Specificity: PPV: NPV: LR+: LR-: Accuracy: 91 AUC: Rater agreement: Kappa: Internal consistency: Alpha:</td>
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<td>Internal consistency: Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
<td>Costs:</td>
<td><strong>Index test 3:</strong> EEG EEG recorded during a visual attention task; weighted directed graphs constructed using the Phase Transfer Entropy measure; Naive Bayes classifier, 10-fold cross validation; Feature matrix of all local graph measures (local efficiency, clustering coefficient)</td>
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<td><strong>Index test 4:</strong> EEG EEG recorded during a visual attention task; weighted directed graphs constructed using the Phase Transfer Entropy measure; K-Nearest Neighbor classifier, 10-fold cross validation; Feature matrix of all global graph measures (global efficiency, characteri</td>
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<td>Sensitivity: Specificity: PPV; NPV; LR+: Accuracy: 90 AUC:</td>
<td>Rater agreement:</td>
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<td></td>
<td></td>
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<td>Sensitivity:</td>
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AUC:
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<tbody>
<tr>
<td>EEG</td>
<td>Hager, 2021&lt;sup&gt;109&lt;/sup&gt; Case series N = 130 Multiple countries Setting: Specialty care</td>
<td><strong>Target</strong>: Free of somatic conditions that could alternatively explain symptoms such as a diagnosed brain injury/ neurological disorder, and/or autism spectrum disorder. IQ must be &gt;=70. Patients were not excluded if they had common comorbidities such as learning disabilities, language disorders, Tourette syndrome, behavioral- and emotional disorders. Patients were not on ADHD medication when tested. <strong>Other</strong>: Age and gender matched typically developing children, mostly drawn from Human Brain Indicies database <strong>ADHD presentation</strong>: inattentive: 21, combined: 79 <strong>Diagnosed by</strong>: Specialist <strong>Comorbidity</strong>: N/A <strong>Female</strong>: 39% <strong>Age mean</strong>: Mean (SD): ADHD 10.52 (1.2) and Typically developing children 10.58 (1.2)</td>
<td><strong>Reference standard</strong>: Clinical diagnosis Diagnosed at three different child psychiatry outpatient clinics in Norway in accordance with DSM 5 criteria. Some patients had participated in earlier studies applying DSM IV. <strong>Timing</strong>: Prior diagnosis <strong>Index test</strong>: EEG 3 min eyes-closed condition, 3 min eyes-opened, and 20 min during a cued go/no-go task. Combined behavioral test scores from a cued visual go/no-go task and Event Related Potentials</td>
<td>Specificity: PPV: NPV: AUC: Index text 5:</td>
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</table>

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<td></td>
<td>EEG</td>
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<tr>
<td></td>
<td>Helgadottir, 2015</td>
<td><strong>Min age:</strong> 9 <strong>Max age:</strong> 12</td>
<td><strong>Reference standard:</strong> Clinical diagnosis Diagnosed according to DSM-IV using the K-SADS-PL semistructured interview, performed by experienced clinicians. <strong>Index test:</strong> EEG 3 min with eyes closed at rest. EEG coherence measures and chronological age features, statistical pattern recognition (SPR) based on support vector machines, cross-validation and separate test group.</td>
<td><strong>Index test 4:</strong> Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: <strong>Index test 5:</strong> Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC:</td>
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<tr>
<td></td>
<td>Case series</td>
<td><strong>Ethnicity:</strong> Other info on race or ethnicity: N/A</td>
<td><strong>Sensitivity:</strong></td>
<td><strong>Specificity:</strong></td>
</tr>
<tr>
<td></td>
<td>N = 661 Iceland Setting: Mixed</td>
<td><strong>Target:</strong> Diagnosed with ADHD and free of moderate or severe intellectual disability. No exclusions due to medication status: included medication-naïve patients, patients receiving treatment at the time of the recording, and patients on medication but not actually receiving treatment at the time of the recording. Children with comorbidities included. Recruited in two specialised centres in Reykjavik, Iceland. <strong>Other:</strong> Typically developing children were reported to be free of any mental or developmental disorders by their parents and had a score of less than 1.5 SDs above the age-appropriate norm on the ADHD Rating Scale-IV recruited in three schools</td>
<td><strong>Specificity:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ADHD presentation: inattentive : 33, hyperactive : 2, combined : 65</td>
<td><strong>Diagnosed by:</strong> Specialist <strong>Comorbidity:</strong> N/A <strong>Female:</strong> %</td>
<td><strong>PPV:</strong></td>
<td><strong>NPV:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>LR+:</strong></td>
<td><strong>LR-:</strong></td>
<td><strong>Accuracy:</strong> 76 Independent test cohort, 81% cross validation</td>
</tr>
</tbody>
</table>
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Population:</th>
<th>Results:</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study:</strong> Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Male:female ratio 3:1 ADHD group, 1:1 for control. Age mean: 9.6 years for the ADHD group and 9.5 years for the control (typically developing) group. Min age: 5.8 Max age: 14. Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Reference standard: Clinical diagnosis Medical diagnosis determined using neurophysiological examination based on the criteria in DSM-4. Timing: Prior diagnosis. <strong>Index test:</strong> EEG Event-related Potential signals were recorded by three electrodes located in the midline of the head (Pz, Cz, and Fz) according to 10–20 international system in two modalities, auditory and visual, at sampling rate of 640 samples per second. Fra-wave characterization with v_SVM classifier, 10 fold cross validation. Sensitivity: 96 Specificity: 87 PPV: NPV: LR+: Accuracy: 91 AUC: 0.94</td>
<td>LR+: Accuracy: AUC: Rater agreement:</td>
</tr>
<tr>
<td><strong>Index text 4:</strong> EEG event-related potentials using 3 sets of features: morphological, wavelets, and nonlinear dynamics based, best combination of features. Support vector machine (SVM) classification, leave one out cross validation. Sensitivity: 96 Specificity: 87 PPV: NPV: LR+: Accuracy: 91 AUC: 0.94</td>
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<tr>
<td><strong>Index text 5:</strong> EEG event-related potentials using 3 sets of features: morphological, wavelets, and nonlinear dynamics based, best combination of features. Support vector machine (SVM) classification, leave one out cross validation. Sensitivity: 96 Specificity: 87 PPV: NPV: LR+: Accuracy: 91 AUC: 0.94</td>
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</tr>
</tbody>
</table>

Jahanshahloo, 2017
Castro-Cabrera, 2010
Ghasemi, 2022

**Case series**

N = 60
Colombia
Setting: School

**Target:** Nothing abnormal in their physical, normal hearing/vision and and IQ of 80 or higher, those on medication were not to take medication for 24 hours before test. Comorbidities were accounted for; ODD, phobias, and learning problems.

**Other:** Control group. All participants recruited from educational institutions of the metropolitan area of Manizales.

**ADHD presentation:** N/A
**Diagnosed by:** Unclear/NR
**Comorbidity:** N/A
**Female:** %
N/A
**Age mean:** N/A
### Index Type

<table>
<thead>
<tr>
<th>Study:</th>
<th>Population:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Results:</th>
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</thead>
<tbody>
<tr>
<td>Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kappa:</td>
</tr>
<tr>
<td>Internal consistency:</td>
</tr>
<tr>
<td>Alpha:</td>
</tr>
<tr>
<td>Costs:</td>
</tr>
</tbody>
</table>

**Index test 3:** EEG Event-related potential (ERP) signals were recorded according to the criteria of the Oddball paradigm in two modes of auditory and visual stimulation; Deep learning classifier using the features Absolute Band Power that is normalized by maximum power (ABP)

**Index test 4:** EEG Event-related potential (ERP) signals were recorded according to the criteria of the Oddball paradigm in two modes of auditory and visual stimulation; Deep learning classifier using the...
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<tr>
<td></td>
<td>Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
<td>features Absolute Band Power that is normalized by maximum power (ABP)</td>
</tr>
<tr>
<td>EEG</td>
<td>Johnstone, 2021 Case series N = 214 China Setting: Other</td>
<td>Target: First-presentation, drug-naive, full-scale IQ scores &gt;80. No (a) diagnosis or history of head trauma with loss of consciousness, (b) history of neurological illness or other severe disease, and (c) diagnosis of schizophrenia, affective disorders, anxiety, tic disorders, pervasive developmental disorders, or mental retardation Other: Typically-developing children ADHD presentation: inattentive : 100 Diagnosed by: Specialist Comorbidity: N/A Female: 18.9% Age mean: 8.85 (range 7-12) Control mean age 8.92 years (range 7-12) Min age: 7 Max age: 12 Ethnicity: % Asian : 100 Other info on race or ethnicity:</td>
<td>Reference standard: Clinical diagnosis DSM-V diagnosis, using the KSADS Timing: Concurrent Index test: EEG Contributions to classification were from child tasks assessing working memory, inhibitory control, and task-shifting, child questionnaires, parent questionnaires including the SNAP-IV, and EEG. Stepwise discriminant function analysis, leave-one-out cross validation Sensitivity: 91 After leave-one-out cross-validation, 85% sensitivity Specificity: 94 After leave-one-out cross-validation, 92% specificity PPV: NPV: LR+: LR: Accuracy: 93 AUC:</td>
<td>Index test 2: Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement: Kappa: Internal consistency: Alpha: Costs:</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>Index test 3: Sensitivity: Specificity: PPV: NPV: LR+: Accuracy:</td>
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### Appendix C. Evidence Tables

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<tbody>
<tr>
<td></td>
<td>Author, year;</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiple publications;</td>
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<tr>
<td></td>
<td>Study design; Study size; Location</td>
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<tr>
<td>EEG</td>
<td>Khoshnoun, 2018³⁵⁹</td>
<td>Target: Right-handed</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Case series N = 24 Iran Setting: Specialty care</td>
<td>Other: Healthy age-matched right-handed children ADHD presentation: N/A: included hyperactive-impulsive, inattentive, and combined subtypes Diagnosed by: Unclear/NR Comorbidity: N/A Female: %</td>
<td>Reference standard: Clinical diagnosis Diagnosed with ADHD at Atieh Comprehensive Centre for Psychology and Nerve Disorders, Tehran, Iran Timing: Prior diagnosis</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Index text 2 Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement:</td>
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</table>

#### Index text 4:
- Sensitivity: 
- Specificity: 
- PPV: 
- NPV: 
- LR+: 
- Accuracy: 
- AUC: 
- Rater agreement:
### Appendix C. Evidence Tables

| Index Type | Study:  
Author, year;  
Multiple publications;  
Study design;  
Study size;  
Location | Population:  
Setting;  
Study target;  
ADHD presentation;  
Diagnosis;  
Comorbidity;  
% Female;  
Age mean;  
Minimum age;  
Maximum age;  
Ethnicity | Results:  
Reference standard;  
Index test;  
Diagnostic accuracy;  
Rater agreement;  
Other outcomes | Additional index tests |
|---|---|---|---|---|
| | N/A  
**Age mean:**  
N/A  
**Min age:** 7  
**Max age:** 12  
**Ethnicity:**  
Other info on race or ethnicity: N/A | height and width of the multifractal singularity spectrum of the EEG time series.  
Classification using support vector machine (SVM) classifier, 4 fold cross validation.  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
LR-:  
Accuracy: 83  
AUC:  
Rater agreement:  
Kappa:  
ICC:  
Internal consistency:  
Alpha:  
Test-retest:  
Costs:  
Misdiagnosis:  
Labeling:  
Costs: |  
Kappa:  
Internal consistency:  
Alpha:  
Costs:  
**Index test 3:**  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy:  
AUC:  
Rater agreement:  
**Index text 4:**  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
AUC:  
**Index text 5:** |
<table>
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<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| EEG        | Kim, 2015<sup>102</sup> Case series N = 97 Korea Setting: Specialty care | Target: Attending a camp for hyperactive children; IQ > 70; no brain damage, a neurological disorder, a genetic disorder, substance dependence, epilepsy or any other mental disorder; not receiving drug treatment  
Other: Children who exhibited no abnormalities based on the DISC-IV criteria and who had no personal history of any psychological disorder or accompanying disease  
ADHD presentation: N/A  
Diagnosed by: Specialist  
Comorbidity: N/A  
Female: 13%  
Age mean: 10.16 (1.90) for ADHD group, and 9.62 (1.72) for control group  
Min age: Max age:  
Ethnicity: Other info on race or ethnicity: N/A | Reference standard: Clinical diagnosis ADHD diagnosis was based on a Korean version of the Diagnostic Interview Schedule for Children Version IV (DISC-IV), and was confirmed by multiple child and adolescent psychiatrists  
Timing: Prior diagnosis  
Index test: EEG Theta-phase gamma-amplitude coupling  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
LR-:  
Accuracy: 72  
AUC:  
Rater agreement:  
Kappa:  
Internal consistency:  
Alpha:  
Costs: | Index test 2:  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy:  
AUC:  
Rater agreement:  
Kappa:  
Internal consistency:  
Alpha:  
Costs: |
|            |                                                                            |                                                                                                                              |                                                                                                                             | Index test 3:                                                                                                               |
|            |                                                                            |                                                                                                                              |                                                                                                                             | Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy:  
AUC:  
Rater agreement:  |
|            |                                                                            |                                                                                                                              |                                                                                                                             | Index test 4:  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
AUC:  |
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEG</td>
<td>Kim, 2015&lt;sup&gt;561&lt;/sup&gt; Case series N = 157 Korea Setting: Other Target: IQ&gt;70; no brain damage, neurological disorders, genetic disorders, substance dependence, epilepsy or any other mental disorder reported during a personal history and anamnesis; not on medication; children diagnosed with ADHD-not otherwise specified were excluded from the study Other: Children with no Korean version of the Diagnostic Interview Schedule for Children diagnosis and no personal history of psychological disorder or accompanying disease ADHD presentation: inattentive : 42, hyperactive : 24, combined : 34, N/A : Children diagnosed with ADHD-not otherwise specified were excluded from the study Diagnosed by: Specialist Comorbidity: N/A Female: 19% Age mean:</td>
<td>Reference standard: Clinical diagnosis ADHD diagnosis was based on a Korean version of the Diagnostic Interview Schedule for Children Version IV (DISC-IV), and diagnoses were confirmed by more than one child and adolescent psychiatrists Timing: Prior diagnosis Index test: EEG Quantitative electroencephalography Sensitivity: Specificity: PPV: NPV: LR+: LR-: Accuracy: 61% for the delta power and 56% for the theta wave AUC: Rater agreement: Kappa: ICC:</td>
<td>Index text 5:</td>
<td>Index text 2: CPT Integrated Visual and Auditory Continuous Performance Test Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: 82% for commission error, and 79% for omission error AUC: Rater agreement: Kappa: Internal consistency: Alpha: Costs: Index text 3: Sensitivity: Specificity:</td>
</tr>
<tr>
<td>Index Type</td>
<td>Study</td>
<td>Population</td>
<td>Results</td>
<td>Additional index tests</td>
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<td></td>
<td>Li, 2005&lt;sup&gt;106&lt;/sup&gt;</td>
<td>Case series N = 113 China Setting: Specialty care</td>
<td><strong>Index text 4:</strong> Clinical diagnosis Diagnosed with ADHD according to DSM-IV criteria Timing: Prior diagnosis</td>
<td>PPV: NPV: LR+: Accuracy: AUC: Rater agreement: Kappa:</td>
</tr>
<tr>
<td>EEG</td>
<td></td>
<td>Target: Outpatient children in Psychology Hyperactivity Department of the Central Hospital of Anshan City diagnosed with ADHD; excluding those with nervous system organic disease, pervasive developmental disorder, mental retardation, epilepsy, psychotic disorder, acoustical and visual abnormalities Other: Outpatient children in Psychology Hyperactivity Department of the Central Hospital of Anshan City not diagnosed with ADHD ADHD presentation: N/A Diagnosed by: Specialist Comorbidity: N/A Female: 22.1%</td>
<td>Internal consistency: Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
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<tr>
<td></td>
<td></td>
<td>Reference standard: Clinical diagnosis Diagnosed with ADHD according to DSM-IV criteria Timing: Prior diagnosis</td>
<td><strong>Index text 5:</strong></td>
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<tr>
<td></td>
<td></td>
<td><strong>Index test:</strong> EEG</td>
<td><strong>Index text 2:</strong> Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement: Kappa: Internal consistency: Alpha: Costs:</td>
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<tr>
<td>Index Type</td>
<td>Study: Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
<td>Additional index tests</td>
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## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Other info on race or ethnicity: N/A</td>
<td>LR+:</td>
<td>AUC:</td>
<td>Index text 3: EEG EEG signals collected during a Simon-spatial Stroop task. Multiple event-related potential (ERP) feature channels combining time domain and frequency domain features. BP neural network classifier.</td>
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<tr>
<td></td>
<td></td>
<td>LR-:</td>
<td>Rater agreement: Kappa:</td>
<td>Sensitivity:</td>
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<td>AUC:</td>
<td>AUC:</td>
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<td>Rater agreement: Kappa:</td>
<td>Internal consistency: Alpha:</td>
<td>Sensitivity:</td>
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<td>Kappa:</td>
<td>Costs:</td>
<td>Specificity:</td>
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<tr>
<td></td>
<td></td>
<td>ICC:</td>
<td>Test-retest: Costs: Misdiagnosis:</td>
<td>PPV: NPV:</td>
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<tr>
<td></td>
<td></td>
<td>Internal consistency: Alpha:</td>
<td>Labeling: Costs:</td>
<td>LR+: Accuracy: 94 AUC:</td>
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<td></td>
<td></td>
<td>Alpha:</td>
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<td>Test-retest: Costs: Misdiagnosis:</td>
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<td>Costs:</td>
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</table>

C-54
| Index Type | Study: Liechti, 2013<sup>38</sup> Case series N = 62 Switzerland Setting: Other | Population: Target: IQ $\geq 80$; medication free or suspended treatment at least 48 hours before testing Other: Typically developing children matched on age, gender, and IQ ADHD presentation: N/A Diagnosed by: Unclear/NR Comorbidity: N/A Female: 37.5% Age mean: 11.1 (2.1) for ADHD group, 11.2 (2.1) for control group Min age: 8 Max age: 16 Ethnicity: Other info on race or ethnicity: N/A | Results: Reference standard: Clinical diagnosis ADHD combined subtype (DSM-IV) were diagnosed using the clinical diagnostic interview PACS (parental account of children’s symptoms) plus Conners' teacher rating scale—revised Timing: Prior diagnosis | Additional index tests |
| --- | --- | --- | --- |

Index test 5: EEG


Index test 3: Sensitivity: Specificity: PPV: NPV: LR+: Accuracy:
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEG</td>
<td>Luo, 2022&lt;sup&gt;199&lt;/sup&gt; Case series N = 161 China Setting: Specialty care</td>
<td>Target: Enrolled from Peking University Sixth Hospital in Beijing; IQ&gt;80 Other: Age and sex-matched controls recruited from communities in Beijing ADHD presentation: inattentive : 51, combined : 49 Diagnosed by: Specialist Comorbidity: N/A Female: 20% Age mean: 12.0 (1.71) for the ADHD group, 11.6 (1.81) for the control group Min age: 8 Max age: 15 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Reference standard: Clinical diagnosis Diagnosed by a qualified psychiatrist using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) Timing: Prior diagnosis Index test: EEG Resting-state eye-closed EEG; microstate features (temporal microstate dynamics) and delta and TBR power components entered into the algorithm, support vector machine with recursive feature elimination (SVM-RFE), 5-fold cross-validation Sensitivity: 67 Specificity: 76 PPV: NPV:</td>
<td>Index test 2: Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement: Kappa: Internal consistency: Alpha: Costs:</td>
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</tbody>
</table>
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<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| EEG        | Marcano, 2018<sup>242</sup> Case series N = 7 US Setting: Other | **Target:** Children part of an ongoing longitudinal study focused on frontal lobe development from infancy through childhood diagnosed with ADHD and on medication **Other:** Children part of an ongoing longitudinal study focused on frontal lobe development from infancy through childhood without a diagnosis of ADHD **ADHD presentation:** N/A **Diagnosed by:** Unclear/NR **Comorbidity:** N/A **Female:** 0% **Age mean:** N/A | **Reference standard:** Other Diagnosis of ADHD was obtained via maternal report **Timing:** Prior diagnosis **Index test:** EEG EEG data collected during the child version of the Attention Network Task; classification using a Universal Background Model, sample split with 4 participants for training (2 ADHD, 2 control) and 3 for validation (2 ADHD, 1 control) **Sensitivity:** **Specificity:** **PPV:** **NPV:** | **PPV:** **NPV:** **LR+:** **Accuracy:** **AUC:** **Rater agreement:** **Index text 4:** **Sensitivity:** **Specificity:** **PPV:** **NPV:** **AUC:** **Index text 5:** **Internal consistency:** **Alpha:** **Test-retest:** **Costs:** **Misdiagnosis:** **Labeling:** **Costs:** **Costs:** **Costs:**
### Index Type

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<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEG</td>
<td>Markovska-Simoska, 2017&lt;sup&gt;403&lt;/sup&gt; Case series N = 60 Macedonia Setting: Specialty care</td>
<td><strong>Target:</strong> All male, right handed with no serious medical or neurological problems like seizures, or recent head trauma&lt;6 months; not on psychostimulants <strong>Other:</strong> Age-matched children selected from the Human Brain Index (HBI) database <strong>ADHD presentation:</strong> N/A : No subtypes in the article <strong>Diagnosed by:</strong> Specialist <strong>Comorbidity:</strong> N/A <strong>Female:</strong> 0% <strong>Age mean:</strong></td>
<td><strong>Reference standard:</strong> Clinical diagnosis Children diagnosed by Neuropsychologist, pediatrician and clinical psychologist plus Conners Rating Scale for teachers and parents <strong>Timing:</strong> Prior diagnosis <strong>Index test:</strong> EEG 5 minute eyes open resting state EEG, absolute theta central Sensitivity: 100 Specificity: 71 PPV: NPV:</td>
</tr>
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<td></td>
<td><strong>Index test 4:</strong> Sensitivity: Specificity: PPV: NPV: AUC:</td>
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<td><strong>Index test 5:</strong></td>
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C-58
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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9 (2.44) for ADHD group, 10.46 (2.27) for control group</td>
<td>Min age: 6 Max age: 14</td>
<td>LR+:</td>
<td>Kappa:</td>
</tr>
<tr>
<td></td>
<td>Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Accuracy: AUC: 0.876</td>
<td>LR-:</td>
<td>Internal consistency:</td>
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<td>Rater agreement: Kappa:</td>
<td>Alpha:</td>
<td>Alpha:</td>
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<td></td>
<td>Internal consistency: Alpha:</td>
<td>Test-retest: Costs:</td>
<td>Costs:</td>
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<td>Misdiagnosis:                                      Costs:</td>
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<td></td>
<td></td>
<td>Labeling:</td>
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<td>Costs:</td>
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<td>Index test 5:</td>
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<td>Costs:</td>
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### Index Type

<table>
<thead>
<tr>
<th>Study:</th>
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<th>Results:</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Index test: EEG records from children with typical ADHD symptomatology</td>
<td>Reference standard:</td>
<td>Index test 2: EEG Eyes-closed resting EEG analyzed by the Theta/ Beta Ratio method after decomposition with the Fast Fourier Transformation.</td>
</tr>
<tr>
<td>Martín-Brufau, 2017 Case series N = 50 Spain Setting: Specialty care</td>
<td>Other: EEG records from sex-matched typically developing children ADHD presentation: N/A Diagnosed by: Unclear/NR Comorbidity: N/A Female: % Reports subjects matched by sex, no other information Age mean: N/A Min age: 6 Max age: 15 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Diagnostic accuracy; Rater agreement; Other outcomes</td>
<td></td>
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<tr>
<td></td>
<td>Reference standard: Clinical diagnosis Diagnosed with ADHD Timing: Prior diagnosis Index test: EEG Eyes-closed resting EEG. Direct analysis of EEG specific montages performed by untrained individuals in EEG interpretation.</td>
<td>Sensitivity: Specificity: PPV: NPV: LR+: LR-: Accuracy: AUC: 0.868 Achieved by 55.5% of the untrained individuals (p&lt;0.01). AUC = 0.726 (p&gt;0.05) for the remaining 44.5%.</td>
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<td>Index test 3: EEG Eyes-closed resting EEG analyzed with the Delta + Theta / Alpha index obtained by visual position decomposition-Verley method.</td>
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<td>Sensitivity: Specificity: PPV: NPV: LR+: Accuracy:</td>
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Appendix C. Evidence Tables

<table>
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<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEG</td>
<td>Moghaddari, 2020&lt;sup&gt;236&lt;/sup&gt;&lt;br&gt;National Brain Mapping Lab, 2019&lt;sup&gt;252&lt;/sup&gt;&lt;br&gt;Mohammadi, 2016&lt;sup&gt;219&lt;/sup&gt;&lt;br&gt;Allahverdy, 2016&lt;sup&gt;236&lt;/sup&gt;&lt;br&gt;Sho‘oun, 2022&lt;sup&gt;239&lt;/sup&gt;&lt;br&gt;Case series&lt;br&gt;N = 61&lt;br&gt;Iran&lt;br&gt;Setting: Other</td>
<td><strong>Target:</strong> Children with ADHD; taking ritalin for up to 6 months&lt;br&gt;<strong>Other:</strong> Healthy children&lt;br&gt;<strong>ADHD presentation:</strong> N/A&lt;br&gt;<strong>Diagnosed by:</strong> Specialist&lt;br&gt;<strong>Comorbidity:</strong> N/A&lt;br&gt;<strong>Female:</strong> 29%&lt;br&gt;<strong>Age mean:</strong> 9.64 (1.73) for ADHD group, 9.85 (1.77) for control group&lt;br&gt;<strong>Min age:</strong> 7&lt;br&gt;<strong>Max age:</strong> 12&lt;br&gt;<strong>Ethnicity:</strong> Other info on race or ethnicity: N/A</td>
<td><strong>Reference standard:</strong> Clinical diagnosis&lt;br&gt;Child and adolescent psychiatrist determined diagnosis - using criteria from DSM-IV&lt;br&gt;<strong>Timing:</strong> Prior diagnosis&lt;br&gt;<strong>Index test:</strong> EEG EEG recording was performed according to the international 10–20 standard using 19 channels with reference electrodes located on earlobes while participants were doing a continuous mental task for four minutes at 512Hz. Frequency band separation making RGB images with three channels, deep learning convolution neural networks (CNN) classifier, 5 fold cross validation, subject-based test sample.&lt;br&gt;<strong>Sensitivity:</strong>&lt;br&gt;<strong>Specificity:</strong>&lt;br&gt;<strong>PPV:</strong>&lt;br&gt;<strong>NPV:</strong>&lt;br&gt;<strong>LR+:</strong>&lt;br&gt;<strong>Accuracy:</strong> 94&lt;br&gt;<strong>AUC:</strong>&lt;br&gt;<strong>Rater agreement:</strong>&lt;br&gt;<strong>Kappa:</strong>&lt;br&gt;<strong>Internal consistency:</strong></td>
<td>AUC: 0.917&lt;br&gt;Rater agreement:&lt;br&gt;<strong>Index text 4:</strong>&lt;br&gt;Sensitivity:&lt;br&gt;Specificity:&lt;br&gt;PPV:&lt;br&gt;NPV:&lt;br&gt;AUC:</td>
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</table>
### Appendix C. Evidence Tables

<table>
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<th>Additional index tests</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
<td>Alpha; Costs;</td>
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<td>LR+: LR-: Accuracy: 98 AUC:</td>
<td><strong>Index test 3</strong>: EEG EEG data, multilayer perceptron neural network as a classifier with one hidden layer by 5 neurons, the output function of the neural network was sigmoidal function, features extracted from the frontal region of scalp EEG&lt;sup&gt;550&lt;/sup&gt; Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: 97 AUC:</td>
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<td>Rater agreement: Kappa: ICC: Internal consistency: Alpha: Test-retest: Costs:</td>
<td><strong>Index text 4</strong>: Other: EOG signals Electrooculogram signals; approximate entropy and Petrosian's fractal dimension features, support vector machine classification, 10-fold cross validation structure, only 10 samples from the control group were used to train the SVM and 117 samples were use</td>
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</tbody>
</table>
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
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<th>Population:</th>
<th>Results:</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| EEG        | Muthuraman, 2019<sup>14</sup>  
Case series  
N = 22  
Germany  
Setting: N/A | Target: All male, right handed, with normal or corrected-to-normal vision.  (I) ADHD without conduct disorders or tic disorders as diagnosed by an experienced child and adolescent psychiatrist; (II) No other neuropsychiatric as well as no documented comorbidities in a structured psychiatric interview ‘Kinder-DIPS’<sup>29</sup>; (III) Sufficient compliance of child and family; (IV) Normal school achievement; (V) IQ>85; and (VI) No MEG exclusion criteria (i.e. ferromagnetic body objects, or a history of claustrophobia). Medication was stopped at least 48 h before recordings.  
Other: Male age-matched non-ADHD controls  
ADHD presentation: N/A : All ADHD children met the criteria for combined type or hyperactive-impulsive type  
Diagnosed by: Specialist  
Comorbidity: N/A  
Female: 0%  
Age mean: | Reference standard: Clinical diagnosis  
The diagnosis of ADHD was supported by the parents’ version of a German adaptive Diagnostic Checklist for ADHD (FBB-ADHD)<sup>31,32</sup> and by the psychiatric interview ‘Kinder-DIPS’  
Timing: Prior diagnosis  
Index test: EEG Multimodal  
electroencephalography (EEG): Eyes closed, resting state. 56 channels were selected from 61 equidistantly placed scalp Ag–AgCl electrodes using a standard cap sampled with 1200 Hz. Support vector machine (SVM) classifier using renormalized partial directed coherence, temporal partial directed coherence, source power, and source coherence parameters and all five frequency bands (delta, theta, alpha, beta, and gamma). 10-fold cross validation.  
Sensitivity: 85  
Specificity: 79  
PPV:  
NPV:  
AUC: 0.82 | Sensitivity: 85  
Specificity: 79  
PPV:  
NPV:  
AUC: 0.82  
Index text 2: EEG  
Multimodal magnetoencephalography (MEG): Eyes closed, resting state recordings were performed using a whole-head system at a sampling rate of 1200Hz in a synthetic third-order gradiometer configuration. Support vector machine (SVM) classifier using renorm  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy: 97  
AUC:  
Rater agreement:  
Kappa:  
Internal consistency: |
### Appendix C. Evidence Tables

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<tr>
<td></td>
<td>Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
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<td><strong>Index test 3:</strong> Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement:</td>
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<td><strong>Index test 4:</strong> Sensitivity: Specificity: PPV: NPV: AUC:</td>
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<td><strong>Index text 5:</strong></td>
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<td></td>
<td>Target: IQ&gt;=70 Other: Normal gender and age-matched controls with no psychiatric diagnosis, developmental disorders, learning disability, or brain injury ADHD presentation: inattentive : 32,combined : 68 Diagnosed by: Specialist Comorbidity: N/A</td>
<td>Reference standard: Clinical diagnosis Diagnoses were according to DSM IV-TR and accepted clinical guidelines. A senior neuropsychologist, pediatrician, and a clinical psychologist were responsible for diagnostic conclusions Timing: Prior diagnosis</td>
<td><strong>Index test 2:</strong> CPT, EF Go/NoGo task recording omission and commission errors, reaction time, and variability of response Sensitivity: Specificity: PPV: NPV: LR+:</td>
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<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
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</table>
|            | Female: 32%  
Age mean: 11 (3)  
Min age: 7 Max age: 16  
Ethnicity: Other info on race or ethnicity: N/A | Specificity:  
PPV:  
NPV:  
LR+:  
LR-:  
Accuracy: 63% for theta, 58% for theta/beta ratio  
AUC:  
Rater agreement:  
Kappa:  
ICC:  
Internal consistency:  
Alpha:  
Test-retest:  
Costs:  
Misdiagnosis:  
Labeling:  
Costs:  | Accuracy: 85 For omission errors  
AUC:  
Rater agreement:  
Kappa:  
Internal consistency:  
Alpha:  
Costs:  | Index text 3:  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy:  
AUC:  
Rater agreement:  
Index text 4:  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
AUC:  |
<p>|            |                                                                              |                                                                                                 |                                                                              | Index text 5: |</p>
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<tr>
<th>Index Type</th>
<th>Study: OÖztoprak, 2017&lt;sup&gt;47&lt;/sup&gt;</th>
<th>Population:</th>
<th>Results:</th>
<th>Additional index tests</th>
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<tr>
<td></td>
<td>Case series N = 108 Turkey Setting: N/A</td>
<td>Target: Male unmedicated first referrals, not using drug therapy, all without comorbidities, and without uncorrected visual or hearing defects. IQ range 90-129 Other: Male age-matched healthy controls ADHD presentation: combined : 100 Diagnosed by: Unclear/NR Comorbidity: N/A Female: 0% Age mean: N/A Min age: 6 Max age: 12 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Reference standard: Clinical diagnosis ADHD-C subtype was diagnosed using the DSM-IV Timing: Prior diagnosis</td>
<td>Index test 2: Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Costs:</td>
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<tr>
<td>EEG</td>
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<td>Index test: EEG Event-related potentials (ERPs) extracted from EEG recordings during performance of Stroop task. Electrodes located according to the 10–10 system (reference: combined mastoids). Feature extraction using the Time-Frequency Hermite Atomizer technique, and classification by support vector machine with recursive feature elimination (SVM RFE). 5-fold cross validation.</td>
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## Appendix C. Evidence Tables

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<th>Results</th>
<th>Additional index tests</th>
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<tbody>
<tr>
<td>EEG</td>
<td>Pereda, 2018&lt;sup&gt;61&lt;/sup&gt; Gonzalez, 2013&lt;sup&gt;767&lt;/sup&gt; Case series N = 33 Spain Setting: Specialty care</td>
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<td>Index text 5:</td>
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<tr>
<td></td>
<td>Target: All males with combined type ADHD Other: Male children of hospital staff ADHD presentation: combined : 100 Diagnosed by: Unclear/NR Comorbidity: N/A Female: 0% 100% male Age mean: 8(0.3) for ADHD group, 8.1 (0.48) for control group Min age: 6 Max age: 10 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Reference standard: Clinical diagnosis DSM-IV criteria of ADHD combined type or ICD-10 criteria of Hyperkinetic Disorder Timing: Prior diagnosis Index test: EEG 1.5 hour eyes open and eyes closed resting-state EEG recordings at 256 Hz, international 10/20 extended system, 8 channels. Functional connectivity pattern using phase locking value (PLV) phase synchronisation from dataset including the 5 most stationary segments, population-based Scatter Search algorithm, and K2 and Hill Climbing search strategies in Bayesian Network Classifier. Cross validation. Sensitivity: 95 Specificity: 93 PPV: NPV: LR+: LR-: Accuracy: 94</td>
<td>Index test 2: Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement: Kappa: Internal consistency: Alpha: Costs: Index test 3: Sensitivity: Specificity: PPV: NPV: LR+: Accuracy:</td>
</tr>
<tr>
<td>Index Type</td>
<td>Study: Rezaeezadeh, 2020&lt;sup&gt;102&lt;/sup&gt;</td>
<td>Population: Target: Patients of Atieh Comprehensive Centre for Psychology and Nerve Disorders, Tehran, Iran Other: Age-matched neurotypical children ADHD presentation: N/A Diagnosed by: Unclear/NR Comorbidity: N/A Female: % N/A Age mean: NA Min age: 7 Max age: 12 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Results: Reference standard: Clinical diagnosis Diagnosed with ADHD AT Atieh Comprehensive Centre for Psychology and Nerve Disorders, Tehran, Iran Timing: Prior diagnosis Index test: EEG Resting state eyes closed EEG, classification by Radial Basis Function support vector machine (RBF SVM) based on a combination of non-linear univariate features, 75/25 training/testing split rearranged randomly 20 times for validation Sensitivity: Specificity: PPV: NPV: LR+: LR:- Accuracy: 90.63 AUC:</td>
</tr>
<tr>
<td>Index Type</td>
<td>Study: Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
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</table>
|            |                                                                             | Accuracy: 99.58  
AUC:  
Rater agreement:  
Kappa:  
ICC:  
Internal consistency:  
Alpha:  
Test-retest:  
Costs:  
Misdiagnosis:  
Labeling:  
Costs: | Internal consistency:  
Alpha:  
Costs: | Index test 3:  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy:  
AUC:  
Rater agreement: | Index test 4:  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
AUC: |
<p>|            |                                                                             |                                                                                  | Index text 5:                                                                 |                                  |</p>
<table>
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<th>Population:</th>
<th>Results:</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEG</td>
<td>Smith, 2003[^335]</td>
<td>Target: Children and adolescents referred to a private ADHD clinic; comorbidities excluded, all drug naive prior to testing Other: Children and adolescents recruited from the local community and reported by their parents to be free of psychiatric and neurological disorders ADHD presentation: inattentive: 50, combined: 50 Diagnosed by: Specialist Comorbidity: N/A Female: % Male:Female ratio 4:1 Age mean: Min age: 8 Max age: 18 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Reference standard: Clinical diagnosis Diagnosis made by an experienced psychologist using DSM-IV criteria and confirmed by an independent pediatrician who was blind to the participant's status; Connoers' Parent and Teacher Rating Scales, the Child Behavior Checklist, and a developmental inter Timing: Prior diagnosis Index test: EEG Event-related potential data collected using EEG while participants completed two blocks of an auditory odd-ball task; discriminant function analysis using 7 variables; leave-one-out cross-validation; children 8-12 years old Sensitivity: 71 Specificity: 77 PPV: NPV: LR+: LR-: Accuracy: 73 AUC: Rater agreement: Kappa: Internal consistency: Alpha: Test-retest: Costs:</td>
<td>Index test 2: EEG Event-related potential data collected using EEG while participants completed two blocks of an auditory odd-ball task; discriminant function analysis using 4 variables; leave-one-out cross-validation; adolescents 13-18 years old Sensitivity: 57 Specificity: 63 PPV: NPV: LR+: Accuracy: 59 AUC: Rater agreement: Kappa: Internal consistency: Alpha: Costs:</td>
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</table>

[^335]: Smith, 2003
### Appendix C. Evidence Tables

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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEG</td>
<td>Snyder, 2008&lt;sup&gt;157&lt;/sup&gt; Case series N = 159 US Setting: Specialty care</td>
<td>Target: Presented to one of four psychiatric and pediatric clinics because of the suspected presence of attention and behavior problems; diagnosed with ADHD; 66% had comorbidities; study required medication wash out (&gt;72 hours) so patients stabilized by multiple medications and individuals on non-stimulants directed toward conditions other than ADHD were excluded</td>
<td>Reference standard: Clinical diagnosis performed by clinicians assisted with a semi-structured clinical interview (Kiddie Schedule of Affective Disorders and Schizophrenia -Present and Lifetime Version) including the supplements for behavioral disorders, affective disorders, and anxiety disorder Timing: Concurrent</td>
<td>Rater agreement:</td>
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<td>Other: Children diagnosed with disorders other than ADHD or no diagnosis ADHD presentation: inattentive: 43, hyperactive: 5, combined: 52 Diagnosed by: Specialist Comorbidity: N/A Female: % 36% in entire sample Age mean: 10.5 (3.4) Min age: 6 Max age: 18 Ethnicity:</td>
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<td>Misdiagnosis: Labeling: Costs:</td>
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<td>Index text 4: Sensitivity: Specificity: PPV: NPV: AUC:</td>
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<td>Index text 5:</td>
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<td>Index test 2: Combined rating ADHD Rating Scales-IV (N=101) Sensitivity: 55 Specificity: 43 PPV: 63 NPV: 36 LR+: Accuracy: 50 AUC:</td>
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<td>Rater agreement: Parent versus teacher ratings Kappa: Internal consistency: Alpha: Costs:</td>
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<td>Index test 3: Combined rating Conners Rating Scales-Revised (N=103)</td>
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</tbody>
</table>

### EEG

- **Target:** Presented to one of four psychiatric and pediatric clinics because of the suspected presence of attention and behavior problems; diagnosed with ADHD; 66% had comorbidities; study required medication wash out (>72 hours) so patients stabilized by multiple medications and individuals on non-stimulants directed toward conditions other than ADHD were excluded
- **Other:** Children diagnosed with disorders other than ADHD or no diagnosis
- **ADHD presentation:** inattentive: 43, hyperactive: 5, combined: 52
- **Diagnosed by:** Specialist
- **Comorbidity:** N/A
- **Female:** %
- 36% in entire sample
- **Age mean:** 10.5 (3.4)
- **Min age:** 6 **Max age:** 18
- **Ethnicity:**

#### Reference standard
- Clinical diagnosis performed by clinicians assisted with a semi-structured clinical interview (Kiddie Schedule of Affective Disorders and Schizophrenia -Present and Lifetime Version) including the supplements for behavioral disorders, affective disorders, and anxiety disorder

#### Timing
- Concurrent

#### Index test
- **EEG Eyes-open and eyes-closed resting state EEG (N=159):** theta/beta ratio, compared to normative database values with ADHD predicted at a standard deviation cutoff of 1.5
- **Sensitivity:** 87
- **Specificity:** 94
- **PPV:** 95
- **NPV:** 82
- **LR+:**
- **LR-:**
- **Accuracy:** 89

#### Additional index tests
- **Index test 2:** Combined rating ADHD Rating Scales-IV (N=101)
- **Sensitivity:** 55
- **Specificity:** 43
- **PPV:** 63
- **NPV:** 36
- **LR+:**
- **Accuracy:** 50
- **AUC:**

#### Rater agreement
- **Parent versus teacher ratings**
- **Kappa:**
- **Internal consistency:**
- **Alpha:**
- **Costs:**

#### Index test 3
- **Conners Rating Scales-Revised (N=103)**
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEG</td>
<td>Snyder, 2015&lt;sup&gt;56&lt;/sup&gt; Case series N = 275 US Setting: Mixed</td>
</tr>
</tbody>
</table>

#### Population:
- **Target:** Children and adolescents consecutively presenting with attentional and behavior concerns to 13 geographically distinct clinics who were diagnosed with ADHD by reference standard; participants needed to be willing to stop medication; IQ>=70; no history of seizure disorder, EEG abnormalities, or anticonvulsant use for seizure control; metal plate or device in the head; suicidal ideation or gesture and/or homicidal ideation or gesture; and known serious medical problems
- **Other:** Children and adolescents consecutively presenting with attentional and behavior concerns to 13 geographically distinct clinics

#### Results:
- **Reference standard:** Clinical diagnosis Multidisciplinary team consensus diagnosis comprised a clinical psychologist, a neurodevelopmental pediatrician, and a child/adolescent psychiatrist using DSM- IV-TR criteria and AACAP practice parameters Timing: Prior diagnosis
- **Index test:** EEG Combination of theta/beta ratio (TBR) from EEG with a clinician’s regular ADHD evaluation. Ten minute eyes open resting-state EEG. Clinical evaluation included: (1) Physical examinations, (2) Clinician interviews, with initial impressions

#### Additional index tests
- Sensitivity: 89 (83, 93) Specificity: 36 (29, 44) PPV: 56 NPV: 79 LR+: Accuracy: 61 AUC: Rater agreement: Kappa: Internal consistency:
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>who were not diagnosed with ADHD by reference standard</td>
<td>ADHD presentation: N/A</td>
<td>and reference to DSM-IV-TR criteria, (3) Kiddie-Schedule of Affective Disorders and Schizophrenia–Present and Lifetime Version (K-SADSPL) and Supplements with interviewer notes, (4) Children’s Global Assessment Scale, (5) Clinical Global Impression–Severity subscale, (6) ADHD-IV Rating Scales completed by investigator with parent informant and 1–2 teachers, (7) Wechsler Abbreviated Scale for Intelligence-long version, (8) Wide Range Achievement Test-4, (9) Questionnaires on socioeconomic status, education and family histories, and (10) any further testing if deemed necessary by the clinician on a patient-by-patient basis. Clinician’s diagnostic conclusions were summarized as “positive”, “negative” or “uncertain” for ADHD. EEG result categories were labeled for reference as “low”, “moderate”, or “high” for TBR level.</td>
<td>Alpha: Costs:</td>
</tr>
<tr>
<td></td>
<td>Female: 36%</td>
<td>% Hispanic or Latino : 4</td>
<td></td>
<td>Index text 4: Sensitivity: Specificity: PPV: NPV: AUC:</td>
</tr>
<tr>
<td></td>
<td>Age mean: 10.1 (2.9) Min age: 6 Max age: 17.99</td>
<td>% Black/African American : 17</td>
<td></td>
<td>Index text 5:</td>
</tr>
<tr>
<td></td>
<td>Ethnicity: % American Indian or Alaska Native : 2</td>
<td>% Asian : 1</td>
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<tbody>
<tr>
<td>EEG</td>
<td>Vahid, 2019&lt;sup&gt;580&lt;/sup&gt; Case series N = 144 Germany Setting: N/A</td>
<td>Target: No other severe or acute psychiatric comorbidities (e.g., autism, tics, depressive episode, etc.). Either diagnosed as ADD (ICD-10 F9838) or ADHD (ICD-10 F90.0 or F90.1) Other: Healthy control children ADHD presentation: inattentive: 52, inattentive_other: Referred to as ADD in study, combined: 48, combined_other: Referred to as ADHD in study Diagnosed by: Specialist Comorbidity: N/A Female: 22%</td>
<td>Reference standard: Clinical diagnosis Standard clinical guidelines by child/adolescent psychiatrists using family, school interviews and IQ, attention testing, and questionnaires Timing: Prior diagnosis Index test: EEG Event-related EEG recording during an interval-timing task, deep learning (EEGNet) classifier, leave one out subject (LOOS) cross validation, 2 class problem classification ADHD inattentive type from healthy control</td>
<td>Index test 2: EEG Event-related EEG recording during an interval-timing task, deep learning (EEGNet) classifier, leave one out subject (LOOS) cross validation, 2 class problem classification ADHD combined type from healthy control Sensitivity: 83 Specificity: 82 PPV: NPV:</td>
</tr>
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<tbody>
<tr>
<td></td>
<td>Age mean: 10.9 (2.4) for ADD group, 10.6 (1.9) for ADHD-combined group, 11.3 (2.2) for control group</td>
<td>Sensitivity: 89 Specificity: 84 PPV: NPV: LR+: LR-: Accuracy: 83 2 class classification AUC: Rater agreement: Kappa: ICC: Internal consistency: Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
<td>LR+: Accuracy: 80 2 class classification AUC: Rater agreement: Kappa: Internal consistency: Alpha: Costs:</td>
<td><strong>Index test 3:</strong> EEG Event-related EEG recording during an interval-timing task, deep learning (EEGNet) classifier, leave one out subject (LOOS) cross validation, 3 class problem classification ADHD inattentive type, ADHD combined type, healthy control Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: 69 AUC: Rater agreement:</td>
</tr>
</tbody>
</table>
|            | Min age: Max age: Ethnicity: Other info on race or ethnicity: N/A | | | **Index text 4:** Sensitivity:
<table>
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<tr>
<td>Imaging</td>
<td>Bansal, 2012&lt;sup&gt;17&lt;/sup&gt; Case series N = 83 US Setting: Specialty care</td>
<td>Target: Children with no lifetime diagnosis of Obsessive Compulsive Disorder, Tourette Syndrome or Tic disorder, and no premature birth (gestation &lt;=36 weeks); recruited through the general outpatient clinic at the Yale Child Study Center or through advertisements with a local chapter of ChADD (Children with Attention Deficit Disorder) Other: Healthy children with no lifetime or current DSM-IV Axis 1 or 2 disorder; IQ&gt;=80 ADHD presentation: N/A Diagnosed by: Specialist Comorbidity: N/A Female: 19.5% Age mean: 12.6 (3.18) for ADHD group, 10.5 (2.43) healthy children Min age: Max age: Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Reference standard: Clinical diagnosis Diagnosed with ADHD, diagnostic assessments were supplemented using the Conners ADHD Parent, Teacher Rating Scales, and the DuPaul-Barkley ADHD rating scale Timing: Prior diagnosis Index test: Imaging Anatomical MRI brain imaging; semi-supervised: applied leave-one-out cross validation to select a set of features that differed significantly between groups of individuals who were already clinically diagnosed, and then we applied hierarchical clustering to the feature vectors to discover naturalistic groupings of individuals in the dataset; 10 independent split-half replication analyses and leave-one-out cross-validation Sensitivity: 94 ADHD children from healthy children Specificity: 89 ADHD children from healthy children</td>
<td>Index test 2: Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement: Kappa: Internal consistency: Alpha: Costs: Index test 3: Sensitivity: Specificity: PPV: NPV: LR+: Accuracy:</td>
</tr>
</tbody>
</table>
### Imbalanced Index Tests

<table>
<thead>
<tr>
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<tr>
<td>Imaging</td>
<td>Chen, 2020&lt;sup&gt;129&lt;/sup&gt;; Wang, 2018&lt;sup&gt;112b,1121&lt;/sup&gt; Case series N = 86 China Setting: Other</td>
<td>Target: ADHD-200 dataset, Peking University subset 1 only (PU_1) Other: Healthy controls ADHD presentation: N/A : Dataset includes all subtypes Diagnosed by: Specialist Comorbidity: N/A Female: 42% Age mean: N/A Min age: 8 Max age: 17</td>
<td>Reference standard: Clinical diagnosis ADHD-200 Dataset Diagnosis Timing: Prior diagnosis Index test: Imaging fMRI resting-state functional connectivity, feature selection via support vector machine with recursive feature elimination (SVM-RFE), deep learning dual subspace classification algorithm (binary hypothesis testing), leave one out cross-validation Sensitivity: 100 Range 69%-95% [Subset Analysis]</td>
<td>Index test 2: Imaging Raw features derived from the temporal variability between intrinsic connectivity networks as well as demographic and covariate variables, model based on the support vector machines (SVMs), leave-one-out cross-validation and 10-folds cross-validations; be Sensitivity: 76 Specificity: 81 PPV:</td>
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</table>

| Ethnicity: Other info on race or ethnicity: N/A | | | |

| Index text 4: | Sensitivity: 75  Specificity: 74  PPV:  NPV:  LR+:  Accuracy: 75  AUC: | Rater agreement: | |

| | Costs: | | |

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</table>
| Imaging    | Crippa, 2017<sup>15</sup> Case series N = 44 Italy Setting: Mixed | **Target:** IQ>80 with normal or corrected-to-normal vision and not taking any medication.  
**Other:** Gender, age, and IQ matched typically developing children with no DSM-4 diagnoses recruited by local pediatricians and from schools  
**ADHD presentation:** inattentive : 18.2, hyperactive : 36.4, combined : 45.5  
**Diagnosed by:** Specialist  
**Comorbidity:** N/A  
**Female:** 0%  
**Age mean:** 11.5 (1.5) for ADHD group, 11.4 (1.9) for comparison group  
**Min age:** Max age:  
**Ethnicity:** % White : 100  
Other info on race or ethnicity: | **Reference standard:** Clinical diagnosis  
Diagnosis of ADHD based on DSM-IV TR  
Timing: Prior diagnosis  
**Index test:** Imaging Multi-domain profile of measures including blood fatty acid profiles, neuropsychological measures, and functional measures from near-infrared spectroscopy. Feature extraction using principal components analysis, support vector machine (SVM) classifier, nested 10-fold cross validation. Model with best accuracy trained on neuropsychological, fatty acid profiles, and deoxygenated-hemoglobin features.  
**Sensitivity:** 73  
**Specificity:** 87  
**PPV:**  
**NPV:**  
**LR+:**  
**Accuracy:** AUC  
**Rater agreement:** Kappa  
**Internal consistency:** Alpha  
**Costs:** | **Index test 2:**  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy:  
AUC:  
Rater agreement: Kappa  
Internal consistency: Alpha  
Costs:  
**Index test 3:**  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy:  |
## Appendix C. Evidence Tables

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<tbody>
<tr>
<td>Imaging</td>
<td>Gao, 2020; Bethlehem, 2017; Qureshi, 2016; Riaz, 2018; Miao, 2019; Zou, 2017; Dey, 2014; Case series N = 83 US</td>
<td><strong>Target:</strong> Children age 8-13, ADHD-200 database, Kennedy Krieger Institute (KKI) <strong>Other:</strong> Typically developing children <strong>ADHD presentation:</strong> N/A : All subtypes included <strong>Diagnosed by:</strong> Unclear/NR <strong>Comorbidity:</strong> N/A <strong>Female:</strong> 45% <strong>Age mean:</strong> N/A</td>
<td><strong>Reference standard:</strong> Clinical diagnosis Diagnosed with ADHD from the ADHD-200 datasets <strong>Timing:</strong> Prior diagnosis <strong>Index test:</strong> Imaging Combination of functional connectivity from resting state fMRI and phenotypic data (phenotypic-attribute attentional brain connectivity, age, and gender), support vector machine (SVM)</td>
<td>AUC: Rater agreement: <strong>Index text 4:</strong> Sensitivity: Specificity: PPV: NPV: AUC: <strong>Index text 5:</strong></td>
</tr>
</tbody>
</table>

| LR+: |
| LR-: |
| Accuracy: 81 Model containing cognitive profile, fatty acid profile, and near-infrared spectroscopy deoxygenated-hemoglobin AUC: 0.80 Model containing cognitive profile, fatty acid profile, and near-infrared spectroscopy deoxygenated-hemoglobin |

Rater agreement:
- Kappa:
- ICC:
- Internal consistency:
  - Alpha:
  - Test-retest:
- Costs:
- Misdiagnosis:
- Labeling:
- Costs:

**Index test 2:** Imaging Fusion of fMRI and non-imaging data, functional connectivity calculation, feature selection, fusion of non-imaging data (age, gender, IQ), and classification, SVM classifier

Sensitivity: 90
Specificity: 77
PPV: NPV:
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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
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</table>
| Setting: Other | **Min age: 8 Max age: 13**  
**Ethnicity:** Other info on race or ethnicity: N/A | classification. Used ADHD-200 provided KKI test dataset for validation  
Sensitivity: 93  
Specificity: 95  
PPV:  
NPV:  
LR+:  
LR-:  
Accuracy: 95  
AUC:  
Rater agreement:  
Kappa:  
ICC:  
Internal consistency:  
Alpha:  
Test-retest:  
Costs:  
Misdiagnosis:  
Labeling:  
Costs: | LR+:  
Accuracy: 87  
AUC:  
Rater agreement:  
Kappa:  
Internal consistency:  
Alpha:  
Costs: | **Index test 3:** Imaging Fractional amplitude of low-frequency fluctuation reflecting intensity of spontaneous neuronal activity combined with feature selection on fMRI  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy: 82  
AUC:  
Rater agreement: | **Index text 4:** Imaging Deep learning-based classification method via 3-D convolutional neural networks applied to MRI, first extracting meaningful 3-D low-level features from fMRI and structural MRI (sMRI). |
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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
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<tbody>
<tr>
<td>Imaging</td>
<td>Lin, 2023&lt;sup&gt;392&lt;/sup&gt; Zhou, 2021&lt;sup&gt;1153&lt;/sup&gt; Case series N = 7,805 US Setting: Other</td>
<td><strong>Target:</strong> U.S. population-based cohort from longitudinal Adolescent Brain and Cognitive Development (ABCD) study 3.0 release <strong>Other:</strong> U.S. population-based cohort from longitudinal Adolescent Brain and Cognitive Development (ABCD) study 3.0 release <strong>ADHD presentation:</strong> N/A <strong>Diagnosed by:</strong> Researcher <strong>Comorbidity:</strong> N/A <strong>Female:</strong> 36% <strong>Age mean:</strong> 9.9 (0.6) <strong>Min age:</strong> 8 <strong>Max age:</strong> 11 <strong>Ethnicity:</strong> % Hispanic or Latino : 20 % Black/African American : 14 % Asian : 2 % White : 55 % Multiracial : 8, Other : Mixed/Others</td>
<td><strong>Reference standard:</strong> Clinical diagnosis Parent Diagnostic Interview scales for the Kiddie-Schedule for affective Disorders and Schizophrenia (K-SADS) from the ABCD database <strong>Timing:</strong> Prior diagnosis <strong>Index test:</strong> Imaging Neuroimaging features selected from multimodal MRI data (resting-state fMRI, structural MRI, and diffusion MRI); RIDGE regularized logistic regression feature selection, extreme gradient boosting (XGB) classifier; 4:1 training/ testing split with 5 repeats of 10-fold cross validation; N=1,561 in validation test set <strong>Sensitivity:</strong> 57 <strong>Specificity:</strong> 65 <strong>PPV:</strong> <strong>NPV:</strong> <strong>LR+:</strong> <strong>LR-:</strong></td>
<td><strong>Index test 2:</strong> Imaging Combined clinical features (age, sex, race, highest parental education, and handedness) and neuroimaging features selected from multimodal MRI data (resting-state fMRI, structural MRI, and diffusion MRI); Hierarchical Clustering feature selection, Support <strong>Sensitivity:</strong> 60 <strong>Specificity:</strong> 56 <strong>PPV:</strong> <strong>NPV:</strong> <strong>LR+:</strong> <strong>LR-:</strong> <strong>Accuracy:</strong> <strong>AUC:</strong> 0.613 <strong>Rater agreement:</strong> <strong>Kappa:</strong></td>
</tr>
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<td>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
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<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Other info on race or ethnicity: Other: Undetermined &lt;1%</td>
<td>Accuracy: AUC: 0.576 Rater agreement: Kappa: ICC: Internal consistency: Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
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<tr>
<td></td>
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<td></td>
<td>Internal consistency: Alpha: Costs:</td>
<td>Index test 3: Imaging integration of multimodal features of structural and functional MRIs and Diffusion Tensor Images, Boruta based feature selection, multiple kernel learning, and support vector machine classifier, 10-fold cross validation and repeated nested 5-fold cross validation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rater agreement:</td>
<td>Sensitivity: 61 61 Specificity: 68 PPV: NPV: LR+: Accuracy: 64 AUC: 0.698 Rater agreement:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Index text 4:</td>
<td>Sensitivity: Specificity: PPV: NPV: AUC: Index text 5:</td>
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</thead>
</table>
| Imaging Riaz, 2020; Riaz, 2018; Itani, 2019; Sun, 2020; Itani, 2018 Case series N = 222 US Setting: Other | **Target:** Children 7-18, New York University medical center dataset (NYU) from ADHD-200 dataset  
**Other:** Healthy children  
**ADHD presentation:** N/A  
**Diagnosed by:** Specialist  
**Comorbidity:** N/A  
**Female:** 35%  
**Age mean:** N/A  
**Min age:** 7  
**Max age:** 18  
**Ethnicity:** Other info on race or ethnicity: N/A | **Reference standard:** Clinical diagnosis ADHD-200 dataset  
**Timing:** Prior diagnosis  
**Index test:** Imaging End-to-end deep learning model using pre-processed fMRI time-series signals. Used ADHD-200 provided NYU test set for validation.  
**Sensitivity:** 66  
**Specificity:** 92  
**PPV:**  
**NPV:**  
**LR+:**  
**LR-:**  
**Accuracy:** 73  
**AUC:**  
**Rater agreement:**  
**Kappa:**  
**Internal consistency:**  
**Alpha:**  
**Test-retest:**  
**Costs:**  
**Misdiagnosis:**  
**Labeling:**  
**Costs:**  | **Index test 2:** Imaging Decision tree machine learning predictive models based on phenotypic characteristics and resting-state functional Magnetic Resonance Images, validated using test set  
**Sensitivity:** 79  
**Specificity:** 58  
**PPV:**  
**NPV:**  
**LR+:**  
**Accuracy:** 73  
**AUC:**  
**Rater agreement:**  
**Kappa:**  
**Internal consistency:**  
**Alpha:**  
**Costs:**  |
| | | | **Index test 3:** Imaging Whole-brain resting-state functional connectivity patterns, support vector machine (SVM) classification, leave one out cross validation  
**Sensitivity:** 82  
**Specificity:** 82  
**PPV:**  
**NPV:**  
**LR+:**  |
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<tr>
<td>Imaging</td>
<td>Schirmer, 2021&lt;sup&gt;506&lt;/sup&gt;</td>
<td>Target: 25 children with primary diagnosis of Autism spectrum disorder who met diagnostic criteria for ADHD and 25 children with ADHD in test set. Part of The Connectomics in NeuroImaging Transfer Learning Challenge using data amassed retrospectively across multiple studies conducted by the Center for Neurodevelopmental and Imaging andResearch (CNIR) at the Kennedy Krieger Institute (KKI) in Baltimore, MD. Considered high-functioning based on having a full-scale IQ at or above the normal range. Other: Age and full-scale IQ matched neurotypical controls with no immediate family members diagnosed with ADHD or autism spectrum disorder ADHD presentation: N/A</td>
<td>Reference standard: Clinical diagnosis Diagnostic Interview for Children and Adolescents (DICA-IV), Fourth Edition or the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) for School-Aged Children-Present and Lifetime Version, in addition Conners’ Parent or Teacher Rating Sca Timing: Prior diagnosis</td>
<td>Accuracy: 85 AUC: Rater agreement: Index text 4: Imaging Computer-aided diagnosis, multi-level decision tree&lt;sup&gt;522&lt;/sup&gt; Sensitivity: Specificity: PPV: NPV: AUC:</td>
</tr>
</tbody>
</table>

Sensitivity: 95 75% in test set. False negative rate ranged from 0.05 to 0.3, false discovery rate ranged from 0.16 to 0.33

**Index text 5:**

**Index test 2:** Imaging fMRI, resting state, Tangent Pearson connectivity, SVM trained regularized by the statistical independence between the classifier decision scores and 3 types of demographic information: gender, age, and handedness score Sensitivity: 75 50% in test set Specificity: 70 50% in test set PPV: 71 NPV: 74 LR+: Accuracy: 73 53% in test set AUC: 0.85 0.54 in test set
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<td>Diagnosed by: Specialist Comorbidity: Other: 25 children with primary diagnosis of Autism spectrum disorder who met diagnostic criteria for ADHD in test set, N/A Female: 28% Age mean: 10.4 (1.3) Min age: 8 Max age: 12 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Specificity: 55 25% in test set PPV: 68 50% in test set NPV: 92 50% in test set LR+: LR-: Accuracy: 75 50% in test set AUC: 0.73 0.48 in test set Rater agreement: Matthews correlation coefficient 0.55 in validation set Kappa: ICC: Internal consistency: Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
<td>Rater agreement: Matthews correlation coefficient 0.45 in validation set Kappa: Internal consistency: Alpha: Costs: Index test 3: Imaging fMRI, resting state, mean and standard deviation, Pearson correlation, Tangent, covariance, and Tangent Pearson Sensitivity: 80 80 Specificity: 85 PPV: 84 NPV: 81 LR+: Accuracy: 83 AUC: 0.89 Rater agreement: Matthews correlation coefficient 0.65 in validation set</td>
<td>Index test 4: Imaging fMRI, resting state, long short-term memory network was used, AAL ROIs were first selected based on consistent connectivity differences</td>
</tr>
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</thead>
</table>
| Imaging   | Serrallach, 2016<sup>12</sup>  
Case series  
N = 147  
Germany  
Setting: Specialty care | Target: Part of a larger longitudinal project addressing the effects of musical practice on the brain and cognition from the primary school age to adolescence; ADHD group broken into separate categories, ADHD and ADD  
Other: Age matched healthy children, children with dyslexia  
ADHD presentation: inattentive: 49, inattentive_other: F 98.8 (ADD) ICD-10 classification, combined: 51, combined_other: F 90.0/F90.1 (ADHD) ICD-10 classification  
Diagnosed by: Specialist  
Comorbidity: N/A  
Female: 22%  
Age mean: 10.8 (1.9) for ADHD group, 11.0 (2.6) for ADD group, 10.7 (1.8) for dyslexic group, and 11.0 (1.3) for control group | Reference standard: Clinical diagnosis DSM IV (ICD-10), re-validated with informal interviews by specialist and "Parent assessment sheet for hyperactivity disorder, which is part of 'Diagnostic System for Psychiatric Disorders in Children and Adolescents' (DISYPS-K)  
Timing: Prior diagnosis  
Index test: Imaging MRI, T1-weighted structural magnetic MRI was performed to investigate the anatomy of the auditory cortex; Neuromag-122 whole-head MEG system was used to measure and analyze the response of the auditory cortex to acoustic stimuli, audiometric and psychoacoustic tests stimuli were presented binaurally with a Hammerfall DSP Multiface System and closed dynamic headphones.  
Index test 2: Sensitivity: 70  
Specificity: 65  
PPV: 67  
NPV: 68  
AUC: 0.72  
Index test 3: Sensitivity: 85  
Specificity: 70  
PPV: 75  
NPV: 80 | between ADHD and controls in bootstrapped samples, time-series from these ROIs were input to an LSTM, with the demograp  
Sensitivity: 70  
Specificity: 65  
PPV: 67  
NPV: 68  
AUC: 0.72 |
<table>
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<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
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<td>Min age: Max age:</td>
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<td>LR+; Accuracy: AUC; Rater agreement:</td>
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<td>Sensitivity: Specificity: PPV: NPV:</td>
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<tr>
<td>Imaging</td>
<td>Soliva, 2010&lt;sup&gt;338&lt;/sup&gt;</td>
<td>Target: IQ&gt;=80; no severe psychiatric illness including anxiety, mood disorders, developmental disorder, or dissociative disorder; no brain damage, neurological illness, head trauma, deafness, blindness, severe language delay, cerebral palsy, seizures, or autism; all on methylphenidate</td>
<td>Reference standard: Clinical diagnosis Diagnosed by a team consisting of a psychologist and a psychiatrist. Scoring was based on parent and teacher rating scales as well as a semi-structured clinical interview. Timing: Prior diagnosis</td>
<td>Index test 2:</td>
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<td>Tremols, 2008&lt;sup&gt;1085&lt;/sup&gt;</td>
<td>Other: Handedness and IQ matched controls ADHD presentation: inattentive : 18, hyperactive : 20, combined : 62 Diagnosed by: Specialist Comorbidity: N/A Female: 10% Age mean: 10.90 (2.83) for the ADHD group, 11.46 (2.86) for the control group Min age: Max age: Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Imaging Morphometric MRI using a novel semi-automated caudate segmentation procedure to obtain volumetric caudate nucleus data. Analyzed the right caudate nucleus body volume/ total bilateral caudate volume and right caudate nucleus body volume/ bilateral caudate body volume ratios. Split sample for training/testing. 40 participants in training group, 38 in test group. Sensitivity: 42 (20, 66) For optimal cut-off value &lt;=0.4818 of the right caudate nucleus body volume/ bilateral caudate body volume ratio in the test group Specificity: 95 (74, 99) For optimal cut-off value &lt;=0.4818 of the right caudate nucleus body volume/ bilateral caudate body volume ratio in the test group PPV: 89 For optimal cut-off value &lt;=0.4818 of the right caudate nucleus body volume/ bilateral caudate body volume ratio in the test group NPV: 62</td>
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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
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<td>For optimal cut-off value &lt;=0.4818 of the right caudate nucleus body volume/ bilateral caudate body volume ratio in the test group</td>
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<td>LR+:</td>
<td>AUC: 0.84 For optimal cut-off value &lt;=0.4818 of the right caudate nucleus body volume/ bilateral caudate body volume ratio in the test group</td>
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<td>LR-:</td>
<td>Rater agreement: Inter-rater reliability of the caudate segmentation procedure</td>
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<td>Kappa:</td>
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<td>AUC: 0.84</td>
<td>ICC: 0.87 for the caudate head and 0.89 for the caudate body at the beginning of the study using 10 randomly selected subjects (5 ADHD and 5 controls)</td>
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<td>Test-retest:</td>
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Index text 5:
### Appendix C. Evidence Tables

#### Index Type

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<tr>
<th>Study</th>
<th>Population</th>
<th>Results</th>
<th>Additional index tests</th>
</tr>
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</table>
| Sun, 2018<sup>19</sup> | **Target:** Newly diagnosed and never-treated, consecutively recruited from September 2009 to October 2015 from the Department of Psychiatry, West China Hospital, Sichuan University; IQ≥90, right-handed, no Axis I psychiatric comorbid disorders; no current or past treatment with psychotropic medication; no substance abuse; no physical illness that might affect brain anatomy and function (including neurologic illness; head injury; and liver, renal or cardiac abnormalities); and contraindications to MR imaging  
**ADHD presentation:** inattentive: 48, combined: 52  
**Diagnosed by:** Specialist  
**Comorbidity:** N/A  
**Female:** 14%  
**Age mean:** 10.83 (2.30) ADHD group, 11.21 (2.51) control group  
**Min age:** 7  
**Max age:** 15  
**Ethnicity:** Other info on race or ethnicity: N/A | **Reference standard:** Clinical diagnosis  
Diagnosis of ADHD by two clinical psychiatrists using the Chinese version of the Structured Clinical Interview for Diagnostic and Statistical Manual 4 Text Revision Axis I Disorders, or SCID  
**Timing:** Prior diagnosis  
**Index test:** Imaging Structural and diffusion-tensor MRI, anatomic and diffusion-tensor magnetic resonance imaging, cerebral radiomic features based random forest models, repeated 10-fold cross validation  
**Sensitivity:** 70  
**Specificity:** 77  
**PPV:**  
**NPV:**  
**LR+:**  
**LR-:**  
**Accuracy:** 74  
**AUC:**  
**Rater agreement:** 100 runs of 10-fold cross-validation (1000 training-testing cycles)  
**Kappa:** 0.47  
**Internal consistency:**  
**Alpha:**  
**Costs:** |  
| **Index test 2:** | Sensitivity:  
Specificity:  
**PPV:**  
**NPV:**  
**LR+:**  
**LR-:**  
**Accuracy:**  
**AUC:**  
**Rater agreement:**  
**Kappa:**  
**Internal consistency:**  
**Alpha:**  
**Costs:** |  
| **Index test 3:** | Sensitivity:  
Specificity:  
**PPV:**  
**NPV:**  
**LR+:**  
**LR-:**  
**Accuracy:**  
**AUC:**  
**Rater agreement:**  
**Internal consistency:**  
**Alpha:**  
**Costs:** |  
| **Index test 4:** | Sensitivity:  
Specificity:  
**PPV:**  
**NPV:**  
**AUC:** |
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<th>Index Type</th>
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<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
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<tbody>
<tr>
<td>Imaging</td>
<td>Tang, 2022\cite{367} Case series N = 194 China Setting: Other</td>
<td>Target: Children age 8 to 17 with ADHD, Peking University (PU) dataset from ADHD-200 Other: Healthy control children from ADHD-200 PU dataset ADHD presentation: N/A Diagnosed by: Specialist Comorbidity: N/A Female: 27% Age mean: N/A Min age: 8 Max age: 17 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Reference standard: Clinical diagnosis ADHD-200 Consortium identified children with ADHD Timing: Prior diagnosis Index test: Imaging fMRI, brain functional connectivities, deep-learning classification architecture based on a binary hypothesis testing framework and a modified auto-encoding network, leave one out cross validation Sensitivity: 99 Specificity: 100 PPV: NPV: LR+: LR-: Accuracy: 99.6 AUC: 0.997 Rater agreement: Kappa: ICC:</td>
<td>Index test 5:</td>
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<tr>
<td>Index Type</td>
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<tr>
<td>Imaging</td>
<td>Yao, 2018&lt;sup&gt;18&lt;/sup&gt; Case series N = 62 China Setting: Mixed</td>
<td>Target: Children: male drug-naive, right handed, full-scale IQ score &gt; 80, attend Peking University Sixth Hospital psychiatrist clinics Other: Age-matched healthy controls from local primary schools ADHD presentation: N/A Diagnosed by: Specialist Comorbidity: N/A Female: 0% all male in children dataset Age mean: 9.79 (1.86) for ADHD group, 10.29 (1.67) for control group Min age: Max age: Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Reference standard: Clinical diagnosis ADHD participants from child and adolescent psychiatric clinics of Peking University Sixth Hospital Timing: Concurrent Index test: Imaging Functional connectivity pattern derived from resting-state fMRI. Used novel Feature Selection method based on Relative Importance and Ensemble Learning (FS_RIEL), 10-fold cross validation Sensitivity: 95 Using FS_RIEL feature selection method Specificity: 76 Using FS_RIEL feature selection method PPV: NPV: LR+: LR-:</td>
<td>AUC: Rater agreement: Index text 4: Sensitivity: Specificity: PPV: NPV: AUC: Index text 5:</td>
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</table>
### Appendix C. Evidence Tables

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<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
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</thead>
<tbody>
<tr>
<td>Imaging</td>
<td>Yasumura, 2020&lt;sup&gt;249&lt;/sup&gt; Yasumura, 2014&lt;sup&gt;149&lt;/sup&gt; Case series N = 99 Japan Setting: Mixed</td>
<td>Target: No severe comorbidities (e.g., ASD or learning disability); IQ &gt;=80 Other: Typically developing children without ADHD ADHD presentation: N/A Diagnosed by: Specialist Comorbidity: N/A Female: 15.0% 15% female in ADHD training group, gender not reported for test group Age mean: Test set: 10.27 (2.2) for ADHD group, 10.16 (1.55) for control group Min age: Max age:</td>
<td>Accuracy: 86.36 Using FS_RIEL feature selection method AUC: Rater agreement: Kappa: ICC: Internal consistency: Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
<td>LR+: Accuracy: AUC: Rater agreement:</td>
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<td>Reference standard: Clinical diagnosis The Japanese version of the 26-item Swanson, Nolan and Pelham–IV + neurologist evaluation Timing: Prior diagnosis Index test: Imaging Near-infrared spectroscopy (NIRS) was used to quantify change in prefrontal cortex oxygenated hemoglobin during reverse Stroop task Classification using support vector machine. Items for machine learning were based on past research: age group (&lt;10 years, 10-12 years, &gt;=13 years), task results (number of responses and reaction time on the noninterference condition; number of responses, reaction time, number of errors,</td>
<td>Index test 2: Sensitivity: Specificity: PPV: NPV: AUC:</td>
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<td>Index text 3:</td>
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## Appendix C. Evidence Tables

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<th>Index Type</th>
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<tr>
<td>Imaging</td>
<td>Yoo, 2020&lt;sup&gt;21&lt;/sup&gt; Seoul National University Childrens Hospital, 2015&lt;sup&gt;1001&lt;/sup&gt; Case series N = 130 Korea Setting: Other</td>
<td><strong>Target:</strong> IQ&gt;=70, no hereditary genetic disorders, current/past history of brain trauma, organic brain disorders, seizure or any neurological disorders, autism spectrum disorder, communication disorder or learning disorder, schizophrenia or any other childhood-onset psychotic disorder, major depressive disorder or bipolar disorder, Tourette’s syndrome or chronic motor/vocal tic disorder,</td>
<td><strong>Reference standard:</strong> Clinical diagnosis DSM-IV criteria confirmed with the Korean Kiddie Schedule for Affective Disorders and Schizophrenia – Present and Lifetime version Timing: Prior diagnosis</td>
<td><strong>Index test 2:</strong> Imaging Structural, functional, and diffusion-tensor MRI, age, sex, and IQ. Lesser feature with Equivalent performance (LE): Machine learning algorithms on multi-measures, multi-modal neuroimaging data (structural</td>
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<td><strong>Sensitivity:</strong> 89 <strong>Specificity:</strong> 84 <strong>PPV:</strong> <strong>NPV:</strong> <strong>LR+:</strong> 5.47 <strong>LR-:</strong> 0.13 <strong>Accuracy:</strong> 86 <strong>AUC:</strong> 0.898 Rater agreement: Kappa: ICC: Internal consistency: Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
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<td>Other info on race or ethnicity: N/A and interference ratio on the interference condition) and NIRS data.</td>
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<td>obsessive-compulsive disorder, and no history of methylphenidate treatment for &gt;1 year or having taken methylphenidate in the previous 4 weeks; test set subjects were selected from independent neuroimaging data called “A cohort study for neurodevelopmental disorder” Other: Age and IQ-matched typically developing children ADHD presentation: inattentive: 46.8, inattentive_other: 27.8% in test group, hyperactive: 6.4, hyperactive_other: 22.2% in test group, combined: 29.8, combined_other: 27.8% in test group, N/A: 17% not otherwise specified Diagnosed by: Specialist Comorbidity: N/A Female: % 33% female in test set, 21% female in training set Age mean: Test set: 9.44 (2.41) for ADHD group, 10.06 (2.69) for control group. Training set: 10.06 (2.24) for ADHD group, 10.00 (2.60) for control group. Min age: 6 Max age: 17 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Best Accuracy Model: Machine learning algorithms on multi-measures, multi-modal neuroimaging data (structural MRI, Resting-state fMRI, diffusion tensor imaging). Selected variables ‘All tensors + CT/CTV + SA/MC + Volume’ [CT, Cortical thickness; CTV, Cortical thickness variability; SA, Surface area; MC, Mean curvature]. Multiple linear SVM recursive feature elimination for feature selection, random forest classifier, leave one out cross validation. Age, sex and IQ were also entered as predictors for random forest regression. Sensitivity: Specificity: PPV: NPV: LR+: LR-: Accuracy: 78 AUC: 0.70</td>
<td>MRI, Resting-state fMRI, diffusion tensor imaging Sensitivity: Specificity: PPV: NPV: LR+: AUC: 0.65 Rater agreement: Kappa: Internal consistency: Alpha: Costs:</td>
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<tr>
<td>neuropsychological</td>
<td>Li, 2016\textsuperscript{84} Yale University, 2012\textsuperscript{147} Case series N = 60 China Setting: Other</td>
<td>Target: Selected to participate if they met diagnostic criteria for any presentation of ADHD or who were considered to be subthreshold for ADHD, defined as one symptom short of meeting diagnostic criteria. Free of any other co-morbid psychiatric condition. Mediation naive or had discontinued medication 6 months prior to study. Other: Age and gender-matched typically developing children ADHD presentation: inattentive : 17, hyperactive : 13, combined : 63, combined other : 3.5% subthreshold combined type, and 3.5% subthreshold inattentive type Diagnosed by: Specialist Comorbidity: N/A Female: 7% Age mean: 8.95 (1.88) Min age: 6 Max age: 12 Ethnicity:</td>
<td>Reference standard: Clinical diagnosis Diagnosis based on DSM-5 criteria for ADHD Timing: Prior diagnosis Index test: neuropsychological Movement intensity measures included a composite measure of total movement intensity and a movement intensity distribution measure, infrared motion tracking system to monitor and record movement intensity during a modified Go/No-Go Task Sensitivity: 97 Specificity: 83 PPV: NPV: LR+: LR-: Accuracy: AUC: 0.904 Rater agreement: Kappa:</td>
<td>AUC: Index text 5:</td>
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### Appendix C. Evidence Tables

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<td>% Asian: 100, Other: All participants were of Han ancestry Other info on race or ethnicity:</td>
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<td>Alpha: Costs:</td>
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<td><strong>Index test 3:</strong> neuropsychological, activity Performance measures on the Go/No-Go task, 6 measures omission errors, commission errors, accuracy, multiple response errors, reaction time, and reaction time variability Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC:</td>
<td>Rater agreement:</td>
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<td><strong>Index text 4:</strong> neuropsychological Go/No-Go task accuracy Sensitivity: Specificity: PPV: NPV: AUC: 0.844</td>
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# Appendix C. Evidence Tables

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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
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</table>
| Case series | Adams, 2009<sup>119</sup> Case series N = 35 US Setting: Specialty care | Target: Boys diagnosed with ADHD recruited through newspaper advertising, children with comorbidities excluded, 10 of the 19 participants were on medication on the day of testing  
ADHD presentation: N/A  
Diagnosed by: Specialist  
Comorbidity: N/A  
Female: 0%  
Age mean: 10.1 (1.74) for the ADHD group, 10.5 (0.89) for the control group  
Min age: 8 Max age: 14  
Ethnicity: % White: 100  
Other info on race or ethnicity: | Reference standard: Clinical diagnosis Diagnoses provided by licensed mental health professionals or pediatric physicians and parents provided consent to have medical records reviewed for confirmation of diagnosis, Behavior Assessment System for children (BASC) Monitor parent rating  
Timing: Prior diagnosis  
Index test: neuropsychological, CPT The Virtual Classroom virtual reality continuous performance test including visual and/or auditory distracters; logistic regression with percent correct as the predictor (difference between ADHD and control groups trended toward significance)  
Sensitivity: 50  
Specificity: 88  
PPV:  
NPV:  
LR+:  
LR-:  
Accuracy: 68  
AUC: | Attention, Impulsivity, Response variability, Reaction time  
Index test 2: neuropsychological, CPT The Vigil continuous performance test; logistic regression with percent correct as the predictor (no statistically significant difference between ADHD and control groups)  
Sensitivity: 50  
Specificity: 69  
PPV:  
NPV:  
LR+:  
Accuracy: 59  
AUC:  
Rater agreement: Kappa:  
Internal consistency: Alpha:  
Costs: |
### Appendix C. Evidence Tables

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<tr>
<th>Index Type</th>
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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
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</table>
| neuropsychological, CPT | Berger, 2010<sup>143</sup> Hadassah Medical Organization, 2008<sup>142</sup> Case series N = 58 Israel Setting: Specialty care | **Target:** All the children in the study were drug naïve; no mental retardation, chronic condition other than ADHD, chronic use of medications, or diagnosis of depression, anxiety or psychosis  
**Other:** Healthy children without any symptoms or signs of ADHD  
**ADHD presentation:** N/A  
**Diagnosed by:** Specialist  
**Comorbidity:** N/A  
**Female:** 29%  
**Age mean:** | **Reference standard:** Clinical diagnosis ADHD diagnosis was established by a certified pediatric neurologist based on DSM-IV-TR criteria  
**Timing:** Prior diagnosis  
**Index test:** neuropsychological, CPT  
Computerized continuous performance functions test, which includes a multi-task approach  
Sensitivity: 100  
Test of reliability, percentage of true positive results among the 45 children with ADHD | **Index test 3:**  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy:  
AUC:  
Rater agreement:  
**Index text 4:**  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
AUC:  
**Index text 5:** |
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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
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</table>
| neuropsychological, CPT | Berger, 2017<sup>147</sup> Case series N = 798 US Setting: N/A | **Target:** Referred to the outpatient pediatric clinics of a neurocognitive center; drug-naïve; no intellectual disability, other chronic condition, chronic use of medications, or primary psychiatric diagnosis (e.g., depression, anxiety, and psychosis)  
**Other:** Randomly recruited typically developed children who study in regular classes at primary schools  
**ADHD presentation:** N/A  
**Diagnosed by:** Specialist | **Reference standard:** Clinical diagnosis  
Child met the criteria for ADHD according to DSM- IV- TR, as assessed by a certified pediatric neurologist  
**Timing:** Prior diagnosis  
**Index test:** neuropsychological, CPT  
MOXO-Continuous Performance Test (CPT) Total Score including 4 indices: attention, timing, hyperactivity, and impulsivity for all age groups | **Index test 3:**  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
LR-:  
Accuracy: 95  
AUC:  
Rater agreement:  
**Index text 4:**  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
AUC:  
**Index text 5:**  
Sensitivity:  
Specificity:  
PPV:  |
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<tr>
<td></td>
<td>Comorbidity: N/A Female: 39.5% Age mean: 9.27 (1.65) in ADHD group, 9.71 (1.64) in control group Min age: 7 Max age: 12 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Sensitivity: Specificity: PPV: NPV: LR+: LR-: Accuracy: AUC: 0.92 0.91-0.96 over the 6 age groups Rater agreement: Kappa: ICC: Internal consistency: Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
<td>NPV: LR+: Accuracy: AUC: 0.92 Rater agreement: Kappa: Internal consistency: Alpha: Costs:</td>
<td><strong>Index test 3:</strong> neuropsychological MOXO-Continuous Performance Test (CPT) Timing for 12 year old participants; number of correct responses given while the target stimulus is still presented on the screen Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: 0.80 Rater agreement: <strong>Index text 4:</strong> MOXO-Continuous Performance Test (CPT) Hyperactivity for 12 year old participants; the number of</td>
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<td>Bledsoe, 2020&lt;sup&gt;160&lt;/sup&gt; Case series N = 35 US Setting: N/A</td>
<td><strong>Target:</strong> Did not meet diagnostic criteria for other psychiatric or psychological disorder including Learning Disorders, Anxiety Disorders, Mood Disorder, or Oppositional Defiant Disorder. IQ&gt;=80. ADHD participants who were prescribed stimulant medication were subjected to at least a 24- to 48-hr washout period prior to testing, and were not taking any other medications during testing <strong>Other:</strong> Healthy age and IQ matched typically developing children.; all participants were recruited from a diversity of socioeconomic status (SES) and ethnic backgrounds to control for potential group differences <strong>ADHD presentation:</strong> combined : 100 <strong>Diagnosed by:</strong> Specialist <strong>Comorbidity:</strong> N/A <strong>Female:</strong> 26% <strong>Age mean:</strong></td>
<td><strong>Reference standard:</strong> Clinical diagnosis Participants were diagnosed with ADHD-C using the Diagnostic Interview Schedule for Children–IV–Parent Version (DISC-IV-P) with agreement between two investigators <strong>Timing:</strong> Prior diagnosis <strong>Index test:</strong> neuropsychological,CPT Support vector machine classification using Conners Global Index-Restless/ Impulsive composite score and d2 Test of Attention/Concentration total score. Leave-one-(participant)-out cross-validation. <strong>Sensitivity:</strong> 100 After leave-one-(participant)-out cross-validation <strong>Specificity:</strong> 100 After leave-one-(participant)-out cross-validation <strong>PPV:</strong> NPV: AUC: 0.82</td>
<td>all types of commission responses that are not coded as impulsive responses <strong>Sensitivity:</strong> Specificity: PPV: NPV: AUC: 0.82 <strong>Index text 5:</strong> Neuropsychological Attention,Impulsivity</td>
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</table>

**Index text 2:** neuropsychological,CPT Support vector machine classification using Behavior Assessment System for Children- 2nd edition hyperactivity scale and d2 Test of Attention/Concentration total score. Leave-one-(participant)-out cross-validation. **Sensitivity:** 100 After leave-one-(participant)-out cross-validation **Specificity:** 96 After leave-one-(participant)-out cross-validation **PPV:** NPV: LR+: |
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<th>Additional index tests</th>
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<tr>
<td></td>
<td>N/A</td>
<td>LR-: Accuracy: 100 After leave-one-(participant)-out cross-validation AUC:</td>
<td>Accuracy: 97 After leave-one-(participant)-out cross-validation AUC:</td>
<td>Accuracy: 97 After leave-one-(participant)-out cross-validation AUC:</td>
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<td>Min age: Max age:Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Rater agreement: Kappa: ICC: Internal consistency: Alpha:</td>
<td>Rater agreement: Kappa: Internal consistency: Alpha:</td>
<td>Costs:</td>
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<td>Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
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<td>Index test 3: Costs</td>
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- **Index test 3:**
  - Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC:
  - Rater agreement:

- **Index test 4:**
  - Sensitivity: Specificity: PPV: NPV: AUC:

- **Index text 5:**
### Appendix C. Evidence Tables

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<tr>
<td></td>
<td>Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Target: Children referred by a neurologist or a child psychiatrist for a neurocognitive evaluation in order to substantiate a possible diagnosis of ADHD; no known diagnosis of mental retardation or major psychopathology (namely, major affective disorder, psychotic disorder, pervasive developmental disorder, substance abuse, posttraumatic stress disorder, obsessive-compulsive disorder, panic disorder)</td>
<td>Reference standard: Clinical diagnosis of ADHD was based on consensus between the research team based on SNAP-IV, DAWBA, and clinical interview all based on DSM-IV criteria. Timing: Concurrent</td>
<td>Index test 2: neuropsychological,EF Subtests of The Cambridge Neuropsychological Test Automated Battery (CANTAB) Sensitivity: 57% for Working Memory, Spatial Working Memory, 71% for Stocking of Cambridge, and 71% for Cognitive Set-Shifting-Intradimensional/Extradimensional Shift subtests Specificity: 22% for Working Memory, Spatial Working Memory, 11% for Stocking of Cambridge, and 7% for Cognitive Set-Shifting-Intradimensional/Extradimensional Shift subtests</td>
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<td>Multiple publications; Study design; Study size; Location</td>
<td>Other: Children referred by a neurologist or a child psychiatrist for a neurocognitive evaluation in order to substantiate a possible diagnosis of ADHD; for 7 patients, the diagnosis of ADHD was excluded (patients were subsequently diagnosed, two with dysthymia, ADHD presentation: N/A</td>
<td>Reference standard: Clinical diagnosis of ADHD was based on consensus between the research team based on SNAP-IV, DAWBA, and clinical interview all based on DSM-IV criteria. Timing: Concurrent</td>
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<td>Study: Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Diagnosed by: Researcher</td>
<td>Index test: neuropsychological,CPT The Test of Variables of Attention (TOVA)</td>
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<td>Study: Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Comorbidity: N/A</td>
<td>Sensitivity: 63 Specificity: 85 PPV: 94 NPV: 37 Lr+: LR-: Accuracy: AUC: Rater agreement: Kappa: ICC: Internal consistency: Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
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<td>Study: Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Female: 44% Age mean: 11.5 Min age: 7 Max age: 17 Ethnicity: Other info on race or ethnicity: N/A</td>
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<td>Study: Author, year; Multiple publications; Study design; Study size; Location</td>
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| Reference standard: Clinical diagnosis of ADHD was based on consensus between the research team based on SNAP-IV, DAWBA, and clinical interview all based on DSM-IV criteria. Timing: Concurrent | |

**Index test 3:**

| Reference standard: Clinical diagnosis of ADHD was based on consensus between the research team based on SNAP-IV, DAWBA, and clinical interview all based on DSM-IV criteria. Timing: Concurrent | |

**Index test 2:**

| Reference standard: Clinical diagnosis of ADHD was based on consensus between the research team based on SNAP-IV, DAWBA, and clinical interview all based on DSM-IV criteria. Timing: Concurrent | |

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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
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</thead>
</table>
| neuropsychological, CPT | Chen, 2022<sup>109</sup> Case series N = 109 China Setting: School | **Target:** Recruited from 6 primary schools and 6 junior high schools diagnosed with ADHD or subclinical ADHD **Other:** Recruited from 6 primary schools and 6 junior high schools **ADHD presentation:** N/A **Diagnosed by:** Researcher **Comorbidity:** N/A **Female:** 28% **Age mean:** 10.6 (1.9) for the ADHD group, 11.0 (1.9) for the subthreshold ADHD group, 11.6 (1.5) for the typically developing group | **Reference standard:** Clinical diagnosis Chinese version of the Swanson Nolan and Pelham Rating Scale (SNAP-IV) parent rating and teacher rating, Conners Abbreviated Symptom Questionnaire parent rating and teacher rating, teacher interviews **Timing:** Prior diagnosis | **Index text 4:** Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement: **Index text 5:** | **Index text 2:** neuropsychological, CPT Attention Network Test-Interaction, support vector machine classifier using the attentional effects of Alerting, Orienting, Conflict in Response Time, and overall Response Time, 10-fold cross validation, binary classification ADHD versus typically develop Sensitivity: Specificity: PPV: NPV:
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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
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<td>Index test 3: neuropsychological, CPT Attention Network Test- Interaction and Backward-Making Majority Function Task, support vector machine classifier using the attentional effects of Alerting, Orienting, Conflict in Response Time, overall Response Time, and Cognitive Control Capacity (there</td>
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<td>Chu, 2017&lt;sup&gt;202&lt;/sup&gt; Case series N = 107 Taiwan Setting: Specialty care</td>
<td>Target: Children who have been diagnosed with ADHD based on clinical diagnosis according to DSM-IV Other: Healthy children without ADHD ADHD presentation: inattentive_other: n=32, hyperactive_other: n=4, combined_other: n=34 Diagnosed by: Specialist Comorbidity: N/A Female: % N/A Age mean:</td>
<td>Reference standard: Clinical diagnosis Diagnosed with ADHD by a medical professional using DSM-IV diagnostic standards Timing: Prior diagnosis Index test: neuropsychological, CPT Diagnosis-supported attention deficit hyperactivity disorder (DS-ADHD) is a self-built diagnosis-supported ADHD screening system based on the Test of Variables of Attention (TOVA) Sensitivity: 85 Specificity: 63</td>
<td>Index text 4: neuropsychological, CPT Attention Network Test-Interaction, support vector machine classifier using the attentional effects of Alerting, Orienting, Conflict in Response Time, and overall Response Time, 10-fold cross validation, binary classification subclinical ADHD versus typic Sensitivity: Specificity: PPV: NPV: AUC:</td>
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<td>Index text 5:</td>
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<tr>
<td></td>
<td>Age reported for each sub-type separately, Inattentive 9 (1.58) / Hyperactive 8.5 (1.91) / Combined 9.8 (1.52)</td>
<td>Min age: 6 Max age: 12</td>
<td>PPV: 82 NPV: 67 LR+: LR-: Accuracy: 78 AUC: 0.867</td>
<td>Index test 3: Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement:</td>
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<td>Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Rater agreement: Kappa: ICC: Internal consistency: Cronbach’s alpha ranged from 0.906 to 0.987 over 15 variables in the DS-ADHD. Variables include items such as response time, response time variability, omission errors, commission errors, and response sensitivity. Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
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### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| neuropsychological,CPT | Emser, 2018<sup>256</sup>  
Case series  
N = 60  
Germany  
Setting: Mixed | Target: IQ >=80; no other medical conditions such as hyperthyroidism, autism, epilepsy, brain disorders and any genetic or medical disorder associated with externalizing behavior; may have oppositional defiance disorder, conduct disorder, learning disorders, anxiety, or depression as long as ADHD was the primary diagnosis; participants taking medication were asked to stop taking it 2 days before testing; recruited through an ADHD outpatient clinic  
Other: Age and gender-matched children, no established or suspected ADHD diagnosis, or family history of ADHD, recruited through local schools  
ADHD presentation: inattentive : 27, hyperactive : 3, combined : 60, N/A : 10% subtype information not available  
Diagnosed by: Specialist  
Comorbidity: N/A  
Female: 30%  
Age mean: 8.9 (1.4) for the ADHD group, 8.7 (1.2) for the control group  
Min age: 6.9  
Max age: 11  
Ethnicity: Other info on race or ethnicity: N/A | Reference standard: Clinical diagnosis ADHD diagnoses were based on a DSM-IV-oriented clinical interview  
Timing: Prior diagnosis  
**Index test:** neuropsychological,CPT Linear support vector machine and feature selection using variables from the Conners-3 parent ratings, the Quantified Behavior Test for children, and the Test Battery of Attention for children. Leave-one-out cross validation  
Sensitivity: 83  
Specificity: 90  
PPV:  
NPV:  
LR+:  
LR-:  
Accuracy: 87  
AUC:  
Rater agreement:  
Kappa:  
Internal consistency:  
Alpha:  
Costs: | Index test 2:  
neuropsychological,CPT  
Linear support vector machine and feature selection using variables from the Conners Behavior Test for children and the Test Battery of Attention for children only. Leave-one-out cross validation  
Sensitivity: 80  
Specificity: 77  
PPV:  
NPV:  
LR+:  
Accuracy: 78  
AUC:  
Rater agreement:  
Kappa:  
Internal consistency:  
Alpha:  
Costs: |
| Index test 3:  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy:  
AUC: |
### Appendix C. Evidence Tables

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<td>Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
<td>Misdiagnosis: Labeling: Costs: Rater agreement:</td>
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<tr>
<td>neuropsychological, CPT</td>
<td>Hall, 2016&lt;sup&gt;112&lt;/sup&gt; Pre-post study N = 80 UK Setting: Specialty care</td>
<td>Target: Pre vs post-test audit design, case records were examined in 40 cases diagnosed without the QbTest [pre-QbTest group] and 40 cases diagnosed with the QbTest [QbTest group] Other: None; study examined time to diagnoses of ADHD with and without QbTest results ADHD presentation: N/A: All diagnoses made for Hyperkinetic disorder (F90), equivalent to &quot;severe combined subtype&quot; Diagnosed by: Specialist Comorbidity: N/A Female: % 20% female in the pre-QbTest group, 30% female in the QbTest group Age mean: QbTest group - 9.2 (2.3) / pre-QbTest group - 8.1 (2.4) Min age: 4.5 Max age: 14.6</td>
<td>Reference standard: Clinical diagnosis Diagnosis completed using ICD-10 codes from patient records Timing: Prior diagnosis Index test: neuropsychological, CPT QbTest is a neuropsychological test that measures the three main symptoms of ADHD, requires subjects to respond to stimulus while ignoring other stimuli Sensitivity: Specificity: PPV: NPV: LR+: LR-: Accuracy: AUC: Rater agreement: Kappa: Internal consistency: Alpha: Costs: pounds</td>
<td>Index test 2: Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement: Kappa: Internal consistency: Alpha: Costs: pounds</td>
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| Heller, 2013<sup>119</sup>  
Case series  
N = 52  
US  
Setting: Specialty care | **Target:** Recruited from two outpatient clinics, diagnosed with ADHD, IQ>55, stimulant medications for ADHD were withheld on the day of testing  
**Other:** Age and sex-matched comparison subjects without ADHD recruited from two outpatient clinics, IQ>55  
**ADHD presentation:** inattentive: 35, inattentive_other: 100% of the ADHD participants had inattentive symptoms, combined: 65, combined_other: 65% of the ADHD participants had hyperactive symptoms in addition to inattentive symptoms  
**Diagnosed by:** Specialist  
**Comorbidity:** N/A  
**Female:** 38%  
**Age mean:** 12.6 for the ADHD group, 14.7 for the no ADHD group | **Reference standard:** Clinical diagnosis  
Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version semistructured diagnostic interview, Conners' Brief Rating Scale- Parent version and Teacher version, previous Conner's CPT scores if available  
**Timing:** Concurrent  
**Index test:** neuropsychological, CPT  
"Groundskeeper" video game using the Sifteo Cubes gaming platform; AdaBoost meta-algorithm, JRip rule-making algorithm, and J48 and RandomForest decision tree algorithms tested, binary classification=
Sensitivity: 77  
Specificity: 81  
PPV:  
NPV:  
LR+: | **AUC:**  
Rater agreement:  
**Index text 4:**  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
AUC:  
**Index text 5:**  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
AUC:  
Rater agreement: |
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<th>Additional index tests</th>
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<tr>
<td></td>
<td>Min age: 6 Max age: 17</td>
<td>LR-: Accuracy: 75</td>
<td>Kappa:</td>
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<td>Ethnicity: % Hispanic or Latino : 2</td>
<td>AUC:</td>
<td>Internal consistency: Alpha:</td>
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<td>% Black/African American : 15</td>
<td>Rater agreement: Kappa:</td>
<td>Costs:</td>
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<td>% White : 77</td>
<td>ICC:</td>
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<td>Other info on race or ethnicity: Other : 6% Other Race</td>
<td>Internal consistency: Alpha:</td>
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**Index text 3:**
- Sensitivity:
- Specificity:
- PPV:
- NPV:
- LR+:

**Accuracy:**
- AUC:
- Rater agreement:
- Costs:

**Index text 4:**
- Sensitivity:
- Specificity:
- PPV:
- NPV:
- AUC:

**Index text 5:**
### Appendix C. Evidence Tables

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<th>Results: Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| neuropsychological,CPT | Hult, 2018<sup>11</sup>  
Case series  
N = 182  
Sweden  
Setting: Specialty care | **Target:** Children referred to specialty clinic with suspected ADHD, autism, or another neurodevelopmental disorder; IQ > 70; unmedicated at time of assessment; comorbid ASD, tic disorders, developmental coordination disorder, borderline intellectual functioning, dyslexia, language disorder, and depression/anxiety disorder included  
**Other:** Children not diagnosed with ADHD referred to and selected from same specialty clinic as the ADHD group; 81% of these children diagnosed with ASD; tic disorders, developmental coordination disorder, borderline intellectual functioning, dyslexia, language disorder  
**ADHD presentation:** inattentive: 24, hyperactive: 2, combined: 71, N/A: 3  
ADHD-not otherwise specified  
**Diagnosed by:** Specialist  
**Comorbidity:** Autism: Non-ADHD clinical comparison (CC) group participants had ASD (81%)  
**Female:** 22%  
**Age mean:** 10.3 (1.7) ADHD group, 10.8 (1.8) comparison group  
**Min age:** 8.4, **Max age:** 13.7  
**Ethnicity:** Other info on race or ethnicity: N/A | **Reference standard:** Clinical diagnosis  
Diagnosis of ADHD performed by a multi-professional team, based on DSM-IV behavioral criteria  
Timing: Concurrent  
**Index test:** neuropsychological,CPT  
**QbTest**  
Sensitivity: With cutoff set to 1.25 Q-score as recommended by the manufacturer, sensitivity ranged from 47% to 67%  
Specificity: With cutoff set to 1.25 Q-score as recommended by the manufacturer, specificity ranged from 72% to 84%  
PPV: 76%-86%  
NPV: 37%-50%  
LR+:  
LR-:  
Accuracy:  
AUC: 0.62-0.76 over three test parameters with cutoff set at recommended 1.25 Q-score  
Rater agreement:  
Kappa:  
ICC:  
Internal consistency:  
Alpha:  
Test-retest:  
Costs: | Index test 2:  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy:  
AUC:  
Rater agreement:  
Kappa:  
Internal consistency:  
Alpha:  
Costs: |

Index test 3:  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy:  
AUC:  
Rater agreement:  
Kappa:  
Internal consistency:  
Alpha:  
Costs: |

Index test 4:  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
AUC: |
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<td><strong>Index test 3</strong>: activity Actigraph measures taken during CPT task; ADHD versus neurotypical controls</td>
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<td><strong>Index test 4</strong>: activity Actigraph measures taken during CPT task; ADHD versus non-ADHD</td>
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<td><strong>Index text 5</strong>:</td>
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<td></td>
<td>Sensitivity: 25 Specificity: 95 PPV: 77 NPV: 63 AUC:</td>
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<td>Neuropsychological, CPT Attention, Impulsivity, Other: Dyscontrol</td>
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<td><strong>Index test 5</strong>:</td>
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C-117
| Index Type | Study: Mitchell, 1990[^25]  
| Case series  
| N = 204  
| US  
| Setting: School | Population: Target: Selected from five elementary schools, in special education placement or regular class with resource specialist, no coexisting major medical problems or centrally active medications other than stimulants, IQ >=80, asked to omit medication for 2 to 3 days prior to testing  
| Other: Selected from two elementary schools  
| ADHD presentation: N/A  
| Diagnosed by: Specialist  
| Comorbidity: N/A  
| Female: 19%  
| Age mean: 10.2 (1.77) for the hyperactive group, 9.08 (2.14) for the control group  
| Min age: 5 Max age: 13  
| Ethnicity: Other info on race or ethnicity: N/A | Results: Reference standard: Clinical diagnosis  
| Diagnosis by psychologist or physician of hyperactivity and/or attention deficit disorder, review of school files including all psychometric testing, Conners Abbreviated Teacher Questionnaire, the Matching Familiar Figures Test  
| Timing: Prior diagnosis  
| Index test: neuropsychological, CPT Four tasks designed for use on the Apple Ile microcomputer described to subjects as a game on which they could earn points, similar to video game; summary score representing the number of measures on which the child scored above the 95th percentile with a cutoff point of 4 of 21 measures  
| Sensitivity: 60  
| Specificity: 95  
| Allowed false positive rate of 5%  
| PPV:  
| NPV:  
| LR+:  
| LR-:  
| Accuracy:  
| AUC:  
| Rater agreement: Agreement was defined as the proportion of subjects with abnormal scores on the Matching Familiar Figures Test who were also abnormal using the video game summary score | Additional index tests | Index test 2:  
| Sensitivity:  
| Specificity:  
| PPV:  
| NPV:  
| LR+:  
| Accuracy:  
| AUC:  
| Rater agreement:  
| Kappa:  
| Internal consistency:  
| Alpha:  
| Costs:  
| Index test 3:  
| Sensitivity:  
| Specificity:  
| PPV:  
| NPV:  
| LR+:  
| Accuracy:  
| AUC:  
| Rater agreement:  
| Index test 4:  
| Sensitivity:  
| Specificity:  
| PPV:  
| NPV:  
| AUC:  |
### Appendix C. Evidence Tables

| Index Type | Study: Mwamba, 2019<sup>19</sup>  
| Case series  
| N = 30  
| South Africa  
| Setting: Specialty care | Population:  
| Target: No known history of severe mental illness  
| Other: Controls, non-ADHD youth  
| ADHD presentation: N/A  
| Diagnosed by: Specialist  
| Comorbidity: N/A  
| Female: 54%  
| Gender ratio was kept as closely as possible to 1:1  
| Age mean: 10  
| Min age: 5 Max age: 16  
| Ethnicity: Other info on race or ethnicity: N/A | Results:  
| Reference standard: Other  
| Subjects had been consulted by a specialist at a private paediatric practice at the Cape Gate Medi-Clinic.  
| Timing: Prior diagnosis  
| Index test: neuropsychological,CPT  
| Paediatric Attention-Deficit/Hyperactivity Disorder Application Software (PANDAS): Tablet-based game, Support vector machine (SVM) classifier. 75/25 train/test split | Additional index tests  
| Agreement = 75%  
| Kappa:  
| ICC:  
| Internal consistency:  
| Alpha:  
| Test-retest:  
| Costs:  
| Misdiagnosis:  
| Labeling:  
| Costs:  | Index text 5:  
| Neuropsychological Attention, Impulsivity, Response variability, Reaction time, Other: Hand errors  
| Index test 2:  
| Sensitivity:  
| Specificity:  
| PPV:  
| NPV:  
| LR+:  
| LR-:  
| Accuracy:  
| AUC:  
| Rater agreement:  
| Kappa:  
| Internal consistency:  
| Alpha:  
| Costs:  | Index test 3:  
| Sensitivity:  
| Specificity:  
| PPV: |
# Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| neuropsychological, CPT | Park, 2019<sup>457</sup> Case series N = 114 Korea Setting: Specialty care | **Target:** IQ>=70, not on ADHD medication within the past 3 months, no past or current history of schizophrenia, organic mental disorder, or pervasive developmental disorder, or presence of seizure or other neurologic disorders. May have comorbid disorders such as tics, and depressive or anxiety disorder; consecutively recruited from outpatient pediatric psychiatry clinic  
**Other:** Children with a negative ADHD diagnosis, IQ>=70. May have comorbid disorders such as tics, and depressive or anxiety disorder, but no past or current history of schizophrenia, organic mental disorder, or pervasive developmental disorder, or presence of se | **Reference standard:** Clinical diagnosis Diagnosed as ADHD using DSM-IV-TR and Kiddie- Schedule for Affective Disorders and Schizophrenia– Present and Lifetime version (K-SADS-PL)  
**Timing:** Prior diagnosis  
**Index test:** neuropsychological, CPT The Advanced Test of Attention  
Sensitivity: 85  
Specificity: 46  
PPV: 78  
NPV: 57  
LR+:  
LR-:  
Accuracy: 72.8  
AUC: 0.653 | |
<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rodriguez, 2018⁴⁸⁸ Case series Spain Setting: Mixed</td>
<td>ADHD presentation: inattentive: 45.6, hyperactive: 5.1, combined: 36.6, N/A: 12.7% ADHD- not otherwise specified</td>
<td>Rater agreement: Kappa: ICC: Internal consistency: Alpha: Test-retest: Test-retest no ICC greater than 0.5 was found in ADHD retest participants</td>
<td>Costs: Misdiagnosis: Labeling: Costs:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diagnosed by: Specialist Comorbidity: N/A Female: 25.3% Age mean: 7.6 (1.5) for ADHD group, 8.6 (2.1) for control group Min age: 6 Max age: 12 Ethnicity: Other info on race or ethnicity: N/A</td>
<td></td>
<td>Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement:</td>
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<td>Reference standard: Clinical diagnosis ADHD group was composed of children with a diagnostic report (by a Clinical Center) specifying the type of ADHD presentation. Using this information, the researchers confirmed the diagnosis and its presentation using the symptomatology described in DSM-5 Timing: Prior diagnosis</td>
<td>Index test 4: Sensitivity: Specificity: PPV: NPV: AUC:</td>
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<tr>
<td></td>
<td></td>
<td>Index test 5: Neuropsychological, CPT Aula Nesplora Virtual Reality Continuous Performance Test; discrimination between ADHD-IH vs ADHD-I vs ADHD-C vs controls</td>
<td>Index test 2: Neuropsychological, CPT Test of Variables of Attention (TOVA); discrimination between ADHD-IH vs ADHD-I vs ADHD-C vs controls</td>
<td>sensitivity: Specificity: PPV: NPV: LR+: Accuracy: 34 Discrimination between ADHD-IH vs ADHD-I vs ADHD-C vs controls AUC:</td>
</tr>
</tbody>
</table>
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Study type; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Other info on race or ethnicity: N/A</td>
<td>Specificity: PPV; NPV; LR+: LR-; Accuracy: 57 Discrimination between ADHD-IH vs ADHD-I vs ADHD-C vs controls AUC; Rater agreement: Kappa; ICC; Internal consistency: Alpha: 0.72; Test-retest: Costs; Misdiagnosis: Labeling: Costs;</td>
<td>Rater agreement: Kappa; Internal consistency: Alpha; Costs;</td>
<td><strong>Index test 3:</strong> Sensitivity; Specificity; PPV; NPV; LR+: Accuracy; AUC; Rater agreement;</td>
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<td></td>
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<td><strong>Index text 4:</strong> Sensitivity; Specificity; PPV; NPV; AUC;</td>
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<td><strong>Index text 5:</strong></td>
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</tbody>
</table>
### Schatz, 2001

- **Index Type**: neuropsychological, CPT
- **Study**: Schatz, 2001
- **Setting**: Case series
- **Population**: N = 48
- **US**: Setting: Mixed

#### Target:
Attentional symptoms must be primary to a learning disability if present, individuals with a pervasive neurological condition such as autism or comorbid psychiatric disorders were excluded.

#### Other:
Children with normal neurodevelopmental histories and at an appropriate grade level for their chronological age; recruited from general pediatric clinics, advertisements in parent magazines and at local fairs, radio advertisements, and through contacts with

#### ADHD presentation:
N/A

#### Diagnosed by:
Specialist

#### Comorbidity:
N/A

#### Female:
N/A

#### Age mean:
11.1 (3.6) for ADHD group, 9.8 (2.7) for control group

#### Min age: 5 Max age: 17

#### Ethnicity:
Other: Predominantly white

#### Reference standard:
Clinical diagnosis

#### Medical history, neurological exam, parent and teacher historical reports, and psychological testing

#### Timing:
Prior diagnosis

#### Index test:
neuropsychological, CPT Test of Variables of Attention (TOVA), cutoff at least one T score >=65

#### Sensitivity: 86
#### Specificity: 70
#### PPV:
#### NPV:
#### LR+:
#### LR-:
#### Accuracy:
#### AUC:

#### Rater agreement:
Kappa:

#### Internal consistency:
Alpha:

#### Test-retest:
Costs:

#### Misdiagnosis: TOVA miss rate 14.3% and false positive rate 30.0%, Conners Hyperactivity Index miss rate 21.4% and false positive rate 0%

#### Labeling:
Costs:

---

**Index test 2**: Parental rating scale
- Conners Parent Rating Scale, Hyperactivity Index, cutoff T score =>65 (1.5 SD above the mean)

- Sensitivity: 79
- Specificity: 100
- PPV:
- NPV:
- LR+:
- Accuracy:
- AUC:

- Rater agreement:
- Kappa:

- Internal consistency:
- Alpha:

- Costs:

---

**Index test 3**:
- Sensitivity:
- Specificity:
- PPV:
- NPV:
- LR+:
- Accuracy:
- AUC:

- Rater agreement:

---

**Index test 4**: 

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# Appendix C. Evidence Tables

<table>
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<tr>
<th>Index Type</th>
<th>Study: Author; year; Multiple publications; Study design; Study size; Location</th>
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<th>Results:</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Target:</strong> Drug naïve, no comorbidities, normal or corrected-to-normal vision; students with developmental delays, poor academic performance, epilepsy, previous history of traumatic brain injury, psychosis, mood disorders, or learning disabilities (including dyslexia, dysgraphia, and dyscalculia) were excluded</td>
<td><strong>Reference standard:</strong> Clinical diagnosis</td>
<td><strong>Index test:</strong> Continuous Visual Attention Test (CVAT). Parameters measured include omission errors (OEs), commission errors (CEs), reaction time (RT), and variability of reaction time (VRT). Coefficient of variation was also calculated (CofV = VRT / RT).</td>
<td><strong>Index test 2:</strong> neuropsychological,CPT Continuous Auditory Attention Test (CAAT). Parameters measured include omission errors (OEs), commission errors (CEs), reaction time (RT), and variability of reaction time (VRT). Coefficient of variation was also calculated (CofV = VRT / RT).</td>
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<tr>
<td></td>
<td><strong>Diagnosed by:</strong> Unclear/NR</td>
<td><strong>Sensitivity:</strong> 70</td>
<td><strong>Specificity:</strong> 56</td>
<td><strong>Accuracy:</strong> 66 AUC:</td>
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<td></td>
<td><strong>Comorbidity:</strong> N/A</td>
<td><strong>PPV:</strong></td>
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<td><strong>Rater agreement:</strong></td>
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<td></td>
<td><strong>Female:</strong> %</td>
<td><strong>NPV:</strong></td>
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<td><strong>Kappa:</strong></td>
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<td></td>
<td><strong>N/A</strong></td>
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<td></td>
<td><strong>Age mean:</strong> 9.3 (1.40) for ADHD group, 9.2(1.41) for healthy control group</td>
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<td><strong>Internal consistency:</strong></td>
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<td><strong>Min age:</strong> 5 <strong>Max age:</strong> 18</td>
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<td><strong>Ethnicity:</strong></td>
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<td>Index Type</td>
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<td></td>
<td>Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
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<td>Slobodin, 2020; Berger, 2020</td>
<td>Other info on race or ethnicity: Other: Sample size is all Brazilian</td>
<td>Accuracy: 70</td>
<td>Alpha:</td>
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<td>Case series N = 458 Israel Setting: Mixed</td>
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<td>AUC:</td>
<td>Costs:</td>
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<td>Target: Clinic-referred children recruited from out-patient pediatric clinics of a Neuro-Cognitive Centre, based in a tertiary care university hospital. Drug naive. No intellectual disability, no chronic use of medications, and no primary psychiatric diagnosis (e.g., depression, anxiety, and psychosis). Other: Typically developed children recruited from regular primary schools</td>
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<td>Rater agreement:</td>
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<td>Reference standard: Clinical diagnosis Diagnosis based on DSM-V criteria for ADHD</td>
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<td>Kappa:</td>
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<td></td>
<td>Index test: neuropsychological,CPT Neuro-Tech Solutions Limited MOXO-CPT which includes visual and auditory stimuli serving as measurable distractors. Analyzed using random forest technique. Machine learning</td>
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<td>ICC:</td>
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<td>Other outcomes:</td>
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<td>Rater agreement:</td>
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## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD presentation: N/A</td>
<td>Diagnosed by: Specialist Comorbidity: N/A Female: 33% Age mean: 8.68 (1.77) Min age: 6 Max age: 12 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>model included four continuous performance test indices (attention, timeliness, hyperactivity, and impulsiveness) and four control variables (age, gender, day of the week, and time of day). 60/40 training/testing split used for validation. Sensitivity: 89 (83, 95) Specificity: 84 (76, 92) PPV: NPV: LR+: LR-: Accuracy: 87 AUC: Rater agreement: Kappa: Internal consistency: Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
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<td>Kappa: Internal consistency: Alpha: Costs:</td>
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<td><strong>Index test 3:</strong> Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement:</td>
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<td><strong>Index text 4:</strong> Sensitivity: Specificity: PPV: NPV: AUC:</td>
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<td><strong>Index text 5:</strong></td>
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<tr>
<th>Study:</th>
<th>Population:</th>
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<th>Additional index tests</th>
</tr>
</thead>
</table>
| Yeh, 2020[^1] | **Target:** Children with good vision, without intellectual or neurological disabilities who have never been on ADHD treatment. No epilepsy, learning disabilities, severe cognitive impairment or other major illnesses  
**Other:** Control group of children without ADHD  
**ADHD presentation:** N/A  
**Diagnosed by:** Provider  
**Comorbidity:** N/A  
**Female:** %  
38% female in entire sample  
**Age mean:** 8.58 (1.48)  
**Min age:** 6  
**Max age:** 12  
**Ethnicity:** Other info on race or ethnicity: N/A | **Reference standard:** Clinical diagnosis Swanson, Nolan, and Pelham, version IV (SNAP-IV) and Conners’ parent symptom questionnaire used in clinician diagnosis  
**Timing:** Prior diagnosis  
**Index test:** neuropsychological,CPT Virtual Reality (VR) classroom: VR cognitive tasks, continuous performance tests, and audio tests were embedded into the virtual environment. Captured task performance and neuro-behavior data. Analyzed with extreme gradient boosting (XGB) machine learning classifier. 5-fold cross validation  
**Sensitivity:**  
**Specificity:**  
**PPV:**  
**NPV:**  
**LR+:**  
**LR-:**  
**Accuracy:** 82  
**AUC:**  | **Index test 2:**  
**Index test:** neuropsychological,CPT Virtual Reality (VR) classroom: VR cognitive tasks, continuous performance tests, and audio tests were embedded into the virtual environment. Captured task performance and neuro-behavior data. Analyzed with support vector machine (SVM) classifier. 5-fold cross validation  
**Sensitivity:**  
**Specificity:**  
**PPV:**  
**NPV:**  
**LR+:**  
**LR-:**  
**Accuracy:** 83  
**AUC:**  | **Index test 3:**  
**Index test:** neuropsychological,CPT Virtual Reality (VR) classroom: VR cognitive tasks, continuous performance tests, and audio tests were embedded into the virtual environment. Captured task performance and neuro-behavior data. Analyzed with support vector machine (SVM) classifier. 5-fold cross validation  
**Sensitivity:**  
**Specificity:**  
**PPV:**  
**NPV:**  
**LR+:**  
**LR-:**  
**Accuracy:** 83  
**AUC:**  |
<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Results:</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zelnik, 2012[23] Case series N = 230 Israel Setting: Specialty care</td>
<td>Target: No major psychiatric conditions, mental retardation, autistic spectrum disorder, and epilepsy and children treated with psychotropic drugs (including central nervous system stimulants); referred to ADHD clinic Other: Children referred to ADHD clinic not diagnosed with ADHD ADHD presentation: inattentive: 39, hyperactive: 15, combined: 46 Diagnosed by: Specialist</td>
<td>Reference standard: Clinical diagnosis Clinical Diagnosis using DSM-IV diagnostic criteria, family interviews about the behavioral and neurodevelopmental history of the child, neurological evaluation, observation at the physician’s office, and employment of the Conners’ Rating Scales (Teacher, Timing: Concurrent</td>
<td>task performance and neurobehavior data. Analyzed with logistic regression. 5-fold cross validation w</td>
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<td>Index text 4:</td>
<td>Index text 5:</td>
</tr>
</tbody>
</table>

### Population

- **Setting:** Specialty care
- **Study target:** No major psychiatric conditions, mental retardation, autistic spectrum disorder, and epilepsy and children treated with psychotropic drugs (including central nervous system stimulants); referred to ADHD clinic
- **Other:** Children referred to ADHD clinic not diagnosed with ADHD
- **ADHD presentation:** inattentive: 39, hyperactive: 15, combined: 46
- **Diagnosed by:** Specialist

### Results

- **Reference standard:** Clinical diagnosis
- **Index test:** Clinical Diagnosis using DSM-IV diagnostic criteria, family interviews about the behavioral and neurodevelopmental history of the child, neurological evaluation, observation at the physician’s office, and employment of the Conners’ Rating Scales (Teacher, Timing: Concurrent
- **Sensitivity:**
- **Specificity:**
- **PPV:**
- **NPV:**
- **LR+:**
- **Accuracy:** 72
- **AUC:**
- **Rater agreement:**
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
|            | **Comorbidity:** N/A
Female: %
29% in entire sample
**Age mean:** 10.0 (2.7)
**Min age:** 6  **Max age:** 17
**Ethnicity:**
Other info on race or ethnicity: N/A |
|            | **Index test:** neuropsychological, CPT Test of Variables of Attention

- Sensitivity: 91
- Specificity: 22
- PPV: 80
- NPV: 41
- LR+:  
- LR-:
- Accuracy:
- AUC:
- Rater agreement: Test of Variables of Attention versus reference standard

- Kappa: 0.152
- ICC:
- Internal consistency:

  - Alpha:
  - Costs:

**Index test 3:**

- Sensitivity:
- Specificity:
- PPV:
- NPV:
- LR+:
- Accuracy:
- AUC:
- Rater agreement:

**Index test 4:**

- Sensitivity:
- Specificity:
- PPV:
- NPV:
- AUC:

**Index test 5:**

- Costs:
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Study Type</th>
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<th>Results</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilbert, 2016&lt;sup&gt;288&lt;/sup&gt;</td>
<td>Target: AD/HD combined type or AD/HD hyperactivity impulsive type, IQ&gt;=80, no disorders of consciousness or head injuries, no comorbid mental disorders, asked to abstain from taking any stimulant medication for two weeks prior to testing. Other: Healthy control children recruited from a local primary school, IQ&gt;=80</td>
<td>Reference standard: Clinical diagnosis Diagnosed by clinician using DSM-IV criteria Timing: Prior diagnosis</td>
<td>Index text 5:</td>
</tr>
<tr>
<td>Clinical trial</td>
<td>ADHD presentation: N/A Diagnosed by: Specialist Comorbidity: N/A Female: 8.6% 91.4 Age mean: 9.3 mean age Min age: 7 Max age: 11 Ethnicity: Other info on race or ethnicity: N/A</td>
<td></td>
<td>Outcome standard: Clinical diagnosis 289</td>
</tr>
<tr>
<td>N = 70</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>China Setting: Mixed</td>
<td></td>
<td></td>
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<td></td>
<td>Index text 2: neuropsychological,CPT,Activity Continuous performance test quotient scores (Full-Scale Response Control Quotient from the Integrated Visual and Auditory Test, Full-Scale Response Attention Quotient) Sensitivity: 59 Specificity: 81 PPV: NPV: LR+: Accuracy: 70 AUC:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rater agreement: Kappa:</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Internal consistency: Alpha:</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>Costs:</td>
</tr>
</tbody>
</table>
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC:</td>
<td>Rater agreement: Kappa: ICC: Internal consistency: Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
<td><strong>Index test 3:</strong> neuropsychological,CPT,activity Continuous performance test quotient scores (Full-Scale Response Control Quotient from the Integrated Visual and Auditory Test, Full-Scale Response Attention Quotient) plus actigraph data (converted into kilocalories, i.e., units of energy expenditure)</td>
<td>Sensitivity: 83 Specificity: 91 PPV: NPV: LR+: Accuracy: 84 AUC: Rater agreement:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Index text 4:</strong> activity Continuous performance test scores (Full-Scale Response Control Quotient from the Integrated Visual and Auditory Test, Full-Scale Response Attention Quotient) plus actigraph data (converted into kilocalories, i.e., units of energy expenditure) plus age</td>
<td>Sensitivity: 80 Specificity: 90</td>
</tr>
</tbody>
</table>
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; Female; Age mean; Minimum age; Max age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| Luo, 2022<sup>195</sup> Case series N = 110 China Setting: Specialty care | **Target:** Outpatients of Beijing Anding Hospital, IQ>=70, no previous use of medication for ADHD; no comorbidity with various developmental disorders such as mental retardation and autism spectrum disorder or comorbid severe psychiatric disorders such as schizophrenia and bipolar disorder  
**Other:** The control group recruited children with normal development and excluded other disorders and also included children with symptoms of ADHD scored by the SNAP-IV but did not meet the diagnosis of ADHD under the gold standard  
**ADHD presentation:** N/A  
**Diagnosed by:** Specialist  
**Comorbidity:** N/A  
**Female:** 15%  
**Age mean:** 8.8 (1.76) for the ADHD group, 8.95 (1.50) for the control group  
**Min age:** 6  
**Max age:** 16 | **Reference standard:** Clinical diagnosis  
Detailed clinic interview between the two senior specialists and the subject’s family, as well as from clinical observations of the subject, combined with certain physical examinations to rule out other causes of the symptoms  
**Timing:** Prior diagnosis  
**Index test:** neuropsychological, CPT, Activity  
Self-developed Wearable Diagnostic Assessment System (WeDA) based on the DSV-5; the user wears 6 motion sensors on their head, hands, feet and waist and complete ten tasks by interacting with a touch screen or 3D printed device within a set time frame; performance is scored based on the completion of the tasks (including accuracy, error rate, time consumption and other information), on the user’s body posture (obtained through the wearable device), and on the user’s body movements observed via the six motion sensors; Information was integrated and | **PPV:**  
**NPV:**  
**AUC:**  
**Index text 5:** |
| | | | | |

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### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Breaux, 2016&lt;sup&gt;170&lt;/sup&gt; Case series N = 168 US Setting: Primary Care</th>
<th>Population: <strong>Ethnicity:</strong> Other info on race or ethnicity: N/A</th>
<th>Results: <strong>Reference standard:</strong> Clinical diagnosis Trained psychology graduate students assigned diagnoses of ADHD and ODD based on measures administered at age 6: Diagnostic Interview Schedule for Children–IV (NIMH DISC-IV), BASC (for mother, father, and teacher), and Disruptive Behavior Rating Scale (for timing: Concurrent</th>
<th>Additional index tests</th>
<th><strong>Index text 4:</strong> Sensitivity: 65 Specificity: 69 PPV: 63</th>
<th><strong>Index text 5:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target:</strong> Children presenting with elevated levels of externalizing problems at age 3 who were diagnosed with ADHD or ADHD+ODD at age 6; no intellectual disability, deafness, blindness, language delay, cerebral palsy, epilepsy, autism, and/or psychosis; children were not asked to discontinue medication <strong>Other:</strong> Children presenting with elevated levels of externalizing problems at age 3 who were</td>
<td>Random forest and Bayesian network were employed to build diagnosis models Sensitivity: 98 (89, 100) Specificity: 95 (84, 99) PPV: 98 NPV: 95 LR+: 52 LR-: 0.06 Accuracy: 96 AUC: 0.964 Rater agreement: Kappa: ICC: Internal consistency: Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
<td>LR+: Accuracy: AUC: Rater agreement:</td>
<td></td>
<td></td>
<td></td>
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</table>
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>not not diagnosed with ADHD at age 6; 13% of participants diagnosed with ODD only</td>
<td><strong>ADHD presentation</strong>: inattentive : 8, hyperactive : 17, combined : 75&lt;br&gt;<strong>Diagnosed by</strong>: Other (specify) Graduate student&lt;br&gt;<strong>Comorbidity</strong>: N/A&lt;br&gt;<strong>Female</strong>: 38.67%&lt;br&gt;16 ADHD only, 13 ADHD + ODD&lt;br&gt;<strong>Age mean</strong>: NA&lt;br&gt;<strong>Min age</strong>: 3 Max age: 6&lt;br&gt;<strong>Ethnicity</strong>: % Hispanic or Latino : 22.6, Other : predominately Puerto Rican&lt;br&gt;% Black/African American : 10.1&lt;br&gt;% White : 53.6&lt;br&gt;% Multiracial : 13.7&lt;br&gt;Other info on race or ethnicity:</td>
<td><strong>Index test</strong>: neuropsychological, CPT, EF&lt;br&gt;Battery of measures including NEPSY&lt;br&gt;Statue, Present task, and the Conners Kiddie Continuous Performance Test ADHD Confidence Index plus hyperactivity/impulsivity and inattention symptoms at age 3&lt;br&gt;Sensitivity: 64&lt;br&gt;Specificity: 75&lt;br&gt;PPV: 67&lt;br&gt;NNP: 72&lt;br&gt;LR+:&lt;br&gt;LR-:&lt;br&gt;Accuracy: 70&lt;br&gt;AUC:&lt;br&gt;Rater agreement: Kappa:&lt;br&gt;Internal consistency: Alpha:&lt;br&gt;Test-retest:&lt;br&gt;Costs:&lt;br&gt;Costs:</td>
<td>NPV: 71&lt;br&gt;LR+:&lt;br&gt;Accuracy: 67&lt;br&gt;AUC:&lt;br&gt;Rater agreement: Kappa:&lt;br&gt;Internal consistency: Alpha:&lt;br&gt;Costs:</td>
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<td></td>
<td><strong>Index test 3</strong>: neuropsychological Delay Aversion: Present task&lt;br&gt;Sensitivity: 55 55&lt;br&gt;Specificity: 66&lt;br&gt;PPV: 57&lt;br&gt;NNP: 64&lt;br&gt;LR+:&lt;br&gt;Accuracy: AUC&lt;br&gt;Rater agreement:</td>
<td><strong>Index test 4</strong>: neuropsychological, CPT&lt;br&gt;Inhibition/Attention: K-CPT ADHD Confidence Index; produced by a discriminant function analysis consisting of percent omissions, gender, age, standard error by ISI, hit reaction time, response style,</td>
</tr>
</tbody>
</table>
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Study:</th>
<th>Population:</th>
<th>Results:</th>
<th>Additional index tests</th>
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</thead>
<tbody>
<tr>
<td><strong>Index Type</strong></td>
<td><strong>Setting:</strong></td>
<td><strong>Reference standard:</strong></td>
<td><strong>Index text 5:</strong></td>
</tr>
<tr>
<td><strong>Study:</strong></td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td><strong>Index test:</strong></td>
<td>Neuropsychological Attention, Impulsivity, Working memory</td>
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</tr>
<tr>
<td><strong>Author, year; Multiple publications; Study design; Study size; Location</strong></td>
<td><strong>Setting:</strong></td>
<td><strong>Reference standard:</strong></td>
<td><strong>Index text 5:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Clinical diagnosis Kiddie-Schedule of Affective Disorders and Schizophrenia- Present and Lifetime (K-SADS-PL), Version 19, a semistructured diagnostic interview by a psychiatric nurse and reviewed by two psychiatrists</strong></td>
<td>Neuropsychological Attention, Impulsivity, Working memory</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Timing:</strong> Concurrent</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Index text 2:</strong> Parental rating scale, Parent-rated Conners subscales as a predictor of ADHD diagnoses</td>
</tr>
<tr>
<td><strong>Faraone, 2016</strong></td>
<td><strong>Target:</strong> Consecutive patients referred to a child psychiatrist diagnosed with ADHD; no history of psychosis or neurological disorder, low intellectual functioning, substance use disorders, conduct disorder, tic disorders, or physical impairments precluding game play; participants did not take stimulant medication on the testing days</td>
<td><strong>Index test:</strong></td>
<td>Parental rating scale, Parent-rated Conners subscales as a predictor of ADHD diagnoses</td>
</tr>
<tr>
<td><strong>Case series</strong></td>
<td><strong>Other:</strong> Consecutive patients referred to a child psychiatrist not diagnosed with ADHD; may have major depressive disorder, dysthymia, generalized anxiety disorder, anxiety disorder not otherwise specified (NOS), social phobia, oppositional defiant disorder, panic</td>
<td><strong>Diagnostic accuracy:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Setting:</strong> Specialty care</td>
<td><strong>ADHD presentation:</strong> N/A</td>
<td><strong>Rater agreement:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>N = 113</strong></td>
<td><strong>Diagnosed by:</strong> Specialist</td>
<td><strong>Other outcomes</strong></td>
<td></td>
</tr>
<tr>
<td><strong>US</strong></td>
<td><strong>Comorbidity:</strong> N/A</td>
<td><strong>Other:</strong> Consecutive patients referred to a child psychiatrist not diagnosed with ADHD; may have major depressive disorder, dysthymia, generalized anxiety disorder, anxiety disorder not otherwise specified (NOS), social phobia, oppositional defiant disorder, panic</td>
<td></td>
</tr>
<tr>
<td><strong>Case series</strong></td>
<td><strong>Female:</strong> 43%</td>
<td><strong>Index test 2:</strong> Parental rating scale, Parent-rated Conners subscales as a predictor of ADHD diagnoses</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Age mean:</strong></td>
<td><strong>Accuracy:</strong></td>
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<tr>
<td></td>
<td></td>
<td><strong>AUC:</strong> 0.76</td>
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<td></td>
<td></td>
<td><strong>Rater agreement:</strong></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Kappa:</strong></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Internal consistency:</strong></td>
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<td></td>
<td></td>
<td></td>
<td><strong>Alpha:</strong></td>
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<td></td>
<td></td>
<td></td>
<td><strong>Costs:</strong></td>
</tr>
<tr>
<td>Index Type</td>
<td>Study: Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
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<tr>
<td>------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>groups differed significantly in age (12.3 vs. 13.6; p=0.01)</td>
<td>Accuracy: AUC: 0.79</td>
<td>Index test 3: neuropsychological,CPT Conners Continuous Performance Test II (CPT II)</td>
</tr>
<tr>
<td></td>
<td><strong>Min age:</strong> 6 <strong>Max age:</strong> 17</td>
<td>Rater agreement: Kappa 0.15 for Groundskeeper versus Conners (z = 1.6, p = 0.06), 0.18 for Groundskeeper versus CPT (z = 1.9, p = 0.9), and 0.3 for Conners versus CPT (z = 3.2, p = 0.0007)</td>
<td>Sensitivity:</td>
</tr>
<tr>
<td></td>
<td><strong>Ethnicity:</strong> % White: 88, Other: in ADHD group, 82% in control group</td>
<td>Kappa: ICC: Internal consistency: Alpha:</td>
<td>Specificity:</td>
</tr>
<tr>
<td></td>
<td>Other info on race or ethnicity:</td>
<td>Test-retest: Costs:</td>
<td>PPV: NPV: LR+: Accuracy: AUC: 0.62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Misdiagnosis: Costs:</td>
<td>Rater agreement:</td>
</tr>
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<tr>
<td></td>
<td></td>
<td><strong>Index text 4:</strong> neuropsychological,CPT,EF</td>
<td>Combined the significant Groundskeeper factors with the Conners inattention subscale and the CPT percent correct in the same model</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sensitivity: Specificity: PPV: NPV: AUC: 0.87</td>
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### Appendix C. Evidence Tables

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<td></td>
<td>Author, year; Multiple publications; Study design; Study size; Location</td>
</tr>
<tr>
<td></td>
<td>Jimenez-Figueroa, 2017*</td>
</tr>
<tr>
<td></td>
<td>Case series</td>
</tr>
<tr>
<td></td>
<td>N = 103</td>
</tr>
<tr>
<td></td>
<td>Colombia</td>
</tr>
<tr>
<td></td>
<td>Setting: School</td>
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</table>

<table>
<thead>
<tr>
<th>Population:</th>
<th>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Target: Spanish native speakers; attend school of medium socio-economic stratum in Barranquilla, Colombia; both parents alive; parents and teachers complete the screening ADHD checklist; IQ &gt;=70; no clinical history of any major neurologic disease and/or developmental disorders or psychotic disorders</td>
</tr>
<tr>
<td></td>
<td>ADHD presentation: inattentive: 30.1, combined: 69.9</td>
</tr>
<tr>
<td></td>
<td>Diagnosed by: Specialist</td>
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<tr>
<td></td>
<td>Comorbidity: N/A</td>
</tr>
<tr>
<td></td>
<td>Female: 29.1%</td>
</tr>
<tr>
<td></td>
<td>Age mean: 7.75 (1.46) ADHD group, 8.84 (1.54) control group</td>
</tr>
<tr>
<td></td>
<td>Min age: 6 Max age: 11</td>
</tr>
<tr>
<td></td>
<td>Ethnicity: Other info on race or ethnicity: Other: Community has predominantly mix ethnicity (racial intermix between white European [Andalusian-Spanish], black African, Syrian-Lebanese [Arabian], Jewish, and Amerindian people)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results:</th>
<th>Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Reference standard: Clinical diagnosis Diagnosis made by neuropsychologist using DSM-V criteria Timing: Concurrent</td>
</tr>
<tr>
<td></td>
<td><strong>Index test:</strong> neuropsychological,CPT,EF Multi-operational apparatus for reaction times (MOART): the visual signal reaction times for prepotent response (PR–RT) and Go/No-Go tasks. PR-based variables were used in a predictive setting to determine their potential for discriminating ADHD-affected individuals from healthy controls.</td>
</tr>
<tr>
<td></td>
<td>Sensitivity: 68 (60, 80) Specificity: 84 (74, 93) PPV: 90 NPV: 55 LR+: 4.16 LR-: 0.38 Accuracy: 79 AUC: 0.73</td>
</tr>
<tr>
<td></td>
<td>Rater agreement: Kappa:</td>
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<tr>
<td></td>
<td>Internal consistency: Alpha:</td>
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<td></td>
<td>Costs:</td>
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<tr>
<th>Additional index tests</th>
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<tbody>
<tr>
<td><strong>Index test 2:</strong></td>
</tr>
<tr>
<td>Sensitivity:</td>
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<tr>
<td>Specificity:</td>
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<tr>
<td>PPV:</td>
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<tr>
<td>NPV:</td>
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<tr>
<td>LR+:</td>
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<td>Accuracy:</td>
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<td>AUC:</td>
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<td>Rater agreement:</td>
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<td>Kappa:</td>
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<tr>
<td>Internal consistency:</td>
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<tr>
<td>Alpha:</td>
</tr>
<tr>
<td>Costs:</td>
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</tbody>
</table>

| **Index test 3:** |
| Sensitivity: |
| Specificity: |
| PPV: |
| NPV: |
| LR+: |
| Accuracy: |
| AUC: |
| Rater agreement: |

| **Index test 4:** |
| Sensitivity: |
| Specificity: |
| PPV: |
| NPV: |
| AUC: |
# Appendix C. Evidence Tables

| Index Type | Study: Newman, 2017<sup>49</sup> Case series N = 152 US Setting: N/A | Population: Target: No diagnosis of brain injury or seizure disorder and/or treated pharmacologically for psychiatric conditions other than ADHD Other: Age, gender, and race-matched children not diagnosed with ADHD ADHD presentation: N/A Diagnosed by: Specialist Comorbidity: N/A Female: 31.6% Age mean: 8.68 (1.84) Min age: 6 Max age: 12 Ethnicity: % Black/African American: 51.3 % White: 48.7 Other info on race or ethnicity: | Results: Reference standard: Clinical diagnosis ADHD diagnosis from a pediatric neurologist, psychiatrist, and/or psychologist using DSM-IV-TR criteria Timing: Prior diagnosis Index test: neuropsychological, CPT, EF The Pediatric Attention Disorders Diagnostic Screener (PADDS) includes 4 components: A Computer Administered/Scored Diagnostic Interview, the Swanson, Nolan, and Pelham-IV (SNAP-IV) questionnaire (parent and/or teacher), the Target Tests of Executive Functioning (3 computer-based tasks), and a Nomographic Evidence-Based Report Analysis that combines the incremental validation of information from parent and teacher ratings with results from the three executive functioning tests to determine the likelihood of an ADHD diagnosis Sensitivity: 88 Specificity: 84 | Additional index tests Index test 2: Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement: Kappa: Internal consistency: Alpha: Costs: Index test 3: Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: |
| --- | --- | --- | --- |
| | | | |
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| Neuropsychological, CPT, EF | Peijnenborgh, 2016<sup>49</sup> Case series N = 136 Netherlands Setting: Mixed | **Target:** Patients of the outpatient clinic Center for Neurological Learning Disabilities, without comorbid DSM-V diagnosis, without medication for attentional problems and hyperactive behavior  
**Other:** Typically developing children  
**ADHD presentation:** N/A  
**Diagnosed by:** Unclear/NR  
**Comorbidity:** N/A  
**Female:** 25%  
**Age mean:** 6.90 (0.74)  
**Min age:** 6 **Max age:** 8 | **Reference standard:** Clinical diagnosis  
Diagnosis of ADHD according to DSM-V  
Timing: Prior diagnosis  
**Index test:** neuropsychological, CPT, EF A computer-based game developed to assess specific cognitive functions (e.g., attention, planning, and working memory), time perception, and reward mechanisms in young school-aged children  
Sensitivity: 89  
Specificity: 69  
**PPV:** 85  
**NPV:** 88  
**LR+:**  
**LR-:**  
**Accuracy:** 86  
**AUC:**  
**Rater agreement:**  
Kappa:  
**ICC:**  
Internal consistency:  
Alpha:  
**Test-retest:**  
**Costs:**  
**Misdiagnosis:**  
**Labeling:**  
**Costs:** | **AUC:**  
**Rater agreement:**  
**Index text 4:**  
Sensitivity:  
Specificity:  
**PPV:**  
**NPV:**  
**AUC:**  
**Index text 5:**  
Sensitivity:  
Specificity:  
**PPV:**  
**NPV:**  
**AUC:**  
**Internal consistency:**  
Alpha: |
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Williams, 2010</strong>&lt;sup&gt;20&lt;/sup&gt; Case series N = 350 Australia Setting: N/A</td>
<td><strong>Target:</strong> IQ &gt;= 80; no personal or family history of Axis I psychiatric disorder other than oppositional defiant disorder, learning disorder, conduct disorder, depression, and anxiety; free of a physical brain injury, neurologic disorder, genetic disorder, other serious medical conditions, drugs, and alcohol <strong>Other:</strong> Age, sex, school grade, and IQ matched healthy control subjects <strong>ADHD presentation:</strong> inattentive : 38, hyperactive : 3, combined : 59</td>
<td><strong>Reference standard:</strong> Clinical diagnosis Clinical interview using DSM-IV criteria by referring pediatrician, and Conner’s Parent Rating Scales: Revised-Long Version Timing: Prior diagnosis <strong>Index test:</strong> neuropsychological, CPT, EF Cognitive and brain-function assessments using proprietary testing software &quot;IntegNeuro&quot; and &quot;LabNeuro&quot; from Brain Resource Ltd. Combination of sustained attention, impulsivity, intrusions, inhibition, and response variability. Severity threshold for det</td>
<td><strong>Costs:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Ethnicity:</strong> Other info on race or ethnicity: N/A</td>
<td><strong>NPV:</strong></td>
<td><strong>Index test 3:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>LR+:</strong></td>
<td>Sensitivity:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>LR-:</strong></td>
<td>Specificity:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Accuracy: 78 (76/97) of the children were correctly classified as being in the ADHD group or in the control group <strong>AUC:</strong></td>
<td><strong>PPV:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rater agreement:</td>
<td><strong>NPV:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Kappa:</td>
<td><strong>LR+:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ICC:</td>
<td>Accuracy:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Internal consistency:</td>
<td><strong>AUC:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Alpha:</td>
<td>Rater agreement:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Test-retest:</td>
<td><strong>Index text 4:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Costs:</td>
<td>Sensitivity:</td>
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<td></td>
<td></td>
<td>Labeling:</td>
<td>PPV:</td>
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<td></td>
<td></td>
<td>Costs:</td>
<td>NPV:</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td><strong>AUC:</strong></td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Index text 5:</strong></td>
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# Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study:</th>
<th>Population:</th>
<th>Results:</th>
<th>Additional index tests</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
<td></td>
</tr>
</tbody>
</table>

**Diagnosed by:** Provider

**Comorbidity:** N/A

**Female:** 23%

**Age mean:**
12.29 (3.08) for ADHD group, 12.24 (3.10) for control group

**Min age:** 6 **Max age:** 18

**Ethnicity:**
- % Asian: 37
- % White: 63

Other info on race or ethnicity:

and response variability. Severity threshold for determining impairment <= 1.0 SD below the mean.

**Sensitivity:** 88
**Specificity:** 91
**PPV:** 96
**NPV:** 80
**LR+:**
**LR-:**

**Accuracy:**

**AUC:**

**Rater agreement:**

**Kappa:**

**Internal consistency:**

**Alpha:**

**Costs:**

Index test 3:

**Sensitivity:**
**Specificity:**
**PPV:**
**NPV:**
**LR+:**
**LR-:**

**Accuracy:**

**AUC:**

**Rater agreement:**

Index test 4:

**Sensitivity:**
**Specificity:**
**PPV:**
**NPV:**
**AUC:**
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Study:</th>
<th>Population:</th>
<th>Results:</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boucugnani, 1989</td>
<td>Target: Children with ADHD and free of medication at least 16 hours before testing</td>
<td>Reference standard: Clinical diagnosis</td>
<td><strong>Index text 5:</strong> Neuropsychological Attention</td>
</tr>
<tr>
<td>Case series</td>
<td>Other: Age and gender-matched neurotypical developing children; identified by teacher report as achieving on grade level or above and as experiencing no significant behavioral or attentional problems in the classroom</td>
<td>Diagnosis made by a psychologist, physician, or psychiatrist using DSM-III criteria and Child Behavior Checklist Inattentive subscale, Bristol Social Adjustment Guides Inconsequence scale, and the Connors Rating Scale Hyperactivity Index parent or teacher</td>
<td></td>
</tr>
<tr>
<td>N = 56</td>
<td>ADHD presentation: N/A</td>
<td>Timing:</td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>Diagnosed by: Specialist</td>
<td><strong>Index test:</strong> neuropsychological,EF</td>
<td></td>
</tr>
<tr>
<td>Setting: N/A</td>
<td>Comorbidity: N/A</td>
<td>Stepwise discriminant function analysis; final multivariate linear equation included the Trail-Making test-Part B and the Wisconsin Card Sorting Test perseverative responses, failure to maintain set, and perseverative errors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female: 14%</td>
<td>Sensitivity:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age mean:</td>
<td>Specificity:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min age: 7 Max age:</td>
<td>PPV:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ethnicity:</td>
<td>NPV:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other info on race or ethnicity: N/A</td>
<td>LR+:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LR-:</td>
<td></td>
</tr>
</tbody>
</table>

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**Index test 2:**

- Sensitivity:
- Specificity:
- PPV:
- NPV:
- LR+:
- Accuracy:
- Rater agreement:
- Kappa:
- Internal consistency:
- Alpha:
- Costs:

**Index test 3:**

- Sensitivity:
- Specificity:
- PPV:
- NPV:
- LR+:
- Accuracy:
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| Canivez, 2016 | **Target:** 15% receive special education  
**Other:** Control group children randomly selected and attempted matching of sex, age, race, and special education classification  
**ADHD presentation:** N/A  
**Diagnosed by:** Unclear/NR  
**Comorbidity:** N/A  
**Female:** 20%  
**Age mean:** 6.60 (1.14) for ADHD group, 7.45(0.51) for control group  
**Min age:**  
**Max age:**  
**Ethnicity:**  
% Hispanic or Latino: 2.5  
% White: 77.5 | **Reference standard:** Clinical diagnosis  
**Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.; DSM-IV-TR) criteria for ADHD**  
**Timing:** Prior diagnosis  
**Index test:** neuropsychological,EF The Das–Naglieri Cognitive Assessment System is a test of cognitive abilities based on the Planning, Attention, Simultaneous, and Successive Theory  
Sensitivity: 80  
Specificity: 75  
PPV: 76  
NPV: 79  
LR+:  
LR-:  | AUC:  
Rater agreement:  
Kappa:  
ICC:  
Internal consistency:  
Alpha:  
Test-retest:  
Costs:  
Misdiagnosis:  
Labeling:  
Costs:  | **Index test 2:**  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy:  
AUC:  
Rater agreement:  
Kappa:  
Internal consistency:  
Alpha:  
Costs:  | **Index test 3:**  
Sensitivity:  

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<tbody>
<tr>
<td>Study: Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
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</tbody>
</table>
## Appendix C. Evidence Tables

<table>
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<th>Index Type</th>
<th>Study: Chelune, 1986&lt;sup&gt;189&lt;/sup&gt;</th>
<th>Population:</th>
<th>Results:</th>
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<tbody>
<tr>
<td></td>
<td>Case series</td>
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<tr>
<td></td>
<td>N = 48</td>
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<tr>
<td></td>
<td>US</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Setting: N/A</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td><strong>Target:</strong> Medication free for at least 16 hours prior to testing</td>
<td>Reference standard: Clinical diagnosis</td>
<td><strong>Index test 2:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Other:</strong> Normal controls from previous study; matched for age, sex, and both maternal and paternal educational backgrounds</td>
<td>The ADD subjects all met minimal DSM-III criteria for ADD as determined by their treating physicians. Parent and/or teacher Conners' Rating Scales were available on 19 of the ADD children (16 having both); two psychiatrists independently reviewed the ADD c</td>
<td>Sensitivity:</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>ADHD presentation:</strong> N/A</td>
<td><strong>Timing:</strong></td>
<td>Specificity:</td>
<td>PPV:</td>
</tr>
<tr>
<td></td>
<td><strong>Diagnosed by:</strong> Specialist</td>
<td></td>
<td>NPV:</td>
<td>NPV:</td>
</tr>
<tr>
<td></td>
<td><strong>Comorbidity:</strong> N/A</td>
<td></td>
<td>LR+:</td>
<td>LR+:</td>
</tr>
<tr>
<td></td>
<td><strong>Female:</strong> 28%</td>
<td></td>
<td>Accuracy:</td>
<td>AUC:</td>
</tr>
<tr>
<td></td>
<td><strong>Age mean:</strong> 9.55 (2.01) for the ADHD group, 9.56 (2.52) for the typically developing group</td>
<td>AUC:</td>
<td>Rater agreement:</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Min age:</strong> 5 <strong>Max age:</strong> 17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Ethnicity:</strong> Other info on race or ethnicity: N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>from parents on children's difficulty in attention or self-control; recruited through posting</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td><strong>ADHD presentation:</strong> N/A</td>
<td>ROC analysis</td>
<td>Sensitivity:</td>
<td>76</td>
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<tr>
<td></td>
<td><strong>Diagnosed by:</strong> Specialist</td>
<td>Specificity:</td>
<td>51</td>
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</tr>
<tr>
<td></td>
<td><strong>Comorbidity:</strong> N/A</td>
<td>PPV:</td>
<td>NPV:</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Female:</strong> 28%</td>
<td>LR+:</td>
<td>LR-:</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Age mean:</strong> 9.55 (2.01) for the ADHD group, 9.56 (2.52) for the typically developing group</td>
<td>Accuracy:</td>
<td>AUC: 0.67</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Min age:</strong> 5 <strong>Max age:</strong> 17</td>
<td></td>
<td>Rater agreement:</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Ethnicity:</strong> Other info on race or ethnicity: N/A</td>
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</tbody>
</table>
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<table>
<thead>
<tr>
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<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
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<tr>
<td></td>
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<tr>
<td></td>
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<td>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
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<td></td>
<td>Study: Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
<td>Additional index tests</td>
</tr>
</tbody>
</table>

### Female: 29%

**Age mean:** 9.4

**Min age:** 6  **Max age:** 12

**Ethnicity:** Other info on race or ethnicity: N/A

### Index test: neuropsychological, EF

Stepwise discriminant function analysis; final variables in the multivariate linear equation were the Wisconsin Card Sorting Test Perseverative Errors and Failures to Maintain Set, Color Forms Time and Errors, and the Kaufman Assessment Battery for Children Number Recall and Gestalt Closure.

**Sensitivity:**

**Specificity:**

**PPV:**

**NPV:**

**LR+:**

**LR-:**

**Accuracy:** 85

**AUC:**

**Rater agreement:** Two psychiatrists independently reviewed the ADD children's charts and made ratings on 5-point scales for 1) how well each child's clinical presentation fit with DSM-III criteria; and 2) response to medication.

**Kappa:** 0.71 for the pooled DSM-III ratings and 0.75 for the pooled medication response ratings.

**ICC:**

**Internal consistency:**

**Alpha:**

**Test-retest:**
# Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
|            | Culbertson, 1998<sup>217</sup> Case series N = 155 US Setting: Mixed            | **Target**: Children drawn from consecutive referrals to a clinic specializing in the neuropsychological evaluation and treatment of ADHD; no history of mental retardation, severe psychiatric disturbance, or neurological injury/disorder; comorbidities present in 46 of the ADHD children including oppositional defiant/conduct disorders, anxiety disorders, depressive disorders, adjustment disorders, and learning disabilities  
**Other**: Children nominated by teachers from a suburban, middle-class community who exhibited at least average academic performance in the classroom and no behavioral or work study problems  
**ADHD presentation**: N/A  
**Diagnosed by**: Specialist  
**Comorbidity**: N/A  
**Female**: 27%  
**Age mean**:  
**Min age**: 7  
**Max age**: 12 | **Reference standard**: Clinical diagnosis  
**Diagnosis**: using DSM-III-R criteria determined by structured parent interview, teacher and parent rating scales, and objective neuropsychological testing by a licensed psychologist  
**Timing**: Prior diagnosis  
**Index test**: neuropsychological,EF Tower of London - Drexel (total move and rule violation scores)  
**Sensitivity**: 64  
**Specificity**: 80  
**PPV**: 85  
**NPV**:  
**LR+**:  
**LR-**:  
**Accuracy**: 70  
**AUC**:  
**Rater agreement**:  
**Kappa**:  
**Internal consistency**:  
**Alpha**:  | **Index test 2**:  
**Sensitivity**:  
**Specificity**:  
**PPV**:  
**NPV**:  
**LR+**:  
**Accuracy**:  
**AUC**:  
**Rater agreement**:  
**Kappa**:  
**Internal consistency**:  
**Alpha**:  
**Costs**:  |
|            |                                                                                   |                                                                                                 |                                                                                               |                      |
|            |                                                                                   |                                                                                                 |                                                                                               |                      |
|            |                                                                                   |                                                                                                 |                                                                                               |                      |
|            |                                                                                   |                                                                                                 |                                                                                               |                      |

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### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Results</th>
<th>Additional index tests</th>
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<tbody>
<tr>
<td><strong>Index Type</strong></td>
<td><strong>Setting:</strong> Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td><strong>Reference standard:</strong> Clinical diagnosis</td>
<td><strong>AUC:</strong></td>
</tr>
<tr>
<td><strong>Ethnicity:</strong></td>
<td><strong>Internal consistency:</strong> Alpha:</td>
<td><strong>Rater agreement:</strong></td>
<td><strong>Costs:</strong></td>
</tr>
<tr>
<td>% White : 96</td>
<td>30 ADHD participants (ages 7 to 10) were assessed on two occasions in a standardized manner with the temporal interval between assessment averaging 16.3 days (SD 8.9, range 7 to 41 days) Test-retest: 0.81 (p&lt;0.05) for total test score, 0.79 (p&lt;0.05) for total time violations, and 0.42 (p&lt;0.005) for total rule violations</td>
<td></td>
<td><strong>AUC:</strong></td>
</tr>
<tr>
<td>Other info on race or ethnicity:</td>
<td>Costs:</td>
<td><strong>Index text 4:</strong></td>
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</tr>
<tr>
<td></td>
<td></td>
<td><strong>Sensitivity:</strong></td>
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<td></td>
<td></td>
<td><strong>Specificity:</strong></td>
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<td></td>
<td></td>
<td><strong>PPV:</strong></td>
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<td></td>
<td></td>
<td><strong>NPV:</strong></td>
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<td></td>
<td></td>
<td><strong>LR+:</strong></td>
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<td></td>
<td></td>
<td><strong>LR−:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Accuracy:</strong></td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Target: Consecutive cases with ADHD selected from 3 sites</th>
<th>Reference standard: Clinical diagnosis Timing: Prior diagnosis</th>
<th><strong>Index text 2:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>El-Sayed, 1999</strong></td>
<td><strong>ADHD presentation:</strong> combined : 100</td>
<td><strong>Index test:</strong> neuropsychological,EF Gordon Diagnostic System Delay Task measuring impulse control, strategic planning, motivational effect, sense of time and readiness to respond generating an &quot;Efficiency Ratio&quot; score, cut-off &lt;=0.78</td>
<td><strong>Sensitivity:</strong> 59 <strong>Specificity:</strong> 81 <strong>PPV:</strong> N/A <strong>NPV:</strong> N/A <strong>LR+:</strong> N/A <strong>LR−:</strong> N/A <strong>Accuracy:</strong> AUC: 0.72</td>
</tr>
<tr>
<td><strong>Case series</strong></td>
<td><strong>Diagnosed by:</strong> Specialist</td>
<td></td>
<td><strong>Rater agreement:</strong></td>
</tr>
<tr>
<td><strong>N = 159</strong></td>
<td><strong>Comorbidity:</strong> N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sweden</strong></td>
<td><strong>Female:</strong> 14%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Setting: Mixed</strong></td>
<td><strong>Age mean:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10.5 for ADHD group, 10.2 for neurotypical group</td>
<td></td>
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</tr>
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<td></td>
<td><strong>Min age:</strong> 6 <strong>Max age:</strong> 17</td>
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<td><strong>Ethnicity:</strong> Other info on race or ethnicity: N/A</td>
<td></td>
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<tr>
<td></td>
<td><strong>Index text 5:</strong></td>
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<tr>
<th>Study</th>
<th>Additional index tests</th>
<th><strong>Index text 2:</strong></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>**neuropsychological,CPT Gordon Diagnostic System Vigilance Task measuring the ability to sustain attention over a 9 minute period generating a &quot;Correct Responses&quot; score, cut-off &lt;=38</td>
<td><strong>Sensitivity:</strong> 49 <strong>Specificity:</strong> 87 <strong>PPV:</strong> N/A <strong>NPV:</strong> N/A <strong>LR+:</strong> N/A <strong>LR−:</strong> N/A <strong>Accuracy:</strong> AUC: 0.72</td>
</tr>
<tr>
<td></td>
<td>Rater agreement:</td>
<td><strong>Costs:</strong></td>
</tr>
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</table>
### Appendix C. Evidence Tables

<table>
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<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
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</thead>
<tbody>
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<td><strong>Index test 3:</strong> neuropsychological, CPT Gordon Diagnostic System Vigilance Task measuring the ability to sustain attention over a 9 minute period generating a &quot;Errors of Commission&quot; score, cut-off &gt;7 Sensitivity: 51 51 Specificity: 85 PPV: NPV: LR+: Accuracy: AUC: 0.73 Rater agreement:</td>
</tr>
<tr>
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<td><strong>Index text 4:</strong> Sensitivity: Specificity: PPV: NPV: AUC:</td>
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<td><strong>Index text 5:</strong></td>
</tr>
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</table>

C-150
| Index Type | Study: Ferrin, 2012<sup>270</sup>  
Case series  
N = 1,185  
Australia  
Setting: Mixed | Population: Target: All stimulant medication naive at the time of their assessment and had only received school-based individual and/or group psychosocial treatments.  
Other: Typically developing children and adolescents  
ADHD presentation: inattentive: 24.8, hyperactive: 7.2, combined: 67.9  
Diagnosed by: Specialist  
Comorbidity: N/A  
Female: 22%  
Age mean: 131.44 months (38.93) for the ADHD group and 133.16 months (27.95) for the comparison group  
Min age: 6 Max age: 16  
Ethnicity: Other info on race or ethnicity: N/A | Results: Reference standard: Clinical diagnosis ADHD status was categorically defined by the semistructured clinical interview of their parent’s K–SADS–PL, and dimensionally by the Conners’ Global Index (CGI) based on DSM–IV criteria  
Timing: Prior diagnosis  
Index test: neuropsychological, EF Scored Developmental Neurological Examination, total score of 13 or over  
Sensitivity: 67  
Specificity: 89  
PPV: 98  
NPV: 25  
LR+: 6.16  
LR−: 0.37  
Accuracy: AUC: 0.779 (95% CI 0.742–0.816)  
Rater agreement:  
Kappa:  
ICC:  
Internal consistency: Alpha:  
Test-retest:  
Costs:  
Misdiagnosis:  
Labeling:  
Costs: | Additional index tests:  
Index test 2:  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy: AUC:  
Rater agreement:  
Kappa:  
Internal consistency: Alpha:  
Costs:  
Index test 3:  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy: AUC:  
Rater agreement:  
Index test 4:  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
AUC: |
### Appendix C. Evidence Tables

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<th>Population:</th>
<th>Results:</th>
<th>Additional index tests</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Target: Teenagers diagnosed with ADD with hyperactivity or ADD without hyperactivity by school psychologists using DSM-III criteria</td>
<td>Reference standard: Clinical diagnosis</td>
<td>Index text 5:</td>
</tr>
<tr>
<td></td>
<td>Garcia-Sanchez, 1997&lt;sup&gt;23&lt;/sup&gt; Case series N = 60 Spain Setting: School</td>
<td>Other: Schoolmates of ADD group ADHD presentation: N/A : 64% ADD with hyperactivity, 36% ADD without hyperactivity Diagnosed by: Specialist Comorbidity: N/A Female: 40% Age mean: 14.8 (0.5) for ADHD group, 14.9 (0.7) for control group Min age: 14 Max age: 16 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Diagnosis by school psychologists, family interview; Conners Teacher Rating Scale, Paced Auditory Addition Task, and Continuous Performance Test with and without auditory interference Timing: Prior diagnosis</td>
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<td>Index test: neuropsychological_EF Neuropsychological tests developed for the assessment of visuospatial skills and are sensitive tasks for right hemisphere functions. Discriminant function analysis; final model included correct score from the WAIS Block-Design, correct score from the Benton's Line Orientation, and the correct score from the Raven's Progressive Matrices; 3 way classification (ADD with hyperactivity vs ADD without hyperactivity vs controls) Sensitivity: 53% for ADD with hyperactivity, 56% for ADD without hyperactivity Specificity: 74</td>
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**Index test 3:**
- Sensitivity: Specificity: PPV: NPV: LR+: Accuracy:
### Appendix C. Evidence Tables

<table>
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<th>Results:</th>
<th>Additional index tests</th>
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<tbody>
<tr>
<td></td>
<td>Geurts, 2004&lt;sup&gt;293&lt;/sup&gt;</td>
<td><strong>Target:</strong> Children with ADHD and children with ADHD+ODD/CD; recruited from parents affiliated with the national parent association of children with ADHD or from 11 special educational services for children with extreme behavioral problems; required not to use any medication; IQ&gt;=80; children with OCD, Tourette syndrome, and pervasive developmental disorders were excluded; medication discontinued at least 20 hours prior to testing&lt;br&gt;<strong>Other:</strong> Neurotypical developing children from 4 regular schools and another research sample with the same recruitment methods, IQ&gt;=80, no</td>
<td><strong>Reference standard:</strong> Clinical diagnosis&lt;br&gt;Child Communication Checklist parent and teacher, Disruptive Behavior Disorder rating scale parent and teacher, Diagnostic Interview Schedule for Children for DSM-IV parent version, and Revised Autism Diagnostic Interview&lt;br&gt;<strong>Timing:</strong> Prior diagnosis&lt;br&gt;<strong>Index test:</strong> neuropsychological, EF 3 group discriminant function analysis (ADHD vs high functioning autism vs neurotypical); z-scores of the following variables were included as predictors: Stop Signal Reaction Time, Self-Ordered Pointing task beta errors, Tower of London beta execution time, Wisconsin Ca&lt;br&gt;<strong>Sensitivity:</strong>&lt;br&gt;<strong>Specificity:</strong></td>
<td><strong>AUC:</strong>&lt;br&gt;Rater agreement:&lt;br&gt;<strong>Index test 2:</strong> neuropsychological, EF 2 group discriminant function analysis (ADHD vs high functioning autism); z-scores of the following variables were included as predictors: Stop Signal Reaction Time, Self-Ordered Pointing task beta errors, Tower of London beta execution time, Wisconsin Ca&lt;br&gt;<strong>Sensitivity:</strong>&lt;br&gt;<strong>Specificity:</strong></td>
</tr>
<tr>
<td>Index Type</td>
<td>Study: Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
<td>Additional index tests</td>
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<tr>
<td></td>
<td>history of behavioral problems or a learning disability; Children with high functioning autism recruited from institutions sp ADHD presentation: inattentive: 30, hyperactive: 3, combined: 67 Diagnosed by: Unclear/NR Comorbidity: N/A Female: 0% Age mean: 9.3 (2.0) for ADHD group, 9.1 (1.7) for normal control group, and 9.4 (1.8) for high functioning autism group Min age: 6 Max age: 12 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Reaction Time, Self-Ordered Pointing task beta errors, Tower of London beta execution time, Wisconsin Card Sorting test percentage, perseverative responses, aggregated verbal fluency score, and aggregated non-executive function task score; leave-one-out cross-validation Sensitivity: 69 Specificity: PPV: NPV: LR+: LR-: Accuracy: 61 56% using leave-one-out cross validation AUC:</td>
<td>PPV: NPV: LR+: Accuracy: 71 69% using leave-one-out cross validation AUC:</td>
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<td></td>
<td>Rater agreement: In order to take into account chance agreement, the kappa coefficient was computed. A value of 1 for Kappa indicates perfect prediction, while a value of 0 indicates chance-level prediction Kappa: 0.38 Internal consistency: Alpha: Costs:</td>
<td>Rater agreement: In order to take into account chance agreement, the kappa coefficient was computed. A value of 1 for Kappa indicates perfect prediction, while a value of 0 indicates chance-level prediction Kappa: 0.38 Internal consistency: Alpha: Costs:</td>
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<tr>
<td>Study: Grodzinsky, 1992&lt;sup&gt;st&lt;/sup&gt;</td>
<td>Population:</td>
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<tr>
<td>Case series</td>
<td>Study: Grodzinsky, 1992&lt;sup&gt;st&lt;/sup&gt;</td>
<td>Setting: Specialty care</td>
<td>Study: Grodzinsky, 1992&lt;sup&gt;st&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>N = 130</td>
<td>Target: Consecutive referrals to an outpatient unit specializing in the treatment of hyperactive children diagnosed with ADHD; children with language-based learning disabilities or clinically significant conduct disorder were excluded; all male; FSIQ between 85 and 125</td>
<td>Reference standard: Clinical diagnosis Medical history, parental interview, Children's Attention Profile; a teacher-completed inventory consisting of the 12 most discriminating features selected from the Inattention and Overactive subscales of the Child Behavior Checklist-Teacher Form Timing: Prior diagnosis</td>
<td>Sensitivity:</td>
<td></td>
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<tr>
<td>US</td>
<td>Other: &quot;Snowball&quot; technique: Parents of ADHD boys referred peer(s) of their son's parents of these children referred other children; also recruited through a local newspaper ad; all male; FSIQ between 85 and 125</td>
<td>Index test: neuropsychological,EF Stepwise discriminant function analysis; variables included are commissions and omissions scores from the vigilance portion of the Gordon Diagnostic System and the Interference subtest of the Stroop test</td>
<td>Specificity:</td>
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<tr>
<td>ADHD presentation: N/A</td>
<td>ADHD presentation: N/A</td>
<td>Sensitivity: 82 Specificity: 80 PPV:</td>
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<tr>
<td>Diagnosed by: Specialist</td>
<td>Diagnosed by: Specialist</td>
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<tr>
<td>Comorbidity: N/A</td>
<td>Comorbidity: N/A</td>
<td>LR+:</td>
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<tr>
<td>Female: 0%</td>
<td>Female: 0%</td>
<td>LR-:</td>
<td></td>
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<tr>
<td>Age mean: 6 Max age: 11</td>
<td>Age mean: 6 Max age: 11</td>
<td>Accuracy: 81</td>
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<td>Ethnicity: Other info on race or ethnicity: N/A</td>
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**Index text 5:**

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<td>Sensitivity:</td>
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<tr>
<td>Specificity:</td>
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<tr>
<td>PPV:</td>
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<td>NPV:</td>
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**Index text 2:**

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<tr>
<td>LR+:</td>
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<td>Accuracy:</td>
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**Index text 3:**

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<td>PPV:</td>
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<tr>
<td>NPV:</td>
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<tr>
<td>LR+:</td>
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<tr>
<td>Accuracy:</td>
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### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study:</th>
<th>Population:</th>
<th>Results:</th>
<th>Additional index tests</th>
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<tr>
<td></td>
<td>Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
<td>AUC; Rater agreement; Kappa; ICC; Internal consistency; Alpha; Test-retest; Costs; Misdiagnosis; Labeling; Costs;</td>
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<tr>
<td></td>
<td>Hinshaw, 2002</td>
<td>Target: Recruited from multiple sources to attend one of three consecutive summer research programs; all female; testing performed without stimulant medication (minimum 24 hour washout period); IQ&gt;=70; common comorbidities not excluded (disruptive behavior disorders, anxiety disorders, depression)</td>
<td>Index text 4: neuropsychological,EF Three category (ADHD combined vs ADHD inattentive vs comparison) discriminant function analysis</td>
<td>AUC: Rater agreement:</td>
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<tr>
<td></td>
<td>Case series N = 228 US Setting: Other</td>
<td>Other: Recruited from multiple sources to attend one of three consecutive summer research programs; age and ethnicity-matched; all female; IQ&gt;=70; girls with ODD or internalizing disorders not excluded from comparison group ADHD presentation: inattentive : 34,combined : 66 Diagnosed by: Specialist Comorbidity: N/A</td>
<td>Sensitivity: 63% for ADHD combined, 16% for ADHD inattentive Specificity: 73 PPV: NPV: LR+: Accuracy: 57 AUC:</td>
<td>Index text 2: neuropsychological,EF Binary (ADHD vs comparison) discriminant function analysis</td>
</tr>
<tr>
<td></td>
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<td>Reference standard: Clinical diagnosis Swanson, Nolan, and Pelham (SNAP) Parent and Teacher Scales, Child Behavior Checklist, Teacher Report Form, Diagnostic Interview Schedule for Children (DISC-IV) Timing: Prior diagnosis Index test: neuropsychological,EF Binary (ADHD vs comparison) discriminant function analysis; variables included in final model were Rey-Osterrieth Complex Figure Design errors, Porteus Maze test age, Cancel Underlining Test, Word Attack, Grooved Pegboard, Continuous Performance Test omissions, and Rapid Automatized Naming scores Sensitivity: 78 Specificity: 58</td>
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<td>Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
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<tr>
<td>Female: 100%</td>
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<td>PPV:</td>
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<td>Min age: 6 Max age: 12</td>
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<td>LR+:</td>
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<tr>
<td>% Hispanic or Latino: 11</td>
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<td>% Black/African American: 27</td>
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<td>% Asian: 9</td>
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<td>% White: 53</td>
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<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Results: Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| Juneja, 2019[16] | Case series N = 100 India Setting: Specialty care | Target: Children presenting with features suggestive of ADHD at a pediatric outpatient department; IQ>=70; No neurological disorders likely to affect upper limb motor performance or compliance with directions for the test, and had not received any treatment for behavioral problems/ADHD | Reference standard: Clinical diagnosis ADHD was diagnosed by a developmental pediatrician using the DSM-V criteria, after interviewing the child and the parents. CPRS and CTRS were administered, and scores on various sub-scales were obtained Timing: Prior diagnosis | Index test 2: neuropsychological,EF
In part 2 (CCTT2) of the test, numbers from 2-15 are presented twice, as both pink and yellow circles. The child has to rapidly connect the numbered circles in sequence, alternating between pink and yellow circles. CCTT takes 15-20 minutes for administration
Sensitivity: 84 (71, 93)
Specificity: 72 (58, 84)
PPV: NPV: LR+: LR-:
Accuracy: AUC: 0.854
Rater agreement: Kappa:
Internal consistency: Alpha:
Costs: |
| | | Other: Age and sex-matched controls enrolled from a pediatric outpatient department ADHD presentation: inattentive: 20, hyperactive: 2, combined: 78 Diagnosed by: Specialist Comorbidity: N/A Female: 0% Age mean: Median (IQR) of whole sample (n=100): 9 (8,12) years Min age: 8 Max age: 15 Ethnicity: Other info on race or ethnicity: N/A | | |
| | | | Sensitivity: 74 (60, 85)
Specificity: 74 (60, 85)
PPV: NPV: LR+: LR-:
Accuracy: AUC: 0.800
Rater agreement: |

---

# Additional index tests

**Index test 2:**
- neuropsychological,EF

In part 2 (CCTT2) of the test, numbers from 2-15 are presented twice, as both pink and yellow circles. The child has to rapidly connect the numbered circles in sequence, alternating between pink and yellow circles. CCTT takes 15-20 minutes for administration

- **Sensitivity:** 84 (71, 93)
- **Specificity:** 72 (58, 84)
- **PPV:** NPV:
- **LR+:** LR-:
- **Accuracy:** AUC: 0.854
- **Rater agreement:** Kappa:
- **Internal consistency:** Alpha:
- **Costs:**

---

**Index test 3:**
- Sensitivity:
- Specificity:
- PPV:
- NPV:
- LR+:
- LR-:
- Accuracy:
### Appendix C. Evidence Tables

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<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
<td>Kappa: ICC: Internal consistency: Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
</tr>
<tr>
<td>Krieger, 2021&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Case series</td>
<td>N = 260 Spain Setting: Specialty care</td>
<td>Target: No history of tics; neurological disorders, or sensory impairments (seizures or brain injury); mental health conditions including autism spectrum disorder, motor or communication disorders and Tourette’s syndrome, IQ (General Ability Index) &gt; 85. Participants taking psychostimulant medication were asked to withhold medication for 24 hours prior to each testing session. Other: Typically developing children ADHD presentation: inattentive : 50.7,combined : 49.3 Diagnosed by: Specialist Comorbidity: N/A Female: 26.09% Age mean: ADHD-Combined 12.91 (12.04), ADHD-Inattentive 11.26 (2.34), Typically developing 11.70 (2.35)</td>
</tr>
</tbody>
</table>

<sup>1</sup>Index test 4: neuropsychological,EF For 13-16 year olds: working memory and processing speed assessed with Wechsler Intelligence Scale for Children (WISC-IV) and attention with the d2 attention test; discriminant function analysis. Stepwise discriminant analysis.

<sup>2</sup>Index test 2: neuropsychological,EF For 13-16 year olds: working memory and processing speed assessed with Wechsler Intelligence Scale for Children (WISC-IV) and attention with the d2 attention test; discriminant function analysis. Stepwise discriminant analysis.
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th><strong>Index Type</strong></th>
<th><strong>Study:</strong></th>
<th><strong>Population:</strong></th>
<th><strong>Results:</strong></th>
<th><strong>Additional index tests</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Index</strong></td>
<td>Study: Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
<td></td>
</tr>
<tr>
<td><strong>Index</strong></td>
<td><strong>Mayes, 2004</strong>&lt;sup&gt;412&lt;/sup&gt;</td>
<td><strong>Min age: 8 Max age: 16</strong></td>
<td><strong>Index test 3:</strong></td>
<td><strong>Index test 4:</strong></td>
</tr>
<tr>
<td><strong>Case series</strong></td>
<td>N = 809</td>
<td><strong>Ethnicity:</strong> Other info on race or ethnicity: N/A</td>
<td><strong>Sensitivity:</strong></td>
<td><strong>Sensitivity:</strong></td>
</tr>
<tr>
<td><strong>US</strong> Setting: Specialty care</td>
<td><strong>Target:</strong> IQ&gt;=80, referred for learning, attention, and/or behavior problems, off medication for testing, and no head injury with loss of consciousness, 54% had a comorbid mood or behavior disorder, 76% had a comorbid learning disorder</td>
<td><strong>Specificity:</strong></td>
<td><strong>Specificity:</strong></td>
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</tr>
<tr>
<td><strong>Other:</strong> Children with autism, brain injury, or mood and behavior disorders with or without learning disorders</td>
<td><strong>Reference standard:</strong> Clinical diagnosis DSM-IV diagnoses agreed upon by both a child psychologist and child psychiatrist</td>
<td><strong>PPV:</strong></td>
<td><strong>PPV:</strong></td>
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<tr>
<td><strong>Timing:</strong> Prior diagnosis</td>
<td><strong>Index test:</strong> neuropsychological,EF 12 Wechsler Intelligence Scale for Children-Third Edition (WISC-III) subtests comprising the four Indexes, Verbal Comprehension, Perceptual Organization, Freedom from</td>
<td><strong>NPV:</strong></td>
<td><strong>NPV:</strong></td>
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<td><strong>LR+:</strong></td>
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<td><strong>Accuracy:</strong> AUC:</td>
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<td><strong>Rater agreement:</strong></td>
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<td><strong>Index test 5:</strong></td>
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</table>
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<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
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<tbody>
<tr>
<td>Study:</td>
<td>Author, year; Multiple publications; Study design; Study size; Location</td>
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<tr>
<td>Moura, 2017</td>
<td>Case series N = 116 Portugal Setting: Specialty care</td>
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</table>

<table>
<thead>
<tr>
<th>Population:</th>
<th>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
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</thead>
<tbody>
<tr>
<td>Target: Children with ADHD only and with ADHD+developmental dyslexia; (a) IQ ≥ 85; (b) native speakers of European Portuguese; (c) absence of a visual, hearing, or motor handicap; and (d) never diagnosed with a language impairment; emotional disturbance; developmental dyscalculia; disruptive, impulse-control, and conduct disorders; neurological impairment or other psychiatric disorder Other: Typically developing children; children with developmental dyslexia only not included in abstracted outcomes ADHD presentation: N/A Diagnosed by: Provider Comorbidity: N/A Female: 75% ADHD+DD group 77.8% female Age mean: 8.79 (0.73) Min age: 8 Max age: 10 Ethnicity: Other info on race or ethnicity: N/A</td>
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<thead>
<tr>
<th>Results:</th>
<th>Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference standard: Clinical diagnosis Diagnosis of ADHD only was confirmed by a comprehensive clinical diagnostic assessment made by two qualified neurodevelopmental pediatricians. The assessments were based on a clinical evaluation during an interview session using the DSM–4th edition (Ameri Timing: Prior diagnosis Index test: neuropsychological, EF Shifting - Trail-B: The Trail–B subtest from the BANC was administered to examine participants’ shifting ability. The Trail–B subtest requires the child to draw a line connecting 25 circles containing numbers or letters randomly distributed on a sheet of paper, alternating between numbers and letters (1, A, 2, B, etc.). ADHD only vs typically developing children Sensitivity: 56 Specificity: 79 PPV: NPV: LR+: LR:- Accuracy: AUC: 0.727 Rater agreement: Kappa: Internal consistency: Alpha: Costs: Index test 3: neuropsychological, EF Naming speed - RAN: The Naming Speed subtest from the BANC comprises two tasks. In the RAN task, the child was asked to name 50 visual stimuli (numbers 2, 4, 6, 7, and 9) as</td>
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<tr>
<th>Additional index tests</th>
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<tbody>
<tr>
<td>Index test 2: neuropsychological, EF Visuospatial short-term memory - corsi blocks: The Corsi Blocks and the Rey Complex Figure subtests from the BANC were administered to measure visuospatial short-term memory. ADHD only vs typically developing children Sensitivity: 63 Specificity: 62 PPV: NPV: LR+: LR:- Accuracy: AUC: 0.744 Rater agreement: Kappa: Internal consistency: Alpha: Costs: Index test 3: neuropsychological, EF Naming speed - RAN: The Naming Speed subtest from the BANC comprises two tasks. In the RAN task, the child was asked to name 50 visual stimuli (numbers 2, 4, 6, 7, and 9) as</td>
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## Appendix C. Evidence Tables

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<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population:</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
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<tr>
<td></td>
<td>Study: Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
<td>Additional index tests</td>
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<tr>
<td></td>
<td>Alpha: Test-retest: Cost: Misdiagnosis: Labeling: Costs:</td>
<td>Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
<td>quickly as possible, which were randomly displayed on a card in a 10 × 5 matrix. Sensitivity: 75 75 Specificity: 88 PPV: NPV: LR+: Accuracy: AUC: 0.844 Rater agreement:</td>
<td></td>
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<tr>
<td></td>
<td>Index text 4: neuropsychological, EF Naming speed - RAS: The Naming Speed subtest from the BANC comprises two tasks. In the Rapid Alternating Stimulus (RAS) task, the child was asked to name 50 visual stimuli (circle, rectangle, square, and triangle, which were colored yellow, red, black, an</td>
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<td></td>
<td>Index text 5: Neuropsychological Processing speed, Working memory</td>
<td>Other outcomes</td>
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</tbody>
</table>

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<p>| Index Type | Study: Moura, 2019 Case series N = 179 Portugal Setting: Primary Care | Population: Target: Native speakers of European Portuguese, with no neurological impairment, no visual, motor, or hearing impairments, no language impairment, no oppositional defiant disorder or conduct disorders; children on psychostimulants did not receive medication during the week of evaluation Other: Age and gender matched children ADHD presentation: inattentive: 36.7, hyperactive: 36.7, combined: 26.5 Diagnosed by: Specialist Comorbidity: N/A Female: 23.5% Age mean: 8.55 (1.92) Min age: 6 Max age: 12 Ethnicity: Other info on race or ethnicity: N/A | Results: Reference standard: Clinical diagnosis Diagnosed using the DSM-5, ADHD confirmed by psychologist Timing: Prior diagnosis | Additional index tests |</p>
<table>
<thead>
<tr>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pauli-Pott, 2021&lt;sup&gt;556&lt;/sup&gt;  Case series  N = 138  Germany Setting: Community</td>
<td><strong>Target:</strong> Children who scored in the upper quartile an ADHD screening questionnaire completed by their parent at age 4-5; IQ&gt;=80; no chronic diseases involving brain functions, any continuous pharmacological treatment, and insufficient German language skills of the parent or child; diagnosed with ADHD at age 8  <strong>Other:</strong> Children who scored in the upper quartile an ADHD screening questionnaire completed by their parent at age 4-5; not diagnosed with ADHD at age 8  <strong>ADHD presentation:</strong> N/A  <strong>Diagnosed by:</strong> Specialist  <strong>Comorbidity:</strong> N/A  <strong>Female:</strong> % 41% in entire sample  <strong>Age mean:</strong> 4.9 (0.5)  Age at follow up assessment 8.4 (0.3)  <strong>Min age:</strong> 4  <strong>Max age:</strong> 5  <strong>Ethnicity:</strong> Other info on race or ethnicity: N/A</td>
<td><strong>Reference standard:</strong> Clinical diagnosis  Parents and child care teachers completed the ADHD rating scale (FBB-ADHS-V) of the Diagnostic System for Psychiatric Disorders (DISYPS-II) done at first assessment at 4 to 5 years old. Investigator (psychologist), who was blind to all data of the first a  <strong>Timing:</strong> Later diagnosis  <strong>Index test:</strong> neuropsychological,EF Task-based neuropsychological impulsivity measure. Two tasks on hot inhibitory control and one task on behavioral approach tendency done at first assessment at 4 to 5 years old. Impulsivity measure cut-point used to predict ADHD diagnosis at 8 years old  <strong>Sensitivity:</strong> 76  <strong>Specificity:</strong> 70  <strong>PPV:</strong>  <strong>NPV:</strong></td>
<td><strong>Index text 4:</strong> Sensitivity: Specificity: PPV: NPV: AUC: <strong>Index text 5:</strong>  <strong>Index test 2:</strong> Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC:  <strong>Rater agreement:</strong> Kappa:  <strong>Internal consistency:</strong> Alpha:  <strong>Costs:</strong>  <strong>Index test 3:</strong> Sensitivity: Specificity: PPV: NPV: LR+: Accuracy:</td>
</tr>
</tbody>
</table>
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Pineda, 2011*465 Case series N = 288 Colombia Setting: Specialty care</th>
<th>Population: Target: Children with ADHD selected from Paisa families inhabiting the Medellín metropolitan area of the State of Antioquia, Colombia; required to have Paisa descent for more than two generations and more than two members affected with ADHD; pedigrees with bilineal transmission of ADHD were excluded; IQ&gt;=81 Other: Children without ADHD selected from Paisa families inhabiting the Medellín metropolitan area of the State of Antioquia, Colombia; required to have Paisa descent for more than two generations and more than two members affected with ADHD; pedigrees with bilineal transmission of ADHD were excluded.</th>
<th>Results: Reference standard: Clinical diagnosis The diagnostic interview for children and adolescents-revised-parent version (DICA-IV-P) Timing: Prior diagnosis Index test: neuropsychological,EF Generalized linear model with a binomial link including sex, the Wechsler intelligence scale for children-revised block design, the A cancelation and vigilance test correct response, the Rey-Osterrieth complex figure test copy time, copy, and memory time, the semantic Verbal fluency test, and the Token test Sensitivity: 81 at 0.2759 cutoff</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index Type</td>
<td>Study: Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
<td>Additional index tests</td>
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</tbody>
</table>

LR-: Accuracy: AUC: Rater agreement: Kappa: ICC: 
Internal consistency: Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs: 
AUC: Rater agreement: 

Index text 4: 
Sensitivity: Specificity: PPV: NPV: AUC: 

Index text 5: 

AUC: Rater agreement: 

Index test 2: 
Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: 
Rater agreement: Kappa: Internal consistency: Alpha: Costs: 

Index test 3: 

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<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
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</tr>
</thead>
<tbody>
<tr>
<td>neuropsychological,EF</td>
<td>Qin , 2018 Case series N = 275 China Setting: Mixed</td>
<td>Target: IQ&gt;=85. No intellectual disability, learning disorder, tic disorders and autism spectrum disorder, and no history of treatment for ADHD using medications Other: Healthy children ADHD presentation: N/A</td>
<td>Reference standard: Clinical diagnosis Clinical diagnosis made by psychiatrists using DSM-IV criteria Timing: Prior diagnosis</td>
<td>Index test 2: neuropsychological,EF The Das-Naglieri Cognitive Assessment System (DN: CAS). Test of cognitive abilities based on four cognitive processes. Two different sets of tests were carried out according to various age groups (5–7 year-olds and 8–17 year-olds). Classification performance of</td>
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<td></td>
<td>Diagnosed by: Specialist Comorbidity: N/A Female: 17%</td>
<td>Diagnosis:</td>
<td></td>
<td>Sensitivity: 79</td>
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</table>
## Appendix C. Evidence Tables

<table>
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<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
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<tbody>
<tr>
<td></td>
<td>Case series</td>
<td>N = 130  Norway Setting: Specialty care</td>
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<td>529</td>
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<td></td>
<td>Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
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<tr>
<td>neuropsychological, EF</td>
<td>Webster, 2000&lt;sup&gt;597&lt;/sup&gt; Case series N = 132 US Setting: Specialty care</td>
<td>Target: Children referred to a private clinic for psychoeducational evaluations who had been previously identified by at least two professionals as having ADHD only, ADHD+learning disability, or ADHD-predominantly inactive type Other: Children referred for other reasons such as underachievement, family problems, or emotional concerns ADHD presentation: inattentive : 25,combined : 46,N/A : ADHD+ Learning Disability 29% Diagnosed by: Unclear/NR Comorbidity: N/A Female: 21.21% Age mean: 12.57 ( 3.10) Min age: 8 Max age: 16 Ethnicity:</td>
<td>Costs: Misdiagnosis: Labeling: Costs:</td>
<td>LR+: Accuracy: AUC: Rater agreement:</td>
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<td></td>
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<td>Reference standard: Clinical diagnosis ADHD group had been previously diagnosed by at least 2 professionals as having the disorder Timing: Prior diagnosis Index test: neuropsychological,EF Learning Efficiency Test -II</td>
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<td>Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC:</td>
<td>Index test 2:</td>
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<td>Internal consistency: Alpha: Costs:</td>
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<td>Index test 3:</td>
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<td>Sensitivity: Specificity:</td>
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</thead>
<tbody>
<tr>
<td>neuropsychological, EF</td>
<td>Westerberg, 2004&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Target: Children taking stimulant medication refrained for 24 hours before testing, no major neurological or psychiatric co-diagnoses, IQ&gt;80 Other: Age-matched neurotypical children ADHD presentation: N/A Diagnosed by: Specialist Comorbidity: N/A Female: 0% Age mean: 11.4 (2.2) for ADHD group, 11.4(2.0) for control group Min age: 8 Max age: 15 Ethnicity: N/A</td>
<td>Reference standard: Clinical diagnosis Diagnosed by experienced physicians specialised in pediatric neurology or child-psychiatry Timing: Prior diagnosis Index test: neuropsychological, EF Choice reaction time and visuo-spatial working memory tests Sensitivity: 74 Specificity: 94 PPV: 19 NPV: 99 LR+:</td>
<td>PPV: NPV: LR+: Accuracy: AUC: Rater agreement:</td>
</tr>
</tbody>
</table>

| | | % Hispanic or Latino : 1 % Black/African American : 34 % White : 65 Other info on race or ethnicity: | ICC: Internal consistency: Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs: | |
| | | | | |

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<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>neuropsychological, EF</td>
<td>Weyandt, 1994694 Case series N = 115 US Setting: School</td>
<td>Target: Children diagnosed with ADHD enrolled in a regular education classroom and not receiving special education services with average to above-average intelligence as assessed by the Raven's Coloured Progressive Matrices Other: Children with developmental language disorder and neurotypical children; both groups had average to above-average intelligence as assessed by the Raven's Coloured Progressive Matrices ADHD presentation: N/A Diagnosed by: Specialist Comorbidity: N/A</td>
<td>Reference standard: Clinical diagnosis Diagnosed by a pediatrician or psychologist using DSM criteria, Revised Conners Teacher Rating Scale and Parent Rating Scale, ADHD Rating scale Timing: Index test: neuropsychological, EF Six executive function tasks: Visual search, verbal fluency, the Wisconsin Card Sorting Test, Matching Familiar Figures Test, Tower of Hanoi, and mazes; Two nonexecutive function tasks: Peabody Picture Vocabulary</td>
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<td>Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement:</td>
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<td>Index text 4: Sensitivity: Specificity: PPV: NPV: AUC:</td>
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<td>Index text 5:</td>
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<td>Index Type</td>
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</table>
|            | **Female: 0%**<br>Age mean: Min age: 6 Max age: 12<br>Ethnicity: % White: 100<br>Other info on race or ethnicity: | Test-Revised and the Boston Naming test; discriminant function analysis<br>Sensitivity: 67%<br>Specificity: 78%<br>Percent of ADHD group correctly classified<br>Percent of neurotypical developing group correctly classified<br>PPV: <br>NPV: <br>LR+: <br>LR-: <br>Accuracy: <br>AUC: <br>Rater agreement: <br>Kappa: <br>ICC: <br>Internal consistency: <br>Alpha: <br>Test-retest: <br>Costs: <br>Misdiagnosis: <br>Labeling: <br>Costs: | **Index test 3:**<br>Sensitivity: <br>Specificity: <br>PPV: <br>NPV: <br>LR+: <br>LR-: <br>Accuracy: <br>AUC: <br>Rater agreement: | **Index test 4:**<br>Sensitivity: <br>Specificity: <br>PPV: <br>NPV: <br>AUC: | **Index test 5:**
| Index Type | Study:  
Wodka, 2008  
Case series  
N = 123  
US  
Setting: Specialty care | Population:  
Target: Participants were recruited from outpatient clinics at the Kennedy Krieger Institute, and from local area pediatricians, local chapters of Children and Adults with Attention Deficit/Hyperactivity Disorder (CHADD), schools, social/service organizations (e.g., Boy/Girl Scouts), and advertisements in the community (e.g., postings at libraries) as part of a larger project examining brain–behavior relationships in children; IQ>=80; no history of speech/language disorder or a reading disability; no evidence of visual or hearing impairment, or history of other neurological or psychiatric disorder; children with DSM-IV diagnoses other than oppositional defiant disorder or specific phobias were excluded; oversampling for the type of ADHD less likely to occur in each sex (combined presentation for girls and inattentive presentation for boys); participants taking stimulant mediation were asked to withhold medication the day of testing and the day prior | Results:  
Reference standard: Clinical diagnosis  
Structured parent interview that utilized DSM-IV criteria (Diagnostic Interview for Children and Adolescents, Fourth Edition (DICA-IV), Conners' Parent Rating Scale-Revised, Long Form  
Timing: Concurrent  
Index test: neuropsychological, EF  
Four subtests from the Delis-Kaplan Executive Function System (D-KEFS): Trail Making, Verbal Fluency, Color-Word Interference, and Tower tests  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
LR-:  
Accuracy:  
AUC:  
Rater agreement:  
Kappa:  
Internal consistency:  
Alpha:  
Costs:  
Index test 2:  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy:  
AUC:  
Rater agreement:  
Kappa:  
Internal consistency:  
Alpha:  
Costs:  
Index test 3:  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy:  
AUC:  
Rater agreement:  
Kappa:  
Internal consistency:  
Alpha:  
Costs:  
Index test 4:  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
AUC:  |
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<td>neuropsychological, EF</td>
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### Index Type

<table>
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<tr>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
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<tr>
<td><strong>Observation</strong></td>
<td><strong>Bunte, 2013</strong>&lt;sup&gt;175&lt;/sup&gt; Case series N = 251 Netherlands Setting: N/A</td>
<td><strong>Target:</strong> Referred preschool children with externalizing behavioral problems; IQ&gt;=70; no current medications; diagnosed with ADHD or disruptive behavior disorder plus ADHD <strong>Other:</strong> Typically developing children recruited from regular elementary schools and daycare centers <strong>ADHD presentation:</strong> N/A <strong>Diagnosed by:</strong> Specialist <strong>Comorbidity:</strong> Other : sample with disruptive behavior or ADHD <strong>Female:</strong> 24% <strong>Age mean:</strong> 54.7 (8.8) <strong>Min age:</strong> 3.5 <strong>Max age:</strong> 5.5 <strong>Ethnicity:</strong> % Black/African American : 2 % Asian : 0.5 % White : 86 % Multiracial : 12, Other : Turkish/Moroccan <strong>Other info on race or ethnicity:</strong></td>
<td><strong>Reference standard:</strong> Clinical diagnosis Clinical diagnosis made by child psychiatrist and child psychologist <strong>Timing:</strong> Prior diagnosis <strong>Index test:</strong> Observation Disruptive Behavior Diagnostic Observation Schedule <strong>Sensitivity:</strong> 87 % <strong>Specificity:</strong> 79 % <strong>PPV:</strong> <strong>NPV:</strong> <strong>LR+:</strong> <strong>LR-:</strong> <strong>Accuracy:</strong> <strong>AUC:</strong> 0.92</td>
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### Appendix C. Evidence Tables

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<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
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<th>Results: Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
|            | **Other**: Claim-based algorithms  
Straub, 2021  
Case series  
N = 350  
US  
Setting: Other | **Target**: Children 14 years or younger identified from a medical encounter in hospitals who met a clinical definition for specific neurodevelopmental disorders including ADHD; required 2 or more medical encounters to qualify with a diagnostic code using ICD-9, and ICD-10  
**Other**: Study also included children with other disorders, but they were not compared to ADHD group; study objective to validate healthcare claim-based algorithms using medical records as the reference  
**ADHD presentation**: N/A  
**Diagnosed by**: Specialist  
**Comorbidity**: N/A  
**Female**: %  
**Age mean**: | **Reference standard**: Clinical diagnosis  
Study used medical records as the fold standard, data comes from ICD-9 codes used to develop algorithms based on ICD-9, and translated to ICD-10 to make data applicable to more current years  
**Timing**: Prior diagnosis  
**Index test**: Other: Claim-based algorithms  
Claim-based algorithms for neurodevelopmental disorders including ADHD  
**Sensitivity**: 88%  
**Specificity**: 88%  
**PPV**: 88%  
**NPV**: 88%  
**LR+**:  
**LR-**:  
**Accuracy**: | **Index text 4**:  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
AUC:  
**Index text 5**:  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
AUC:  
**Alpha**: 0.82  
**ICC**: children retested after 8 weeks  
**Test-retest**: 0.64  
**Costs**:  
**Misdiagnosis**:  
**Labeling**:  
**Costs**: |
|            | Alpha: 0.82  
ICC: children retested after 8 weeks  
Test-retest: 0.64  
Costs:  
Misdiagnosis:  
Labeling:  
Costs: | Alpha: 0.82  
ICC: children retested after 8 weeks  
Test-retest: 0.64  
Costs:  
Misdiagnosis:  
Labeling:  
Costs: | Accuracy:  
AUC:  
Rater agreement:  
**Index text 4**:  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
AUC:  
**Index text 5**:  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
AUC: |
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<tr>
<td></td>
<td>Koh, 2022&lt;sup&gt;14&lt;/sup&gt;</td>
<td>N/A Min age: 1 Max age: 14 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>AUC:</td>
<td>NPV:</td>
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<tr>
<td></td>
<td>Raine, 2019&lt;sup&gt;160&lt;/sup&gt;; Tor, 2021&lt;sup&gt;183&lt;/sup&gt;</td>
<td>Target: ADHD only (45 participants), ADHD + conduct disorder (62 participants), subset from the randomized Omega-3 Supplements and Social Skills Intervention Study (ClinicalTrials.gov Identifier: NCT00819429) Other: Conduct disorder only (16 participants) ADHD presentation: N/A Diagnosed by: Provider Comorbidity: ODD Female: 11.2% Age mean: N/A Min age: 7 Max age: 16 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Reference standard: Clinical diagnosis Primary diagnosis made by child's attending physician Timing: Prior diagnosis</td>
<td>LR+:</td>
</tr>
<tr>
<td>Other: ECG</td>
<td>Other: ECG Continuous 12-channel electrocardiography (ECG) signals recorded over 3 min during complete relaxation with eyes open, K-nearest neighbor three class classification (ADHD vs ADHD+CD vs CD only), 10-fold cross validation Sensitivity: 88 Specificity: 86 PPV: NPV: LR+:</td>
<td>Index test: Other : ECG Continuous 12-channel electrocardiography (ECG) signals recorded over 3 min during complete relaxation with eyes open, bagged tree three class classification (ADHD vs ADHD+CD vs CD only), 10-fold cross validation</td>
<td>Accuracy: 84</td>
<td></td>
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<td></td>
<td>Index test 2: Other : ECG Continuous 12-channel electrocardiography (ECG) signals recorded over 3 min during complete relaxation with eyes open, K-nearest neighbor three class classification (ADHD vs ADHD+CD vs CD only), 10-fold cross validation Sensitivity: 83 Specificity: 85 PPV: NPV: LR+:</td>
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## Appendix C. Evidence Tables

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<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
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<td><strong>Index test 3: EEG</strong> Electroencephalogram (EEG) during resting-state, eyes open for 3 minutes, K-nearest neighbor three class classification (ADHD vs ADHD+CD vs CD only), 10-fold cross validation 1083 Sensitivity: 97 97 Specificity: 100 PPV: NPV: LR+: Accuracy: 98 AUC: Rater agreement:</td>
<td><strong>Index test 4: EEG</strong> Electroencephalogram (EEG) during resting-state, eyes open for 3 minutes, bagged tree three class classification (ADHD vs ADHD+CD vs CD only), 10-fold cross validation 1083 Sensitivity: 94</td>
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</table>

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<table>
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<tr>
<th>Study Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slaby, 2022</td>
<td>Slaby, 2022⁵³⁰ Case series N = 27,270 US Setting: Other</td>
<td>Target: Mined EHRs from 2009 to 2016 using ICD codes, medication history and keywords specific to ADHD, and comorbid psychiatric disorders; subjects that were cases of both ADHD and one or more psychiatric disorders were considered comorbid ADHD cases Other: Controls lacked psychiatric and other neurological disorders; learning disabilities and mild/moderate intellectual disability were not excluded ADHD presentation: N/A Diagnosed by: Unclear/NR Comorbidity: Other: 54% of ADHD participants had psychiatric comorbidities Female: % 49% female in entire sample Age mean: 11(6) Min age: Max age: Ethnicity: % Black/African American: 44 % White: 52</td>
<td>Reference standard: Other Chart abstractions and behavioral surveys added evidence in support of the psychiatric diagnoses. Conducted an independent electronic medical record review for random cases that were pulled out by the algorithms to confirm they were “true” cases. The numb Timing: Prior diagnosis Index test: Other: EHR phenotype algorithm Multi-source/multi-approach electronic health record (EHR) rule-based phenotype algorithm with natural language processing text mining developed to discriminate cases with ADHD in isolation from cases with ADHD with comorbidities Sensitivity: Specificity: PPV: NPV: LR+: LR-: Accuracy:</td>
<td>Specificity: 100 PPV: NPV: AUC: Index text 5:</td>
</tr>
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</table>

| Other: EHR phenotype algorithm | | | | |
### Appendix C. Evidence Tables

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<tr>
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<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electro interstitial scans (EIS)</td>
<td>Caudal, 2011&lt;sup&gt;363&lt;/sup&gt; Case series N = 112 France Setting: N/A</td>
<td>Target: Participants had to be without a parent who had a neurological disorder, excluded if the clinician decided that the child was clinically unsuitable as a candidate, and/or if there were any contraindications to use the EIS system; children needed to have diagnosis of ADHD following psychiatric examination Other: Children without ADHD symptoms ADHD presentation: N/A Diagnosed by: Unclear/NR Comorbidity: N/A Female: 26.92% Age mean: 8 Min age: 3 Max age: 18 Ethnicity: Other info on race or ethnicity: Other : Electro interstitial scans (EIS) Electro interstitial scans to measure bioimpedance</td>
<td>Reference standard: Clinical diagnosis Diagnosed with ADHD according to the DSM-IV and further examinations Timing: Prior diagnosis Index test: Other : Electro interstitial scans (EIS) Electro interstitial scans to measure bioimpedance Sensitivity: 80 Cutoff 7.4 micro Siemens Specificity: 98 Cutoff 7.4 micro Siemens PPV: NPV: LR+: LR-: Accuracy: AUC: 0.876 Rater agreement: Kappa:</td>
<td>AUC: Rater agreement: Index text 4: Sensitivity: Specificity: PPV: NPV: AUC: Index text 5:</td>
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</table>

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## Appendix C. Evidence Tables

<table>
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<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
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<tbody>
<tr>
<td>Eye movement</td>
<td>Merzon, 2022&lt;sup&gt;219&lt;/sup&gt; Case series N = 73 Other Setting: N/A</td>
<td>Target: No medication within 24 hours prior to assessment; comorbidities present in some participants include oppositional defiant disorder, unspecified conduct disorder, panic disorder, unspecified affective disorders, and chronic motor or vocal tic disorder Other: Typically developing children, matched on age and gender ADHD presentation: N/A Diagnosed by: Provider Comorbidity: N/A Female: 22% Age mean: 10.4 (1.0) for the ADHD group, 10.8 (1.2) for the typically developing group</td>
<td>Reference standard: Clinical diagnosis ADHD diagnosis made by a licensed medical doctor and verified via the National Medical Database Timing: Prior diagnosis Index test: Other: Eye movement Eye movement data collected during Executive Performance in Everyday Living (EPELI) VR task; includes 13 task scenarios where the participants perform everyday chores in a virtual environment; support vector machine classifier using the eye movement features Fixation Duration, Saccade Duration, and Saccade Amplitude; 10-fold cross validation Sensitivity: 84 Specificity: 78</td>
<td>Index test 2: Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement: Kappa: Internal consistency: Alpha: Costs:</td>
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<td></td>
<td></td>
<td>ICC:</td>
<td>PPV: NPV: LR+: Accuracy: AUC: Rater agreement:</td>
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<td>Internal consistency: Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
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<tr>
<td></td>
<td>Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
<td>Sensitivity; Specificity; PPV; NPV; LR+: LR-; Accuracy; AUC; Rater agreement:</td>
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<tr>
<td></td>
<td>Other: Eye vergence</td>
<td>Other: Eye vergence BGaze system to test eye vergence ADHD versus healthy controls. Two-layer classification model: First layer= Radial Basis Function support vector machine (RBF-SVM), second layer = two k-nearest-neighbor models. 30-fold stratified cross-validation routin</td>
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</table>

**Target:** Not on medication; free of a history of head injury with loss of consciousness or other neurological illness, mental retardation or other significant disorders like a pervasive developmental disorder and visual or auditory problems; recruited through the Child and Adolescent Health Mental Center from the Hospital Mataró of the Consorci Sanitari del Maresme

**Other:** Non-ADHD clinical controls referred to the hospital for attentional and/ or conduct problems, healthy children showing no attention

**Reference standard:** Clinical diagnosis All the clinical diagnoses of ADHD were made by clinical psychiatrists using the DSM-IV-TR criteria

**Timing:** Prior diagnosis

**Index test:** Other: Eye vergence BGaze system to test eye vergence ADHD versus clinical controls. Two-layer classification model: First layer= Radial Basis Function support vector machine (RBF-SVM), second layer = two k-nearest-neighbor models. 30-fold stratified cross-validation routin

**Index test 2:** Other: Eye vergence BGaze system to test eye vergence ADHD versus clinical controls. Two-layer classification model: First layer= Radial Basis Function support vector machine (RBF-SVM), second layer = two k-nearest-neighbor models. 30-fold stratified cross-validation routin

### Varela Casal, 2019th
- **Case series**
- **N = 92**
- **Spain**
- **Setting:** Mixed
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<tr>
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<td>or conduct problems recruited from a public school</td>
<td>ADHD presentation: N/A Diagnosed by: Specialist Comorbidity: N/A Female: % N/A Age mean: 10.67 (2.64) Min age: 7 Max age: 17 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>routine over the S1 subsample, which, at each iteration, was further split into an 80-20 train-test random resampling. Then, the resulting model was tested on the S2 subsample, which so far had been unseen by it. Sensitivity: Specificity: PPV: NPV: LR+: LR-: Accuracy: 96 AUC: 0.99 Rater agreement: Kappa: Internal consistency: Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
<td>Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: 86 AUC: 0.90 Rater agreement: Kappa: Internal consistency: Alpha: Costs:</td>
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<tbody>
<tr>
<td></td>
<td>Mikolas, 2022 [23] Case series N = 299 Germany Setting: Specialty care</td>
<td><strong>Target:</strong> Individuals who were referred to a secondary care outpatients unit with a suspected ADHD diagnosis, or in whom an ADHD diagnosis was the suspected diagnosis after the initial consultation <strong>Other:</strong> Patients who did not fulfill diagnostic criteria for ADHD <strong>ADHD presentation:</strong> N/A: 64% predominantly hyperactive-impulsive type, 27.5% predominantly inattentive type, 8.5% comorbid with conduct disorder <strong>Diagnosed by:</strong> Specialist <strong>Comorbidity:</strong> N/A <strong>Female:</strong> 14% <strong>Age mean:</strong> 10.0 (2.4) for the ADHD group, 10.5 (2.5) for the non-ADHD group <strong>Min age:</strong> Max age: 18 <strong>Ethnicity:</strong> Other info on race or ethnicity: N/A</td>
<td><strong>Reference standard:</strong> Clinical diagnosis The standardized diagnostic process included several consultations with the child and caregivers together and individually. Parents and (nursery) school teachers completed general and ADHD-specific rating scales. Further, general intelligence and attention Timing: Later diagnosis <strong>Index test:</strong> Other: Medical record data 30 features extracted from medical record data, linear support vector machine classifier, 10-fold cross-validation. Features include: age and gender; symptom ratings from Conners-3 parent/teacher ratings and a computed set of ‘consistency indices’ describing the consistency between parent and teacher ADHD specific Conners-3 ratings; neuropsychological measures from 3 TAP subtests (GoNogo, Divided Attention, and Alertness) and the Wechsler Intelligence Scale for Children IV or V</td>
<td><strong>Index test 5:</strong> Other: Medical record data 19 most predictive features selected from the original 30 using sequential floating forward selection, linear support vector machine classifier, 10-fold cross-validation <strong>Sensitivity:</strong> <strong>Specificity:</strong> <strong>PPV:</strong> <strong>NPV:</strong> <strong>LR+:</strong> <strong>Accuracy:</strong> 68 <strong>AUC:</strong> <strong>Rater agreement:</strong> Kappa: <strong>Internal consistency:</strong> Alpha: <strong>Costs:</strong></td>
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<tr>
<td></td>
<td>Vogt, 2011</td>
<td>Case series</td>
<td>Target: Individuals with a referral for ADHD made to a local generic child and adolescent mental health services (CAMHS) clinic over 2 years; ADHD assessments in the year prior to using objective measurements (2006-2007 control group, n = 46) were compared with ADHD assessments in the first year of adding objective measures to the assessment (2007-2008 QbTest group, n = 62)</td>
<td>Reference standard: Clinical diagnosis Clinical interview by the child and adolescent psychiatrists at the clinic, a medical examination and the administration of rating scales by parents and teachers</td>
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<td>N = 108</td>
<td>Other: Individuals from same referral group not diagnosed with ADHD ADHD presentation: N/A : QbTest group; 16% combined, 14% inattentive; control group 11% inattentive</td>
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<tr>
<td></td>
<td>UK Setting: Specialty care</td>
<td>Diagnosed by: Specialist</td>
<td></td>
<td>Index text 5:</td>
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<tr>
<td></td>
<td></td>
<td>Comorbidity: N/A</td>
<td>Sensitivity: Specificity: PPV: NPV: LR+: LR-: Accuracy: AUC:</td>
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<td>Female: %</td>
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<td>16% female in the QbTest group</td>
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<td>Age mean:</td>
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<td>10.5 for the QbTest group, 9 for the control group</td>
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<tr>
<td></td>
<td>Min age: Max age: Ethnicty: Other info on race or ethnicity: N/A</td>
<td>Rater agreement: Mixed SDQ rating (disagreement between parent and teacher ratings) versus clinician’s diagnosis Among those with a positive/negative SDQ in both the control and QbTest groups the majority of parents’ SDQs (10/13, 77%) agreed with the clinician’s diagnosis of ADHD, whereas the majority of teacher’s SDQs (13/18, 72%) agreed with the clinician’s reject Kappa: ICC: Internal consistency: Alpha: Follow-up over 1 year of the participants referred for an attention-deficit hyperactivity disorder (ADHD) assessment with a diagnosis rejected at the initial assessment Test-retest: n=19; lost to follow-up n=3, reassessed and diagnosed with ADHD at 1-year follow-up n=7; The majority of the revised assessments were for girls (n = 4) Costs:</td>
<td>attention-deficit hyperactivity disorder (ADHD) assessment with a diagnosis rejected at the initial assessment n=19; lost to follow-up n=3, reassessed and diagnosed with ADHD at 1-year follow-up n=7; The majority of the revised assessments were for girls (n = 4) Costs:</td>
<td>Index test 3: Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement:</td>
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<td>Costs: Misdiagnosis: The results from this audit suggest that through greater symptom specification with the use of objective measurements clinical decisions remained more consistent and were less likely to be revised over 1 year Labeling: Costs:</td>
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**Index text 5:**

Labeling: Costs:
## Appendix C. Evidence Tables

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<th>Study: Parent interview guide</th>
<th>Population:</th>
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<th>Additional index tests</th>
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<tr>
<td>Case series</td>
<td>Other: Normal control subjects recruited from advertisements placed in a hospital staff newsletter, IQ&gt;=80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 620</td>
<td>ADHD presentation: N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>Diagnosed by: Specialist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Setting: Specialty care</td>
<td>Comorbidity: N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boy-to-girl ratio of 3.2:1 in clinic-referred cases</td>
<td>Female: %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age mean: 8.67 (1.81) clinic-referred cases, 9.04 (1.63) control sample</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min age: 6 Max age: 16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity: Other info on race or ethnicity: N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Results:</strong></td>
<td><strong>Reference standard:</strong></td>
<td><strong>Index test:</strong></td>
<td><strong>Additional index tests</strong></td>
</tr>
<tr>
<td><strong>Index test:</strong> Parent interview guide Parent Interview for Child Symptoms (PICS)</td>
<td>6-hour evaluation divided into two, 3-hour sessions, Teacher Telephone Interview, Conners' Rating Scales-Revised and Revised ontario Child Health Study Scales from parents and teachers Timing: Concurrent</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sensitivity:</strong></td>
<td><strong>Specificity:</strong></td>
<td><strong>PPV:</strong></td>
<td><strong>NPV:</strong></td>
</tr>
<tr>
<td><strong>Costs:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[^1]: Reference standard: Clinical diagnosis 6-hour evaluation divided into two, 3-hour sessions, Teacher Telephone Interview, Conners' Rating Scales-Revised and Revised ontario Child Health Study Scales from parents and teachers Timing: Concurrent

**Index test 2:** Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement: Kappa: Internal consistency: Alpha: Costs:

**Index test 3:** Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement:

**Index test 4:** Sensitivity: Specificity: PPV: NPV: AUC:
### Appendix C. Evidence Tables

**Index Type**

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Results</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study:</strong> Author, year; Multiple publications; Study design; Study size; Location</td>
<td><strong>Index test:</strong> Cost</td>
<td><strong>Index text 5:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Index test:</strong></td>
<td><strong>Labeling:</strong></td>
<td><strong>Index test 2:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Study:</strong></td>
<td><strong>Reference standard:</strong></td>
<td><strong>Index test 3:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Index test:</strong></td>
<td><strong>Index test:</strong></td>
<td><strong>Index test:</strong></td>
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<td><strong>Study:</strong></td>
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<tr>
<td><strong>Study:</strong></td>
<td><strong>Index test:</strong></td>
<td><strong>Index test:</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Parent rating**

<table>
<thead>
<tr>
<th>Algorta, 2016</th>
<th>Target: Children with ADHD; all participants data from The British Child and Adolescent Mental Health Survey 1999</th>
<th>Reference standard: Clinical diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case series N = 18,232 UK Setting: Other</td>
<td>ADHD presentation: inattentive : 27,hyperactive : 8,combined : 65</td>
<td>Reference standard: Clinical diagnosis</td>
</tr>
<tr>
<td>Diagnosis:</td>
<td>Diagnosed by: Specialist</td>
<td>Reference standard: Clinical diagnosis</td>
</tr>
<tr>
<td>Comorbidity: N/A</td>
<td>Female: 18%</td>
<td>Reference standard: Clinical diagnosis</td>
</tr>
<tr>
<td>Age mean:</td>
<td>Mean and SD reported by subtype - ADHD-C= 10.02 (3.09) / ADHD- I = 10.07 (2.81) / ADHD- H = 9.32 (2.92)</td>
<td>Reference standard: Clinical diagnosis</td>
</tr>
<tr>
<td>Min age: 5 Max age: 15</td>
<td>Other: Children without ADHD</td>
<td>Reference standard: Clinical diagnosis</td>
</tr>
<tr>
<td>Ethnicity:</td>
<td>Other info on race or ethnicity:</td>
<td>Reference standard: Clinical diagnosis</td>
</tr>
<tr>
<td>% White : 89</td>
<td></td>
<td>Reference standard: Clinical diagnosis</td>
</tr>
</tbody>
</table>

**Additional index tests**

<table>
<thead>
<tr>
<th><strong>Index test 5:</strong></th>
<th><strong>Index test 2:</strong></th>
<th><strong>Index test 3:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Labeling:</strong></td>
<td><strong>Sensitivity:</strong></td>
<td><strong>Sensitivity:</strong></td>
</tr>
<tr>
<td><strong>Costs:</strong></td>
<td><strong>Specificity:</strong></td>
<td><strong>Specificity:</strong></td>
</tr>
<tr>
<td></td>
<td><strong>PPV:</strong></td>
<td><strong>PPV:</strong></td>
</tr>
<tr>
<td></td>
<td><strong>NPV:</strong></td>
<td><strong>NPV:</strong></td>
</tr>
<tr>
<td></td>
<td><strong>LR+:</strong></td>
<td><strong>LR+:</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Accuracy:</strong></td>
<td><strong>Accuracy:</strong></td>
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<tr>
<td></td>
<td><strong>AUC:</strong></td>
<td><strong>AUC:</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Rater agreement:</strong></td>
<td><strong>Rater agreement:</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Kappa:</strong></td>
<td><strong>Kappa:</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Internal consistency:</strong></td>
<td><strong>Internal consistency:</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Alpha:</strong></td>
<td><strong>Alpha:</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Costs:</strong></td>
<td><strong>Costs:</strong></td>
</tr>
</tbody>
</table>

**Index test 5:**

- Sensitivity:
- Specificity:
- PPV:
- NPV:
- LR+:
- LR-:
- Accuracy:
- AUC:
- Rater agreement:
- Kappa:
- Internal consistency:
- Alpha:
- Costs:
Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Study: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent rating</td>
<td>Babinski, 2021&lt;sup&gt;135&lt;/sup&gt;</td>
<td><strong>Target</strong>: Participation not limited by gender, race, income, or geography due to desire of sample to represent US population; all participants had ADHD</td>
<td><strong>Reference standard</strong>: Other Disruptive Behavior Disorders Rating Scale-Parent rating</td>
<td><strong>Index test 2</strong>: Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC:</td>
</tr>
<tr>
<td></td>
<td>Case series</td>
<td><strong>Other</strong>: None</td>
<td><strong>Rater agreement</strong>:</td>
<td><strong>Kappa</strong>:</td>
</tr>
<tr>
<td></td>
<td>N = 1050 US Setting: N/A</td>
<td><strong>ADHD presentation</strong>: N/A</td>
<td><strong>Index text 4</strong>: Sensitivity: Specificity: PPV: NPV: AUC:</td>
<td><strong>Index test 5</strong>:</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Diagnosed by</strong>: Unclear/NR</td>
<td><strong>Internal consistency</strong>: Alpha:</td>
<td><strong>Test-retest</strong>: Costs:</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Comorbidity</strong>: N/A</td>
<td><strong>Rater agreement</strong>:</td>
<td><strong>Costs</strong>:</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Female</strong>: 48.5%</td>
<td><strong>Kappa</strong>:</td>
<td><strong>Misdiagnosis</strong>:</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Age mean</strong>: 8.42 (2.31)</td>
<td><strong>Internal consistency</strong>: Alpha:</td>
<td><strong>Labeling</strong>:</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Min age</strong>: 5 Max age: 12</td>
<td><strong>Test-retest</strong>: Costs:</td>
<td><strong>Costs</strong>:</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Ethnicity</strong>: % White: 78.8% Other info on race or ethnicity: Other: Non-Hispanic: 84.2%</td>
<td><strong>Rater agreement</strong>:</td>
<td><strong>Costs</strong>:</td>
</tr>
</tbody>
</table>

- **Results**: female subsamples and at different age ranges
- **Rater agreement**: Kappa: ICC:
- **Internal consistency**: Alpha:
- **Test-retest**: Costs:
- **Misdiagnosis**: Labeling:
- **Costs**: AUC:

**Index text 2**: Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC:

**Index test 3**: Sensitivity:
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study:</th>
<th>Population:</th>
<th>Results:</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Author, year;</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
<td></td>
</tr>
</tbody>
</table>

**Reference standard**: Clinical diagnosis. The Validation ADHD Group diagnoses were based on consensus between a psychiatrist and clinical psychologist following assessment; in the community sample the group was previously diagnosed with ADHD. **Timing**: Prior diagnosis. **Index test 2**: Teen/child self report. Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Rating Scale (SWAN) Self report, optimal cut-point >0.81. Self-reports done by adolescents ages 13-17 from population-based sample only. Sensitivity: 57 Specificity: 81 PPV: NPV: LR+: |

**Index text 4**: |

**Index text 5**: |
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
|            | **Female**: 26.23% 21.43% in validation sample  
**Age mean**: 11.0 (2.8) 9.1 (2.2) in validation sample  
**Min age**: 6  
**Max age**: 17  
**Ethnicity**: Other info on race or ethnicity: N/A | point created using population-based sample tested using validation sample.  
Sensitivity: 82 84% in clinical validation sample  
Specificity: 81 92% in clinical validation sample  
PPV:  
NPV:  
LR+:  
LR-:  
Accuracy: AUC: 0.88  
Rater agreement:  
Kappa:  
ICC:  
Internal consistency: Alpha: 0.95  
Test-retest:  
Costs:  
Misdiagnosis:  
Labeling:  
Costs: | Accuracy: AUC: 0.71  
Rater agreement:  
Kappa:  
Internal consistency: Alpha: 0.88  
Costs:  
**Index test 3:**  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy: AUC:  
Rater agreement:  
**Index test 4:**  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
AUC:  
**Index text 5:** |
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Results:</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent rating</td>
<td>Bussing, 1998[77] Case series N = 499 US Setting: School</td>
<td>Target: Total special ed population in one school district. 70% participation rate. All underwent Diagnostic Interview Schedule for Children (DISC) for DSM IV diagnosis plus two index instruments. Other: Other special ed students. (See above). ADHD presentation: inattentive: 18, hyperactive: 14, combined: 40 Diagnosed by: Researcher Comorbidity: Learning disability: Special education students, N/A Female: 28% Age mean: 9.7 (1.0) Min age: 7 Max age: 12 Ethnicity: % White: 51 Other info on race or ethnicity: Other: 49% &quot;non-white&quot;</td>
<td>Reference standard: Clinical diagnosis ADHD per DSM IV diagnosis Timing: Concurrent Index test: Parent rating Attention Deficit Disorders Evaluation Scale (ADDES), parent rating Data abstracted for 15th percentile Sensitivity: When administered two months before DISC for DSM IV, sensitivity was 58% (SE 3.8%) to discriminate from other special ed students. Specificity: When administered two months before DISC for DSM IV, specificity was 82% (SE 1.9%) to discriminate from other special ed students. PPV: When administered two months before DISC for DSM IV, PPV was 64% (SE 0.5%) to discriminate from other special ed students. NPV: When administered two months before DISC for DSM IV, NPV was 77% (SE 3.4%) to discriminate from other special ed students. LR+: When administered two months before DISC for DSM IV, LR+ was 77% (SE 3.4%) to discriminate from other special ed students. LR-: Accuracy: 73 &quot;efficiency&quot; = 73% at 2 months before DSM-IV administered. Data is for 15th percentile on ADDES AUC: Index test 2: Parental rating scale Conners Abbreviated Symptom Questionnaire (ASQ), parent rating Data abstracted for 60 T score Sensitivity: When administered simultaneous with DSM IV, sensitivity was 84% (SE 3%) to discriminate from other special ed students. Specificity: When administered simultaneous with DISC for DSM IV, specificity was 71% (SE 2.2%) to discriminate from other special ed students. PPV: NPV: LR+: Accuracy: 76% &quot;efficiency&quot; when administered simultaneous with DISC for DSM IV, 76% &quot;efficiency&quot; to discriminate from other special ed students. AUC: Rater agreement: Kappa: Internal consistency: Alpha:</td>
<td></td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Index Type</th>
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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parent rating</strong></td>
<td>Chen, 1994&lt;sup&gt;294&lt;/sup&gt; Doyle, 2000&lt;sup&gt;271&lt;/sup&gt; Case series N = 260 US Setting: Mixed</td>
<td><strong>Target</strong>: All male, met diagnostic criteria for current ADHD at time of clinical referral with active symptoms for which they were receiving treatment; excluded if they had been adopted or if their nuclear family was not available for study; no major sesomotor handicaps (paralysis, deafness, blindness), psychosis, autism; IQ&gt;80 <strong>Other</strong>: Children without ADHD selected from active outpatients at pediatric medical clinics;</td>
<td><strong>Reference standard</strong>: Clinical diagnosis Kiddie Schedule for Affective Disorders and Schizophrenia, Epidemiologic version (SADS-E), interview with mother and direct interview with children older than 12 <strong>Timing</strong>: Prior diagnosis <strong>Index test</strong>: Parent rating Child Behavior Checklist (CBCL) Attention Problems Scale, T score cutoff of 55; logistic regression,</td>
<td><strong>Index test 2</strong>: Parental rating scale Child Behavior Checklist (CBCL) Attention Problems Scale, T score cutoff of 55; logistic regression, validation using brothers of ADHD and pediatric comparison probands</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study:</th>
<th>Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
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<td><strong>Parent rating</strong></td>
<td>Chen, 1994&lt;sup&gt;294&lt;/sup&gt; Doyle, 2000&lt;sup&gt;271&lt;/sup&gt; Case series N = 260 US Setting: Mixed</td>
<td><strong>Target</strong>: All male, met diagnostic criteria for current ADHD at time of clinical referral with active symptoms for which they were receiving treatment; excluded if they had been adopted or if their nuclear family was not available for study; no major sesomotor handicaps (paralysis, deafness, blindness), psychosis, autism; IQ&gt;80 <strong>Other</strong>: Children without ADHD selected from active outpatients at pediatric medical clinics;</td>
<td><strong>Reference standard</strong>: Clinical diagnosis Kiddie Schedule for Affective Disorders and Schizophrenia, Epidemiologic version (SADS-E), interview with mother and direct interview with children older than 12 <strong>Timing</strong>: Prior diagnosis <strong>Index test</strong>: Parent rating Child Behavior Checklist (CBCL) Attention Problems Scale, T score cutoff of 55; logistic regression,</td>
<td><strong>Index test 2</strong>: Parental rating scale Child Behavior Checklist (CBCL) Attention Problems Scale, T score cutoff of 55; logistic regression, validation using brothers of ADHD and pediatric comparison probands</td>
</tr>
<tr>
<td>Index Type</td>
<td>Study: Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
<td>Additional index tests</td>
</tr>
<tr>
<td>------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------------------</td>
</tr>
</tbody>
</table>
|            | models validated using siblings of ADHD probands and pediatric comparison probands | ADHD presentation: N/A  
Diagnosed by: Specialist  
Comorbidity: N/A  
Female: 0%  
Age mean: Min age: 6 Max age: 18  
Ethnicity: % White : 100  
Other info on race or ethnicity: | split-half cross validation sample using ADHD and pediatric comparison probands  
Sensitivity: 84  
Specificity: 93  
PPV: 93  
NPV: 84  
LR+:  
LR-:  
Accuracy: AUC: 0.925  
Rater agreement:  
Kappa:  
Internal consistency: Alpha:  
Test-retest:  
Costs:  
Misdiagnosis:  
Labeling:  
Costs: | NPV: 93  
LR+:  
Accuracy: AUC: 0.855  
Rater agreement:  
Kappa:  
Internal consistency: Alpha:  
Costs: |
|            | Index test 3: Parental rating scale Child Behavior Checklist (CBCL) Attention Problems Scale, T score cutoff of 55; logistic regression, validation using sisters of ADHD and pediatric comparison probands | Sensitivity: 67  
Specificity: 94  
PPV: 50  
NPV: 97  
LR+:  
Accuracy: AUC: 0.902  
Rater agreement: | |
<p>|            | Index text 4: Neuropsychological tests administered to ADHD and pediatric comparison probands | | |</p>
<table>
<thead>
<tr>
<th>Study Type</th>
<th>Population</th>
<th>Results</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| **Parent rating** | Deb, 2008\(^{222}\) Case series  
N = 151  
UK  
Setting: Specialty care | **Target:** Children who received clinical assessments for ADHD and intellectual disabilities in a specialist outpatient clinic; Intellectual disability defined as IQ <=70 associated with inadequate adaptive functioning, borderline IQ defined as IQ above 70 but below 80 on either verbal or performance tasks  
**Other:** Children not diagnosed with ADHD at a specialist outpatient clinic for intellectual disability and behavior problems  
**ADHD presentation:** inattentive : 24, hyperactive : 24, combined : 52  
**Diagnosed by:** Specialist  
**Comorbidity:** Other : All participants had borderline IQ or intellectual disability  
**Female:** %  
28% female in entire sample | **Reference standard:** Clinical diagnosis  
Timing: Prior diagnosis  
**Index test:** Parent rating Conners’ Parent Rating Scales-Revised, cut-off score of 50  
Sensitivity: 83  
Specificity: 89  
PPV:  
NPV:  
LR+:  
LR-:  
Accuracy: AUC: 0.875  
Rater agreement: Parent versus teacher total scores  
Kappa:  
ICC: 0.19 | at 4-year follow-up visit:  
Wechsler Intelligence Scale for Children-Revised (<17 years old) or Wechsler Adult Intelligence Scale-Revised (>=17 years old) Freedom from Distract  
Sensitivity: 76  
Specificity: 46  
PPV: 63  
NPV: 62  
AUC: 0.69  
**Index text 5:**  
**Index test 2:** Teacher rating scale  
Conners’ Teacher Rating Scales-Revised, cut-off score of 48  
Sensitivity: 56  
Specificity: 83  
PPV:  
NPV:  
LR+:  
Accuracy: AUC: 0.665  
Rater agreement: Kappa:  
Internal consistency: Alpha: 0.80  
Costs: |
| Index Type | Study:  
Author, year;  
Multiple publications;  
Study design;  
Study size;  
Location | Population:  
Setting;  
Study target;  
ADHD presentation;  
Diagnosis;  
Comorbidity;  
% Female;  
Age mean;  
Minimum age;  
Maximum age;  
Ethnicity | Results:  
Reference standard;  
Index test;  
Diagnostic accuracy;  
Rater agreement;  
Other outcomes | Additional index tests |
|---|---|---|---|---|
| Parent rating | Deserno, 2022  
Case series  
N = 434  
Netherlands  
Setting: Other | **Target:** Part of a larger cohort of the Healthy Brain Network Biobank based on a community-referred recruitment model of children with developmental psychopathology; a third had an additional diagnosis such as oppositional defiant disorder, autism spectrum disorder, specific learning disorder with impairment in reading, language disorder, and generalized anxiety disorder; replication sample from the Oregon ADHD and Autism project  
**Other:** Children with autism spectrum disorder, neurotypical developing children | **Reference standard:** Clinical diagnosis  
Extensive clinicians-administered assessments including the Autism Diagnostic Observation Schedule, computerized Schedule for Affective Disorders and Schizophrenia-Children’s Version (KSADS-COMP) parent interview and child interview  
**Timing:** Concurrent  
**Index test:** Parent rating The Strengths and Weaknesses of ADHD symptoms and Normal-behaviors ratings scale (SWAN) | **Index test 2:** Parental rating scale  
The Strengths and Weaknesses of ADHD symptoms and Normal-behaviors ratings scale (SWAN) hyperactivity/impulsivity subscale and the Social Responsiveness Scale restricted interests and repetitive behaviors, social |

**Age mean:**  
Min age: 3  
Max age: 17  
**Ethnicity:**  
Other info on race or ethnicity: N/A  
Internal consistency:  
Alpha: 0.84  
Test-retest:  
Costs:  
Misdiagnosis:  
Labeling:  
Costs:  
Index test 3:  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy:  
AUC:  
Rater agreement:  
**Index test 4:**  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
AUC:  
**Index test 5:**
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD presentation: N/A</td>
<td>Diagnosed by: Specialist</td>
<td>Comorbidity: N/A</td>
<td>Female: 20%</td>
<td>Age mean: 9.4 (1.7) for the ADHD group, 9.3 (1.6) for the ASD group, 9.4 (1.5) for the typically developing group; 10.11 (0.092) for replication sample, range 8-12</td>
</tr>
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</table>

**Index test 3:** Parental rating scale The Strengths and Weaknesses of ADHD symptoms and Normal-behaviors ratings scale (SWAN) hyperactivity/impulsivity subscale and the Social Responsiveness Scale restricted interests and repetitive behaviors, social awareness, social cognition, social commun
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| Parent rating | Duda, 2016<sup>239</sup>  
Case series  
N = 2925  
US  
Setting: Other | **Target:** Mainly siblings of the autism probands that reported a prior clinical diagnosis of ADHD; no documented diagnosis of autism  
**Other:** Children with autism and no comorbidity with ADHD  
**ADHD presentation:** N/A  
**Diagnosed by:** Unclear/NR  
**Comorbidity:** Autism: 95%  
**Female:** 37%  
**Age mean:** Median age range between the three different databases = 64.5-134.5 months  
**Min age: Max age:** | **Reference standard:** Clinical diagnosis  
Parent-reported clinical diagnosis  
**Timing:** Prior diagnosis  
**Index test:** Parent rating Social Responsiveness Scale, Support Vector Classification, 10-fold cross validation, classification of ADHD vs ASD  
**Sensitivity:** Specificity:  
**PPV:** NPV:  
**LR+: LR-:**  
**Accuracy:** | **Sensitivity:** 77  
**Specificity:** 74  
**PPV:**  
**NPV:**  
**LR+: LR-:**  
**Accuracy:** 71  
**AUC:**  
**Rater agreement:** |

<table>
<thead>
<tr>
<th><strong>Index text 4:</strong></th>
<th><strong>Index text 5:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Index text 2:</strong></td>
<td><strong>Index text 3:</strong></td>
</tr>
</tbody>
</table>
| **Sensitivity:**  
**Specificity:**  
**PPV:**  
**NPV:**  
**LR+: LR-:**  
**Accuracy:**  
**AUC:**  
**Rater agreement:**  
**Kappa:**  
**Internal consistency:**  
**Alpha:**  
**Costs:** |
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| Parent rating | Duda, 2017<sup>238</sup> Case series N = 422 US Setting: Mixed | **Target:** Selected the subset of responses from parents of children with only ADHD (n = 174) to serve as the survey sample; for this survey data set, diagnoses of ADHD were provided as parent report  
**Other:** Selected the subset of responses from parents of children with only ASD (n = 248) to serve as the survey sample, diagnoses of ASD were provided as parent report  
**ADHD presentation:** N/A  
**Diagnosed by:** Unclear/NR  
**Comorbidity:** N/A | **Reference standard:** Other Survey sample: diagnoses of ASD or ADHD were provided as parent report. Archival data set: diagnoses of ASD were physician-confirmed and diagnoses of ADHD were reported as part of an extensive family medical history. **Timing:** Prior diagnosis  
**Index test:** Parent rating Subset of items from the Social Responsiveness Scale (SRS). Best AUC obtained with Elastic Net and Linear discriminant analysis classifiers. Machine-learning pipeline consisted of three | **Index test 3:**  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy:  
AUC:  
Rater agreement:  
**Index text 4:**  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
AUC:  
**Index text 5:** |
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<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female: 34.5%</td>
<td>trials using subsamples of archival data, survey data, or a mixture of both. Model used to discriminate between ADHD and ASD</td>
<td>Sensitivity: Specificity: PPV: NPV: LR+: LR-: Accuracy: AUC: 0.89 ADHD versus ASD</td>
<td>Costs:</td>
</tr>
<tr>
<td></td>
<td>Min age: Max age:</td>
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<tr>
<td></td>
<td>Ethnicity: Other info on race or ethnicity: N/A</td>
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</tbody>
</table>

**Index test 3:**
- Sensitivity:
- Specificity:
- PPV:
- NPV:
- LR+:
- LR-:
- Accuracy:
- AUC:
- Rater agreement:

**Index test 4:**
- Sensitivity:
- Specificity:
- PPV:
- NPV:
- AUC:

**Index test 5:**

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<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent rating</td>
<td>Ebosutani, 2010&lt;sup&gt;245&lt;/sup&gt; Case series N = 476 US Setting: Specialty care</td>
<td><strong>Target:</strong> Consecutively referred children and adolescents to two mental health clinics <strong>Other:</strong> Consecutively referred children and adolescents to two mental health clinics <strong>ADHD presentation:</strong> inattentive: 34, hyperactive: 2, combined: 45, N/A: ADHD-not otherwise specified 19% <strong>Diagnosed by:</strong> Specialist <strong>Comorbidity:</strong> N/A <strong>Female:</strong> % 32.8% female in entire sample <strong>Age mean:</strong> 11.4 (2.5) <strong>Min age:</strong> 6 <strong>Max age:</strong> 18 <strong>Ethnicity:</strong> Other info on race or ethnicity: N/A</td>
<td><strong>Reference standard:</strong> Clinical diagnosis Children's Interview for Psychiatric Syndromes, Parent Version (P-ChIPS) <strong>Timing:</strong> Concurrent <strong>Index test:</strong> Parent rating Child Behavior Checklist (CBCL) DSM-oriented ADHD Problems scale, ADHD vs No ADHD <strong>Sensitivity:</strong> <strong>Specificity:</strong> <strong>PPV:</strong> <strong>NPV:</strong> <strong>LR+:</strong> <strong>LR-:</strong> <strong>Accuracy:</strong> <strong>AUC:</strong> 0.75 <strong>Rater agreement:</strong> <strong>Kappa:</strong> <strong>Internal consistency:</strong> <strong>Alpha:</strong> <strong>Test-retest:</strong> <strong>Costs:</strong></td>
<td><strong>Index test 2:</strong> Parental rating scale Child Behavior Checklist (CBCL) Attention Problems syndrome scale, ADHD vs No ADHD <strong>Sensitivity:</strong> <strong>Specificity:</strong> <strong>PPV:</strong> <strong>NPV:</strong> <strong>LR+:</strong> <strong>Accuracy:</strong> <strong>AUC:</strong> 0.76 <strong>Rater agreement:</strong> <strong>Kappa:</strong> <strong>Internal consistency:</strong> <strong>Alpha:</strong> <strong>Costs:</strong></td>
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</table>
### Appendix C. Evidence Tables

#### Index Type

<table>
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<th>Study:</th>
<th>Population:</th>
<th>Results:</th>
<th>Additional index tests</th>
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</thead>
<tbody>
<tr>
<td>Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
<td>Sensitivity; Specificity; PPV; NPV; AUC: Index text 5:</td>
</tr>
</tbody>
</table>
| **Parent rating** | **Target:** Consecutive referrals to an ADHD evaluation and treatment program located in a university-affiliated pediatric hospital diagnosed with ADHD **Other:** Consecutive referrals to an ADHD evaluation and treatment program located in a university-affiliated pediatric hospital not diagnosed with ADHD **ADHD presentation:** inattentive: 24, hyperactive: 6, hyperactive_other: hyperactive presentation not included in analysis, combined: 48 **Diagnosed by:** Specialist **Comorbidity:** N/A **Female:** % 21% female in entire sample **Age mean:** 8.7 (1.7) **Min age:** 6 **Max age:** 13 **Ethnicity:** % Hispanic or Latino: 3 % Black/African American: 21 | **Reference standard:** Clinical diagnosis Diagnostic Interview for Children and Adolescents-Revised-Parent Version and Attention Problems subscale of the Teacher's Report Form Timing: Concurrent **Index test:** Parent rating Devereux Scales of Mental Disorders (DSMD) Attention subscale; children with any presentation of ADHD versus controls, cutoff T>=65 **Sensitivity:** 77 **Specificity:** 78 **PPV:** 95 **NPV:** 39 **LR+:** **LR-:** **Accuracy:** **AUC:** | **Index test 2:** Parental rating scale Child Behavior Checklist (CBCL) Attention Problems subscale; children with any presentation of ADHD versus controls, cutoff T>=70 **Sensitivity:** 51 **Specificity:** 83 **PPV:** 94 **NPV:** 24 **LR+:** **Accuracy:** **AUC:** **Rater agreement:** Kappa: **Internal consistency:** Alpha: **Costs:** | **Index test 3:**

---

Eiraldi, 2000 | 248 | 21% female in entire sample | 21% female in entire sample | 8.7 (1.7) | 6 to 13 | Hispanic or Latino: 3 | Black/African American: 21 | Devereux Scales of Mental Disorders (DSMD) Attention subscale; children with any presentation of ADHD versus controls, cutoff T>=65 | Parent rating Devereux Scales of Mental Disorders (DSMD) Attention subscale; children with any presentation of ADHD versus controls, cutoff T>=70 | Parent rating Devereux Scales of Mental Disorders (DSMD) Attention subscale; children with any presentation of ADHD versus controls, cutoff T>=70 |

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## Appendix C. Evidence Tables

| Index Type | Study: Elkins, 2014<sup>251</sup>  
Case series  
N = 46  
US  
Setting: Specialty care | Population:  
% White: 76  
Other info on race or ethnicity: | Results:  
Reference standard: Clinical diagnosis  
Diagnosed with ADHD per DSM-IV-R  
Timing: Prior diagnosis | Additional index tests | Additional index tests

| | Target: Children and adolescents with generalized anxiety disorder and diagnosed ADHD; those exhibiting symptoms of thought disorders, pervasive developmental disorders, organic brain syndromes, intellectual disabilities, or suicidal ideation were excluded  
Other: Children with generalized anxiety disorder and symptoms of inattention but no ADHD diagnosis  
ADHD presentation: N/A  
Diagnosed by: Specialist  
Comorbidity: Mood disorder  
Female: 54% | Internal consistency:  
Alpha:  
Test-retest:  
Costs:  
Misdiagnosis:  
Labeling:  
Costs: | Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy:  
AUC:  
Rater agreement:  
Index text 4:  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
AUC:  
Index text 5: | | |
### Parent rating

<table>
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<tr>
<th>Study</th>
<th>Population</th>
<th>Results</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gardner, 2007&lt;sup&gt;285&lt;/sup&gt;</td>
<td>Target: Children and adolescents diagnosed with ADHD who consecutively presented at primary care offices for well-child care, the evaluation of recurrent abdominal pain, or the assessment and management of other minor illnesses. Participants selected into one of two studies based on positive screening results for the conditions of interest for each study. Sample includes more children with psychosocial problems, particularly anxiety and depression, than would be found in an unselected primary care sample.</td>
<td>Reference standard: Clinical diagnosis Schedule for affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL) Timing: Concurrent</td>
<td>Index test 2: Parental rating scale Child Behavior Checklist (CBCL) Attention subscale Sensitivity: 68 Specificity: 90 PPV: 26 NPV: 98 LR+: Accuracy: AUC: 0.88 Rater agreement:</td>
</tr>
<tr>
<td>Parent rating</td>
<td>Age mean: 12.03 (3.3) Min age: 7 Max age: 18 Ethnicity: % White : 80.4 Other info on race or ethnicity:</td>
<td>LR-: Accuracy: 82.6 Overall Correct Classification AUC: 0.84 SE 0.06 Rater agreement: Kappa: ICC: Internal consistency: Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
<td>Index test 3: Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement:</td>
</tr>
<tr>
<td>Gardner, 2007&lt;sup&gt;285&lt;/sup&gt;</td>
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<tr>
<td>Parent rating</td>
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<tr>
<td>Gardner, 2007&lt;sup&gt;285&lt;/sup&gt;</td>
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<th>Additional index tests</th>
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<tbody>
<tr>
<td></td>
<td>Author, year; Multiple publications; Study design; Study size; Location</td>
<td><strong>Index test 3:</strong></td>
<td>Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
<td></td>
</tr>
<tr>
<td><strong>Other:</strong></td>
<td>Children and adolescents not diagnosed with ADHD from same recruitment and selection process as ADHD participants</td>
<td>ADHD presentation: N/A</td>
<td>NPV: 98 5% prevalence LR+: LR-: Accuracy: AUC: 0.86 Rater agreement: Kappa: ICC: Internal consistency: Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
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<tr>
<td></td>
<td><strong>ADHD presentation:</strong> N/A</td>
<td>Diagnosed by: Researcher</td>
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<tr>
<td></td>
<td><strong>Comorbidity:</strong> N/A</td>
<td>Comorbidity:</td>
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<tr>
<td></td>
<td><strong>Female:</strong> %</td>
<td>Female:</td>
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</tr>
<tr>
<td></td>
<td>53% female in entire sample</td>
<td>53% female in entire sample</td>
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<tr>
<td></td>
<td><strong>Age mean:</strong> 8.1 (2.1)</td>
<td>Age mean: 8.1 (2.1)</td>
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<tr>
<td></td>
<td><strong>Min age:</strong> 8 <strong>Max age:</strong> 15</td>
<td>Min age: 8 Max age: 15</td>
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<tr>
<td></td>
<td><strong>Ethnicity:</strong></td>
<td>Ethnicity:</td>
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<tr>
<td></td>
<td>% Black/African American: 6</td>
<td>% Black/African American: 6</td>
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<tr>
<td></td>
<td>% White: 90</td>
<td>% White: 90</td>
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<td>Other info on race or ethnicity: Other: 4</td>
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### Appendix C. Evidence Tables

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<th>Study Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gargaro, 2014&lt;sup&gt;287&lt;/sup&gt; Case series N = 49 Australia Setting: N/A</td>
<td><strong>Target:</strong> Children with ADHD (N = 13) or ADHD plus autism (N = 12). Participants were excluded if they had previously experienced the following conditions: comorbid medical (e.g. tuberous sclerosis), hearing or visual, neurological (e.g. Epilepsy), psychiatric (e.g. Tourette’s, Conduct Disorder, Oppositional Defiant Disorder) or genetic disorders (e.g. Fragile X disorder), other than the primary diagnoses of autism and/or ADHD. <strong>Other:</strong> Children with autism alone (N = 12) or neurotypical (N = 12) <strong>ADHD presentation:</strong> combined : 100 <strong>Diagnosed by:</strong> Specialist <strong>Comorbidity:</strong> <strong>Female:</strong> 18.4% All 12 children with comorbid autism and ADHD were male <strong>Age mean:</strong> 11.2 (3.6) Autism 11.3 (3.6); ADHD 10.9 (3.2); comorbid autism and ADHD 11.1 (3.9); neurotypical 11.4 (3.6) <strong>Min age:</strong> 6 <strong>Max age:</strong> 18 <strong>Ethnicity:</strong> Other info on race or ethnicity: N/A</td>
<td><strong>Reference standard:</strong> Clinical diagnosis Diagnosed with ADHD per DSM IV TR Timing: Prior diagnosis <strong>Index test:</strong> Parent rating Developmental Behaviour Checklist Hyperactivity Index (DBC-HI), parent version, cut point = 4 Sensitivity: 100 Sensitivity for differentiating ADHD + autism from autism alone = 83.3% for cut point at 7 Specificity: 92 Specificity for differentiating ADHD + autism from autism alone = 50.0% for cut point at 7 <strong>PPV:</strong> <strong>NPV:</strong> <strong>LR+:</strong> <strong>Accuracy:</strong> AUC: 0.997 AUC 0.722 (CI .507–.937) for discriminating autism + ADHD from autism alone <strong>Rater agreement:</strong> <strong>Kappa:</strong> <strong>Internal consistency:</strong> Alpha: 0.931 <strong>Test-retest:</strong> <strong>Costs:</strong></td>
<td><strong>Index test 2:</strong> Parental rating scale Conner’s Parent Rating Scale-Revised Short Form (CPRS-RS) Sensitivity: 100 Sensitivity for differentiating autism + ADHD from autism alone = 75% for cut point score of 72 Specificity: 92 Specificity for differentiating autism + ADHD from autism alone = 67% for cut point score of 72 <strong>PPV:</strong> <strong>NPV:</strong> <strong>LR+:</strong> <strong>Accuracy:</strong> AUC: 0.994 AUC 0.782 (CI 0.596–0.979) for discriminating autism + ADHD from autism alone <strong>Rater agreement:</strong> <strong>Kappa:</strong> <strong>Internal consistency:</strong> Alpha: <strong>Costs:</strong></td>
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## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study:</th>
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<th>Results:</th>
<th>Additional index tests</th>
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<tbody>
<tr>
<td>Parent rating</td>
<td>Gomez, 2018⁵⁹⁹</td>
<td>Target: Archival records of patients referred to an outpatient psychiatric unit between 2008 and 2016</td>
<td>Reference standard: Clinical diagnosis DSM-IV TR Timing: Prior diagnosis</td>
<td>NPV:</td>
</tr>
<tr>
<td></td>
<td>Cohort study</td>
<td>ADHD presentation: inattentive: 28.3, hyperactive: 6.7, combined: 65.0</td>
<td>Index test: Parent rating Modified version of the Strengths and Weaknesses of ADHD-Symptoms and Normal Behavior (SWAN-M) Scale, all maternal ratings, test-retest study of measurement invariance over a 12-month interval</td>
<td>LR+:</td>
</tr>
<tr>
<td></td>
<td>Australia</td>
<td>Comorbidity: N/A Female: 22.5% Age mean: N/A</td>
<td></td>
<td>AUC:</td>
</tr>
<tr>
<td></td>
<td>Setting: Specialty care Min age: 7 Max age: 17 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Rater agreement:</td>
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<td>Index test 3: Sensitivity:</td>
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<tr>
<td>Index Type</td>
<td>Study: Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
<td>Additional index tests</td>
</tr>
<tr>
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<td>--------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------</td>
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<tr>
<td></td>
<td>AUC: Rater agreement: Kappa: ICC: Internal consistency: Internal consistency coefficient alpha values were .89, .89, .92 for the IA and HI and combined (IA plus HI) scales, respectively, at Time 1; and 77, .80, .79, respectively, for Time 2 Alpha: 12 months apart Test-retest: Test-retest measurement invariance not reliability was tested Costs: Misdiagnosis: For the bifactor model, measurement invariance testing using multiple-group confirmatory factor analysis (CFA) indicated support for configural and full scalar test-retest invariance when the chi-square difference test was applied. Labeling: Costs:</td>
<td>Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement:</td>
<td>Index text 4: Sensitivity: Specificity: PPV: NPV: AUC:</td>
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Index text 5:
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<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent rating</td>
<td>Hong, 2019&lt;sup&gt;126&lt;/sup&gt; Case series N = 44 US Setting: Specialty care</td>
<td>Target: Children presenting to university affiliated outpatient clinics with early disruptive behavior problems diagnosed with ADHD+ disruptive behavior disorder <strong>Other</strong>: Children presenting to university affiliated outpatient clinics with early disruptive behavior problems not diagnosed with ADHD (diagnosed with disruptive behavior disorder only) <strong>ADHD presentation</strong>: hyperactive : 57.1, combined : 42.9 <strong>Diagnosed by</strong>: Specialist <strong>Comorbidity</strong>: ODD : 95.5% ODD, 25% CD <strong>Female</strong>: 20.5% <strong>Age mean</strong>: 4.61 (0.87) <strong>Min age</strong>: 3 <strong>Max age</strong>: 5 <strong>Ethnicity</strong>: % Hispanic or Latino : 29.4 % Black/African American : 4.5 % Asian : 2.3 % White : 56.8 % Multiracial : 4.5, Other : Defined by Other Other info on race or ethnicity:</td>
<td><strong>Reference standard</strong>: Clinical diagnosis Kiddie-Disruptive Behavior Disorders Schedule (K-DBDS) by supervised by a licensed clinical psychologist and diagnoses were confirmed through consensus <strong>Timing</strong>: Concurrent <strong>Index test</strong>: Parent rating Child Behavior Checklist for ages 1.5 to 5 Attention-Deficit/Hyperactivity Problems scale <strong>Sensitivity</strong>: 71 <strong>Specificity</strong>: 91 <strong>PPV</strong>: 88 <strong>NPV</strong>: 78 <strong>LR+</strong>: 80 <strong>LR-</strong>: 0.83 <strong>Accuracy</strong>: 80 <strong>AUC</strong>: 0.83 <strong>Rater agreement</strong>: Kappa: <strong>Internal consistency</strong>: Alpha: <strong>Test-retest</strong>: Costs: <strong>Misdiagnosis</strong>: <strong>Labeling</strong>: <strong>Costs</strong>:</td>
<td><strong>Index test 2</strong>: Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement: Kappa: Internal consistency: Alpha: Costs: <strong>Index test 3</strong>: Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement: <strong>Index test 4</strong>: Sensitivity: Specificity: PPV: NPV: AUC:</td>
</tr>
</tbody>
</table>
### Appendix C. Evidence Tables

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<tr>
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<th>Population: Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent rating</td>
<td>Hudziak, 2004 Case series N = 370 US Setting: Mixed</td>
<td><strong>Target:</strong> Probands participating in a family genetic study of attention and aggressive behavior problems; lives with at least one biological parent, has at least one sibling between ages 6 and 18, IQ &gt;= 70, T-scores above 67 on the attention problems syndrome and/or the aggressive behavior syndrome scales of the Child Behavior Checklist  <strong>Other:</strong> Probands with T-scores below 60 on both the attention problems syndrome and the aggressive behavior syndrome scales of the Child Behavior Checklist; randomly selected siblings of probands (one sibling from each family) used as cross validation sample  <strong>ADHD presentation:</strong> N/A  <strong>Diagnosed by:</strong> Specialist  <strong>Comorbidity:</strong> N/A  <strong>Female:</strong> % 42% female in entire sample  <strong>Age mean:</strong> 6  <strong>Min age:</strong> 6  <strong>Max age:</strong> 18</td>
<td><strong>Reference standard:</strong> Clinical diagnosis Vermont Structured Diagnostic interview with mothers of the probands and siblings  <strong>Timing:</strong> Prior diagnosis  <strong>Index test:</strong> Parent rating Child Behavior Checklist (CBCL) attention problems scale, T-score cutoff = 55, ROC analysis using attention problems syndrome scale  Sensitivity: 83 Sibling group  Specificity: 88 Sibling group  PPV: 80 Sibling group  NPV: 90 Sibling group  LR+:  LR-:  Accuracy: AUC: 0.841 for proband group, 0.904 for sibling group  Rater agreement: Kappa:</td>
<td><strong>Index test 2:</strong>  <strong>Sensitivity:</strong>  <strong>Specificity:</strong>  <strong>PPV:</strong>  <strong>NPV:</strong>  <strong>LR+:</strong>  <strong>Accuracy:</strong>  <strong>AUC:</strong>  <strong>Rater agreement:</strong>  <strong>Kappa:</strong>  <strong>Internal consistency:</strong>  <strong>Alpha:</strong>  <strong>Costs:</strong>  <strong>Index test 3:</strong>  <strong>Sensitivity:</strong>  <strong>Specificity:</strong>  <strong>PPV:</strong>  <strong>NPV:</strong>  <strong>LR+:</strong>  <strong>Accuracy:</strong>  <strong>Index test 5:</strong></td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| Parent rating | Jacobson, 2020\(^{1,3,5}\) Case series N = 787 US Setting: Specialty care | **Target:** Youth referred for outpatient neuropsychological assessment in a large outpatient neuropsychology clinic  
**Other:** Non-ADHD clinical comparison group; part of same referral process as ADHD group  
**ADHD presentation:** inattentive: 50, hyperactive: 10, combined: 40  
**Diagnosed by:** Specialist  
**Comorbidity:** N/A  
**Female:** % 37.5% in entire sample  
**Age mean:** 11.29 (3.15), 8.71 (2.68), 9.65 (2.88) across groups  
**Min age:** 5  
**Max age:** 18  
**Ethnicity:**  
% Hispanic or Latino: 2.25  
% Black/African American: 24.46 | **Reference standard:** Clinical diagnosis Categorized using modified Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5) ADHD symptom criteria, including caregiver-report symptom count on the ADHD Rating Scale-IV after neuropsychological assessment in a large outpatient neuropsychology clinic  
**Timing:** Concurrent  
**Index test:** Parent rating Behavior Rating Inventory of Executive Function, Second Edition (BRIEF2) global executive composite summary score  
Sensitivity: 38  
Specificity: 96  
PPV: 93  
NPV: 54  
LR+:  
LR-:  
Accuracy: 63 | **Index test 2:**  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy:  
AUC:  
Rater agreement:  
Kappa:  
Internal consistency:  
Alpha:  
Costs:  
**Index test 3:**  
Sensitivity:  
Specificity:  
PPV:  
NPV:  |
| **Ethnicity:** Other info on race or ethnicity: N/A | **ICC:**  
Internal consistency:  
Alpha:  
Test-retest:  
Costs:  
Misdiagnosis:  
Labeling:  
Costs:  | **AUC:**  
Rater agreement:  
Index text 4:  
Sensitivity:  
Specificity:  
PpV:  
NPV:  
AUC:  | **Index text 5:**  
Sensitivity:  
Specificity:  
PpV:  
NPV:  
AUC:  
Rater agreement:  
Kappa:  
Internal consistency:  
Alpha:  
Costs:  |
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</tr>
</thead>
<tbody>
<tr>
<td>Parent rating</td>
<td>Jensen-Doss, 2013</td>
<td>Study:</td>
<td>Target: Children presenting for treatment at county community mental health clinics in Texas; recruitment took place through the mental health authority’s Eligibility Center (EC), a clinic where all new clients are screened for service eligibility. <strong>Other:</strong> Children presenting for treatment at county community mental health clinics in Texas; recruitment took place through the mental health authority’s Eligibility Center (EC), a clinic where all new clients are screened for service eligibility. <strong>ADHD presentation:</strong> inattentive: 4, combined: 74, N/A: ADHD-not otherwise specified 22%. <strong>Diagnosed by:</strong> Provider. <strong>Comorbidity:</strong> N/A. <strong>Female:</strong> %</td>
<td>Reference standard: Clinical diagnosis. 15 clinicians conducted the initial eligibility evaluations for the clients; Four of them were licensed mental health professionals, five were interns, and six were called “Qualified Mental Health Professionals” by the state, representing individuals with experience in the state. <strong>Index test:</strong> Parent rating Child Behavior Checklist Attention deficit/ hyperactivity problems subscale.</td>
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<td></td>
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<td>Setting: Community</td>
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<td>Setting:</td>
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<td>Location:</td>
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<tr>
<td></td>
<td></td>
<td>% Asian: 2.3</td>
<td>AUC: 0.806</td>
<td>LR+:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% White: 59.63</td>
<td>Rater agreement:</td>
<td>Accuracy:</td>
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<tr>
<td></td>
<td></td>
<td>% Multiracial: 5.45</td>
<td>Kappa:</td>
<td>AUC:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other info on race or ethnicity: Other: 4.8% unknown</td>
<td>ICC:</td>
<td>Rater agreement:</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Internal consistency: Alpha: 0.965</td>
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<td>Test-retest:</td>
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<td>Costs:</td>
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<td>Misdiagnosis:</td>
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</table>

## Additional index tests

**Index text 4:**
- Sensitivity: 
- Specificity: 
- PPV: 
- NPV: 
- AUC: 

**Index text 5:**
- Sensitivity: 
- Specificity: 
- PPV: 
- NPV: 
- AUC: 

**Index test 2:**
- Sensitivity: 
- Specificity: 
- PPV: 
- NPV: 
- LR+: 
- Accuracy: 
- AUC: 

**Index test 3:**
- Sensitivity: 
- Specificity: 

---

The table above provides a detailed overview of the evidence tables, including study design, population characteristics, and results. The data includes information on study authors, years, multiple publications, study design, study size, location, population setting, study target, ADHD presentation, diagnosis, comorbidity, percentage of females, age mean, minimum age, maximum age, ethnicity, reference standard, index test, diagnostic accuracy, rater agreement, and other outcomes. Additional index tests are also mentioned, along with their respective accuracy metrics.
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent rating</td>
<td>Levy, 2017&lt;sup&gt;2&lt;/sup&gt; Case series N = 139 US Setting: Specialty care</td>
<td>Target: Validation sample consisted of consecutive patients seen in a comprehensive psychological testing clinic (for cognitive and/or personality assessment) over approximately an 8-year period of time Other: Children without ADHD, part of same referral and selection process as ADHD group, diagnosed with other disorders such as ODD, CD, anxiety disorder, or depressive disorder ADHD presentation: inattentive_other : 42, combined_other : 36 Diagnosed by: Specialist Comorbidity: N/A Female: %</td>
<td>Reference standard: Clinical diagnosis SI-4 scores for parent and teacher Timing: Prior diagnosis Index test: Parent rating Conduct-Hyperactive-Attention Problem-Oppositional Symptom (CHAOS) scale parent. Subscales include attention problems, hyperactivity-impulsivity, oppositional behavior, and conduct problems. Sensitivity: Specificity: PPV: NPV:</td>
<td>Index test 2: Teacher rating scale Conduct-Hyperactive-Attention Problem-Oppositional Symptom (CHAOS) scale teacher. Subscales include attention problems, hyperactivity-impulsivity, oppositional behavior, and conduct problems. Sensitivity: Specificity: PPV: NPV:</td>
</tr>
</tbody>
</table>
### Appendix C. Evidence Tables

#### Index Type

<table>
<thead>
<tr>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>41% female in entire validation sample</td>
<td>LR+: LR-: Accuracy: AUC: Rater agreement: Mother versus father rating Ranged from 0.58 to 0.63 over three subscales, the fourth subscale, conduct problems, interrater agreement was not statistically significant Kappa: ICC: Internal consistency: Cronbach's alpha ranged from 0.80 to 0.91 over four subscales Alpha: Test-retest between 1 and 829 days Test-retest: Ranged from 0.74 to 0.87 over four subscales Costs: Misdiagnosis: Labeling: Costs:</td>
<td>Accuracy: AUC: Rater agreement: Teacher versus parent rating Ranged from 0.28 to 0.41 over three subscales. The fourth subscale, oppositional behavior, was only marginally statistically significant (r=0.17, p&lt;0.1) Kappa: Internal consistency: Cronbach's alpha ranged from 0.64 to 0.91 over four subscales Alpha: Costs:</td>
<td></td>
</tr>
</tbody>
</table>

#### Index text 3:

- Sensitivity:
- Specificity:
- PPV:
- NPV:
- LR+:
- Accuracy:
- AUC:
- Rater agreement:

#### Index text 4:

- Sensitivity:
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| Parent rating | Mayfield, 2018<sup>411</sup> Case series N = 337 US Setting: Other | **Target:** Children with no co-morbid intellectual disability, pervasive developmental disorder, or history of neurological disorder including seizures, convulsions, epilepsy, cerebral palsy, encephalitis, traumatic brain injury, and loss of consciousness, and a standardized rating scale for the assessment of ADHD symptoms was completed by both the mother and the father  
**Other:** None; study comparing mother and father ratings  
**ADHD presentation:** inattentive: 62.9, combined: 37.1  
**Diagnosed by:** Unclear/NR  
**Comorbidity:** N/A  
**Female:** 27.9%  
**Age mean:** 10.3 (2.83)  
**Min age:** 6  
**Max age:** 16  
**Ethnicity:** Other info on race or ethnicity: N/A | **Reference standard:** Clinical diagnosis DSM-IV diagnosis of ADHD  
**Timing:** Concurrent  
**Index test:** Parent rating DSM-ADHD-SRS (symptom rating scale) total score mother rating  
**Sensitivity:**  
**Specificity:**  
**PPV:**  
**NPV:**  
**LR+:**  
**LR-:**  
**Accuracy:**  
**AUC:**  
**Rater agreement:** DSM-ADHD-SRS (symptom rating scale) mother-rating versus father-rating  
Mother and father ratings (ICC) correlated .51 for inattention, .56 for hyperactivity, and .58 for impulsivity  
**Kappa:**  
**Index test 2:** Parent rating DSM-ADHD-SRS (symptom rating scale) total score father rating  
**Sensitivity:**  
**Specificity:**  
**PPV:**  
**NPV:**  
**LR+:**  
**LR-:**  
**Accuracy:**  
**AUC:**  
**Rater agreement:** Kappa  
**Internal consistency:**  
**Alpha:** 0.91  
**Costs:**  | **Specificity:**  
**PPV:**  
**NPV:**  
**AUC:**  
**Index test 5:** |
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: McCarthy, 2016&lt;sup&gt;14&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case series</td>
</tr>
<tr>
<td></td>
<td>N = 1622</td>
</tr>
<tr>
<td></td>
<td>US</td>
</tr>
<tr>
<td></td>
<td>Setting: Specialty care</td>
</tr>
</tbody>
</table>

**Target:** Youth who entered outpatient treatment and who had ADHD as their DSM-IV Axis I primary or secondary diagnosis  
**Other:** Patients who had at least one psychiatric DSM-IV diagnosis at the time of their intake interview, but whose diagnosis/diagnoses did not include ADHD  
**ADHD presentation:** N/A  
**Diagnosed by:** Specialist  
**Comorbidity:** N/A  
**Female:** 33.6%  
**Age mean:** 10.51 (3.75) for ADHD group, 11.46 (4.10) for non-ADHD group  
**Min age:** 3 Max age: 17

<table>
<thead>
<tr>
<th>Population:</th>
<th>Setting: Specialty care</th>
</tr>
</thead>
</table>
|             | Target: Youth who entered outpatient treatment and who had ADHD as their DSM-IV Axis I primary or secondary diagnosis  
|             | Other: Patients who had at least one psychiatric DSM-IV diagnosis at the time of their intake interview, but whose diagnosis/diagnoses did not include ADHD  
|             | ADHD presentation: N/A  
|             | Diagnosed by: Specialist  
|             | Comorbidity: N/A  
|             | Female: 33.6%  
|             | Age mean: 10.51 (3.75) for ADHD group, 11.46 (4.10) for non-ADHD group  
|             | Min age: 3 Max age: 17

| Results: | Reference standard: Clinical diagnosis ADHD as primary or secondary DSM-IV Axis I diagnosis. Clinician-completed Brief Psychiatric Rating Scale for Children (BPRS-C) and Children's Global Assessment Scale (CGAS), consists of 21 distinct symptoms, each rated for severity on a 7-point Likert-type scale.  
|          | Timing: Concurrent  
|          | Index test: Parent rating The Pediatric Symptom Checklist (PSC) Attention Subscale parent-completed measure of child and adolescent psychosocial functioning  
|          | Sensitivity: 55  
|          | Specificity: 81

| Additional index tests | ICC:  
|                       | Internal consistency: Alpha: 0.90  
|                       | Test-retest: Costs:  
|                       | Misdiagnosis: Labeling: Costs:  
|                       | PPV:  
|                       | NPV:  
|                       | LR+:  
|                       | Accuracy: AUC: Rater agreement:  
|                       | Index text 4: Sensitivity: Specificity: PPV: NPV: AUC:  
|                       | Index text 5:  

|              | Internal consistency: Alpha: Costs:  
|              | Index test 3:  

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<table>
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</tr>
</thead>
</table>
| Parent rating | McIntosh, 1995<sup>17</sup> Case series N = 265 US Setting: School | **Target:** Selected from two suburban public school districts, no other medical problems (i.e. Tourettes, seizures, cerebral palsy, mental retardation), not adopted  
**Other:** Randomly selected neurotypical children who were in regular education classrooms and were not receiving remedial or special education services  
**ADHD presentation:** N/A  
**Diagnosed by:** Specialist | **Reference standard:** Clinical diagnosis  
Diagnosed by physicians and licensed psychologists and verified by the investigators through school health and testing records  
**Timing:** Prior diagnosis | **Index test 2:**  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy:  
AUC:  
Rater agreement: |

### Parent rating

| McIntosh, 1995<sup>17</sup> Case series N = 265 US Setting: School | PPV:  
NPV:  
LR+:  
LR−:  
Accuracy:  
AUC:  
Rater agreement: Kappa:  
ICC:  
Internal consistency:  
Alpha: 0.90  
Test-retest:  
BPRS-C-PE and PSC-AS correlated 0.56 at intake and 0.53 at a 3-month follow up appointment.  
Costs:  
Misdiagnosis:  
Labeling:  
Costs: | Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy:  
AUC:  
Rater agreement: | **Index text 4:**  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
AUC:  
Rater agreement: |

### Index text 5:

**McIntosh, 1995**

417

Case series

N = 265

US

Setting: School

**Target:** Selected from two suburban public school districts, no other medical problems (i.e. Tourettes, seizures, cerebral palsy, mental retardation), not adopted

**Other:** Randomly selected neurotypical children who were in regular education classrooms and were not receiving remedial or special education services

**ADHD presentation:** N/A

**Diagnosed by:** Specialist

**Reference standard:** Clinical diagnosis  
Diagnosed by physicians and licensed psychologists and verified by the investigators through school health and testing records  
**Timing:** Prior diagnosis

**Index test:** Parent rating The Maternal Perinatal Scale consisting of questions and a condition checklist  

**Index test 2:**  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy:  
AUC:  
Rater agreement:
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<tbody>
<tr>
<td></td>
<td>Female: 15%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age mean: 9.6 (1.6) for the ADHD group, 10.4 (1.7) for the undifferentiated ADD group, 9.5 (1.8) for the neurotypical group</td>
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<td></td>
<td>Min age: 6 Max age: 13</td>
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<td></td>
<td>Ethnicity: % Black/African American : 1 % White : 94 Other info on race or ethnicity: Other : 5% Other</td>
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<th>Results</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| Parent rating | Mouti, 2019\(^{435}\) Case series N = 162 Australia Setting: Mixed | **Target:** Children with ADHD and children with dual diagnoses of ADHD and autism spectrum disorder, IQ above 70  **Other:** Children with autism spectrum disorder severity levels 1 and/or 2 and typically developing children  **ADHD presentation:** N/A  **Diagnosed by:** Specialist  **Comorbidity:** Autism: 29 with dual diagnosis  **Female:** 10.8%  **Age mean:** 11.27 (3.28)  **Min age:** 6  **Max age:** 17  **Ethnicity:** Other info on race or ethnicity: N/A | **Reference standard:** Clinical diagnosis ADHD group provided documentation of their diagnosis that included evidence of pediatric/psychiatric assessment using DSM criteria  **Timing:** Prior diagnosis  **Index test:** Parent rating Social Communication Questionnaire- Lifetime version, total score cutoff of 13 to differentiate between autism spectrum disorder and ADHD  **Sensitivity:** 96% autism spectrum disorder vs ADHD groups  **Specificity:** 87% autism spectrum disorder vs ADHD groups  **PPV:**  **NPV:**  **LR+:**  **LR-:**  **Accuracy:**  **AUC:** AUC 0.96 (0.91, 1.0) autism spectrum disorder vs ADHD groups  **Rater agreement:** Kappa:  **Internal consistency:** Alpha: | **Index test 2:**  **Sensitivity:**  **Specificity:**  **PPV:**  **NPV:**  **LR+:**  **Accuracy:**  **AUC:**  **Rater agreement:** Kappa:  **Internal consistency:** Alpha:  **Costs:**  **Index test 3:**  **Sensitivity:**  **Specificity:**  **PPV:**  **NPV:**  **LR+:**  **Accuracy:**  **AUC:**  **Rater agreement:**  **Index test 4:**  **Sensitivity:**  **Specificity:**  **PPV:**  **NPV:**  **AUC:**
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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent rating</td>
<td>Mukherjee, 2014&lt;sup&gt;436&lt;/sup&gt; Case series N = 156 India Setting: Specialty care</td>
<td>Target: Recruited from the Child Development/Neurology outpatient clinics Other: Children with various Neurodevelopmental Disorders were recruited from the Child Development/Neurology outpatient clinics; those with typical development were recruited from the pediatric outpatient departments. ADHD presentation: inattentive: 46, hyperactive: 19, combined: 35 Diagnosed by: Specialist Comorbidity: N/A Female: % 31% female in entire sample Age mean: 7.4 (0.99) Min age: 6 Max age: 9 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Reference standard: Clinical diagnosis Each child was assessed by a two member expert team (pediatric neurologist and child psychiatrist) who based their diagnosis on DSM-IV-TR criteria comprising interviews and direct observations; each evaluator was blinded to original diagnosis and to the a Timing: Concurrent Index test: Parent rating INCLEN Diagnostic Tool for ADHD (INDT-ADHD); ADHD versus typically developing children Sensitivity: 88 (81, 89) Specificity: 97 (87, 100) PPV: 98 NPV: 83 LR+: 31.5 LR-: 0.12 Accuracy: AUC: Rater agreement:</td>
<td>Index test 2: Parental rating scale INCLEN Diagnostic Tool for ADHD (INDT-ADHD); ADHD versus other neurodevelopmental disorders Sensitivity: 88 (79, 94) Specificity: 43 (35, 49) PPV: 58 NPV: 79 LR+: Accuracy: AUC: Rater agreement: Kappa: Internal consistency: Alpha: Costs: Index test 3: Parental rating scale INCLEN Diagnostic Tool</td>
</tr>
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</table>
### Appendix C. Evidence Tables

<table>
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<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
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</thead>
</table>
| Parent rating Mulhern, 1994<sup>433</sup> Post-only N = 245 US Setting: N/A | **Target:** Children consecutively referred to a university hospital-based pediatric practice between 1981 and 1992 for school related learning and/or behavior problems diagnosed with ADHD  
**Other:** Children consecutively referred to a university hospital-based pediatric practice between 1981 and 1992 for school related learning and/or behavior problems not diagnosed with ADHD  
ADHD presentation: N/A  
Diagnosed by: Provider | Convergent validity with Conner’s Parents Rating Scale was moderate ($r =0.73$, $P=0.001$).  
Kappa:  
ICC:  
Internal consistency:  
Alpha: 0.91  
Test-retest:  
Costs:  
Misdiagnosis:  
Labeling:  
Costs: | for ADHD (INDT-ADHD); total score >=8  
Sensitivity: 88  
Specificity: 96  
PPV: 38  
NPV: 11  
LR+:  
Accuracy:  
AUC: 0.98  
Rater agreement:  
**Index text 4:**  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
AUC:  
**Index text 5:** |
### Appendix C. Evidence Tables

| Index Type | Study: 
| Author, year; Multiple publications; Study design; Study size; Location | Population: 
| Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity | Results: 
| Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes | Additional index tests |
| --- | --- | --- | --- | --- |
| Parent rating | Nolan, 1999[^1] 
Case series 
N = 222 
US Setting: Specialty care | **Target:** Consecutive referrals to a child psychiatry outpatient clinic; children and adolescents who received a diagnosis of ADHD and who exhibited some symptoms of ADHD, but the clinician was uncertain if all of the DSM-IV diagnostic criteria were met were included in the sample  
**Other:** | **Reference standard:** Clinical diagnosis 
Interviews with the care provider and child patient, informal observations of parent-child interaction, observations of the child in clinic-based simulated classrooms and in public school settings, review of school history, school reports, and psychoeduca 
Timing: Concurrent | **Index test 2:** Teacher rating scale 
Symptom Inventories- Teacher rating 
Sensitivity: Specificity: PPV: NPV: AUC: |
|  |  | **Comorbidity:** Other: Significant school-related problems were diagnosed in 92% of subjects  
**Female:** 19%  
**Age mean:** 8.1  
**Min age:** 4  
**Max age:** 15  
**Ethnicity:**  
% White: 92  
Other info on race or ethnicity: | **LR-:**  
**Accuracy:**  
**AUC:**  
**Rater agreement:**  
Kappa:  
**ICC:**  
**Internal consistency:**  
Alpha:  
**Test-retest:**  
Costs:  
**Misdiagnosis:**  
**Labeling:**  
Costs: | **Alpha:**  
**Costs:**  
**Index test 3:**  
**Sensitivity:**  
**Specificity:**  
**PPV:**  
**NPV:**  
**AUC:**  
**Rater agreement:** |
|  | Parent rating |  |  |  |
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<tbody>
<tr>
<td></td>
<td>Author, year; Multiple publications; Study design; Study size; Location</td>
<td>ADHD presentation: inattentive: 48, hyperactive: 10, combined: 42</td>
<td>Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
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<td></td>
<td>Diagnosed by: Specialist</td>
<td>Comorbidity: N/A</td>
<td>Index test: Parent rating Symptom Inventories- Parent rating</td>
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<td>Ethnicity: % Hispanic or Latino: 6 % Black/African American: 10 % White: 82</td>
<td>Other info on race or ethnicity: Other: 2% Other race</td>
<td>Rater agreement: Parent versus Teacher Kappa: Inattentive category 0.68, Hyperactive-impulsive category 0.42, Combined category 0.56 ICC: Internal consistency: Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
<td>Rater agreement:</td>
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**Index test 3:**
- Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement:

**Index test 4:**
- Sensitivity: Specificity: PPV: NPV: AUC: Rater agreement:

**Index test 5:**
- Sensitivity: Specificity: PPV: NPV: AUC: Rater agreement:
### Appendix C. Evidence Tables

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<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
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<tbody>
<tr>
<td>Parent rating</td>
<td>O’Neill, 2021(^{452}) Case series N = 70 US Setting: Specialty care</td>
<td>Target: Children with IQ of at least 70 and off-medication at least 24 h prior to testing, including children with ADHD plus prenatal alcohol exposure and familial ADHD without prenatal alcohol exposure; children in the ADHD without prenatal alcohol exposure group had to have one or more first-degree relatives with diagnosed ADHD Other: Typically developing controls; compared to the two ADHD groups separately ADHD presentation: N/A : Met DSM-V criteria for ADHD, any subtype Diagnosed by: Researcher Comorbidity: Other : ADHD+prenatal alcohol exposure Female: 33% Age mean: 9.7 (1.6), 10.7 (0.9), 11.3 (1.6) across subgroups Min age: 8 Max age: 13 Ethnicity: % Hispanic or Latino : 18.6 % Black/African American : 5.7 % Asian : 5.7 % White : 44.3 % Multiracial : 20 Other info on race or ethnicity:</td>
<td>Reference standard: Clinical diagnosis Clinician-administered Schedule for Affective Disorders and Schizophrenia for School-Aged Children Parent Version Timing: Prior diagnosis Index test: Parent rating Conners 3 Parent Rating Scale Inattention and Hyperactivity/Impulsivity scores and Behavioral Regulation Index of the Behavior Rating Inventory of Executive Function (BRIEF2) used to discriminate between children with ADHD+Prenatal alcohol exposure and typically developing children Sensitivity: Specificity: PPV: NPV: LR+: LR-: Accuracy: AUC: 0.90 All 3 scale measures alone AUC &gt;0.90, p&lt;0.0005 Rater agreement: Kappa: Internal consistency: Alpha: Test-retest: Costs:</td>
<td>Index test 2: Parental rating scale Conners 3 Parent Rating Scale Inattention (CIn) and Hyperactivity/Impulsivity (CHp) scores and Behavioral Regulation Index (BRI) of the Behavior Rating Inventory of Executive Function (BRIEF2) used to discriminate between children with ADHD+familial histo Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: 0.95 All 3 scale measures alone AUC &gt;0.95, p&lt;0.0005 Rater agreement: Kappa: Internal consistency: Alpha: Costs:</td>
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### Appendix C. Evidence Tables

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<td>Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
<td>ADHD+Prenatal alcohol exposure and typically developing children</td>
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<td></td>
<td>Misdiagnosis: Labeling: Costs:</td>
<td>Rater agreement:</td>
<td>Imaging Magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI) used to discriminate between children with ADHD+familial history of ADHD (no prenatal alcohol exposure) and typically developing children</td>
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<tr>
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<td>Index text 4: Imaging Magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI) used to discriminate between children with ADHD+familial history of ADHD (no prenatal alcohol exposure) and typically developing children</td>
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<td>Index text 5:</td>
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### Appendix C. Evidence Tables

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<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Study target; ADHD presentation; Diagnosis; Comorbidity; Gender; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
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</thead>
</table>
| Parent rating       | Quintana, 2007<sup>1,6</sup> Case series N = 26 US Setting: Specialty care     | **Target:** Children who presented to a child psychiatric clinic because a parent and/or school official suspected they might have ADHD who were diagnosed with ADHD with or without associated disorders or co-morbidities; not on medication at time of study or in the prior 6 months  
**Other:** Children who presented to a child psychiatric clinic because a parent and/or school official suspected they might have ADHD who were not diagnosed with ADHD; diagnosed with other disorder or no diagnosis  
**ADHD presentation:** inattentive: 63, hyperactive: 6, combined: 31  
**Diagnosed by:** Specialist  
**Comorbidity:** N/A  
**Gender:** 12.5%  
**Age mean:**  
**Min age:** 6  
**Max age:** 16  
**Ethnicity:**  
% Black/African American: 15.4  
% Asian: 3.8  
% White: 76.9  
Other info on race or ethnicity: Other: 3.8% Middle Eastern | **Reference standard:** Clinical diagnosis Psychiatric evaluation; Schedule for Affettive Disorders and Schizophrenia-Lifetime Version and Supplement for Behavioral Disorders, Clinical Global Assessment Scale and clinical Global Impression-Severity subscale  
**Timing:** Concurrent  
**Index test:** Parent rating The Attention-Deficit/Hyperactivity Disorder Rating Scale, Version-IV  
Sensitivity: 81  
Specificity: 22  
PPV: 65  
NPV:  
LR+:  
LR-:  
Accuracy: 60  
AUC:  
Rater agreement:  
Kappa:  
**Costs:**  
**Index test 2:** EEG  
Eyes closed and eyes open resting state, frontal beta power with 2 SD cutoff, theta/beta ratio with 1.5 SD cutoff; performed blinded to psychiatric evaluation and rating scale results  
Sensitivity: 94  
Specificity: 100  
PPV:  
NPV:  
LR+:  
Accuracy: 96  
AUC:  
Rater agreement:  
Kappa:  
**Costs:**  
**Index test 3:**  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
Accuracy:  
AUC:  
Rater agreement:  |
### Appendix C. Evidence Tables

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<th>Index Type</th>
<th>Study: Rishel, 2005 Case series N = 236 US Setting: Community</th>
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<td><strong>Target:</strong> Children and adolescents with attention deficit disorder treated at community mental health clinic</td>
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<td><strong>Other:</strong> &quot;Non psychotic&quot; children treated at community mental health clinic</td>
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<td><strong>ADHD presentation:</strong> N/A</td>
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<td><strong>Diagnosed by:</strong> Provider</td>
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<td></td>
<td><strong>Comorbidity:</strong> N/A</td>
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<td></td>
<td><strong>Female:</strong> 43%</td>
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<td><strong>Age mean:</strong> 11.3 (3.4)</td>
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<td><strong>Min age:</strong> 6 <strong>Max age:</strong> 17</td>
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<td><strong>Ethnicity:</strong> % Black/African American: 11.8, Other: Mother's race</td>
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<td>% White: 86, Other: Mother's race</td>
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<td>Other info on race or ethnicity:</td>
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| Results: | **Reference standard:** Clinical diagnosis DSM IV per Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) Timing: Concurrent |
|          | **Index test:** Parent rating Child Behavior Checklist (CBCL), parent rating |
|          | Sensitivity: 72.0% differentiating "ADD" from non-ADD children in mental health clinic |
|          | Specificity: 80.9% differentiating "ADD" from non-ADD children in mental health clinic |
|          | **PPV:** 66.7% differentiating "ADD" from non-ADD children in mental health clinic |
|          | **NPV:** 84.4% differentiating "ADD" from non-ADD children in mental health clinic |

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<th>Additional index tests</th>
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## Appendix C. Evidence Tables

| Index Type | Study: Scheeringa, 2020<sup>504</sup>  
Case series  
N = 58  
US  
Setting: Specialty care | Population:  
Target: Children recruited from one private outpatient child and adolescent psychiatry clinic that specialized in very young children without primary diagnosis of ASD  
Other: None  
ADHD presentation: N/A  
Diagnosed by: Researcher  
Comorbidity: N/A  
Female: 25%  
Age mean: 4.67(1.15)  
Min age: 1  
Max age: 6  
Ethnicity:  
% Hispanic or Latino : 8  
% Asian : 1  
% White : 87  
% Multiracial : 4 | Results:  
Reference standard: Other ADHD measured using SNAP and administered by trained RA  
Timing: Concurrent  
Index test: Parent rating The Diagnostic Infant and Preschool Assessment was revised to include Likert ratings (DIPA-L) <= 30 days between interviews  
Sensitivity:  
Specificity:  
PPV:  
NPV:  
LR+:  
LR-:  
Accuracy:  
AUC:  
Rater agreement: | Additional index tests |
## Appendix C. Evidence Tables

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<td></td>
<td>Other info on race or ethnicity:</td>
<td>Kappa: ICC: Internal consistency: Alpha: 0.92 The Diagnostic Infant and Preschool Assessment including LIkertratings (DIPA-L) first interview versus second interview. Interval between interviews based on scheduling availability. Test-retest: ICC 0.91 Kappa 0.79 Costs: Misdagnosis: Labeling: Costs:</td>
<td>Alpha: The Diagnostic Infant and Preschool Assessment including LIkertratings (DIPA-L) first interview versus second interview. Interval between interviews &lt;=30 days ICC 0.91 Kappa 0.84 Costs:</td>
<td>Index test 3: Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Rater agreement: Index test 4: Sensitivity: Specificity: PPV: NPV: AUC: Index test 5:</td>
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<td>Index text 4: Sensitivity: Specificity: PPV: NPV: AUC:</td>
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<tr>
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<td><strong>Parent rating</strong></td>
<td><strong>Target:</strong> Children recruited during a well-child visit at an urban pediatric practice and diagnosed with ADHD; 55% comorbid with ODD; 30% with two or more comorbidities <strong>ADHD presentation:</strong> N/A <strong>Diagnosed by:</strong> Other (specify) <strong>Staff</strong> <strong>Comorbidity:</strong> N/A <strong>Female:</strong> 49.3% <strong>Age mean:</strong> 7.0 (1.4) <strong>Min age:</strong> 6 <strong>Max age:</strong> 10 <strong>Ethnicity:</strong> % Hispanic or Latino : 84.7 % Black/African American : 4.3 % American Indian or Alaska Native : 0.5 % Asian : 0.0 % Native Hawaiian or Pacific Islander : 1.0 % White : 9.6</td>
<td><strong>Reference standard:</strong> Other <strong>MINI-KID (Miniature International Neuropsychiatric Interview) for Children</strong> <strong>Timing:</strong> Later diagnosis <strong>Index test:</strong> Parent rating Pediatric Symptom Checklist (PSC-35) <strong>Sensitivity:</strong> 82 <strong>Specificity:</strong> 50 <strong>PPV:</strong> 64 <strong>NPV:</strong> 73 <strong>LR+:</strong> <strong>LR-:</strong> <strong>Accuracy:</strong> AUC: 0.700 <strong>Rater agreement:</strong> <strong>Kappa:</strong></td>
<td><strong>Index text 5:</strong></td>
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<td><strong>Spencer, 2018</strong>&lt;sup&gt;142&lt;/sup&gt; <strong>Case series N = 41 US Setting: Community</strong></td>
<td><strong>Index test 2:</strong> Parental rating scale <strong>Child Behavior Checklist (CBCL)</strong> <strong>Sensitivity:</strong> 80 <strong>Specificity:</strong> 81 <strong>PPV:</strong> 80 <strong>NPV:</strong> 81 <strong>LR+:</strong> <strong>Accuracy:</strong> AUC: 0.837 <strong>Rater agreement:</strong> <strong>Kappa:</strong></td>
<td><strong>Index test 2:</strong> Parental rating scale <strong>Child Behavior Checklist (CBCL)</strong> <strong>Sensitivity:</strong> 80 <strong>Specificity:</strong> 81 <strong>PPV:</strong> 80 <strong>NPV:</strong> 81 <strong>LR+:</strong> <strong>Accuracy:</strong> AUC: 0.837 <strong>Rater agreement:</strong> <strong>Kappa:</strong></td>
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<th>Index Type</th>
<th>Study</th>
<th>Population</th>
<th>Results</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Ethnicity: % Hispanic or Latino: 4 % Black/African American: 7 % White: 88 Other info on race or ethnicity: Other: 1% Other</td>
<td>Internal consistency: Coefficient alpha 0.92 for inattentive scale, 0.87 for hyperactive/impulsive scale Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
<td>0.95 for hyperactive/impulsive scale Alpha: Costs: <strong>Index test 3:</strong> Teacher rating scale ADHD Symptom Checklist-4 Teacher, randomized-order version given to cohort 2 (N=104) Sensitivity: 66 Specificity: 57 PPV: 75 NPV: 57 LR+: Accuracy: AUC: Rater agreement:</td>
</tr>
<tr>
<td></td>
<td>Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
<td></td>
<td></td>
<td><strong>Index test 4:</strong> Teacher rating scale ADHD Symptom Checklist-4 Teacher, standard diagnostic-cluster version given to cohort 1 (N=103) Sensitivity: 70 Specificity: 59 PPV: 67 NPV: 62 AUC:</td>
</tr>
</tbody>
</table>

**Index test 5:**
<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study</th>
<th>Population</th>
<th>Results</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent rating</td>
<td>Thompson, 2017&lt;sup&gt;69&lt;/sup&gt;</td>
<td>Target: Recruitment specialists identified participants (parents of individuals aged 5-19 with ADHD) through advertising, patient advocacy groups, and treating physicians; each individual ADHD status was recorded based on a self-report by a parent or caregiver. &lt;br&gt;Other: Age matched healthy children. &lt;br&gt;ADHD presentation: N/A &lt;br&gt;Diagnosed by: Provider &lt;br&gt;Comorbidity: N/A &lt;br&gt;Female: 20% &lt;br&gt;Age mean: Control: 11.5 (3.4); ADHD: 11.4 (3.4) &lt;br&gt;Min age: 5 Max age: 12 &lt;br&gt;Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Reference standard: Clinical diagnosis &lt;br&gt;Self-Report physician-diagnosed ADHD &lt;br&gt;Timing: Prior diagnosis. &lt;br&gt;Index test: Parent rating The Weiss Functional Impairment Rating Scale Parent Form (WFIRS-P), a tool to differentiate ADHD from normal controls based on functional impairment scores. &lt;br&gt;Sensitivity: 83 &lt;br&gt;Specificity: 85 &lt;br&gt;PPV: &lt;br&gt;NPV: &lt;br&gt;LR+: &lt;br&gt;LR-: &lt;br&gt;Accuracy: &lt;br&gt;AUC: 0.91</td>
<td>Index test 2: &lt;br&gt;Sensitivity: &lt;br&gt;Specificity: &lt;br&gt;PPV: &lt;br&gt;NPV: &lt;br&gt;LR+: &lt;br&gt;Accuracy: &lt;br&gt;AUC: &lt;br&gt;Rater agreement: &lt;br&gt;Kappa: &lt;br&gt;Internal consistency: &lt;br&gt;Alpha: &lt;br&gt;Costs: &lt;br&gt;Index test 3: &lt;br&gt;Sensitivity: &lt;br&gt;Specificity: &lt;br&gt;PPV: &lt;br&gt;NPV: &lt;br&gt;LR+: &lt;br&gt;Accuracy: &lt;br&gt;AUC: &lt;br&gt;Rater agreement: &lt;br&gt;Index test 4: &lt;br&gt;Sensitivity: &lt;br&gt;Specificity: &lt;br&gt;PPV: &lt;br&gt;NPV: &lt;br&gt;AUC:</td>
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### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study:</th>
<th>Population:</th>
<th>Results:</th>
<th>Additional index tests</th>
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<tbody>
<tr>
<td></td>
<td>Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</td>
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</tbody>
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### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Parent rating</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Wassenberg, 2004&lt;sup&gt;193&lt;/sup&gt; Case series N = 72 US Setting: Primary Care</td>
</tr>
</tbody>
</table>

**Target:** Children diagnosed with ADHD; study design consisted of a consecutive series of subjects who survived a severe traumatic brain injury compared with an individually matched comparison group of subjects who sustained a mild traumatic brain injury, and a second matched control group of subjects who sustained an orthopaedic injury with no evidence of traumatic brain injury; most of the ADHD children had at least one comorbid disorder including depression and/or anxiety disorders, ODD, or CD

**Other:** Children not diagnosed with ADHD; study design consisted of a consecutive series of subjects who survived a severe traumatic brain injury compared with an individually matched comparison group of subjects who sustained a mild traumatic brain injury, and a

#### Results:

**Reference standard:** Clinical diagnosis Kiddie Schedule for Affective Disorders and Schizophrenia for Shool-Age Children-Epidemiology Verion supplemented by a posttraumatic stress disorder module

**Timing:** Concurrent

**Index test:** Parent rating Child Behavior Checklist; scores for ADHD (n=19) versus no ADHD (n=51) groups, social problems subscale, cutoff t>=60

**Sensitivity:** 74

**Specificity:** 86

**PPV:**

**NPV:**

**LR+:**

**LR-:**

**Accuracy:** 83

**Index text 2:** Parental rating scale

Child Behavior Checklist; scores for ADHD (n=19) versus no ADHD (n=51) groups, attention problems subscale, cutoff t>=60

**Sensitivity:** 84

**Specificity:** 84

**PPV:**

**NPV:**

**LR+:**

**LR-:**

**Accuracy:** 84

**AUC:**

**Rater agreement:**

**Kappa:**

**Index text 4:**

#### Additional index tests

AUC:

Rater agreement:

Kappa:

ICC:

Internal consistency:

Alpha:

Test-retest:

Costs:

Misdiagnosis:

Labeling:

Costs:

AUC:

Rater agreement:
# Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
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<tr>
<td>Parent rating</td>
<td>Zelko, 1991n26 Case series N = 89 US Setting: Mixed</td>
<td>Target: Boys with ADHD drawn from pediatric neurology and child guidance clinics. Other: Two groups: a) subjects with psychodiagnoses such as adjustment disorder, depression, anxiety disorder, conduct disorder, etc. b) normal subjects drawn from regular educational settings. ADHD presentation: N/A : 27 ADD with hyperactivity, 3 ADD without hyperactivity</td>
<td>Reference standard: Clinical diagnosis Diagnosis by pediatric neurologist, child psychiatrist or psychologist. Verified by author interview of child and parents based on DSM III&gt; Timing: Prior diagnosis Index test: Parent rating Conners Abbreviated Rating Scale (ARS) parent Sensitivity:</td>
<td>Index test 2: Parental rating scale Child Behavior CheckList (CBCL) parent Sensitivity: Specificity: PPV: NPV: LR+: Accuracy:</td>
</tr>
</tbody>
</table>
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
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<td></td>
<td>Index text 4: Sensitivity: Specificity: PPV: NPV: AUC:</td>
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<td>Index text 5:</td>
</tr>
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**Appendix C. Evidence Tables**

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study/Author, year; Multiple publications; Study design; Study size; Location</th>
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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| Teacher rating scale              | Alloway, 2009126 Case series N = 91 UK Setting: School                         | **Target:** Only included children who score in the normal range on the Developmental, Diagnostic and Dimensional Interview, a computerized assessment for autistic spectrum disorders; all receiving stimulants but were taken off 24 hours prior to testing  
**Other:** Healthy typically developing children and children with low working memory; age-matched to within 60 days (plus or minus 30 days) of children in the ADHD group  
**ADHD presentation:** combined : 100  
**Diagnosed by:** Specialist  
**Comorbidity:** N/A  
**Female:** 13%  
**Age mean:** 9.75 (1.0) for the ADHD group, 9.91 (0.92) for the working memory-impaired group, 9.91 (0.92) for the typically developing group  
**Min age:** 8  
**Max age:** 11  
**Ethnicity:** Other info on race or ethnicity: N/A | **Reference standard:** Clinical diagnosis  
Comprehensive clinical diagnostic assessment by pediatric psychiatrists and community pediatricians  
Timing: Concurrent  
**Index test:** Teacher rating scale Conners' Teacher Rating Scale (CTRS) short form; discriminant function analysis ADHD index  
Sensitivity: 72  
Specificity: 95  
PPV:  
NPV:  
LR+:  
LR-:  
Accuracy:  
AUC:  
Rater agreement:  
Kappa:  
**Internal consistency:**  
Alpha:  
Test-retest:  
Costs:  
Misdiagnosis:  
Labeling:  
Costs: | **Index test 2:** Teacher rating scale  
The Behavior Rating Inventory of Executive Function (BRIEF) teacher rating; discriminant function analysis all three indices  
Sensitivity: 78  
Specificity: 90  
PPV:  
NPV:  
LR+:  
Accuracy:  
AUC:  
Rater agreement:  
Kappa:  
**Internal consistency:**  
Alpha:  
Costs: | **Index test 3:** Teacher rating scale  
The Working Memory Rating Scale (WMRS) teacher rating; discriminant function analysis  
Sensitivity: 82  
Specificity: 100  
PPV:  
NPV:  
LR+:  
Accuracy:  
Costs: |
### Appendix C. Evidence Tables

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<thead>
<tr>
<th>Index Type</th>
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<th>Population:</th>
<th>Results:</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| Teacher rating scale | Edwards, 2015\(^{246}\)  Case series  
N = 95  
US  
Setting: Specialty care | **Target:** Consecutively referred to a developmental center at a university medical center for evaluation of suspected ADHD; not on medication; diagnosed with ADHD  
**Other:** Consecutively referred to a developmental center at a university medical center for evaluation of suspected ADHD; not on medication; not diagnosed with ADHD  
**ADHD presentation:** N/A  
**Diagnosed by:** Specialist  
**Comorbidity:** N/A  
**Female:** % | **Reference standard:** Clinical diagnosis ADHD module from the parent version of the Computer-Diagnostic Interview Schedule for Children (C-DISC) and the parent and teacher versions of the Conners' ADHD/DSM-IV Scales (CADS)  
**Timing:** Concurrent | **Index text 4:**  
neuropsychological, CPT The Conners' Continuous Performance Test; The K test was administered to assess performance on a vigilance task; discriminant function analysis  
Sensitivity: 41  
Specificity: 65  
PPV:  
NPV:  
AUC:  
**Index text 5:** |

<table>
<thead>
<tr>
<th>Teacher rating scale</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
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| Teacher rating scale | Edwards, 2015\(^{246}\)  Case series  
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Setting: Specialty care | **Target:** Consecutively referred to a developmental center at a university medical center for evaluation of suspected ADHD; not on medication; diagnosed with ADHD  
**Other:** Consecutively referred to a developmental center at a university medical center for evaluation of suspected ADHD; not on medication; not diagnosed with ADHD  
**ADHD presentation:** N/A  
**Diagnosed by:** Specialist  
**Comorbidity:** N/A  
**Female:** % | **Reference standard:** Clinical diagnosis ADHD module from the parent version of the Computer-Diagnostic Interview Schedule for Children (C-DISC) and the parent and teacher versions of the Conners' ADHD/DSM-IV Scales (CADS)  
**Timing:** Concurrent | **Index text 4:**  
neuropsychological, CPT The Conners' Continuous Performance Test; The K test was administered to assess performance on a vigilance task; discriminant function analysis  
Sensitivity: 41  
Specificity: 65  
PPV:  
NPV:  
AUC:  
**Index text 5:** |
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
|            | 24% in entire sample<br>**Age mean:** 8.7 (1.9)<br>**Min age:** 6 **Max age:** 12<br>**Ethnicity:**<br>% Hispanic or Latino : 2<br>% Black/African American : 18<br>% American Indian or Alaska Native : 1<br>% White : 79<br>Other info on race or ethnicity: | NPV: 79<br>LR+:<br>LR-:<br>Accuracy:<br>AUC:<br>Rater agreement: Cohen's kappa; recalibrated efficiency (adjusted for base rates; 0= random test, 1.0= perfect test)<br>Kappa: 0.537 (95% CI: 0.519, 0.567)<br>ICC:<br>Internal consistency:<br>Alpha:<br>Test-retest:<br>Costs:<br>Misdiagnosis:<br>Labeling:<br>Costs: | Rater agreement: Cohen's kappa; recalibrated efficiency (adjusted for base rates; 0= random test, 1.0= perfect test)<br>Kappa:0.396 (95% CI: 0.375, 0.424)<br>Internal consistency:<br>Alpha:<br>Costs:<br>**Index test 3:** Teacher rating scale Teacher Report Form (TRF) Attention Problems Scale; cutoff T-score 67<br>Sensitivity: 57 57<br>Specificity: 88<br>PPV: 81<br>NPV: 68<br>LRI+:<br>Accuracy:<br>AUC:<br>Rater agreement: Cohen's kappa; recalibrated efficiency (adjusted for base rates; 0= random test, 1.0= perfect test)<br>**Index test 4:** Parental rating scale Child Behavior Checklist (CBCL) Attention Problems Scale; cutoff T-score 67<br>Sensitivity: 57 57<br>Specificity: 88<br>PPV: 81<br>NPV: 68<br>LRI+:<br>Accuracy:<br>AUC:
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Results: Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teacher rating scale</td>
<td>Gomez, 2021&lt;sup&gt;100&lt;/sup&gt; Case series N = 264 Australia Setting: Specialty care</td>
<td>Target: Children referred to a hospital outpatient psychiatric who were diagnosed with ADHD; more individuals in the ADHD group with comorbid-specific phobia, panic disorder, ODD and conduct disorder compared to those without ADHD Other: Children referred to a hospital outpatient psychiatric unit who were not diagnosed with ADHD ADHD presentation: inattentive: 17, hyperactive: 12, combined: 71 Diagnosed by: Specialist Comorbidity: N/A Female: 26% Age mean: 9.21 (1.22) for ADHD group, 9.29 (1.18) for non-ADHD group Min age: 6 Max age: 11 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Reference standard: Clinical diagnosis Diagnoses of ADHD and ODD based on the ADIS-C-IV (Anxiety Disorders Interview Schedule for Children); a semistructured interview, based on the DSM-IV-TR diagnostic system Timing: Prior diagnosis Index test: Teacher rating scale Conners 3 Teacher Short Form and Teacher’s Report Form, score of 17 used as cut-off Sensitivity: 72 (64, 79) Specificity: 75 (59, 87) PPV: 92 NPV: 41 LR+: LR-: Accuracy: AUC: 0.77 Rater agreement: Kappa: ICC: Internal consistency: Alpha:</td>
<td>Sensitivity: 78 Specificity: 63 PPV: 67 NPV: 76 AUC: 5 Index text 5:</td>
</tr>
</tbody>
</table>

**Index text 2:** Parental rating scale
Conners 3 Parent Short Form and Child Behavior Checklist

Sensitivity: 79 (73, 85)
Specificity: 77 (63, 87)
PPV: 92
NPV: 50

Rater agreement:
Kappa:
Internal consistency:
Alpha:

**Index text 3:** Parental rating scale Child Behavior Checklist aggressive behavior scale

Sensitivity: 60
Specificity: 75
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| Teacher rating scale | Hall, 2020<sup>11</sup> RCT N = 250 UK Setting: Mixed | **Target:** Children referred for their first ADHD assessment to a child and adolescent mental health service or community pediatric clinic; participants and their assessing clinician were randomized to either immediately receiving the QbTest report (QbOpen group) or having the report withheld until the study end (QbBlind group)  
**Other:** None  
**ADHD presentation:** N/A  
**Diagnosed by:** Provider  
**Comorbidity:** N/A  
**Female:** 21% | **Reference standard:** Clinical diagnosis  
Clinician’s diagnosis was made in accordance with DSM-IV/DSM-5 criteria using a short clinical record pro forma after each consultation  
**Timing:** Concurrent  
**Index test:** Teacher rating scale SNAP-IV teacher rating  
Sensitivity: 97  
Specificity: 26  
PPV: 83  
NPV: 67  
LR+:  
LR-: | PPV: 83.9  
NPV: 46.9  
LR+:  
Accuracy:  
AUC:  
Rater agreement: |

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<sup>11</sup> Teacher rating scale Teacher's Report Form = aggressive behavior scale;  
Sensitivity: 48  
Specificity: 91  
PPV: 91.5  
NPV: 44.9  
AUC:  
**Index text 4:** Teacher rating scale SNAP-IV parental rating  
Sensitivity: 100  
Specificity: 4  
PPV: 82  
NPV: 100  
LR+:  
Accuracy:  
AUC:  
Rater agreement: Kappa:  
Internal consistency:
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Teacher rating scale</td>
<td>Jarrett, 2018&lt;sup&gt;11&lt;/sup&gt; Case series N = 388 US Setting: Specialty care</td>
<td><strong>Target:</strong> Consecutive referrals to an outpatient clinic diagnosed with ADHD: 18.3% taking stimulant medication, instructed not to take medication on day of assessment. 5.8% on nonstimulant medication, not asked to stop medication for assessment <strong>Other:</strong> Children referred from community pediatricians, schools, and mental health professionals presenting at an outpatient clinic</td>
<td><strong>Reference standard:</strong> Clinical diagnosis Participants were diagnosed with ADHD using the Diagnostic Interview Schedule for Children–IV–Parent Version (DISC-IV-P) with agreement between two investigators. <strong>Timing:</strong> Concurrent <strong>Index test:</strong> Teacher rating scale Teacher Report Form Attention Problems <strong>Sensitivity:</strong></td>
<td><strong>Index test 2:</strong> Parental rating scale Child Behavior Checklist Attention Problems <strong>Sensitivity:</strong> <strong>Specificity:</strong> <strong>PPV:</strong> <strong>NPV:</strong> <strong>AUC:</strong> <strong>LR+:</strong> Diagnostic likelihood ratio of 1.98 for individuals in the</td>
</tr>
</tbody>
</table>
### Appendix C. Evidence Tables

| Index Type | Study: 
Author, year; Multiple publications; Study design; Study size; Location | Population: 
Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity | Results: 
Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes | Additional index tests |
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<tbody>
<tr>
<td></td>
<td>for a psychoeducational assessment not diagnosed with ADHD</td>
<td>SPECIFICITY:</td>
<td></td>
<td>highest risk group (scores &gt;=71)</td>
</tr>
<tr>
<td></td>
<td>ADHD presentation: inattentive: 29, hyperactive: 3, combined: 68</td>
<td>PPV:</td>
<td></td>
<td>Accuracy:</td>
</tr>
<tr>
<td></td>
<td>Diagnosed by: Specialist</td>
<td>NPV:</td>
<td></td>
<td>AUC: 0.66</td>
</tr>
<tr>
<td></td>
<td>Comorbidity: N/A</td>
<td>LR+:</td>
<td>Diagnostic likelihood ratio of 1.55 for individuals in the highest risk group (scores &gt;=66.28)</td>
<td>Rater agreement:</td>
</tr>
<tr>
<td></td>
<td>Female: 32%</td>
<td>LR-:</td>
<td></td>
<td>Kappa:</td>
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<tr>
<td></td>
<td>Age mean: 10.21 (2.73)</td>
<td>Accuracy:</td>
<td></td>
<td>Internal consistency:</td>
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<tr>
<td></td>
<td>Min age: 5 Max age: 17</td>
<td>AUC: 0.65</td>
<td></td>
<td>Alpha: 0.76</td>
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<td></td>
<td>Ethnicity: % Hispanic or Latino: 1.5</td>
<td>Rater agreement:</td>
<td></td>
<td>Costs:</td>
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<td></td>
<td>% Black/African American: 4</td>
<td>Kappa:</td>
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<tr>
<td></td>
<td>% White: 93</td>
<td>ICC:</td>
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<td></td>
<td>Other info on race or ethnicity: Other: 1.5%</td>
<td>Internal consistency:</td>
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<tr>
<td></td>
<td>Race other</td>
<td>Alpha: 0.95</td>
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<td>Test-retest:</td>
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<td>Costs:</td>
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<td>Misdiagnosis:</td>
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<td>Labeling:</td>
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<td>Costs:</td>
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</table>

**Index text 3:** CPT Conners

CPT Hit Reaction Time

**Index text 4:**

Sensitivity: Specificity: PPV: NPV: LR+: Diagnostic likelihood ratio of 1.87 for individuals with high scores (>=74.5) Accuracy: AUC: Rater agreement:
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| Teacher rating scale | Karr, 2021; Kibby, 2015; Kibby, 2014 | **Target:** IQ $\geq$ 80, diagnosed with ADHD or ADHD with comorbid reading disorder (children with comorbidities not included in ROC analysis)  
**Other:** Healthy children; study also included children with reading disorder and children with "other diagnoses" but they were not part of ROC analysis  
**ADHD presentation:** N/A : n=85 children in sample w/ADHD  
**Diagnosed by:** Specialist  
**Comorbidity:** Learning disability : Reading disability  
**Female:** 43.1%  
**Age mean:** 9.49 (1.35)  
**Min age:** 8  
**Max age:** 12  
**Ethnicity:**  
  - % Hispanic or Latino : 2.7  
  - % Black/African American : 4.9  
  - % White : 85.8  
  - Other info on race or ethnicity: Other : 6.7 | **Reference standard:** Clinical diagnosis  
Clinical neuropsychologist conducted assessment according to DSM-IV criteria  
**Timing:** Prior diagnosis  
**Index test:** Teacher rating scale Behavior Assessment System for Children, Second Edition, Executive Function screener (BASC-2-EF) teacher rating scale global sum score; analysis of ADHD vs healthy children  
Sensitivity: 79  
Specificity: 71  
PPV: NPV:  
LR+: LR-:  
Accuracy: AUC: 0.831  
Rater agreement: Kappa:  
ICC: | **Index text 5:** |
| | | | | |
| | | | | **Index test 2:** Parental rating scale  
Behavior Assessment System for Children, Second Edition, Executive Function screener (BASC-2-EF) parent rating scale global sum score; analysis of ADHD vs healthy children  
Sensitivity: 91  
Specificity: 84  
PPV: NPV: LR+:  
Accuracy: AUC: 0.919  
Rater agreement: Kappa:  
Internal consistency: Alpha: 0.91  
Costs: |
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| Teacher rating scale| Kennerley, 2018[35]                                                            | **Target:** Recruited from a preexisting database within the Department of Psychology at the University of Otago, New Zealand or referred from the Southern District Health Board’s Paediatric Outpatients and Child and Family Mental Health Services; 15 children were on medication (Ritalin, Rubifen, Concerta, and Methamphetamine) | **Internal consistency:** Alpha: 0.95  
 **Test-retest:** Costs:  
 **Misdiagnosis:**  
 **Labeling:**  
 **Costs:** | **Index test 3:**  
 Sensitivity:  
 Specificity:  
 PPV:  
 NPV:  
 LR+:  
 Accuracy:  
 AUC:  
 Rater agreement:  |
|                     | Case series  
 N = 55  
 New Zealand  
 Setting: Specialty care | **Other:** None  
 **ADHD presentation:** inattentive: 43, hyperactive: 11, combined: 39, N/A: 7%  
 ADHD-not otherwise specified | **Reference standard:** Clinical diagnosis  
 Kiddie Schedule for Affective Disorders and Schizophrenia  
 Timing: Prior diagnosis  
 **Index test:** Teacher rating scale Attention-Deficit/Hyperactivity Disorder Rating Scale–Fourth edition teacher rating  
 Sensitivity:  
 Specificity:  
 PPV:  
 NPV: | **Index test 2:** Parental rating scale  
 Attention-Deficit/Hyperactivity Disorder Rating Scale–Fourth edition parent rating  
 Sensitivity:  
 Specificity:  
 PPV:  
 NPV:  
 LR+:  
 Accuracy:  
 AUC: |
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosed by: Specialist</td>
<td>Comorbidity: N/A</td>
<td>Female: 20%</td>
<td>Age mean: 104.33 months (23.67 months)</td>
<td>Min age: 6 Max age: 12</td>
</tr>
<tr>
<td><strong>Index text 4:</strong></td>
<td></td>
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</table>

Sensitivity:
### Appendix C. Evidence Tables

<table>
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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teacher rating scale</td>
<td>Raiker, 2017</td>
<td>Target: Recruited using a prospective, consecutive case series design from all intakes at an urban, community mental health center; youth self-report only completed by adolescent group age 12-18</td>
<td>Reference standard: Clinical diagnosis Diagnoses of ADHD were made in accordance with DSM-IV-TR Timing: Prior diagnosis</td>
<td>Specificity: PPV: NPV: AUC:</td>
</tr>
<tr>
<td></td>
<td>Case series</td>
<td>Other: Children and adolescents recruited using a prospective, consecutive case series design from all intakes at an urban, community mental health center not diagnosed with ADHD ADHD presentation: inattentive_other : Age 5 to 11: 9%. Age 12 to 18: 10%,hyperactive_other : Age 5 to 11: 4%. Age 12 to 18: 4,combined_other : Age 5 to 11: 53%. Age 12 to 18: 25%,N/A : ADHD not otherwise specified Age 5 to 11: 7%. Age 12 to 18: 13%. Diagnosed by: Specialist Comorbidity: N/A Female: % Age 5 to 11 32% female, age 12 to 18 46% female</td>
<td>Index test: Teacher rating scale Teacher Report Form Achenbach System of Empirically Based Assessment (ASEBA) Sensitivity: Specificity: PPV: NPV: LR+: LR-: Accuracy: AUC: Age 5 to 11: AUC 0.62 (0.55-0.70), age 12 to 18: AUC 0.56 (0.50-0.62) Rater agreement: Kappa: ICC: Internal consistency:</td>
<td>Index test 2: Parental rating scale Child Behavior Checklist Achenbach System of Empirically Based Assessment (ASEBA) Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: Age 5 to 11: AUC 0.72 (0.65-0.80), age 12 to 18: AUC 0.73 (0.67-0.78) Rater agreement: Kappa: Internal consistency: Alpha: Costs:</td>
</tr>
</tbody>
</table>
Appendix C. Evidence Tables

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</thead>
<tbody>
<tr>
<td>Teacher rating scale</td>
<td>Schneider, 2020&lt;sup&gt;(87)&lt;/sup&gt;</td>
<td><strong>Target:</strong> ADHD symptoms present for at least 6 months and cross-situational impairment; IQ &gt;=80; free of intellectual disability or autism spectrum disorder, visual impairment, treatment with psychotropic medications other than for ADHD. history of DSM-IV or DSM-V Axis I diagnosis other than oppositional defiant disorder or adjustment disorder, neurological disorder, documented hearing loss &gt;= 25 decibels loss in either ear, reported history of</td>
<td><strong>Reference standard:</strong> Clinical diagnosis Adapted from the NIH Preschoolers with Attention-Deficit/ Hyperactivity Disorder Treatment Study. Diagnostic Interview Schedule for Children-Young Child used for 4-year-olds and Diagnostic Interview for Children and Adolescents, Fourth Edition used for 5</td>
<td><strong>Index test 3:</strong> Teen/child self report Youth Self-Report Achenbach System of Empirically Based Assessment (ASEBA) Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC: 0.56 Rater agreement:</td>
</tr>
<tr>
<td></td>
<td>Case series</td>
<td>N = 84</td>
<td><strong>Alpha:</strong></td>
<td></td>
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<tr>
<td></td>
<td>Setting: Mixed</td>
<td></td>
<td>Test-retest:</td>
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<td>Costs:</td>
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<td>Misdiagnosis:</td>
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<td>Labeling:</td>
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<td></td>
<td></td>
<td></td>
<td>Cost:</td>
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</tr>
</tbody>
</table>

### Study Details

**Population:**
- **Min age:** Age 5 to 11: 7.63 (1.65), age 12 to 18: 13.43 (1.85)
- **Max age:** 18

**Ethnicity:**
- % Hispanic or Latino: Age 5 to 11: 3%. Age 12 to 18: 0%
- % Black/African American: Age 5 to 11: 87%. Age 12 to 18: 89%
- % White: Age 5 to 11: 6%. Age 12 to 18: 6%
- Other info on race or ethnicity: Other: Ethnicity Other age 5 to 11: 4%. Age 12 to 18: 4%

### Results

- **Sensitivity:**
- **Specificity:**
- **PPV:**
- **NPV:**
- **AUC:**

### Additional Index Tests

- **Index test 2:** Parental rating scale Behavior Rating Inventory of Executive Function- Preschool Version (same form for teachers and parents)
- **Sensitivity:**
- **Specificity:**
- **PPV:**

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Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population:</th>
<th>Results:</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
|            |                                                                                   |             | Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes | NPV: 
|            | physical sexual, or emotional abuse, and history of a developmental language disorder |             |         | Accuracy: |
|            | Other: Typically developing children                                               |             |         | AUC:                  |
|            | ADHD presentation: N/A                                                             |             |         | Rater agreement: |
|            | Diagnosed by: Unclear/NR                                                           |             |         | Kappa:             |
|            | Comorbidity: N/A                                                                  |             |         | Internal consistency: |
|            | Female: 40.8%                                                                     |             |         | Alpha:              |
|            | Age mean: ADHD group: 5.0 (0.6), comparison group: 4.9 (0.5)                      |             |         | Costs:               |
|            | Min age: 4 Max age: 5                                                             |             |         |                       |
|            | Ethnicity: % Black/African American : 5 % Asian : 3 % White : 90 % Multiracial : 1 |             |         |                       |
|            | Other info on race or ethnicity: Other : Other 1%                                 |             |         |                       |
| Index test 1: | Teacher rating scale Behavior Rating Inventory of Executive Function-Preschool Version (same form for teachers and parents) |             |         |                       |
|            | Sensitivity:                                                                       |             |         |                       |
|            | Specificity:                                                                       |             |         |                       |
|            | PPV:                                                                               |             |         |                       |
|            | NPV:                                                                               |             |         |                       |
|            | LR+:                                                                               |             |         |                       |
|            | LR-:                                                                               |             |         |                       |
|            | Accuracy:                                                                          |             |         |                       |
|            | AUC:                                                                               |             |         |                       |
|            | Rater agreement: Teacher versus parent Using standardized score totals, analysis of group-by-rater interaction effects revealed significant interactions for two scales: Working Memory, and Plan/Organize. Of note, the effect size for group differences (ADHD vs. TD) for these two scales was small. Within the ADHD group, there were significant associations between parent and teacher ratings on four of the five scales (correlations ranging from 0.30 to 0.34), with only the Shift scale showing non-significant inter-rater association ($r = -0.01$). In con Kappa: |
|            | ICC:                                                                               |             |         |                       |
|            | Internal consistency: Alpha:                                                       |             |         |                       |
|            | Test-retest:                                                                       |             |         |                       |
| Index test 2: | Teacher rating scale Behavior Rating Inventory of Executive Function-Preschool Version (same form for teachers and parents) |             |         |                       |
|            | Sensitivity:                                                                       |             |         |                       |
|            | Specificity:                                                                       |             |         |                       |
|            | PPV:                                                                               |             |         |                       |
|            | NPV:                                                                               |             |         |                       |
|            | LR+:                                                                               |             |         |                       |
|            | LR-:                                                                               |             |         |                       |
|            | Accuracy:                                                                          |             |         |                       |
|            | AUC:                                                                               |             |         |                       |
|            | Rater agreement: Teacher versus parent Using standardized score totals, analysis of group-by-rater interaction effects revealed significant interactions for two scales: Working Memory, and Plan/Organize. Of note, the effect size for group differences (ADHD vs. TD) for these two scales was small. Within the ADHD group, there were significant associations between parent and teacher ratings on four of the five scales (correlations ranging from 0.30 to 0.34), with only the Shift scale showing non-significant inter-rater association ($r = -0.01$). In con Kappa: |
|            | ICC:                                                                               |             |         |                       |
|            | Internal consistency: Alpha:                                                       |             |         |                       |
|            | Test-retest:                                                                       |             |         |                       |
## Appendix C. Evidence Tables

<table>
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<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| Teacher rating scale | **Shemmassian, 2016**<sup>13</sup>  
Shemmassian, 2012<sup>14</sup>  
Case series  
N = 195  
US  
Setting: Other | **Target:** Youths recruited through talks at self-help groups for ADHD, and study fliers distributed to local mental health service providers with language specifically targeting youth with elevated levels of attention and hyperactivity problems; with or without psychotropic medications; IQ<=70  
**Other:** Neurotypical children without ADHD recruited from local elementary schools and pediatric offices using fliers containing “neutral” language (i.e., did not refer to ADHD-related problems); youth who met criteria for any disorder other than ADHD (e.g., an ADHD presentation: inattentive: 42, hyperactive: 12, combined: 46)  
**Diagnosed by:** Researcher  
**Comorbidity:** N/A  
**Female:** 30%  
**Age mean:** 7.4 (1.1)  
**Min age:** 6  
**Max age:** 10  
**Ethnicity:** | **Reference standard:** Clinical diagnosis  
Any subtype of ADHD according to DISC-IV  
**Timing:** Concurrent  
**Index test:** Teacher rating scale Teacher Disruptive Behavior Disorder (DBD) Ratings Scale  
Sensitivity: 48  
Specificity: 70  
PPV: 65  
NPV: 54  
LR+:  
LR-:  
Accuracy:  
AUC:  
Rater agreement:  
Kappa:  
Internal consistency:  
Alpha:  
Test-retest: | **Index test 2:** Parental rating scale  
Parent Disruptive Behavior Disorder (DBD) Ratings Scale  
Sensitivity: 73  
Specificity: 93  
PPV: 93  
NPV: 75  
LR+:  
Accuracy:  
AUC:  
Rater agreement:  
Kappa:  
Internal consistency:  
Parent-rated inattention Cronbach's alpha 0.94, Parent rated hyperactivity/impulsivity Cronbach's alpha 0.91  
Alpha:  
Costs: |
## Appendix C. Evidence Tables

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<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
|            | % Hispanic or Latino : 10 % Black/African American : 7 % White : 53 % Multiracial : 22 Other info on race or ethnicity: Other : 4 | Costs: Misdiagnosis: Labeling: Costs: | Costs: Misdiagnosis: Labeling: Costs: | **Index test 3:** Combined rating OR rule, i.e., teacher or parent rating indicates ADHD (Teacher Disruptive Behavior Disorder (DBD) Ratings Scale or Parent Disruptive Behavior Disorder (DBD) Ratings Scale)  
Sensitivity: 88 88  
Specificity: 63  
PPV: 73  
NPV: 83  
LR+:  
Accuracy:  
AUC:  
Rater agreement:  
**Index test 4:** Combined rating AND rule, i.e., teacher and parent rating indicates ADHD (Teacher Disruptive Behavior Disorder (DBD) Ratings Scale or Parent Disruptive Behavior Disorder (DBD) Ratings Scale)  
Sensitivity: 25  
Specificity: 98  
PPV: 93  
NPV: 53  
AUC:  |  
**Index test 5:**  |
<table>
<thead>
<tr>
<th>Study:</th>
<th>Author, year; Multiple publications; Study design; Study size; Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index Type</td>
<td>Study:</td>
</tr>
<tr>
<td>Teacher rating scale</td>
<td>Shemmassian, 2017</td>
</tr>
<tr>
<td>Case series</td>
<td>N = 151</td>
</tr>
<tr>
<td>US</td>
<td>Setting: Mixed</td>
</tr>
<tr>
<td>Population: Target: IQ&gt;=70, free from a previous pervasive developmental, seizure, or neurological disorder, or any medical condition that prevented full participation in the study; recruited through presentations to self-help groups and advertisements mailed to local elementary schools, pediatric offices, and clinical service providers. Other: Youth who met criteria for any disorder other than ADHD, as well as those with a subclinical ADHD included in comparison group: IQ&gt;=70, free from a previous pervasive developmental, seizure, or neurological disorder, or any medical condition that prevent ADHD presentation: inattentive: 43, hyperactive: 12, combined: 45. Diagnosed by: Unclear/NR. Comorbidity: N/A. Female: 29%. Age mean: 7.4 (1.2). Min age: 5 Max age: 10. Ethnicity: % Hispanic or Latino: 9. % Black/African American: 10. % Asian: 4. % White: 54. % Multiracial: 21. Other: Biracial. Other info on race or ethnicity: Other: 2% race category other.</td>
<td></td>
</tr>
<tr>
<td>Results: Reference standard: Clinical diagnosis. Diagnostic Interview Schedule for Children, 4th edition. Timing: Prior diagnosis. Index test 1: Disruptive Behavior Disorder Rating Scale, teacher rating. Total predictive value (TPV) was calculated for each level of each teacher-rated ADHD symptom against ADHD versus non-ADHD status derived from the DISC-IV. &quot;Observed&quot; classification algorithm: &gt;=6 of 9 inattentive and/or hyperactive/impulsivity symptoms endorsed at their highest TPV level. Sensitivity: 82. Specificity: 55. PPV: 67. NPV: 73. LR+: 73. LR-: 0.11. Accuracy: 0.79. Rater agreement: Kappa: 0.94. Internal consistency: Cronbach's alpha 0.94 for both teacher-rated inattention and hyperactivity symptom counts on the Disruptive Behavior Disorder Rating Scale. Alpha:</td>
<td></td>
</tr>
<tr>
<td>Additional index tests</td>
<td>Index test 2: Parental rating scale. Disruptive Behavior Disorder Rating Scale, parent rating. Total predictive value (TPV) was calculated for each level of each parent-rated ADHD symptom against ADHD versus non-ADHD status derived from the DISC-IV. &quot;Observed&quot; classification algorithm: &gt;=6 of 9 inattentive and/or hyperactivity/impulsivity symptoms endorsed at their highest TPV level. Sensitivity: 88. Specificity: 80. PPV: 82. NPV: 87. LR+: 8.99. Accuracy: 0.87. Rater agreement: Kappa: 0.94. Internal consistency: Cronbach's alpha 0.94 for parent-rated inattention symptoms and 0.91 for parent-rated hyperactivity symptoms on the Disruptive Behavior Disorder Rating Scale. Alpha:</td>
</tr>
<tr>
<td>Costs:</td>
<td>index test 3:</td>
</tr>
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</table>
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<table>
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<tr>
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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teacher rating scale</td>
<td>Tripp, 2006&lt;sup&gt;174&lt;/sup&gt; Case series N = 184 New Zealand Setting: Specialty care</td>
<td><strong>Target:</strong> Children diagnosed with ADHD at specialized clinic. No exclusion criteria listed. <strong>Other:</strong> Children referred to the ADHD Research Clinic at the University of Otago for assessment that did not meet ADHD diagnosis criteria. <strong>ADHD presentation:</strong> inattentive: 17.6, hyperactive: 4.6, combined: 77.8 <strong>Diagnosed by:</strong> Specialist <strong>Comorbidity:</strong> N/A <strong>Female:</strong> 23.4% <strong>Age mean:</strong> 7.9 (1.6) <strong>Min age:</strong> 5 <strong>Max age:</strong> 12</td>
<td><strong>Reference standard:</strong> Clinical diagnosis DSM IV by clinical psychologist experienced in ADHD assessment Timing: Concurrent <strong>Index test:</strong> Teacher rating scale Teacher Report Form (TRF) Sensitivity: 78.7 Specificity: 63.5 PPV: N/A LR+: LR-: Accuracy: 72.5</td>
<td><strong>Index test 2:</strong> Parental rating scale Child Behavior Checklist (CBCL), parent rating Sensitivity: 76.9 Specificity: 32.9 PPV: N/A LR+: LR-: Accuracy: 58.7 AUC: Rater agreement: Kappa: Internal consistency:</td>
</tr>
</tbody>
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<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ethnicity: % Native Hawaiian or Pacific Islander : 12.0 % White : 76.1 Other info on race or ethnicity: N/A : 8.7,Other : Other 3.2</td>
<td>AUC: Rater agreement: Kappa: ICC: Internal consistency: Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
<td>Alpha: Costs:</td>
<td>Index test 3: Teacher rating scale Conners Teacher Rating Scale Sensitivity: 81.3 Specificity: 81.3 PPV: NPV: LR+: Accuracy: 76.4 AUC: Rater agreement:</td>
</tr>
<tr>
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<td></td>
<td>Index test 4: Parental rating scale Conners Parent Rating Scale Sensitivity: 78.5 Specificity: 32.4 PPV: NPV: AUC:</td>
</tr>
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</table>

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# Appendix C. Evidence Tables

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<thead>
<tr>
<th>Study</th>
<th>Population</th>
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<th>Additional index tests</th>
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<tbody>
<tr>
<td>Teacher rating scale</td>
<td></td>
<td></td>
<td>Index test 4:</td>
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<th>Population: Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
</table>
| Teen/child self report | **Doyle, 2007**<sup>236</sup>  
Case series  
N = 251  
US  
Setting: Other | **Target:** Probands and siblings participating in a longitudinal study of youth diagnosed with ADHD  
**Other:** Probands and siblings participating in a longitudinal study of youth without ADHD  
**ADHD presentation:** N/A  
**Diagnosed by:** Specialist  
**Comorbidity:** N/A  
**Female:** %  
25% female in entire sample, all probands were males, sibling sets included both boys and girls  
**Age mean:** 14.6 (1.9)  
**Min age:** 12  
**Max age:** 18  
**Ethnicity:** Other: All probands were white, non-Hispanic  
Other info on race or ethnicity: N/A | **Reference standard:** Clinical diagnosis Schedule for Affective Disorders and Schizophrenia for School-Aged Children and Adolescents Epidemiologic Version (Kiddie SADS-E), independent interviews with the mother and direct interviews of children  
**Timing:** Concurrent  
**Index test:** Teen/child self report Achenbach youth self-report (YSR) | **Index text 4:** Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC:  
**Index text 5:**  
**Index test 2:** Sensitivity: Specificity: PPV: NPV: LR+: Accuracy: AUC:  
**Index test 3:** Sensitivity: Specificity: PPV: |
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<table>
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<tr>
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<th>Results:</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study:</td>
<td>Author, year; Multiple publications; Study design; Study size; Location</td>
<td>Target: Referred to a private pediatric neurologic clinic between January 2018 and December 2020; exclusion criteria were an intellectual disability, severe neurological or developmental disabilities, and psychosis</td>
<td>Reference standard: Clinical diagnosis Interview with the child and the parents, medical/neurological examination, CPT administration, and ADHD diagnostic questionnaires (Conners ADHD Index Rating scales, 3rd edition, short-form-parent and teacher, Child Behavior Checklist and Teacher's Report Form)</td>
<td></td>
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<tr>
<td></td>
<td>Slobodin, 2022&lt;sup&gt;31&lt;/sup&gt; Case series N = 190 Israel Setting: Specialty care</td>
<td>Other: ADHD presentation: N/A Diagnosed by: Specialist Comorbidity: N/A Female: 40% Age mean: 8.48 (0.90) Min age: 7 Max age: 10 Ethnicity: Other info on race or ethnicity: Other : All of Jewish background living in northern Israel</td>
<td>Reference standard: Clinical diagnosis Interview with the child and the parents, medical/neurological examination, CPT administration, and ADHD diagnostic questionnaires (Conners ADHD Index Rating scales, 3rd edition, short-form-parent and teacher, Child Behavior Checklist and Teacher's Report Form)</td>
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<tr>
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<td>Index test: Teen/child self report Child self-report ratings compared to parent ratings (Conners and Child Behavior Checklist)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Sensitivity: Specificity: PPV: NPV: LR+: AUC:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rater agreement: Child self-report versus teacher reports Spearman correlation: Inattention self-report with</td>
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<td>index text 2: Teen/child self report Child self-report ratings compared to teacher ratings (Conners and Teacher's Report Form)</td>
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<td>Rater agreement: Child self-report versus teacher reports Spearman correlation: Inattention self-report with</td>
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## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Index Type</th>
<th>Study: Author, year; Multiple publications; Study design; Study size; Location</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LR: Accuracy:</td>
<td>Rater agreement: Child self-report versus parent reports Spearman correlation: Inattention r= 0.179, p&lt;0.05; hyperactivity r= 0.246, p &lt;0.01; social problems r=0.206, p&lt;0.01; child self-report of social problems with parent report of anxiety r=0.164, p&lt;0.05; anxiety r=0.178, p&lt;0.05; child self-report of depression Kappa: ICC: Internal consistency: Alpha: Test-retest: Costs: Misdiagnosis: Labeling: Costs:</td>
<td>social problems teacher report r=0.174, p&lt;0.05; social problems r=0.283, p &lt;0.01; children's self-report of social problems with teacher's report of depression r=0.270, p &lt;0.01; learning difficulties r= 0 Kappa: Internal consistency: Alpha: Costs:</td>
<td></td>
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<tr>
<td></td>
<td>AUC:</td>
<td></td>
<td>Index test 3: Teen/child self report Child self-report ratings compared to performance on MOXO-CPT indices</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Rater agreement: Child self-report versus MOXO-CPT performance Spearman correlation: child self-report of inattention with at least one impaired CPT index r=0.211, p&lt;0.01; child self-report of learning difficulties with CPT</td>
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</tbody>
</table>
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<tr>
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<th>Results: Reference standard; Index test; Diagnostic accuracy; Rater agreement; Other outcomes</th>
<th>Additional index tests</th>
</tr>
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<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td>accuracy r=-0.162, p&lt;0.05 and CPT impulsiveness r=0.212, p&lt;0.01; child self-report of disli</td>
</tr>
</tbody>
</table>

**Index text 4:**
- Sensitivity:
- Specificity:
- PPV:
- NPV:
- AUC:

**Index text 5:**
### Table C.2. KQ2 evidence table

<table>
<thead>
<tr>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAM</strong></td>
<td><strong>Target:</strong> Children aged 6–14 years diagnosed with ADHD according to DSM-5 criteria, their CSI-4 score, clinical judgment of a psychiatrist, and a family physician; scores on the CSI-4 questionnaire scores for the AD section needed to exceed 6, and the HA section needed to exceed 5 to meet the inclusion criteria  <strong>Other:</strong> ADHD presentation: N/A  <strong>Diagnosis:</strong> Confirmation by specialist DSM-V  <strong>Comorbidity:</strong> N/A  <strong>Female:</strong> 18.2%  <strong>Age mean:</strong> 9.8 (2)  <strong>Minimum age:</strong> 6  <strong>Maximum age:</strong> 14  <strong>Ethnicity:</strong> Other info on race or ethnicity: N/A</td>
<td><strong>Intervention:</strong> Auricular therapy was performed at six ear acupoints, stimulated bilaterally for 20 sec at each point, each participant evaluated and received stimulation for 15 min, repeated once a week for 6 weeks, after stimulation, each point labeled with small sections of adhesive tape that contained a small granule (Vaccaria seeds), participants’ supervisors were asked to apply medium pressure once a day for 1 min on each of the seeds  <strong>Control:</strong> Attention-matched control Nonacupuncture points were not electrically stimulated and only the seedless adhesive tapes were attached, adhesive replacement was performed once a week for 6 weeks  <strong>Comparator:</strong> NA  <strong>Follow-up:</strong> 2.5 months</td>
<td>Hyperactivity Scores, Comprehensive Behavior Rating Scale, Parent’s version Hyperactivity impulsiveness, and anger improvement improvement, investigator evaluation  Patients exhibited significantly greater improvement after receiving auricular therapy than did children in the sham control group (p &lt; .05).</td>
</tr>
<tr>
<td>CAM</td>
<td><strong>Target:</strong> Patients ADHD with a CGI of 14 or higher were included in the study; if there was any doubt concerning the diagnosis of ADHD, patients were referred to a child and adolescent psychiatrist or</td>
<td><strong>Intervention:</strong> Homeopathic liquid LM-potencies (LM-3 to LM-30) every day or every second day, used for 4 weeks, moving on to the next higher level (eg LM-6) after a treatment free interval of several days to one week</td>
<td>CGI (Clinical Global Impression) scale During homeopathic treatment the mean CGI rating fell to 9.27 corresponding to an amelioration of 55%, and with MPD to 10.96, corresponding to an amelioration of 48%.</td>
</tr>
<tr>
<td><strong>Frei, 2001</strong></td>
<td><strong>ID:</strong> NA  <strong>Clinical trial</strong>  <strong>Single center</strong>  <strong>N = 115</strong></td>
<td><strong>Intervention:</strong> LM-potencies (LM-3 to LM-30) every day or every second day, used for 4 weeks, moving on to the next higher level (eg LM-6) after a treatment free interval of several days to one week</td>
<td><strong>Outcome and results</strong></td>
</tr>
<tr>
<td><strong>Binesh, 2020</strong></td>
<td><strong>Research Institute for Islamic and Complementary Medicine, 2019</strong></td>
<td><strong>ID:</strong> IRCT20090527001957N9  <strong>RCT</strong>  <strong>Single center</strong>  <strong>N = 50</strong>  <strong>Iran</strong></td>
<td><strong>Setting:</strong> N/A</td>
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</tbody>
</table>
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
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</thead>
<tbody>
<tr>
<td>CAM Frei, 2005&lt;sup&gt;290&lt;/sup&gt; ID: NA Crossover trial Single center N = 83 Switzerland Setting: Specialty care</td>
<td>Target: Children with ADHD with neuropsychological correlates (greater difficulty in learning, memory, non-automated language tasks, and traditional frontal executive measures), the necessity for treatment, and absence of any chronic physical, neurological or psychiatric disorders. Other: ADHD presentation: N/A Diagnosis: Confirmation by specialist DSM-IV by neuropsychologist Comorbidity: N/A</td>
<td>Intervention: Verum homeopathic treatment daily for 6 weeks Control: Placebo Comparator: NA Follow-up: 5.5 months</td>
<td>Conners’ Global Index (CGI) Intervention group had significantly more improvement than control group (p=0.0479).</td>
</tr>
<tr>
<td>Switzerland Setting: Specialty care psychologist or a pediatric neurologist for further testing Other: ADHD presentation: N/A Diagnosis: Confirmation by specialist DSM-IV Comorbidity: N/A Female: 20 % Age mean: mean age 8.3 Minimum age: 3 Maximum age: 17 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Control: NA Comparator: Medication Methylphenidate for patients who did not reach sufficient clinical improvement, or whose behavior remained unacceptable despite a certain response to homeopathy after reevaluation, optimal dosage was adjusted over 3 months Follow-up: 3 months</td>
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### Appendix C. Evidence Tables

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<thead>
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<th>Intervention</th>
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<tbody>
<tr>
<td><strong>Study:</strong> Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td><strong>Female:</strong> 12.8 %&lt;br&gt;Arm 1 = 14.81% / Arm 2 = 10.71%&lt;br&gt;<strong>Age mean:</strong>&lt;br&gt;Arm A: 10 (range 7–15); Arm B: 10 (range 7–15)&lt;br&gt;<strong>Minimum age:</strong> 6&lt;br&gt;<strong>Maximum age:</strong> 16&lt;br&gt;<strong>Ethnicity:</strong> Other info on race or ethnicity: N/A</td>
<td><strong>Intervention:</strong> Acupuncture treatment for twenty minutes, twice per week for six weeks&lt;br&gt;<strong>Control:</strong> Wait list&lt;br&gt;<strong>Comparator:</strong> NA</td>
<td>Child Behavior Checklist (CBCL), change from baseline&lt;br&gt;No significant difference between groups (p = 0.393).&lt;br&gt;ADHD-RS change&lt;br&gt;Change in score did not differ significantly between groups (p = 0.561).&lt;br&gt;3 headaches in acupuncture group, none in control group; no other adverse events reported.</td>
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<tr>
<td><strong>Target:</strong> ADHD diagnosis (of any subtype); any intervention (pharmacological, psychosocial therapy, educational, occupational therapies etc.) without change in ADHD treatments/ symptoms for last 2 weeks or no current treatment. Exclusion criteria: diagnosis of mental retardation or pervasive developmental disorders; past history of epilepsy or other neurotic disorder; pregnancy; any change in medications during the course of the study.&lt;br&gt;<strong>Other:</strong> Parent reported some outcomes&lt;br&gt;<strong>ADHD presentation:</strong> N/A : Mean Hyperactivity/Impulsivity score = 11.0 in each group.&lt;br&gt;<strong>Diagnosis:</strong> Confirmation by specialist DSM IV criteria</td>
<td><strong>Follow-up:</strong> 1.5 months</td>
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[^1]: Hong, 2016
[^2]: Cochrane Central Register of Controlled Trials, 2010
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<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
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<th>Outcome and results</th>
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<tr>
<td>Cognitive training</td>
<td>Benzing, 2019&lt;sup&gt;146&lt;/sup&gt; Universität Bern, 2016&lt;sup&gt;1091&lt;/sup&gt; ID: KEK 393/15, DRKS00010171 RCT Single center N = 51 Switzerland Setting: Other</td>
<td>Comorbidity: N/A Female: 18.7 % Age mean: 11.0 (2.8) Minimum age: 7 Maximum age: 18 Ethnicity: % Asian: 100 Other info on race or ethnicity:</td>
<td></td>
<td>Conners-3 Scale, German version, Global Index Score, parents Significant effects favoring the intervention were detected on the total global index score (p=0.022). ADHD symptoms (DSM-IV-TR scales) No significant group effects (p &gt; .05). For the Motor ability - German Motor test the intervention group showed a significantly better total performance than the control group (p=0.008).</td>
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<td>Intervention; Control; Comparator; Follow-up</td>
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<td>Other info on race or ethnicity:</td>
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<tr>
<td>Cognitive training</td>
<td>Bigorra, 2016&lt;sup&gt;156&lt;/sup&gt; Bigorra, 2016&lt;sup&gt;674&lt;/sup&gt; ID: ISRCTN00767728 RCT Single center N = 66 Spain Setting: Specialty care</td>
<td>Target: Children with ADHD, comorbidity with other disruptive behavior disorders was accepted, all diagnoses were confirmed using the semi-structured Kiddie-Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version (K-SADS-PL) interview that was administered to parents; T scores on the Conners ADHD index for parents and teachers &gt;70 at the time of diagnosis; no previous psychological or pharmacological treatment for ADHD Other: ADHD presentation: combined : 100 Diagnosis: Confirmation by specialist DSM-IV-TR by clinician Comorbidity: N/A Female: 55 % Age mean: 8.92 (1.75) Minimum age: 7 Maximum age: 12</td>
<td>Intervention: Adaptive training with Cogmed Working Memory Training: visual-spatial, auditory, and location memory and tracking of moving visual objects as working memory tasks, each training session included 90 trials and had a duration of 30–45 min, participants attended 5 sessions per week over a 5-week period for a total of 25 sessions Control: Attention-matched control Control group (non-adaptive training) engaged in the MegaMemo, which consists of the same working memory tasks but without the adjustment for difficulty, i.e. they performed simpler tasks Comparator: NA Follow-up: 6 months</td>
<td>Behaviour Symptoms Index (mean parent, teacher) ADHD Composite Index (Conners, SDQ) A significant improvement was noted for the intervention group compared to the control group (p = 0.01). Weiss Functional Impairment Rating Scale (WFIRS-P)- Parent Significant improvements for the intervention group compared to the control group were registered on the school learning behavior subscale (p=0.02) but not on any other subscale. With respect to executive functions scales (BRIEF), the the experimental group improved significantly more than the control group (p=0.01). No statistically significant differences between the groups for Theory of Mind composite score were recorded at any point in time (p=0.57).</td>
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<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
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</thead>
<tbody>
<tr>
<td>Cognitive training</td>
<td>Bikic, 2018&lt;sup&gt;19&lt;/sup&gt; Region Syddanmark, 2012&lt;sup&gt;39&lt;/sup&gt; ID: NCT01752530 RCT Multicenter N = 78 Denmark Setting: Mixed</td>
<td><strong>Target:</strong> Children fulfilling DSM-IV criteria for ADHD (in DAWBA interview, and verified with K-SADS); age between 6 and 13 years; access to a computer and internet connection; no diagnosis of comorbid conduct disorder, autism spectrum disorders, depression or schizophrenia; no medical history of head injury or a verified neurological disorder; intelligence quotient (IQ) not less than 80; no motor or perceptual handicaps which would interfere with computer use; no medical condition requiring primary treatment; and no informed consent from custody <strong>Other:</strong> Parents <strong>ADHD presentation:</strong> inattentive : 42.6, hyperactive : 5.7, combined : 50 <strong>Diagnosis:</strong> Confirmation by specialist interviewed by one of three trained psychologists, to confirm the ADHD diagnosis, using the ADHD section of the Kiddie-Schedule for Affective Disorder</td>
<td><strong>Intervention:</strong> Computer program ACTIVATE used 6 times a week for 8 weeks using only used the cognitive computer games part, not use the physical exercises, the group received ADHD treatment as usual <strong>Control:</strong> Other Treatment as usual alone, which consisted of diagnostic and cognitive assessment, psycho-education, pedagogical counseling, and questionnaires for parents and teachers, home and school visits and, for some children, medical treatment <strong>Comparator:</strong> NA <strong>Follow-up:</strong> 5.8 months</td>
<td>ADHD-RS-IV (ADHD-Rating Scale-IV), parent rating There was no significant effect for training (p=0.69). Weiss functional impairment rating scale-parent report form (WFIRS-P) There were no significant differences between the intervention and the control group (p=0.54). No significant effect of training on sustained attention, parent-rated-BRIEF, or teacher-rated-BRIEF.</td>
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## Appendix C. Evidence Tables

### Intervention

<table>
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<tr>
<th>Study</th>
<th>Population</th>
<th>Comparison</th>
<th>Outcome and results</th>
</tr>
</thead>
</table>
| Bul, 2016<sup>173</sup>  
Bul, 2018<sup>64</sup>  
ID: ISRCTN62056259  
RCT  
Multicenter  
N = 170  
Multiple countries  
Setting: Mixed | Disorders and Schizophrenia (K-SADS)  
Comorbidity: N/A  
Female: 16 %  
Age mean: 9.95 (1.7)  
Minimum age: 6  
Maximum age: 13  
Ethnicity: Other info on race or ethnicity: N/A | Intervention: Game intervention in addition to treatment as usual for the first 10 weeks, maximum of 65 minutes approximately 3 times per week  
Control: TAU  
Treatment as usual for the first 10 weeks and the crossed over to the serious game intervention in addition to treatment as usual for the subsequent 10 weeks  
Comparator: NA  
Follow-up: 5 months | Behavior Rating Inventory of Executive Function (BRIEF, subscale Plan/Organized) showed significantly greater improvements (p=0.004).  
10 adverse events that could be related to the intervention, all were mild or moderate severity, including pain in the fingers, irritability, and headache, one participant did not want to play the game anymore because he could not concentrate during his school activities; there were no serious adverse events. |

### Target

- **Children stable on pharmacological and/or psychological treatment for ADHD 8 weeks before baseline**
  (determined by health care professionals on the basis of medication data and behavioral observation)

### Other

- **ADHD presentation:** inattentive: 22.4, hyperactive: 3.5, combined: 74.1
- **Diagnosis:** Confirmation by specialist  
DSM-IV-TR by psychologist  

### Comorbidities

- **Comorbidity:** N/A  
Female: 19.4 %  
Age mean: 9.85 (1.26)  
Minimum age: 8  
Maximum age: 12
# Appendix C. Evidence Tables

| Intervention | Study:  
|--------------|---------------------------------|
|              | Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting | Population:  
|              | Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity | Comparison:  
|              | Intervention; Control; Comparator; Follow-up | Outcome and results |
|--------------|---------------------------------|
| Cognitive training | Chu, 2021\[2021\]^\[2021\]   
|              | Shanghai Childrens Hospital, 2021\[2021\]^\[2021\]   
|              | ID: ChiCTR2100052803 RCT Unclear/Not reported N = 145 China Setting: N/A | Target: IQ should be 70 or above established with the Wechsler Intelligence Scale for children–fifth edition (WISC-V). Moreover, parents or primary caregivers did not want to receive drug therapy, could read and write the Chinese language, were legally able to sign informed consent, and signed the informed consent. Children with autism spectrum disorder, schizophrenia, epilepsy, head injury, or verified neurological disorder, intellectual disability (IQ <70, based on WISC-V), and sensory impairment (hearing/vision problems) and those receiving other ADHD treatments were excluded. Neither the intervention nor waitlist group were treated with medication.  
|              | Other: ADHD presentation: inattentive : 60, hyperactive : 14, combined : 26 Diagnosis: Confirmation by specialist DSM-V | Intervention: Eight weekly sessions of a hospital-based executive function training program for participants, each session 90 minutes long, and an online parent training program, each session 30 minutes long  
|              | Control: Wait list Comparator: NA Follow-up: 2 months | SNAP-IV total score (Chinese version), parent Weiss Functional Impairment Scale, parent There was no significant difference between groups.  
|              | The intervention had significantly greater differences of improvement compared to control (p = 0.009). The intervention group had greater reduction in the scores of behavioral regulation index (inhibition, emotional control) and metacognition index (working memory, planning/organization, monitoring) in executive function than those in the control group (p < 0.05). |
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
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<th>Comparison:</th>
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<tbody>
<tr>
<td>Cognitive training</td>
<td>Denton, 2020&lt;sup&gt;125&lt;/sup&gt; The University of Texas Health Science Center, Houston, 2010&lt;sup&gt;183&lt;/sup&gt;; Dvorsky, 2021&lt;sup&gt;127&lt;/sup&gt; ID: NCT01133847 RCT Multicenter N = 222 US Setting: School</td>
<td><strong>Target:</strong> Patients with ADHD and a standard score ≤ 25th percentile on either the Woodcock-Johnson III Letter-Word Identification or Word Attack subtests or the Basic Reading Skills composite <strong>Other:</strong> Parents received training and provided some outcomes <strong>ADHD presentation:</strong> Inattentive: 46.1, Combined: 53.9 <strong>Diagnosis:</strong> Confirmation by specialist DSM-IV <strong>Comorbidity:</strong> Learning disability <strong>Female:</strong> 39.0 % <strong>Age mean:</strong> 8.8 (1.3) <strong>Minimum age:</strong> 5 <strong>Maximum age:</strong> 7 <strong>Ethnicity:</strong> % Black/African American: 72.1</td>
<td><strong>Intervention:</strong> Reading intervention plus medication plus parent training; the reading intervention was provided individually or in groups of two students in 45-minute lessons, 4 days per week, a possible total of 64 lessons over 16 weeks; medication treatment in children typically began with a low dose of extended-release methylphenidate, which was titrated up in weekly visits to a dosage at which the child had a satisfactory response with limited side effects for a total of 12 weeks; the behavioral parent training consisted of 9 group sessions over 10 weeks, topics included psychoeducation about ADHD and evidence-based strategies for behavior management <strong>Control:</strong> Other</td>
<td>Inattention, SNAP (Swanson, Nolan, and Pelham Checklist for DSM-IV), parent rating Combined intervention group improved more than group receiving reading instruction alone. Same for SNAP Parent Rating of Hyperactivity-Impulsivity, SNAP- Teacher Rating of Inattention, and SNAP- Teacher Rating of Hyperactivity-Impulsivity. Test of Word Reading Efficiency (TOWRE) Phonemic Decoding Efficiency: combined intervention (p 0.03) and reading group alone (p 0.007) had significantly higher posttest means than medication and parent treatment alone. Improvement in WIAT-3 Reading Comprehension means was superior for medication plus parent training group compared to both groups receiving a reading intervention (p 0.008).</td>
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<tr>
<td>Dental training</td>
<td>Dentz, 2020&lt;sup&gt;236&lt;/sup&gt; Université du Québec à Montréal, 2017&lt;sup&gt;1992&lt;/sup&gt; ID: NCT03335748 RCT Single center N = 52 Canada Setting: Other</td>
<td>% White: 19.6 % Multiracial: 6.4 Other info on race or ethnicity: Parent training plus medication only; treatment typically began with a low dose of extended-release methylphenidate, which was titrated up in weekly visits to a dosage at which the child had a satisfactory response with limited side effects; the behaviora Comparator: NA Follow-up: 4 months</td>
<td></td>
<td>Inattention, Conners 3 There was no significant difference between groups (p=0.18).</td>
</tr>
</tbody>
</table>

**Target:** Youths 7-13 years of age diagnosed with ADHD combined type with comorbid learning disability, oppositional defiance disorder, or Tourette syndrome, and under pharmacological treatment for ADHD, which had been stabilized for at least the past 2 months

**Other:**
- ADHD presentation: N/A
- Diagnosis: Confirmation by specialist DSM-IV
- Comorbidity: N/A
- Female: 13%
- Age mean:
  - Intervention: 10.44 (1.18), control: 9.60 (2.08)
  - Minimum age: 7

**Intervention:** Cogmed program: a cognitive training software designed with exercises targeting the verbal and visuospatial components of working memory specifically, each training session lasted from 30 to 45 min, participants had to complete at least five sessions per week for five consecutive weeks

**Control:** Placebo Comparison version of the Cogmed program with a low and invariable level of difficulty, which was expected to dampen the program's effects.

**Comparator:** NA

**Follow-up:** 2.5 months
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
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<tbody>
<tr>
<td>Cognitive training</td>
<td>Dovis, 2015&lt;sup&gt;214&lt;/sup&gt; Dovis, 2015&lt;sup&gt;720&lt;/sup&gt; ID: NTR2728 RCT Multicenter N = 89 Netherlands Setting: Specialty care</td>
<td>Maximum age: 13 Ethnicity: % White: 86.5 Other info on race or ethnicity:</td>
<td></td>
<td>There was no significant difference of treatment outcome on any executive function measures..</td>
</tr>
<tr>
<td></td>
<td>Target: DSM-IV-TR diagnosis of ADHD combined time diagnosed by a child psychologist or child psychiatrist, score on Disruptive Behavioral Disorder Rating Scale (Dutch translation) in 9th to 100th percentile for both parent and teacher version ADHD scale, met criteria for ADHD combined type on ADHD section of Diagnostic Interview Schedule for Children, parent version; IQ score greater than or equal to 80 on Dutch (WISC-III); Exclusion criteria - conduct disorder, autism spectrum disorder, neurological disorder, sensory or motor impairment reported by parents, medications other than methylphenidate or dextroamphetamine Other: ADHD presentation: combined: 100 Diagnosis: No Prior diagnosis per DSM-IV confirmed by child psychologist or</td>
<td>Intervention: Executive functioning training (&quot;Braingame Brian&quot;) total of 25 training sessions, each session taking between 35-50 minutes each, all tasks were in training mode and level is adjusted to child's level of performance Control: Placebo Braingame Brain in placebo condition: working memory, inhibition, and cognitive-flexibility tasks were presented in the same way as training mode except the stop-trials and switch-trials were replaced by go-trials and non-switch trials and difficulty level Comparator: Cognitive trainingPartially-active condition in which the working memory tasks were in placebo mode which did not adjust difficulty to performance while the inhibition and cognitive-flexibility tasks were in training mode Follow-up: 4.25 months</td>
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</table>
| Cognitive training | Egeland, 2013<sup>247</sup> Hovik, 2013<sup>81</sup>  ID: ISRCTN19133620  RCT  Single center  N = 75  Norway  Setting: School | psychiatrist, but did not describe process of confirmation  
Comorbidity: N/A  
Female: 20 %  
Age mean: Table 1 labeled value as "M", suspect this is the "mean age,"; mean age of full-active intervention 10.6 (SD 1.4), partially-active intervention 10.3 (SD 1.3), and placebo group 10.5 (SD 1.3)  
Minimum age: 8  
Maximum age: 12  
Ethnicity: Other info on race or ethnicity: N/A | | ADHD-RS-IV (ADHD-Rating Scale IV), parent  
There was no significant difference between groups.  
Strengths & Difficulties Questionnaire (SDQ), parent  
There was no significant difference between groups.  
Training group had significant gains in working memory performance measures. |

| Target: Children in treatment for ADHD, exclusion criteria were IQ below 70, or a comorbid diagnosis of Pervasive Developmental Disorders, Tourette’s Disorder, evidence of psychosis or Bipolar Disorder and Conduct Disorder  
Other:  
ADHD presentation: N/A  
Diagnosis: Confirmation by specialist F-90 ICD-10 Hyperkinetic Disorder (equivalent to DSM-IV)  
Comorbidity: N/A  
Female: 24 %  | Intervention: The Working Memory training (RoboMemo) performed on a daily basis at school for 5–7 weeks, sessions last for 30–45 minutes  
Control: Wait list  
Offered the possibility to train after the completion of the study  
Comparator: NA  
Follow-up: 8 months | | |
## Intervention Study

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<tr>
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<tr>
<td>Estrada-Plana, 2019[^1] ID: NA RCT Single center N = 29 Spain Setting: Other</td>
<td>Target: Attending primary school, and having diagnosis of ADHD, without having any other mental disorders, and having an IQ of more than 80 Other: ADHD presentation: inattentive: 23.1, hyperactive: 76.9 Diagnosis: Confirmation by specialist Psychiatrists or Clinical Psychologists Comorbidity: N/A Female: 46.2 % Age mean: 9.46 (1.20) Minimum age: 8 Maximum age: 12 Ethnicity: % Hispanic or Latino: 97 Other info on race or ethnicity: Other: Does not specify the other 3%</td>
<td>Intervention: Cognitive training based on board games, closed groups of 6-8 participants, 5 weekly training sessions, 60 minutes each, 1 game per week Control: Wait list Comparator: NA Follow-up: 1 month</td>
<td>Conners CPRS-48 Conduct Problems Subscale There was no significant difference between groups. Hyperactivity Index, Conners CPRS-48 (CPRS-48) Strengths and Difficulties Questionnaire (SDQ) Intervention participants showed lower conduct problems in the SDQ subscale compared to control group participants (p&lt;0.001). Number of participants with adverse events No patients with adverse events. No adverse effects were found during the intervention.</td>
</tr>
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<tr>
<td>Cognitive training</td>
<td>Hahn-Markowitz, 2020; Hahn-Markowitz, 2017; Hadassah Medical Organization, 2013</td>
<td>Target: Children in second to fourth grade with ADHD Other: Parents and teachers provided some outcomes ADHD presentation: inattentive: 48.6, hyperactive: 4.7, combined: 46.7 Diagnosis: Confirmation by specialist DSM-IV, assessed by a certified pediatric neurologist/psychiatrist, including a semi-structured interview with the child and parents, medical/neurological/psychiatric examination, and completion of a ADHD diagnostic questionnaire Comorbidity: N/A Female: 38% Age mean: 8.5 (0.85) Minimum age: 7 Maximum age: 10 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Intervention: Cog-Fun: integrative intervention using effortful executive strategies and supplemented by environmental adaptations, weekly 1-hr sessions with child and parent over 12 weeks Control: Wait list Comparator: NA Follow-up: 3 months</td>
</tr>
<tr>
<td>Cognitive training</td>
<td>Kofler, 2020</td>
<td>Target: DSM-5 diagnosis of ADHD by the directing clinical psychologist based on K-SADS; and clinical/borderline elevations on at least 1 parent and one teacher ADHD rating scale, or previous psychoeducational</td>
<td>Intervention: Inhibitory control training: 10-week protocol included weekly in-office sessions with the child (1 hour), combined with parent-supervised, in-home training (goal: 15-min/day, 2–3 days/week) Control: NA</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
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<tr>
<td>Cognitive training</td>
<td>Kollins, 2020&lt;sup&gt;46&lt;/sup&gt; Akili Interactive Labs, Inc., 2016&lt;sup&gt;46&lt;/sup&gt; ID: NCT02674633 RCT Multicenter</td>
<td>US Setting: Other</td>
<td>Comparator: Cognitive training Central executive training targeting central executive working memory deficits in ADHD; each matched pair of ICT/CET training games is identical in terms of website address, name, art, animations, storylines, layouts, interfaces, and use of adaptive train</td>
</tr>
</tbody>
</table>

**Target:** Children aged 8–12 years with a confirmed diagnosis of ADHD according to DSM-5 and Intelligence Quotient 80 or above; no significant comorbid psychiatric diagnoses and no use of ADHD

**Intervention:** Digital therapeutic AKL-T01 at home for 5 sessions per day (total time on task about 25 min), 5 days per week, for 4 weeks

**Control:** Attention-matched control

Control was designed to match AKL-T01 on expectancy.

**Dosage:**

**Comparison:** Intervention; Control; Comparator; Follow-up

**Follow-up:** 2.5 months

**Other info on race or ethnicity:**

- % Hispanic or Latino: 11
- % Black/African American: 9
- % White: 74
- % Multiracial: 6

**Study:** Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting

**Population:** Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity

**Comparison:** Intervention; Control; Comparator; Follow-up

**Outcome and results:**

- **Evaluation documenting cross-informant symptoms:** children with scores in the average range or higher on all pretreatment working memory tests were excluded; no inhibitory control thresholds were set
- **Other:**
  - **ADHD presentation:** inattentive: 28, hyperactive: 3.7, combined: 69
  - **Diagnosis:** Confirmation by specialist K-SADS
  - **Comorbidity:** N/A
  - **Female:** 22%
  - **Age mean:** 10.41 (1.46)
  - **Minimum age:** 8
  - **Maximum age:** 12
  - **Ethnicity:**
    - % Hispanic or Latino: 11
    - % Black/African American: 9
    - % White: 74
    - % Multiracial: 6

- **Follow-up:** 2.5 months

- No difference in improvement between groups.

**ADHD-RS-IV, number with at least 30% improvement**
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<tr>
<td>Cognitive training</td>
<td>Nejati, 2021&lt;sup&gt;443&lt;/sup&gt; Nejati, 2020&lt;sup&gt;921&lt;/sup&gt; ID: NA RCT Single center N = 30 Iran Setting: Specialty care</td>
<td>Target: Children with ADHD. Those with psychiatric comorbidities excluded. Other: ADHD presentation: inattentive: 16.7, hyperactive: 23.3, combined: 60.0 Diagnosis: Confirmation by specialist Diagnosis by psychiatrist via DSM-V Comorbidity: N/A</td>
<td>Intervention: Cognitive training with paper and pencil tasks, twelve to fifteen sessions of intervention, three sessions per week during 4–5 weeks, each session took about 40–50 minutes Control: No intervention Comparator: NA Follow-up: 1.25 months</td>
<td>ADHD score, SNAP IV There was no significant difference. No effect of group on Persian Attention Registration Test, total time (p = .744) or Stroop Test, Selective Attention Index (p = .285) or Trail Making Test.</td>
</tr>
<tr>
<td>N = 348 US Setting: Other</td>
<td>medications that could not be discontinued Other: Parents ADHD presentation: N/A Diagnosis: Confirmation by specialist Participants diagnosis of ADHD according to DSM-5 criteria was confirmed. Comorbidity: N/A Female: 28.7 % Age mean: Intervention 9.7 (1.3), control 9.6 (1.3) Minimum age: 8 Maximum age: 12 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>engagement, and time on task in the form of a challenging and engaging digital word game, targeting cognitive domains not targeted by the AKL-T01 intervention and not primarily associated with ADHD; th Comparator: NA Follow-up: 1 month</td>
<td>No difference in improvement between groups (p = 0.23). Impairment Rating Scale improved by 1 point Marginal effect on impairment (p 0.049). No significant difference in improvement between groups in working memory (p 0.62) or inhibit (p 0.75) scales. Participants experiencing intervention emergent adverse events The rate was 7% in the intervention compared to 2% in the control group. There were no serious intervention-related adverse events or discontinuations due to adverse events in either group.</td>
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</table>
| Cognitive training | Nejati, 2022; ID: RCT Multicenter N = 35 Iran Setting: School | **Target:** Children with ADHD; in each kindergarten children with behavioral problems were selected by their teachers for the study and then clinically assessed  
**Other:** Blinded parents completed outcome instruments  
**ADHD presentation:** N/A  
**Diagnosis:** Confirmation by specialist DSM V  
**Comorbidity:** N/A  
**Female:** 13.3%  
**Age mean:** 6.23 (0.32)  
**Minimum age:** 6  
**Maximum age:** 7  
**Ethnicity:** | **Intervention:** PARISA (Program for Attentive Rehabilitation of Inhibition and Selective Attention), 6 progressive computerized tasks targeting 3 types of inhibitory control, 10-12 sessions, each 30-45 minutes, over a 4 to 5 week period  
**Control:** Attention-matched control Story telling group with opportunity for intervention after study ended  
**Comparator:** NA  
**Follow-up:** 1.5 months | **Child Behavior Checklist total** Significant (p 0.001) intervention effect compared to control.  
**SNAP-IV ADHD scale** Significant (p 0.001) intervention effect compared to control.  
Flanker test (assessing selective attention) scores favor intervention (p = .05). Go/No-go task (measuring prepotent inhibition) scores favor intervention (p = .001). |

- Poor reporting. Authors report mean age for experimental group = 11.16 (1.52), control group = 11.40 (1.99). Yet mean age for total = 10.74 (1.81).  
- **Minimum age:** 8  
- **Maximum age:** 14  
- **Ethnicity:** Other info on race or ethnicity: N/A, Other: Presumably 100% Persian

**Female:** 47%  
**Age mean:** 10.74 (1.81)
## Appendix C. Evidence Tables

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</table>
| Cognitive training | Raghuveer, 2020<sup>178</sup>  
ID: NA  
RCT  
Multicenter  
N = 70  
India  
Setting: School | **Target:** Children with ADHD who were not on medication; children with learning disabilities, autism spectrum disorders, musculoskeletal impairments, developmental delay, visual or audio impairments were excluded  
**Other:** Therapists or parents  
**ADHD presentation:** N/A  
**Diagnosis:** Confirmation by specialist DSM-IV criteria per clinician interview  
**Comorbidity:** N/A  
**Female:** %  
Not reported  
**Age mean:** 4.5 (1.06)  
**Minimum age:** 3  
**Maximum age:** 6  
**Ethnicity:** Other info on race or ethnicity: N/A | **Intervention:** Structured games which utilize visual-spatial sketch pad and phonological loop, 4 sessions per week for 5 weeks  
**Control:** NA  
**Comparator:** Parent training  
Training of one or both parents on behavioral controls strategies including praising, organizing the child's possessions (toys, clothing, etc.) and keep a routine schedule. One session of training was providing. Parents received a list of do's and don'ts  
**Follow-up:** 1.25 months | Intervention group performed significantly better (p <0.05) on the Sequin Form Board Test Time. |
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<td>Cognitive training</td>
<td>Shuai, 2020(^{118})</td>
<td>Target: 96 native Chinese speaking preschool children with DSM-V diagnosed ADHD, ranging from ages 4 years 0 months to 5 years 11 months. No major sensory-motor disorders, no history of brain damage, epilepsy, no diagnosis of autism spectrum disorder, no intelligence quotient (IQ) score &lt;80, and no pharmacological or nonpharmacological treatment. Other: Parents ADHD presentation: inattentive: 8.3, hyperactive: 19.8, combined: 71.9</td>
<td>Intervention: Executive Function Training for Preschool is structured psychotherapy 90-min sessions (60-min for children, 30-min for parents) once a week for 8 weeks. Sessions contained four parts: tasks and games aiming to practice executive function (40 min), paper-pencil tasks (15 min), relaxation (5 min) for children; parents received session on guiding their child (30 min). Control: Wait list Put on waitlist and received treatment as usual. Comparator: NA</td>
<td>SNAP-IV (Swanson, Nolan, and Pelham Rating Scale Chinese version) The intervention group had significantly reduced ODD symptoms compared to control group (p=.02), but differences in inattention scores were not significant (p=0.24). Differences in BRIEF-P scores between intervention group and control group were not significant (p=0.47).</td>
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<td>Cognitive training</td>
<td>van der Donk, 2015&lt;sup&gt;53&lt;/sup&gt;</td>
<td><strong>Target:</strong> Children with ADHD, some with comorbid learning disabilities and/or oppositional defiant disorder <strong>Other:</strong> ADHD presentation: inattentive: 25.0, combined: 64.0, N/A: not specified- 11% <strong>Diagnosis:</strong> Confirmation by specialist Parents were also asked to send a copy of the diagnostic psychiatric report of their child to establish the subtype of ADHD and rule out other potential psychiatric problems <strong>Comorbidity:</strong> N/A <strong>Female:</strong> 28.0 % <strong>Age mean:</strong> 9.9 (1.3) <strong>Minimum age:</strong> 8 <strong>Maximum age:</strong> 12 <strong>Ethnicity:</strong> Other info on race or ethnicity: N/A</td>
<td><strong>Intervention:</strong> Combined working memory and compensatory training (Paying Attention in Class): participants trained individually outside the classroom for 5 weeks, five times a week, about 45 min a day <strong>Control:</strong> NA <strong>Comparator:</strong> Cognitive trainingCogmed Working Memory Training is a computerized training program consisting of a variety of game format tasks. 5 weeks, five times a week, about 45 min a day <strong>Follow-up:</strong> 6 months</td>
<td>CBCL (Child Behavior Checklist), parent report There were no significant differences between groups for either subscale (attention problems, p=0.593, externalizing problems, p=0.243). No significant differences between groups at follow-up for BRIEF, Behavioral Regulation Index, parent report (p 0.46), BRIEF (Behavioral Regulation Index, teacher report; p 0.217) and Learning efficiency quotient, word reading fluency score.</td>
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<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
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<td>Intervention; Control; Comparator; Follow-up</td>
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</tbody>
</table>
| Cognitive training | Wennberg, 2018<sup>102</sup>  
ID: NA  
RCT  
Multicenter  
N = 46  
Sweden  
Setting: N/A | Target: Diagnosis of ADHD, age 9–15 years and parent-reported difficulties with daily time management, despite medication for ADHD. No autism spectrum disorder; no intelligence quotient <70; able to answer questions in Swedish.  
Other: Parents of children with ADHD  
ADHD presentation: N/A  
Diagnosis: Confirmation by specialist  
ADHD diagnosis was determined in accordance with DSM-IV criteria by an experienced clinician  
Comorbidity: N/A  
Female: 26 %  
Age mean:  
Intervention group mean age (11.7) and SD (1.83). Control group mean age (11.1) and SD (1.71).  
Minimum age: 9  
Maximum age: 15  
Ethnicity: Other info on race or ethnicity: N/A | Intervention: Compensation and remediation lasted about 12 weeks: compensation were 1.5-hour sessions with 3-4 sessions in the study period, remediation training sessions were 3 times per week with 20 minutes per day assigned outside of sessions  
Control: Other  
Received standard methods of care alone.  
Comparator: NA  
Follow-up: 8 months | The Kit for assessing time-processing ability (KaTid) assesses time perception, time orientation and time management. The intervention group improved more on total score (p = 0.019), time perception score (p = 0.046), time orientation (p = 0.010), but not time management (p = 0.764). |
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| Cognitive training | Wu, 2023<sup>16</sup> | Target: Children with ADHD; those with serious medical conditions or neuropsychiatric diseases were excluded, as were those on any ADHD meds  
Other: Parents reported outcomes  
ADHD presentation: inattentive_other : Mean ADHD-RS inattention score: intervention 17.3 (4.50), comparator 18.2 (3.79),hyperactive_other : Mean ADHD-RS hyperactivity score: intervention 13.9 (5.30), comparator 13.8 (6.09)  
Diagnosis: Confirmation by specialist DSM IV by child psychiatrists, via K-SADS-PL  
Comorbidity: N/A  
Female: 15 %  
Age mean: 8.35 (1.26)  
Minimum age: 6  
Maximum age: 12  
Ethnicity: % Asian : 100  
Other info on race or ethnicity: | Intervention: Executive function training (AET), designed and developed by Infinite Brain Technology, is a battery of several digital cognitive trainings designed to improve impaired executive functions; training tasks were adapted from N-back task, visual-spatial memory task, Schulte Grid, Go/No-go task, and mental calculation; difficulty is automatically adjusted to match participants’ progressive skills; participants were required to complete 48 training sessions within a two-month period  
Control:  
Comparator: General executive function training (GET) is a multiple component training targeting cognitive functions which are not closely associated with ADHD, such as processing speed, reasoning, and planning; participants were required to complete 48 training sess  
Follow-up: 2 months | CBCL-attention problems  
ADHD-RS total, parent report  
No significant difference in improvement  
No significant difference in improvement on Behavior Rating Inventory of Executive Function (BRIEF)—Parent scores or Cambridge Neuropsychological Test Automated Battery (CANTAB) scores |
| Study: | Author, year;  
Multiple publications;  
Trial ID;  
Study design;  
Sites;  
Study size;  
Location Setting | Population: | Study design;  
Sites;  
Study size;  
Location Setting | Comparison:  
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<td>Combined pharmacological + behavioral</td>
<td>Abikoff, 2004&lt;sup&gt;114&lt;/sup&gt; Hechtman, 2004&lt;sup&gt;708&lt;/sup&gt;; Klein, 2004&lt;sup&gt;585&lt;/sup&gt; ID: N/A RCT Multicenter N = 103 Multiple countries Setting: Mixed</td>
<td>Target: Children with ADHD free of conduct and learning disorders, who responded to short-term methylphenidate who had a current or had a previous positive response to methylphenidate Other: Parents ADHD presentation: N/A Diagnosis: Confirmation by specialist DSM-III-R criteria by child psychologists Comorbidity: N/A Female: 7 % Age mean: 8.2 (0.8) Minimum age: 7 Maximum age: 9 Ethnicity: % Hispanic or Latino : 2 % Black/African American : 13 % White : 84 Other info on race or ethnicity:</td>
<td>Intervention: Methylphenidate plus intensive multimodal psychosocial treatment; methylphenidate maximum dose design up to maximum 50mg/day divided 3 times per day, multimodal treatment modules manual-based delivered once weekly during the first year (requiring 2 clinic visits per week) and once monthly during the second year (requiring 2 clinic visits per month), treatment period of 2 years Control: Other Methylphenidate alone, no other intervention (except for crisis sessions when required); after the child was stabilized on medication, children and parents were seen once per month by a child psychiatrist; the dose was maintained, precluding side effects Comparator: NA Follow-up: 24 months</td>
<td>Observation with Classroom Observation Code during academic classes Classroom behaviors yielded no significant group or interaction effects. C-GAS (Children’s Global Assessment Scale) There was no significant difference between groups. ADHD diagnosis Social functioning No advantage was found on any measure of social functioning for the combination treatment over methylphenidate alone or methylphenidate plus attention control; significant improvement occurred across all treatments and continued over 2 years.</td>
</tr>
<tr>
<td>Combined pharmacological + behavioral</td>
<td>Blader, 2021&lt;sup&gt;159&lt;/sup&gt; Joseph Blader, 2008&lt;sup&gt;841&lt;/sup&gt; ID: NCT00794625 RCT Multicenter N = 175</td>
<td>Target: Diagnosed with ADHD (any subtype) and either oppositional defiant disorder or conduct disorder according to DSM-IV-TR; required an R-MOAS total score &gt;24 at both the initial telephone screening and the in-person evaluation with recent or</td>
<td>Intervention: Stimulant medication and behavioral therapy plus risperidone, dose started at 0.25 mg each evening for 3 days, with a morning dose of 0.25 mg added on the fourth day, dose adjustments were elective and based on response and tolerability</td>
<td>Retrospective Modified Overt Aggression Scale (R-MOAS), parent % in remission from aggression (R-MOAS &lt;15) Intervention and comparator had larger reductions in aggression relative to the placebo group (risperidone p &lt;0.003; divalproex sodium p&lt;0.046). Percent in</td>
</tr>
</tbody>
</table>
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>Setting: Specialty care</td>
<td>current treatment with stimulant medication at a minimum daily total dose equivalent of 30 mg of immediate-release methylphenidate for at least 30 days; required no current or previous major depressive disorder, bipolar I or II disorder, Tourette’s disorder, autism spectrum disorder, or any psychotic disorder as defined by DSM-IV-TR, and IQ greater than or equal to 70; no seizure disorders; no pregnancy; and no contraindications to treatment with stimulants Other: ADHD presentation: N/A Diagnosis: Confirmation by specialist Completion of the Schedule of Affective Disorders and Schizophrenia for School-Age Children (K-SADS) with a parent and the child by a clinical child psychologist or a child and adolescent psychiatrist. A second clinician (child and adolescent psychiatrist Comorbidity: ODD Female: 19 % Age mean: 9.63 (2.02)</td>
<td>Control: Placebo Stimulant medication and behavioral therapy plus placebo Comparator: Medication + behavioral Stimulant medication and behavioral therapy plus divalproex sodium, aimed to achieve approximately 18 mg/kg by the end of the first week; when permitted by valproic acid level, dose increases by 125 mg or 250 mg occurred based on clinical response through Follow-up: 2 months</td>
<td>remission from aggression—remission was met by 69% of the risperidone group, 40% of the divalproex There were no instances of serious adverse events.</td>
</tr>
</tbody>
</table>
### Intervention

<table>
<thead>
<tr>
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<th>Comparison:</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Coelho, 2017</td>
<td>Crossover trial; Unclear/Not reported; N = 67; Brazil; Setting: Specialty care</td>
<td>Target: ADHD as a primary disorder and no signs of neurodevelopmental delay, epilepsy, genetic syndromes, HIV, hydrocephalus, brain damage, and not currently taking other medications</td>
<td>Intervention: Group cognitive-behavioral therapy and medication, prolonged-release methylphenidate 20 mg for 20 weeks, group cognitive-behavioral therapy attended by parents and children, family sessions lasted 40 minutes and sessions with children about 80 minutes</td>
<td>CBCL (Child Behavior Checklist), total problems Cognitive and behavioral outcome measures showed no differences between treatment groups. On social skills, multimodal showed more improvement in frequency indicators on empathy, assertiveness, and self-control subscales and in the difficulty on assertiveness and self-control subscales</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other: ADHD presentation: inattentive: 47, combined: 54</td>
<td>Control: Other Prolonged-release methylphenidate 20 mg for 20 weeks alone</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Diagnosis: Confirmation by specialist DSM-4, clinicians who specializes in diagnosing children and adolescents with neurodevelopmental disorders</td>
<td>Comparator: NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comorbidity: N/A</td>
<td>Follow-up: 5 months</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Female: 25 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age mean: 10.2 (2.0)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Minimum age: 7</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Maximum age: 14</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Ethnicity: % White: 100</td>
<td></td>
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<table>
<thead>
<tr>
<th>Minimum age: 6</th>
<th>Maximum age: 12</th>
<th>Ethnicity: % Hispanic or Latino : 30.29 % Black/African American : 16.57 % White : 46.29 Other info on race or ethnicity: Other : 6.86 other</th>
</tr>
</thead>
</table>

**Footnote:**

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### Intervention

<table>
<thead>
<tr>
<th>Study:</th>
<th>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>David, 2021 Babes-Bolyai University, 2018 ID: ISRCTN92640175 RCT Single center N = 59 Romania Setting: Specialty care</td>
</tr>
</tbody>
</table>

#### Population:

<table>
<thead>
<tr>
<th>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setting: Specialty care</td>
</tr>
<tr>
<td>Comparator: NA Follow-up: 4 months</td>
</tr>
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</table>

#### Comparison:

<table>
<thead>
<tr>
<th>Intervention; Control; Comparator; Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined pharmacological + behavioral</td>
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</table>

Other info on race or ethnicity:

- Other info on race or ethnicity:
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<tr>
<th>Intervention</th>
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<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined pharmacological + behavioral</td>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Target: Children with ADHD combined type (MTA)</td>
<td>Intervention: Multimodal Treatment Study of Children With ADHD (MTA), intensive multicomponent behavior therapy consisting of medication management and behavior modification, treatment period of 36 months</td>
<td>Parent and teacher average rating of oppositional defiant disorder symptoms from the SNAP Ratings were similar across groups. SWAN Both groups improved from baseline. Columbia Impairment Scale (CIS) No significant moderator effects of comorbidity were found in the treatment comorbidity group interactions (p = 0.21). Wechsler Individual Achievement Test (WIAT) Both groups improved from baseline. None of the treatment groups differed significantly on the social skills rating system (SSRS). After 14 months, children treated with methylphenidate had gained less height and less weight (-1.23 cm per year and -2.48 kg per year) than untreated children; Followup into young adulthood (25 yo) within naturalistic subgroups of ADHD cases, ext Children with ADHD and manic symptoms respond robustly to methylphenidate during the first month of treatment and are not more likely to have an adverse response to methylphenidate.</td>
</tr>
<tr>
<td></td>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Other:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADHD presentation: combined : 87.5, N/A : comm control 79.5</td>
<td>Intervention: Multimodal Treatment Study of Children With ADHD (MTA), intensive multicomponent behavior therapy consisting of medication management and behavior modification, treatment period of 36 months</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Diagnosis: Confirmation by specialist DSM-IV</td>
<td>Control: TAU</td>
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<tr>
<td></td>
<td></td>
<td>Comorbidity:</td>
<td>Comparator: NA</td>
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<tr>
<td></td>
<td></td>
<td>Female: 21 %</td>
<td>Follow-up: 36 months</td>
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<tr>
<td></td>
<td></td>
<td>Age mean: 11.8 (0.95)</td>
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<tr>
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<td>Minimum age: 11</td>
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<td></td>
<td></td>
<td>Ethnicity:</td>
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<tr>
<td></td>
<td></td>
<td>% Hispanic or Latino : 36</td>
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<tr>
<td></td>
<td></td>
<td>% Black/African American : 20.2</td>
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<tr>
<td></td>
<td></td>
<td>% White : 61.7</td>
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<tr>
<td></td>
<td></td>
<td>Other info on race or ethnicity: Other : 10.7 %</td>
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<tr>
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<tbody>
<tr>
<td>Combined pharmacological + behavioral</td>
<td>Karakaya, 2019&lt;sup&gt;150&lt;/sup&gt; ID: NA RCT Single center N = 41 Turkey Setting: Specialty care</td>
<td>Target: Adolescents receiving treatment ADHD, on medication, residing in the city center Other: ADHD presentation: N/A Diagnosis: Confirmation by specialist diagnosed prior to study; were already receiving medication tx through clinic Comorbidity: N/A Female: 19.5 % Age mean: 13.2 (1.25) Minimum age: 12 Maximum age: 18 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Intervention: Solution-focused approach comprised of 6 sessions, each 45-60 minutes, 1 per week for 6 weeks, individually and face-to-face, in addition to ADHD medication treatment with psychostimulants and clinic follow-up Control: Other No intervention, but ADHD medication treatment with psychostimulants as usual Comparator: NA Follow-up: 3 months</td>
<td>General Self-Efficacy Scale (GSE) evaluates the extent to which individuals perceive themselves as adequate in coping with difficulties. Intervention group score was higher at follow up (p&lt;0.001).</td>
</tr>
<tr>
<td>Combined pharmacological + behavioral</td>
<td>Perez-Alvarez, 2009&lt;sup&gt;402&lt;/sup&gt; ID: NA RCT Single center N = 96 Spain Setting: Specialty care</td>
<td>Target: Children and adolescents with SNAP IV teacher rating scores of at least 2.5 and parent ratings of at least 1.8, all had planning dysfunction according to PASS (planning, attention, successive and simultaneous) scales; patients with medical and psychiatric comorbidities were excluded Other: Parents and teachers provided some outcome data ADHD presentation: inattentive: 79, hyperactive: 0, combined: 21</td>
<td>Intervention: Methylphenidate plus humanistic intervention; extended release methylphenidate hydrochloride administered at an optimal dose plus humanistic psychological intervention conducted as 24 sessions, 1 every 15 days, treatment followed up for 12 months Control: Other Extended release methylphenidate hydrochloride alone</td>
<td>Swanson, Nolan, and Pelham scale 18 (SNAP-IV-18), number in remission (score &lt;= 1.0) Intervention scored better than control (p &lt; .05). PASS (planning, attention, successive, and simultaneous processes) cognitive assessment: only significant difference at follow-up was for planning scale; intervention group improved more (p &lt; .05).</td>
</tr>
</tbody>
</table>
## Appendix C. Evidence Tables

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<tr>
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<tr>
<td><strong>Study:</strong></td>
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<td><strong>Population:</strong> Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td><strong>Comparison:</strong> Intervention; Control; Comparator; Follow-up</td>
<td><strong>Outcome and results</strong></td>
</tr>
<tr>
<td><strong>Diagnosis:</strong></td>
<td>Confirmation by specialist ADHD diagnostic interview schedule for children module was completed face-to-face with the child’s principal caregiver by trained research interviewers.</td>
<td><strong>Comparator:</strong> NA</td>
<td><strong>Follow-up:</strong> 12 months</td>
<td></td>
</tr>
<tr>
<td><strong>Comorbidity:</strong></td>
<td>N/A</td>
<td><strong>Follow-up:</strong> 12 months</td>
<td><strong>Outcome and results</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Female:</strong></td>
<td>20 %</td>
<td><strong>Follow-up:</strong> 12 months</td>
<td><strong>Outcome and results</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Age mean:</strong></td>
<td>ADHD-Combined 9 (2), ADHD-Inattentive 12 (3)</td>
<td><strong>Follow-up:</strong> 12 months</td>
<td><strong>Outcome and results</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Minimum age:</strong></td>
<td>7</td>
<td><strong>Follow-up:</strong> 12 months</td>
<td><strong>Outcome and results</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Maximum age:</strong></td>
<td>15</td>
<td><strong>Follow-up:</strong> 12 months</td>
<td><strong>Outcome and results</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity:</strong></td>
<td>Other info on race or ethnicity: N/A</td>
<td><strong>Follow-up:</strong> 12 months</td>
<td><strong>Outcome and results</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Target:** Adolescents meeting DSM-IV criteria for current ADHD and at least one nontobacco Substance User Disorder (SUD). Exclusion criteria were current or past psychotic disorder, bipolar disorder, suicide risk, opiate dependence, methamphetamine abuse or dependence, cardiac illness or serious medical illness, pregnancy, past month use of psychotropic medications or participation in other substance or mental health treatment **Other:**

**Intervention:** Cognitive behavioral therapy plus osmotic-release methylphenidate (OROS); 72mg methylphenidate once daily and manual-standardized, individual CBT using motivational enhancement approaches, for 16 weeks **Control:** Other Cognitive behavioral therapy plus matching placebo, manual-standardized, individual CBT using motivational enhancement approaches

Treatment responders based on CGI-I (score of 1 or 2) Rates of treatment response were not significantly different (P=0.418) between treatment (23.4%) and control (19.1%). **ADHD-RS** There were no group differences on reduction in ADHD-RS scores. Substance use in the past 28 days: there was no between-group difference (p 0.321). Adolescents treated with OROS-MPH + CBT had significantly more negative urine drug screens compared to participants treated with placebo + CBT (p 0.05).
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<tr>
<td>Combined pharmacological + behavioral</td>
<td>Sprich, 2016[48] Massachusetts General Hospital, 2009[77] ID: NCT01019252 Crossover trial Single center N = 46 US Setting: Specialty care</td>
<td>Target: Adolescents 14-18, with ADHD on a stable dose (defined as no change in dose for at least 2 months) of an FDA-approved medication without severe comorbid disorders that could interfere with participation, active suicidality, conduct disorder, active substance abuse or dependence, organic mental disorder, mental retardation, pervasive</td>
<td>Comparator: NA Follow-up: 4 months</td>
<td>Treatment-emergent study-related adverse events Participants treated with OROS-MPH reported more treatment-emergent study-related AEs than control group (p=0.02). No statistically significant differences between groups on self-reported medication abuse (taking more medication than prescribed, 4.8% vs 2.8%, p&gt;0.05) or diversion (selling medication to others, 2.1% vs 1.4%, p&gt;0.05; letting others take your medication,</td>
</tr>
</tbody>
</table>

ADHD presentation: inattentive: 28.1, hyperactive: 2.6, combined: 68.6

Diagnosis: Confirmation by specialist DSM-IV per Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiologic Version (K-SADS-E)

Comorbidity: Other: SUD

Female: 21.1%

Age mean: 16.5 (1.3)

Minimum age: 13

Maximum age: 18

Ethnicity:

- % Hispanic or Latino: 15.2
- % Black/African American: 23.2
- % White: 61.7

Other info on race or ethnicity:

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<tr>
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<td>Comparator: NA Follow-up: 4 months</td>
<td>Treatment-emergent study-related adverse events Participants treated with OROS-MPH reported more treatment-emergent study-related AEs than control group (p=0.02). No statistically significant differences between groups on self-reported medication abuse (taking more medication than prescribed, 4.8% vs 2.8%, p&gt;0.05) or diversion (selling medication to others, 2.1% vs 1.4%, p&gt;0.05; letting others take your medication,</td>
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<tbody>
<tr>
<td></td>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>developmental disorder, or prior CBT for ADHD</td>
<td>Intervention; Control; Comparator; Follow-up</td>
<td>Comparator: NA</td>
</tr>
<tr>
<td></td>
<td>Abikoff, 2007&lt;sup&gt;1&lt;/sup&gt;6; Greenhill, 2006&lt;sup&gt;7&lt;/sup&gt;22; Ghuman, 2007&lt;sup&gt;7&lt;/sup&gt;66; Swanson, 2006&lt;sup&gt;6&lt;/sup&gt;071; Wigal, 2006&lt;sup&gt;1&lt;/sup&gt;480; Kollins, 2006&lt;sup&gt;6&lt;/sup&gt;86; ID: N/A</td>
<td>Other: ADHD presentation: N/A Diagnosis: Confirmation by specialist Kiddie-Schedule for Affective Disorders and Schizophrenia-Epidemiologic Version No Comorbidity: N/A Female: 21.7 % Age mean: Intervention 15.17 (1.01), control 15.09 (1.11) Minimum age: 14 Maximum age: 18 Ethnicity: % Black/African American : 2.17 % Asian : 0 % Native Hawaiian or Pacific Islander : 2.17 % White : 93.5 Other info on race or ethnicity:</td>
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</tr>
</tbody>
</table>

**Target:** Children between the ages of 3-5.5 years and an impairment scale score of less than or equal to 55 on the Children Global Assessment Scale

**Other:** Parents and teachers of the children

**Intervention:** Methylphenidate 1.25, 2.5, 5, or 7.5 mg 3 times per day for 4 weeks

**Control:** Placebo Placebo treatment

**Comparator:** NA

CGI-S (Clinical Global Impression-Severity) Proportion of excellent responders Scale scores were significantly better for children in the treatment group compared to the placebo group (p < 0.0001) but only 21% on best-dose MPH and 13% on placebo
### Appendix C. Evidence Tables

<table>
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<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
</table>
| RCT          | Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting | ADHD presentation: hyperactive: 29.51, combined: 70.49 | Follow-up: 1 month | achieved MTA-defined categorical criterion for remission set for school-age children with ADHD. 
SWAN (Strengths and Weaknesses of ADHD-Symptoms and Normal Behaviors), parent version. There was no significant difference in treatment group and placebo group for parents. 
Social Skills Rating System (Parent) (SSRS-P) change, measures social function. Effect size 0.14, ANCOVA treatment effect not statistically significant. 
There was no significant difference in parental stress across the treatment and placebo groups. 
Growth rates. During methylphenidate treatment, slope indicated a reduction of growth rates. 
There were eight serious adverse events, but only one, a possible seizure, was thought to be related to medication. There were no episodes of mania, hypomania, depression, or suicidality. |
|              | N = 114 | Diagnosis: Confirmation by specialist. Used the DSM-IV edition, the psychiatrists interviewed children and made them take examinations to determine their scale scores. Comorbidity: N/A | Control; Comparator; Follow-up | 
|              | US     | Female: 19.67 % | | 
|              | Setting: School | Age mean: 4.39 (0.72) | | 
|              |         | Minimum age: 3 | | 
|              |         | Maximum age: 5.5 | | 
|              |         | Ethnicity: % Hispanic or Latino: 19.67 | | 
|              |         | % Black/African American: 19.67 | | 
|              |         | % White: 59.02 | | 
|              |         | Other info on race or ethnicity: | | 
| Abikoff, 2009 | Target: Medication naive children with ADHD who had problems with organization, time management, and planning. Other: Parents and teachers provided outcome data. | SNAP IV (Swanson, Nolan, and Pelham, Version IV) total score, parent rating. Mean SNAP IV parent rating, total score, and mean SNAP IV teacher rating, total score, were significantly lower in intervention group at follow-up (p < .005 for both outcomes). Lower is better. | | 
| NA           | Intervention: Methylphenidate osmotic-release oral system 48.3 mg (range 18-54 mg) daily for 2 weeks | Control: Placebo Placebo Comparator: NA | | 
| ID: Crossover trial Single center | N = 19 | US | |
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
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<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen, 2005123</td>
<td>FDA-approved pharmacological</td>
<td>Setting: Specialty care Diagnosis: Confirmation by specialist DSM IV criteria based on Diagnostic Interview Schedule for Children IV (DISC-IV)-Parent version Comorbidity: Other : impaired organizational skills per Children's Organizational Skills Scale Female: 21 % Age mean: 10.05 (1.62) Minimum age: 8 Maximum age: 13 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Follow-up: 2 months</td>
<td>Mean Children’s Organizational Skills Scale (COSS) total score, teacher rating, was significantly higher at follow-up for the intervention group (p &lt; .01). Mean Children’s Organizational Skills Scale (COSS) total score, parent rating, was also significantly higher at follow-up for the intervention group (p &lt; .05). Higher is better.</td>
</tr>
<tr>
<td>Multicenter N = 148 US Setting: Mixed</td>
<td>Target: Children 7-17 years old with diagnosis of ADHD according to DSM-IV and concurrent Tourette syndrome or chronic motor tic disorder, have scores on the Attention Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) had to be at least 1.5 SD above the age and sex norm, have scores of at least 5 on the Yale Global Tic Severity Scale (YGTSS). Exclusion: have a Children’s Yale–Brown Obsessive Compulsive Scale (C-YBOCS) total score larger or equal to 15, have a</td>
<td></td>
<td>ADHD-RS Total Significant treatment effects were obtained on all ADHD measures. Reduction in Yale Global Tic Severity Scale total score between placebo and atomoxetine is not statistically significant (p = 0.063). Decreased appetite Decrease appetite was reported in 15.9% of intervention and 2.8% of placebo participants. Discontinuations due to an adverse were 2 in the atomoxetine group (headache, vomiting) and 1 in the placebo group (upper abdominal pain); none was evaluated as serious.</td>
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</table>
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention Study:</th>
<th>Population:</th>
<th>Comparison:</th>
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<tbody>
<tr>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td></td>
<td>Intervention; Control; Comparator; Follow-up</td>
<td>Children's Depression Rating Scale–Revised (CDRS-R) total score of larger than 40, have a history of bipolar disorder or psychosis; seizure disorder; or current use of any psychotropic medication other than study drug</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other: ADHD presentation: inattentive: 35.8, hyperactive: 3.4, combined: 60.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diagnosis: Confirmation by specialist Schedule for Affective Disorders and Schizophrenia for School-age Children–Present and Lifetime Version16 (K-SADSPL) Comorbidity: Tic disorder</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Female: 11.5% Age mean: 11.2 (2.5) Minimum age: 7 Maximum age: 17</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ethnicity: % Hispanic or Latino: 6.1 % Black/African American: 4.7 % Asian: 0.7 % White: 87.8 Other info on race or ethnicity: Other: Other: 4/148 (2.7%)</td>
</tr>
<tr>
<td>Study:</td>
<td>Population:</td>
<td>Comparison:</td>
<td>Outcome and results</td>
</tr>
<tr>
<td>--------</td>
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</tr>
</tbody>
</table>
| Ashkenasi, 2011<sup>133</sup>  
ID: N/A  
RCT  
Single center  
N = 26  
US  
Setting: Other | **Target:** Children aged 6-12 years who met the DSM IV Edition criteria for attention deficit hyperactivity disorder (any subtype) and who demonstrated difficulty sleeping (as reported by the caregiver) were eligible; patients with previous intolerance, adverse response, or allergy to methylphenidate or skin sensitivity to the methylphenidate transdermal system, and those with severe comorbid psychiatric disorders were excluded  
**Other:**  
**ADHD presentation:** N/A  
**Diagnosis:** Confirmation by specialist DSM-IV  
**Comorbidity:** N/A  
**Female:** 27 %  
**Age mean:** 9.8 (1.8), 9.6 (1.8), 7.5, 10.3 (1.8) across groups  
**Minimum age:** 6  
**Maximum age:** 12  
**Ethnicity:** Other info on race or ethnicity: N/A | **Intervention:** Methylphenidate transdermal patch sequence of 9 hours, 10 hours, 11 hours, and 12 hours for 4 week, patch wear times maintained Monday through Thursday of each week, alternating wear times across 4 consecutive weeks with standard 9-hour wear time schedule Friday through Sunday  
**Control:** NA  
**Comparator:** MedicationMethylphenidate transdermal 12 hours, 11 hours, 10 hours, 9 hours for 4 weeks, patch wear times maintained Monday through Thursday of each week, alternating wear times across 4 consecutive weeks with standard 9-hour wear time schedule Friday through Sunday  
**Follow-up:** 1 month | There was no significant difference between groups (p=0.114).  
ADHD-RS-IV (Attention Deficit Hyperactivity Disorder Rating Scale-IV)  
There was no significant difference between groups (p=0.466).  
No significant effects of patch wear time on sleep latency (p=0.558) or total sleep time (p=0.382) were evident.  
No adverse event related treatment discontinuations were evident and no individuals reported a reaction greater than dark red and itchy. |
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA-approved pharmacological</td>
<td>Banaschewski, 2013[^157] Coghill, 2013[^702]; Coghill, 2014[^703]; Coghill, 2021[^705]; Shire, 2008[^1013] ID: NCT00763971 RCT Multicenter N = 336 Multiple countries Setting: Mixed</td>
<td>Target: Children and adolescents 6-17 years old who meet DSM-IV criteria for ADHD diagnosis, with baseline ADHD-RS-IV total score of 28 or higher. Key exclusion criteria included failure to respond to a previous course of OROS-MPH (but not of other formulations of methylphenidate) and the presence of a comorbid psychiatric diagnosis with significant symptoms (not including oppositional defiant disorder); patients whose current ADHD medication provided effective control of symptoms with acceptable tolerability were also excluded. Other: ADHD presentation: inattentive: 15.96, hyperactive: 3.01, combined: 80.72 Diagnosis: Confirmation by specialist ADHD-RS-IV Comorbidity: N/A Female: 19.3% Age mean: LDX 10.9 (2.9), placebo 11.0 (2.8), OROS-MPH 10.9 (2.6) Minimum age: 6</td>
<td>Intervention: Lisdexamfetamine dimesylate once daily (30, 50, or 70 mg/day) for 7 weeks Control: Placebo Placebo pill identical to study drugs given daily at 07:00 to participants Comparator: Medication Osmotic-release oral system methylphenidate (OROS) once daily, 18, 36, or 54 mg/day dose Follow-up: 2 months</td>
<td>CPRS-R (Conners Parent Rating Scale-Revised) change The intervention and comparator groups had significantly more improvement than the placebo group (p&lt;0.001). ADHD-RS-IV change The intervention and comparator groups had significantly more improvement than control group (p&lt;0.001). Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P) The intervention and comparator groups had significantly more improvement than control group (p&lt;0.001). Decreased appetite Active treatments reported more appetite suppression than placebo, no difference between treatment medications. Participants experiencing treatment emergent adverse events The rate was 72.1% for LDX, 64.9% for OROS-MPH, and 57.3% for placebo. The proportion of patients who reported serious treatment emergent adverse events were low across all groups.</td>
</tr>
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</table>
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study:</th>
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<tbody>
<tr>
<td>Bangs, 2007</td>
<td>FDA-approved pharmacological</td>
</tr>
<tr>
<td>ID: N/A</td>
<td>RCT</td>
</tr>
<tr>
<td>Multicenter</td>
<td>N = 142</td>
</tr>
<tr>
<td>Setting: N/A</td>
<td>US</td>
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<table>
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<tr>
<td>Maximum age: 17</td>
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<tr>
<td>Ethnicity:</td>
</tr>
<tr>
<td>% Hispanic or Latino : 1.20</td>
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<tr>
<td>% Black/African American : 0.30</td>
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<tr>
<td>% Asian : 0.30</td>
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<tr>
<td>% White : 97.0</td>
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<td>Other info on race or ethnicity:</td>
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<td>Other : 2.41</td>
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<table>
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<th>Comparison:</th>
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<tr>
<td>Intervention: Atomoxetine 1.2-1.8 mg/kg per day for 9 weeks</td>
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<tr>
<td>Control: Placebo</td>
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<tr>
<td>Placebo once daily</td>
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<tr>
<td>Comparator: NA</td>
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<tr>
<td>Follow-up: 2 months</td>
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</table>

<table>
<thead>
<tr>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD-RS-IV-Parent: Inv scale</td>
</tr>
<tr>
<td>Mean decrease was significantly greater in the intervention group (p=0.001).</td>
</tr>
<tr>
<td>There were no significant differences between treatment groups in Children’s Depression Rating Scale–Revised total scores at any time point.</td>
</tr>
<tr>
<td>Decreased appetite</td>
</tr>
<tr>
<td>Nausea and decreased appetite occurred significantly more often during the acute phase in the ATX treatment group compared with the placebo group.</td>
</tr>
<tr>
<td>One serious adverse event, worsening of depression, occurred during the acute treatment phase in the placebo group and led to the patient discontinuing the study due to lack of efficacy.</td>
</tr>
</tbody>
</table>
### Appendix C. Evidence Tables

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<th>Population</th>
<th>Comparison</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA-approved pharmacological</td>
<td>Bangs, 2008&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Target: Children with ADHD and oppositional defiance disorder (ODD). Those with serious psychiatric disorders or medical conditions were excluded.</td>
<td>Intervention: Atomoxetine, 1.2 mg/kg per day for ~8 weeks</td>
<td>Clinical Global Impression - Improvement (CGI-I) Atomoxetine group improved more on CGI-I (p = 0.037) and CGI-Severity (p=0.013).</td>
</tr>
<tr>
<td></td>
<td>RCT</td>
<td>ADHD presentation: inattentive: 9.7, hyperactive: 5.8, combined: 84.5</td>
<td>Control: Placebo</td>
<td>SNAP-IV Mean improvement in SNAP-IV ODD total score was not significantly different between groups (p = 0.252). Mean improvement in SNAP-IV Combined, Inattentive, and Hyperactivity score was significantly greater in the intervention groups (p &lt; 0.001, p &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td>Multicenter N = 226</td>
<td>Diagnosis: Confirmation by specialist DSM IV by an investigator's clinical assessment via structured interview (Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Version)</td>
<td>Comparator: NA</td>
<td>Decreased appetite Significantly more atomoxetine patients reported decreased appetite (p &lt; .001).</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Comorbidity: ODD: 100% ODD Female: 6.6 %</td>
<td>Follow-up: 2 months (8 weeks)</td>
<td>Nausea and fatigue were significantly higher for atomoxetine than for placebo (p= 0.033 and p = 0.021, respectively).</td>
</tr>
<tr>
<td></td>
<td>Specialty care Setting:</td>
<td>Age mean: 9.6 (1.9) Minimum age: 6 Maximum age: 12 Ethnicity:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Specialty care</td>
<td>% White: 95.2 Other info on race or ethnicity:</td>
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</table>
FDA-approved pharmacological

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: <em>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</em></th>
<th>Population: <em>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</em></th>
<th>Comparison: <em>Intervention; Control; Comparator; Follow-up</em></th>
<th>Outcome and results</th>
</tr>
</thead>
</table>
| Bedard, 2015*144*  
Mount Sinai, 2005*158*  
ID: NCT00183391  
Crossover trial Unclear/Not reported N = 102 US Setting: Other | Target: *Youth with ADHD, excluded were IQ below 75, non-English speaking parent or child, neurological dysfunction, systemic medical illness, uncorrected sensory impairments, and history of psychosis or bipolar disorder; other comorbidity was permitted provided ADHD was the primary disorder and the comorbid condition did not require medication treatment; participants may have been previously treated with ATX or MPH, but must not have been nonresponders to an adequate trial and must not have experienced disabling adverse effects with either medication*  
Other:  
ADHD presentation: inattentive : 37, hyperactive : 3, combined : 60  
Diagnosis: Confirmation by specialist  
DSM-IV  
Comorbidity: N/A  
Female: 25 %  
Age mean: 10.5 (2.7)  
Minimum age: 6  
Maximum age: 17  
Ethnicity: % Hispanic or Latino : 20 | Intervention: Atomoxetine 0.5 mg/kg, 1.0 mg/kg, 1.4 mg/kg, 1.8 mg/kg, administered each morning for 4-6 weeks  
Control: NA  
Comparator: MedicationMethylphenidate, 2 capsules of OROS MPH administered each morning, 18 mg, 36 mg, 54 mg, 72 mg  
Follow-up: 3.5 months | ADHD-RS  
Both medications produced significant improvement (p<0.001).  
For commission errors, there were no significant main effects of Drug or Time, and the Drug by Time was not significant. For omission errors, there was a significant Drug by Time interaction and a significant main effect of Time with no main effect of Drug, significant reduction in omission errors following MPH (p 0.001) but not ATX (p 0.69). There was a significant Drug by Time interaction such that youth treated with MPH had a greater speeding of RT than those treated with ATX. There was no main effect of Drug, but there was a main effect of Time. A post hoc paired t-test showed no significant change in RT for ATX (p = .99). There were main effects for Time and Drug on reaction time variability. There was also a significant Drug by Time interaction. MPH had a significantly larger impact than ATX. |
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Comparison</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td><strong>Study:</strong> Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td><strong>Population:</strong> Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td><strong>Outcome and results</strong></td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Clinical Global Impression (CGI) scale Ratings were either very much improved or much improved in over 70% of patients in the active treatment groups, compared with 18% in the placebo group. ADHD Rating Scale The 70mg group had the greatest symptom improvement compared to the placebo (p&lt;0.001). Decreased appetite Rates were 49.3% in the 70mg, 36.6% in the 30mg, and 4.2% in the placebo group (p&lt;0.05). Number of participants that experienced any adverse events Rates were 83.6% in the 70mg, 71.8% in the 30mg, and 47.2% in the placebo group. Statistically significant different adverse events in treatment groups vs. placebo: decreased appetite, insomnia, irritability, vomiting, weight loss, dry mouth.</td>
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<tr>
<td>Biederman, 2007&lt;sup&gt;152&lt;/sup&gt;</td>
<td><strong>Target:</strong> Children aged 6-12 with inadequate treatment or no previous treatment of ADHD and an ADHD Rating Scale version IV score greater than or equal to 28 <strong>Other:</strong> ADHD presentation: hyperactive : 4, combined : 96 Diagnosis: No Unspecified interviewer Comorbidity: N/A Female: 30.7 % Age mean: 9 (1.8) Minimum age: 6 Maximum age: 12 Ethnicity: % Hispanic or Latino : 17 % Black/African American : 24 % American Indian or Alaska Native : 0.7 % Asian : 1 % Native Hawaiian or Pacific Islander : 0.3 % White : 53 Other info on race or ethnicity:</td>
<td><strong>Intervention:</strong> Lisdexamfetamine dimesylate 70mg orally once per day for 4 weeks <strong>Control:</strong> Placebo Placebo <strong>Comparator:</strong> Medication Lisdexamfetamine dimesylate 30mg orally once per day for 4 weeks <strong>Follow-up:</strong> 1 month</td>
<td></td>
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<tr>
<td>ID: RCT Multicenter N = 290 US Setting: N/A</td>
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<tr>
<td>Intervention</td>
<td>Study:</td>
<td>Population:</td>
<td>Comparison:</td>
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</tr>
<tr>
<td>FDA-approved pharmacological</td>
<td>Biederman, 2008\textsuperscript{153}  Shire, 2003\textsuperscript{1022}  ID: NCT00152009  RCT  Multicenter  N = 345  US  Setting: N/A</td>
<td>Target: Children with ADHD, patients were excluded for a current, uncontrolled, comorbid psychiatric diagnosis (except oppositional defiant disorder) with significant symptoms, or when other symptomatic manifestations would contraindicate GXR treatment or confound efficacy or safety assessments; patients who weighed&lt;55 lb or were morbidly overweight or obese, pregnant, lactating, or hypertensive were also excluded, patients were not enrolled when they had any of the following: QTc interval of &gt;440 milliseconds, history of seizure during the past 2 years (exclusive of febrile seizures), tic disorder; family history of Tourette’s disorder; positive urine drug screen; abnormal thyroid function not adequately treated, any cardiac condition or family history of cardiac condition that would require exclusion, who had taken an investigational drug within 28 days, were taking medications that affect BP or heart rate, or were taking other medications that have central nervous system effects or affect performance were also not eligible Other:</td>
<td>Intervent: Guanfacine extended release 4 mg/day for 8 weeks  Control: Placebo  Matching placebo tablet  Comparator: MedicationGuanfacine extended release 2mg/day group, began dosing at 1 mg/day, escalated weekly in 1-mg increments  Follow-up: 2 months</td>
</tr>
</tbody>
</table>
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA-approved pharmacological</td>
<td>Block, 2009&lt;sup&gt;162&lt;/sup&gt; ID: N/A RCT Single center N = 288 US Setting: Primary Care</td>
<td>ADHD presentation: inattentive: 26.1, hyperactive: 2, combined: 71.9 Diagnosis: Confirmation by specialist DSM-IV Comorbidity: N/A Female: 25.5% Age mean: 10.5 (6.0–17.0) Minimum age: 6 Maximum age: 17 Ethnicity: % Hispanic or Latino: 9.9 % Black/African American: 13.3 % American Indian or Alaska Native: 0.3 % Asian: 0.6 % White: 70.1 Other info on race or ethnicity: Other: 5.8</td>
<td>Target: Children, 6 to 12 years old who met DSM-IV-TR criteria for ADHD Other: ADHD presentation: inattentive other: 16-26 across arms, hyperactive other: 1-3% across arms, combined other: 68-76% across arms</td>
<td>Intervention: Atomoxetine 1.25mg/kg/day each morning for 6 weeks Control: Placebo Placebo in the morning or evening for 6 weeks</td>
</tr>
</tbody>
</table>
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diagnosis: Confirmation by specialist clinical interview</td>
<td>Comorbidity: N/A</td>
<td>Comparator: Medication Evening dosing, 1.26mg/kg/day of atomoxetine for 6 weeks</td>
<td>Follow-up: 1.5 months</td>
</tr>
<tr>
<td></td>
<td>Female: 30 %</td>
<td>Age mean: Across arms 8.8 (1.7), 9.1 (1.6), 8.9 (1.7)</td>
<td>Minimum age: 6</td>
<td>Maximum age: 12</td>
</tr>
<tr>
<td></td>
<td>Ethnicity: Other: 62-70% across arms Other info on race or ethnicity:</td>
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</table>

Note: AM = morning; PM = evening; ADHD-RS-IV = Attention-Deficit/Hyperactivity Disorder Rating Scale IV; CGIP = Clinician’s Global Impression of Severity; P = Probability.
### Intervention

<table>
<thead>
<tr>
<th>Study:</th>
<th>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Brams, 2018&lt;sup&gt;169&lt;/sup&gt; Shire, 2015&lt;sup&gt;1020&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>ID: NCT02466425 RCT Multicenter N = 264 US Setting: Specialty care</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Population:</th>
<th>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target:</td>
<td>Children with ADHD Other: Clinician reported outcomes ADHD presentation: inattentive: 23.2, hyperactive: 1.1, combined: 75.7 Diagnosis: Confirmation by specialist DSM IV plus ADHD Rating Scale IV (ADHD-RS-IV) total scores &gt;=28 Comorbidity: N/A Female: 38% Age mean: 12.5 (3.24) Minimum age: 6 Maximum age: 17 Ethnicity: % Hispanic or Latino: NR % Black/African American: 28.5 % Asian: 0.3 % White: 61.2 % Multiracial: 8.0 Other info on race or ethnicity:</td>
</tr>
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<table>
<thead>
<tr>
<th>Comparison:</th>
<th>Intervention; Control; Comparator; Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Amphetamine, SHP465 mixed amphetamine salts (12.5 or 25 mg) for 4 weeks</td>
</tr>
<tr>
<td>Control:</td>
<td>Placebo</td>
</tr>
<tr>
<td>Comparator:</td>
<td>NA</td>
</tr>
<tr>
<td>Follow-up:</td>
<td>1 month</td>
</tr>
</tbody>
</table>

### Outcome and results

Abdominal pain, vomiting, somnolence, nausea, and stomach discomfort were reported more often with AM atomoxetine than with placebo; vomiting was reported more often with PM atomoxetine than with placebo; no significant differences between AM and PM atomoxetine in the incidence of any particular adverse event were observed.

CGI-I (Clinical Global Impressions-Improvement) Intervention group improved significantly more than placebo group (p < 0.001).

ADHD-RS-IV change Change from baseline significantly favored intervention over placebo (p<0.001).

Appetite decrease Significantly more participants in the intervention group experienced decreased appetite than control group participants.

Participants with any adverse event The rate was 67% for intervention and 47% for control.

The frequency of treatment-emergent adverse events leading to discontinuation was greater with the intervention treatment than with placebo.
### FDA-approved Pharmacological

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buitelaar, 2007</td>
<td></td>
<td></td>
<td>Intervention: Atomoxetine 0.5-1.8 mg/kg/d for 6 months</td>
<td>CGI-S (Clinical Global Impressions–Severity of Illness) change Statistically significant difference favoring atomoxetine (p 0.003). ADHD-RS-IV Total Score Relapse rate Atomoxetine was superior to placebo in maintaining symptom response (p 0.001). The relapse rate was 2.5% for atomoxetine and 12.2% for placebo. CHQ (Child Health Questionnaire) Psychosocial Summary Score No difference between groups. Effects on sexual development: Tanner stage: No statistically significant differences were observed between treatment groups either in sexual development (mean time, in days, to the first Tanner stage change, p=0.33) or in the duration of treatment exposure (p = 0.90). Weight increase in weight percentile Both groups showed an increase in weight percentile, but the increase was greater in the placebo group (p 0.001). Participants reporting at least 1 new or worsened adverse event The rate was 65.6% (intervention) vs 53.7% (placebo). Two adverse events were reported in more than 5% of subjects in both treatment groups.</td>
</tr>
<tr>
<td>Trzepacz, 2011; Michelson, 2004</td>
<td></td>
<td></td>
<td>Control: Placebo Placebo-controlled Comparator: NA Follow-up: 12 months</td>
<td></td>
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<tr>
<td>ID: N/A RCT Multicenter N = 163 Multiple countries Setting: Other</td>
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<tr>
<td></td>
<td>Target: Children with ADHD: patients with bipolar disorder or psychotic illness were excluded, as were patients with unstable medical illness or conditions requiring ongoing administration of a psychoactive medication (other than atomoxetine)</td>
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<tr>
<td></td>
<td>Other: ADHD presentation: inattentive: 22.9, hyperactive: 4.5, combined: 72.6</td>
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<td>Diagnosis: Confirmation by specialist DSM-IV Comorbidity: N/A Female: 10.6 % Age mean: 10.6 (2.3) Minimum age: 6 Maximum age: 15 Ethnicity: Other info on race or ethnicity: N/A</td>
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<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetin, 2015(^{183}) ID: N/A RCT Single center N = 145 Turkey Setting: Specialty care</td>
<td>Target: Patients without any comorbid psychopathologies Other: ADHD presentation: inattentive: 12.6, hyperactive: 0, combined: 87.4 Diagnosis: Confirmation by specialist DSM-IV-TR by child psychiatrists Comorbidity: N/A Female: 18.4 % Age mean: 9.47 (2.32) Minimum age: 7 Maximum age: 16 Ethnicity: Other info on race or ethnicity: Other: Ethnicity, Turkish patients but not sure of race</td>
<td>Intervention: Atomoxetine, mean dose 1.14±0.13 mg/kg/day Control: NA Comparator: Medication Osmotic release oral system methylphenidate (OROS), mean dose of 0.73±0.22 mg/kg/day for 10 weeks Follow-up: 6 months</td>
<td>Conners Comprehensive Behavior Rating Scale-Behavior Problems, teacher There was no significant difference between groups (p=0.720). Weight loss The rate was 1.6% in both groups. Adverse effects The rate was 31.1% in the OROS-MPH and 27.1% in the ATX group. The most commonly encountered adverse effect was anorexia in both groups, and it was seen in 19.6% of the patients in the OROS-MPH group and 13.5% of the patients in the ATX group.</td>
<td>Headache (atomoxetine, 8 [10.1%]; placebo, 7 [8.6%]) and nasopharyngitis (atomoxetine, 6 [7.6%]; placebo, 7 [8.6%]); all other adverse events were reported by &lt;= 5% of subjects, and none were reported significantly more often by those taking atomoxetine.</td>
</tr>
<tr>
<td>Childress, 2009(^{199}) ID: RCT Multicenter N = 253</td>
<td>Target: Children with ADHD who were drug naive or not treated with any MPH-related medication in the month prior to the study; those with serious psyc disorders were excluded.</td>
<td>Intervention: 30 mg extended release Dexmethylphenidate daily. Control: Placebo Placebo capsule daily</td>
<td>Clinical Global Impression - Improvement (CGI-I), number improved Significantly greater percentage of medication patients improved on CGI-I (p &lt; .001 for both groups). CGI-Severity ratings of each medication group was significantly better (p &lt; 0.001) than placebo group.</td>
<td></td>
</tr>
</tbody>
</table>
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>Setting: Specialty care</td>
<td>Other: Parents and teachers provided outcome information</td>
<td>Comparator: Medication10 mg extended release Dexamethylphenidate daily.</td>
<td>Conners'- ADHD DSM-IV Scales (CADS), teacher report Patients in medication groups demonstrated a significant improvement as compared to placebo (all p &lt; 0.001) on both CADS-T and CADS-P (parent report). Deceased appetite, number Significantly more medication patients experienced appetite decease. Number with any adverse event &quot;Overall incidence of adverse events was generally higher&quot; in medication groups; p values not reported. &quot; Adverse events were mild to moderate in severity&quot;</td>
</tr>
<tr>
<td></td>
<td>ADHD presentation: inattentive: 21.7, hyperactive: 2.8, combined: 73.9</td>
<td>Diagnosis: Confirmation by specialist DSM-IV-TR based on a psychiatric examination and K-SADS PL Comorbidity: N/A Female: 35.6 % Age mean: 8.7 (1.84) Minimum age: 6 Maximum age: 12 Ethnicity: % Black/African American: 0.8 % Asian: 0.8 % White: 57.7 Other info on race or ethnicity: Other: Other 12.6%</td>
<td>Follow-up: 1 month</td>
<td></td>
</tr>
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<td>Diagnosis: Confirmation by specialist DSM-IV-TR based on a psychiatric examination and K-SADS PL Comorbidity: N/A Female: 35.6 % Age mean: 8.7 (1.84) Minimum age: 6 Maximum age: 12 Ethnicity: % Black/African American: 0.8 % Asian: 0.8 % White: 57.7 Other info on race or ethnicity: Other: Other 12.6%</td>
<td>Comparator: Medication10 mg extended release Dexamethylphenidate daily.</td>
<td>Follow-up: 1 month</td>
<td>Conners'- ADHD DSM-IV Scales (CADS), teacher report Patients in medication groups demonstrated a significant improvement as compared to placebo (all p &lt; 0.001) on both CADS-T and CADS-P (parent report). Deceased appetite, number Significantly more medication patients experienced appetite decease. Number with any adverse event &quot;Overall incidence of adverse events was generally higher&quot; in medication groups; p values not reported. &quot; Adverse events were mild to moderate in severity&quot;</td>
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</table>

### Additional Information

- **FDA-approved pharmacological**
- **Childress, 2019**
- **Tris Pharma, Inc., 2017**
- **ID: NCT03088267**
- **RCT**
- **Single center** N = 36 US Setting: Other

<p>| Target: | Intervention: Amphetamine, optimized dose of 5–20 mg/day of amphetamine extended-release oral suspension for 5 days, and then crossed over on day 6 | Control: Placebo Matching placebo drug Comparator: NA Follow-up: 0.5 month | SKAMP-C (Swanson, Kotkin, Agler, M-Flynn, Pelham-Combined) Rating Scale score at 30 minutes postdose At both 30 minutes and 3 hours postdose, changes from baseline in SKAMP-C for AMPHEROS versus placebo were statistically significant (p&lt;0.01 and p=0.0002, respectively). AEs (&gt;10%) during the open-label phase included upper respiratory tract infection, fatigue, upper abdominal pain, headache, |
| Scolored greater or equal to the 90th percentile for sex and age on the ADHD rating scale-5, and needed to have no other disorder included in the DSM-V with the exception of a few other disorders including specific phobias and learning disorders, and have no comorbid medical illnesses such as hypertension, and thyroid disease or family history of sudden death | | | |</p>
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study: Childress, 2022 [198] Shire, 2017 [1021] ID: NCT03260205 RCT Multicenter N = 199 US</td>
<td>Population: ADHD diagnoses per DSM-IV, baseline scores of 28 (boys) or 24 (girls) on the parent reported ADHD-RS-IV-PS-TS and 4 on the Clinical Global Impression–Severity (CGI-S) scale. Required to have undergone nonpharmacologic treatment or to have had symptoms severe</td>
<td>Comparison: Intervention: Lisdexamfetamine 30 mg/day for 6 weeks Control: Placebo Matching placebo for 6 weeks Comparator: Medication Treatment with 5 mg lisdexamfetamine for 6 weeks</td>
<td>Decreased appetite, and affect lability. There were two subjects (11.1%) who reported decreased appetite and no reports of insomnia. No serious AEs or AEs leading to premature withdrawal were reported.</td>
</tr>
</tbody>
</table>

**Intervention:**
- Lisdexamfetamine 30 mg/day for 6 weeks
- Placebo Matching placebo for 6 weeks
- Medication Treatment with 5 mg lisdexamfetamine for 6 weeks

**Target:**
- ADHD diagnoses per DSM-IV, baseline scores of 28 (boys) or 24 (girls) on the parent reported ADHD-RS-IV-PS-TS and 4 on the Clinical Global Impression–Severity (CGI-S) scale. Required to have undergone nonpharmacologic treatment or to have had symptoms severe

**Comparison:**
- Intervention: Lisdexamfetamine 30 mg/day for 6 weeks
- Control: Placebo Matching placebo for 6 weeks
- Comparator: Medication Treatment with 5 mg lisdexamfetamine for 6 weeks

**Outcome and results:**
- CGI Global Impression scale Rates were 41.7% across all active treatment groups and 24.3% with placebo (p 0.0857).
- ADHD-RS-IV-PS Scores decreased more with lisdexamfetamine than placebo (p 0.0074, effect size –0.52).
- Results for the sleep diary were variable across treatment groups, with no notable
### Appendix C. Evidence Tables

| Intervention | Study: 
Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting | Population: 
Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity | Comparison: 
Intervention; Control; Comparator; Follow-up | Outcome and results |
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<tbody>
<tr>
<td>Setting: N/A</td>
<td>enough to warrant enrollment without prior nonpharmacologic treatment and to be engaged in structured group activities that allowed for assessment of ADHD symptoms and impairment outside of the home, Peabody Picture Vocabulary Test standard score 70 and to have lived with the same parent/LAR for 6 months; excluded if need meds for CNS, have a concurrent illness, disability or comorbidity. Other: ADHD presentation: combined : 91.6 Diagnosis: No Comorbidity: N/A Female: 32.3 % depends on placebo/tx group/pooled Age mean: 5.1 (6.54) Minimum age: 4 Maximum age: 5 Ethnicity: Other info on race or ethnicity: Other : depends on tx/placebo/pooled</td>
<td>Follow-up: 1.5 months</td>
<td>trends indicative of differential changes between active treatment and placebo. Decreased weight Weight decreased for two patients with 20 mg LDX but in no other group. Any treatment-emergent adverse event The rates were 57.9% in the intervention receiving 30mg, 33.3% in the comparator receiving 5mg, and 42.2% in the placebo group. Safety and tolerability assessments included treatment-emergent adverse events and changes in pulse (greater in all treatment group vs placebo) and blood pressure (greater in all treatment groups vs placebo).</td>
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</table>
**Appendix C. Evidence Tables**

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<tr>
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<th>Study:</th>
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</thead>
<tbody>
<tr>
<td>FDA-approved pharmacological</td>
<td>Cho, 2011&lt;sup&gt;200&lt;/sup&gt;</td>
<td><strong>Target:</strong> Children aged 6 to 18 years with a diagnosis of ADHD as defined by DSM-IV-TR, enrolled patients had to meet all of the following criteria: did not take any medication for ADHD treatment at least 2 weeks prior to randomization and at least 1 week prior to obtaining baseline ADHD-RS-IV-Parent:Inv and CGI-S scores; had no significant laboratory abnormalities or clinical conditions that would preclude participation at study entry; had no impairment in intelligence as assessed clinically by the investigator; and were able (along with parents or legal guardian) to keep appointments for clinic visits and all examinations as required by the protocol</td>
<td><strong>Intervention:</strong> Atomoxetine 0.5-1.2 mg/kg/day for 6 weeks</td>
<td>CGI-S and CGI-I Atomoxetine 1.2 mg/kg/day was associated with greater improvement compared with atomoxetine 0.2 mg/kg/day (p=0.0025). ADHD-RS-IV-Parent:Inv total score The ANCOVA model for demonstrated a significantly greater improvement in mean change for atomoxetine 1.2 mg/kg/day in a pairwise comparison with atomoxetine 0.2 mg/kg/day (p=0.006). Decreased appetite Rates were 12.5% in the intervention vs 7.41% in the comparator group. Participants with at least one treatment emergent adverse event The rates were 58.33 in the intervention and 40.74 in the comparator. The majority of these events were mild or moderate, and no events related to suicide ideation or self-harm were reported.</td>
</tr>
<tr>
<td></td>
<td>ID: N/A</td>
<td><strong>Setting:</strong></td>
<td><strong>Control:</strong></td>
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<td></td>
<td>RCT</td>
<td><strong>Study target:</strong></td>
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<td></td>
<td>Multicenter</td>
<td><strong>ADHD presentation:</strong></td>
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<td></td>
<td>N = 153</td>
<td><strong>Diagnosis:</strong> Confirmation by specialist DSM-IV</td>
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<td></td>
<td>Korea</td>
<td><strong>Comorbidity:</strong> N/A</td>
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<td></td>
<td>Setting: N/A</td>
<td><strong>Female:</strong> 16.3 %</td>
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<td><strong>Age mean:</strong> 9.8 (2.4)</td>
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<td><strong>Minimum age:</strong> 6</td>
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<td><strong>Maximum age:</strong> 18</td>
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<td><strong>Study design:</strong></td>
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<td><strong>Sites:</strong></td>
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<td></td>
<td><strong>Location:</strong></td>
<td>N/A</td>
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</tbody>
</table>
### Intervention Study

**Author, year:**
- Coghill, 2014
- Banaschewski, 2014
- Shire, 2009

**Trial ID:**
- NCT00784654

**Study design:**
- RCT

**Sites:**
- Multicenter

**Study size:**
- N = 157

**Location Setting:**
- Multiple countries

**Setting:**
- Specialty care

### Population

**Setting:**
- Specialty care

**Study target:**
- All patients had ADHD of at least moderate severity, defined as an ADHD-RS-IV total score of 28 or higher at baseline

**ADHD presentation:**
- inattentive: 17.3%
- combined: 82.2%
- combined_other: 0.5%

**Diagnosis:**
- Confirmation by specialist
- DSM-IV-TR by clinician

**Comorbidity:**
- N/A

**Female:**
- 21.7%

**Age mean:**
- 6-12 years: 66.9%
- 13-17 years: 33.1%

**Minimum age:**
- 6

**Maximum age:**
- 17

**Ethnicity:**
- % White: 94.9%

**Other info on race or ethnicity:**

### Comparison

**Intervention:**
- Lisdexamfetamine dimesylate optimal dose for up to 6 weeks orally

**Control:**
- Placebo

**Comparator:**
- NA

**Follow-up:**
- 8.25 months

### Outcome and results

**Ethnicity:**
- % Asian: 100

**Other info on race or ethnicity:**

**CGI-S treatment failure (at least 2-point increase)**
- The rate was 17.1% in the intervention compared to 68.8% in the placebo group.

**ADHD-RS-IV Total Score**
- Treatment failure (50% or greater increase in ADHD-RS-IV and 2-point increase in CGI-S)

**Significantly less participants in the intervention group met criteria for treatment failure compared to those in the control group (p<0.001).**

**The difference between the LDX and placebo groups changes from baseline to endpoint was significant (p<0.001).**

**CHIP-CE: PRF T-scores deteriorated in all domains in the placebo group, but not in the lisdexamfetamine dimesylate group.**

**Weight, kg**
- Decreased appetite
- The rate was 3.8% in the intervention compared to none in the placebo group.

**Participants with any treatment-emergent adverse events**
- The rate was 39.7% in the intervention compared to 25.3% in the placebo group.
### Intervention

**Study:**
- Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting

**Population:**
- Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity

**Comparison:**
- Intervention; Control; Comparator; Follow-up

**Outcome and results**

<table>
<thead>
<tr>
<th>FDA-approved pharmaceutical</th>
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</thead>
<tbody>
<tr>
<td>Concordia Pharmaceuticals, 2011[^209]</td>
</tr>
<tr>
<td>ID: NCT01439126</td>
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<tr>
<td>RCT</td>
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<tr>
<td>Multicenter</td>
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<tr>
<td>N = 135</td>
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<tr>
<td>US Setting: Mixed</td>
</tr>
</tbody>
</table>

**Target:** Children and adolescents ages 6-17 years old who meet DSM-IV-TR criteria for primary diagnosis for ADHD, IQ at least 70 or higher; exclusion: comorbid psychiatric conditions, other significant health conditions, pharmaceuticals used for ADHD treatment prior to 30 days before begin of study

**Other:**
- ADHD presentation: N/A
- Diagnosis: Confirmation by specialist Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime (MINI-Kid)
- Comorbidity: N/A
- Female: 30.4 %
- Age mean: 10.8 (2.88)
- Minimum age: 6
- Maximum age: 17

**Ethnicity:**
- % Hispanic or Latino : 23.7
- % Black/African American : 27.4
- % American Indian or Alaska Native : 0.0
- % Asian : .7
- % Native Hawaiian or Pacific Islander : 0.0
- % White : 64.4

**Intervention:** Clonidine hydrochloride 0.1 mg, 0.2 mg, 0.3 mg, or 0.4 mg taken daily for 26 weeks

**Control:** Placebo
Subjects randomized to the placebo arm were tapered off their optimal dose of KAPVAY at weekly intervals in decrements of 0.1 mg/day until reaching the dose of 0 mg/day, and then received only placebo for the rest of the study.

**Comparator:** NA

**Follow-up:** 6.5 months

**CGI (Clinical Global Impressions-Severity of Illness)**
- Intervention scores improved (mean 0.4, SD 1.40) when compared to placebo (mean 0.9, SD 1.28)
  - Intervention scores improved more (mean 3.0, SD 10.75) than the control (mean 7.0, SD 12.30).
- Weiss Functional Impairment Rating Scale-Parent (WFIRS-P)
  - N/A
- Change in Epworth Sleepiness Scale for Children (ESS-C) from randomization to end of study period (mean, SD): intervention, -0.6 (3.18), placebo, -0.6 (4.09)
- Number of subjects that responded "Yes" to the question "Do you have a wish to be dead" in Columbia Suicide Severity Rating Scale (C-SSRS) at Visit 20; intervention 0 count, placebo 1 count
- Participants with at least 1 treatment emergent adverse event
  - The rate was 50% for intervention and 46% for control.
### Intervention

**Connor, 2010**<sup>11</sup>
**Shire, 2006**<sup>1013</sup>

**ID:** NCT00367835
**RCT**
**Multicenter**
**N = 217**
**US**
**Setting:** Specialty care

**Target:** Children with ADHD and oppositional symptoms. Those with other psychiatric co-morbidities excluded.

**Other:** Parents provided some outcome data

**ADHD presentation:** inattentive: 12.6, hyperactive: 3.3, combined: 84.1

**Diagnosis:** Confirmation by specialist

**DSM-IV-TR per Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime**

**Comorbidity:** ODD

**Female:** 31.3 %

**Age mean:** 9.4 (1.84)

**Minimum age:** 6

**Maximum age:** 12

**Ethnicity:**
- % Hispanic or Latino: 16.8
- % Black/African American: 22.4
- % American Indian or Alaska Native: 2.8

**Intervention:** Guanfacine extended release 1-4 mg per day for 9 weeks

**Control:** Placebo

**Comparator:** NA

**Follow-up:** 2 months

**Outcome and results**

- A higher percentage of patients in the intervention group had improved on the CGI-S (p < .001).
- ADHD-RS-IV (ADHD Rating Scale IV) total score change, clinician rating
- Reduction in ADHD-RS-IV greater in intervention group than placebo group (p < .001).
- Medication Satisfaction Survey (MSS, number satisfied overall - agree or strongly agree)
- Greater percentage of intervention patients satisfied with treatment (p<0.001).
- Participants with any treatment emergent adverse event
  - The rate was 83.8% in the intervention and 57.7% in the placebo group.
  - Adverse events were more common in the intervention group. A higher percentage of intervention patients reported somnolence, sedation, dizziness, abdominal pain, fatigue, and irritability.
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervent</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
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<tr>
<td>FDA-approved pharmacological</td>
<td>Corkum, 2020[12] ID: NA RCT Unclear/Not reported N = 26 Canada Setting: Specialty care</td>
<td>Target: ADHD participants with or without periodic limb movements during sleep (PLMS) Other: ADHD presentation: inattentive : 34.6, combined_other : hyperactive-impulsive 65.4% Diagnosis: Confirmation by specialist psychologists and pediatricians. DSM-IV-TR Comorbidity: N/A Female: 11.5 % Age mean: 8.57 (2.0) Minimum age: 6 Maximum age: 12 Ethnicity: % Hispanic or Latino : 3.8 % White : 88.8 Other info on race or ethnicity: N/A,Other : Aboriginal 7.7%</td>
<td>Intervention: Methylphenidate hydrochloride for 2 weeks, &lt;20 kg = 20 mg daily dose, 20-30 kg = 30 mg, &gt;30 kg = 40 mg Control: Placebo Placebo Comparator: NA Follow-up: 1 month</td>
<td>ADHD symptoms index, Conners Parent and Teacher Rating Scale-Revised (Long Form) (CP/TRS-R:L) Univariate analyses indicated that CPRS-R:L and CTRS-R:L T-scores were both significantly reduced during MPH treatment compared to placebo: CPRS-R:L: F (1, 25) = 8.11, p = .009; partial η2 = .25; CTRS-R:L: F (1, 25) = 5.64, p = 0.03, partial η2 = .18 Increased sleep onset latency resulting in reduced total sleep time, which has been linked to poorer daytime functioning, is a potential adverse effect of stimulant medication which may require management to optimize outcome.</td>
</tr>
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</table>
### Intervention

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<th>Study:</th>
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<tbody>
<tr>
<td>FDA-approved pharmacological</td>
<td>Daviss, 2008; Palumbo, 2008; University of Cincinnati, 1999; ID: NCT00031395 RCT Multicenter N = 122 US Setting: Other</td>
<td><strong>Target:</strong> All ADHD subtypes who had a designated parent in daily contact with the patient had previously used methylphenidate or clonidine; with no history of the following disorders: tic disorder, major depression, pervasive developmental disorder, autism, psychosis, mental retardation, anorexia nervosa, bulimia, a serious cardiovascular (e.g., significant hypotension, congenital heart disease) or other medical disorder. <strong>Other:</strong> ADHD presentation: inattentive: 19.9, hyperactive: 4.1, combined: 76.0, N/A Diagnosis: Confirmation by specialist DSM-IV by investigator Comorbidity: N/A Female: 19.7 % Age mean: 9.5 (1.6) Minimum age: 7 Maximum age: 12 Ethnicity: % Hispanic or Latino: 7 % Black/African American: 11 % White: 78</td>
<td><strong>Intervention:</strong> Clonidine plus methylphenidate adjusted to optimal doses and continued for 8 weeks; doses were titrated up to 0.6mg/day for clonidine and 60mg/day for methylphenidate in divided doses (up to four times per day for clonidine and up to three times per day for methylphenidate). <strong>Control:</strong> Other Methylphenidate alone <strong>Comparator:</strong> NA <strong>Follow-up:</strong> 4 months</td>
<td>Childrens Global Assessment Scale (CGAS) Clonidine was not found to improve ADHD symptoms, whereas subjects treated with methylphenidate showed significant improvement compared to those not treated with methylphenidate. Conners Abbreviated Symptom Questionnaire for Teachers (ASQ-Teacher) Patients treated with clonidine had greater improvements compared with patients not treated with clonidine. Pittsburgh Side Effect Scale (Drowsiness): Clon and Clon+MPH experienced initial drowsiness relative to others not taking clonidine. However, levels reached equivalent to those in placebo and MPH only. Quality of Life, as measured by Daily Hassles and Impact on Family instruments: in a general linear model repeated measures analysis, treatment groups improved compared to placebo; all treatment groups were combined for this analysis. Weight, kg All groups had mean weight gains during the 16 weeks period, but these gains were significantly less when taking Methylphenidate than those that did not (p 0.0007). Participants with any adverse event Subjects taking clonidine had higher rates of any AE reported (75%) than those not treated with clonidine (41%; p=.0006)</td>
</tr>
</tbody>
</table>
## Appendix C. Evidence Tables

| Intervention | Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting | Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity | Comparison: Intervention; Control; Comparator; Follow-up | Outcome and results |
|--------------|-------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|--------------------------------|------------------------------------------------|-------------------|
| Dell'Agnello, 2009 | FDA-approved pharmacological | Target: Children with ADHD with oppositional defiant disorder Other: Parents and teachers provided some outcome data ADHD presentation: inattentive: 5.8, hyperactive: 5.1, combined: 89.1 Diagnosis: Confirmation by specialist DSM-IV, in addition to Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (K-SADS-PL) | Intervention: Atomoxetine 1.2 mg/kg/day for 6 weeks Control: Placebo Comparator: NA Follow-up: 2 months | Bradycardia on ECG (HR < 60 bpm) significantly higher in subjects treated with clonidine than in subjects not treated with clonidine (p = 0.02), somnolence: subjects treated with clonidine experienced higher rates of somnolence than subjects not treated with clonidine (p < 0.0001); fatigue: subjects treated with clonidine experienced higher rates of fatigue than subjects not treated with clonidine (p = 0.03); nervousness: subjects treated with clonidine experienced higher rates of nervousness than subjects not treated with clonidine (p = 0.04); Pittsburg Side Effects Rating Scale Parent & Teacher: dull/tired/listless subjects treated with clonidine experienced higher rates (p < 0.0001), drowsiness/sedation subjects treated with clonidine experienced higher rates (p < 0.0001). |
### Intervention

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<tr>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
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<tbody>
<tr>
<td>Author, year;</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Intervention; Control; Comparator; Follow-up</td>
<td>Anxiety Related Emotional Disorders (SCARED)-Parent Version, mean changes: Intervention −2.1 (7.6), Control −1.7 (6.5). Health Related Quality of Life (HRQOL): Intervention 30.7, Control 28.2. SDs not reported. Higher score is better. p values not reported. Anorexia Small increase (+0.5 kg) in body weight with placebo and a small decrease (−1.2 kg) with atomoxetine (p &lt; 0.001). Mean height increased more in placebo group (+ 1.5 cm) than in atomoxetine group (+1.0 cm) (p=0.021).</td>
</tr>
<tr>
<td>Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Comorbidity: ODD Female: 7.1 % Age mean: mean 9.9 Minimum age: 6 Maximum age: 15 Ethnicity: Other info on race or ethnicity: N/A</td>
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<tr>
<td>Diamond, 1999(^22) ID: RCT Unclear/Not reported N = 91 Canada Setting: N/A</td>
<td>Target: Children aged 6 to 12 years old with pervasive ADHD (8 or more of the 14 DSM-III-R criteria for ADHD in one setting and at least 5 criteria in another setting), history of ADHD for more than 6 months and beginning before the age of 7, estimated Full Scale IQ greater than 80, no primary anxiety or affective disorder Other: ADHD presentation: N/A Diagnosis: No DSM-III-R, methods only state &quot;interviewer&quot; Comorbidity: Mood disorder Female: 0.2 %</td>
<td>Intervention: Methylphenidate 0.7 mg/kg twice daily with parental training/support Control: Other Placebo with parental training/support Comparator: NA Follow-up: 4 months</td>
<td>Telephone interview probe oppositional behavior, parent rating No statistically significant differences. No difference in the development of clinically significant side effects, only 1 or 2 children in each group developed those.</td>
</tr>
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</table>
### Intervention

**Study:**
- Author, year;
- Multiple publications;
- Trial ID;
- Study design;
- Sites;
- Study size;
- Location Setting

**Population:**
- Setting;
- Study target;
- ADHD presentation;
- Diagnosis;
- Comorbidity;
- % Female;
- Age mean;
- Minimum age;
- Maximum age;
- Ethnicity

**Comparison:**
- Intervention;
- Control;
- Comparator;
- Follow-up

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<tr>
<td>ADHD Score SNAP-IV</td>
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<tr>
<td>Intervention and comparator groups were significantly superior to the control group (p &lt;0.001). The intervention group had significantly reduced scores compared to the control group (p &lt;0.001).</td>
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# Appendix C. Evidence Tables

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<tr>
<th>Intervention</th>
<th>Outcome and results</th>
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</table>
| **Study:** | Dittmann, 2013<sup>33</sup>  
Shire, 2010<sup>1018</sup>  
ID: NCT01106430  
RCT  
Multicenter  
N = 267  
Multiple countries  
Setting: Mixed | **Comparison:**  
MedicationLisdexamfetamine dimesylate, 30, 50 or 70 mg once daily for 9 weeks  
Follow-up: 2.25 months |
| **Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting** | **Target:** Male and female patients (aged 6–17 years) who satisfied DSM-IV-TR criteria for a primary diagnosis of ADHD of at least moderate severity as shown by a baseline ADHD Rating Scale IV (ADHD-RS-IV) total score of 28 or higher  
**Other:**  
ADHD presentation: inattentive : 16.8, hyperactive : 3.4, combined : 79.9  
**Diagnosis:** Confirmation by specialist  
Yes - DSM-IV, Kiddie-Schedule for Affective Disorders and Schizophrenia for School Age Children—Present and Lifetime (KSADS-PL)  
**Comorbidity:** N/A  
**Female:** 24.81 %  
**Age mean:** 10.65 (2.79)  
**Minimum age:** 6  
**Maximum age:** 17  
**Ethnicity:**  
% Hispanic or Latino : 18.7 | **Intervention:** Atomoxetine, mean optimal dose 40.2 mg/day (SD 20.05)  
**Control:** NA  
**Comparator:** MedicationLisdexamfetamine dimesylate, 30, 50 or 70 mg once daily for 9 weeks  
**Outcome and results:**  
CGI-I (Clinical Global Impressions-Improvement), days to first clinical response  
The median time to first clinical response was significantly shorter for patients in the lisdexamfetamine group than those in the atomoxetine group (p= 0.001)  
ADHD-RS-IV total score improvement in ADHD-RS-IV from baseline to follow-up was significantly greater in the LDX group compared to the ADX group (p < 0.001).  
Decreased appetite  
The rate was 26.8% in the lisdexamfetamine dimesylate and 10.4% in the atomoxetine group.  
Any treatment-emergent adverse event  
The rate was 71.9% in the lisdexamfetamine dimesylate and 70.9% in the atomoxetine group.  
No deaths or serious treatment-emergent adverse event were reported. |
### Appendix C. Evidence Tables

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<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
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</thead>
<tbody>
<tr>
<td>Dreakhshanpour, 2022&lt;sup&gt;23&lt;/sup&gt;</td>
<td>FDA-approved pharmacological ID: IRCT2015123025768N1 RCT Single center N = 55 Iran Setting: Specialty care</td>
<td>% White: 88.95 Other info on race or ethnicity:</td>
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<td>Target: Children with ADHD; those with morbid obesity, excessive polyphagia, or unstable physical conditions that prevented drug intake were excluded, as were those who using any psychotropic drug during the two prior weeks or with co-psychiatric disorders such as bipolar mood disorder, mental retardation, and autism Other: Parents provided some outcomes ADHD presentation: N/A Diagnosis: Confirmation by specialist DSM V TR Comorbidity: N/A Female: 23.6 % Age mean: 3.98 (0.93) Minimum age: 3 Maximum age: 6 Ethnicity: Other info on race or ethnicity: N/A</td>
<td><strong>Intervention:</strong> Daily risperidone: started at 0.25 mg/day in one dose and increased based on response and tolerance by 0.25 mg weekly increments, to a maximum dose of 1.25 mg/day <strong>Control:</strong> Comparator: Medication: Aripiprazole started at 2.5 mg per day and gradually increased by 1.25 mg every week based on response and tolerance, to a maximum dose of 6.25 mg/day <strong>Follow-up:</strong> 3 months</td>
<td>Strengths and Difficulties Questionnaire (SDQ), pro-social behavior scale Aripiprazole group improved more than risperidone group (p = 0.031). ADHD-RS, parent report Aripiprazole group improved more than risperidone group (p = 0.019). No difference in improvement in emotional symptoms or peer problems based on the SDQ score. Number with adverse events &quot;No statistically significant differences observed between the adverse effects of the two drugs.&quot;</td>
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<tr>
<td>Intervention</td>
<td>Study</td>
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<tr>
<td>FDA-approved pharmacological</td>
<td>Duke University, 2009&lt;sup&gt;57k&lt;/sup&gt; ID: NCT00889915 RCT Unclear/Not reported N = 228 US Setting: N/A</td>
<td>Target: Children 6-17 years old with diagnosis of ADHD according to DSM-IV criteria, English-speaking, with no history cardiovascular diseases, may receive other medicinal and/or psychosocial interventions for other comorbid disorders; patients with inpatient status are excluded, cannot take another medication for ADHD (psychostimulant, atomoxetine, bupropion); those with psychosis or autism spectrum disorder are excluded Other: ADHD presentation: N/A Diagnosis: Comorbidity: N/A Female: 31.6% Age mean: 10.3 (3.1) 10.3 (3.2), 10.6 (3.1), 10.0 (3.2), Adderall 10.4 (3.0) Minimum age: 6 Maximum age: 17 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Intervention: Methylphenidate transdermal system, optimal dose received for 6 weeks Control: NA Comparator: MedicationMixed amphetamine salts extended release (dosage not described) Follow-up: 1.5 months</td>
<td>Decreased appetite and weight loss Both groups reported an equal number of participants. Intervention had a higher percentage of participants experiencing adverse events compared to the comparator group.</td>
</tr>
<tr>
<td>FDA-approved</td>
<td>Eli Lilly, 2004&lt;sup&gt;799&lt;/sup&gt; ID: NCT00192023 RCT Single center</td>
<td>Target: Children and Adolescents With ADHD and Comorbid Oppositional Defiant Disorder. Those with history of Bipolar,</td>
<td>Intervention: Atomoxetine 0.5 mg per kg per day for 1 week, then 1.2 mg/kg/day for 7 weeks Control: Placebo</td>
<td>Clinical Global Impressions (CGI) Severity Greater improvement for intervention group (p&lt;0.001) as measured by both CGI-S and Conners' Parent Rating Scale-Revised: Short Form, ADHD Index.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Comparison: Intervention; Control; Comparator; Follow-up</td>
<td>Outcome and results</td>
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<tr>
<td>N = 139</td>
<td>Italy Setting: Specialty care</td>
<td>psychosis or pervasive development disorder excluded. <strong>Other:</strong> Parents and teachers provided some outcomes. <strong>ADHD presentation:</strong> N/A <strong>Diagnosis:</strong> Confirmation by specialist DSM-IV <strong>Comorbidity:</strong> ODD : 100% with ODD <strong>Female:</strong> 7.3% <strong>Age mean:</strong> 9.8 (2.3) <strong>Minimum age:</strong> 6 <strong>Maximum age:</strong> 15 <strong>Ethnicity:</strong> % White : 97 Other info on race or ethnicity:</td>
<td>Placebo, daily for 8 weeks <strong>Comparator:</strong> NA <strong>Follow-up:</strong> 2 months</td>
<td>Swanson, Nolan and Pelham Questionnaire (SNAP-IV) Intervention group improved more (p&lt;0.001). Children's Depression Rating Scale-Revised: No difference in improvement between groups (p = 0.870). Decreased appetite Significantly higher proportion of intervention group experienced appetite decrease, anorexia, and weight loss. Adverse events Rate was 73.83% in the atomoxetine and 37.50 in the placebo group. No serious adverse events in either group.</td>
</tr>
<tr>
<td>Eli Lilly, 2006</td>
<td>N/A ID: NCT00406354 RCT Multicenter N = 181 Germany Setting: Specialty care</td>
<td><strong>Target:</strong> Conduct disorder not exclusionary; normal intelligence; able to swallow capsules <strong>Other:</strong> ADHD presentation: inattentive : 19.4, hyperactive : 5, combined : 75.6 <strong>Diagnosis:</strong> Confirmation by specialist DSM-IV criteria by unknown source <strong>Comorbidity:</strong> N/A <strong>Female:</strong> 15.6%</td>
<td><strong>Intervention:</strong> Atomoxetine 0.5 milligram per kilogram (mg/kg) daily dose taken orally for 1 week, then 1.2 mg/kg daily dose taken orally for 8 weeks <strong>Control:</strong> Placebo Matching placebo daily dose taken orally <strong>Comparator:</strong> Medication Atomoxetine Slow Titration arm: 0.5 mg/kg daily dose taken orally for 1 week, then 0.8 mg/kg daily dose taken orally for 1</td>
<td>Investigator-Rated Individual Target Behaviors (ITB-Inv): Intensity Score Intervention and comparator performed better than control group (p=0.010). CGI-S (Clinical Global Impressions - Severity) ADHD Score Intervention and comparator performed better than control group (p&lt;0.001). ADHD Combined Score SNAP-IV (Swanson, Nolan &amp; Pelham Rating Scale - Revised) Intervention and comparator scored better than control group (p&lt;0.001).</td>
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## Appendix C. Evidence Tables

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<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA-approved pharmaceutical</td>
<td>Eli Lilly[^{252}] ID: NCT00568685 RCT Multicenter N = 153 Korea Setting: N/A</td>
<td>Target: Patients with ADHD ages 6-18years, based on the accepted criteria for that disease, must not have taken any medication used to treat ADHD for at least 2 weeks prior to beginning study treatment, must be able to swallow capsules, judged by the study investigator to be reliable to keep appointments for clinic visits and all tests, including blood tests and any other required examinations Other: ADHD presentation: N/A Diagnosis: No Comorbidity: N/A Female: 55.6 % Age mean: 9.41 (1.64) Minimum age: 6 Maximum age: 18 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Intervention: Atomoxetine hydrochloride for 6 weeks total, 0.5 mg/kg/day orally in 2 divided doses for 7 days, then 0.8 mg/kg/day orally in 2 divided doses for 7 days, then 1.2 mg/kg/day orally in 2 divided doses for 28 days Control: NA Comparator: Medication Atomoxetine 0.2 mg/kg/day orally in 2 divided doses for 6-weeks</td>
<td>CGI-S (Clinical Global Impressions-ADHD Severity Scale) change The intervention group had more improvement than comparator group (p=0.0048). ADHD-RS-IV-Parent Total Score change The intervention group had more improvement than comparator group (p=0.024). No incidence of suicide or self-harm in either group. Decreased appetite Decreased appetite was more common in the high dose group. Participants with reported adverse events The rate was 56.25% in the higher dose compared to 29.41% in the lower dose. 8% irritability rate in high dose group, 4% in low dose group, 8% abdominal pain rate in high dose group, 0 in low dose group.</td>
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</table>

| Age mean: 11.0 (3.01) Minimum age: 6 Maximum age: 17 Ethnicity: % Black/African American : 1 % White : 99 Other info on race or ethnicity: | week, then 1.2 mg/kg daily dose taken orally for 7 weeks | Follow-up: 2.25 months | |

| | decreased appetite | |

Note: \[^{252}\] Indicates a study with multiple publications.
<table>
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<tr>
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<tbody>
<tr>
<td>FDA-approved pharmacological</td>
<td>Findling, 2001&lt;sup&gt;274&lt;/sup&gt; ID: NA RCT</td>
<td>Target: There were no formal inclusion or exclusion criteria. Other: ADHD presentation: N/A Diagnosis: No a computerized version of the Diagnostic Interview Schedule for Children and clinical interviews with a psychologist and a psychiatrist. Comorbidity: N/A Female: 0 % Gender separated by age group - male reported only; &lt;7.99 years= 82.61% / 8-10.99 years= 80.36% / 11-17.59 years = 78.85% Age mean: Age mean separated by age group; &lt;7.99 years = 6.35 / 8-10.99 years= 9.47 / 11-17.59 years = 13.64 Minimum age: 4 Maximum age: 18 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Intervention: Mixed amphetamine salts (Adderall) 5 mg per dose, 10 mg per dose, and 15 mg per dose for 4 weeks Control: Placebo Comparator: MedicationMethylphenidate (5 mg per dose, 10 mg per dose, and 15 mg per dose) twice per day (in the morning and at lunch) Follow-up: CPR-S-R (Connors Parent Rating Scale-Revised Short Form) PGA (Parent Global Assessment) rated as improved Compared with placebo, both active treatments showed significant improvements (p&lt;0.0001).</td>
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<tr>
<td>FDA-approved pharmacological</td>
<td>Noven Therapeutics, 2004&lt;sup&gt;275&lt;/sup&gt;; Findling, 2009&lt;sup&gt;276&lt;/sup&gt;; Findling, 2010&lt;sup&gt;277&lt;/sup&gt; ID: NCT00444574 RCT</td>
<td>Target: Children age 6 to 12 inclusive who were diagnosed with ADHD according to DSM-IV-TR criteria (predominantly hyperactive/impulsive, inattentive, or combined type) were eligible for study inclusion</td>
<td>Intervention: Methylphenidate transdermal system 10, 15, 20, or 30 mg/9 hours (dose-optimized) plus placebo capsule for 7 weeks Control: Placebo Placebo capsule plus placebo patch</td>
<td>ASQ (Connors Abbreviated Symptoms Questionnaire, Parent and Teacher versions) Similar efficacy was observed between the medications. Of the 195 youths who entered into this trial, 11 had their participation terminated because of adverse events. Dosage levels that led to discontinuation included placebo (n = 1), 5 mg (n = 3), 10 mg (n = 5), and 15 mg (n = 2). Of note, all youths who withdrew prematurely had multiple adverse events at the dose of treatment that led to study discontinuation. For this reason, a single, specific side effect could not be ascribed as the cause for their trial being discontinued.</td>
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# Appendix C. Evidence Tables

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<th>Comparison:</th>
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<tbody>
<tr>
<td></td>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Intervention; Control; Comparator; Follow-up</td>
<td>ADHD-RS-IV The average magnitude of changes from baseline was a 2-fold greater improvement in active treatments compared to placebo. Compared with placebo, both active treatments showed significant improvements in ADHD-RS-IV scores (p&lt;0.0001). Decreased appetite The rate of decreased appetite was 25.5% in the intervention, 18.7% in the OROS and 4.7% in the placebo group. Participants with at least 1 adverse event The rate was 75.5% for the intervention, 69.2% for the OROS, and 57.6% for the placebo group. The majority of treatment-emergent adverse events were mild or moderate.</td>
</tr>
<tr>
<td>Unclear/Not reported</td>
<td>N = 282 US Setting: N/A</td>
<td>Other: ADHD presentation: inattentive_other : 11-26% across groups, hyperactive_other : 1-2% across groups, combined_other : 71-86% across groups Diagnosis: Confirmation by specialist inclusive who were diagnosed with ADHD according to Diagnostic and Statical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) Comorbidity: N/A Female: 33.7 % 64.9 Age mean: 8.7 (1.94) Minimum age: 6 Maximum age: 12 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Comparator: Medication18mg OROS capsules plus placebo patch for 5 weeks Follow-up: 1.25 months</td>
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<tr>
<td>FDA-approved pharmacological</td>
<td>Findling, 2010\textsuperscript{275}</td>
<td>Target: Adolescent age 13-17 years old with diagnosis of ADHD according to DSM -IV-TR, have a total score of &gt;=26 on the ADHD-RS-IV scale at baseline, IQ of &gt;= 80. Exclusion: have a conduct disorder or comorbid psychiatric illnesses that contraindicated treatment with MTS, history of cardiac problems, history of</td>
<td>Intervention: Methylphenidate transdermal system, patches applied to hips once daily (alternating hips each day), worn for 9 hours per day, titrated to an optimal dose (10,15,20,30 mg) of medication (week 1-5) followed by a 2-week maintenance period Control: Placebo</td>
<td>CGI-I (Clinical Global Impressions-Improvement) very much improved or much improved Intervention group had significantly more participants that improved compared to control group (p&lt;0.001). ADHD-RS-IV (ADHD Rating Scale-IV)</td>
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<tr>
<td>Intervention</td>
<td>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
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<td>substance abuse, history of being nonresponsive to psychostimulant treatment; clonidine, atomoxetine, antidepressants, sedatives, antipsychotics, anxiolytics, P450 enzyme altering agents, or other investigational medications within 30 days prior to screening not eligible Other: ADHD presentation: N/A Diagnosis: Confirmation by specialist Schedule for Affective Disorders and Schizophrenia for School-Age Children– Present and Lifetime Version Comorbidity: N/A Female: 25.3% Age mean: 14.6 (1.3) Minimum age: 13 Maximum age: 17 Ethnicity: % Black/African American: 40 % American Indian or Alaska Native: .5 % Asian: .5 % White: 77 Other info on race or ethnicity: Other: Other: 3.7%</td>
<td>Matching placebo Comparator: NA Follow-up: 2 months</td>
<td>Intervention group had significantly more improvement compared to control group (p&lt;0.001). Decreased appetite The rate was 25.5% in the intervention and 1.4% in the control group. Participants with treatment-emergent adverse events during the study period Adverse events were reported in 77.2% of intervention and 55.6% of placebo participants. A total of three serious adverse events were reported by two participants, one in each treatment group discontinued from the study due to the events (two episodes of syncope, both judged to be of moderate severity and related to study treatment by the investigator, and one incidence of oppositional behavior which was judged as severe but not related to treatment).</td>
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## Intervention Study

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<tr>
<th>Study</th>
<th>Population:</th>
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<th>Outcome and results</th>
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<tbody>
<tr>
<td>Findling, 2011^{273}</td>
<td>Target: Children with ADHD; participants with conduct disorder or a comorbid psychiatric diagnosis requiring medication, a concurrent chronic/acute medical condition that might confound efficacy/safety assessments or pose a safety risk, a history of seizures, tic disorder or family history of Tourette disorder, family history of sudden cardiac death or arrhythmia, abnormal thyroid function (a stable dose of thyroid medication for at least 3 months was permitted), glaucoma, or those considered a suicide risk were excluded; BMI could not be 5th or 97th percentile for age and gender; tested positive on urine drug screen (except current stimulant therapy), or had a recent history of suspected substance abuse (excluding nicotine) were not enrolled; pregnant/lactating females, with clinically significant ECG findings, who required medications with central nervous system effects, with failure to respond to and/or intolerance of amphetamine therapy, and/or who were well controlled on current ADHD medication with acceptable safety and efficacy were disqualified</td>
<td>Intervention: Lisdexamfetamine dimesylate 70 mg/d for 4 weeks Control: Placebo Placebo for 4 weeks Comparator: Medication Lisdexamfetamine dimesylate 30 mg/d for 4 weeks</td>
<td>CGI-I (Clinical Global Impressions–Improvement) score of 1 or 2 A higher number of participants in the intervention and comparator groups were improved versus participants on placebo (p &lt; 0.0001). ADHD-RS-IV A higher number of participants in the intervention and comparator groups were improved versus participants on placebo (p &lt; 0.0001). YQOL-R changes at endpoint scores for LDX groups versus placebo were not significant. Decreased appetite The rate was 37.2% in the 70mg, 37.2% in the 30mg, and 2.6% in the placebo group. Participants with any treatment emergent adverse event The rate was 71.8% in the 70mg, 65.4% in the 30mg, and 58.4% in the placebo group. Commonly reported treatment emergent adverse events greater than or equal to 5% across all doses were decreased appetite, headache, insomnia, decreased weight, and irritability.</td>
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<td>Shire, 2008^{1014}</td>
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<td>ID: NCT00735371</td>
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### Findings

- CG-I (Clinical Global Impressions–Improvement) score of 1 or 2
  - A higher number of participants in the intervention and comparator groups were improved versus participants on placebo (p < 0.0001).
- ADHD-RS-IV
  - A higher number of participants in the intervention and comparator groups were improved versus participants on placebo (p < 0.0001).
- YQOL-R changes at endpoint scores for LDX groups versus placebo were not significant.
- Decreased appetite
  - The rate was 37.2% in the 70mg, 37.2% in the 30mg, and 2.6% in the placebo group.
- Participants with any treatment emergent adverse event
  - The rate was 71.8% in the 70mg, 65.4% in the 30mg, and 58.4% in the placebo group.
- Commonly reported treatment emergent adverse events greater than or equal to 5% across all doses were decreased appetite, headache, insomnia, decreased weight, and irritability.
<table>
<thead>
<tr>
<th>Intervention Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Intervention; Control; Comparator; Follow-up</td>
<td></td>
</tr>
<tr>
<td>Fuentes, 2013&lt;sup&gt;232&lt;/sup&gt; Eli Lilly and Company, 2007&lt;sup&gt;171&lt;/sup&gt; ID: NCT00447278 RCT Multicenter N = 398 Multiple countries Setting: Mixed</td>
<td>ADHD presentation: N/A Diagnosis: Confirmation by specialist ADHD-RS-IV Comorbidity: N/A Female: 29.7 % Age mean: 14.6 (1.31) Minimum age: 13 Maximum age: 17 Ethnicity: % Hispanic or Latino : 14.8 % Black/African American : 14.8 % White : 79 Other info on race or ethnicity:</td>
<td>Intervention: Atomoxetine oral once or twice daily, starting dose 0.5 mg/kg per day increasing to the recommended target dose of 1.2 mg/kg per day, not exceeding a maximum dose of 1.8 mg/kg per day Control: NA Comparator: Medication The OEST group defined as any ADHD treatment including any medication except ATX, including long- and short-acting MPH and antidepressants; allowed switching between different formulations of a Weiss Functional Impairment Rating Scale, Parent (WFIRS-P)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other: ADHD presentation: N/A Diagnosis: Confirmation by specialist</td>
<td></td>
<td>There was no significant difference between groups (p=0.166). Significantly more patients of the ATX group reported fatigue (11.6% ATX vs 2.5% OEST; P G 0.001), somnolence (6.5% vs 1.0%; P = 0.006), and sedation (3.5% vs 0%; P = 0.015). In the OEST group, insomnia (12.6% OEST vs 2.0% ATX; P G 0.001) and irritability (6.5% vs 1.5%; P = 0.019) were reported by significantly more patients; initial insomnia (6.5% OEST, 1.5% ATX; P = 0.053) and sleep disorder (4.5% OEST, 1.0% ATX; P = 0.062) missed significance by a small margin. During study period II (6 months), 2 patients (1.0%) in both</td>
</tr>
</tbody>
</table>
### Intervention

<table>
<thead>
<tr>
<th>Study:</th>
<th>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Population:</th>
<th>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Comparison:</th>
<th>Intervention; Control; Comparator; Follow-up</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Outcome and results</th>
</tr>
</thead>
</table>

#### Gard, 2014[^26]

**ID:** RCT  
**Setting:** Specialty care  
**N = 84**  
**India**

**Target:** Children aged 6-14 diagnosed with ADHD and have moderate to severe illness as assessed by Clinical Global Impressions Severity Scale (CGI-S)  
**Other:** ADHD presentation: inattentive: 21.7, hyperactive: 8.7, combined: 69.6  
**Diagnosis:** No  
**Not reported**  
**Comorbidity:** N/A  
**Female:** 18.8 %  
**Age mean:** 8.47 (2.22) for methylphenidate, 8.66 (2.44) for atomoxetine  
**Minimum age:**  
**Maximum age:**  
**Ethnicity:** Other info on race or ethnicity: N/A

**Intervention:** Atomoxetine 1.2 mg/kg/day, once or twice daily based on response and tolerability  
**Control:** NA  
**Comparator:** MedicationMethylphenidate (immediate release) 1 mg/kg/day  
**Follow-up:** 2 months

Clinical Global Impressions Severity Scale (CGI-S)  
Scores significantly improved for both groups, but there was no statistically significant difference between the groups (p=0.997).  
VADPRS (Vanderbilt ADHD Diagnostic Parent Rating Scale)  
Scores significantly improved for both groups, but there was no statistically significant difference between the two groups (p=0.500) in the parent or the teacher ratings.  
Decreased appetite  
Rate 33.3% in the atomoxetine, 43.8% in the methylphenidate group.

**Side effects**  
56% in the atomoxetine group developed side effects, 55% of the methylphenidate group (n.s.).  
3 patients in each group dropped out due to adverse events.

[^26]: FDA-approved pharmacological

Specific medication, specific doses were not mandated in the  
**Follow-up:** 12 months  

Treatment groups had serious AEs (SAEs). In study period III (12 months), 7 patients experienced SAEs: 4 (2.9%) in the ATX group and 3 (1.9%) in the OEST group. None of the SAEs were considered related to study medication. Seven patients (3.5%) in the ATX group and 2 patients (1.0%) in the OEST group discontinued because of TEAEs during study period II and 4 patients (2 each in the ATX [1.4%] and OEST [1.3%] group) during study period III.
## Appendix C. Evidence Tables

### Intervention

<table>
<thead>
<tr>
<th>Study:</th>
<th>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gau, 2006&lt;sup&gt;129&lt;/sup&gt;</td>
<td>FDA-approved pharmacological</td>
</tr>
<tr>
<td>ID: N/A</td>
<td>RCT</td>
</tr>
<tr>
<td>Single center</td>
<td>N = 64</td>
</tr>
<tr>
<td>Taiwan</td>
<td>Setting: Mixed</td>
</tr>
</tbody>
</table>

### Population:

| Target: | Patients age 6-15 years old with diagnosis of ADHD, taking MPH on a total daily dose of 10-40 mg for the past 3 months; excluded significant gastrointestinal problems, a history of hypertension, known hypersensitivity to MPH, or a co-existing medical condition or concurrent medication likely to interfere with the safe administration of MPH, glaucoma, Tourette’s Syndrome, an active seizure disorder, or a psychotic disorder were excluded, as were girls who had reached menarche Other: Parents were also asked questions about the treatment and usage of ADHD within their children, but were not actively experimented on. ADHD presentation: inattentive: 18.8, hyperactive: 3.1, combined: 78.1 Diagnosis: Confirmation by specialist Chinese Kiddie-Schedule for Affective Disorders and Schizophrenia Comorbidity: N/A Female: 9.4% Age mean: 10.5 (3.2) |

### Comparison:

| Intervention: | Methylphenidate Osmotic Release Oral System with the treatment doses 18 mg or 36mg once daily for 28 days |
| Control: | NA |
| Comparator: | MedicationInstant release MPH at two different doses (5/10 mg/day) |
| Follow-up: | 1 month |

### Outcome and results

<p>| CGI-I rating of 1 or 2 The OROS-MPH group had a significantly greater proportion of subjects being very much or much improved in the CGI-I scale than the IR MPH group (p = 0.014). ADHD Index Score Conner’s Teacher Rating Scale-Revised: Short Form-C change Compared to the IR MPH group, the OROS MPH group showed a significantly greater slope of reductions in ADHD symptoms. SKAMP (Chinese Version of the Swanson, Kotin, Agler, M-Flynn, and Pelham Rating Scale) Attention score mean change (SD) from baseline at endpoint Difference in SKAMP Attention score mean change (SD) from baseline between OROS and IR MPH groups is statistically significant (p &lt; 0.01). Difference in SKAMP Deportment score mean change (SD) from baseline between OROS (-4.65 SD 5.53) and IR (-4.41 SD 6.) Decreased appetite The rate of decreased appetite was 46.9% in the OROS and 59.4% in the immediate release group (p=0.316). There was no difference in the rates of side effects between the two groups. |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population</th>
<th>Comparison</th>
<th>Outcome and results</th>
</tr>
</thead>
</table>
| **Intervention** | **Study:** Gau, 2007<sup>288</sup>  
ID: N/A  
RCT  
Multicenter  
N = 106  
Taiwan  
Setting: Other | **Target:** Children with ADHD, no ADHD treatment medication, or completion of the washout procedures before entering this study. Subjects were excluded if they weighed less than 20 kg or more than 60 kg; had a serious medical illness, such as a cardiovascular disease; had a history of bipolar I or II disorder, psychosis, or pervasive developmental disorder; had anxiety disorder based on the DSMIV criteria at study entry; had a history of any seizure disorder or prior EEG abnormalities related to epilepsy, or taking anticonvulsants for seizure control; had a history of alcohol or drug abuse within the past 3 months; or if they might have to use psychoactive medications | **Intervention:** Atomoxetine once daily in the morning, maximal dose of 1.8 mg/kg per day, for 6 weeks  
**Control:** Placebo  
Placebo once daily in the morning  
**Comparator:** NA  
**Follow-up:** 1.5 months | **Outcome and results** |
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Population</th>
<th>Comparison</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA-approved pharmacological</td>
<td>Geller, 2007&lt;sup&gt;292&lt;/sup&gt;  ID: N/A  RCT  Multicenter  N = 176  US  Setting: Specialty care</td>
<td><strong>Target:</strong> Children between 8-17 with ADHD according to DSM-IV, and one of the following anxiety disorders: separation anxiety disorder, generalized anxiety disorder, or social phobia  <strong>Other:</strong> Parents or legal representatives  <strong>ADHD presentation:</strong> inattentive: 23.0, hyperactive: 1.2, combined: 75.9  <strong>Diagnosis:</strong> Confirmation by specialist  Used the DSM-IV standard. &quot;ADHD diagnoses were confirmed clinically, and anxiety and ADHD diagnoses were confirmed using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime.&quot;  <strong>Intervention:</strong> Atomoxetine 0.8-1.8 mg/kg/day divided into two doses daily for 12 weeks  <strong>Control:</strong> Placebo  Placebo has the same measurements as the treatment dosage  <strong>Comparator:</strong> NA  <strong>Follow-up:</strong> 3 months</td>
<td>CGI (Clinical Global Impression - Severity of Illness) change  CGI results indicated overall symptom improvement.  ADHD-RS-IV-P (Attention-Deficit/Hyperactivity Disorder Rating Scale-IV Parent Version) The mean change scores showed greater improvement with atomoxetine relative to placebo (p&lt;0.001).  Significant reduction in Multidimensional Anxiety Scale for Children (p 0.009).  Decreased appetite  Statistically significant decreased appetite associated with the intervention (p=0.025).  No statistically significant difference in incidence of headache, upper abdominal pain, vomiting, irritability, nasopharyngitis, nausea, cough, influenza, sinusitis across groups.</td>
</tr>
<tr>
<td></td>
<td>Setting: Specialty care</td>
<td><strong>Study:</strong>  Author, year; Multiple publications;  Trial ID;  Study design;  Sites;  Study size;  Location  <strong>Setting:</strong>  N/A  <strong>Study target:</strong>  ADHD presentation;  Diagnosis;  Comorbidity;  % Female;  Age mean;  Minimum age;  Maximum age;  Ethnicity</td>
<td><strong>Study design:</strong>  Multicenter  <strong>Sites:</strong>  N/A  <strong>Study size:</strong>  N = 176  <strong>Location:</strong>  US  <strong>Study target:</strong>  ADHD presentation;  Diagnosis;  Comorbidity;  % Female;  Age mean;  Minimum age;  Maximum age;  Ethnicity</td>
</tr>
</tbody>
</table>
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study</th>
<th>Population</th>
<th>Comparison</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Author, year; Multiple publications; Multiple ID; Study design; Sites; Study size; Location Setting</td>
<td>Lifetime version (K-SADS-PL; Univers)</td>
<td>Intervention; Control; Comparator; Follow-up</td>
<td>Lifetime version (K-SADS-PL; Univers)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Comorbidity:</strong> Mood disorder</td>
<td></td>
<td><strong>Female:</strong> 37.9 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Age mean:</strong> Intervention 12.2 (2.8), placebo 11.8 (2.5)</td>
<td></td>
<td><strong>Minimum age:</strong> 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Maximum age:</strong> 17</td>
<td></td>
<td><strong>Ethnicity:</strong> Other info on race or ethnicity: Other: intervention 79% white, control 82%</td>
</tr>
<tr>
<td></td>
<td>Greenhill, 2006[^1]</td>
<td><strong>Target:</strong> Patients age 6-15 years old with clinical diagnosis of ADHD. For boys, baseline scores on the Conners ADHD/DSM-IV Scale-Teacher version (CADS-T) DSM-IV total subscale were required to be equal or larger than 27 for those 6 to 8 years old, equal or larger than 24 for those 9 to 11 years old, equal or larger than 19 for those 12 to 14 years old, and equal or larger than 14 for those 15 to 17 years old. For girls, the respective baseline cutoff scores on the CADS-T were 16, 13, 12, and 6. All of the patients were attending school in a classroom setting and had the same teacher for the</td>
<td><strong>Intervention:</strong> Dexamphetamine extended release 5, 10, 15, 20, or 30 mg/day once daily for 2 weeks</td>
<td>CGI-I rated 1 or 2</td>
</tr>
<tr>
<td></td>
<td>FDA-approved pharmacological</td>
<td><strong>Control:</strong> Placebo Placebo pills once daily</td>
<td></td>
<td>Statistically significant difference between groups.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Comparator:</strong> NA</td>
<td></td>
<td>Conners ADHD/DSMIV Scale-Teacher version total score Statistically significant difference between groups (p&lt;0.001), effect size 0.79.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Follow-up:</strong> 2 months</td>
<td></td>
<td>Decreased appetite The rate of decreased appetite was 30.2% in the intervention and 8/5% in the control group.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Participants with at least one adverse event reported The rate was 75.5% in the intervention and 57% in the placebo group.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>There were no deaths or serious adverse events.</td>
</tr>
</tbody>
</table>
### Intervention

**Study:**
- Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting

**Population:**
- Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity

**Comparison:**
- Intervention; Control; Comparator; Follow-up

**Outcome and results**

<table>
<thead>
<tr>
<th>Duration of the study who was able and willing to perform symptom assessments</th>
<th>Other: ADHD presentation: inattentive: 21.4, hyperactive: 1.9, combined: 76.7</th>
<th>ADHD presentation: inattentive: 21.4, hyperactive: 1.9, combined: 76.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis: Confirmation by specialist Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version)</td>
<td>Comorbidity: N/A</td>
<td>Comorbidity: N/A</td>
</tr>
<tr>
<td>Female: 35.9%</td>
<td>Age mean: Intervention 9.76 (2.75), placebo 10.4 (2.70)</td>
<td>Age mean: Intervention 9.76 (2.75), placebo 10.4 (2.70)</td>
</tr>
<tr>
<td>Minimum age: 6</td>
<td>Maximum age: 15</td>
<td>Maximum age: 15</td>
</tr>
<tr>
<td>Ethnicity:</td>
<td>Ethnicity:</td>
<td>Ethnicity:</td>
</tr>
<tr>
<td>% Black/African American: 23.3</td>
<td>% White: 60.2</td>
<td>% White: 60.2</td>
</tr>
<tr>
<td>Other info on race or ethnicity:</td>
<td>Other info on race or ethnicity:</td>
<td>Other info on race or ethnicity:</td>
</tr>
<tr>
<td>Other: Other: 17/103 (16.5%)</td>
<td>Other: Other: 17/103 (16.5%)</td>
<td>Other: Other: 17/103 (16.5%)</td>
</tr>
</tbody>
</table>

**Other:**
- Intervention: Atomoxetine dose based on body mass as per prescribing guidelines (mean dose was 1.35 mg.kg−1; range 1.0–1.4 mg.kg−1) taken daily for 6 weeks

**Target:** Diagnosis of ADHD, fluent in English, no current stimulant use, any contraindications to atomoxetine, no substance or alcohol abuse

**Other:**

**FDA-approved**
- Griffiths, 2018
- ID: ANZCTR 12607000535471
- Crossover trial
- Multicenter

**Intervention:** Atomoxetine resulted in significant improvement of response inhibition (p<0.001) and fear identification (p<0.04), but not for sustained attention (p<0.06). The treatment
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 136 Australia Setting: School</td>
<td>ADHD presentation: inattentive: 45, hyperactive: 4, combined: 67 Diagnosis: Confirmation by specialist Patients were evaluated at the beginning of the study using the DSM-IV criteria Comorbidity: N/A Female: 20% Age mean: 11.29 (2.5) Minimum age: 6 Maximum age: 17 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Control: Placebo Placebo, both groups switched and were evaluated again Comparator: NA Follow-up: 1.5 months</td>
<td>Improved ADHD symptoms (p&lt;0.001) as well as anxiety symptoms (p&lt;0.043). Atomoxetine significantly improved response inhibition, assessed using the Go-NoGo test (p&lt;0.001; effect size 0.42). Atomoxetine was associated with significantly reduced symptom severity for anxiety (p=0.043).</td>
</tr>
<tr>
<td></td>
<td>Harfterkamp, 2012 FDA-approved pharmacological ID: RCT Multicenter N = 97 Netherlands Setting: Specialty care</td>
<td>Target: Children and adolescents dually diagnosed with autism spectrum disorders and ADHD Other: Teachers provided some outcomes ADHD presentation: N/A Diagnosis: Confirmation by specialist DSM IV_TR Comorbidity: Autism Female: 14.4% Age mean: 9.9 (10.8) Minimum age: 6 Maximum age: 17 Ethnicity:</td>
<td>Intervention: Atomoxetine titrated in 3 weeks to a fixed once daily dose of 1.2 mg/kg for 8 weeks Control: Placebo Placebo capsules identical to medication Comparator: NA Follow-up: 2 months</td>
<td>CGI-ADHD-I, number classified as much or very much improved Total ADHD score was not statistically difference between groups (p = 0.077); difference in those categorized as improved was not significant (p= 0.14). Decreased appetite The rate was 27.1% in the atomoxetine and 6.1% in the placebo group. At least one adverse event The rate was 81.3% in the intervention vs 653% in the placebo group. None of the patients had a serious adverse event.</td>
</tr>
</tbody>
</table>
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<table>
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<tr>
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<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study:</strong></td>
<td><strong>Setting:</strong></td>
<td><strong>Study target:</strong></td>
<td><strong>Intervention:</strong></td>
</tr>
<tr>
<td>Hazell, 2003</td>
<td><strong>Study target:</strong></td>
<td><strong>Control:</strong></td>
<td><strong>Intervention:</strong></td>
</tr>
<tr>
<td>ID: NA</td>
<td><strong>ADHD presentation:</strong></td>
<td><strong>Comparator:</strong></td>
<td><strong>Clonidine added to</strong></td>
</tr>
<tr>
<td>RCT</td>
<td><strong>Diagnosis:</strong></td>
<td><strong>Follow-up:</strong></td>
<td>ongoing psychostimulant therapy (either methylphenidate or dexamphetamine) 0.05 to 0.10 mg morning and evening for 6 weeks</td>
</tr>
<tr>
<td>Unclear/Not reported</td>
<td><strong>Comorbidity:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 67</td>
<td><strong>Female:</strong></td>
<td></td>
<td>Results favored clonidine (p&lt;0.01).</td>
</tr>
<tr>
<td>Australia</td>
<td><strong>Age mean:</strong></td>
<td></td>
<td>Hyperactive index, parent report</td>
</tr>
<tr>
<td>Setting: N/A</td>
<td><strong>Minimum age:</strong></td>
<td></td>
<td>Number achieving 43% reduction from baseline</td>
</tr>
<tr>
<td></td>
<td><strong>Maximum age:</strong></td>
<td></td>
<td>There was no statistically significant difference between the groups (p = .16)</td>
</tr>
<tr>
<td></td>
<td><strong>Ethnicity:</strong></td>
<td></td>
<td>A significant difference in Parent report conduct symptoms—no. achieving 38% reduction from baseline (p&lt;.01)</td>
</tr>
<tr>
<td></td>
<td>% Black/African American: 1.0</td>
<td></td>
<td>A significant difference in Parent report conduct symptoms—no. achieving 33% reduction from baseline (p&lt;.01)</td>
</tr>
<tr>
<td></td>
<td>% White: 99.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other info on race or ethnicity:</td>
<td></td>
<td>Mean height</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>There were no statistically significant differences between groups.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Transient increase in side effects in the clonidine-treated group compared with the control group for drowsiness and dizziness.</td>
</tr>
</tbody>
</table>
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hervas, 2014&lt;sup&gt;231&lt;/sup&gt;</td>
<td>Target: Male and female children/adolescents ages 6-17 years old with a diagnosis of ADHD of at least severity as defined by a baseline ADHD-RS-IV with a total score of 32 or higher and a minimum Clinical Global Impression Severity (CGI-S) score of 4; intellectual functioning, blood pressure measurements within the 95th percentile for age, sex and height; and the ability to swallow tablets or capsules</td>
<td>Intervention: Guanfacine (extended release), dose-optimized taken once daily in the morning for 6 weeks</td>
<td>Patients showing an improvement (CGI-I, very much improved or much improved) Compared with placebo, the difference in the percentage of patients showing improvement was significant for guanfacine (p&lt;0.001) and atomoxetine (p 0.024). ADHD-RS-IV The change from baseline was greater for guanfacine and atomoxetine compared with placebo. Decreased appetite The rate was 13.2% in the guanfacine, 27.7% in the atomoxetine, and 10.8% in the placebo group. Treatment-emergent adverse events The rate was 77.2% in the guanfacine, 67.9% in the atomoxetine, and 65.8% in the placebo group. Three (1.1%) serious adverse events were reported: one in the placebo group (syncope considered treatment related) and two in the guanfacine group (syncope [considered treatment related] and appendicitis [occurred prior to randomization and not treatment related]).</td>
</tr>
<tr>
<td></td>
<td>ID: n/a</td>
<td>Other info on race or ethnicity: N/A</td>
<td>Control: Placebo Placebo tablets provided taken once daily, at a similar time, each morning for 6 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RCT</td>
<td></td>
<td>Comparator: MedicationAtomoxetine capsules for 6 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multicenter N = 338</td>
<td>Age mean: 10.8 (2.8) Minimum age: 6</td>
<td>Follow-up: 2.25 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiple countries Setting: N/A</td>
<td>% Female: 25 % Age mean: 73.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Intervention**
- **Study:**
  - Author, year;
  - Multiple publications;
  - Trial ID;
  - Study design;
  - Sites;
  - Study size;
  - Location Setting
- **Population:**
  - Setting;
  - Study target;
  - ADHD presentation;
  - Diagnosis;
  - Comorbidity;
  - % Female;
  - Age mean;
  - Minimum age;
  - Maximum age;
  - Ethnicity
- **Comparison:**
  - Intervention;
  - Control;
  - Comparator;
  - Follow-up
- **Outcome and results**
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA-approved pharmacological</td>
<td>Ichikawa, 2020&lt;sup&gt;313&lt;/sup&gt; Ichikawa, 2020&lt;sup&gt;819&lt;/sup&gt; ID: NA RCT Multicenter N = 76 Japan Setting: N/A</td>
<td>Target: Children aged 6–17 with ADHD per DSM V. ADHD-RS-IV total score of at least 28 was required. Exclusion criteria: serious disorders of the blood or bone marrow, heart, kidneys, liver, lungs; psychiatric comorbidity (e.g., bipolar disorder, schizophrenia); CD (excluding ODD); current tics; history of seizures; low or high bodyweight; hypertension; QTc interval (Fridericia adjusted; QTcF) &gt;430 milliseconds; substance use disorder; and pregnancy or lactation Other: ADHD presentation: inattentive: 2.6, hyperactive: 34.2, combined: 63.2 Diagnosis: Confirmation by specialist DSM V plus ADHD-RS-IV Comorbidity: N/A Female: 17.1% Age mean: 10.0 (2.8) Minimum age: 6</td>
<td>Intervention: Lisdexamfetamine, 70 mg/day for 4 weeks, 1 week placebo, and 1 week of follow-up Control: Placebo Placebo pill Comparator: Medication Lisdexamfetamine 30 mg/day for 4 weeks Follow-up: 1 month</td>
<td>ADHD-RS-IV total score, parent, change from baseline All dosages had significantly greater improvements from baseline to all time points than placebo (p&lt;0.0001). Participants with any adverse event The rate was 70% for intervention, 42% for control, and 68% for comparator.</td>
</tr>
</tbody>
</table>
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Comparison</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jain, 2011&lt;sup&gt;137&lt;/sup&gt; Addrenex Pharmaceuticals, 2007&lt;sup&gt;641&lt;/sup&gt; ID: NCT00556959 RCT Multicenter N = 236 US Setting: N/A</td>
<td><strong>Target</strong>: Patients with a diagnosis of ADHD of the hyperactive or combined inattentive/hyperactive subtype and each patient's clinical research physician and a minimum score of 26 on the ADHD Rating Scale–IV (ADHD-RS-IV), having a good health, be able to swallow tablets, be mentally competent, having a body mass index of at least the fifth percentile for the patients' age group, and having concomitant diagnosis of tics or oppositional defiant disorder were eligible for study inclusion. Patients were excluded if they had a clinically significant illness or abnormality that would increase the safety risk of clonidine or if they had a clinically significant abnormality on electrocardiographic readings that were interpreted by a single entity, having a concomitant diagnosis or history of a psychiatric disorder that required psychotropic medication, and having a history of conduct disorders, syncopal episodes, or fainting.</td>
<td><strong>Intervention</strong>: Clonidine hydrochloride extended release tablets of 0.4 mg/day: dose-escalating titration schedule of 0.1 mg/day per week to achieve the target dose for the patient (i.e., 0.2 mg/day at week 2 or 0.4 mg/day at week 4), followed by dose tapering in 0.1-mg/day/week intervals until cessation of treatment at the end of week 8. <strong>Control</strong>: Placebo Placebo for 8 weeks followed the same procedure as the intervention group. <strong>Comparator</strong>: MedicationClonidine hydrochloride extended release 0.2 mg/day, forced dose-escalating titration schedule of 0.1 mg/day per week to achieve the target dose for the patient (i.e., 0.2 mg/day at week 2 or 0.4 mg/day at week 4), followed by dose tapering in 0.1-mg/day/week.</td>
<td>Clinical Global Impression of Improvement (CGI-I) Significant improvement in both treatment groups versus placebo (p=0.0032). ADHD-RS-IV Statistically significant improvements in the intervention groups compared to control. Participants that reported an adverse event 83% of both intervention groups and 72% of placebo patients reported an adverse event. Adverse events that led to discontinuation occurred in 1% of patients in the placebo group, 7% of patients in the 0.2-mg/day group, and 19% in the 0.4-mg/day group. The most common reasons for discontinuation were somnolence and fatigue.</td>
</tr>
</tbody>
</table>

### Table 1: Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
</tr>
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<tbody>
<tr>
<td>Jain, 2011&lt;sup&gt;137&lt;/sup&gt; Addrenex Pharmaceuticals, 2007&lt;sup&gt;641&lt;/sup&gt; ID: NCT00556959 RCT Multicenter N = 236 US Setting: N/A</td>
<td>Maximum age: 17 Ethnicity: Other info on race or ethnicity: N/A</td>
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</tr>
</tbody>
</table>
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
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<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>seizures (except for febrile seizure before 2 years of age). Other: ADHD presentation: N/A Diagnosis: Confirmation by specialist DSM-IV Comorbidity: N/A Female: 28 % Age mean: 9.4 (6–16), 9.6 (6–17), 9.4 (6–17) Minimum age: 6 Maximum age: 17 Ethnicity: % Hispanic or Latino: 8 % Black/African American: 27 % White: 59 Other info on race or ethnicity:</td>
<td></td>
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<tr>
<td></td>
<td>Johnson, 2020[142] Supernus Pharmaceuticals, 2016[156] ID: NCT02633527 RCT Multicenter N = 234 US Setting: Mixed</td>
<td>Target: Children between 6 and 12 with a diagnosis of ADHD per the DSM, medically healthy, free of ADHD medication for at least 1 week prior to baseline, participants should not have a history or presence of neuropsychiatric disease other than ADHD as the primary diagnosis, no history or presence of systemic diseases or other neurologic or psychiatric diseases, no history of suicidal</td>
<td>Intervention: Viloxazine (SPN-812), 400 mg/day of extended-release viloxazine for 8 weeks Control: Placebo Placebo titrated for the same period as the highest dose group, to minimize any potential placebo effects Comparator: Medication/Viloxazine (SPN-812), 100 mg/day of</td>
<td>CGI-I Intervention scores but not comparator scores improved significantly compared to control (p&lt;0.05). ADHD-RS-IV Intervention scores but not comparator scores improved significantly compared to control (p&lt;0.05). Decreased Appetite Adverse Event</td>
</tr>
</tbody>
</table>
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
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<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
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<tbody>
<tr>
<td></td>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Intervention; Control; Comparator; Follow-up</td>
<td>attempt or ideation 6 months prior to screening or at screening</td>
</tr>
<tr>
<td></td>
<td>attempt or ideation 6 months prior to screening or at screening</td>
<td>Other: ADHD presentation: inattentive_other : placebo 21.9 (4.7); 100mg/day: 22.1 (3.9); 200mg/day: 22.2 (3.6); 300mg/day 21.8 (3.8); 400mg/day: 21.0 (4.7); hyperactive_other : hyperactive/impulsivity mean(sd) for 4 groups: placebo: 20.5 (4.4); 100mg/day: 20.3 (5.2); 200mg/day: 21.</td>
<td>extended-release viloxazine for 8 weeks</td>
<td>All groups had at least one participant experience decreased appetite as an adverse event.</td>
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<tr>
<td></td>
<td></td>
<td>Diagnosis: Confirmation by specialist MINI-KID</td>
<td>Follow-up: 2 months</td>
<td>No deaths or serious treatment emergent adverse events were reported at any point during the study.</td>
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<td></td>
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<td>Comorbidity: N/A</td>
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<td></td>
<td></td>
<td>Female: 33 %</td>
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<td></td>
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<td>Age mean: Median 9.0 across all groups except 100mg group (median 8.0 years)</td>
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<td>Minimum age: 6</td>
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<td>Maximum age: 12</td>
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<td></td>
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<td>Ethnicity: % Black/African American : 38.3 % American Indian or Alaska Native : 0.97 % Asian : 0.97 % White : 56.8 % Multiracial : 2.43</td>
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</tbody>
</table>
### Intervention

<table>
<thead>
<tr>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Kelsey, 2004&lt;sup&gt;134&lt;/sup&gt;</td>
<td>Target: Children with ADHD. Those with serious medical illness, a history of psychosis, or bipolar disorder were excluded. Other: Parents provided some outcomes</td>
<td>ADHD presentation: inattentive: 27.4, hyperactive: 3.6, combined: 69.0</td>
<td>Conners' Global Index, Parent Significantly greater mean improvement in atomoxetine group. ADHD RS, parent 25% reduction from baseline Significantly greater improvement in atomoxetine group.</td>
</tr>
<tr>
<td>ID: RCT Multicenter N = 197 US Setting: N/A</td>
<td>Diagnosis: Confirmation by specialist DSM IV per Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Version Comorbidity: N/A Female: 29.4 % Age mean: 9.5 (1.8) Minimum age: 6 Maximum age: 12 Ethnicity: % White: 72.6 Other info on race or ethnicity:</td>
<td>Control: Placebo Placebo once per day in the morning, for 8 weeks Comparator: NA Follow-up: 2 months</td>
<td>Decreased appetite A significantly greater proportion of atomoxetine patients experienced decreased appetite. 4.5% of atomoxetine and 1.6% of placebo patients discontinued as the result of adverse events.</td>
</tr>
</tbody>
</table>

**Intervention:** Atomoxetine once per day in the morning for 8 weeks (max 1.8 mg/kg per day, 120 mg per day) Placebo once per day in the morning, for 8 weeks

**Comparator:** NA

**Follow-up:** 2 months
### Appendix C. Evidence Tables

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<th>Intervention</th>
<th>Study:</th>
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<tbody>
<tr>
<td>FDA-approved pharmacological</td>
<td>Kollins, 2011[^68] Shire, 2005[^1024]</td>
<td><strong>Target:</strong> Reasons for exclusion included any current comorbid psychiatric diagnosis (except oppositional defiant disorder), weight &lt;25 kg (55 lb), cardiac conditions that might have increased the safety risk to the subject, or a Pediatric Daytime Sleepiness Scale (PDSS) score 22 at screening and/or baseline.</td>
<td><strong>Intervention:</strong> Guanfacine extended release, optimal dose (1, 2, or 3mg/day) found in 3 week dose-finding phase, maintained for 2 weeks of maintenance</td>
<td>CGI-I scale much improved or very much improved A significantly greater percentage in the intervention group was rated 'much improved' or 'very much improved' compared with placebo (p&lt;0.007). ADHD-RS-IV total scores Reductions were significantly greater in the intervention than in the placebo group (p&lt;0.001). Reaction time as measured by the Choice Reaction Time (CRT) test indicated that treatment did not impair psychomotor functioning or alertness compared with placebo. Participants with treatment emergent adverse events reported Rate was 79.3% in intervention, 70.2% in placebo group. The majority of adverse events were mild to moderate; there were 2 serious events severe asthma and moderate loss of consciousness (neither was judged to be related to GXR).</td>
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<td></td>
<td>Shire, 2005[^1024]</td>
<td><strong>Other:</strong></td>
<td><strong>Control:</strong> Placebo</td>
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<tr>
<td></td>
<td>ID: NCT00150592 RCT Multicenter N = 182 US Setting: N/A</td>
<td><strong>ADHD presentation:</strong> inattentive : 23.6, hyperactive : 1.7, combined : 74.7</td>
<td><strong>Comparator:</strong> NA</td>
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<td><strong>Follow-up:</strong> 2.5 months</td>
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<td><strong>Diagnosis:</strong> Confirmation by specialist DSM-IV-TR</td>
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<td><strong>Comorbidity:</strong> N/A</td>
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<td></td>
<td></td>
<td><strong>Female:</strong> 30.3 %</td>
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<td></td>
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<td><strong>Age mean:</strong> 12.6 (2.81)</td>
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<td></td>
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<td><strong>Minimum age:</strong> 6</td>
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<td><strong>Maximum age:</strong> 17</td>
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<td><strong>Ethnicity:</strong></td>
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<td></td>
<td></td>
<td>% Hispanic or Latino : 12.4</td>
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<td></td>
<td>% Black/African American : 16.3</td>
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<td></td>
<td></td>
<td>% White : 66.9</td>
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<td>Other info on race or ethnicity:</td>
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</tbody>
</table>

[^68]: Kollins, 2011
[^1024]: Shire, 2005
Appendix C. Evidence Tables

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<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
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</thead>
<tbody>
<tr>
<td>Kollins, 2011 Addrenex Pharmaceuticals, Inc., 2008 ID: NCT00641329 RCT Multicenter N = 198 US Setting: N/A</td>
<td><strong>Target:</strong> Children were required to have inadequate stimulant medication response, defined as a total score 26 on the ADHD-RS-IV questionnaire after a minimum of 4 weeks on a stable stimulant regimen, had intelligence quotient estimated to be 80 by the investigator and a BMI in the 5th percentile for the patient’s gender and age; patients were excluded from participation in the study if they had (1) a current diagnosis or history of a psychiatric disorder that required psychotropic medication or severe comorbid Axis I or Axis II disorder (2) a history of conduct disorder, (3) a history of syncopal episodes or seizures (except for febrile seizures), (4) current or past drug abuse, (5) a history of clonidine intolerance, or (6) used any investigational drug within 30 days of the study initiation or had a positive drug test (except for ADHD medication)</td>
<td><strong>Other:</strong> ADHD presentation: N/A Diagnosis: Confirmation by specialist DSM-IV Comorbidity: N/A</td>
<td><strong>Intervention:</strong> Clonidine hydrochloride extended-release tablets with stimulants (methylphenidate or amphetamine): total daily doses of 0.1 to 0.4 mg per day for 8 weeks, concomitant stimulant medication was prescribed by the patient’s regular physician and was obtained from the patient’s usual pharmacy</td>
<td><strong>Control:</strong> Placebo Placebo plus stimulants for 8 weeks, methylphenidate or amphetamine prescribed by the patient’s regular physician and was obtained from the patient’s usual pharmacy <strong>Comparator:</strong> NA <strong>Follow-up:</strong> 1.25 months CGI-I change from baseline The intervention group had greater improvement than the control group (p=0.006). ADHD-RS-IV (ADHD Rating Scale IV), change The intervention group had greater improvement than the control group (p=0.009). Participants with at least one treatment emergent adverse event The rate was 45% in the intervention and 41% in the concomitant placebo group. Somnolence, headache, fatigue, upper abdominal pain, and nasal congestion were the most commonly reported event in the CLON-XR plus stimulant group. Of the 96 patients in the placebo plus stimulant group, 3 (3%) discontinued because of TEAEs (ie, increased heart rate [n=1], aggression [n=1], and somnolence [n=1]), and only 1 of 102 patients (1%) in the CLON-XR plus stimulant group discontinued because of a TEAE (ie, slowed thought processes).</td>
</tr>
</tbody>
</table>
### Appendix C. Evidence Tables

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</thead>
<tbody>
<tr>
<td><strong>FDA-approved pharmacological</strong></td>
<td><strong>Kratochvil, 2002</strong></td>
<td><strong>Target:</strong> Girls older than 9 years were excluded because the results of preclinical studies of atomoxetine’s effects on pregnant animals were unavailable at the time this study started. Important exclusion criteria included a history of bipolar or psychotic disorders, motor tics or a family history of Tourette syndrome, substance abuse, nonresponse to a previous trial of methylphenidate (significant residual symptoms after at least 2 weeks of treatment with at least 1.2 mg/kg per day), and serious medical illness. Other concurrent psychiatric diagnoses did not exclude patients from the trial; these were assessed with the Diagnostic Interview for Children</td>
<td><strong>Intervention:</strong> Atomoxetine 1-2 mg/kg per day administered as a divided dose in the morning and late afternoon for 10 weeks <strong>Control:</strong> NA <strong>Comparator:</strong> MedicationMethylphenidate was dosed beginning at 5 mg from one to three times daily with an ascending dose titration based on the investigator’s assessment of clinical response and tolerability, total daily dose was not to exceed 60 mg, concomitant use of other psy</td>
<td><strong>CGI ADHD Severity</strong> Both groups improved. <strong>ADHD-RS-IV</strong> No statistically significant differences between treatment groups (p = .66). <strong>Weight loss</strong> The rate of weight loss was 2.7% in the atomoxetine and 5% in the methylphenidate group (p=0.611). Both atomoxetine and methylphenidate were well tolerated, with no statistically significant differences in discontinuations due to adverse events (atomoxetine 5.4%, methylphenidate 11.4%; p=.18); all atomoxetine patients who discontinued due to an adverse event were extensive metabolizers.</td>
</tr>
<tr>
<td><strong>ID:</strong> NA</td>
<td><strong>RCT</strong></td>
<td><strong>Female:</strong> 26% <strong>Age mean:</strong> Intervention 10.4 (2.5), control 10.5 (2.5) <strong>Minimum age:</strong> 6 <strong>Maximum age:</strong> 17 <strong>Ethnicity:</strong> % Hispanic or Latino : 11 % Black/African American : 27 % White : 54 Other info on race or ethnicity: Other : 8</td>
<td></td>
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</table>
| **Study:** | Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting | **Population:** Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity | **Comparison:** Intervention; Control; Comparator; Follow-up | **CGI-I scores of very much improved or much improved rate**
40% of atomoxetine and 22% of placebo participants had CGI-I scores of 1 (very much improved) or 2 (much improved) relative to baseline, which was not a significant difference after adjustment for age and study center (p = .1). A total of 62% of subjects | ADHD-RS total score, parent
Significant mean decreases in parent (P = .009) and teacher (P = .02) ADHD-IV Rating |
| **FDA-approved pharmacological** | Kratochvil, 2011^{172} University of Nebraska, 2007^{1999} ID: NCT00561340 RCT Unclear/Not reported N = 101 US Setting: Other | **Target:** Young children with ADHD, exclusion criteria included concurrent use of psychotropic or other medications with significant central nervous system effects; current effective treatment with atomoxetine; medical contraindication to atomoxetine; current diagnosis of adjustment disorder, autism, psychosis, bipolar disorder, or significant suicidality; history of abuse that may confound symptoms of ADHD; and failure to | **Intervention:** Atomoxetine 0.5-1.8 mg/kg per day for 8 weeks **Control:** Placebo Placebo controlled **Comparator:** NA **Follow-up:** 2 months | |
### Intervention

**Study:**
- Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting

**Population:**
- Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity

**Comparison:**
- Intervention; Control; Comparator; Follow-up

### Outcome and results

- Scale scores with atomoxetine compared with placebo.
- Decreased appetite
  - The rate was 30% in the intervention compared to 8% in the placebo group.
  - There were no significant differences in the mean change in systolic blood pressure with atomoxetine treatment compared with placebo ($p = .09$), in the change in diastolic blood pressure ($p = .8$), or heart rate ($p = .07$) with atomoxetine. There was a significant difference in change in weight ($-0.2$ kg $\pm 0.1$) in atomoxetine and $0.6$ kg $\pm 0.2$ in the placebo group ($P = .0006$); however, this was not clinically significant.

### Other info on race or ethnicity:

- % Black/African American: 1
- % Native Hawaiian or Pacific Islander: 3
- % White: 86
- Other info on race or ethnicity:

### FDA-approved pharmacological

**Kurowski, 2019**
- Children's Hospital Medical Center, Cincinnati, 2013
- ID: NCT01933217
- Crossover trial
- Single center
- N = 26

**Target:**
- Children age 6-17 years old with hospital admission for blunt head trauma, and a confirmed diagnosis of moderate to severe traumatic brain injury (Glasgow Coma Scale $\leq 12$), have 6 of 9 current symptoms on at least one subscale of the VADPRS; children with preinjury diagnoses of developmental or neurological

**Intervention:**
- Methylphenidate long-acting (Concerta), initial dose of $18$ mg, subsequent 3 weeks, titrated based on response and side effects for week 4; $<25$kg = $18$mg (low), $27$mg (medium), and $36$mg (high) dosages, $25$kg = $18$mg (low), $36$mg (medium), $54$mg (high) dosages

**Control:** Placebo

**ADHD total symptom score VADPRS (Vanderbilt ADHD Parent Diagnostic Rating Scale)**
- On optimal dose of medication, greater reductions were found for the medicated condition than for placebo ($p = 0.022$, effect size $0.59$).
- Mean number of participants with change in appetite side effect
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
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<th>Study:</th>
<th>Population:</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>US</strong></td>
<td>Setting: Specialty care</td>
<td>disorders, or hospitalized for psychiatric reasons in the past 12 months, involved in active behavioral and/or medication treatments for attention problems and/or who had contraindications to methylphenidate use or were on medications that had potentially severe interactions with methylphenidate were excluded</td>
<td><strong>Intervention:</strong> Methylphenidate 0.7mg/kg twice daily for 1 year <strong>Control:</strong> Placebo <strong>Comparator:</strong> NA <strong>Follow-up:</strong> 2 months</td>
<td>Compared to the placebo condition, the medication condition was associated with lower weight at the second, third, and fourth week (p&lt;.0001). Methylphenidate was associated with weight loss (~1 kg), increased systolic blood pressure (~3–6 point increase), and mild reported changes in appetite versus the placebo condition. At the last visit, suicidal ideation was reported by one participant while on placebo.</td>
</tr>
</tbody>
</table>

**Other:**
ADHD presentation: inattentive : 69.2, hyperactive : 7.7, combined : 23.1, N/A

**Diagnosis:** Confirmation by specialist K-SADS-P/L

**Comorbidity:** Other: Traumatic brain injury

**Female:** 23.1 %

**Age mean:** 11.5 (2.8)

**Minimum age:** 6

**Maximum age:** 17

**Ethnicity:**
% White : 73.1

Other info on race or ethnicity:

**FDA-approved**
Law, 1999779
ID: N/A
RCT
Single center

**Target:** Children who exhibited pervasive ADHD, defined as 8 or more of the 14 criteria for ADHD according to DSM-III-R based on parent or teacher interview; at least

**Intervention:** Methylphenidate 0.7mg/kg twice daily for 1 year

**Control:** Placebo

**Onset or worsening severity of tics:** from abstract - clinically significant tics developed in 19.6% of the subjects without preexisting tics receiving MPH and in 16.7% of those receiving the placebo (Fisher exact test, p = .59, not
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
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</thead>
<tbody>
<tr>
<td>N = 91 Canada Setting: Other</td>
<td>5 ADHD criteria in another setting; a history of ADHD symptoms for at least 6 months, starting before the age of 7 years; estimated Full Scale IQ greater than 80 (based on subtests of VISC-R); no primary anxiety or affective disorder; no history of prior treatment for ADHD or tics. Excluded children if they had severe motor or vocal tic disorder or Tourette's disorder (mild to moderate tics included); if regularly received medication for a medical problem; if had a chronic medical condition; or if attended a full time residential or day treatment program Other: Parents, teachers, and research assistants; research assistants were trained to achieve high consistency in measurements of tics under supervision of study psychiatrist ADHD presentation: N/A Diagnosis: Comorbidity: Female: 18.68 % Age mean: MPH group mean age 8.4(1.6), Placebo group mean age 8.3(. 1.5) Minimum age:</td>
<td>Comparator: NA Follow-up: 12 months</td>
<td>significant; relative risk = 1.17, confidence interval = 0.31-4.40). Deterioration of tics was observed in 33% of subjects with preexisting tics receiving MPH and in 33% of those receiving the placebo (Fisher exact test, p = .70, not significant; relative risk = 1.0, confidence interval = 0.40-1.85).</td>
<td></td>
</tr>
</tbody>
</table>
### FDA-approved pharmacological

<table>
<thead>
<tr>
<th>Study:</th>
<th>Lilly, 2008\footnote{33}</th>
</tr>
</thead>
<tbody>
<tr>
<td>ID:</td>
<td>NCT00760747</td>
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<tr>
<td>RCT</td>
<td>RCT</td>
</tr>
<tr>
<td>Multicenter</td>
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<tr>
<td>N = 112</td>
<td></td>
</tr>
<tr>
<td>Multiple countries</td>
<td></td>
</tr>
<tr>
<td>Setting:</td>
<td>Mixed</td>
</tr>
</tbody>
</table>

#### Intervention
- **Target:** Children 6-16 years old who meet DSM-IV diagnostic criteria for ADHD and unsatisfactory symptom response to stimulant therapy or experience of adverse events while on stimulant therapy; those who previously participated in an atomoxetine study and those taking anticonvulsants, antihypertensive agents, medication with sympathomimetic activity, psychotropic medications, monoamine oxidase inhibitor were excluded.
- **Other:**
  - **ADHD presentation:** inattentive: 28.2, hyperactive: 3.6, combined: 66.7, combined_other: Not categorized: 1/111
  - **Diagnosis:** No
  - **Not mentioned**
  - **Comorbidity:** N/A
  - **Female:** 16.2 %
  - **Age mean:** 11.5 (2.38)
  - **Minimum age:** 6

#### Comparison
- **Intervention:** Slow switching group (switch from full stimulant dose to atomoxetine, 1.2 mg/kg/day, orally, during 10 weeks then continue treatment up to 1.8 mg/kg/day, to 14 weeks)
- **Control:** NA
- **Comparator:** MedicationFast switching group (switch from full stimulant dose to atomoxetine 1.2 mg/kg/day, PO, during 2 weeks then continue treatment up to 1.8 mg/kg/day, PO to 14 weeks)

#### Outcome and results
- **Follow-up:** 2.5 months
- **CGI-S (Clinical Global Impression Severity) rating scale change**
  - There was no significant difference between groups ($p=0.898$).
- **ADHD-RS-IV (Attention Deficit Hyperactivity Disorder-Rating Scale) Parent Version change**
  - There was no significant difference between groups ($p=0.692$).
- **Treatment Satisfaction Preference**
- **Serious adverse events**
  - The rate was 1.8% in the intervention group and 1.9% for comparator group.
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA-approved pharmacological</td>
<td>Martenyi, 2010&lt;sup&gt;604&lt;/sup&gt; Eli Lilly and Company, 2004&lt;sup&gt;728&lt;/sup&gt; ID: NCT00386581 RCT Multicenter N = 105 Russia Setting: N/A</td>
<td>Maximum age: 16 Ethnicity: % Hispanic or Latino: 18.9 % Black/African American: 0.9 % White: 80.2 Other info on race or ethnicity:</td>
<td></td>
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<tr>
<td></td>
<td>Target: Participants were 6–16 years of age, with a DSM-IV diagnosis of ADHD, a minimum score of 25 for boys and 22 for girls, or &gt; 12 for their diagnostic subtype on the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored, score of &gt;= 4 on CGI-ADHD Severity scale, had not taken any medications for ADHD. Exclusion: weight &lt;20 kg or &gt;60 kg, history of bipolar disorder, anxiety disorder, psychosis, or developmental disorder, suicidal Other: ADHD presentation: inattentive: 22.9, hyperactive: 4.8, combined: 72.4 Diagnosis: Confirmation by specialist Kiddie Schedule for Affective Disorders and Schizophrenia for School-aged Children-Present and Lifetime Version (K-SADS-PL)</td>
<td>Intervention: Atomoxetine 1.2 mg/(kg/day) as a single dose in the morning for 6 weeks Control: Placebo Identical placebo treatment Comparator: NA Follow-up: 1.5 months</td>
<td>CGI-ADHD-S (Clinical Global Impression-ADHD-Severity) change The intervention group had significantly more improved scores compared to control group (p=0.035). ADHD-RS-IV (Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version) change The intervention group had significantly more improved scores compared to control group (p=0.013). Weight loss Rate was 8.3 in the intervention group with none in placebo. Treatment emergent signs and symptoms Rate was 41.9% in the intervention and 33.3% in the control group. No serious adverse events (including deaths or suicidal ideation) were reported in either treatment group. One patient (in the atomoxetine group) discontinued the study due to an adverse event (mild skin itch and eruptions).</td>
<td></td>
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</tbody>
</table>

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### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study:</td>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Intervention; Control; Comparator; Follow-up</td>
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<tr>
<td></td>
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<tr>
<td></td>
<td>Comorbidity: N/A</td>
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<tr>
<td></td>
<td>Female: 14.3 %</td>
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<tr>
<td></td>
<td>Age mean: 9.8 (2.8)</td>
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<tr>
<td></td>
<td>Minimum age: 6</td>
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<tr>
<td></td>
<td>Maximum age: 16</td>
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<td></td>
<td>Ethnicity:</td>
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<tr>
<td></td>
<td>% White: 100</td>
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<tr>
<td></td>
<td>Other info on race or ethnicity:</td>
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<tr>
<td>ADHD presentation:</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis:</td>
<td>Confirmation by specialist ADHD-RS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbidity:</td>
<td>N/A</td>
<td></td>
<td></td>
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<tr>
<td>Female:</td>
<td>22 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age mean:</td>
<td>13.8 (2.2) and 13.6 (2.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum age:</td>
<td>8</td>
<td></td>
<td></td>
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<tr>
<td>Target:</td>
<td>Children using methylphenidate as prescribed in clinical practice in any dosage or form for 2 years or longer; if a child had stopped the medication during, for instance, a weekend or a school holiday, they could still participate if the period of not using methylphenidate had not exceeded 2 continuous months during the past 2 years</td>
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<tr>
<td>Other:</td>
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<tr>
<td></td>
<td>ADHD presentation: N/A</td>
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<tr>
<td></td>
<td>Diagnosis: Confirmation by specialist ADHD-RS</td>
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<tr>
<td></td>
<td>Comorbidity: N/A</td>
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<tr>
<td></td>
<td>Female: 22 %</td>
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<td></td>
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<tr>
<td></td>
<td>Age mean:</td>
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<tr>
<td></td>
<td>13.8 (2.2) and 13.6 (2.2)</td>
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<td></td>
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<tr>
<td></td>
<td>Minimum age: 8</td>
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<tr>
<td>Intervention:</td>
<td>Gradual withdrawal of methylphenidate to placebo over a 3-week period followed by 4 weeks of complete placebo</td>
<td></td>
<td>CGI-I (Clinical Global Impressions improvement scale) not worsened CGI-I indicated worsening in 40.4% of the discontinuation group compared with 15.9% of the continuation group. ADHD-RS (ADHD Rating Scale) A significant between-group difference in change over time of in favor of the group that continued methylphenidate treatment. Strengths and Difficulties Questionnaire (SDQ), total score, parent, change from baseline The intervention group improved significantly compared to comparator group (p&lt;0.03). Change in appetite The rate of patients with changes in appetite was 9.6% in the discontinuation group and 7.4% in the continuation group. Participants with at least one adverse event reported</td>
</tr>
<tr>
<td>Control:</td>
<td>NA</td>
<td></td>
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<tr>
<td>Comparator:</td>
<td>Medication Continued extended-release methylphenidate for 7 weeks, 54 or 36 mg/day</td>
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<tr>
<td>Follow-up:</td>
<td>2.75 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>Population:</td>
<td>Comparison:</td>
<td>Outcome and results</td>
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<tr>
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<tr>
<td>Study:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting | **Population:**
|             | Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity | **Comparison:** Intervention; Control; Comparator; Follow-up | In the discontinuation group, 13.5% reported at least one adverse event, compared with 10.6% in the continuation group (p=0.46). None of the participants had a serious adverse event. |
|             | **Maximum age:** 18
|             | **Ethnicity:** % White : 98.9 Other info on race or ethnicity: | | |
| Mattingly, 2020<sup>699</sup> Shire, 2017<sup>1028</sup> ID: NCT03325881 RCT Multicenter N = 89 US Setting: Specialty care | **Target:** Children (aged 6–12 years) with Diagnostic and Statistical Manual of Mental Disorders, Fifth edition—defined ADHD; baseline ADHD-Rating Scale, Fifth Edition, Child, Home Version total scores (ADHD-RS-5-HV-TS) ≥ 28; and baseline Clinical Global Impressions-Severity scores ≥ 4 were eligible **Other:** ADHD presentation: inattentive : 13.6, hyperactive : 13.6, combined : 72.8 Diagnosis: Confirmation by specialist ADHD-Rating Scale, Fifth Edition, Child, Home Version Comorbidity: N/A Female: 40 % Age mean: 8.8 (2.20) Minimum age: 6 Maximum age: 17 Ethnicity: % Black/African American : 24.4 | **Intervention:** Mixed amphetamine salts extended-release (SHP465), 6.25 mg once daily for 4 weeks **Control:** Placebo Placebo capsules were identical in appearance to maintain blinding **Comparator:** NA **Follow-up:** 1 month | CGI-I (Clinical Global Impressions-Improvement) Difference between groups was not statistically significant (p=0.597). ADHD-RS-5-HV-TS (ADHD-Rating Scale, Fifth Edition, Child, Home Version total scores, hyperactivity/impulsivity and inattention) Difference between groups was not statistically significant. Decreased appetite The rate was 2.2% in the intervention and 4.7% in the placebo group. Participants with treatment emergent adverse events The rate was 16.3% in the placebo and 24.4% in the treatment group. There were no serious or severe treatment emergent adverse events, nor events or leading to discontinuation or death. |
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study:</strong> McCracken, 2016[^1]</td>
<td><strong>Target:</strong> Male or female individuals 7 to 14 years of age; ADHD (any subtype) diagnosed by semi-structured diagnostic interview (Kiddie-Schedule for Affective Disorders and Schizophrenia -PL [K-SADS-PL]) and clinical interview; and Clinical Global Impression Severity (CGI-S) score 4 for ADHD</td>
<td><strong>Intervention:</strong> Guanfacine (1-3 mg/day) plus d-methylphenidate extended-release (5-20 mg/day), with fixed-flexible dosing</td>
<td>CGI-I treatment response (very much improved or much improved) There were significant differences in treatment response for the 3 treatment sequences, with rates of 81% for methylphenidate alone, 69% for guanfacine alone, and 91% for guanfacine plus methylphenidate (p = 0.01). ADHD-RS-IV (ADHD-Rating Scale-IV) total score Guanfacine plus methylphenidate showed superiority versus guanfacine alone (p = 0.049), but did not differ statistically from methylphenidate (p = 0.066). Any adverse event The rate was 99% for intervention versus 96% for control.</td>
</tr>
<tr>
<td><strong>Author, year:</strong> McCracken, 2016[^1]</td>
<td><strong>Diagnosis:</strong> Confirmation by specialist DSM-IV ADHD by clinician</td>
<td><strong>Control:</strong> Other Placebo plus d-methylphenidate extended-release (5-20 mg/day)</td>
<td></td>
</tr>
<tr>
<td><strong>Multiple publications:</strong> McCracken, 2016[^1]</td>
<td><strong>Comorbidity:</strong> N/A</td>
<td><strong>Comparator:</strong> NA</td>
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<tr>
<td><strong>Trial ID:</strong> NCT00429273</td>
<td><strong>Female:</strong> 32%</td>
<td><strong>Follow-up:</strong> 2 months</td>
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<tr>
<td><strong>Study design:</strong> RCT</td>
<td><strong>Age mean:</strong> 10.0 (2.1)</td>
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<tr>
<td><strong>Sites:</strong> Single center</td>
<td><strong>Minimum age:</strong> 7</td>
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<tr>
<td><strong>Study size:</strong> N = 212</td>
<td><strong>Maximum age:</strong> 14</td>
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<tr>
<td><strong>Location Setting:</strong> US</td>
<td><strong>Ethnicity:</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Setting:</strong> Specialty care</td>
<td>% Hispanic or Latino : 21.3</td>
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<tr>
<td></td>
<td>% Black/African American : 17</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>% Asian : 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>% White : 69</td>
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</tbody>
</table>

[^1]: FDA-approved pharmacological

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[^2]: McCracken, 2016
[^3]: Sayer, 2016
[^4]: University of California, Los Angeles, 2007

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[^1]: FDA-approved pharmacological
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Comparison</th>
<th>Outcome and results</th>
</tr>
</thead>
</table>
| Michelson, 2001<sup>122</sup>  
Matza, 2004<sup>879</sup>  
ID: NA  
RCT  
Multicenter  
N = 297  
US  
Setting: Other | **Target:** Children with ADHD from the DSM-IV by clinical assessment and structured interview  
**Other:**  
ADHD presentation: inattentive: 31, hyperactive: 2, combined: 67  
Diagnosis: Confirmation by specialist  
DSM-IV  
Comorbidity: ODD  
Female: 29%  
Age mean: 11.2 (2.3)  
Minimum age: 8  
Maximum age: 18  
Ethnicity:  
% Hispanic or Latino: 2  
% Black/African American: 17.9  
% Asian: 1  
% White: 75.8  
Other info on race or ethnicity: Other: 6 | **Intervention:** Atomoxetine 1.8 mg/kg/day for 8 weeks  
**Control:** Placebo  
Placebo-controlled  
**Comparator:** Medication Atomoxetine 0.5 mg/kg/day  
**Follow-up:** 2 months | Behavior rating, Psychological Summary Score  
Atomoxetine groups were statistically significantly better than placebo.  
CGI-S  
Outcomes in the 1.2 and 1.8 mg/kg/day groups were superior to placebo on almost all measures but for the 0.5 mg/kg/day group CGI-S scale outcomes were not statistically significantly different from those of the placebo group.  
ADHD-RS, parent  
Atomoxetine groups were statistically significantly better than placebo.  
Psychosocial summary score  
Atomoxetine groups were statistically significantly better than placebo.  
Reduction in affective symptoms, as measured by the CDRS-R, was greater among those in the 2 higher dose groups of atomoxetine compared with placebo.  
Anorexia  
The rate of anorexia was 12% in the high dose, 6.8% in the low dose, and 4.8% in the placebo group. |
Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michelson, 2002</td>
<td>ID: NA, RCT, Multicenter, N = 171, US, Setting: Specialty care</td>
<td>Target: Children and adolescents with ADHD. Other: Parents and teachers provided outcome data. ADHD presentation: inattentive: 40.6, hyperactive: 1.8, combined: 57.6. Diagnosis: Confirmation by specialist. DSM-IV, assessed by clinical interview and confirmed by Schedule for Affective Disorders and Schizophrenia for School-aged Children (K-SADS-PL). Comorbidity: N/A. Female: 29.4%. Age mean: 10.3 (2.4). Minimum age: 6. Maximum age: 16. Ethnicity: Other info on race or ethnicity: N/A.</td>
<td>Intervention: Atomoxetine 1-1.5 mg/kg per day at 4 weeks. Control: Placebo. Comparator: NA. Follow-up: 1.5 months.</td>
<td>Atomoxetine was well tolerated at all doses. No adverse event was statistically significantly more frequent among either of the 1.2 mg/kg/day or 1.8 mg/kg/day atomoxetine dose groups compared with placebo. CGI-S Intervention group improved more (p &lt; .001). ADHD-RS-IV (ADHD Rating Scale IV), total score, parent report. Intervention group improved more (p &lt; .001). Decreased appetite. More intervention patients reported decreased appetite (p=0.02).</td>
</tr>
</tbody>
</table>

**Intervention**

- **Study:** Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location; Setting.
- **Population:** Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity.
- **Comparison:** Intervention; Control; Comparator; Follow-up.

**Outcome and results**

Atomoxetine was well tolerated at all doses. No adverse event was statistically significantly more frequent among either of the 1.2 mg/kg/day or 1.8 mg/kg/day atomoxetine dose groups compared with placebo. CGI-S Intervention group improved more (p < .001). ADHD-RS-IV (ADHD Rating Scale IV), total score, parent report. Intervention group improved more (p < .001). Decreased appetite. More intervention patients reported decreased appetite (p=0.02).
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
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<th>Population:</th>
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<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montoya, 2009&lt;sup&gt;130&lt;/sup&gt; Escobar, 2009&lt;sup&gt;138&lt;/sup&gt; ID: NCT00191945 RCT Multicenter N = 151 Spain Setting: Specialty care</td>
<td>Target: Medication naive children and adolescents with ADHD. Patients with psychiatric comorbidities excluded. Other: Parents provided some outcome data ADHD presentation: inattentive : 32.9, hyperactive : 4.0, combined : 63.1 Diagnosis: Confirmation by specialist Diagnosed per DSM-IV-TR). Confirmed by Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version (K-SADS-PL). Comorbidity: N/A Female: 20.5 % Age mean: 10.3 (2.5) Minimum age: 6 Maximum age: 15 Ethnicity: % Hispanic or Latino : 3.3 % Black/African American : 0.7 % White : 96 Other info on race or ethnicity:</td>
<td>Intervention: Atomoxetine, target dose of 1.2 mg/kg/day taken once daily for 12 weeks Control: Placebo Comparator: NA Follow-up: 3 months</td>
<td>CPRS-R:S (Conners’ Parent Rating Scale-Revised: Short Form), Total CGI-S (Clinical Global Impression - Severity) severely ill Total Conners score was significantly lower in intervention group at 12 weeks. A significantly lower percentage of intervention group participants were determined to be ‘severely ill’ compared to the control group. ADHD-RS-IV (ADHD-Rating Scale-IV) total score, parent report Statistically significant improvements with atomoxetine compared to placebo from baseline to follow up on total and subscale scores of the ADHD- RS-IV (p &lt; .001). Atomoxetine improved Health Related Quality of Life risk avoidance (p &lt; .001) and achievement (p = .042) domains compared to placebo, as assessed by parents. Difference in satisfaction, comfort, and resilience domains not statistically significant. Number with decreased appetite Significantly lower percentage of placebo patients experienced appetite decrease (p = 0.006). Participants with at least one adverse event The rate was 65% for intervention and 37% for control.</td>
<td></td>
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</tbody>
</table>
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
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<tbody>
<tr>
<td></td>
<td>Motaharifard, 2019&lt;sup&gt;122&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Vice Chancellor for research of Tehran university of Medical Sciences, 2015&lt;sup&gt;108&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>ID: IRCT2015050922165N1</td>
<td>Target: diagnosed with mild or moderate ADHD according to DSM-5, had no significant chronic medical condition, had no development disorders, had no other psychiatric disorders, had no intellectual disabilities (intelligence quotient &lt;70), not clinically current drug abusers or dependent on drugs within the last 6 months</td>
<td>Intervention: Methylphenidate dose of 1 mg/kg/day, initial dose of 5 mg twice daily in the first week, followed by a 10-mg tablet twice daily, participants weighing beyond 30 kg received a 10-mg tablet thrice daily from the third week of the study, tablets mixed into 5 cc/day of therapeutically ineffective syrup</td>
<td>ADHD-RS-IV (ADHD Rating Scale-IV), parent-Hyperactivity Subscale There was no significant difference between groups (p=0.78). Decreased Appetite Side Effect Intervention group had significantly more participants who had a side effect of decreased appetite (p&lt;0.001). Reported side effects of sweet almond syrup, reported (N, %): Insomnia (2, 8%); Increased sleep (4, 16%); Difficulty falling asleep (3, 12%); Abdominal pain (2, 8%); Impulsiveness (1, 4%); Irritability (1, 4%); Nausea (1, 4%). Side effects of MPH reported (N, %): Insomnia (6, 24%); Increased sleep (1, 4%); Difficulty falling asleep (9, 36%); Abdominal pain (6, 24%); Headache (6, 24%); Impulsiveness (3, 12%); Irritability (6, 24%); Nausea (1, 4%); Constipation (1, 4%); Dry mouth (1, 4%); Sadness (6, 24%); Tic (1, 4%); Itching (1, 4%)</td>
</tr>
<tr>
<td></td>
<td>RCT</td>
<td>Diagnosis: Confirmation by specialist Child and adolescent psychiatrist confirmed diagnosis of ADHD according to DSM-5</td>
<td>Control: NA Comparator: Nutrition, supplementsReceived sweet almond syrup 5 cc/day (three times a day). Follow-up: 2 months</td>
<td></td>
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<tr>
<td></td>
<td>Single center N = 59 Iran Setting: Primary Care</td>
<td>Comorbidity: N/A Female: 34 % Age mean: 7.1 (1.36) Minimum age: 6 Maximum age: 14 Ethnicity: Other info on race or ethnicity:</td>
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<tr>
<td></td>
<td>Mount Sinai, 2012&lt;sup&gt;227&lt;/sup&gt;</td>
<td>Target: Aged 7-17 years, Wechsler Intelligence Scale for Children ≥ 75, diagnosis of ADHD, any subtype, determined by Kiddie Schedule for Affective Disorders and</td>
<td>Intervention: Atomoxetine, flexible-dose titration for 6-8 weeks</td>
<td>CGI-S (Clinical Global Impressions-Severity) Intervention scores improved when compared to comparator. ADHD-RS</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
<td>Diagnosis: Confirmation by specialist Child and adolescent psychiatrist confirmed diagnosis of ADHD according to DSM-5</td>
<td>Control: NA Comparator: MedicationMethylphenidate, flexible-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ID: NCT01678209 RCT</td>
<td>Comorbidity: N/A Female: 34 % Age mean: 7.1 (1.36) Minimum age: 6 Maximum age: 14 Ethnicity: Other info on race or ethnicity:</td>
<td></td>
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</tr>
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</table>

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## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Intervention scores improved compared to comparator.</td>
</tr>
<tr>
<td>Control:</td>
<td>Percentage of correct inhibition in the Go-No go task favored methylphenidate (81.81%) compared to atomoxetine (80.72%).</td>
</tr>
<tr>
<td>Comparator:</td>
<td>Decreased appetite</td>
</tr>
<tr>
<td>Follow-up:</td>
<td>The rate was 9.09% for atomoxetine and 18.18% for methylphenidate.</td>
</tr>
<tr>
<td>Follow-up:</td>
<td>Participants with adverse events</td>
</tr>
<tr>
<td>Follow-up:</td>
<td>The rate was 27.7% for atomoxetine and 18.18% for methylphenidate.</td>
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<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
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<tbody>
<tr>
<td>N = 127</td>
<td>Single center</td>
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<tr>
<td>US</td>
<td>Setting: Specialty care</td>
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<tr>
<td>Schizophrenia for School-Aged Children-Present and Lifetime Versions (K-SADS-PL); ADHD Rating Scale-IV-Parent Version: Investigator Administered (ADHD-RSIV) total score ≥ 1.5 SD above age and gender means for subtype; Clinical Global Impressions-ADHD-Severity (CGI-S) score &gt; 4; ADHD must be the primary diagnosis and focus of treatment, and the treatments offered in the study must not be contraindicated for the comorbid disorder</td>
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<tr>
<td>Other:</td>
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<td>ADHD presentation: N/A</td>
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<tr>
<td>Diagnosis: Confirmation by specialist</td>
<td>Diagnosis of ADHD, any subtype, determined by Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Versions (K-SADS-PL)</td>
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<tr>
<td>Comorbidity: N/A</td>
<td>Female: 27.3 %</td>
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<tr>
<td>Age mean: 11 (2.94)</td>
<td>Minimum age: 7</td>
<td></td>
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<tr>
<td>Maximum age: 17</td>
<td>Ethnicity:</td>
<td></td>
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<tr>
<td>% Hispanic or Latino : 56.8</td>
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### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Comparison</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasser, 2020&lt;sup&gt;42&lt;/sup&gt; Supernus Pharmaceuticals, 2017&lt;sup&gt;103&lt;/sup&gt; &lt;br&gt; ID: NCT03247530 RCT Single center N = 477 US Setting: Other</td>
<td><strong>Target:</strong> Children between 6 and 11 years of age and had a primary diagnosis of ADHD as defined according to the DSM-5, which was confirmed by the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID), children should not currently have a diagnosis of a major psychiatric/neurologic disorder other than ADHD (excluding oppositional defiant disorder, or major depressive disorder if the subject was free of major depressive episodes both currently and for the 6 months before screening), significant systemic disease, a history of allergic reaction to viloxazine, any food allergy or intolerance that can impede treatment, and/or evidence of suicidality within 6 months of screening &lt;br&gt; <strong>Other:</strong> ADHD presentation: inattentive_other : mean(sd) 22.7 (3.5), hyperactive_other :</td>
<td><strong>Intervention:</strong> Viloxazine (SPN-812) 200 mg/day, viloxazine extended-release daily in the morning, with or without food, for 6-weeks &lt;br&gt; <strong>Control:</strong> Placebo &lt;br&gt; Placebo, 2 capsules daily for 6 weeks &lt;br&gt; <strong>Comparator:</strong> MedicationViloxanzine (SPN-812), one 100-mg SPN-812 and one placebo capsule daily for 6 weeks</td>
<td>Conners-3 Composite Score, parent: Significant improvement for Conners 3-PS Composite T-score (P =0.0003 and P =0.0002) when compared to placebo. ADHD-RS-5: Statistically significant improvements in ADHD-RS-5: Total score were observed in both the 100- and 200-mg/day SPN-812 treatment groups compared to placebo at week 1 of treatment (P=0.0004 and P=0.0244, respectively), which was maintained through EOS (P=0). Weiss Functional Impairment Rating Scale - Parent, change from baseline: Significant improvement was shown in both the intervention and comparator groups compared to the placebo (p=0.0019 for comparator, p=0.0002 for intervention). Decreased appetite: There was no incidence of decreased appetite in the placebo group but a rate of 7.5 in the 200mg group and 4.5 in the 100mg group. Participants with at least 1 adverse event: The rate was 48% for intervention, 30% for control, and 48% for comparator.</td>
</tr>
</tbody>
</table>
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasser, 2021</td>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Intervention; Control; Comparator; Follow-up</td>
<td>Discontinuations due to AEs were infrequent with 1.3% in the placebo, 1.2% in the 200mg, and 3.2% in the 100mg group discontinuing the trial.</td>
</tr>
<tr>
<td>FDA-approved pharmacological</td>
<td>Study:</td>
<td>Population:</td>
<td>Comparison:</td>
<td>Outcome and results</td>
</tr>
<tr>
<td>Supernus Pharmaceuticals, 2017</td>
<td>NCT03247556</td>
<td>hyperactive/impulsivity mean(sd) 21.5 (4.9)</td>
<td>Intervention: Viloxazine extended-release (SPN-812), 600 mg/day group, one 200-mg capsule and two placebo capsules daily during week 1, two 200-mg capsules and one placebo capsule daily during week 2, followed by three 200-mg capsules daily for the remaining 5 weeks</td>
<td>ADHD-RS-5 (ADHD Rating Scale-5) change ADHD-RS-5 responders The difference in mean improvement was statistically significant for comparator vs</td>
</tr>
<tr>
<td>RCT</td>
<td>Multicenter</td>
<td>Target: Adolescents age 12-17 years old with diagnosis of ADHD according to DSM-5, weight &gt;= 35 kg, have an ADHD-RS-5 Total score &gt;= 28, and a Clinical Global Impression-Severity of Illness (CGI-S) score &gt;= 4. Exclusion: have a current diagnosis of a major psychiatric disorder, a major neurological disorder (including seizures), a significant systemic disease, evidence of suicidality, have an intolerance or allergic</td>
<td>CGI-I (Clinical Global Impression-Improvement) There was a higher proportion of responders for each week of treatment in both the intervention and comparator groups compared to the placebo group. This difference was statistically significant in the intervention group at Week 3 and in the comparator group</td>
<td></td>
</tr>
</tbody>
</table>
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>reaction to viloxazine, received any investigational drugs within 30 days of trial</td>
<td>Comparator: Medication Viloxazine, 400-mg/day viloxazine extended-release taken daily for 7 weeks Follow-up: 2 months</td>
<td>control group (p&lt;0.05), as was the proportion of responders (p &lt; 0.0340). Weiss Functional Impairment Rating Scale (WFIRS-P), parent, change from baseline Total scores were improved in intervention and comparator groups compared to the placebo group, but this difference was not statistically significant for either the 600-mg/day or 400-mg/day SPN-812 treatment arms (p = 0.9756 and p =0.0698, respectively). Stress Index for Parents of Adolescents (SIPA) scores were lower in the comparator arm compared to placebo (p 0.1259). Appetite changes The rate was 6.1% in the intervention, 6.0% in the comparator, and 2.1% in the control group. Participants with at least one adverse event The rate was 55.6% in the intervention, 58.0% in the comparator, and 40.2% in the placebo group. The most common treatment-related adverse events that occurred in at least 5% of subjects in any of the active treatment groups were somnolence (15.1%), fatigue (10.6%), headache (8.0%), nausea (6.5%), and decreased appetite (6.0%),</td>
<td></td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Intervention</th>
<th>Population</th>
<th>Comparison</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasser, 2021(^{444}) Supernus Pharmaceuticals, Inc., 2017(^{1067}); Supernus Pharmaceuticals, 2017(^{1066}) ID: NCT03247543, NCT03247556 RCT Multicenter N = 313 US Setting: Mixed</td>
<td><strong>Target:</strong> Male and female children aged 6-11 years old with a body weight of at least 20 kg and a primary diagnosis of ADHD, as defined in the DSM-5, confirmed using the Mini International Neuropsychiatric Interview for Children and Adolescents, and an ADHD-Rating Scale-5 score of at least 28 and a Clinical Global Impression-Severity of Illness (CGI-S) score of at least 4 at screening <strong>Other:</strong> Parents/guardians of children with ADHD completed parent rating scales and clinicians completed clinician rating scales <strong>ADHD presentation:</strong> N/A <strong>Diagnosis:</strong> Confirmation by specialist primary diagnosis of ADHD as defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), confirmed using the Mini International Neuropsychiatric Interview for Children and Adolescents, and an ADHD-RS-5 score of 28 or higher <strong>Comorbidity:</strong> N/A <strong>Female:</strong> 35.5 % <strong>Age mean:</strong> 8.4 (1.7) <strong>Minimum age:</strong> 6</td>
<td><strong>Intervention:</strong> Vloxazine, 400 mg FDA-approved viloxazine extended-release, once daily for 8 weeks (including 3 weeks titration period) <strong>Control:</strong> Placebo Four matching placebo capsules daily <strong>Comparator:</strong> Medication Vloxazine, 200 mg mg FDA-approved viloxazine extended-release, once daily for 8 weeks (including 3 weeks titration period) <strong>Follow-up:</strong> 2 months</td>
<td>CGI-I (Clinical Global Impression-Improvement) Intervention and comparator groups had significantly more improvement compared to the control group (p=0.009, p=0.0028). ADHD-RS-5 (ADHD Rating Scale -5) ADHD-RS-5 responders (patients who had a reduction in total score of 50%) Intervention and comparator groups had significantly more improvement compared to the control group (p=0.0063, p=0.0038). Weiss Functional Impairment Rating Scale-Parent (WFIRS-P) There was no significant difference between comparator and placebo (p=0.065) or between intervention and placebo (p=0.168). Decreased Appetite Treatment Related Adverse Event Both intervention and comparator group participants had a higher percentage of participants experiencing decreased appetite compared to control group participants. No participants in any treatment group were noted to misuse or overuse medication. The rate of discontinuations due to adverse events in both SPN- 812 treatment groups combined was &lt;5%. All groups had at least 1 or greater adverse events that led to discontinuation of the study.</td>
</tr>
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### Intervention

<table>
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<tr>
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<tbody>
<tr>
<td>ID:</td>
<td>NCT02736656 RCT</td>
</tr>
<tr>
<td>Multicenter</td>
<td></td>
</tr>
<tr>
<td>N = 310</td>
<td>US Setting: N/A</td>
</tr>
</tbody>
</table>

### Target:
- ADHDRS-5 Total score ≥28 and a Clinical Global Impression—Severity of Illness (CGI-S) score ≥4; refrain from taking other ADHD medications for a minimum of 1 week before randomization and for the study duration; considered medically healthy by the study investigator via assessment of physical examination, medical history, clinical laboratory tests, vital signs, and electrocardiogram (ECG); females of childbearing potential had to either be sexually inactive (abstinent) or agree to use one of the acceptable birth control methods beginning 30 days before the first dose and throughout the study

### Other:
- ADHD presentation: N/A

### Comparison:
- **Intervention:**
  - Viloxazine, 400 mg viloxazine extended-release capsules, taken once daily for 6 weeks; one 200-mg Viloxazine extended-release capsule and one placebo capsule daily during week 1, followed by two 200-mg capsules daily for the remaining 5 weeks
- **Control:**
  - Placebo Capsules were identical in appearance, 2 placebo capsules daily for 6 weeks
- **Comparator:**
  - Medication Viloxazine, 200-mg viloxazine extended-release capsules for 6 weeks

### Follow-up: 3 months

### Outcome and results

**CGI-I**
- The scores were significantly better in each VLX-ER treatment group compared with placebo (p<0.05).
- ADHD-RS-5 (ADHD Rating Scale Edition 5)
  - At least 50% reduction ADHD-RS-5 Intervention and comparator groups had significantly greater improvement compared to the control group (p<0.05).
- Weiss Functional Impairment Rating Scale—Parent (WFIRS-P)
  - There were no significant differences between groups.

**Decreased appetite**
- The rate was 8.6% in the 400mg, 5.1% in the 200mp, and 0 in the placebo group.

**Participants with at least 1 adverse event**
- The rate was 53.3% in the 400mg, 43.4% in the 200mg, and 36.5% in the placebo group.
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newcorn, 2005 [44]</td>
<td>FDA-approved pharmacological N = 297 US</td>
<td>Diagnosis: Confirmation by specialist DSM-V</td>
<td></td>
<td>The most common treatment-related adverse events were somnolence, headache, decreased appetite, nausea, and fatigue. The adverse event–related discontinuation rates were &lt;5% in all groups.</td>
</tr>
<tr>
<td></td>
<td>Target: Children and adolescents age 8-18 years old with clinical diagnosis of ADHD according to DSM-IV, have a symptom severity score of &gt;=1.5SDs above age and gender norms on the Attention-Deficit/Hyperactivity Disorder</td>
<td>Comorbidity: N/A</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Female: 32.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age mean: 200mg 13.9 (1.48), 400mg 14.0 (1.59)</td>
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<tr>
<td></td>
<td></td>
<td>Minimum age: 6</td>
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<tr>
<td></td>
<td></td>
<td>Maximum age: 17</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ethnicity: Other : Reported for 200mg= 28.7% / 400mg=31.1% Other : Reported for 200mg=39.4% / 400mg=40.8% Other : reported for 200mg= 1.1% / 400mg=1.9% Other : Reported for 200mg=1.1% / 400mg=1.0% Other : Reported for 200mg=56.4% / 400mg=53.4% Other : reported for 200mg= 2.1% / 400mg=2.9% Other info on race or ethnicity:</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Intervention: Atomoxetine 1.8 mg/kg/day for 8 weeks administered equally divided doses in the morning and late afternoon</td>
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<tr>
<td></td>
<td></td>
<td>Control: Placebo Matching placebo for 8 weeks</td>
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<tr>
<td></td>
<td></td>
<td>CGI-S (Clinical Global Impressions of Severity) Tests for a linear dose-response showed a statistically significant effect, suggesting increased efficacy as a function of increasing atomoxetine dose.</td>
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</table>
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Rating Scale-IV-Parent version (ADHDRS-IV-Parent:Inv), have a IQ &gt;= 80 according to the full WISC-III. Exclusion: any serious medical illness, comorbid psychosis or bipolar disorder, history of a seizure disorder, or ongoing use of psychoactive medications other than the study drug</td>
<td>Comparator: Medication Atomoxetine 1.2 mg/kg/day</td>
<td>ADHD-RS-IV-Parent, investigator rated and scored Atomoxetine at 1.8 mg/kg/day, but not 1.2 mg/kg/day, was superior to placebo in reducing symptoms of ADHD among youths with ADHD and ODD, effect sizes were ADHD + ODD (placebo versus ATMX1.2 = 0.49; placebo versus ATMX1.8 = 0.69; placebo versus ATMX1.2 + CHQ Psychosocial Summary scale Changes in ADHD and oppositional symptoms were associated with improvements in broader functioning for youths with ADHD with and without ODD. There was significant improvement on the CPRS-R:S Oppositional subscale for patients with ADHD and ODD receiving atomoxetine doses 0.5 and 1.8 mg/kg/day (effect sizes, ODD: placebo versus ATMX1.2 = 0.39; placebo versus ATMX1.8 = 0.68; placebo versus ATMX1.2 + ATMX1.8 = 0.56; non-ODD: placebo versus ATMX1.2 = 0.55; placebo versus ATMX1.8 = 0.40; placebo versus ATMX1.2 + ATMX1.8 = 0.46.</td>
</tr>
<tr>
<td></td>
<td>Setting: Mixed</td>
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<td>Follow-up: 2 months</td>
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<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newcorn, 2008&lt;sup&gt;448&lt;/sup&gt;</td>
<td>ID: N/A Crossover trial Multicenter N = 516 US Setting: N/A</td>
<td>Target: Patients 6-16 years with ADHD; children who had seizures, bipolar disorder, a psychotic illness, or a pervasive developmental disorder or who were taking concomitant psychoactive medications, anxiety and tic disorders were excluded, other concurrent psychiatric diagnoses, including major depressive disorder, were permitted as long as ADHD was the primary diagnosis and therefore an appropriate target of treatment. Participants were excluded if they had been treated previously with an adequate trial of methylphenidate or amphetamine and either did not experience at least some improvement in ADHD signs and symptoms (nonresponders) or had intolerable adverse events Other: ADHD presentation: inattentive: 28, hyperactive: 2, combined: 70 Diagnosis: Confirmation by specialist DSM-IV KSADS-PL Comorbidity: N/A Female: 26% Age mean:</td>
<td>Intervention: Atomoxetine for 6 weeks, 0.8–1.8 mg/kg per day Control: Placebo Identically appearing capsules Comparator: Medication Osmotically released methylphenidate, 18–54 mg/day, initiated at 18 mg/day, with increases to 36 mg and 54 mg allowed at the first and second visits Follow-up: 1.5 months</td>
<td>Daily Parent Ratings of Evening and Morning Behavior—Revised, Evening score, change from baseline There was no difference between comparator and intervention (p=0.21). CGI ADHD severity scale Patients on methylphenidate changed more than patients on atomoxetine or placebo. ADHD-RS (ADHD Rating Scale) total score Treatment favored atomoxetine compared to osmotically released methylphenidate. Change in weight (kg) Difference from placebo was statistically significant for both active interventions (p&lt;0.05). Adverse events that occurred in at least 5% of the patients in any treatment group or that occurred significantly more often for either drug than for placebo: Insomnia was more common for patients assigned to methylphenidate than for those taking placebo. Somnolence was reported more often for atomoxetine than for methylphenidate, while insomnia was reported more often for methylphenidate than for atomoxetine. The mean increase in diastolic blood pressure, relative to placebo, was statistically significant for both atomoxetine and osmotically released methylphenidate. No differences were observed in mean change of systolic blood pressure between placebo and either drug.</td>
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### Evidence Tables

**Intervention**

<table>
<thead>
<tr>
<th>Study:</th>
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<tr>
<td>Newcorn, 2016[^147]</td>
</tr>
<tr>
<td>Shire, 2010[^1026]</td>
</tr>
<tr>
<td>ID: NCT01081145</td>
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<tr>
<td>RCT</td>
</tr>
<tr>
<td>Multicenter</td>
</tr>
<tr>
<td>N = 316</td>
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<tr>
<td>Multiple countries</td>
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<tr>
<td>Setting: Mixed</td>
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</tbody>
</table>

**Population:**

- **Setting:**
- **Study target:**
- **ADHD presentation:**
- **Diagnosis:** Confirmation by specialist
- **Comorbidity:** N/A
- **Female:** 25.7%
- **Age mean:** 10.8 (2.67)
- **Minimum age:**
- **Maximum age:**

**Comparison:**

- **Intervention:**
- **Control:**
- **Comparator:** NA

**Follow-up:** 9 months

**Outcome and results**

- Increase in heart rate was significantly greater for atomoxetine than for either placebo or methylphenidate.

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[^147]: FDA-approved pharmaceutical

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**Intervention**

<table>
<thead>
<tr>
<th>Study:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author, year;</td>
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<td>Trial ID;</td>
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<td>Study design;</td>
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<tr>
<td>Sites;</td>
</tr>
<tr>
<td>Study size;</td>
</tr>
<tr>
<td>Location Setting</td>
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</tbody>
</table>

**Population:**

- **Setting:**
- **Study target:**
- **ADHD presentation:**
- **Diagnosis:**
- **Comorbidity:** % Female;
- **Age mean:**
- **Minimum age:**
- **Maximum age:**
- **Ethnicity**

**Comparison:**

- **Intervention:**
- **Control:**
- **Comparator:**

**Follow-up**

**Outcome and results**

- CGI-S, rated as normal or borderline mentally ill
- A larger proportion of participants in the GXR group was rated as normal or borderline mentally ill compared with placebo (p = 0.001).
- ADHD-RS-IV (ADHD Rating Scale-IV) total score
- The difference between GXR and placebo was significant (p < 0.001), indicating that the effect of treatment was better maintained with GXR than placebo.
- Weiss Functional Impairment Rating Scale, Parent (WFIRS-P)
- There was no difference between groups in global domain score.
- Treatment failure (defined as ≥50% increase in ADHD Rating Scale version IV total score and ≥2-point increase in Clinical Global Impression-Severity compared with baseline) occurred in 49.3% of the GXR and 64.9% of the placebo group (p = 0.006).
- Treatment-emergent adverse events

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[^1026]: Newcorn, 2016

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Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
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<tr>
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<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Intervention; Control; Comparator; Follow-up</td>
<td>The rate was 56.7% in the intervention, and 48.1% in the placebo group. TEAEs led to discontinuation in 1.9% in the GXR group (grand mal convulsion, sedation, somnolence) and 1.3% in the placebo group (one with irritability, the other with chest pain, dizziness, dyspnoea, nausea and tremor). Six participants (GXR, n = 2; placebo, n = 4) reported seven severe adverse events (SAEs), one of which was judged to be related to treatment (GXR: grand mal convulsion). The majority of TEAEs were mild to moderate, with 5 (3.2%) GXR and 2 (1.3%) placebo participants reporting a severe treatment-emergent adverse events.</td>
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<td></td>
<td>Prasad, 2007</td>
<td>Ethnicity:</td>
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<td>Weight decreased, number No statistical differences in percent with weight decrease or decreased appetite.</td>
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<td></td>
<td>FDA-approved pharmacological</td>
<td>% White : 79.5 Other info on race or ethnicity: Other : 20.5</td>
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<td></td>
<td>Prasad, 2007</td>
<td>Target: Children and adolescents with ADHD; patients with: a history of bipolar disorder, psychotic disorders, pervasive development disorder (autistic spectrum disorder), any seizure disorder or alcohol/drug abuse; with significant prior/current medical conditions or at serious suicidal risk; or taking medication that could potentially interfere with study outcomes were excluded Other: Parents supplied some outcome data ADHD presentation: inattentive : 7.5, hyperactive : 2.0, combined : 90.5</td>
<td>Intervention: Atomoxetine 0.5 to 1.8 mg/kg/day for 10 weeks Control: TAU Standard current therapy Comparator: NA Follow-up: 2.5 months</td>
<td>CGI-I (Clinical Global Impression Improvement) much improved The intervention group had significantly more improvement compared to the control group (p&lt;0.001). ADHD-RS (ADHD Rating Scale), investigator rated ADHD RS, number showing at least 25% improvement Percent improving at least 25% on investigator-rated ADHD-RS total score was statistically superior for atomoxetine group (p&lt;0.001). Weight decreased, number No statistical differences in percent with weight decrease or decreased appetite.</td>
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<tr>
<td>Study:</td>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Population:</td>
<td>Comparison:</td>
<td>Outcome and results</td>
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<td>Rubio Morell, 2019[^2]</td>
<td>Diagnosis: Confirmation by specialist DSM-IV criteria by clinical investigator and confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Versions (K-SADS-PL)</td>
<td>Intervention: Atomoxetine, effective clinical dose, titration initiated with a standard dose based on weight (0.8–1.5 mg/kg/day for ATX) and adjusted by clinical response until an optimal clinical response with minimum side effects was reached, mean dose 40 mg/day</td>
<td>There were no deaths and no serious adverse events.</td>
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<td>FDA-approved pharmacological ID: N/A RCT Single center N = 45 Spain Setting: Other</td>
<td>Comorbidity: N/A Female: 11.4 % Age mean: 10.9 (2.2) Minimum age: 6.9 Maximum age: 15.9 Ethnicity: % Black/African American : 0.5 % Asian : 0.5 % White : 99.0 Other info on race or ethnicity:</td>
<td>Control: NA Comparator: MedicationModified-release methylphenidate (long-acting), dose titration initiated with a standard dose based on weight (1</td>
<td>Risk taking behavior evaluated by the Cambridge Gambling Task. There was no difference between groups. Both MPH and ATX significantly improved scores in verbal working memory (p 0.71, d 0.12), spatial working memory (p 0.44; d 0.03), planning (p 0.6, d 0.18), decision making (p 0.06, d 0.12) and inhibition (p 0.08, d 0.00). No beneficial effect on delay aversion and risk taking was found with MPH and neither with ATX. Long-term treatment in range of optimal clinical dosages with either MPH or ATX.</td>
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## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
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</thead>
<tbody>
<tr>
<td>Sallee, 2009</td>
<td>FDA-approved pharmacological</td>
<td>Other:</td>
<td>Intervention: Guanfacine extended-release (SPD503) 4 mg g for 9 weeks</td>
<td>improves EF, but not DAv in children with ADHD. No ADHD participant dropped out the study due to adverse effects or other any other reason</td>
</tr>
<tr>
<td>Shire, 2004</td>
<td>RCT</td>
<td>ADHD presentation: N/A</td>
<td>Control: Placebo</td>
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<tr>
<td></td>
<td>Multicenter</td>
<td>Diagnosis: Confirmation by specialist DSM-IV</td>
<td>Comparator: MedicationGuanfacine extended-release (SPD503) 1 mg g for 9 weeks</td>
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<tr>
<td></td>
<td>N = 324</td>
<td>Comorbidity: N/A</td>
<td>Follow-up: 6 months</td>
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<td></td>
<td>US</td>
<td>Female: %</td>
<td>Follow-up: 4 months</td>
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<td></td>
<td>Setting: Specialty care</td>
<td>Age mean:</td>
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<td>Intervention: 10.46 (0.66), comparator: 10.0 (0.40)</td>
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<td>Minimum age: 9</td>
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<td>Maximum age: 12</td>
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<td>Ethnicity: Other info on race or ethnicity:</td>
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<td>ADHD presentation: inattentive : 26, hyperactive : 2, combined : 73</td>
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<td>Diagnosis: Confirmation by specialist DSM IV - TR per psyc evaluation</td>
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<td>Target: Children 6-17 with ADHD, those with co-morbid psyc disorders (other than ODD) were excluded, as were those currently on medications that might affect blood pressure, morbids obesity or abnormal vital signs, or prior treatment with guanfacine</td>
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<td>Other:</td>
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<td>ADHD presentation:</td>
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<td>Confirmation by specialist</td>
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<th>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
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<th>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
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Appendix C. Evidence Tables

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<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
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<tbody>
<tr>
<td>Sangal, 2006&lt;sup&gt;500&lt;/sup&gt;</td>
<td>FDA-approved pharmacological</td>
<td>Comorbidity: N/A</td>
<td>Adverse events occurring in 5% or greater in participants taking medication were somnolence, headache, fatigue, sedation, dizziness, irritability, upper abdominal pain, and nausea.</td>
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<tr>
<td>US</td>
<td>Crossover trial Multicenter</td>
<td>Female: 28 %</td>
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<tr>
<td>N = 85</td>
<td>Target: Children with ADHD. Patients with pre-existing sleep disorders or serious medical conditions were excluded.</td>
<td>Age mean: 11 (3.0)</td>
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<tr>
<td>Setting: Other</td>
<td>Other: ADHD presentation: inattentive: 29.8, hyperactive: 2.4, combined: 67.9</td>
<td>Minimum age: 6</td>
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<td>Diagnosis: Confirmation by specialist DSM IV diagnosis. a. Diagnosis per investigator’s clinical evaluation and by the administration of several modules of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age</td>
<td>Maximum age: 17</td>
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<td></td>
<td>Ethnicity:</td>
<td>Other: &quot;Other&quot; 4.3%</td>
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<td>% Hispanic or Latino: 9</td>
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<td>% Black/African American: 17</td>
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<td>% American Indian or Alaska Native: 0.003</td>
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<td>Other: 0.3% Asian or Pacific Islander</td>
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<td>% White: 67</td>
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<td>Other info on race or ethnicity:</td>
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<td></td>
<td>Intervention: Atomoxetine 1.0-1.8 mg/kg/day divided into twice daily doses for 7 weeks</td>
<td>Control: NA</td>
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<td>Comparator: Medication Methylphenidate, three times per day</td>
<td>Comparator: Methylphenidate, three times per day</td>
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<td>Follow-up: 1.8 months</td>
<td>Follow-up: 1.8 months</td>
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# Appendix C. Evidence Tables

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<th>Intervention</th>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA-approved pharmacological</td>
<td>Shang, 2020&lt;sup&gt;113&lt;/sup&gt; Shang, 2015&lt;sup&gt;1005&lt;/sup&gt;; Wu, 2021&lt;sup&gt;1145&lt;/sup&gt;; Shih, 2019&lt;sup&gt;1009&lt;/sup&gt;, Hospital, National Taiwan University, National Science Council, 2009&lt;sup&gt;919&lt;/sup&gt; ID: NCT00916786 RCT Single center N = 168 Taiwan Setting: Specialty care</td>
<td>Target: Drug naive children aged 7 to 16 with ADHD. Exclusions: comorbid psychiatric conditions, including psychosis, bipolar disorders, autism spectrum disorders, substance use disorders, intellectual disability (full-scale intelligence quotient &lt;80), or had a history of major medical or neurological problems Other: Parents ADHD presentation: N/A Diagnosis: Confirmation by specialist DMS IV, Chinese version of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children– Epidemiological Version (K-SADS-E) to confirm ADHD</td>
<td>Intervention: Atomoxetine: an initial dosage of 0.5 mg/(kg per day), administered as once-daily dose, titrated at visits 2–7 (weeks 2–24) according to clinical response and adverse effects; max dose 1.2 mg/kg daily Control: NA Comparator: MedicationMethylphenidate, initial dosage of 18 mg/day, administered as a single morning dose, titrated at visits 2–7 (weeks 2–24) according to clinical response and adverse effects, max dose 54 mg/day Follow-up: 8 months</td>
<td>(p=0.004), and less time to fall asleep (p=0.001) with atomoxetine. Number of patients with decreased appetite Greater incidence of decreased appetite with methylphenidate (p=0.03). No significant difference in percent reporting headache, irritability, congestion, cough, and intestinal pain. More methylphenidate patients reported insomnia (p &lt; .001).</td>
</tr>
</tbody>
</table>

### Children-Present and Lifetime Version structured interview
- **Comorbidity:** N/A
- **Female:** 24.7 %
- **Age mean:** 10.1 (2.0)
- **Minimum age:** 6
- **Maximum age:** 14
- **Ethnicity:** % White: 72.9 Other info on race or ethnicity: Other: 27.1% non-white Home Behaviors subcale of the Social Adjustment Inventory for Children and Adolescents (SAICA), parent, change from baseline There was no significant difference between groups (p=0.097).

**CBCL (Child Behavior Checklist)** The intervention group improved more on aggressive behavior subscale ( p = 0.032) and somatic complaint subscale (0.008) than the comparator group but none of the other subscales.

Both treatment groups showed improvement in executive functions (p-value <0.05 for the major indices of each domain). Magnitude of increasing detectability (p< 0.01) and reducing commission errors (p<0.05) was significantly greater in the intervention group vs comparator group.
<table>
<thead>
<tr>
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<th>Comparison:</th>
<th>Outcome and results</th>
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</thead>
<tbody>
<tr>
<td>FDA-approved pharmacological</td>
<td>Shaywitz, 2017\textsuperscript{114}</td>
<td>Comorbidity: N/A</td>
<td>intervention; control; comparator; follow-up</td>
<td>ADHD-RS-IV-Parent:Inv scores ADHD symptom decreases were significantly greater for patients treated with atomoxetine. Reading abilities change from baseline measured using Gray Oral Reading Tests-4. N of participants intervention group (51). Academic rating scale least-squares mean change scores intervention group (-2.19). N of participants control group (55). Academic r</td>
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<tr>
<td></td>
<td>Eli Lilly and Company, 2008\textsuperscript{72}</td>
<td>Female: 13%</td>
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<tr>
<td></td>
<td>ID: NCT00607919</td>
<td>Age mean: 8.7 (2.56)</td>
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<td></td>
<td>RCT</td>
<td>Minimum age: 7</td>
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<td>Multicenter</td>
<td>Maximum age: 16</td>
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<td>N = 124</td>
<td>Ethnicity:</td>
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<td>Other info on race or ethnicity:</td>
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<td>Setting: Other</td>
<td>ADHD presentation:</td>
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<td>inattentive: 46, hyperactive: 2.4, combined: 51.6</td>
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<td>Diagnosis: Confirmation by specialist DSM-IV-TR criteria for ADHD diagnosis confirmed during the first screening visit</td>
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<td></td>
<td>ADHD presentation: inattentive: 46, hyperactive: 2.4, combined: 51.6</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Diagnosis: Confirmation by specialist DSM-IV-TR criteria for ADHD diagnosis confirmed during the first screening visit</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Target: Met DSM-IV-TR criteria for ADHD diagnosis confirmed during the first screening visit. Also met criteria for dyslexia at the second screening visit. Had intelligence quotient score of at least 80, were 10 to 16 years. No history of bipolar I or bipolar II disorder, psychosis, autism, Asperger’s syndrome, or pervasive developmental disorder, or were currently taking anticonvulsants for seizure control.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| | | Other: ADHD presentation: inattentive: 46, hyperactive: 2.4, combined: 51.6 | | }

C-377
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA-approved pharmacological</td>
<td>Simonoff, 2013</td>
<td>Target: Children 7–15 years of age with a diagnosis of ICD-10 hyperkinetic disorder and a full-scale IQ of 30–69 who were living in a stable situation and had regular school attendance</td>
<td>Intervent: Methylphenidate, dose titration comprised at least 1 week each of low (0.5 mg/kg/day), medium (1.0 mg/kg/day) and high dose (1.5 mg/kg/day), taken for 16 weeks</td>
<td>CGI-I improved 40% of participants receiving methylphenidate compared to 7% of placebo were rated as improved. ADHD Index Conners Rating Scale-Short Version-Parent Methylphenidate was superior to placebo for the parent Conners ADHD index. Methylphenidate was superior to placebo for the teacher Conners ADHD index. Poor appetite 15% of patients receiving methylphenidate compared to 2% on placebo reported poor appetite.</td>
</tr>
<tr>
<td></td>
<td>ID: N/A RCT</td>
<td>Other: ADHD presentation: N/A : 100% with a diagnosis of ICD-10 hyperkinetic disorder Diagnosis: Confirmation by specialist Diagnosis of hyperkinetic disorder was made using the Child and Adolescent Psychiatric Assessment</td>
<td>Control: Placebo Placebo medication, offered active medication after the trial Comparator: NA Follow-up: 4 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Single center N = 122 UK Setting: Specialty care</td>
<td>Ethnicity: % Hispanic or Latino : 15.3 % Black/African American : 13 % Asian : 2 % White : 69.4 Other info on race or ethnicity:</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Comorbidity: Learning disability: Dyslexia alone group and dyslexia + ADHD subgroup Female: 36.3 % Age mean: Intervention mean age 12.2, control mean age 12.3 Minimum age: 10 Maximum age: 17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study:</td>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Population:</td>
<td>Comparison:</td>
<td>Outcome and results</td>
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<tr>
<td></td>
<td>Study:</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Comparison: Intervention; Control; Comparator; Follow-up</td>
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<td></td>
<td>Study:</td>
<td>Population:</td>
<td>Comparison:</td>
<td>Outcome and results</td>
</tr>
<tr>
<td></td>
<td>Study:</td>
<td>Target: Children with Tourette's Syndrome and ADHD between the ages 7 to 13 years and of normal intellect</td>
<td>Comparator: Medication Desipramine (25 mg four times daily), each child started with one capsule per day (evening) and added 1 additional capsule every week to a maximum daily dose of one capsule 4 times a day; patients then were maintained on the highest daily dose for an addi</td>
<td>16 withdrew from the trial, 5 were due to adverse events following methylphenidate; 21% vs 3% had trouble getting to sleep (P&lt;0.01) but there was no difference in looks sad/miserable, crying, looks anxious, meaningless repetitive behavior, talks less with other children.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Study:</td>
<td>Other: ADHD presentation: N/A Diagnosis: Confirmation by specialist DSM-IV Comorbidity: Tic disorder Female: 8 % Age mean: mean age 10.6 Minimum age: 7 Maximum age: 13 Ethnicity: % Black/African American: 3 % White: 89 Other info on race or ethnicity:</td>
<td>Intervention: Clonidine 0.05 mg 4 times daily for 6 weeks Control: Placebo Uniform-appearing capsule Comparator: Desipramine was significantly better than placebo and clonidine (p &lt;0.05). A global linear analogue comparing the child’s current tics to tics anytime in the past, showed a statistically significant drug effect (P &lt;.05), with orthogonal contrasts demonstrating that desipramine was superior to clonidine (P &lt; .01). Results with clonidine did not differ from placebo, whereas desipramine significantly reduced tics compared to placebo (P &lt;.05). Participants with at least one drug-related problem</td>
<td>Hyperactivity scale CBCL (Child Behavior Checklist) Desipramine was significantly better than placebo and clonidine (p &lt;0.05). A global linear analogue comparing the child’s current tics to tics anytime in the past, showed a statistically significant drug effect (P &lt;.05), with orthogonal contrasts demonstrating that desipramine was superior to clonidine (P &lt; .01). Results with clonidine did not differ from placebo, whereas desipramine significantly reduced tics compared to placebo (P &lt;.05). Participants with at least one drug-related problem</td>
</tr>
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### Interventions

<table>
<thead>
<tr>
<th>FDA-approved pharmacological</th>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
</table>
| **Spencer, 2002**<sup>44</sup> | Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting | Target: Children with ADHD. Patients who weighed less than 55 pounds, were on psych medication, or had a history of psychosis or bipolar disorder were excluded. Those who were prognostic to be poor metabolizers of medication based on a genetic test were excluded. Other: Parents provided some outcomes. ADHD presentation: inattentive: 18, hyperactive: 1, combined: 81 | Intervention: Atomoxetine 3 times per day, drug dosage based on weight | CGI-S
Significantly greater mean improvement in CGI-S scores (p < .001) and Conners Parent Rating Scale in atomoxetine patients than placebo patients. ADHD RS total, mean improvement
ADHD RS, response (25% decrease in total score)
Atomoxetine patients had greater mean improvement than placebo patients (p < .001) and a significantly greater rate of response.
Decreased appetite, number with
Significantly greater rate of decreased appetite in atomoxetine group.

Headache
No significant difference between groups in headache, abdominal pain, rhinitis, pharyngitis, vomiting, cough, nervousness, somnolence, or nausea. |
| **Spencer, 2006**<sup>45</sup> | Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting | Target: Adolescents with ADHD. Patients who were known to be nonresponsive to stimulants or naive to stimulant treatment were eligible for enrollment. Exclusion | Intervention: Mixed amphetamine salts extended release 40 mg per day for 4 weeks | CGI-I (Clinical Global Impression – Improvement scale) improved
A higher percentage of patients in the medication groups were considered improved |
| **FDA-approved** | ID: | N = 291 | Control: Placebo | **Placebo. See administration info above.** |
| **Unclear/Not reported** | Setting: Specialty care | | Comparator: Medication Methylphenidate. See administration information above. Outcomes not reported for this arm, as this was a proof-of-concept study where methylphenidate was used in the stimulant naive stratum to validate the study design if atomoxetine was not superior to | Follow-up: 2 months (9 weeks) | |
| | | | | |
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 287 US Setting: Specialty care</td>
<td>criteria included: comorbid psychiatric diagnosis except oppositional defiant disorder; hypertension; history of seizure disorder within the last 2 years; tic disorder; Tourette's syndrome; abnormal thyroid function; cardiac disorder; and significant laboratory abnormalities. <strong>Other:</strong> ADHD presentation: inattentive : 41.0, hyperactive : 2.5, combined : 56.5 Diagnosis: Confirmation by specialist DSM-IV-TR Comorbidity: N/A Female: 34.5 % Age mean: 14.2 (1.2) Minimum age: 13 Maximum age: 17 Ethnicity: % Hispanic or Latino: 6.8 % Black/African American: 15.8 % White: 73.7 Other info on race or ethnicity: Other: Other 3.6</td>
<td>Placebo <strong>Comparator:</strong> Medication Mixed amphetamine salts extended release (Adderall MX) 10 mg per day <strong>Follow-up:</strong> 1 month</td>
<td>compared with those receiving placebo (p &lt; 0.001). ADHD-RS-IV (Attention-Deficit/Hyperactivity Disorder Rating Scale-IV) Statistically significant (p &lt; 0.001) improvement in mean ADHD-RS-W total scores in medication groups compared with placebo. Anorexia/decreased appetite, number of patients Significantly more medication patients experienced decreased appetite and weight loss compared to placebo patients. p value not reported. Insomnia and abdominal pain more prevalent in medication patients. p value not reported.</td>
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<tr>
<td>Intervention</td>
<td>Study:</td>
<td>Population:</td>
<td>Comparison:</td>
<td>Outcome and results</td>
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<tr>
<td>Spencer, 2008</td>
<td>Author, year;</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Intervention; Control; Comparator; Follow-up</td>
<td>CGI-ADHD/Psych-S ADHD-RS-IV, parent</td>
</tr>
<tr>
<td>ID: N/A RCT Multicenter</td>
<td>Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td></td>
<td></td>
<td>Intervention participants showed significantly greater improvement compared to controls (p=0.011). The intervention group showed a significantly greater decrease from baseline in tic severity relative to control (p=0.027). Body weight change Decreased appetite The rate was 18% in the atomoxetine vs 10.3% in the placebo group. Discontinuations because of an adverse event were rare, with 2 in the atomoxetine group (headache, vomiting) and 1 in the placebo group (upper abdominal pain).</td>
</tr>
<tr>
<td>N = 117 US Setting: N/A</td>
<td>Target: Children with Tourette's syndrome and scoring 1.5 SD above sex norm for their diagnostic subtype at enrollment and at randomization for the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent version</td>
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<td>Other: ADHD presentation: inattentive: 30.8, hyperactive: 3.4, combined: 65.8</td>
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<td>Diagnosis: Confirmation by specialist met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for ADHD and concurrent TS. Subjects' scores on the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-administered and -scored (ADHDRS-IV-P)</td>
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<td></td>
<td>Comorbidity: Tic disorder</td>
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<td></td>
<td>Female: 12.8 %</td>
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<td>Age mean: 11.2 (2.4)</td>
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<td></td>
<td>Minimum age: 7</td>
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<td>Maximum age: 17</td>
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<td></td>
<td>Ethnicity: % Hispanic or Latino: 4.3 % Black/African American: 4.3 % Asian: 0.9 % White: 88.0</td>
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<tr>
<td></td>
<td>Intervention: Atomoxetine 0.5-1.5 mg/kg/day, as a divided dose, for 15 weeks</td>
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<td>Control: Placebo Placebo</td>
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<tr>
<td></td>
<td>Comparator: NA</td>
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<td></td>
<td>Follow-up: 3 months</td>
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</table>
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
</table>
| FDA-approved pharmacological | Steele, 2006[^149]  
ID: n/a  
RCT  
Multicenter  
N = 147  
Canada  
Setting: Specialty care | Target: Physically healthy male and female outpatients, aged 6-12 years with DSM-IV diagnosis of ADHD; medication naïve, Clinical Global Impression Severity score of 4 or greater and had behavioral difficulties  
Other:  
ADHD presentation: inattentive: 18.37, hyperactive: 2.04, combined: 78.23  
Diagnosis: Confirmation by specialist  
The criteria were confirmed by a clinical and structured interview  
Comorbidity: N/A  
Female: 16.3%  
Age mean: 9.0 (2.1) and 9.1 (1.8)  
Minimum age: 6  
Maximum age: 12  
Ethnicity:  
% Black/African American: 3.4  
% Asian: 0.6  
% White: 85.7 | Intervention: Methylphenidate osmotic release oral system 18-54 mg once daily for 8 weeks  
Control: NA  
Comparator: Medication Immediate release methylphenidate initiated at whatever dose the clinician felt was appropriate and over the weeks each individual dose was titrated weekly by 5mg or 10mg increments, according to manufacturer’s recommendations and the investigator’s clin  
Follow-up: 2 months | Homework visual analog scale  
There was no statistically significant difference between groups.  
CGI-I Clinical Global Severity  
There was a statistically significant difference favoring intervention group.  
Snap-IV, parent  
There was a statistically significant reduction in scores favoring OROS.  
Parent satisfaction with current ADHD medication  
There was a statistically significant difference in parent satisfaction favoring OROS.  
Parent Stress Index scores showed significant differences in favor or OROS.  
Decreased appetite  
Rates were similar in both groups.  
Participants with any adverse event  
The rate was 82% for intervention and comparator.  
Adverse events (any possible medication related event, headache, insomnia, abdominal pain, nervousness, emotional lability, agitation, |
### Appendix C. Evidence Tables

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<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA-approved pharmacological</td>
<td>Su, 2016; Peking University, 2010; Yang, 2012; ID: NCT01065259</td>
<td>Target: Youth with ADHD, either treatment naive or untreated for at least 6 months; subjects were excluded if they had a history of poor response with adequate treatment or intolerance to either treatment medication; medical contraindications to stimulants or who had seizure disorder or an abnormal EEG associated with epilepsy, bipolar disorder, psychosis, anxiety disorder, depression disorder, TD, pervasive developmental disorder, or an IQ &lt;70, children taking concomitant psychoactive medications including dietary supplements with central nervous system activity in the past 30 days were also excluded</td>
<td>Other info on race or ethnicity: Other: 8.8</td>
<td>Other: ADHD presentation: inattentive: 48,hyperactive: 3,combined: 49</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diagnosis: Confirmation by specialist DSM-IV Comorbidity: N/A Female: 17%</td>
<td></td>
<td>Control: NA Comparator: Medication Osmotic Release Oral System Methylphenidate optimized dose (18, 36, or 54 mg/day) for 4 weeks Follow-up: 12 months</td>
</tr>
</tbody>
</table>
### Intervention

**Study:**
- Author, year;
- Multiple publications;
- Trial ID;
- Study design;
- Sites;
- Study size;
- Location

**Population:**
- Setting;
- Study target;
- ADHD presentation;
- Diagnosis;
- Comorbidity;
- % Female;
- Age mean;
- Minimum age;
- Maximum age;
- Ethnicity

**Comparison:**
- Intervention;
- Control;
- Comparator;
- Follow-up

### Outcome and results

**Target:** Children with ADHD and comorbid impulsive aggression already using monotherapy treatment with FDA-approved optimized ADHD medication (psychostimulant or non-stimulant).

Current or lifetime diagnosis of epilepsy, major depressive disorder, bipolar disorder, schizophrenia or a related disorder, personality disorder, Tourette's disorder, or psychosis excluded.

**Other:** Parents provided some outcomes.

**ADHD presentation:** N/A

**Diagnosis:** Confirmation by specialist

DSM-5 confirmed by the Schedule for Affective Disorders and Schizophrenia for School-aged Children - Present and Lifetime Version 2013

**Comorbidity:** ODD : Impulsive aggression

**Female:** 24.9 %

**Age mean:** 9.0 (1.84)

**Intervention:** Molindone Hydrochloride Extended-Release (SPN-810) high dose (36 mg) twice each day, in the morning and in the evening, in addition to usual ADHD medication

**Control:** Placebo

Placebo twice each day, in the morning and in the evening, in addition to usual ADHD medication

**Comparator:** MedicationMolindone Hydrochloride Extended-Release (SPN-810) 18 mg twice each day, in the morning and in the evening, in addition to usual ADHD medication

**Follow-up:** 1 month

Clinical Global Impression-Improvement (CGI-I) Scale Investigator Rated

No significant difference (p = 0.0742) in improvement measured by investigator rated CGI-I or CGI-S (p = 0.1729). Significantly greater improvement on parent rated CGI-I for high dose medication group (p = 0.0384).

Swanson, Nolan, Pelham Rating Scale-Revised (SNAP-IV) Rating Scale, parent

No significant difference between groups (p = 0.1418).

Increased appetite

None of 65 low dose patients experienced appetite increase, compared to 9 of 137 high dose patients, and 6 of 126 in placebo group.

Adverse events

Rates were 18.98% in the high dose, 15.38% in the low dose, and 14.29% in the placebo group.

2/13 participants experienced a serious adverse event (eye disorder, appendicitis perforated) in the high dose group, none in the other groups.
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
</table>
| Svanborg, 2009<sup>560</sup> | Minimum age: 6  
Maximum age: 12  
Ethnicity:  
% Hispanic or Latino: 14.2  
% Black/African American: 26.5  
% American Indian or Alaska Native: 2.2  
% Asian: 0.3  
% White: 65.8  
Other info on race or ethnicity: Other: Categories not mutually exclusive | Intervention: Psychoeducation for caregivers plus atomoxetine, 1.2 mg/kg day (70 kg) or 80 mg/day (>70 kg) for 10 weeks  
Control: Other Psychoeducation for caregivers plus placebo capsules for 10 weeks  
Comparator: NA  
Follow-up: 2.75 months | CGI-I (Clinical Global Impression Improvement), change from baseline  
An improvement was observed in the atomoxetine group whereas in the placebo group the score changed only slightly (p < 0.001).  
ADHD-RS-IV (Attention-Deficit/Hyperactivity Disorder Rating Scale IV)–Parent Version: Investigator Administered and Scored Treatment responders  
Statistically significant between-treatment differences in favor of atomoxetine at each visit (P < 0.001) from visit 4 (week 3) onwards.  
The global parental assessment of most aspects of psychoeducation was very positive; items were mostly rated as very good/very satisfied or rather good/satisfied.  
Decreased appetite |
| Svanborg, 2009<sup>568</sup> | | | |
| FDA-approved pharmacological | Target: Male and female patients 7–15 years of age were included if they met the criteria for ADHD of the (DSM-IV)  
Other: ADHD presentation: inattentive_other: 18.2% across all arms, hyperactive_other: 4% across all arms, combined_other: 77.8% across all arms  
Diagnosis: Confirmation by specialist clinical interview  
Comorbidity: N/A  
Female: 19.2%  
Age mean: Mean 12.8  
Minimum age: 7 | | |
| Study: | Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity | Intervention; Control; Comparator; Follow-up | |
| Study design; Sites; Study size; Location Setting | Minimum age: 6  
Maximum age: 12  
Ethnicity:  
% Hispanic or Latino: 14.2  
% Black/African American: 26.5  
% American Indian or Alaska Native: 2.2  
% Asian: 0.3  
% White: 65.8  
Other info on race or ethnicity: Other: Categories not mutually exclusive | CGI-I (Clinical Global Impression Improvement), change from baseline  
An improvement was observed in the atomoxetine group whereas in the placebo group the score changed only slightly (p < 0.001).  
ADHD-RS-IV (Attention-Deficit/Hyperactivity Disorder Rating Scale IV)–Parent Version: Investigator Administered and Scored Treatment responders  
Statistically significant between-treatment differences in favor of atomoxetine at each visit (P < 0.001) from visit 4 (week 3) onwards.  
The global parental assessment of most aspects of psychoeducation was very positive; items were mostly rated as very good/very satisfied or rather good/satisfied.  
Decreased appetite | |
| FDA-approved pharmacological | Target: Male and female patients 7–15 years of age were included if they met the criteria for ADHD of the (DSM-IV)  
Other: ADHD presentation: inattentive_other: 18.2% across all arms, hyperactive_other: 4% across all arms, combined_other: 77.8% across all arms  
Diagnosis: Confirmation by specialist clinical interview  
Comorbidity: N/A  
Female: 19.2%  
Age mean: Mean 12.8  
Minimum age: 7 | Intervention: Psychoeducation for caregivers plus atomoxetine, 1.2 mg/kg day (70 kg) or 80 mg/day (>70 kg) for 10 weeks  
Control: Other Psychoeducation for caregivers plus placebo capsules for 10 weeks  
Comparator: NA  
Follow-up: 2.75 months | CGI-I (Clinical Global Impression Improvement), change from baseline  
An improvement was observed in the atomoxetine group whereas in the placebo group the score changed only slightly (p < 0.001).  
ADHD-RS-IV (Attention-Deficit/Hyperactivity Disorder Rating Scale IV)–Parent Version: Investigator Administered and Scored Treatment responders  
Statistically significant between-treatment differences in favor of atomoxetine at each visit (P < 0.001) from visit 4 (week 3) onwards.  
The global parental assessment of most aspects of psychoeducation was very positive; items were mostly rated as very good/very satisfied or rather good/satisfied.  
Decreased appetite | |
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<tr>
<th>Intervention</th>
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<th>Comparison:</th>
<th>Outcome and results</th>
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</thead>
<tbody>
<tr>
<td>FDA-approved pharmacological</td>
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</tr>
<tr>
<td>Takahashi, 2009</td>
<td>Author, year;</td>
<td>Setting;</td>
<td>Intervention;</td>
<td>The rate was 6.1% in the intervention and 0 in the placebo group (p 0.117).</td>
</tr>
<tr>
<td>Multiple publications;</td>
<td>Study target;</td>
<td>Study target;</td>
<td>Control;</td>
<td>Patients with at least 1 treatment emergent adverse event</td>
</tr>
<tr>
<td>Trial ID;</td>
<td>ADHD presentation;</td>
<td>ADHD presentation;</td>
<td>Comparator;</td>
<td>The rate was 89.8% in the intervention, and 74% in the placebo group (p 0.066).</td>
</tr>
<tr>
<td>Study design;</td>
<td>Diagnosis;</td>
<td>Diagnosis;</td>
<td>Follow-up</td>
<td>No serious adverse events occurred in either group.</td>
</tr>
<tr>
<td>Sites;</td>
<td>Comorbidity;</td>
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<tr>
<td>Study size;</td>
<td>% Female;</td>
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<tr>
<td>Location</td>
<td>Age mean;</td>
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<td>Setting</td>
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<tr>
<td>Maximum age: 15</td>
<td>Other: 0-1% across all arms</td>
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<tr>
<td>Ethnicity:</td>
<td>Other: 3% across all arms</td>
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<tr>
<td>Other: 93.9% across all arms</td>
<td>Other: 2.2% across all arms</td>
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<tr>
<td>Other info on race or ethnicity:</td>
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<tr>
<td>Target: Japanese children and adolescents age 6-17 years old with DSM-IV diagnosis of ADHD, CGI-ADHD-S score of &gt;= 3, have symptom severity score at least 1.5 standard deviations (SD) above Japanese pediatric age and gender norms on the Attention-Deficit=Hyperactivity Disorder Rating Scale-IV–Parent Version: Investigator Administered and Scored=Translated and Validated in Japanese (ADHD RS-IVJ:I), IQ &gt;= 80. Exclusion: anyone who took antipsychotic medication within 26 weeks of study visit 1, had a history of bipolar disorder or psychosis, or were determined by the investigator to be at suicidal risk.</td>
<td>Intervention: Atomoxetine 1.8 mg/kg per day for 8 weeks</td>
<td>ADHD RS-IVJ:I (Attention-Deficit Hyperactivity Disorder Rating Scale-IV–Parent Version: Investigator Administered and Scored-Translated and Validated in Japanese) 1.8 mg per day atomoxetine was superior to placebo (p 0.010).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other: ADHD presentation: inattentive: 61.2, hyperactive: 4.5, combined: 34.5</td>
<td>Control: Placebo</td>
<td>Decreased appetite</td>
<td>Decreased appetite</td>
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<tr>
<td></td>
<td>Placebo pills 2 times a day for 8 weeks</td>
<td>The rate was 21.3% in the intervention, 4.8% in the comparator, and 3.2% in the placebo group.</td>
<td>The rate was 21.3% in the intervention, 4.8% in the comparator, and 3.2% in the placebo group.</td>
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<tr>
<td></td>
<td>Comparator: MedicationAtomoxetine 0.5 mg/kg per day for 8 weeks</td>
<td>Two serious adverse events occurred, both in the same patient in the intervention group (hospitalization due to headache and vomiting).</td>
<td>Two serious adverse events occurred, both in the same patient in the intervention group (hospitalization due to headache and vomiting).</td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>Study</td>
<td>Population</td>
<td>Comparison</td>
<td>Outcome and results</td>
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<td>Diagnosis: Confirmation by specialist Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children—Present and Lifetime Versions (KSADS-PL)</td>
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<tr>
<td></td>
<td></td>
<td>Comorbidity: N/A</td>
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<tr>
<td></td>
<td></td>
<td>Female: 14.7%</td>
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<td></td>
<td></td>
<td>Age mean: 10.53 (2.52)</td>
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<td></td>
<td></td>
<td>Minimum age: 6</td>
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<td>Maximum age: 17</td>
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<td></td>
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<td>Ethnicity: % Asian: 100</td>
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<td></td>
<td>FDA-approved pharmacological</td>
<td>Target: Children meeting the DSM-IV criteria for ADHD and for Tourette disorder, chronic motor tic disorder or chronic vocal tic disorder; excluded if there was evidence of secondary tic disorder (e.g., tardive tics, neuroacanthocytosis, Huntington disease), major depression, pervasive developmental disorder, autism, psychosis, mental retardation, anorexia nervosa, bulimia, a serious cardiovascular (e.g., significant hypotension, congenital heart disease) or other medical disorder that would preclude the safe use of the medication, impaired renal function</td>
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<td>Intervention: Methylphenidate 60mg/day plus clonidine 0.6mg/day for 8 weeks</td>
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<td>Control: Placebo Placebo in gelatin capsules</td>
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<tr>
<td></td>
<td></td>
<td>Comparator: Medication Methylphenidate (Ritalin), maximum allowable daily drug dosages were 60 mg for MPH and 0.6 mg</td>
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<td></td>
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<td>Follow-up: 4 months</td>
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<td></td>
<td>Tourette’s Syndrome Study Group, 2002</td>
<td>Classroom observation disruptive behavior MPH (but not CLON) improved “on task” behavior. CGI (Clinical Global Impression) investigator judged improvement of ADHD Combined intervention had 87.5% improvement, comparator had 80.6% and placebo had 32.3%. Children’s Global Assessment Scale (C-GAS) Intervention and comparator groups significantly improved over control group (p=0.002, p=0.0005). No significant difference was observed when comparing CLON alone and MPH alone. No gender differences were found in the identified treatment effects.</td>
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<tr>
<td></td>
<td>ID: NA RCT Multicenter N = 136 US Setting: N/A</td>
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</tbody>
</table>
### Intervention

<table>
<thead>
<tr>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
</table>
| Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale (SKAMP), change from baseline The intervention significantly improved compared to control group (p<0.0001). PERMP (Permanent Product Measure of Performance) - The PERMP consists of 400 math questions and each are scored. PERMP scores are expressed as the number of questions correct. Predose PERMP Tests are similar pattern of treatment effect was found when analyzing some of our secondary outcome measures for ADHD, including Iowa Conners. 20% with MPH reported a worsening of tics as an adverse event (8 when used alone, 6 when given in combination with CLON) compared with 26% treated with CLON alone and 22% receiving placebo. Tics were reported to limit further dosage increases more often for subjects assigned to MPH alone (35%) than those assigned to MPH combined with CLON (15%), CLON alone (18%), or placebo (19%). Compared with placebo at the final visit, the severity of tics as assessed by the YGTSS-total, GTRS, and TSSR decreased in all active treatment groups. There was no overall evidence of cardiac toxicity by ECG monitoring. |}

- **Intervention**
  - TRI102 formulation containing active moiety (amphetamine), i.e. amphetamine extended-release oral suspension, 10 to 20 mg/day for 5 weeks

- **Control**
  - Placebo
  - Placebo formulation without active moiety

<table>
<thead>
<tr>
<th>FDA-approved pharmacological</th>
<th>Target: Children aged 6 to 12 years with ADHD who require pharmacologic treatment for this condition. Exclusion Criteria: Other serious illnesses or conditions that would put the patient at particular risk for safety events or would interfere with treatment/assessment of ADHD</th>
<th>Other:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tris Pharma, 2014&lt;sup&gt;175&lt;/sup&gt; ID: NCT02083783 RCT Multicenter N = 108 US Setting: Other</td>
<td>(a routine urinalysis was performed), or pregnancy (a urine pregnancy test was performed for all adolescent girls Other:</td>
<td></td>
</tr>
<tr>
<td><strong>Other:</strong> ADHD presentation: inattentive: 71, hyperactive: 2, combined: 27</td>
<td>Diagnosis: Confirmation by specialist DSM-IV Comorbidity: Tic disorder Female: 15% Age mean: Placebo 9.7 (1.8), MPH 10.7 (2.0), CLON 9.7 (1.8), Combination 10.6 (1.9) Minimum age: 7 Maximum age: 14 Ethnicity: % White: 72 Other info on race or ethnicity:</td>
<td></td>
</tr>
</tbody>
</table>

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### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA-approved pharmacological</td>
<td>van Stralen, 2020</td>
<td>ADHD presentation: inattentive: 20, hyperactive_other: impulsive 1, combined: 78</td>
<td>Comparator: NA</td>
<td>compared with post-dose PERMP scores at prespecified time (p&lt;0.0001). Significant improvement compared to placebo in the upper abdomen, 3.85% epistaxis, 3.85% rhinitis; only one person (2.08%) in the placebo group reported pain in the upper abdomen.</td>
</tr>
<tr>
<td>van Stralen Medicine Professional, 2013</td>
<td>JPM van Stralen</td>
<td>Diagnosis: No</td>
<td>Follow-up: 1.25 months</td>
<td></td>
</tr>
<tr>
<td>ID: NCT01985581</td>
<td>Crossover trial</td>
<td>Comorbidity: N/A</td>
<td></td>
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</tr>
<tr>
<td>Single center</td>
<td>N = 50</td>
<td>Female: 31 %</td>
<td></td>
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</tr>
<tr>
<td>Canada</td>
<td></td>
<td>Age mean: 9.4 (1.86)</td>
<td></td>
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<tr>
<td>Setting: Specialty care</td>
<td></td>
<td>Minimum age: 6</td>
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<td></td>
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<td>Maximum age: 12</td>
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<td></td>
<td></td>
<td>Ethnicity: % Hispanic or Latino: 39</td>
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<td></td>
<td></td>
<td>% Black/African American: 34</td>
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<td></td>
<td></td>
<td>% White: 55</td>
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<tr>
<td></td>
<td></td>
<td>% Multiracial: 10</td>
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<td></td>
<td>Other info on race or ethnicity:</td>
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<tr>
<td>Target:</td>
<td>Pediatric patients with a diagnosis of inattentive, hyperactive, or combined subtype of ADHD, being treated with stimulant medication and presenting with 'suboptimal' executive function</td>
<td>Comparator: NA</td>
<td></td>
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<tr>
<td>Other:</td>
<td>ADHD presentation: N/A</td>
<td>Follow-up: 2 months</td>
<td></td>
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<tr>
<td>Diagnosis: Confirmation by specialist</td>
<td>DSM-IV-TR diagnosed via clinical assessment and ADHD-RS-IV</td>
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<tr>
<td>Comorbidity: N/A</td>
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<tr>
<td>Female: 16.0 %</td>
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<tr>
<td>Intervention:</td>
<td>Guanfacine extended-release 4 mg/day for 8 weeks as adjunct therapy to usual care stimulant therapy</td>
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<tr>
<td>Control:</td>
<td>Placebo</td>
<td></td>
<td>CGI-S (Clinical Global Impressions - Severity) Intervention group had significantly lower severity at follow-up (p = .0007). ADHD-RS-IV, total score Intervention had significantly lower symptom score at follow-up (p &lt; .001). Participants with any adverse event The rate was 87% in the intervention and 85% in the control group. Intervention group reported more abdominal pain, fatigue, affect lability, and somnolence.</td>
<td></td>
</tr>
<tr>
<td>Comparator:</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up:</td>
<td>2 months</td>
<td></td>
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</tr>
<tr>
<td>Intervention Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Comparison: Intervention; Control; Comparator; Follow-up</td>
<td>Outcome and results</td>
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<tr>
<td>Wang, 2007&lt;sup&gt;593&lt;/sup&gt; FDA-approved pharmacological</td>
<td>Meds then placebo group: 12% female; Placebo then meds group: 20% female (all have ADHD) <strong>Age mean:</strong> Meds then placebo group: 9.4 (1.6) / Placebo then meds: 9.0 (1.4) <strong>Minimum age:</strong> 6 <strong>Maximum age:</strong> 12 <strong>Ethnicity:</strong> N/A</td>
<td>Both groups improved. ADHD-RS-IV (Attention Deficit Hyperactivity Disorder Rating Scale-IV-Parent Version), investigator-administered, change Similar improvement between the treatment groups. Weight loss Decreased appetite The rate for appetite suppression was 28% in the atomoxetine and 19% in the methylphenidate group (p 0.070). Atomoxetine reported -1.2 kg vs. methylphenidate -0.4 kg weight loss (p 0.001). Participants experiencing treatment emergent adverse events A significantly greater percentage of patients in the atomoxetine treatment group (87%)</td>
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</tbody>
</table>
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Comparison</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong>&lt;br&gt;Study: Wehmeier, 2012&lt;sup&gt;99&lt;/sup&gt; &lt;br&gt;Eli Lilly and Company, 2007&lt;sup&gt;10&lt;/sup&gt; &lt;br&gt;ID: NCT00546910 &lt;br&gt;RCT &lt;br&gt;Multicenter &lt;br&gt;N = 128 &lt;br&gt;Germany</td>
<td><strong>Target:</strong> Eligible were girls and boys aged 6 to 12 years with a diagnosis of ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition TR &lt;br&gt;<strong>Other:</strong>&lt;br&gt;ADHD presentation: inattentive: 22.4, hyperactive: 7.2, combined: 70.4</td>
<td><strong>Intervention:</strong> Atomoxetine 0.5-1.2 mg/kg per day once daily in the morning for 8 weeks &lt;br&gt;<strong>Control:</strong> Placebo &lt;br&gt;Placebo-controlled &lt;br&gt;<strong>Comparator:</strong> NA &lt;br&gt;<strong>Follow-up:</strong> 2 months</td>
<td>experienced events compared with methylphenidate (67%; p&lt;0.001).&lt;br&gt;No deaths were reported, a simple partial seizure was reported for a patient in the atomoxetine group (discontinued from the study).</td>
</tr>
<tr>
<td><strong>Comparison:</strong></td>
<td><strong>Outcome and results</strong></td>
<td></td>
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<tr>
<td>Intervention; Control; Comparator; Follow-up</td>
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<tr>
<td><strong>Outcome and results</strong></td>
<td></td>
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<tr>
<td>Weekly Ratings of Evening and Morning Behavior (WREMB)</td>
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<tr>
<td>The severity of ADHD symptoms was reduced to a statistically significantly greater degree in the treatment group compared to placebo (p&lt;0.001).</td>
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<tr>
<td>CGI-S</td>
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<tr>
<td>The severity of ADHD symptoms was reduced to a statistically significantly greater degree in</td>
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</tbody>
</table>
### Intervention

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Comparison</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Intervention; Control; Comparator; Follow-up</td>
<td>the treatment group compared to placebo ($p&lt;0.001$). ADHD-RS-IV The severity of ADHD symptoms was reduced to a statistically significantly greater degree in the treatment group compared to placebo ($p&lt;0.0001$). Treatment was significantly superior to placebo in reducing hyperactivity, inattention, and impulsivity as measured by q-scores of 10 primary variables of the cb-CPT/MT (infrared motion-tracking devise). Decreased appetite The rate of decreased appetite was 1.6 in the intervention and 3.2 in the placebo group. Participants with treatment emergent adverse events The rate of participants with adverse events was 51% in the intervention and 44% in the control group. No serious treatment emergent adverse event or death occurred.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Diagnosis</th>
<th>Setting: Mixed</th>
<th>ADHD-RS-IV-Teacher (Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Teacher) total score change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atomoxetine up to 1.8 mg/kg/day for 7 weeks</td>
<td>Confirmation by specialist</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCT</td>
<td>N/A</td>
<td>Mixed</td>
<td>Connors Global Index-Teacher, change from baseline</td>
</tr>
<tr>
<td>Multicenter</td>
<td></td>
<td></td>
<td>Statistically significant change favored the treatment group change compared to the placebo group ($p=0.008$).</td>
</tr>
<tr>
<td>N = 153</td>
<td></td>
<td></td>
<td>ADHD-RS-IV-Teacher</td>
</tr>
<tr>
<td>Multiple countries</td>
<td></td>
<td></td>
<td>(Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Teacher) total score change</td>
</tr>
<tr>
<td>Setting: Mixed</td>
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<td></td>
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<tr>
<td>Target: Children with a standard deviation score of 1.0 for ADHD-RS-IV-Teacher Version and score at least 1.5 SDs above age and sex norm for the CPRS-R:S ADHD Index</td>
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<tr>
<td>Control: Placebo Identical in appearance, once-daily for 7 weeks</td>
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<tr>
<td>Comparator: NA</td>
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<tr>
<td>Follow-up: 1.75 months</td>
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</table>

#### FDA-approved pharmacological

- Weiss, 2005
- ID: N/A
- RCT
- Multicenter
- N = 153
- Multiple countries
- Setting: Mixed

- Connors Global Index-Teacher, change from baseline
- Statistically significant change favored the treatment group change compared to the placebo group ($p=0.008$). ADHD-RS-IV-Teacher (Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Teacher) total score change
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Intervention; Control; Comparator; Follow-up</td>
<td>Only the standardized symptoms scores for the continuous data is available. Treatment group responded with a reduction in score by 20% compared to the placebo group (Fisher exact test p 0.003). Decreased appetite Decreased appetite was 24.0% vs 3.8% (p 0.001). 5.9% in the atomoxetine group discontinued due to adverse events, including abdominal pain, emotional disturbance, feeling abnormal, irritability, and vomiting; no patients in the placebo group discontinued due to adverse events.</td>
</tr>
<tr>
<td></td>
<td>Other: Teachers had to be available for telephone interviews and updates on the progress</td>
<td>ADHD presentation: inattentive : 26.8, hyperactive : 0.7, combined : 72.5 Diagnosis: Confirmation by specialist Followed the DSM-IV: “Diagnostic criteria were evaluated by clinic assessment and confirmed using a structured parent interview, the behavioral module of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime V Comorbidity: N/A Female: 19.6% Age mean: 9.9 (1.3) Minimum age: 8 Maximum age: 12 Ethnicity: Other info on race or ethnicity: N/A: Not mentioned or brought up.</td>
<td></td>
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</tr>
<tr>
<td>Weiss, 2007</td>
<td>FDA-approved pharmacological</td>
<td>Target: Children with ADHD, score of 1.5 or greater SD from the norm on the Conners’ ADHD Index; patients were excluded if they were allergic to MPH or amphetamines or had a history of serious adverse reactions to MPH or had a lack of</td>
<td>Intervention: Methylphenidate long-duration multilayer-release once daily based on weight (10 mg for 20 kg, 20 mg for between 20 and 35 kg, and 30 mg for greater than 35 kg) for 2 weeks Control: Placebo</td>
<td>Home Situations Questionnaire (HSQ), number of problem situations Both groups improved significantly form baseline but there was no difference between groups. CGI (Clinical Global Impressions), investigator rating</td>
</tr>
<tr>
<td>ID: N/A</td>
<td>Crossover trial Multicenter</td>
<td>N = 90</td>
<td></td>
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</table>
Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author, year; Multiple publications;</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Intervention; Control; Comparator; Follow-up</td>
<td>No difference between active groups. ADHD Index, CPRS (Conners' Parent and Teacher Rating Scales) Both active groups improved compared to baseline (p&lt;0.05). PSS (Parent Satisfaction Survey), satisfied or very satisfied with treatment 77% of parents were satisfied or very satisfied with MLR-MPH treatment and 82% with IR-MPH. Decrease in ADHD Index and oppositional scales, which was of similar magnitude for MLR- and IR-MPH in patients. Decreased appetite There was no statistically significant difference between active treatment groups. There were no significant differences between treatments in the adverse effects.</td>
</tr>
<tr>
<td>Trial ID; Study design; Sites; Study size; Location Setting</td>
<td></td>
<td></td>
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<tr>
<td>Canada Setting: Mixed</td>
<td>response to MPH, serious or unstable medical illness, co-morbid psychiatric illness of sufficient severity to require treatment, or currently receiving psychotropic medications or herbal treatments, a history of drug abuse, alcohol abuse, disorders of the sensory organs (particularly deafness), autism, psychosis, or any unstable psychiatric conditions</td>
<td>Placebo in the morning and at midday</td>
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<tr>
<td></td>
<td>Other: ADHD presentation: N/A Diagnosis: Confirmation by specialist DSM-IV Comorbidity: N/A Female: 18% Age mean: 11.0 (2.5) Minimum age: 6.4 Maximum age: 17.5 Ethnicity: % Black/African American: 6 % Asian: 4 % White: 83 Other info on race or ethnicity: Other: 7</td>
<td>Comparator: Medication Immediate-release MPH administered daily at 08:00 hour +/- 1 hour and 12:00 hour +/- 1 hour, initial daily dose was based on body weight (10 mg for &lt;= 20 kg, 20 mg for between 20 and 35 kg, and 30 mg for greater than 35 kg), daily dose was titrated in 10-</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Follow-up: 2.75 months</td>
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</tbody>
</table>

C-395
### Intervention

<table>
<thead>
<tr>
<th>Study:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
</tr>
</tbody>
</table>

#### Population:

<table>
<thead>
<tr>
<th>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
</tr>
</thead>
</table>
| Target: Children diagnosed with of any presentations of ADHD (hyperactive/impulsive, inattentive, or combined); either treatment naïve or dissatisfied with their current ADHD pharmacotherapy; age-appropriate intellectual functioning (IQ ≥80 based on the Wechsler Abbreviated Scale of Intelligence or Kaufman Brief Intelligence Test; provide a negative pregnancy test (if female); demonstrate that they could successfully swallow the largest capsule size. Other:

ADHD presentation: inattentive: 26.2, hyperactive: 1.9, combined: 71.5

Diagnosis: Confirmation by specialist

Comorbidity: N/A

Female: 33.0%

Age mean: 14.2 (1.58)

Minimum age: 12

Maximum age: 17

Ethnicity:

Other info on race or ethnicity: N/A |

#### Comparison:

<table>
<thead>
<tr>
<th>Intervention; Control; Comparator; Follow-up</th>
</tr>
</thead>
</table>
| Intervention: Methylphenidate long-acting formulation (PRC-063) 85 mg/day for 4 weeks

Control: Placebo Identical in appearance

Comparator: Medication Long-acting methylphenidate formulation (PRC-063) 25 mg/day for 4 weeks

Follow-up: 1 month |

#### Outcome and results:

- CGI-I (Clinical Global Impression-Improvement) responders (much or very much improved)
- About 52.7% of participants randomized to PRC-063 were responders versus 32.4% on placebo (p 0.0004).
- ADHD-5-RS
- Treatment groups showed a statistically significant improvement compared to placebo.
- Decreased appetite
- Across doses, 20.1% of participants reported decreased appetite (none in placebo).
- Participants with any treatment related adverse event
- Across doses, the rate was 48.6% for placebo and 65.6% across all doses.
- Two serious adverse events (both during the open-label study), one of which (aggressive behavior) was assessed as related to study drug.
### Intervention

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Comparison</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention:</strong> Atomoxetine slow titration starting dose 0.5 mg/kg/day for 7–9 days, followed by 1.0 mg/kg/day for 7–9 days, then 1.2 mg/kg/day for remainder of the 8-week period, fast titration group received atomoxetine at a starting dose of 0.5 mg/kg/day for a minimum of 3 days followed by 1.2 mg/kg/day for the remainder of the 8-week study period, a low dose of 0.8 mg/kg/day or the maximum label dose of 1.4 mg/kg/day for 40 week maintenance</td>
<td><strong>Control:</strong> NA</td>
<td><strong>Youth Risk Behavior Surveillance (YRBS)</strong> Total scores of the highest quartile patients did not improve significantly from baseline (p=0.116) <strong>CGI-ADHD-S (Clinical Global Impressions-Attention-Deficit-Hyperactivity Disorder-Severity), clinician</strong> Significant benefit was demonstrated with both titration schedules (p &lt;0.001) and there was no significant difference between groups (p=0.205). <strong>ADHD-RS (ADHD Rating Scale), clinician rating</strong> Significant benefit was demonstrated with both titration schedules and there was no significant difference between groups. Decreased appetite (8 week acute period) No statistically significant differences were observed in any of the vital signs or in weight between the 0.5=1.2 mg=kg=day and 0.5=1.0=1.2 mg=kg=day groups.</td>
<td></td>
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<tr>
<td><strong>Target:</strong> Adolescents 13-16 years old, who met DSM-IV criteria for ADHD, score of at least 1.5 SD above age and gender normative sample for ADHD-RS-IV Parent version, score of 70 or more on Kaufman Brief Intelligence Test (K-BIT). Patients who responded to the study medication during the acute treatment period (8 weeks) were eligible to continue on to an additional 40-week maintenance treatment period. Exclusion: patients currently taking psychotropic medications; have a history of bipolar disorder, psychosis, autism, Asperger’s syndrome, pervasive developmental disorder; patients who previously participated in a study of atomoxetine were excluded <strong>Other:</strong> ADHD presentation: inattentive : 49.8, hyperactive : 2.2, combined : 47.9 <strong>Diagnosis:</strong> Confirmation by specialist Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (K-SAD-PL: Behavioral)</td>
<td><strong>Comparator:</strong> MedicationFast titration group received atomoxetine at a starting dose of 0.5 mg/kg/day for a minimum of 3 days followed by 1.2 mg/kg/day for the remainder of the 8-week study period, a low dose of 0.8 mg/kg/day or the maximum label dose of 1.4 mg/kg/day for 40 week maintenance</td>
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</tbody>
</table>
### FDA-approved Pharmacological Intervention

<table>
<thead>
<tr>
<th>Study:</th>
<th>Wigal, 2004&lt;sup&gt;696&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>ID:</td>
<td>NA</td>
</tr>
<tr>
<td>N:</td>
<td>132</td>
</tr>
<tr>
<td>Setting:</td>
<td>Specialty care</td>
</tr>
</tbody>
</table>

#### Intervention

* Dexmethylphenidate hydrochloride (d-MPH, FocalinTM) twice daily for 4 weeks, with titration of the dose based on weekly clinic visits, a maximum of 10 mg twice daily

#### Control

* Placebo, twice daily for 4 weeks.

#### Comparator

* Medication d,l-threo-Methylphenidate Hydrochloride twice daily for 4 weeks, with titration of the dose based on weekly clinic visits.

#### Follow-up

* 1 month

#### Outcome and results

CGI-I, proportion much improved or very much improved

The percentage of patients with a therapeutic response was significantly higher in the group treated with d-MPH (p = .0010) and the group treated with d,l-MPH (p = .0130) than placebo.

SNAP-ADHD (abbreviated version of the full SNAP-IV Rating Scale) change, teacher reported

Treatment with either d-MPH (p = .0004) or d,l-MPH (p = .0042) significantly improved Teacher SNAP ratings compared with placebo. The d-MPH group showed significant improvements compared with placebo on afternoon Parent SNAP ratings (p = .0003) as did the

Anorexia

4 intervention patients, 2 placebo patients, and 6 comparator patients had clinically significant weight losses ranging from 5% to 18% of
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>ADHD presentation: inattentive : 34.8, hyperactive : 0.8, combined : 64.4</td>
<td>Intervene; Control; Comparator; Follow-up</td>
<td>baseline values. Four intervention patients, 0 placebo patients, and 5 comparator patients had anorexia. P values n</td>
</tr>
<tr>
<td></td>
<td>multiple publications; trial id; study design; sites; study size; location setting</td>
<td>Diagnosis: Confirmation by specialist DSM IV diagnosis, confirmed by NIMH Diagnostic Interview Schedule for Children (DISC-IV) administered to parents</td>
<td></td>
<td>70% of patients experienced at least one adverse event, more medication patients experienced headache and nausea.</td>
</tr>
<tr>
<td></td>
<td>population: setting; study target; ADHD presentation; diagnosis; comorbidity; % female; age mean; minimum age; maximum age; ethnicity</td>
<td>Comorbidity: N/A Female: 12% Age mean: 9.8 (2.65) Minimum age: 6 Maximum age: 17 Ethnicity: % Black/African American: 13.6 % White: 78.0 Other info on race or ethnicity: Other: Other race: 8.3</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Target: Subjects receiving medication to treat their ADHD at the time of study enrollment exhibited an inadequate response to their then-current stimulant dose and completed a washout equivalent to 5 half-lives of the given medication before completing baseline assessments. Additional requirements included attendance of regular school and the ability to read and understand English.</td>
<td>Intervention: Methylphenidate Osmotic-Release Oral System (OROS) optimized dose of 18, 36, or 54 mg/day for 6 weeks</td>
<td></td>
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<tr>
<td></td>
<td>Intervention: Methylphenidate Osmotic-Release Oral System (OROS) optimized dose of 18, 36, or 54 mg/day for 6 weeks</td>
<td>Control: Placebo</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>In the crossover design, subjects who completed both laboratory school assessments served as their own control and provided data for both OROS MPH and placebo Comparator: NA</td>
<td>Comparator: NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) - Composite score The intervention group had significantly better scores compared to the control group (p&lt;0.0001). Permanent Product Measure of Performance (PERMP) - Correct Answers The intervention group had significantly better scores compared to the control group (p&lt;0.0001).</td>
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</table>
### Intervention

<table>
<thead>
<tr>
<th>Study:</th>
<th>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population:</strong></td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
</tr>
<tr>
<td><strong>Comparison:</strong></td>
<td>Intervention; Control; Comparator; Follow-up</td>
</tr>
<tr>
<td><strong>Outcome and results</strong></td>
<td></td>
</tr>
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</table>
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>parent or caregiver; history of response to stimulant medication; and oppositional defiant disorder diagnosis was acceptable Other: ADHD presentation: N/A : for 6 months open-label MAS XR arm Diagnosis: Confirmation by specialist DSM-IV by either a child psychiatrist or psychologist Comorbidity: N/A Female: 29 % Age mean: Open-label mixed amphetamine salts extended release (MAS XR) mean age (year) at 14.4. No SD provided. Minimum age: 13 Maximum age: 17 Ethnicity: % White: 72.0 Other info on race or ethnicity: N/A: no other info provided</td>
<td>Comparator: Medication60 mg of MAS XR (mixed amphetamine salts extended-release) Follow-up: 6 months</td>
<td>systolic BP (1.7 mm Hg; P=.0252) and pulse (4.4 bpm; P&lt;.0001) were statistically, but not clinically, significant; diastolic BP was not significantly changed (0.6 mm Hg). A decrease in QTcB interval (-4.6±19.9 msec) was statistically (P=.009), but not clinically, significant. There were no serious cardiovascular adverse events.</td>
<td></td>
</tr>
<tr>
<td>FDA-approved</td>
<td>Wilens, 2008\textsuperscript{60} Noven Therapeutics, 2005\textsuperscript{81} ID: NCT00151970 Crossover trial</td>
<td>Target: Children with ADHD; children with conduct disorder or comorbid illnesses that contraindicated or could confound medication treatment, or a history of failing to respond to</td>
<td>Intervention: Methylphenidate transdermal patch, dose optimized over 5 weeks, 6 hour patch Control: Placebo Placebo transdermal patch</td>
<td>CPRS-R (Conners Parent Rating Scale-Revised) Mean total score decreased by &gt;67% from baseline to follow-up when patients wore the patch (p &lt;.0001).</td>
</tr>
</tbody>
</table>
### Intervention

<table>
<thead>
<tr>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multicenter N = 117 US Setting: Specialty care</td>
<td>psychostimulant treatment were excluded Other: Parents provided some outcomes ADHD presentation: N/A Diagnosis: Confirmation by specialist Diagnosed per DSM-IV-TR criteria. Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version interview was also conducted Comorbidity: N/A Female: 35.9% Age mean: 8.8 (0.2) Minimum age: 6 Maximum age: 12 Ethnicity: % Black/African American: 15.4 % American Indian or Alaska Native: 0 % Asian: 0 % Native Hawaiian or Pacific Islander: 0 % White: 63.2 Other info on race or ethnicity:</td>
<td>Comparator: Medication Methylphenidate transdermal patch, dose optimized over 5 weeks, 4 hour patch Follow-up: 2 months</td>
<td>ADHD-RS-IV (Attention-Deficit/Hyperactivity Disorder Rating Scale-IV) change, clinician rating Mean total score decreased at follow-up when patients wore the patch (p &lt; .0001). Permanent Product Measure of Performance (PERMP) math problem score A significant increase in the number of attempted math problems was seen during the 4- and 6-hour medicated patch wear times compared with placebo patch (p &lt; .0001). Correct scores for the 4- and 6-hour medicated patch wear times were significantly high 326 treatment-emergent adverse events were reported during the entire study for subjects in the safety population, majority were mild (62%) or moderate (37%) in intensity; there were no serious adverse events.</td>
</tr>
</tbody>
</table>
### FDA-approved pharmacological

<table>
<thead>
<tr>
<th>Study</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilens, 2012&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Target: Children and adolescents with ADHD with suboptimal but partial response to stimulant medication&lt;br&gt;Other: Parents provided some outcome data</td>
<td>Intervention: Guanfacine extended release 1-4mg in morning as adjunct to usual stimulant medication for 9 weeks&lt;br&gt;Control: Placebo&lt;br&gt;Comparator: MedicationGuanfacine extended release in evening as adjunct to usual stimulant medication</td>
<td>Oppositional symptoms, measured by oppositional subscale of the Conners’ Parent Rating Scale-Revised: Long Form (CPRS-R:L) GXR + stimulant taken in AM (p&lt;0.001) or PM (p&lt;0.003) led to significantly greater improvement in oppositional symptoms than versus placebo + psychostimulant.</td>
</tr>
<tr>
<td>Wilens, 2017&lt;sup&gt;141&lt;/sup&gt;, Shire, 2008&lt;sup&gt;116&lt;/sup&gt;</td>
<td>ADHD presentation: N/A&lt;br&gt;Diagnosis: Confirmation by specialist&lt;br&gt;DSM-IV-TR per Kiddie Schedule for Affective Disorder - Present and Lifetime (K-SADS-PL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ID: NCT00734578 RCT Multicenter N = 461 US Setting: Specialty care</td>
<td>Comorbidity: N/A&lt;br&gt;Female: 28.4 %&lt;br&gt;Age mean: 10.8 (2.4)&lt;br&gt;Minimum age: 6&lt;br&gt;Maximum age: 17&lt;br&gt;Ethnicity: % Hispanic or Latino : 13.4 % Black/African American : 22.0 % American Indian or Alaska Native : 0.2 % Asian : 1.3 % Native Hawaiian or Pacific Islander : 0.7 % White : 67.7 Other info on race or ethnicity:</td>
<td>Follow-up: 2 months</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Participants reporting any adverse event</td>
</tr>
</tbody>
</table>
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA-approved pharmacological</td>
<td>Wilens, 2015</td>
<td>The inclusion criteria adolescent outpatients aged 13 to 17 years with a diagnosis of ADHD (any subtype). Consistent with the DSM-IV-TR criteria, a primary ADHD diagnosis was confirmed by clinical evaluation using the behavior module of the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime version at screening.</td>
<td>Intervention: Guanfacine extended-release once-daily less than or equal to 7mg for 13 weeks</td>
<td>More intervention participants showed improvement than control participants (p=0.10). ADHD-RS-IV Intervention participants showed improvement compared to control group (p&lt;0.001). Weiss Functional Impairment Rating Scale, parent (WFIRS-P) There was no significant difference between groups.</td>
</tr>
<tr>
<td></td>
<td>Shire, 2011</td>
<td>Target: Guanfacine extended-release once-daily less than or equal to 7mg for 13 weeks</td>
<td>Control: Placebo Placebo ratio 1:1 same as baseline of 1 mg depending on weight group and was allowed to increase 1 mg weekly Comparator: NA Follow-up: 0.25 months</td>
<td>CGI-I score of equal to or greater than 2</td>
</tr>
</tbody>
</table>
### Intervention

**Study:**
- Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting

**Population:**
- Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity

**Comparison:**
- Intervention; Control; Comparator; Follow-up

**Outcome and results**

<table>
<thead>
<tr>
<th>% Black/African American</th>
<th>16.88</th>
</tr>
</thead>
<tbody>
<tr>
<td>% American Indian or Alaska Native</td>
<td>0.63</td>
</tr>
<tr>
<td>% Asian</td>
<td>1.59</td>
</tr>
<tr>
<td>% White</td>
<td>72.29</td>
</tr>
<tr>
<td>Other info on race or ethnicity: Other</td>
<td>7.96</td>
</tr>
</tbody>
</table>

### FDA-approved pharmacological

- Wolraich, 2001<sup>1</sup>  615
- Faraone, 2005<sup>1</sup>  744; Spencer, 2006<sup>1</sup>  1052; Baren, 2000<sup>1</sup>  662
- ID: N/A  RCT  Multicenter
- N = 282  US  Setting: Specialty care

**Target:** Children with ADHD who were taking MPH or had taken it in the past; a total daily MPH dose of at least 10 mg but not more than 60 mg. Patients with glaucoma, Tourette's syndrome, an ongoing seizure disorder, or a psychotic disorder also were excluded, as were girls who had reached menarche. Other: Parents and teachers provided outcome data

**ADHD presentation:** Inattentive: 19.5, Hyperactive: 7.1, Combined: 73.4

**Diagnosis:** Confirmation by specialist DSM diagnosed confirmed by Diagnostic Interview Schedule for Children (Version 4)

**Comorbidity:** N/A

**Female:** 17.4 %

**Age mean:** 9.0 (1.8)

**Minimum age:** 6

**Intervention:** Methylphenidate extended-release OROS tablets, 18 to 54 mg per day for 28 days

**Control:** Placebo

**Comparator:** Medication Immediate release methylphenidate, 5 to 15 mg per day

**Follow-up:** 1 month

CGI (Clinical Global Impression) much improved or very much improved

Both medications groups had more improvement in mean teacher (p < .05) and parent (p < .05) Conners ratings than placebo group. OROS MPH and immediate release MPH did not differ significantly (p < .539).

Inattention SNAP-IV, teacher report

The medication groups improved more than the placebo on SNAP-IV Inattention - Teacher Report, SNAP-IV Hyperactivity/Impulsivity - Teacher Report, SNAP-IV Inattention - Parent report and SNAP-IV Hyperactivity/Impulsivity - Parent Report p < .001 for all s

Proportion of patients eating less than usual The percentage of patients eating less than usual was significantly higher (p < .001) for the 2 medication groups compared with placebo. There was not difference between the medication groups.

Participants experiencing at least one adverse event The rate was 43% for intervention, 35% for control, and 47% for comparator.
### Appendix C. Evidence Tables

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<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
</table>
| FDA-approved pharmacological | Young, 2014<sup>232</sup>; Newcorn, 2013<sup>213</sup>; Stein, 2015<sup>1054</sup> | Maximum age: 12  
Ethnicity:  
% Hispanic or Latino : 3.5  
% Black/African American : 7.4  
% Asian : 0.4  
% White : 84.4  
Other info on race or ethnicity:  
Other : Other 4.3% | | CPRS-RS total scores  
Intervention group and comparator group had a significantly greater improvement from baseline in total score than control group (p<0.001).  
ADHD-RS-IV score  
At end of treatment, participants receiving guanfacine had a significantly greater reductions in mean ADHD-RS-IV total scores compared with the placebo group, regardless of the time of administration (p < .001 for all intervention groups versus placebo).  
Weiss Functional Impairment Rating Scale–Parent Report (WFIRS-P)  
Both medication groups showed significantly greater improvement in mean WFIRS-P Total scores versus placebo (p < 0.001).  
Decreased appetite |
| | | Target: Children with a primary diagnosis of ADHD according to DSM-IV-TR; a baseline ADHD-RS-IV total score 28 and a Clinical Global Impressions–Severity of Illness Scale score 4; no current diagnosis of controlled or uncontrolled comorbid psychiatric disorders; no previous or present risk for suicide; no history or active presence of cardiac abnormalities or a primary sleep disorder  
Other: Parents  
ADHD presentation: inattentive : 2.1, hyperactive : 1.8, combined : 96.1  
Diagnosis: Confirmation by specialist ADHD diagnosis according to DSM-IV-TR based on psychiatric assessment  
Comorbidity: N/A  
Female: 29.4 % | Intervention: Guanfacine extended release administered in the morning and placebo administered in the evening for 8 weeks, 1-4 mg/day based on dose optimization  
Control: Placebo  
Placebo administered in the morning and evening for 8 weeks  
Comparator: Medication Guanfacine extended release administered in the evening and placebo administered in the morning for 8 weeks; 5 week dose-optimization period, 3 week dose-maintenance period, and 9 day dose-taper period, dose optimization starting dose of 1 mg/day was titr  
Follow-up: 2 months |
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhu, 2017</td>
<td>FDA-approved pharmacological</td>
</tr>
<tr>
<td>ID: N/A</td>
<td>RCT</td>
</tr>
<tr>
<td>N = 104</td>
<td>Single center</td>
</tr>
<tr>
<td>Setting: Other</td>
<td>China</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Population:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target: Patients who aged from six to fourteen and conformed to the ADHD diagnostic criteria of the DSM5, fourth edition.</td>
</tr>
<tr>
<td>Other: ADHD presentation: inattentive: 49.03, hyperactive: 29.80, combined: 21.15</td>
</tr>
<tr>
<td>Diagnosis: Confirmation by specialist Confirmed by clinician using DSM 5.</td>
</tr>
<tr>
<td>Comorbidity: N/A</td>
</tr>
<tr>
<td>Female: 20.19%</td>
</tr>
<tr>
<td>Age mean: 58.65</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention: Atomoxetine with initial dose 0.5 mg/kg per day then gradually increased to 1.2 mg/kg according to the participant's condition and tolerance, taken after breakfast for 2 months</td>
</tr>
<tr>
<td>Control: NA</td>
</tr>
<tr>
<td>Comparator: Medication Methylphenidate with initial dose 0.2 mg/kg per day and then gradually increased to 0.5 mg/kg, taken after breakfast every day for 2 months</td>
</tr>
<tr>
<td>Follow-up: 2 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of decreased appetite was 4% in the active arms and 2.7% in the placebo arm.</td>
</tr>
<tr>
<td>Participants with treatment-emergent adverse events: The rate of events was 79% in the active groups and 57% in placebo.</td>
</tr>
<tr>
<td>4.1% reported severe AEs (4 in the AM, 5 in the PM group, 0 in placebo).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGI-ADHD-S Both groups improved but there was no statistical significance in difference values between the two groups.</td>
</tr>
<tr>
<td>ADHD-RS (ADHD rating scale for parent version) total score: At the end of treatment, a significant decrease from baseline was observed in two groups in scores of ADHDRS-IV-Parent: Inv, 2 subscales and CPRS-R: S (ADHD index, learning problems, hyperactivity-impulsivity, and confrontation), with considerable clinical significance.</td>
</tr>
<tr>
<td>Loss of appetite: There was no statistically significant difference in loss of appetite between groups (p=0.239).</td>
</tr>
</tbody>
</table>
### Neurofeedback

**Intervention**

- **Study:** Arnold, 2022<sup>12</sup>, Kerson, 2020<sup>330</sup>
- **ID:** RCT
- **Location:** Multicenter
- **Setting:** Specialty care
- **Population:**
  - **Setting:**
  - **Study target:** Children with ADHD.
  - **ADHD presentation:**
    - Inattentive: 37.5
    - Combined: 62.5
  - **Diagnosis:** Confirmation by specialist
  - **DSM per Child Interview for Psychiatric Syndromes (CHIPS)**
  - **Comorbidity:** N/A
  - **Female:** 23.3%
  - **Age mean:** 8.6 (1.14)
  - **Minimum age:** 7
- **Comparison:**
  - **Intervention:** Theta-beta ratio neurofeedback protocol in which theta power was down-trained and beta power was reinforced at scalp site Cz or Fz, 38 sessions total, at 3 times per week.
  - **Control:** Attention-matched control treatment of identical appearance, intensity/frequency, and duration, differing only in that reinforcement for controls was based on a pre-recorded electroencephalogram (EEG) of another child.
  - **Comparator:** NA
- **Follow-up:** 25 months
- **Outcome and results:**
  - Clinical Global Impression (CGI) global index, parent
  - Clinical Global Impression (CGI) - Severity, number in remission
  - No significant difference between groups.

**Neurofeedback**

- **Population:**
  - **Setting:**
  - **Study target:**
  - **ADHD presentation:**
    - Inattentive: 37.5, combined: 62.5
  - **Diagnosis:** Confirmation by specialist
  - **DSM per Child Interview for Psychiatric Syndromes (CHIPS)**
  - **Comorbidity:** N/A
  - **Female:** 23.3%
  - **Age mean:** 8.6 (1.14)
  - **Minimum age:** 7

- **Comparison:**
  - **Intervention:** Atomoxetine 9.92 (2.98), methylphenidate 9.75 (3.14)
  - **Control:**
  - **Comparator:**
  - **Follow-up:**

  The incidence of lethargy of atomoxetine group was significantly higher than that of methylphenidate group (p=0.027).
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
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<tr>
<td>Neurofeedback</td>
<td>Bakshayesh, 2011&lt;sup&gt;136&lt;/sup&gt; ID: NA RCT Unclear/Not reported N = 35 Germany Setting: N/A</td>
<td>Target: Children with a primary diagnosis of hyperkinetic disorder (disturbance of activity and attention (ICD-10:F90.0); or attention deficit without hyperactivity (ICD-10:F90.8); an IQ of &gt;80; no known neurological or gross organic diseases; no hyperkinetic conduct disorders (ICD-10:F90.1) or pervasive developmental disorders; children currently taking stimulant medication were not excluded. Other: Parents, teachers; assessed the behavior of pre-and post-treatment ADHD presentation: N/A Diagnosis: Confirmation by specialist ICD-10:F90.0; (ICD-10:F98.8 Comorbidity: N/A Female: 26 %</td>
<td>Intervention: EEG neurofeedback: each session lasted 30 min with a 30-s break between the different games, each game consisted of three trials lasting 3 min each, total of 30 sessions Control: NA Comparator: OtherEMG biofeedback (BF) aiming at forehead muscle relaxation: Both groups experienced similar treatment conditions except for the location of electrodes. Children received instructions on a computer screen to familiarize them with the exercises based on the intervention</td>
<td>FBB-HKS (German ADHD rating scales) total scores, parent report Improvement of the NF group in the FBB-HKS total score was superior to EMG group (p=0.062; effect size -0.77) per parent rating. There were no significant differences between treatment groups in the teacher ratings. Computer Continuous Performance Test: Commission Errors: Significant differences in commission errors between pre- and post-treatment (F(1,33) = 11.865; p = .002); significant interaction between treatment group and time for reaction time (F(1,33) = 7.359; p = .011) with a medium effect size of -0.70 (dcorr); overall, performance in the BF group decreased, while performance of the NF group improved after treatment; the effect sizes vary from dcorr = -0.32 (reaction time variability) to dcorr = -0.79 (reaction time).</td>
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Maximum age: 10  
Ethnicity:  
% Hispanic or Latino : 10.83  
% Black/African American : 7.63  
% Asian : 4.24  
% White : 76.3  
% Multiracial : 8.47  
Other info on race or ethnicity: Other : Other: 3.39
<table>
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<tbody>
<tr>
<td>Neurofeedback</td>
<td>Bluschke, 2022 ID: Clinical trial Single center N = 129 Germany Setting: Specialty care</td>
<td><strong>Target:</strong> Children and adolescents with ADHD according to ICD-10 criteria. 14 had an axis I comorbidity and 22 had an additional axis II diagnosis. <strong>Other:</strong> Parents reported one outcome measure. <strong>ADHD presentation:</strong> N/A <strong>Diagnosis:</strong> Confirmation by specialist determined according to standard clinical guidelines by a team of experienced child and adolescent psychiatrists and psychologists <strong>Comorbidity:</strong> N/A <strong>Female:</strong> % Not reported <strong>Age mean:</strong> 10.76 (0.37) Age range not reported. <strong>Minimum age:</strong> <strong>Maximum age:</strong> <strong>Ethnicity:</strong> Other info on race or ethnicity: N/A</td>
<td><strong>Intervention:</strong> Neurofeedback. Downregulation of theta and upregulation of beta. Two one-hours sessions per week for 8 weeks. 58.6% were on ADHD medication. <strong>Control:</strong> No intervention No neurofeedback. 60.9% were on ADHD medication <strong>Comparator:</strong> Neurofeedback. Upregulation of beta. Two one-hours sessions per week for 8 weeks. 46.4% were on ADHD medication. <strong>Follow-up:</strong> 2 months (8 weeks)</td>
<td>ADHD Symptom Checklist, parent rating, Inattention scal No significant difference in effect by group. Flanker test: the no neurofeedback group demonstrated significantly faster reaction times than those in the $\theta^u\beta^u$ group ($p=0.007$) or the $\beta^u$ group ($p=0.033$).</td>
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| **Age mean:** 9.34 (1.92) **Minimum age:** 6 **Maximum age:** 14 **Ethnicity:** Other info on race or ethnicity: N/A | | | | |

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<tr>
<th>Intervention</th>
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<tr>
<td>Neurofeedback</td>
<td>Dashbozorgi, 2021&lt;sup&gt;1,2&lt;/sup&gt; Faculty of Rehabilitation, 2018&lt;sup&gt;3&lt;/sup&gt; ID: IRCT20160717028964N 2 RCT Unclear/Not reported N = 40 Iran Setting: Other</td>
<td>Target: Male elementary school children with ADHD with IQ&gt;90, no history of cerebral trauma/injuries, learning disability, and behavioral disorders, taking a stable dose of psychostimulant under the supervision of a child psychiatrist, no history of receiving any other types of non-medical therapies Other: ADHD presentation: N/A Diagnosis: Confirmation by specialist Child Psychiatrist DSM-IV Comorbidity: N/A Female: 0 % Age mean: 11.17 (0.97) Minimum age: Maximum age: Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Intervention: 12 (60min) neurofeedback training sessions for six consecutive weeks, completed twice a week Control: Attention-matched control No treatment and watched animations that had no therapeutic potency; they waited to receive neurofeedback training sessions after the study. Comparator: NA Follow-up: 1.5 months</td>
<td>Buss-Perry Aggression Questionnaire (BPAQ) The intervention group (NF) showed a significant 60.2% decrease in aggression (p=0.001) from pre to post-test; the control group had so significant changes. BIS (Barrat Impulsiveness Scale) The intervention group (NF) showed a significant 60.9% decrease in impulsivity (p=0.001), the control group had no significant changes.</td>
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<tr>
<td>Neurofeedback</td>
<td>Duric, 2017&lt;sup&gt;4&lt;/sup&gt; Duric, 2014&lt;sup&gt;5&lt;/sup&gt; ID: NCT01252446 RCT Unclear/Not reported N = 130 Norway Setting: N/A</td>
<td>Target: Children clinically diagnosed with ADHD using the ICD-10 research diagnostic criteria and cognitive function above an IQ&gt;70; no involvement in another intervention group, including CBT and Stop Now And Plan (SNAP); no co-morbid disorders other than ODD or anxiety disorder; no</td>
<td>Intervention: Neurofeedback three times a week, with a total of 30 sessions, plus methylphenidate at a dosage of 1mg/kg/day in the form of long-acting methylphenidate capsules between 20–60mg, 6 months of follow-up Control: Other Neurofeedback alone; unipolar sensors were placed on the patient's</td>
<td>ADHD core symptoms, Barkley's Defiant Children rating scale, parent All groups improved over time but no difference was found between groups (p=0.385). School performance in the NF group did show a significant improvement (mean difference 1.5, CI 0.1 to 0.29).</td>
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<tr>
<td>Neurofeedback</td>
<td>Gelade, 2017&lt;sup&gt;291&lt;/sup&gt; Gelade, 2016&lt;sup&gt;61&lt;/sup&gt;; Janssen, 2016&lt;sup&gt;226&lt;/sup&gt;; Janssen, 2016&lt;sup&gt;226&lt;/sup&gt;; Janssen, 2017&lt;sup&gt;330&lt;/sup&gt;; Janssen, 2020&lt;sup&gt;832&lt;/sup&gt;; Gelade, 2018&lt;sup&gt;62&lt;/sup&gt;; van Mourik, 2011&lt;sup&gt;1106&lt;/sup&gt;; van Mourik, 2010&lt;sup&gt;1106&lt;/sup&gt; ID: NCT01363544 RCT</td>
<td>Target: Children with confirmed ADHD, free of stimulant use for 1 month, IQ&gt;80, no comorbidity restrictions Other: Parents and teachers provided outcome data ADHD presentation: N/A Diagnosis: Confirmation by specialist DSM-IV-TR diagnosis required; parent- and teacher ratings on the Disruptive Behavior Disorders</td>
<td>Inattention score, SWAN, parent report SWAN Inattention score, Parent report: MPH group had better score at follow-up than neurofeedback (p = .002). SWAN Hyperactivity / Impulsivity score, Parent report: MPH group had better score at follow-up than neurofeedback (p = .005). SWAN Inattention sc Response speed at follow-up as measured by stop-signal reaction time (SSRT) and mean reaction time (MRT) was better for</td>
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</table>
| Neurofeedback| Gevensleben, 2010[294]  
Gevensleben, 2009[765]; Wangler, 2011[125]  
ID: ISRCTN87071503  
RCT  
Multicenter  
N = 102  
Germany  
Setting: Specialty care | Target: Children aged 8 to 12 with ADHD; vast majority (over 90%) were medication naive. Comorbid disorders included: conduct disorder, emotional disorders, tic disorder and dyslexia. All children lacked gross neurological, other organic disorders, and comorbidities not specified above.  
Other: Parents provided some outcome data  
ADHD presentation: Inattentive: 29.8, Combined: 70.2  
Diagnosis: Confirmation by specialist  
Diagnoses were based on a semi-structured clinical interview (CASCAP-D[6]) and confirmed using the Diagnostic Checklist for Hyperkinetic Disorders/ADHD[7] by a child and adolescent | Comparator: Neurofeedback system SAM ('self-regulation and attention management') with 36 units of 50 minutes each, divided in two blocks of 18 units, the units were combined in 9 sessions which took place 2–3 times a week, break of 2–3 weeks between the two treatment blocks  
Control: NA  
Comparator: Cognitive trainingComputerized attention skills training which primarily exercises visual and auditory perception, vigilance, sustained attention, and reactivity; 36 units of 50 minutes each, divided in 2 blocks of 18 units; the units were combined in 9 sessions which too | Problem behavior during homework, Homework Problem Checklist  
No statistically significant difference.  
FBB-HKS (German ADHD rating scale) total score  
At one week post 8 week treatment, improvement in German ADHD rating scale (FBB-HKS) total score, parent rating, was greater for neurofeedback group compared to attention training group (p < .005).  
Improvement in teacher rating was also greater for neurofeedback training.  
SDQ (Strength and Difficulties Questionnaire)  
Effect size was 0.32 indicating a small positive effect of the intervention.  
For the problem situations in family (HSQ-D) questionnaire, no significant effects were seen. |
| Multicenter | N = 112  
Netherlands  
Setting: Specialty care | Rating Scale (DBDRS) confirmed diagnosis  
Comorbidity: N/A  
Female: 24.1%  
Age mean: 9.63 (1.76)  
Minimum age: 7  
Maximum age: 13  
Ethnicity: Other info on race or ethnicity: N/A | Comparator: MedicationShort-acting methylphenidate; during the 4 weeks titration phase, children were randomly assigned to one of five groups: 5 mg, 10 mg, 15 mg, 10 mg MPH, or placebo for 1 week, twice daily  
Follow-up: 6 months | intervention compared to neurofeedback and physical activity (p < .001 for all). |
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<tr>
<td>Neurofeedback</td>
<td>Gonzalez-Castro, 2016&lt;sup&gt;[30]&lt;/sup&gt; ID: N/A Clinical trial Unclear/Not reported N = 131 Spain Setting: Mixed</td>
<td>Target: Children with ADHD and an IQ of 80 or higher Other: ADHD presentation: N/A Diagnosis: Confirmation by specialist Neuro-pediatrician Comorbidity: N/A Female: 37 % Age mean: 9.61 (1.11) Minimum age: 8 Maximum age: 11 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Neurofeedback: Neurofeedback plus pharmacological support, neurofeedback consisted of a 15 min session, 3 days per week, for 3 months, methylphenidate administered according to neuropediatricians’ recommendations Control: No intervention Control group did not receive neurofeedback or pharmacological support Comparator: NA Follow-up: 3 months ADHD Scale of Assessment of Attention Deficit with Hyperactivity (EDAH) There were significant differences between control group and neurofeedback (p &lt;0.001), between control group and combined (p = 0.016), but not between control group and pharmacological support (p = 0.289). Statistically significant differences between control group and intervention and comparator groups (p&lt;0.001) for Test of Variables of Attention (TOVA) and the neurofeedback group improved to a greater extent in executive control than the pharmacological support group. Executive Function Scores, cortical activation assessed with QEEG at Cz. there were statistically significant group differences between control group and the treatment groups: neurofeedback (p 0.001), pharmacological support (p 0.001), and combined (p&lt; 0.001). For Fp1, there were statistically significant group differences between control group and the three treatment groups.</td>
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<td>Neurofeedback</td>
<td>Hasslinger, 2021&lt;sup&gt;316&lt;/sup&gt; Karolinska Institutet, 2019&lt;sup&gt;343&lt;/sup&gt; ID: NCT01841151 RCT Single center N = 217 Sweden Setting: Other</td>
<td>Target: Individuals with ADHD as primary diagnosis, IQ&gt;80, had sufficient Swedish proficiency, and stable pharmacologic treatment; neurodevelopmental comorbidities such as autism spectrum disorder, learning disabilities and language impairments were not reasons for exclusion Other: ADHD presentation: N/A Diagnosis: Confirmation by specialist Kiddie Schedule for Afective Disorders and Schizophrenia Interview Comorbidity: N/A Female: 24 % Age mean: 12.21 and 12.61 (2.30 and 2.74) Minimum age: 9 Maximum age: 17 Ethnicity: Other info on race or ethnicity:</td>
<td>Intervention: Slow cortical potentials neurofeedback: intentionally creating negative or positive slow cortical potentials, each trial lasted 10s, each session consisted of 144 trials split into 4 blocks (36 trial per block), lasted around 60 min, 5 sessions per week for 5 weeks Control: TAU Treatment as usual; in accordance with regional guidelines for treatment of ADHD, many of the children’s parents underwent psychoeducational parent group-training Comparator: Cognitive training Working Memory Training: a computerized software program with visuospatial and auditory tasks called Minneslek Flex (based on CogMed); participants could choose between a Junior and a Senior version that differed in the thematic content while sharing the Follow-up: 6 months</td>
<td>groups: neurofeedback (p&lt;0.001), pharmacological support (p = 0.005), and combined (p&lt;0.001). Inattention, Conners 3 Swedish Version, parent Intervention and comparator were significantly superior to control. There were no significant differences between intervention and comparator. Live Z-score neurofeedback outperformed slow cortical potential for teacher-rated hyperactivity (p 0.028; effect No severe adverse events were reported during the trial, whereas transient stress-related problems were quite frequent.</td>
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</tr>
</thead>
</table>
| Neurofeedback | Korfmacher, 2022[^1^]  
ID: NCT 01879644]  
RCT  
Single center  
N = 115  
Germany  
Setting: Specialty care | **Target:** Children with ADHD. Children with disorders or conditions that may mimic ADHD such as autism, brain disorders, epilepsy, hyperthyreosis, and any genetic or medical disorder associated with externalizing behavior were excluded.  
**Other:** Parents and teachers provided some outcomes.  
**ADHD presentation:** inattentive: 34, hyperactive: 11, combined: 55  
**Diagnosis:** Confirmation by specialist DSM-III-R and DSM-IV via semi-structured diagnostic interview (K-SADS-PL)  
**Comorbidity:** N/A  
**Female:** 23%  
**Age mean:** 9.1  
**Minimum age:** 7.0  
**Maximum age:** 11.8  
**Ethnicity:** Other info on race or ethnicity: N/A | **Intervention:** SCP (slow cortical potential) neurofeedback training aims at first learning to control and self-regulate certain brain activity parameters (via real-time feedback and operant principles), and as the next step utilizing this ability (by transfer) to improve everyday life functioning. Three sessions per week over 3 months. Three booster sessions were scheduled 6 months after end of therapy to activate the strategies learned.  
**Control:** NA  
**Comparator:** OtherSelf management training (SMT) Three sessions per week over 3 months. Three booster sessions were scheduled 6 months after end of therapy to activate the strategies learned.  
**Follow-up:** 12 months | Conners Parent Rating Scale  
No significant differences between groups in any Conner's Parent or Teacher Rating Scales (p > 0.34)  
Quality of life assessed via KINDL-R self-report showed SMT superior to neurofeedback regarding quality of life in school. |
| Neurofeedback | Lim, 2019[^2^]  
ID: NCT01344044  
RCT | **Target:** Children with ADHD; excluded children with intellectual disability, epilepsy and severe sensorineural deficits or co-existing psychiatric disorder. | **Intervention:** Brain computer interface-based attention training program for total 20 weeks, first 8 weeks of 3 sessions per week (24 sessions total), next 12 weeks of 4-weekly sessions (3 sessions total), each training session consists of 10 | CBCL (Child Behavior Checklist) - Externalizing reduction  
The intervention group had significantly greater reductions than the control group (p<0.001).  
ADHD-RS, clinician-rated |
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<td>Neurofeedback</td>
<td>Luo, 2022&lt;sup&gt;410&lt;/sup&gt; ID: ChiCTR 1900021891 RCT Single center N = 121 China Setting: Specialty care</td>
<td>Target: Children with ADHD. Those with other serious neuropsychiatric diseases or IQ&lt;80 excluded. Other: Parents provided outcomes ADHD presentation: N/A Diagnosis: Confirmation by specialist DSMIV criteria by a qualified psychiatrist Comorbidity: N/A Female: 20%</td>
<td>Intervention: Neurofeedback (NF) plus computerized cognitive training (CCT). Focus Pocus training program includes neurofeedback games and cognitive training(CT) games, . Each training session consisted of 14 randomly ordered mini-games, and, as each mini-game took approximately 1 min to complete, the total time per session was approximately 15 minutes. NF games aimed to promote awareness and control of brain activity with EEG recorded via ADHD Rating Scale IV (ADHD-RS IV), parent Weiss Functional Impairment Scale-Parent Report Behavior Rating Inventory of Executive Function (BRIEF): no significant difference in change among groups.</td>
<td>ADHD Rating Scale IV (ADHD-RS IV), parent All groups improved; no significant difference in change among groups. Weiss Functional Impairment Scale-Parent Report All groups improved; no significant difference in change among groups. Behavior Rating Inventory of Executive Function (BRIEF): no significant difference in change among groups.</td>
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<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
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</table>
| Neurofeedback | Minder, 2018; Zuberer, 2018; University of Zurich, 2015 | % only reported for completers  
Age mean: 8.94  
Minimum age: 7  
Maximum age: 12  
Ethnicity:  
% Asian: 100, Other: assumed; conducted in China  
Other info on race or ethnicity: | | |
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<td>Neurofeedback</td>
<td>NF Coll. Group, 2021</td>
<td>Target: Participants with ADHD and an IQ greater than or equal to 80; and an eyes-open theta/beta power ratio greater than or equal to 4.5 at Cz or Fz by the LubarMonastra Assessment Suite, participants could continue stimulants during the study but discontinued for 5 days, before major assessments, no comorbid disorder requiring psychoactive medication other than psychostimulant; no medical disorder requiring systemic chronic medication with confounding psychoactive effects</td>
<td>Comparator: Cognitive trainingCognitive training with CogniPlus, a software program developed for the rehabilitation of neurological patients consisting of adaptive game-like training tasks that target neuropsychological functions such as alertness, sustained attention, working memory</td>
<td>Follow-up: 3.5 months</td>
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<td>Ohio State University, 2014</td>
<td>ADHD presentation: inattentive: 35.9, combined: 64.1</td>
<td></td>
<td>Conners 3 Aggression, teacher ratingThe difference between groups was not statistically significant. CGI-I (Clinical Global Impression-Improvement) improvement of more than 2 Responders were 61% in the intervention and 54% in the control group (p =0.36). DSM Inattentive Symptoms on Conners 3 Long Version (average of teacher and parent ratings), change from baseline Both groups improved and there was no significant difference between groups (p=0.412) Functional assessment checklist, parent ratingThe difference between groups was not statistically significant. Appetite decreaseThe rate was 26.2% in the intervention and 13.8% in the control group.</td>
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<td></td>
<td>ID: NCT02251743</td>
<td>Diagnosis: Confirmation by specialist</td>
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<td>Multicenter</td>
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<td>N = 144</td>
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<td>Setting: N/A</td>
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<tr>
<td><strong>Intervention</strong></td>
<td><strong>DSM-V</strong>&lt;br&gt;Comorbidity: N/A&lt;br&gt;Female: 21.8 %&lt;br&gt;Age mean: 8.58 (1.14)&lt;br&gt;Minimum age: 7&lt;br&gt;Maximum age: 10&lt;br&gt;Ethnicity:&lt;br&gt;% Black/African American: 7.9&lt;br&gt;% Asian: 3.6&lt;br&gt;% White: 76.3&lt;br&gt;% Multiracial: 9.4&lt;br&gt;Other info on race or ethnicity:</td>
<td><strong>Intervention:</strong>&lt;br&gt;At-home neurofeedback training consisted of five 4-minute-long active blocks (with real-time feedback) and two 2.5 minute-long transfer blocks (with only intermittent feedback), two treatment phases of 16 to 20 sessions (4 per week)&lt;br&gt;<strong>Control:</strong>&lt;br&gt;NA&lt;br&gt;<strong>Comparator:</strong>&lt;br&gt;Medication Methylphenidate, open titration period of 3 weeks and a treatment period with titration started at 10 mg of extended-release methylphenidate per day and a maximum possible dose of 60 mg/day; treatment lasted 2 months, the optimal dose was maintained&lt;br&gt;<strong>Follow-up:</strong>&lt;br&gt;CGI improvement The comparisons between neurofeedback and medication were significant, indicating a better CGI Improvement in the medication group; 76.3% were much or very much improved with medication and 21.1% with neurofeedback. ADHD-Rating Scale-Clinician-rated total score The study failed to demonstrate noninferiority of neurofeedback vs methylphenidate (mean between-group difference 8.09; 90% CI 8.09, 10.56). Executive functions (BRIEF) showed significant decreases in both groups, the comparison showed greater effects in the medication group (p=0.002).</td>
<td>Adverse events that were possibly attributable to treatment were distributed proportionally between the treatments, with no significant difference in any.</td>
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<td><strong>Neurofeedback</strong></td>
<td><strong>Target:</strong> Children diagnosed with an inattentive or combined presentation of ADHD; without established diagnosis of autism, schizophrenia, severe generalized anxiety disorder, major depression, tics, epilepsy, or other neurological disorders; no antecedents of treatment with NF or medications for ADHD; no systemic chronic medication; IQ&gt;80&lt;br&gt;<strong>Other:</strong>&lt;br&gt;ADHD presentation: N/A: inattentive and combined presentation but no breakdown&lt;br&gt;Diagnosis: Confirmation by specialist&lt;br&gt;Made by a clinician using Kiddie-SADS (K-SADS)</td>
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<td>Purper-Ouakil, 2021&lt;sup&gt;472&lt;/sup&gt;&lt;br&gt;Mensia Technologies SA, 2016&lt;sup&gt;886&lt;/sup&gt;&lt;br&gt;ID: NCT02778360&lt;br&gt;RCT&lt;br&gt;Multicenter&lt;br&gt;N = 186&lt;br&gt;Multiple countries&lt;br&gt;Setting: Mixed</td>
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## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurofeedback</td>
<td>Qian, 2018&lt;sup&gt;173&lt;/sup&gt; ID: N/A RCT Single center N = 29 Singapore Setting: Specialty care</td>
<td>Target: ADHD participants who had combined or inattentive subtypes on medicine were only allowed to participate after at least 1 month of washout Other: ADHD presentation: N/A Diagnosis: Confirmation by specialist DSM-IV Comorbidity: N/A Female: 0 % all boys Age mean: 9 (1.5) and 9.45 (1.29) in the groups Minimum age: Maximum age: Ethnicity:</td>
<td>Intervention: Brain computer-interface training: 3 sessions per week for 8 weeks, each session lasting 30 minutes with breaks included Control: No intervention MRI scan and clinical assessment were performed in the control group although no intervention was done Comparator: NA Follow-up: 2 months</td>
<td>Participants with spontaneous reporting or Pediatric Adverse Event Rating Scale adverse events 91% of patients in the MPH group versus 21.6% in the NF group had at least one adverse event related to treatment with a significant between-group difference (chi-square test (1) = 80.71, p &lt; .0001); Severe adverse events occurred in 20.9% of patients in the MPH vs 29.7% in the NF group (p=0.195). CBCL (Child Behavior Checklist) The reduction of internalizing problems in the intervention group was slightly greater than that in the control group, but not significant (p = 0.44). ADHD-RS, clinician rated inattention The intervention group had significantly greater reduction in the ADHD-RS clinician inattention scores compared to the control group (p=0.038).</td>
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<td>Neurofeedback</td>
<td><strong>Intervention</strong></td>
<td><strong>Comparison</strong></td>
<td><strong>Outcome and results</strong></td>
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<td>Rajabi, 2020</td>
<td><strong>Study:</strong></td>
<td><strong>Population:</strong></td>
<td><strong>CPRS-R (Conners Parent Rating Scales-Revised)</strong></td>
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<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>There was a statistically significant effect favoring the intervention group. The intervention significantly improved total attention and total response control (impulsivity) measured by the Integrated Visual and Auditory Continuous Performance compared to the control group (p &lt;0.05).</td>
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<td>Other info on race or ethnicity: N/A</td>
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### Neurofeedback

#### Study:
- Steiner, 2014
- Steiner, 2014
- Tufts Medical Center, 2012
- ID: NCT01583829
- RCT
- Multicenter
- N = 104
- US
- Setting: School

#### Population:
- **Target:** Children in grade 2 or 4 with ADHD, IQ of 80 or higher; with no coexisting diagnosis of conduct disorder, autism spectrum disorder, or other serious mental illness (eg, psychosis); child ADHD medication use was not suspended for treatments or assessments
- **Other:** Parents provided some outcome data
- **ADHD presentation:** N/A
- **Diagnosis:** Confirmation by specialist clinical diagnosis of ADHD made by the child’s clinician,
- **Comorbidity:** N/A
- **Female:** 26.0 %
- **Age mean:** 8.57 (1.0)
- **Minimum age:** 7
- **Maximum age:** 10
- **Ethnicity:**
  - % Black/African American : 6.7
  - % Asian : 18.3
  - % White : 73.1
- Other info on race or ethnicity:

#### Comparison:
- **Intervention:** Neurofeedback training (Play Attention) in-school 45-minute intervention sessions 3 times per week, monitored by a trained research assistant for 40 sessions over 5 months
- **Control:** No intervention
- **Comparator:** Cognitive training via computer (Captain’s Log, BrainTrain) with 14 auditory and visual exercises targeting areas of attention and working memory; each exercise is interactive and lasts ~5 minutes; in-school 45-minute intervention sessions 3 times per week
- **Follow-up:** 6 months

#### Outcome and results
- Behavioral Observation of Students in Schools (BOSS), Off-task, teacher
  - Significant improvements were found in the intervention condition compared with the control (p = 0.04) but there were no differences found between the intervention and comparator.
  - Inattention score Conners 3, parent report
    - Intervention participants had significantly greater than gains than control group on the Connor’s 3 Inattention, Executive Functioning and Hyperactivity/Impulsivity scales (p < .01 for all).
  - Swanson, Kotkin, Agler, M-Flynn and Pelham scale (SKAMP) total score
    - No significant differences between groups in SKAMP total score at follow up.
    - Intervention (neurofeedback) group had greater improvement at follow-up compared to control group on the following Behavior Rating Inventory of Executive Function (BRIEF) rating summary scales: Behavior Regulation (p < .03), Metacognition (p < .04), and Global Executive Composite (p < .01).

- No adverse side effects of either intervention were reported on the standardized session checklists.
## Intervention

<table>
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<tr>
<th>Study:</th>
<th>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
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<tbody>
<tr>
<td>Neurofeedback</td>
<td>Strehl, 2017; Holtmann, 2014; Aggensteiner, 2019</td>
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<tr>
<td>ID: ISRCTN76187185</td>
<td>RCT</td>
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<tr>
<td>Multicenter</td>
<td>N = 150</td>
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<tr>
<td>Germany</td>
<td>Setting: School</td>
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### Population:

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<tr>
<th>Target:</th>
<th>Ages 7 to 9, diagnosed with ADHD combined type according to the DSM-IV; excluded were diagnosis of bipolar disorder, obsessive compulsive disorder, psychosis, chronic severe ticks, Tourette syndrome, major physical or neurological illness, and IQ of less than 80</th>
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<tr>
<td>Other:</td>
<td>ADHD presentation: combined: 100</td>
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<td>Diagnosis:</td>
<td>Confirmation by specialist</td>
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<td>Diagnosis confirmed by licensed psychologists/clinical psychiatrists</td>
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<td>Comorbidity:</td>
<td>N/A</td>
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<td>Female:</td>
<td>16.7 %</td>
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<td>Age mean:</td>
<td>mean (SD) Neurofeedback group 8.6 (0.92), EMG feedback 8.57 (0.88)</td>
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<td>Maximum age:</td>
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<td>Ethnicity:</td>
<td>Other info on race or ethnicity: N/A</td>
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### Comparison:

| Intervention: | Neurofeedback where participants were prompted to either produce negative (reducing the excitability threshold of the underlying cortex) or positive shifts (inhibition of excitation) in a randomized order; after session 12, the ratio of negativity to positivity trials was increased from 50 to 80%, total of 25 training sessions within 3 months with two to three sessions per week |
| Control: | Other |
| Comparator: | NA |
| Follow-up: | 6 months |

### Outcome and results

ADHD Symptom Severity, parent-rated Neurofeedback showed a significant superiority over EMG (treatment difference 0.17, 95% CI 0.02–0.3, p = 0.02); yielding an effect size (ES) of d = 0.57 without and 0.40 with baseline observation carried forward (BOCF); the sensitivity analysis confirmed In the safety population (N = 140) 119 AE were reported.; at least one AE was reported in 33% of NF participants and 35% of EMG participants; children reported headaches (N = 4, both groups), skin reactions (n = 3, NF), myalgia (n = 1, EMG), and nausea (n = 1, EMG).
Intervention Study: Aevi Genomic Medicine, 2016 ID: NCT02777931 RCT Multicenter N = 101 US Setting: Mixed

Population: Target: Children and adolescents age 12-17 years old with diagnosis of ADHD based on DSM-V criteria, ADHD-RS-5 score > 28 at baseline, IQ at least 79, have disruptive mutations in genes within the glutamate receptor metabotropic (GRM)-network as determined by the presence of copy number variations (CNVs) (GRM biomarker-positive subjects), no substance use (alcohol, nicotine products, illicit drugs), no comorbid psychiatric disorders, no serios chronic or physical health conditions (stroke, syncope, CVD, etc.)
Other: ADHD presentation: N/A Diagnosis: Confirmation by specialist ADHD-RS-5 score larger or equal to 28 at baseline Comorbidity: Other : Genetic disorders Female: 37.1 % Age mean: 14.1 (1.58) Minimum age: 12 Maximum age: 17 Ethnicity: 

Comparison: Intervention: NFC-1 (Fasoracetam) 100-400 mg twice daily as capsules (size 2 hard gelatin capsules); dosing was be optimized during the first 4 weeks of treatment, based on clinical response and tolerability, and maintained for an additional 2 weeks Control: Placebo Matching placebo capsules Comparator: NA Follow-up: 1.5 months

Outcome and results CGI-S Placebo performed better than intervention on CGI-S scores. ADHD-RS-5 Symptoms were reduced in the intervention group compared to control. Non serious adverse events The rate was 70% for intervention and 56% for control.
## Appendix C. Evidence Tables

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<tr>
<th>Intervention</th>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
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<tbody>
<tr>
<td>New pharmaceutical agent</td>
<td>Aevi Genomic Medicine, 2018&lt;sup&gt;[1]&lt;/sup&gt;</td>
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<td>ID: NCT03609619</td>
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<td>RCT Multicenter</td>
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### Appendix C. Evidence Tables

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<th>Intervention</th>
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<th>Comparison:</th>
<th>Outcome and results</th>
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<tbody>
<tr>
<td></td>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Intervention; Control; Comparator; Follow-up</td>
<td>ADHD-RS-IV (ADHD Rating Scale-IV) parent and teacher report Responders (at least 40% decrease in ADHD-RS scores) Both groups showed a significant improvement over the 6 weeks of treatment for the parent and teacher ratings. Decreased appetite Observed more frequently in the methylphenidate group (p 0.03). Ten side effects were observed over the trial that all of them were mild to moderate and tolerable. The difference between the modafinil and methylphenidate groups in the frequency of side effects was not significant except for decreased appetite and difficulty falling asleep that were observed more frequently in the methylphenidate group.</td>
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<td>Multiple publications;</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Maximum age: 17 Ethnicity: % Hispanic or Latino : 18.5 % Black/African American : 14.8 % American Indian or Alaska Native : 0.9 % Asian : 0.00 % White : 75.9 % Multiracial : 4.6 Other info on race or ethnicity: Other : Not reported: 4/108 (3.7%)</td>
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<tr>
<td>New pharmaceutical agent</td>
<td>Amiri, 2008</td>
<td>Target: Children with ADHD, children were excluded if they had a history or current diagnosis of pervasive developmental disorders, schizophrenia or other psychiatric disorders; any current psychiatric comorbidity that required pharmacotherapy; any evidence of suicide risk and mental retardation (I.Q.&lt;70 based on clinical judgment), a clinically significant chronic medical condition, including organic brain disorder, seizures and, current abuse or dependence on drugs within 6 months, hypertension, hypotension and habitual consumption of more than 250 mg/day of caffeine Other: ADHD presentation: N/A Diagnosis: Confirmation by specialist</td>
<td>Intervention: Modafinil film coated tablet in doses of 200–300 mg/day depending on weight (200 mg/day for &lt;30 kg and 300 mg/day for &gt;30 kg) for 6 weeks Control: NA Comparator: MedicationMethylphenidate (in doses of 20–30 mg/day) depending on weight (20 mg/day for &lt;30 kg and 30 mg/day for &gt;30 kg), titrated up: week 1: 10 mg/day (5 mg in the morning and 5 mg at midday); week 2: 20 mg/day (10 mg in the morning and 10 mg at midday) and week</td>
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### Appendix C. Evidence Tables

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<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
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<th>Outcome and results</th>
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<tbody>
<tr>
<td>New pharmaceutical agent</td>
<td>Barrickman, 1995&lt;sup&gt;12&lt;/sup&gt; ID: NA Crossover trial Unclear/Not reported N = 15 US Setting: N/A</td>
<td>DSM-IV-TR Comorbidity: N/A Female: 22 % Age mean: Modafinil 9.20 (2.53), methylphenidate 8.96 (2.34) Minimum age: 6 Maximum age: 15 Ethnicity: Other info on race or ethnicity: N/A</td>
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<td>Clinical Global Impression-Severity (CGI-S) Methylphenidate had greater improvements over bupropion (P &lt; .05) Iowa-Conners Teacher’s Rating Scale The changes in scores did not differ significantly between the two treatment arms of the study for either drug. Anorexia No changes were noted on ECG measurements or vital signs, and adverse effects were few, mild, and transient</td>
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<td>Target: Subjects could also have coexisting diagnoses of conduct, oppositional defiant, or developmental learning disorders. The following exclusion criteria were used: IQ &lt; 70 (mental retardation), and any other major Axis I, II, or III diagnoses. Since bupropion is contraindicated in subjects with seizure disorders, any subject with a seizure history was excluded. Other: ADHD presentation: N/A Diagnosis: No DSM-III-R Comorbidity: N/A Female: 20 % Age mean: 11.8 (3.3)</td>
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<td>Intervention: Bupropion 1.4 to 5.7 mg/kg per day for 6 weeks Control: NA Comparator: Medication Methylphenidate was titrated to the maximum effective dose of 0.4 to 1.3 mg/kg per day (mean 0.7 mg/kg per day). Dose was fixed for the final 3 weeks of bupropion therapy. Methylphenidate was administered in a dose of 0.4 mg/kg per day during the first week Follow-up: 1.5 months</td>
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<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Intervention; Control; Comparator; Follow-up</td>
<td>CGI-I (Clinical Global Impressions Scale-Improvement) responders Proportion of participants who were classified as responders based on CGI-I rating (rating of 1 or 2) at final visit between modafinil and placebo groups were statistically significant (p&lt;0.0001). Modafinil showed significantly greater improvement than pa ADHD-RS-IV School Version total score Difference between Modafinil and placebo groups in ADHD-RS-IV School Version total score at final visit was statistically significant (p &lt; 0.0001). Decreased appetite The rate was 16% in the intervention and 4% in the placebo group (p=&lt;0.05). Serious adverse events were reported for 2 patients in the modafinil group (Stevens-Johnson syndrome possibly related to study; duodenitis, peptic ulcer, and hypertonia unrelated to study drug).</td>
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<td>Biederman, 2005&lt;sup&gt;15&lt;/sup&gt; ID: NA RCT Multicenter N = 248 US Setting: Mixed</td>
<td>Minimum age: 7 Maximum age: 16 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Intervention: Modafinil film–coated tablets 170-425 mg/day for 9 weeks Control: Placebo Matching placebo pills for 9 weeks Comparator: NA Follow-up: 2.5 months</td>
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### Intervention

**Study:**
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- Multiple publications;
- Trial ID;
- Study design;
- Sites;
- Study size;
- Location

**Population:**
- Setting;
- Study target;
- ADHD presentation;
- Diagnosis;
- Comorbidity;
- % Female;
- Age mean;
- Minimum age;
- Maximum age;
- Ethnicity

**Comparison:**
- Intervention;
- Control;
- Comparator;
- Follow-up

**Outcome and results**

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<th>ADHD presentation</th>
<th>Diagnosis</th>
<th>Comorbidity</th>
<th>Female</th>
<th>Age mean</th>
<th>Minimum age</th>
<th>Maximum age</th>
<th>Ethnicity</th>
<th>Other info on race or ethnicity</th>
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New pharmaceutical agent

**Biederman, 2006**

- ID: NA
- RCT
- Multicenter
- N = 248
- US
- Setting: N/A

**Target:** Children age 6-13 years old with diagnosis of ADHD according to DSM-IV, stimulant-naive or who had manifested an unsatisfactory response to stimulant therapy, IQ of at least 80, a score of 80 or higher on the screener version of the Wechsler Individual Achievement Test, CGI-S score of 4 or more at baseline visit

**Other:**
- ADHD presentation: inattentive: 20.6, hyperactive: 2.0, combined: 76.6

**Intervention:**
- Modafinil 400 mg total, 200 mg twice daily (morning and midday) for 4 weeks

**Control:**
- Placebo
- 5 placebo pills daily

**Comparator:**
- Medication Modafinil 100 mg followed by 200 mg at midday (modafinil 100/200-mg divided dose)

**Follow-up:**
- 1 month

**Outcome and results**

CGI-I (Clinical Global Impressions of Improvement) much improved or very much improved.

The intervention and comparator groups had significantly greater improvement compared to the control group (p=0.04 and p=0.01). Both the intervention and comparator groups had a higher percentage of participants rated as improved compared to the placebo.

ADHD-RS-IV (ADHD Rating Scale-IV), school version.

The intervention group had significantly greater improvement compared to the control group (p=0.006).

Decreased appetite
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<tbody>
<tr>
<td></td>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Diagnosis: Confirmation by specialist Psychiatric evaluation and the Diagnostic Interview Schedule for Children, Fourth Edition Comorbidity: N/A Female: 26.6 % Age mean: 8.8 (2.0), 8.8 (2.1), 9.2 (2.1), 10.5 (1.6), 8.9 (2.0) across groups Minimum age: 6 Maximum age: 13 Ethnicity: % White: 81.5 Other info on race or ethnicity: Other: Other: 46/248 (18.5%)</td>
<td>Intervention: Zolpidem, recommended dose of 0.25 mg/kg, prepared as an oral formulation at 2.5 mg/mL, once per day at night for 8 weeks Control: Placebo Placebo was matched with respect to color and flavor Comparator: NA Follow-up: 2 months</td>
<td>The rates were 2% in the intervention and the placebo group and 12% in the comparator. Insomnia was the only adverse event that occurred with significantly greater prevalence in a group assigned to modafinil (200/100-mg divided dose) than in the placebo group (p = 0.03). One child who received modafinil 400 mg experienced serious dehydration, gastroenteritis, and vomiting on day 14; these adverse events were considered by the investigator to be unrelated to modafinil.</td>
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<td>Blumer, 2009&lt;sup&gt;163&lt;/sup&gt; Sanofi, 2006&lt;sup&gt;988&lt;/sup&gt; ID: NCT00318448 RCT Multicenter N = 201 US Setting: Other</td>
<td>Target: Patients were required to have latency to persistent sleep of 30 minutes, according to baseline polysomnographic results, and a sleep disturbance not attributable to direct physiologic effects of an abused drug or misused prescription medication. Patients were excluded if they had other sleep disorders diagnosed with baseline polysomnography, other major psychiatric disorders (but not obsessive-compulsive disorder), or a history of substance abuse and/or dependence. Previous</td>
<td>CGI-I (Clinical Global Impressions Scale), parent There was no significant difference between groups (p=0.076). ADHD Rating Scale-IV Baseline-adjusted mean changes did not differ between groups. No significant difference between treatment groups in latency to persistent sleep of more than 30 minutes was detected. Participants with at least one treatment emergent adverse event</td>
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<td><strong>Intervention</strong></td>
<td>adverse experience with zolpidem, use of pharmacologic sleep aids that the patient was unwilling to discontinue, or current use of rifampicin and/or sertraline also disqualified patients</td>
<td><strong>Rate of 62.5% in treatment and 47.7% in placebo group.</strong> Administration was terminated because of adverse events for 7.4% in the intervention and none in the placebo group; the main reason was hallucination.</td>
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<td><strong>New pharmaceutical agent</strong></td>
<td><strong>Target:</strong> Children with ADHD, exclusion criteria included any clinically significant medical conditions or abnormal baseline laboratory liver function tests, mental retardation, organic brain disorders, unstable psychiatric conditions, bipolar disorder, psychosis, drug or alcohol abuse or dependence within the prior 6 months</td>
<td><strong>Intervention:</strong> Pemoline for 4 weeks, morning and after school dosing as 18.75-mg and 37.5-mg tablets (3mg/kg/day) <strong>Control:</strong> Placebo Identical appearing and tasting 18.75-mg and 37.5-mg tablets morning and after school dosing <strong>Comparator:</strong> NA</td>
<td>CGI score very much improved or much improved A significantly higher proportion experienced improvement on pemoline relative to placebo (60% versus 11%, p 0.013). Hyperactivity, Inattentiveness, Impulsivity, DSM-IV-derived ADHD rating scale Progressive improvement in the intervention group compared to placebo (p 0.001).</td>
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</tbody>
</table>

| Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting | Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity | Comparison: Intervention; Control; Comparator; Follow-up | |

N/A

Confirmation by specialist DSM-IV

N/A

6

17

Other info on race or ethnicity: N/A

Bostic, 2000

ID: N/A

Crossover trial Unclear/Not reported

N = 21

US

Setting: Other

C-432
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
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<tbody>
<tr>
<td>Buitelaar, 1996</td>
<td>Study: Crossover trial Unclear/Not reported N = 52 Netherlands Setting: N/A</td>
<td>Target: Children with ADHD according to DSM-III-R criteria, scores in the clinical range on both the CBCL and CTRS hyperactivity factors, deficits in attention performance on either a reaction-time task or a continuous performance task in the neuropsychological testing, no previous treatment with psychotropic medication, and a clinical indication for drug treatment; children were excluded for a diagnosis of tic disorder or pervasive developmental disorder, a family history of tic disorder, and ADHD presentation: N/A Diagnosis: Confirmation by specialist DSM-IV Comorbidity: N/A Female: 14 % Age mean: 14.14 (1.6) Minimum age: 12 Maximum age: 17 Ethnicity: % White : 90 Other info on race or ethnicity:</td>
<td>Follow-up: 2.5 months</td>
<td>Using standard cutoff points for depression (HAM-D . 16, BDI . 19) and anxiety (HAM-A.21), no subjects had scores indicative of clinical depression or anxiety. Furthermore, none of the three depression or anxiety measures changed to a clinically or statistically significant degree over the course of this study (all p . 0.05). Loss of appetite Rates were 38% in intervention and 10% in placebo (p 0.014). The only adverse effects specifically associated with pemoline relative to placebo were mild insomnia (62% versus 5%, p &lt; 0.001) and mild loss of appetite (38% versus 10%, p 0.014).</td>
</tr>
</tbody>
</table>

**Intervention:** Pindolol 20 mg twice per day for 4 weeks

**Control:** Placebo

Matching placebo administered at breakfast and at noon

**Comparator:** Medication Methylphenidate 10 mg b.i.d, during the first 3 days a single dose of 10 mg, then treated in a fixed-dosage schedule 10 mg b.i.d at breakfast and at noon

**Follow-up:** 1 month

**CGI-S**

No difference between the two active treatments

Hyperactivity scale CPRS (Conners Parent Rating Scale)

No difference between groups.

Anorexia

The rate was 15% for pindolol, 24% for methylphenidate, and 25% for placebo.

Paresthesias were significantly more often reported with pindolol than with methylphenidate or with placebo; for all other adverse effects the frequencies did not differ significantly across drug status.
Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
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<tr>
<td>Ceresoli-Borrioni, 2021</td>
<td>Ceresoli-Borrioni, 2021</td>
<td>Target: ADHD participants with persistent impulsive aggression</td>
<td>Rate of remission for aggressive behavior (Retrospective-Modified Overt Aggression Scale (R-MOAS) scale score ≤ 0)</td>
<td>Rates of remission for aggressive behavior were greater in intervention and comparator groups compared with placebo. CGI Global Impression scale There was no significant difference between any groups. Weight and BMI</td>
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<td>Supernus Pharmaceuticals, 2011</td>
<td>Supernus Pharmaceuticals, 2011</td>
<td>Other: ADHD presentation: N/A</td>
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<td>ID: NCT01364662</td>
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## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>New pharmaceutical agent</td>
<td>Conners, 1996&lt;sup&gt;210&lt;/sup&gt; ID: RCT Multicenter N = 109 US Setting: Specialty care</td>
<td>Target: Children with ADHD in good physical health with no lab abnormalities Other: Parents and teachers provided data ADHD presentation: N/A Diagnosis: Confirmation by specialist DSM III Comorbidity: N/A Female: 10.0 % Age mean: 66% in 3rd grade or lower Minimum age: Maximum age: Ethnicity: % White: 75 Other info on race or ethnicity:</td>
<td>Comparator: Medication SPN-810, 12 mg/18 mg extended-release molindone (low dose) Follow-up: 1.5 months</td>
<td>All treatment groups exhibited increases in mean weight and BMI. Participants with adverse events The intervention group had 68% of participants with any adverse events, the comparator group had 38%, and the placebo group had 58%.</td>
</tr>
</tbody>
</table>
| | | | Intervention: Bupropion 50 mg or 75 mg, depending on body weight, twice daily at 7 AM and 7 PM for 4 weeks Control: Placebo Placebo tablet Comparator: NA Follow-up: 1 month | Clinical Global Impression The pooled results from the sites failed to demonstrate a significant treatment effect. Conners Parent Questionnaire, hyperactive-immature, restless-impulsive, and conduct disorder Improvements in the intervention group. Significant treatment effects for the continuous performance test and memory retrieval. Bupropion appeared to be well tolerated in most children; dermatological reactions were twice as frequent in the drug group than the placebo group with 4 reactions prompting discontinuation.
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<tr>
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<th>Outcome and results</th>
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<tbody>
<tr>
<td>New pharmaceutical agent</td>
<td>Dehbozorghi, 2019&lt;sup&gt;123&lt;/sup&gt; Roozbeh Psychiatric Hospital, 2018&lt;sup&gt;983&lt;/sup&gt;</td>
<td>Target: Patients with the diagnosis of ADHD based on DSM-5 alongside the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS) 25 and medical history; patients with history or current diagnosis of a psychiatric comorbidity except for oppositional defiant disorder, pervasive development mental disorders, mental retardation; history or allergy to tipepide or methylphenidate hydrochloride (Ritalin); use or any medication or supplement for psychotropic disorders; presence or uncontrolled seizures; abnormal systolic blood pressure, resting pulse rate, or liver function; neurological or cardiac disorders were excluded</td>
<td>Intervention: Tipepide (Asverin) at a dose of 15-30 mg/day divided into 3 doses before breakfast, supper, and bedtime plus 0.3-1.5 mg/kg/day of methylphenidate hydrochloride divided into two separate doses at 30 min before breakfast and lunch, treatment over a period of 8 weeks</td>
<td>CGI-S Score The effect for time by treatment interaction was not significant (p=0.182). ADHD-IV-RS, parent On general linear model repeated measures analysis a significant effect was seen for time by treatment interaction (p=0.049). Increased appetite The rate was 4.16% in the intervention compared to none in the control group. The frequencies of adverse events were similar between the groups.</td>
</tr>
<tr>
<td></td>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Study:</td>
<td>Intervention; Control; Comparator; Follow-up</td>
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<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
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<tr>
<td>New pharmaceutical agent</td>
<td>Farmer, 2017&lt;sup&gt;16&lt;/sup&gt; Michael Aman, 2008&lt;sup&gt;18&lt;/sup&gt; ID: NCT00796302 RCT Unclear/Not reported N = 165 US Setting: N/A</td>
<td>Target: Children 6 to 12 years old with a DSM-4 diagnosis of any subtype of ADHD and evidence of severe physical aggression, either conduct disorder or oppositional defiant disorder, and a CGI-S score equal or greater than 4; excluded were IQ was less than 71, any condition that was a contraindication for medication, family history of type-2 diabetes, using any psychotropic medications that would cause risk to the participant if stopped, suicidal ideation, eating disorder, autism disorder diagnosed using the DSM-4 criteria, or a mood disorder Other: ADHD presentation: N/A Diagnosis: Confirmation by specialist DSM-4 diagnosis was required for participation Comorbidity: ODD Female: 22 % Age mean: 8.94 (2.01)</td>
<td>Intervention: Risperidone plus psychostimulant (usually osmotic release oral system [OROS] methylphenidate) for 6 weeks, titrated to an optimal dose Control: Other Psychostimulant alone (usually osmotic release oral system [OROS] methylphenidate; STIM) plus placebo for 6 weeks titrated to an optimal dose Comparator: NA Follow-up: 2.25 months</td>
<td>No difference in h Conners’ Continuous Performance Test (CPT-II) or Digit Span performance was observed between groups.</td>
</tr>
<tr>
<td>Intervention</td>
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<td>Comparison:</td>
<td>Outcome and results</td>
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<tr>
<td>New pharmaceutica lagent</td>
<td>Findling, 2019</td>
<td>Minimum age: 6</td>
<td>Intervention: Dasotraline 4 mg</td>
<td>ADHD-RS-IV (ADHD Rating Scale-IV) Home Version total score change</td>
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<tr>
<td></td>
<td>Sunovion, 2015; Sunovion, 2015</td>
<td>Maximum age: 12</td>
<td>administered once-daily in the</td>
<td>There was a significant difference in 6 week</td>
</tr>
<tr>
<td></td>
<td>ID: NCT02457819, NCT02428088</td>
<td>Ethnicity:</td>
<td>morning for 6 weeks total</td>
<td>change from baseline between the placebo</td>
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<tr>
<td></td>
<td>RCT</td>
<td>% Black/African American : 41</td>
<td>Control: Placebo</td>
<td>and 4mg/day group (p&lt;0.001), but not when</td>
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<td></td>
<td>Multicenter</td>
<td>% White : 61</td>
<td>Placebo for 6 weeks</td>
<td>compared to the 2mg/day. This significance</td>
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<tr>
<td></td>
<td>N = 342</td>
<td>Other info on race or ethnicity:</td>
<td>Comparator: MedicationDasotraline</td>
<td>was also observed between the placebo and</td>
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<tr>
<td></td>
<td>US</td>
<td>Other : Non-Hispanic 93%</td>
<td>2 mg administered once-daily in the</td>
<td>4mg/day groups in the CGI-S score (p=0.04)</td>
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<tr>
<td></td>
<td>Setting: N/A</td>
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<td>morning for 6 weeks</td>
<td>Weight change</td>
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<td>Follow-up: 1.5 months</td>
<td>Decreased appetite</td>
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<td>The rate was 21.7% in the 4mg, 15.3% in the</td>
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<td>2mg, and 4.3% in placebo.</td>
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<td>Discontinuation rates were higher in the</td>
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<td>4mg/day group (12.2%) than 2mg/day (6.3%)</td>
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<td>and placebo (1.7%) groups. Psychosis</td>
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<td>symptoms were reported in 7 participants.</td>
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<td>For events with a higher incidence on</td>
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<td>dasotraline compared with placebo, the three</td>
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<td>most frequent AEs in the dasotraline 2 and 4</td>
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<td>mg/day groups (vs. placebo) were insomnia</td>
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<td>(15.3% [NNH = 10] and 21.7% [NNH = 6] vs.</td>
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<td>4.3%), decreased appetite (12.6% [NNH = 7]</td>
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<td>and 21.7% [NNH = 14] vs. 5.2%), and weight</td>
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<td>decreased (5.4% [NNH = 19] and 8.7%</td>
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</table>

**Notes:**
- ADHD presentation: N/A
- Diagnosis: Confirmation by specialist participants were evaluated based on the DSM-V criteria at the beginning of the trial
- Comorbidity: N/A
- Female: 33.3 %
### Appendix C. Evidence Tables

<table>
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<tr>
<th>Intervention</th>
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<th>Outcome and results</th>
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</thead>
<tbody>
<tr>
<td>New pharmaceutical agent</td>
<td>Greenhill, 2006[^1] ID: NA RCT Multicenter N = 200 US Setting: Mixed</td>
<td>Age mean: 2mg/day 8.9 (1.7), 4mg/day 9.1 (1.9), placebo 9.2 (2.1) Minimum age: 6 Maximum age: 12 Ethnicity: % Black/African American : 29.5 % White : 62.9 % Multiracial : 7.6 Other info on race or ethnicity:</td>
<td>[NNH = 12] vs. 0%.</td>
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<td>Target: Patients age 6-17 years old with clinical diagnosis of ADHD, a CGI-S rating of 4+, weight and height between 5-95th percentile, IQ at least 80, no learning disabilities, attending school full-time, have a investigator-rated ADHD-RS-IV (School Version) score of at least 1.5 SD above the norm for the patient's age and gender. Exclusion: history or current diagnosis of pervasive developmental disorder, schizophrenia, or other psychotic disorders (DSM-IV axis I), any current psychiatric comorbidity that required pharmacotherapy, presence of suicide risk, ADHD symptoms well controlled on current therapy with tolerable side effects, or failed 2+ courses of stimulant therapy for ADHD</td>
<td>Intervention: Modafinil film-coated tablets 170-425mg once daily in the morning for 9 weeks Control: Placebo Matching placebo tablets once daily in the morning for 9 weeks Comparator: NA Follow-up: 2.5 months</td>
<td>CGI-I rated 1 or 2 52% of modafinil and 18% of placebo met criteria for responder on the CGI-I (p&lt;0.0001). ADHD-RS-IV School Version change Modafinil produced significant reductions in ADHD-RS-IV total scores at school compared with placebo (p&lt;0.0001). Decreased appetite The rate of decreased appetite as 18% in the intervention and 3% in the placebo group. Modafinil was associated with significantly more insomnia, headache, decreased appetite, and weight loss than placebo, but discontinuation attributed to adverse events did not differ statistically between treatment groups (modafinil, 5%; placebo, 6%).</td>
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[^1]: Reference
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<th>New pharmacutic</th>
<th>Intervention</th>
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<tr>
<td>Kahbazi, 2009</td>
<td>Modafinil, 200–300 mg/day (once daily) depending on weight for 6 weeks</td>
<td>Children newly diagnosed with ADHD; children were excluded if they had a history or current diagnosis of pervasive developmental disorders, schizophrenia, or other psychiatric</td>
<td>ADHS-RS-IV (ADHD Rating Scale-IV) change, parent report ADHD Rating Scale-IV (ADHD-RS-IV), parent report, % responding (at least 40% decrease in score)</td>
<td>MODAFINIL</td>
<td>PLACEBO</td>
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<td>ID: NA RCT Single center</td>
<td>Placebo</td>
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<td>Other:</td>
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<td>ADHD presentation: inattentive : 23.7, hyperactive : 5.1, combined : 70.2</td>
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<td>Diagnosis: Confirmation by specialist the National Institute of Mental Health Diagnostic Interview Schedule for Children, Fourth Edition (DISC-IV) was used to establish the patients' diagnosis of ADHD using the full DSM-IV diagnostic criteria.</td>
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<td>Comorbidity: N/A</td>
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<td>Female: 27.3 %</td>
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<td>Age mean: Modafinil 9.9 (6-16), placebo 9.9 (6-16)</td>
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<td>Minimum age: 6</td>
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<td>Maximum age: 17</td>
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<td>Ethnicity: % Black/African American : 18.2 % White : 71.7</td>
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<td>Other info on race or ethnicity: Other : Other: 20/198 (10.1%)</td>
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<td>Intervention</td>
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<td>N = 46 Iran</td>
<td>Setting: Specialty care disorders or if they had a clinically significant chronic medical condition. Other: Parents and teachers provided outcome data ADHD presentation: combined : 100 Diagnosis: Confirmation by specialist DSM-IV-TR diagnosis confirmed by psychiatrist Comorbidity: N/A Female: 23.9 % Age mean: 9.07 (2.03) Minimum age: 6 Maximum age: 15 Ethnicity: Other info on race or ethnicity: N/A Comparator: NA Follow-up: 1.5 months</td>
<td>Change in ADHD Rating Scale-IV (ADHD-RS-IV) total, teacher report favored intervention (p &lt; 0.001), as did ADHD-RS-IV total score, parent report (p &lt; 0.001). The difference in % responding (at least 40% decrease in score) was significantly higher in the Decreased appetite More children in the modafinil group reported decreased appetite (p=0.05). No statistically significant differences between groups regarding abdominal pain, anxiety or nervousness, sadness, difficulty falling asleep, weight loss, nausea, dry mouth, irritability, or headaches.</td>
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| New pharmaceutical agent | Kratochvil, 2005[71] ID: NA RCT Multicenter N = 173 US Setting: Mixed Target: Patients age 7-17 years old with diagnosis of ADHD according to DSM-IV and comorbid anxiety or depression symptoms (Children's Depression Rating Scale-Revised (CDRS-R) total score of >36 or Multidimensional Anxiety Scale for Children (MASC) total score at least 1 SD above age and gender norms). Exclusion: any history of psychosis, bipolar disorder, or serious medical illness, history of substance abuse | Intervention: Fluoxetine 20 mg administered once daily for 8 weeks plus atomoxetine 1.8mg/kg/day evenly divided into two doses for the final 5 weeks of treatment Control: Other Atomoxetine alone plus placebo, after 3 weeks of treatment, atomoxetine was added to each patient's regimen for the final 5 weeks of treatment, initiated at 0.5 mg/kg/day and increased at weekly CGI-S (Clinical Global Impressions- Severity) change Difference in CGI-S score mean change from baseline between groups were not statistically significant (p 0.065). ADHD-RS-IV (Attention-Deficit/Hyperactivity Disorder Rating Scale-IV) total change Difference in ADHD-RS-IV Total T-score mean change from baseline between A/F and A/P groups were not statistically significant (p 0.121) ADHD-RS-IV Total score mean (SD)
<table>
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<tr>
<th>Intervention</th>
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<td></td>
<td><strong>Other:</strong></td>
<td><strong>Other:</strong></td>
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<td>intervals to 0.8 mg/kg/day and then to 1.2 mg/kg/day; maximu</td>
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<td></td>
<td>ADHD presentation: inattentive : 23.2, hyperactive : 2.9, combined : 73.8</td>
<td>Diagnosis: Confirmation by specialist Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version Comorbidity: Mood disorder Female: 27.7 % Age mean: Atomoxetine + Fluoxetine 11.2 (2.7), Atomoxetine + Placebo 11.6 (2.4) Minimum age: 7 Maximum age: 17 Ethnicity: % White: 83.8 Other info on race or ethnicity: Other: Other: 16.2 %</td>
<td>Comparator: NA Follow-up: 2 months</td>
<td>change from baseline: A/F (n = 113) –24.0 (13.6), A/P (n=44) –20.5 (12.9), p =.101. Children’s Depression Inventory (CDI) score mean (SD) change from baseline: A/F (n = 81) –8.8 (8.1), A/P (n=33) –6.4 (10.0), p =.043. CDRS-R (Children’s Depression Rating Scale-Revised) total score mean (SD) change from baseline: A/F (n = 113) –20.4 (13.6), A/P (n=44) –17.6 (11.8), p =.342. CDRS-R (Children’s Depression Rating Scale-Revised) total T-score mean (SD) change from baseline: A/F (n = 113) –22.9 (15.2), A/P (n=44) –19.8 (13.3), p =.342. Multidimensional Anxiety Scale for Children (MASC) score mean (SD) change from baseline: A/F (n = 109) –13.4 (16.0), A/P (n=42) –11.3 (19.0) p =.489. Multidimensional Anxiety Scale for Children (MASC) total T-score mean (SD) change from baseline: A/F (n = 109) –8.7 (10.3), A/P (n=42) –7.5 (12.9) p =.527. Decreased appetite The rate was 20% in intervention vs 6.8% in placebo approaching significance (p=.055); patients in the combined treatment group also experienced greater weight loss (mean [SD] weight change in kilograms: A/F –1.0 [1.7], A/P –.4 [1.3], p =.009).</td>
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</table>
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<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Intervention; Control; Comparator; Follow-up</td>
<td>The proportion of patients who discontinued because of an adverse event was low and similar between groups (A/F 2.4%, A/P 2.2%); Mean heart rate increased more in the A/F group as compared with the A/P group (mean [SD] change in beats/minute: A/F 11.9 [11.2], A/P 6.5 [15.5]; p = .008); Mean blood pressure was also increased more in the combined treatment group (mean [SD] diastolic change in mm Hg: A/F 5.2 [9.4], A/P 0.3 [9.1], p = .008; mean [SD] systolic change in mm Hg: A/F 3.1 [8.9], A/P −0.14 [9.3]; p = .070)</td>
</tr>
<tr>
<td>New pharmaceutical agent</td>
<td>Lin, 2014 El Lilly and Company, 2009</td>
<td>Target: Female and male patients greater than or equal to 6 years and &lt;17 years and 9 months of age at the time of informed consent Other: ADHD presentation: inattentive : 24.16, hyperactive : 3.68, combined : 72.18 Diagnosis: Confirmation by specialist DSM-IV-TR Comorbidity: N/A Female: 29 % Age mean: mean age 11.46 Minimum age: 6 Maximum age: 17 Ethnicity:</td>
<td>Intervention: Edivoxetine 0.3mg/kg administered daily for 8 weeks Control: Placebo Placebo-controlled Comparator: MedicationOROS MPH was administered at the label-recommended doses Follow-up: 2 months</td>
<td>Clinical Global Impressions-Attention-Deficit/Hyperactivity Disorder-Improvement (CGI-ADHD-I): Scores at the end-point for the edivoxetine 0.3 mg/kg/day arm was significantly lower relative to the placebo arm (lower score indicating greater clinical improvement) ADHD-RS-IV The edivoxetine 0.2 mg/kg/day and 0.3 mg/kg/day arms had statistically significantly greater improvement than the placebo arm in mean ADHD-RS total score change at end-point (placebo - 10.35; edivoxetine 0.2 mg/kg/day - 16.09, p &lt; 0.010; edivoxetine 0.3 mg/kg/day - 16.09, p &lt; 0.010; edivoxetine 0.3 mg/kg/day - 16.09, p &lt; 0.010). Statistically significant differences relative to placebo were observed for all edivoxetine dose arms with respect to changes in weight. (p &lt; 0.05)</td>
</tr>
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Appendix C. Evidence Tables

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<tr>
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<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
</table>
| New pharmaceutical agent | Mohammadi, 2010<sup>423</sup>  
Tehran University, 2010<sup>1073</sup>  
ID: NCT01099059  
RCT  
Single center  
N = 40  
Iran  
Setting: Mixed | Target: Participants age 6-14 with a diagnosis of ADHD based on DSM-IV criteria, have ADHD-RS-IV School version score of at least 1.5 SD above the norm for patient's gender and age. Exclusion: history of pervasive developmental disorders, schizophrenia or other psychiatric disorders, any current psychiatric comorbidity that required pharmacotherapy, IQ < 70, have a significant chronic medical condition.  
Other:  
ADHD presentation: combined : 100  
Diagnosis: Confirmation by specialist  
Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime diagnostic interview  
Comorbidity: N/A | Intervention: Amantadine for 6 weeks, dose of 100–150 mg/day depending on weight, 50 mg twice per day for <30 kg and 50 mg three times per day for >30 kg  
Control: NA  
Comparator: MedicationMethylphenidate at a dose of 20–30 mg/day depending on weight (20 mg/day for <30 kg and 30 mg/day for >30 kg), titrated up: week 1: 10 mg/day (5 mg in the morning and 5 mg at midday); week 2: 20 mg/day (10 mg in the morning and 10 mg at midday) and week 3 | ADHD-RS (ADHD Rating Scale) Total Score change, parent rating  
No significant differences were observed between the two groups on the Parent and Teacher Rating Scale scores.  
Decreased appetite  
The rate was 45% in the amantadine group and 84% in the methylphenidate group (p=0.01).  
All side effects were mild to moderate and tolerable. The difference between the amantadine and methylphenidate groups in the frequency of side effects was not significant except for decreased appetite and restlessness that were observed more frequently in the methylphenidate group. | Edivoxetine dose arms demonstrated statistically significantly greater mean increases in sitting heart rates, and sitting systolic and diastolic blood pressure, than the placebo arm (p<0.05). Edivoxetine and placebo treatment arms did not differ in the number of patients who reported at least one treatment-emergent adverse event (TEAE) (p >0.05). |
### Intervention

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<th>Comparison:</th>
<th>Outcome and results</th>
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<tbody>
<tr>
<td>Saito, 2020(^{495}) Taisho Pharmaceutical, 2016(^{1077}) ID: JapicCTI-163244 RCT Multicenter N = 216 Japan Setting: N/A</td>
<td><strong>Target:</strong> Ages 6-17 years old with a diagnosis of ADHD according the DSM-5, a total score equal to or less than 23 on ADHD RS-IV and a score equal to or less than 3 on CGI-ADHD-S. Patients were excluded based on a history of schizophrenia, other psychiatric disorders, intellectual disabilities, or reactive attachment disorder <strong>Other:</strong> ADHD presentation: Inattentive: 41.2%, hyperactive: 0.5%, combined: 58.3 Diagnosis: No Any existing diagnosis was required but nothing was done in the trial Comorbidity: N/A Female: 15.2% Age mean: 9.5 (2.3) Minimum age: 6</td>
<td><strong>Intervention:</strong> Tipepidine, 60 mg twice a day of tipepidine hibenzate (Asverin, non-opioid antitussive), 2 weeks of observation with 8 weeks of treatment <strong>Control:</strong> Placebo Placebo dose <strong>Comparator:</strong> Medication Tipepidine, 30mg/day tipepidine hibenzate (Asverin) <strong>Follow-up:</strong> 16 months</td>
<td>ADHD RS-IV-J-I (ADHD Rating Scale IV Japanese version) Mean Changes No significant difference was observed between the placebo and treatment groups, and no dose-response was observed; 30mg vs placebo (p=0.183) 120mg (p=0.748) No clinically significant changes in body weight were observed Adverse Events Total Count Incidence of AEs: 36.5% (placebo); 51.9% (30mg); 46.2 (60mg); 49.1% (120mg); no significant differences amongst treatment groups (p=0.420) Incidence of side-effects: 3.8% (placebo); 5.6% (30mg); 17.3% (60mg); 3.8% (120mg); no significant differences (p=0.050). No clinically significant changes in laboratory tests or vital signs were observed amongst treatment groups.</td>
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<td><strong>New pharmaceutical agent</strong></td>
<td>Salardini, 2016&lt;br&gt;ID: NA&lt;br&gt;RCT&lt;br&gt;Single center&lt;br&gt;N = 54&lt;br&gt;Iran&lt;br&gt;Setting: Specialty care</td>
<td><strong>Target:</strong> ADHD patients with blood pressure, pulse rate, and liver function tests were within clinically normal range&lt;br&gt;<strong>Other:</strong> &lt;br&gt;<strong>ADHD presentation:</strong> combined : 100&lt;br&gt;<strong>Diagnosis:</strong> Confirmation by specialist ADHD-RS-IV diagnosed by psychiatrist&lt;br&gt;<strong>Comorbidity:</strong> N/A&lt;br&gt;<strong>Female:</strong> 22 %&lt;br&gt;<strong>Age mean:</strong> 10.47 (2.13)&lt;br&gt;<strong>Minimum age:</strong> 6&lt;br&gt;<strong>Maximum age:</strong> 15&lt;br&gt;<strong>Ethnicity:</strong> % White : 100&lt;br&gt;<strong>Other info on race or ethnicity:</strong></td>
<td><strong>Intervention:</strong> Agomelatine was started as 15 mg/day in participants with weight 30 kg and 25 mg/day in patients with weight 45 kg in the morning and followed by placebo at lunch time&lt;br&gt;<strong>Control:</strong> NA&lt;br&gt;<strong>Comparator:</strong> Medication Ritalin (methylphenidate hydrochloride) 10 mg tablet twice daily for 6 weeks, participants who weighed more than 30 kg received a 10 mg methylphenidate hydrochloride tablet thrice daily&lt;br&gt;<strong>Follow-up:</strong> 1.5 months</td>
<td>ADHD-RS-IV, parent, change from baseline&lt;br&gt;Changes from baseline were not significantly different between the agomelatine group and the MPH group (p=0.44).&lt;br&gt;The frequency of side effects was not significantly different between the agomelatine and MPH groups.</td>
</tr>
<tr>
<td><strong>New pharmaceutical agent</strong></td>
<td>Sangal, 2014&lt;br&gt;Sunovion, 2009&lt;br&gt;Sunovion, 2009&lt;br&gt;ID: NCT00856973, NCT00857220&lt;br&gt;RCT</td>
<td><strong>Target:</strong> Children and adolescents with ADHD and insomnia; excluded another primary sleep disorder, other major psychiatric disorders, alcohol or substance abuse, and nicotine use</td>
<td><strong>Intervention:</strong> Eszopiclone high dose (2 mg for children, 3 mg for ado-lescents) for 12 weeks, participants continued on whatever stimulant medication they were on prior to trial enrollment</td>
<td>CGI, parent&lt;br&gt;The intervention group improved significantly over the control group (p=0.009), but the comparator did not (p=0.238).</td>
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<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
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<tr>
<td>Multicenter</td>
<td>N = 486</td>
<td>Other: Parents supplied some outcome data</td>
<td>Control: Placebo Placebo plus whatever stimulant medication patients were on prior to trial enrollment</td>
<td>Inattention score, Conners Comprehensive Behavior Rating Scale (CBRS) change, parent report</td>
</tr>
<tr>
<td></td>
<td>US</td>
<td>ADHD presentation: N/A</td>
<td></td>
<td>No significant difference between groups (p 0.238 for high dose vs placebo, p 0.352 for low dose vs placebo).</td>
</tr>
<tr>
<td></td>
<td>Setting: Specialty care</td>
<td>Diagnosis: Confirmation by specialist DSM-IV criteria and confirmed by the M.I.N.I. Inter-national Neuropsychiatric Interview for Children and Adolescents</td>
<td>Comparator: MedicationEszopiclone low dose (1 mg for children, 2 mg for adolescents), patients also continued on whatever stimulant medication they were on prior to trial enrollment</td>
<td>No significant differences between intervention, comparator, and placebo group in change from baseline to week 12 in latency to persistent sleep based on polysomnography (p 0.375 for high dose, p 0.999 for low dose).</td>
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<tr>
<td></td>
<td></td>
<td>Comorbidity: Sleep</td>
<td>Follow-up: 3 months</td>
<td>Participants with any adverse event The rate was 61% for intervention, 59.5% for comparator, and 46% for placebo.</td>
</tr>
<tr>
<td></td>
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<td>Female: 36.2 %</td>
<td></td>
<td>A dose-response relationship was observed for dysgeusia, abdominal discomfort, dizziness, and nasal congestion.</td>
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<td>Age mean: 11.4 (3.0)</td>
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<td>Minimum age: 6</td>
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<td>Maximum age: 17</td>
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<td></td>
<td></td>
<td>Ethnicity: % Hispanic or Latino : 15.5 % Black/African American : 19.3 % White : 74.5 Other info on race or ethnicity:</td>
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<tr>
<td>New pharmaceutical agent</td>
<td>Swanson, 2006</td>
<td>Target: Clinical Global Impressions-Severity of Illness scale (CGI-S) rating of 4 or higher (&quot;moderately ill&quot; or worse), total and/or subscale scores on the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) School Version22 at least 1.5 standard deviations above norms for the patient’s age and gender, and intelligence quotient of at least 80 as estimated by the</td>
<td>Intervention: Modafinil 340 or 425 mg/day (depending on weight) for 7 weeks</td>
<td>ADHD-RS-IV (Attention-Deficit/ Hyperactivity Disorder Rating Scale-IV) Home Version Modafinil significantly improved symptoms of ADHD as shown by reductions in ADHD-RS-IV School Version total scores compared with placebo at all visits (p ≤ .009), including the final visit of the double-blind phase (p &lt; .0001).</td>
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<tr>
<td></td>
<td>ID: N/A</td>
<td>Control: Placebo</td>
<td>Control: Placebo</td>
<td>Decreased appetite The rate was 14% in the intervention vs 2% in the placebo group.</td>
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<td></td>
<td>RCT</td>
<td>Comparator: NA</td>
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<td></td>
<td>Multicenter</td>
<td>Follow-up: 2.25 months</td>
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<td>N = 190</td>
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<td>US</td>
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<td>Setting: Specialty care</td>
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<td><strong>New pharmaceutical</strong>&lt;br&gt;Wilens, 2011&lt;sup&gt;112&lt;/sup&gt;&lt;br&gt;ID: NCT00640419&lt;br&gt;RCT&lt;br&gt;Multicenter&lt;br&gt;N = 121</td>
<td><strong>Target:</strong> DSM-IV diagnosis of any ADHD subtype, confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL), 15 and a rating of 4 or higher on the Wechsler Intelligence Scale for Children-Third Edition, and a score of at least 80 on the Wechsler Individual Achievement Test, Second Edition, Abbreviated. Patients were eligible if they were attending a full-time school (i.e., they were not eligible if receiving homeschooling) and if a teacher and parent were willing to participate&lt;br&gt;<strong>Other:</strong>&lt;br&gt;<strong>ADHD presentation:</strong> inattentive: 27, hyperactive: 6, combined: 67&lt;br&gt;<strong>Diagnosis:</strong> Confirmation by specialist&lt;br&gt;<strong>DSM-IV-TR</strong>&lt;br&gt;<strong>Comorbidity:</strong> N/A&lt;br&gt;<strong>Female:</strong> 30%&lt;br&gt;<strong>Age mean:</strong> 11.6 (2.6)&lt;br&gt;<strong>Minimum age:</strong> 6&lt;br&gt;<strong>Maximum age:</strong> 17&lt;br&gt;<strong>Ethnicity:</strong> Other info on race or ethnicity:</td>
<td><strong>Intervention:</strong> ABT-089 (neuronal nicotinic receptor partial agonist) 1.4 mg/kg taken daily for 6 weeks&lt;br&gt;<strong>Control:</strong> Placebo&lt;br&gt;<strong>Placebo</strong></td>
<td>Two patients receiving modafinil experienced 3 serious adverse events (asthma attack, influenza syndrome, dehydration), these events resolved spontaneously and were considered to be not related or unlikely related to the study medication.</td>
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```c
New pharmaceutical
Wilens, 2011<sup>112</sup>
ID: NCT00640419
RCT
Multicenter
N = 121
```
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<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparator: MedicationABT-089 (neuronal nicotinic receptor partial agonist) 0.7 mg/kg taken daily for 6 weeks</th>
<th>Outcome and results</th>
</tr>
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<tr>
<td>US</td>
<td>Clinical Global Impression-ADHD-Severity Scale (CGI-ADHD-S); no history of current or past diagnosis of bipolar I, II, or NOS (Not Otherwise Specified) disorder; psychotic disorder; autism, Asperger’s syndrome or pervasive developmental disorder; tics or Tourette syndrome; seizure disorder; traumatic brain injury; current diagnosis of obsessive-compulsive disorder, eating disorder, anxiety disorder, or depressive disorder requiring treatment of any kind; psychotropic medications within 14 days or 5 half-lives (7 days for stimulants), whichever was longer, prior to the Day 1. <strong>Other:</strong> ADHD presentation: inattentive, inattentive_other: %'s broken down by meds, hyperactive, hyperactive_other: %'s broken down by meds, combined, combined_other: %'s broken down by meds <strong>Diagnosis:</strong> Confirmation by specialist <strong>DSM-IV</strong> <strong>Comorbidity:</strong> N/A <strong>Female:</strong> 33 %</td>
<td>Comparator: MedicationABT-089 (neuronal nicotinic receptor partial agonist) 0.7 mg/kg taken daily for 6 weeks</td>
<td>ADHS-RS-IV There was no statistically significant difference between ABT-089 and placebo in the primary efficacy analysis of mean change from baseline to final evaluation of the ADHD-RS-IV (HV) Total Score (Table 2), or on the secondary analysis of mean change from... Any adverse event The rates were 60% in the intervention, 69% in the placebo, and 67.6% in the low dose group.</td>
<td></td>
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</tbody>
</table>
### New pharmaceutical agent

**Study:**
- Author, year: Willens, 2011
- Multiple publications: Yes
- Trial ID: NCT00528697
- RCT: Yes
- Multicenter: Yes
- N = 278
- Setting: N/A

**Population:**
- Setting: N/A
- Study target: DSM-IV diagnosis of any ADHD subtype, confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL), and a rating of 4 or higher on the Clinical Global Impression-ADHD-Severity Scale (CGI-ADHD-S); no history of current or past diagnosis of bipolar I, II, or not otherwise specified) disorder; psychotic disorder; autism, Asperger's syndrome or pervasive developmental disorder; tics or Tourette syndrome; seizure disorder; traumatic brain injury; current diagnosis of obsessive-compulsive disorder, eating disorder, anxiety disorder, or depressive disorder requiring treatment of any kind; psychotropic medications within 14 days or 5 half-lives (7 days for stimulants), whichever was longer, prior to the Day; atomoxetine within 3 months

**Comparison:**
- Intervention: ABT-089 of 0.085 mg/kg, 0.260 mg/kg, 0.520 mg/kg, or 0.700 mg/kg once per day, treatment period of 8 weeks
- Control: Placebo
- Comparator: MedicationAtomoxetine 1.2 mg/kg/day once per day, treatment period of 8 weeks

**Follow-up:** 2 months

**Outcome and results**

There was no statistically significant difference between any ABT-089 dose and placebo for the mean change from baseline to final evaluation for the CGI-ADHD-S, or on the mean change from baseline to each evaluation, with the exception of the 0.520 mg/kg ADHD-RS-IV

There was no statistically significant difference between ABT-089 and placebo in the primary efficacy analysis of mean change from baseline to final evaluation of the ADHD-RS-IV (HV) Total Score, or on the secondary analysis of mean change from baseline to baseline treatment period of 8 weeks

In the atomoxetine group, mean weight and BMI decreased by 0.1 kg and 0.2 kg/m² (mean difference from placebo -1.3 CI-1.99, -0.69 and -0.6 CI -0.96, -0.19]

Any adverse event
The rate were 82% in the intervention, 76.1% in the placebo, and 82% in the atomoxetine group.
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<tr>
<td>ABT-089</td>
<td>Zarinara, 2010</td>
<td>Target: Children with combined subtype of ADHD and were newly diagnosed if they had a history or current diagnosis of pervasive developmental disorders, schizophrenia, or other psychiatric disorders or any current psychiatric comorbidity that required pharmacotherapy; any evidence of suicide risk and mental retardation</td>
<td></td>
<td>ADHD-089 was generally safe and well tolerated, with no statistically significant difference between any ABT-089 dose and placebo in the overall incidence of any specific AE, and no clinically significant changes in other safety measures</td>
</tr>
</tbody>
</table>

Other: ADHD presentation: inattentive_other : %s broken down by meds, hyperactive_other : %s broken down by meds, combined_other : %s broken down by meds

Diagnosis: Confirmation by specialist DSM-IV
Comorbidity: N/A
Female: 33 %
Age mean: mean 8.6
Minimum age: 6
Maximum age: 12
Ethnicity: Other info on race or ethnicity:

New pharmaceutical agent
Zarinara, 2010
ID: N/A
RCT
Single center
N = 38
Iran
Setting: Other

Intervention: Venlafaxine (antidepressant) at doses of 50–75 mg/day depending on weight (25 mg twice per day for <30 kg and 25 mg three times per day for >30 kg), treatment for 6 weeks
Control: NA
Comparator: Medication Methylphenidate at a dose of 20–30 mg/day depending on

ADHD-RS-IV, parent rating
Responder (at least 40% decrease in ADHD-RS-IV)
No significant difference was observed in the two groups (p 0.33).
No significant difference was observed on the reduction of scores of the Teacher ADHD Rating Scale (p 0.30).
Decreased appetite
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<td><strong>Zavadenko, 2019</strong>&lt;sup&gt;25&lt;/sup&gt;</td>
<td>(IQ &lt; 70), a clinically significant chronic medical condition, including organic brain disorder, seizures, or current abuse or dependence on drugs the last 6 months, hypertension or hypotension</td>
<td>weight, titrated up: week 1: 10 mg/day (5 mg in the morning and 5 mg at midday); week 2: 20 mg/day (10 mg in the morning and 10 mg at midday); and week 3: 30 mg/day for children &gt;30 kg (10 mg in the m</td>
<td>The reported rates were 10.52% in the venlafaxine and 10.52% in the methylphenidate group. Nine side effects were observed over the trial, but all of them were mild to moderate and tolerable. The difference between the venlafaxine and methylphenidate groups in the frequency of side effects was not significant except for headaches and insomnia that were observed more frequently in the methylphenidate group.</td>
</tr>
<tr>
<td><strong>New pharmaceutical agent</strong></td>
<td>ADHD presentation: combined; Diagnosis: Confirmation by specialist DSM-IV-TR; Comorbidity: N/A; Female: 29%; Age mean: 9.42 (2.19) and 9.57 (1.86); Minimum age: 6; Maximum age: 13; Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Follow-up: 1.5 months</td>
<td></td>
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<tr>
<td><strong>Study</strong>: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td><strong>Target</strong>: Children 6-12 years old with ADHD diagnosis based on ICD-10 criteria, presence of hyperdynamic (hyperkinetic) syndrome with attention deficit; severity of ADHD on the CGI-S scale of 3–6 points; total score on the ADHD-DSM-IV scale is at least 25 for boys and 22 for girls; patients with comorbid diseases that would require the use of</td>
<td><strong>Intervention</strong>: Pantogam (Hopantenic acid) was given as tablets containing 250 mg at the pediatric therapeutic dose of 30 mg/kg, divided into two split doses taken after meals, for 4 months</td>
<td><strong>CGI-S (Clinical Global Impressions Scale-Severity)</strong> The intervention produced a decrease in disease severity from the placebo level (p=0.014). Proportions of patients with clinical improvements (decreases in total points scores on the DSM-IV ADHD scale by 25% or more from baseline)</td>
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<td><strong>Population:</strong> Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td><strong>Comparison:</strong> Intervention; Control; Comparator; Follow-up</td>
<td>There was no significant difference between groups. Weiss Functional Impairment Rating Scale (WFIRS-P); Family Section-Parent</td>
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<td>barbiturate, anticonvulsants, or any other nootropic agents were excluded</td>
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<td><strong>Other:</strong> ADHD presentation: inattentive: 61.8, hyperactive: 7.9, combined: 30.3</td>
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<tr>
<td></td>
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<td>Diagnosis: No Comorbidity: N/A Female: 18.0% Age mean: Pantogon 8.7 (2.1), placebo 8.24 (1.63) Minimum age: 6 Maximum age: 12 Ethnicity: Other info on race or ethnicity: N/A</td>
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<td></td>
<td>Abbasi, 2011</td>
<td><strong>Target:</strong> Children with combined subtype of ADHD and newly diagnosed (drug naive); children were excluded if they had a history or current diagnosis of pervasive developmental disorders, schizophrenia or other psychiatric disorders, any current psychiatric comorbidity that required pharmacotherapy; or any evidence of suicide risk and mental retardation (I.Q&lt;70). In addition, patients were excluded if they had a clinically significant chronic</td>
<td><strong>Intervention:</strong> Acetyl-L-Carnitine doses ranging from 500 to 1,500 mg/day depending on the weight of the child (13.5–30 kg = 0.5 g twice per day; &gt;30–50 kg = 1.0 g twice per day; and &gt;50 kg = 1.5 g twice per day) plus methylphenidate at a dose of 20–30 mg/day depending on weight (20 mg/day for &lt;30 kg and 30 mg/day for &gt;30 kg), treatment for 6 weeks</td>
<td>ADHD-RS-IV, parent rating The difference between groups was not significant (p 0.74). The difference between the two protocols was not significant for the teacher ratings (p 0.63). Decreased appetite The rate was 35% in the intervention and 40% in the control group. Fourteen side effects were observed, all mild to moderate and tolerable. The difference in the frequency of side effects was not significant except for headache and irritability</td>
</tr>
<tr>
<td></td>
<td>ID: N/A</td>
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<td><strong>Comparator:</strong> NA <strong>Follow-up:</strong> 4 months</td>
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**Nutrition, supplements**

Abbasi, 2011

ID: N/A

RCT

Single center

N = 40

Iran

Setting: Other
### Intervention

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<th>Study:</th>
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<tr>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Intervention; Control; Comparator; Follow-up</td>
<td>that were observed more frequently in the methylphenidate plus placebo group.</td>
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<td></td>
<td>medical condition, including organic brain disorder, seizures or current abuse or dependence on drugs in the last 6 months. Additional exclusion criteria were hypertension or hypotension <strong>Other:</strong> ADHD presentation: combined : 100 Diagnosis: Confirmation by specialist DSM-IV-TR Comorbidity: N/A Female: 30 % Age mean: 8.84(2.03) and 8.36(1.53) Minimum age: 7 Maximum age: 13 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Placebo plus methylphenidate at a dose of 20–30 mg/day depending on weight (20 mg/day for &lt;30 kg and 30 mg/day for &gt;30 kg). Methylphenidate was titrated up: week 1: 10 mg/day (5 mg in the morning and 5 mg at midday), week 2: 20 mg/day (10 mg in the morning and 5 mg at midday). Follow-up: 1.5 months</td>
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### Nutrition, supplements

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<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
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<tbody>
<tr>
<td>Akhondzadeh, 2004</td>
<td>Target: Children aged 5-11, newly diagnosed with ADHD combined subtype and had not yet received any stimulant medication prior to enrollment <strong>Other:</strong> ADHD presentation: combined : 100.0 Diagnosis: Confirmation by specialist</td>
<td>Intervention: Zinc sulfate 55 mg/day (15mg elemental zinc) plus methylphenidate 1 mg/kg/day twice daily Control: Other Methylphenidate 1 mg/kg/day twice daily Comparator: NA Follow-up: 1.5 months</td>
<td>Both groups showed significant improvement and the zinc+methylphenidate group improved significantly more than the placebo+methylphenidate group (p&lt;0.001). Decreased appetite No difference between groups. Metallic taste was experienced more in the zinc group (p=0.0001).</td>
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<tr>
<td>ID: RCT Single center N = 44 Iran Setting: Specialty care</td>
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### Appendix C. Evidence Tables

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<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
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<tr>
<td>Nutrition, supplements</td>
<td>Bazar, 2019&lt;sup&gt;143&lt;/sup&gt; Tehran University of Medical Sciences, 2017&lt;sup&gt;147&lt;/sup&gt; ID: IRCT201701131556N94 RCT Single center Iran Setting: Other</td>
<td>Diagnosed by psychiatrist Comorbidity: N/A Female: 40.9 % Age mean: 7.88 (1.67) Minimum age: 5 Maximum age: 11 Ethnicity: Other info on race or ethnicity: Other : Persian: 100%</td>
<td></td>
<td>ADHD-RS-IV total, parent and teacher No significant difference between the two groups on Parent and Teacher Rating Scale scores. Decreased appetite The rate of decreased appetite was 8% in the saffron group compared to 20% in the methylphenidate group. No serious adverse event was observed in any of the patients and all noticed adverse effects were mild to moderate and tolerable, the frequency of side effects was not significantly different between the saffron and MPH groups.</td>
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<td>Target: Children with a subscale scores on Attention-Deficit/Hyperactivity Disorder Rating Scale-IV of at least 1.5 standard deviations above norms for patient's age and gender. Exclusion criteria were psychiatric comorbidities, mental retardation, clinically significant chronic medical condition, systolic blood pressure over 125 mmHg and/or resting pulse below 60 or over 110 beats/min, history of allergy to saffron, psychotropic medication use in the past 2 weeks, females who were likely to go through pregnancy or lactation, use of any medication that might have adverse reactions with saffron, including warfarin, aspirin, other antiplatelet agents, herbal medicines, and patients who were going to</td>
<td>Intervention: Saffron capsules at a dosage of 20–30 mg/d depending on weight (20 mg/d for &lt;30 kg and 30 mg/d for &gt;30 kg) for 6 weeks Control: NA Comparator: MedicationMethylphenidate (ritalin) at a dose of 0.3–1 mg/(kg*d), titrated up during the trial according to the following schedule: 10 mg/d (5 mg in the morning and 5 mg at midday) in week 1; 20 mg/d (10 mg in the morning and 10 mg at midday) in week 2; 20 mg/d for</td>
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<td>Follow-up: 1.5 months</td>
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C-455
### Appendix C. Evidence Tables

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<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
</table>
| Nutrition, supplements | Behdani, 2013 | **Target:** Children and adolescents with ADHD. Those with co-morbid psychiatric diagnoses or serious medical conditions were excluded  
**Other:** Teachers and parents reported outcomes | **Intervention:** Methylphenidate plus Omega 3; final dose of 1mg/kg (maximum dose 60mg/day), in 2 or 3 divided doses, plus Omega-3, two 1000-miligram capsules (containing 240 mg of DHA and 360 mg of EPA), per day in 2 divided doses  
ADHD Rating Scale-IV, parent  
Difference between groups in terms of parent’s and teacher’s ADHD rating scale scores were not significant.  
1/75 dropped out due to side effects of omega 3, including nausea, vomiting, and abdominal pain. | undergo surgery within 36 hours to 14 days  
**Other:**  
ADHD presentation: N/A  
Baseline ADHD-RS-IV Parent version total, mean(SD): Control=34.20(4.69) Intervention=33.56(6.48)  
Baseline ADHD-RS-IV Teacher version total, mean(SD): Control=24.16(8.32) Intervention=23.64(8.16)  
**Diagnosis:** Confirmation by specialist DSM-V  
**Comorbidity:** N/A  
**Female:** 20%  
**Age mean:** Intervention 9.08 (2.23), control 8.28 (1.59)  
**Minimum age:** 6  
**Maximum age:** 17  
**Ethnicity:** Other info on race or ethnicity: N/A |
<table>
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<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilici, 2004</td>
<td>Setting: Specialty care</td>
<td>ADHD presentation: inattentive: 21.7, hyperactive: 37.7, combined: 40.6</td>
<td>Control: Placebo Methylphenidate plus placebo; final dose of 1mg/kg (maximum dose 60mg/day), in 2 or 3 divided doses plus placebo</td>
<td>ADHDS (Attention Deficit Hyperactivity Disorder Scale) change Therapeutic response Intervention patients showed greater improvement than placebo patients (p=.002). Intervention group also showed significantly more improvement in ADHDS-H (p=.01), ADHDS-I (p=.03), and ADHDS-S (p=.03) subscales compared with placebo groups. Therapeutic Significantly more intervention patients than placebo patients reported metallic taste (p = .01). No significant difference in nausea, vomiting, abdominal pain, and diarrhea.</td>
</tr>
<tr>
<td>Nutrition, supplements</td>
<td>Target: Children with ADHD who have no other mental or medical illness Other: Teachers supplied some outcomes ADHD presentation: N/A Diagnosis: Confirmation by specialist DSM-IV by psychiatrists, pediatrician, and psychologist Comorbidity: N/A Female: 20 % Age mean: 9.4 (1.5) Minimum age: 6</td>
<td>Intervention: Zinc sulfate (150 mg/day) for 12 weeks Control: Placebo Placebo (sucrose, 150 mg) for 12 weeks Comparator: NA Follow-up: 3 months</td>
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### Appendix C. Evidence Tables

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<tr>
<td>Chang, 2019&lt;sup&gt;196&lt;/sup&gt; Hospital, China Medical University, National Science Council, 2016&lt;sup&gt;97&lt;/sup&gt; ID: NCT03542643 RCT Single center N = 103 Taiwan Setting: Specialty care</td>
<td><strong>Target</strong>: Children and adolescents with ADHD who were drug naïve or had no medication for the past 6 months. Those with comorbid psychiatric disorders, such as autism spectrum disorder, anxiety disorder, and conduct disorder were excluded <strong>Other</strong>: ADHD symptoms were rated by parents and teachers <strong>ADHD presentation</strong>: N/A <strong>Diagnosis</strong>: Confirmation by specialist DSM V diagnoses were confirmed by a child and adolescent psychiatrist <strong>Comorbidity</strong>: N/A <strong>Female</strong>: 14.1 % <strong>Age mean</strong>: 9.49 (3.05) <strong>Minimum age</strong>: 6 <strong>Maximum age</strong>: 18 <strong>Ethnicity</strong>: % Asian: 100 Other info on race or ethnicity:</td>
<td><strong>Intervention</strong>: Omega 3 eicosapentaenoic acid (EPA) 1.2 g per day for 12 weeks <strong>Control</strong>: Placebo Placebo <strong>Comparator</strong>: NA <strong>Follow-up</strong>: 3 months</td>
<td>SNAP IV total score, parent version There was no difference between groups in changes in parent or teacher reported inattention (p=.072, .066), hyperactivity (p=.075, .766) and ODD (p=.207, .759) subscale scores. Continuous Performance Test (CPT) variability score (measures focused attention). Intervention group had significantly greater decrease from baseline to 12 weeks (p = 0.041).</td>
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## Appendix C. Evidence Tables

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<tr>
<th>Intervention</th>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
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</thead>
<tbody>
<tr>
<td>Nutrition, supplements</td>
<td>Cornu, 2018&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Target: Children and adolescents ages 6-15 with at least hyperactivity-impulsivity symptoms for 6 months or more and/or at least one of six inattention symptoms for six months or more, all with certain symptoms which were present before age 7 and with a functional impairment in 2 or more environments and clinically significant alteration in social, school, or family functioning.</td>
<td>Intervention: Omega 3 dietary supplement, participants aged 6–8 years given eicosatetraenoic acid 336 mg, participants aged 9–11 years eicosatetraenoic acid 504 mg, participants aged 12–15 years eicosatetraenoic acid 672 mg, capsules also contained 100 µg vitamin A, 1.25 µg vitamin D, and 3.5 mg vitamin E, treatment duration was 3 months, during which other hyperactivity treatments and other omega-3 supplements or psychotropic drugs were not allowed</td>
<td>Connors total score No beneficial effect of omega-3 supplement. ADHD-RS-IV No beneficial effect of omega-3 supplement. There was no significant change in reading skills (L'Aloutte) in both groups (p=0.28). Participants experiencing adverse events 15% vs 11% adverse events favoring placebo. 2/80 patients in the DHA–EPA group experienced a severe adverse event (hospitalisation for worsening ADHD symptoms).</td>
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<td>Crippa, 2018&lt;sup&gt;16&lt;/sup&gt;</td>
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<td>Eugenio Medea, 2012&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Target: Children with ADHD who were drug-naïve and had not consumed omega-3/omega-6 supplements during the 3 months prior to the recruitment</td>
<td>Intervention: Omega 3 supplement of 500 mg algal docosahexaenoic acid (DHA) per day for 6 months</td>
<td>Behavior in Child Health Questionnaire Only the intervention group improved. CGI-S</td>
</tr>
</tbody>
</table>

### Notes:
- **Intervention**: Omega 3 dietary supplement, participants aged 6–8 years given eicosatetraenoic acid 336 mg, participants aged 9–11 years eicosatetraenoic acid 504 mg, participants aged 12–15 years eicosatetraenoic acid 672 mg, capsules also contained 100 µg vitamin A, 1.25 µg vitamin D, and 3.5 mg vitamin E, treatment duration was 3 months, during which other hyperactivity treatments and other omega-3 supplements or psychotropic drugs were not allowed.
- **Control**: Placebo. The placebo capsules were indistinguishable from active capsules and were composed of olive oil, the same amount of vitamin A, D, and E, with traces of marine lipid concentrate: EPA (18%), DHA (12%), totaling 4.83 mg, to give the capsules a similar taste.
- **Comparator**: NA
- **Follow-up**: 28 months
### Appendix C. Evidence Tables

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<th>Study:</th>
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<th>Comparison:</th>
<th>Outcome and results</th>
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<tr>
<td>RCT</td>
<td>Fallah, 2018&lt;sup&gt;2&lt;/sup&gt; Shahid Sadoughi University of Medical Sciences, 2016&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Other: ADHD presentation: inattentive: 15.7, hyperactive: 33.3, combined_other: 51</td>
<td>Intervention; Control; Comparator; Follow-up</td>
<td>Placebo treatment consisted of two pearls per day containing 500 mg wheat germ oil. Placebo pill was stabilized with low concentration of Vitamin E Comparator: NA Follow-up: 6 months Difference between groups was not significant (p &gt; 0.05). ADHD-RS-IV (ADHD rating scale IV) Parent Version, total Difference between groups was not significant (p&gt;0.05). Word Reading Accuracy (errors) difference between groups was not significant (p&gt;0.05). Higher impact of symptoms on functioning evaluated by SDQ in DHA group (p=0.045). Participants with adverse events No adverse events in both groups. Over the course of the 6 months, no instances of either major or minor adverse events were reported.</td>
</tr>
<tr>
<td>Nutrition, supplements</td>
<td>Fallah, 2018&lt;sup&gt;2&lt;/sup&gt; Shahid Sadoughi University of Medical Sciences, 2016&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Target: Children with ADHD and refractory epilepsy. Other: ADHD presentation: N/A Diagnosis: Confirmation by specialist DSM-IV</td>
<td>Intervention: Omega-3 (1000 mg of omega 3 fish oil, 180 mg of eicosapentaenoic acid and 120 mg docosahexaenoic acids) 1 capsule per day plus 0.5 mg of risperidone per day and an antiepileptic drug for 3 months Control: Other Risperidone 0.5 mg and an antiepileptic drug alone Comparator: NA Follow-up: 6 months Monthly seizure frequency was lower in intervention group compared to control group (p=0.03). The rate of good response, defined as a 50% decrease in seizures, was higher in the intervention group (p = 0.001). Participants with side effects No significant difference between groups (p 0.50).</td>
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### Intervention

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<tbody>
<tr>
<td><strong>Author, year</strong>; <strong>Multiple publications</strong>; <strong>Trial ID</strong>; <strong>Study design</strong>; <strong>Sites</strong>; <strong>Study size</strong>; <strong>Location</strong> <strong>Setting</strong></td>
<td><strong>Setting</strong>; <strong>Study target</strong>; <strong>ADHD presentation</strong>; <strong>Diagnosis</strong>; <strong>Comorbidity</strong>; <strong>% Female</strong>; <strong>Age mean</strong>; <strong>Minimum age</strong>; <strong>Maximum age</strong>; <strong>Ethnicity</strong></td>
<td><strong>Intervention</strong>; <strong>Control</strong>; <strong>Comparator</strong>; <strong>Follow-up</strong></td>
<td><strong>ADHD-RS-IV</strong> Significant time by treatment interaction on total and inattention subscales indicating beneficial effects of the adjunct. Seven side effects were recorded during the course of the study; no serious adverse event was observed in any of the patients; the most common side effects were abdominal pain (28%), headache (20%), and insomnia (16%) in the L-carnosine group; and abdominal pain (24%) and headache (24%) in the placebo group. The frequency of side effects did not differ significantly between the two groups.</td>
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| Study ID: IRCT201601031556N84 RCT | % White : 100 Other info on race or ethnicity: | | |

| **Nutrition, supplements** | **Target:** Newly diagnosed patients who met criteria of DSM-V, needed to have no previously diagnosed psychiatric comorbidity (except for ODD), or developmental or physiological disorders (such as high blood pressure or seizures), this includes having an IQ over 70, and without receiving any supplemental medication, or having an allergy to L-carnosine or methylphenidate  **Other:**  **ADHD presentation:** combined : 100  **Diagnosis:** No  **Comorbidity:** N/A  **Female:** 16 %  **Age mean:** 9.12 (2.18)  **Minimum age:** 6  **Maximum age:** 17  **Ethnicity:** Other info on race or ethnicity: Other : All patients were reported as persian | **Intervention:** L-carnosine (800mg/d) plus methylphenidate hydrochloride (20 mg/d in 2 divided doses, 30 mg/d in three divided doses) for 8 weeks  **Control:** Other Methylphenidate alone, 0.5-1.5mg./kg, titrated up during the trial according to the following schedule: 10mg/d (two divided doses) for the first week followed by 20mg/d (two divided doses) from the second week till the rest of the trial. Patients who weig  **Comparator:** NA  **Follow-up:** 2 months | |
### Appendix C. Evidence Tables

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<tr>
<th>Study</th>
<th>Population</th>
<th>Comparison</th>
<th>Outcome and results</th>
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<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td><strong>Nutrition, supplements</strong></td>
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</tbody>
</table>
| Ghanizadeh, 2015<sup>106</sup>  
ID: IRCT201311303930N29  
RCT  
Single center  
N = 106  
Iran  
Setting: Specialty care | **Target:** Children with ADHD. Those with serious medical conditions were excluded.  
**Other:** Parents  
**ADHD presentation:**  
inattentive, other: Mean inattentiveness score at baseline = 15.75 on ADHD Checklist  
**Diagnosis:** Confirmation by specialist  
DSM-IV diagnostic criteria supported by KSADS  
**Comorbidity:** N/A  
**Female:** 26.4%  
**Age mean:** 8.45 (2.1)  
**Minimum age:** 5  
**Maximum age:** 14  
**Ethnicity:** Other info on race or ethnicity: Other: 100% Persian | **Intervention:** Methylphenidate (mean dose 12.7(5.4) mg/day) plus dietary recommendations. Parents received a lists of foods which were recommended (diary, homemade fruit juices, vegetables, low-fat meat) and another list of the foods which were recommended to be eaten as less as possible. Parents were encouraged to provide their children with three regular meals per day.  
**Control:** Other  
Methylphenidate alone, mean dose 11.9(4.6) mg/day.  
**Comparator:**  
**Follow-up:** 1 month | ADHD Checklist, Hyperactivity / Impulsivity Score  
No significant difference between groups in the mean change of hyperactivity/impulsivity and inattentiveness scores. |
| Gustafsson, 2010<sup>107</sup>  
Hela Pharma AB, 2004<sup>108</sup>  
ID: EudraCT No. 2004-003853-13  
RCT  
Multicenter  
N = 92  
Sweden  
Setting: Specialty care | **Target:** ADHD patients with no medical conditions requiring intervention and no neuro or psyc comorbidity.  
**Other:** Parents and teachers provided outcomes  
**ADHD presentation:** N/A  
**Diagnosis:** Confirmation by specialist  
DSM-IV | **Intervention:** Omega 3, one eicosapentaenoic acid (EPA) capsule PlusEPA contained 500 mg EPA + 2.7 mg DHA and 10 mg Vitamin E mixed tocopheroles, 1 capsule per day for 15 weeks  
**Control:** Placebo  
Placebo was a mixture of rape seed oil and medium-chain triglycerides contained in a capsule identical to the one used for PlusEPA containing | Conners Rating Parent rating scale total  
No significant difference between groups (p > .05).  
There were only mild adverse events observed, most of them classified as not related or unlikely to have been related to the drug. Events possibly related to drug treatment, such as abdominal symptoms and nose bleeding did not differ between groups. |
### Interventions

<table>
<thead>
<tr>
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<th>Population:</th>
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<th>Outcome and results</th>
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<tbody>
<tr>
<td><strong>Nutrition, supplements</strong></td>
<td>Comorbidity: N/A</td>
<td>Intervention:</td>
<td>&lt;10% of the PlusEPA content of omega-3 LCPUFA</td>
</tr>
<tr>
<td>Hariri, 2012</td>
<td>Female: % not provided</td>
<td>Control; Comparator; Follow-up</td>
<td>Comparator: NA Follow-up: 3.75 months</td>
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<td>ID: N/A</td>
<td>Age mean: NA</td>
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<td>Minimum age: 7 Maximum age: 12</td>
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<td>Setting: Other</td>
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</table>

**Target:** ADHD patients on Ritalin with Conners' Abbreviated Questionnaires (ASQ-P) scores for hyperactivity greater than 14. Exclusion criteria were infectious diseases, diabetes, hyperthyroidism, convulsion, epilepsy and consumption of n-3 fatty acids supplements. **Other:** Parents provided outcomes **ADHD presentation:** N/A **Diagnosis:** Confirmation by specialist **Comorbidity:** N/A **Female:** 38% **Age mean:** 7.90 (1.5) **Minimum age:** 6

**Intervention:** Omega 3 plus ritalin (any dose); soft gel capsules of n-3 fatty acids with a total daily dose of 900mg n-3 fatty acids (635mg eicosapentaenoic acid, 165mg docosahexaenoic acid and 100mg other n-3 fatty acids), for 8 weeks **Control:** Other Ritalin (any dose) plus placebo (olive oil capsules) **Comparator:** NA **Follow-up:** 2 months

ASQ-P (Conners' Abbreviated Questionnaires) Intervention group improved more than control group (p < .001).

2 intervention group patients withdrew because of steatorrhoea.
### Intervention

<table>
<thead>
<tr>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemamy, 2021&lt;sup&gt;120&lt;/sup&gt; Hemamy, 2020&lt;sup&gt;161&lt;/sup&gt; ID: N/A RCT Single center N = 66 Iran Setting: Mixed</td>
<td>Target: Children with serum level of 25-hydroxyvitamin D3 less than 30 ng/dL, a diagnosis of ADHD based on the presence of at least 6 out of 9 cases of inattention and also at least 6 out of 9 cases of hyperactivity based on DSM IV and serum magnesium levels less than 2.3 mg/dL Other: ADHD presentation: N/A Diagnosis: Confirmation by specialist DSM-IV diagnosed by unknown source Comorbidity: N/A Female: 30.3 % Age mean: 9.06 (1.76) Minimum age: 6 Maximum age: 12 Ethnicity: % White : 100 Other info on race or ethnicity:</td>
<td>Intervention: Vitamin D (50,000 IU/week with lunch meal) and an oral tablet of magnesium (6 mg/kg/day with lunch meal) for a duration of 8-weeks Control: Placebo Participants in the control group received a placebo, similar in appearance, color, and taste to the two supplements (edible paraffin oil as a placebo for vitamin D, microcrystalline cellulose, and stearic acid as a placebo for magnesium) Comparator: NA Follow-up: 2 months</td>
<td>Strength and difficulties questionnaire (SDQ), total difficulties The intervention group showed a significant reduction in total difficulties compared to control group (p = 0.001). No adverse effects of Vitamin D and magnesium supplementation were reported at the end of this study.</td>
</tr>
</tbody>
</table>
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
</table>
| Nutrition, supplements | Hirayama, 2014\(^\text{123}\) ID: RCT Single center N = 36 Japan Setting: Community | **Target:** Children aged 4-14 years old  
**Other:**  
ADHD presentation: N/A  
Diagnosis: Confirmation by specialist diagnosed by child's own psychiatrist  
Comorbidity: N/A  
Female: 5.6%  
Age mean: 9.1 (1.7) for intervention group; 8.7 (3.0) for placebo group  
Minimum age:  
Maximum age:  
Ethnicity: Other info on race or ethnicity: N/A | **Intervention:** Phosphatidylserine (soy-derived) 100mg chewable tablet, 2 chews per day  
**Control:** Placebo Identical-appearing placebo chewable tablets, 2 chews per day  
**Comparator:** NA  
**Follow-up:** 2 months | Inattention Go/No-Go task  
No difference between groups (p 0.29).  
DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) criteria score ADHD symptoms were statistically significantly lower in the phosphatidylserine treated group compared to the placebo group (p<0.01).  
Working memory: phosphatidylserine 0.3, placebo -0.7 (n.s.). |
| Nutrition, supplements | Johnson, 2009\(^\text{13}\) ID: N/A RCT Multicenter N = 75 Sweden Setting: Specialty care | **Target:** Children and adolescents with ADHD, exclusion criteria were autism, psychosis, bipolar disorder, mental retardation, uncontrolled seizure disorder, hyper- or hypothyroidism, significant other medical conditions, weight below 20 kg, alcohol or drug abuse, or the use of any psychoactive drugs or omega 3 preparations in the past 3 months  
**Other:** Parents reported some outcomes | **Intervention:** Omega 3/6 in a dose of three capsules twice daily, corresponding to a daily dose of 558 mg eicosapentaenoic acid, 174 mg docosahexaenoic acid (both are omega-3 fatty acids), 60 mg gamma linoleic acid (an omega 6 fatty acid), and 10.8 mg Vitamin E for 3 months  
**Control:** Placebo Identical capsules containing olive oil  
**Comparator:** NA  
**Follow-up:** CGI (Clinical Global Impression) scale change  
Intervention group improved more than placebo group (p 0.02).  
ADHD-RS-IV (ADHD Rating Scale IV), parent reported change  
Number responding (defined as 25% improvement in ADHD symptoms on ADHD RS IV)  
Difference in mean improvement at follow-up not significant. Higher percentage of intervention group classified as responders.  
11 (3 active, 8 placebo) withdrawals during Study Period (7 were unmotivated to continue... |
### Intervention

<table>
<thead>
<tr>
<th>Study:</th>
<th>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>ADHD presentation:</strong> inattentive: 53, combined: 47</td>
<td><strong>Comparison:</strong> Intervention; Control; Comparator; Follow-up</td>
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<td></td>
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<td><strong>Diagnosis:</strong> Confirmation by specialist DSM-RS-IV</td>
<td>Follow-up: 3 months</td>
<td>or had problems swallowing the capsules [1 active, 6 placebo], 3 had side effects in the form of dyspepsia, vomiting, or diarrhea [2 active, 1 placebo]), and 1 patient (placebo) due to markedly increased irritability.</td>
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<td><strong>Comorbidity:</strong> N/A</td>
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<td></td>
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<td><strong>Female:</strong> 15%</td>
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<td><strong>Age mean:</strong> Intervention 11.8 (2.14), control 12.2 (2.19)</td>
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<td><strong>Minimum age:</strong> 8</td>
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<td><strong>Maximum age:</strong> 18</td>
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<td><strong>Ethnicity:</strong> Other info on race or ethnicity: N/A</td>
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### Comparison

| Intervention: Capsules containing a blend of ingredients comprising all vitamins and known essential minerals, plus amino acids and antioxidants, total of 9 to 12 capsules per day accumulated to doses above the Recommended Dietary Allowance but below the Upper Tolerable Intake Level, 8 weeks of treatment | CGI-S severity reduced 56% of micronutrient group vs 22% of placebo group had illness severity reduced by at least 1 category (p < .001). |
| Control: Placebo Visually identical placebo capsules containing cellulose filler and 0.1 mg of riboflavin per capsule to mimic the color of urine as when supplemented with B-vitamins | Inattention CASI-5 (Child and Adolescent Symptom Inventory-5), parent-rated Between-group difference was not significant. |
| Control: Placebo Visually identical placebo capsules containing cellulose filler and 0.1 mg of riboflavin per capsule to mimic the color of urine as when supplemented with B-vitamins | Impairment scale CASI teacher rating No statistically significant difference between groups (p=0.22). |
| Height (cm) | Intervention patients gained more height (p 0.002). | Participants with any adverse event |

### Other info on race or ethnicity: N/A

### Follow-up

- CGI-S severity reduced 56% of micronutrient group vs 22% of placebo group had illness severity reduced by at least 1 category (p < .001).
- Inattention CASI-5 (Child and Adolescent Symptom Inventory-5), parent-rated Between-group difference was not significant.
- Impairment scale CASI teacher rating No statistically significant difference between groups (p=0.22).
- Height (cm) Intervention patients gained more height (p 0.002).
- Participants with any adverse event
## Evidence Tables

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<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
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<tbody>
<tr>
<td>Nutrition, supplements</td>
<td>Katz, 2010333 Etz-HaChayim Clinic (Israel), 2007339 ID: ISRCTN10628149 RCT Single center N = 120 Israel Setting: Specialty care</td>
<td>Minimum age: 6  Maximum age: 12  Ethnicity: % Black/African American : 3  % Asian : 3  % White : 88  Other info on race or ethnicity: Comparator: NA  Follow-up: 2 months</td>
<td>Comparator: NA  Follow-up: 4 months</td>
<td>Rate was 32% in the intervention and 45% in the placebo group.  No between-group differences for treatment-emergent adverse events were detected.</td>
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<td>Test of Variables of Attention (TOVA), composite score  Improvement for overall TOVA (p &lt; .001) as well as omission (p = .016), commission (p = .026), response time (p &lt; .001) and variability (p &lt; .001) scales was greater for intervention group than placebo group.  Decreased appetite  Decreased appetite reported by 2 people in the control group and only 1 in the intervention group.  No serious adverse events were reported, and the rate of even mild adverse events among intervention patients was less than that of placebo. None of the adverse events were more frequent in the intervention than in the placebo group.</td>
</tr>
</tbody>
</table>
### Appendix C. Evidence Tables

<table>
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<tr>
<th>Intervention</th>
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<tbody>
<tr>
<td>Nutrition, supplements</td>
<td>Khaksarian, 2021[^556] Khoram-Abad University of Medical Sciences, 2020[^151] ID: IRCT20190602043790N 2</td>
<td>Target: Children and adolescents with ADHD Other: Parents and teachers provided outcomes ADHD presentation: N/A Diagnosis: Confirmation by specialist DSM V by Child Psychiatrist Comorbidity: N/A Female: % N/A Age mean: Methylphenidate group: 11.03 (2.31) and for Methylphenidate and Saffron group: 10.57 (2.56) Minimum age: 6 Maximum age: 16 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Intervention: Saffron plus methylphenidate: 20 mg/d (for &lt;30 kg and 30 mg/d for &gt; 30 kg, 10 mg for morning, midday, and evening equally) plus 20-30 mg/d saffron capsules according to the BMI (20 and 30 mg/d for &lt;30kg and &gt; 30kg), treatment over 8 week period Control: Other Methylphenidate alone: In week one, initial dose of 10mg/d (5mg for morning and midday equally); week 2 it was 20 mg/d (10 mg for morning and midday equally), and 20 mg/d (for &lt;30 kg and 30 mg/d for &gt; 30 kg, 10 mg for morning, midday, and evening. Comparator: NA</td>
<td>ADHD-IV (Attention-Deficit/Hyperactivity Disorder Rating Scale-IV) scores, total, parent report Intervention group improved more on all ADHD IV parent and teacher reported scales (p &lt; .001). No significant difference between groups in side effects.</td>
</tr>
<tr>
<td>Nutrition, supplements</td>
<td>Khoshbakht, 2021[^358] Nutrition and Food security research center, 2018[^152] ID: IRCT20130223012571N 6</td>
<td>Target: Treatment naive children with ADHD Other: Parents and teachers provided outcomes ADHD presentation: N/A Diagnosis: Confirmation by specialist DSM-IV by psychiatrist Comorbidity: N/A Female: 0 %</td>
<td>Intervention: Dietary Approaches to Stop Hypertension (DASH) diet for 3 months (12 weeks), diet contains higher amounts of whole grains, fruits, vegetables, low-fat dairy products, nuts, and beans, as well as low amounts of saturated fats, cholesterol, refined grains, sweets, and red meat Control: Attention-matched control</td>
<td>SNAP-IV, combined, parent report Intervention group improved more on both parent reported SNAP IV (p = 0.007) and teacher reported SNAP IV (p = 0.03). SDQ-P (strengths and difficulties questionnaire, parent reported) total score After adjustment for confounders, parent, teacher, and child reported SDQ hyperactivity, emotional symptoms, and total scores significantly improved in the DASH group compared with the control group (p &lt; 0.05).</td>
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</table>
### Intervention

<table>
<thead>
<tr>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
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<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iran Setting: Specialty care</td>
<td>Age mean: N/A Minimum age: 6 Maximum age: 12 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Control diet was similar to the usual diet of Iranian children, allowing for refined grains, full-fat dairy, and meats; it had lower amounts of fruits and vegetables, simple sugars were also allowed Comparator: NA Follow-up: 3 months</td>
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</table>

### Nutrition, supplements

| Target: Confirmed DSM-IV-ADHD diagnosis. No girls who reached menarche; no history or current diagnosis of any serious systemic or neurological condition; no pervasive developmental disorder or nonverbal learning disability; no psychotic disorder; no current psychiatric comorbidity that required psychiatric pharmacotherapy; no history of alcohol or substance abuse. Other: Parents, teachers reported outcomes ADHD presentation: inattentive: 32, hyperactive: 2, combined: 66 Diagnosis: Confirmation by specialist DSM-IV ADHD diagnosis confirmed Comorbidity: N/A Female: 29.3 % Age mean: 9.2 (1.9) | Intervention: Omega 3, 4 capsules (2 capsules twice a day for 15-weeks) of Phosphatidylserine-Omega3 daily; daily dosage provided 300 mg of Phosphatidylserine, 120 mg of Eicosapentaenoic acid + Docosahexaenoic acid (Eicosapentaenoic acid/Docosahexaenoic acid ratio of 2:1) Control: Placebo Four capsules (2 capsules twice a day for 15-weeks) of cellulose as placebo. Comparator: NA Follow-up: 4 months | CTRS/L (Conners’ Teacher Rating Scale Revised Long-Hebrew Version) No significant difference between the intervention and control group (p=0.898). Strengths and Difficulties Questionnaire (SDQ) No significant difference between the intervention and control group. BMI change following 15 weeks of treatment P=0.301 Participants with adverse events No significant differences were detected between the placebo and the intervention group in the incidence or number of adverse events recorded (p = 0.848 and p = 0.982, respectively). |
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Comparison</th>
<th>Outcome and results</th>
</tr>
</thead>
</table>
| Mohammadi, 2012<sup>22s</sup>  
ID: N/A  
RCT  
Single center  
N = 50  
Iran  
Setting: N/A | **Target:** Children aged 7-12 years diagnosed with ADHD (combined form) by a child and adolescent psychologist and did not use any confounding drugs or supplements were recruited into the initial stage of this study. Children with history of major prenatal complications such as prematurity, low birth weight (reported by parents), any past or present psychosis, comorbid Tourette syndrome, celiac, phenylketonuria, autism, or other persistent developmental disorders were excluded. Furthermore, narcotics use was among our exclusion criteria.  
**Other:**  
ADHD presentation: N/A  
Diagnosis: Confirmation by specialist  
DSM-IV  
Comorbidity: N/A  
Female: 28 %  
Age mean: | **Intervention:** Melatonin (3 or 6mg) combined with methylphenidate (Ritalin) (1mg/kg) for 8 weeks  
**Control:** Placebo  
Placebo combined with methylphenidate (Ritalin) (1mg/kg) for 8 weeks  
**Comparator:** NA  
**Follow-up:** 2 months | ADHD-RS (ADHD Rating Scale)  
The mean attention deficiency scores of two groups based on ADHD rating scale at 8 weeks after the treatment showed no statistically significant difference (p=0.974; mean for melatonin was 11.11 and mean for placebo was 11.29).  
SDSC (Sleep Disturbance Scale for Children):  
The mean sleep latency and total sleep disturbance scores were reduced in melatonin group, while the scores increased in the placebo group (p≥0.05).  
Loss of appetite  
The rates were 70% in the melatonin and 61% in the placebo group.  
Mean scores of side effects based on the stimulant drug side effects questionnaire were 11.35 (SD 8.81) in melatonin group and 10.16 (SD 9.05) in placebo group (p=0.686). |
|    | Minimum age: 6  
Maximum age: 13  
Ethnicity: Other info on race or ethnicity: N/A |    |    |

**Nutrition, supplements**

Mohammadi, 2012<sup>22s</sup>  
ID: N/A  
RCT  
Single center  
N = 50  
Iran  
Setting: N/A
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrition, supplements</td>
<td>Mohammadzadeh, 2019&lt;sup&gt;20&lt;/sup&gt; Kurdistan University of Medical Sciences, 2017&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Target: Children with ADHD. Those who had used omega-3 in the last 6 months were excluded.</td>
<td>Intervention: Omega-3 eicosapentaenoic acid (EPA) capsules (180 mg) and docosahexaenoic acid (120 mg) plus optimal dose of methylphenidate up to 30 mg, supplement and medication taken twice a day for 8 weeks</td>
<td>ADHD-RS-IV (ADHD Rating Scale-IV parents), total score. There was no statistically significant difference between groups (p=0.75). There were also no significant intergroup differences between the Inattention (p=0.48) and hyperactivity/impulsivity (p=0.80) subscale scores on the Parents ADHD Rating Scale. Anorexia: No difference between groups (p&gt;0.05). There was no statistically significant difference in incidences of nausea, vomiting, diarrhea, stomach ache, dry mouth, drowsiness, insomnia, anxiety, restlessness, irritability, or seizure between the groups.</td>
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<tr>
<td></td>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Control: Other Placebo plus methylphenidate for 8 weeks Comparator: NA Follow-up: 2 months</td>
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<tr>
<td>Intervention Study</td>
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<td>Comparison</td>
<td>Outcome and results</td>
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<tr>
<td>Author, year;</td>
<td>Setting;</td>
<td>Intervention;</td>
<td>Hyperactivity scale Strengths and Difficulties Questionnaire (SDQ), parent-report</td>
<td></td>
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<tr>
<td>Multiple publications;</td>
<td>Study target;</td>
<td>Control;</td>
<td>Intervention group improved more on hyperactivity scale (p = 0.04). No significant difference in improvement on emotional symptoms (p= .88), conduct problems (p = .55), peer problems (p = .66), or prosocial behavior (p = .62). Regarding teacher report SD</td>
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<tr>
<td>Trial ID;</td>
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<td>Comparator;</td>
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<td>Diagnosis;</td>
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<td>Location</td>
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<td>Setting</td>
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<td>Ethnicity</td>
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<thead>
<tr>
<th>Nutrition, supplements</th>
<th>Target</th>
<th>Intervention</th>
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</thead>
<tbody>
<tr>
<td>Mostajeran, 2020[41]</td>
<td>Children with ADHD on medication. Exclusion criteria were having any significant physical impairment, history of a pervasive developmental disorder, schizophrenia, bipolar disorder, severe depressive episode, epilepsy or heart disease.</td>
<td>Ma'aljobon powder for two months, 25 g in 100 cc water, once daily after breakfast, participants continued their previous standard conventional ADHD medications</td>
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<tr>
<td>Mostajeran, 2018[15]</td>
<td>Other: Parents provided some outcomes</td>
<td>Control: TAU</td>
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<tr>
<td>ID:</td>
<td>ADHD presentation: N/A</td>
<td>Children continued their previous standard conventional ADHD medications.</td>
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<tr>
<td>IRCT20180303038930N1</td>
<td>Diagnosis: Confirmation by specialist</td>
<td>Comparator: NA</td>
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<tr>
<td>RCT</td>
<td>Pediatrician by DSM-V</td>
<td>Follow-up: 2 months</td>
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<tr>
<td>Single center N = 64</td>
<td>Comorbidity: N/A</td>
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<tr>
<td>Iran</td>
<td>Female: 12.5 %</td>
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<tr>
<td>Setting: Specialty care</td>
<td>Age mean: 9.38 (2.18)</td>
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<td>Minimum age: 6</td>
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<td>Maximum age: 13</td>
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<td>Ethnicity: Other info on race or ethnicity: N/A</td>
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<td>Intervention</td>
<td>Study: Author, year; Multiple publications; Title ID; Study design; Sites; Study size; Location Setting</td>
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<tr>
<td>Nutrition, supplements</td>
<td>Pelsser, 2011[160] Wageningen University (The Netherlands), 2008[113] ID: ISRCTN76063113 Crossover trial Unclear/Not reported N = 100 Netherlands Setting: Mixed</td>
<td>Target: Children with ADHD. Exclusion criteria were children receiving drugs or behavioural therapy for ADHD, children already following a diet, or family circumstances that were likely to prevent completion of the study. Other: Parents &amp; teachers supplied some outcomes. ADHD presentation: inattentive: 6, hyperactive: 9, combined: 85 Diagnosis: Confirmation by specialist DSM-IV Comorbidity: N/A Female: 14% Age mean: 6.9 (1.3) Minimum age: 4 Maximum age: 8 Ethnicity: Other info on race or ethnicity:</td>
<td>Intervention: Individually designed restricted elimination diet, consisting of the few- foods diet (ie, rice, meat, vegetables, pears, and water) complemented with specific foods such as potatoes, fruits, and wheat for five weeks Control: Attention-matched control Received healthy food advice according to the guidelines of the Dutch Nutrition Centre. Parents continued to keep an extended diary until the end of the trial. Comparator: NA Follow-up: 3 months</td>
</tr>
<tr>
<td>Nutrition, supplements</td>
<td>Pongpitakdamrong, 2021[166] ID: N/A RCT Single center N = 52 Thailand Setting: Specialty care</td>
<td>Target: Children and adolescents with ADHD and iron deficiency treated with a steady dosage of methylphenidate for at least 1 month Other: Parents &amp; teachers supplied outcomes ADHD presentation: inattentive: 21.2, hyperactive: 1.9, combined: 76.9</td>
<td>Intervention: Iron in the form of ferrous fumarate, 200mg capsules of ferrous fumarate, participants who weighed less than or equal to 30kg received 1 capsule of ferrous fumarate per day for 12 weeks, participants who weighed &gt; 30kg received 2 capsules per day (2–4 mg of elemental iron/kg/d) for 12 months</td>
</tr>
<tr>
<td>Intervention</td>
<td>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
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</tbody>
</table>
| Nutrition, supplements | Rafeiy-Torghabeh, 2021\textsuperscript{177}  
Roozbeh Psychiatric Hospital, 2018\textsuperscript{192}  
ID: IRCT20090117001556N 115  
RCT  
Single center  
N = 66  
Iran  
Setting: Specialty care | Diagnosis: Confirmation by specialist DSM-V  
Comorbidity: Other : Iron deficiency  
Female: 13.5 %  
Age mean: 9.6 (2.0)  
Minimum age: 6  
Maximum age: 18  
Ethnicity: % Asian : 100  
Other info on race or ethnicity: | weeks, methylphenidate continued as already prescribed  
Control: Placebo  
Placebo that tasted and looked similar to the ferrous fumarate capsules, participants who weighed less than or equal to 30kg received 1 capsule of placebo per day for 12 weeks, whereas participants who weighed >30kg received 2 capsules per day for 12 wee  
Comparator: NA  
Follow-up: 3 months | ADHD-RS-IV parent version  
Significant of intervention on parent ADHD-RS (total p 0.015; inattention p 0.032; hyperactivity/impulsivity p 0.036). No significant differences on teacher version of ADHD-RS (total p 0.401; inattention p 0.507; hyperactivity/impulsivity p 0.466).  
Reduced appetite  
No group difference in decreased appetite ( p = 0.76).  
The frequencies of adverse events in the groups were similar. |
| | Target: Children 6 to 12 with ADHD per DSM 5; excluded if any psychiatric comorbidity except oppositional defiant disorder (ODD)  
Other: Guardians (usually parents) and teachers  
ADHD presentation: N/A  
Diagnosis: Confirmation by specialist DSM 5  
Comorbidity: N/A  
Female: 28.3 %  
Age mean: 8.7 (1.7)  
Minimum age: 6  
Maximum age: 12  
Ethnicity: | Intervention: Resveratrol 250mg two times a day in addition to methylphenidate 20mg/day for 8 weeks, participants weighing more than 30kg received methylphenidate 30mg/day  
Control: Placebo  
Placebo plus methylphenidate 20mg/day for 8 weeks, participants weighing more than 30kg received methylphenidate 30mg/day  
Comparator: NA  
Follow-up: 2 months |
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td></td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Intervention; Control; Comparator; Follow-up</td>
<td></td>
</tr>
<tr>
<td>Rucklidge, 2018&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>Other info on race or ethnicity: N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ID: ACTRN12613000896774 RCT</td>
<td></td>
<td></td>
<td></td>
<td>SDQ - Conduct problems, teacher</td>
</tr>
<tr>
<td>Single center</td>
<td></td>
<td></td>
<td></td>
<td>No statistically significant difference between groups (p=0.055).</td>
</tr>
<tr>
<td>N = 93</td>
<td></td>
<td></td>
<td></td>
<td>CGI-I (Clinical Global Impressions- Improvement)</td>
</tr>
<tr>
<td>New Zealand</td>
<td></td>
<td></td>
<td></td>
<td>CGI-I improved or very much improved Intervention group had greater improvement in mean score (p=0.029) and had a higher percentage showing improvement (p&lt;0.05).</td>
</tr>
<tr>
<td>Setting: Specialty care</td>
<td></td>
<td></td>
<td></td>
<td>ADHD-RS-IV, clinician report</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No between-group differences (p=0.415).</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intervention group improved more on Teacher BRIEF–Behavioural Regulation Index (p 0.05) and BRIEF emotional control scale (p 0.01).</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>No difference in Child Mania Rating Scale - Parent report (p 0.10). No difference in Strengths and Difficulties Questionnaire (SDQ) total problem score as reported by parents (p 0.062) or teachers (p 0.064). Intervention group scored better on SDQ conduct problems scale in the parent (p 0.015) but not teacher report (p 0.055).</td>
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<tr>
<td></td>
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<td></td>
<td>Weight (kg) change from baseline</td>
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<tr>
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<td></td>
<td>The change in weight was not statistically significant (p=0.608).</td>
</tr>
</tbody>
</table>

**Nutrition, supplements**

Target: Medication-free children with ADHD aged 7–12 years

Other: Parents and teachers provided some outcome data

ADHD presentation: inattentive : 28.0, hyperactive : 5.4, combined : 66.6

Diagnosis: Confirmation by specialist

DSM IV plus Kiddie Schedule for Affective Disorders and Schizophrenia Lifetime Version (KSADS-PL) plus parent and teacher Conners Rating Scales (CRS-R:L; T score > 65 on parent form and >60 on teacher form)

Comorbidity: N/A

Female: 23.7 %

Age mean: 9.75 (1.5)

Minimum age: 7

Maximum age: 12

Ethnicity: % Native Hawaiian or Pacific Islander : 21.5%, Other info : Maori or Tongan

% White : 78.5%

Intervention: Multivitamin containing a comprehensive range of micronutrients (13 vitamins, 17 minerals, and four amino acids), 15 capsules a day for 10 weeks

Control: Placebo

Comparator: NA

Follow-up: 2.5 months
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
</table>
| Salehi, 2010[^1]    | Target: Children with ADHD; comorbid psychiatric diagnosis that would contraindicate GXR treatment or confound efficacy or safety assessments, were excluded  
Other: Parents & teachers provided outcomes  
ADHD presentation: combined : 100  
Diagnosis: Confirmation by specialist Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime diagnostic interview  
Comorbidity: N/A  
Female: 22 %  
Age mean:  
Ginkgo 9.12 (1.61), methylphenidate 9.61 (2.26)  
Minimum age: 6  
Maximum age: 14  
Ethnicity:  
Other info on race or ethnicity: Other : Persian | Intervention: Gynkgo biloba dose of 80–120 mg/day depending on weight, 40 mg twice per day for < 30 kg and 120 mg three times per day for > 30kg, treatment for 6 weeks  
Control: NA  
Comparator: MedicationMethylphenidate 20–30 mg/day depending on weight (20 mg/day for < 30kg and 30 mg/day for > 30 kg) for 6 weeks; titrated in week 1: 10 mg/day (5 mg in the morning and 5 mg at midday), week 2: 20 mg/day (10 mg in the morning and 10 mg at midday) and week 3: Follow-up: 1.5 months | Across a large number of assessed outcomes, micronutrients had minimal side effects. |

[^1]: Nutrition, supplements

[^2]: Roozbeh Psychiatric Hospital, 2009[^6]  
ID: IRCT138711151556N6  
RCT  
Single center  
N = 50  
Iran  
Setting: Specialty care
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrition, supplements</td>
<td>Salehi, 2016&lt;sup&gt;59s&lt;/sup&gt;</td>
<td>Target: Children with ADHD with no history of psychiatric drug usage and no history of other psychiatric disorders, no limitation or sensitivity for the use of zinc sulfate and omega-3, and absence of mental retardation.</td>
<td>Intervention: Omega 3, eicosapentaenoic fatty acid (100 mg for children &lt;25 kg, 200 mg for 26–35 kg, and 400 mg for children &gt;35 kg/day) with daily methylphenidate, prescribed based on child’s weight (10 mg daily for children under 20 kg; 10 mg, twice a day for children over 20 kg) for 8 weeks. Control: Other. Methylphenidate plus placebo (whitish color capsule containing sugar, as the same shape and volume of omega-3 capsules). Comparator: Nutrition, supplements Zinc sulfate capsule (containing 22 mg zinc sulfate) administered with daily MPH.</td>
<td>Conners’ Parent and Teacher Rating Scales average No difference among groups (p=0.581).</td>
</tr>
<tr>
<td>Nutrition, supplements</td>
<td>Tan, 2016&lt;sup&gt;66&lt;/sup&gt;</td>
<td>Target: Children with ADHD. Those with syndromes, inborn errors of metabolism, structural brain lesions, co-existing chronic liver disease and those on concurrent anticoagulants or antiplatelet drugs were excluded. Children who were unable to</td>
<td>Intervention: Tocotrienol-rich fractions (TRF), a potent antioxidant from the natural Vitamin E family. Two softgel capsules containing 100 mg TRF per day for 6 months. Control: Placebo</td>
<td>Vanderbilt ADHD Parent Rating Scale, Total No significant group differences in parent or teacher rating at 6 months. Number of adverse events No statistical difference in the number of adverse events per group.</td>
</tr>
<tr>
<td></td>
<td>ID: NCT01855984 RCT Multicenter N = 146 Other</td>
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</tbody>
</table>
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Setting: Specialty care</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study:</td>
<td>swallow the capsule were also excluded. <strong>Other:</strong> Parents and teachers provided outcomes. <strong>ADHD presentation:</strong> inattentive: 10.3, hyperactive: 0, combined: 89.7 <strong>Diagnosis:</strong> Confirmation by specialist DSM-IV by physicians <strong>Comorbidity:</strong> N/A <strong>Female:</strong> 15% <strong>Age mean:</strong> 9.4 (1.8) <strong>Minimum age:</strong> 6 <strong>Maximum age:</strong> 12 <strong>Ethnicity:</strong> % Asian: 100, Other: Malaysian Other info on race or ethnicity:</td>
<td><strong>Intervention:</strong> Pycnogenol (extract from the bark of the French maritime pine, consisting of phenolic acids, catechin, taxifolin and procyanidins), 1 mg/kg/day for 4 weeks <strong>Control:</strong> Placebo <strong>Comparator:</strong> NA <strong>Follow-up:</strong> 1 month</td>
<td>Two placebo capsules per day for 6 months. <strong>Comparator:</strong> NA <strong>Follow-up:</strong> 6 months</td>
<td></td>
</tr>
</tbody>
</table>

### Nutrition, supplements

| Trebaticka, 2006\(^5\) | Target: Children with ADHD with at least 6 months of symptoms, general disposition as restless, inattentive, distractible and disorganized; patients with acute inflammatory diseases, renal and cardiovascular disorders, diabetics, and co-morbid psychiatric conditions were excluded **Other:** Parents and teachers provided some outcomes **ADHD presentation:** N/A | **Intervention:** CAP (Child Attention Problems), teacher Intervention group scores improved significantly compared to placebo on hyperactivity (p=0.044) and inattention (p=0.0067) scores. CPRS (Conner’s Parent Rating Scale) No significant difference in reduction between intervention and placebo. |
# Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrition supplements</td>
<td>Tzang, 2016(^{177}) Mackay Memorial Hospital, 2012(^{871})</td>
<td>Diagnosis: No ADHD according to ICD-10 with following diagnoses: Hyperkinetic Disorder, Hyperkinetic Conduct Disorder, Attention Deficit without Hyperactivity&lt;br&gt; Comorbidity: N/A&lt;br&gt; Female: 18 %&lt;br&gt; Age mean: mean 9.5&lt;br&gt; Minimum age: 6&lt;br&gt; Maximum age: 14&lt;br&gt; Ethnicity: Other info on race or ethnicity: N/A : Slovakian</td>
<td>Comparison: Intervention; Control; Comparator; Follow-up</td>
<td>SNAP ODD: Swanson, Nolan, Pelham oppositional defiance disorder scores&lt;br&gt;The sarcosine group had lower mean values on all three subscales compared to placebo.&lt;br&gt;Decreased appetite&lt;br&gt;The difference between groups was not significant (p=0.677).&lt;br&gt;Rates of adverse events</td>
</tr>
<tr>
<td></td>
<td>ID: NCT01725737 RCT Single center N = 116 Taiwan Setting: Primary Care</td>
<td>Target: Children aged between 6–12 years, with a clinical diagnosis of ADHD as defined by DSM-IV; children were deemed healthy by means of medical history, physical examination, vital-sign measurements, and laboratory assessments; children had to be naïve to all treatments for ADHD&lt;br&gt;Other:&lt;br&gt;ADHD presentation: inattentive : 34.5,hyperactive_other : Treatment: 14.0%; Placebo 15.1%,combined : 65.5,N/A : ODD comorbidity in treatment group: 72.4% and placebo: 74.1%</td>
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</table>
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<th>Study:</th>
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<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van der Heijden, 2007</td>
<td>Author, year; Multiple publications;</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Intervention; Control; Comparator; Follow-up</td>
<td>CBCL (Child Behavior Checklist) The melatonin group had significantly smaller improvements compared to the placebo group. TACQOL-P (TNO-AZL Questionnaire for Children's Health-Related Quality of Life, Parent form) showed no statistically significant changes in scores between groups. Adverse events There were no statistically significant differences between the intervention and placebo group (p=1.00)</td>
</tr>
<tr>
<td>ID: RCT Multicenter</td>
<td>N = 107 Netherlands Setting: Specialty care</td>
<td>Diagnosis: Confirmation by specialist The diagnoses of ADHD and other mental disorders were confirmed by a child-and adolescent psychiatrist by using a structured parent interview according to the National Institute of Mental Health Diagnostic Interview Schedule for Children (version 4.0). Comorbidity: N/A Female: 44.8 % Age mean: Treatment group: 9.3 (2.7) Placebo Group: 9.0 (2.2) Minimum age: 6 Maximum age: 12 Ethnicity: Other info on race or ethnicity: N/A</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Target: Children aged 6 to 12 years old with diagnosed ADHD and chronic sleep-onset insomnia Other: ADHD presentation: inattentive : 21.0,hyperactive : 3.8,combined : 73.3</td>
<td>Diagnosis: Confirmation by specialist Psychologist and psychiatrist</td>
<td></td>
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<tr>
<td></td>
<td>Intervention: Fast-release melatonin, 3mg if body weight &lt; 40mg, 6mg if body weight &gt; 40kg Control: Placebo Identical-appearing placebo tablets Comparator: NA Follow-up: 1 month</td>
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</table>
### Appendix C. Evidence Tables

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<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrition, supplements</td>
<td>Weber, 2008&lt;sup&gt;96&lt;/sup&gt; National Center for Complementary and Integrative Health (NCCIH), 2004&lt;sup&gt;916&lt;/sup&gt; ID: NCT00100295 RCT Single center N = 54 US Setting: Other</td>
<td>Comorbidity: Sleep: chronic sleep-onset insomnia Female: 25.7 % Age mean: 9.1 (2.3) for treatment group; 9.3 (1.8) for placebo group Minimum age: Maximum age: Ethnicity: Other info on race or ethnicity: N/A</td>
<td></td>
<td>CGI-I (Clinical Global Impression - Improvement Scale) much or very much improved There was no significant difference between groups (p=0.59). ADHD RS-IV (ADHD Rating Scale–IV), parent report No significant difference between the 2 groups in the change in scores from baseline to follow up (p = 0.68). No significant difference was seen in change in height between the groups during the 8-week trial. Participants with any adverse event The rate was 41% for intervention and 44% for comparator, which was no significantly different between groups.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Target: Children and adolescents with ADHD that scored more than 1.5 standard deviations above age and sex norms on the ADHD RS-IV; those with psychiatric comorbidities were excluded Other: Parents ADHD presentation: N/A Diagnosis: Confirmation by specialist DSM IV criteria based on the Kiddie Schedule for Affective Disorders and Schizophrenia–Epidemiologic Version (K-SADS) Comorbidity: N/A Female: 37 % Age mean: 9.8 (2.0) Minimum age: 6 Maximum age: 17</td>
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</tbody>
</table>
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent education</td>
<td>Abikoff, 2015 NYU Langone Health, 2011 ID: NCT01320098 RCT Single center N = 164 US Setting: Specialty care</td>
<td>Target: Preschool, daycare or nursery school students diagnosed with ADHD. Current medication for ADHD excluded. Other: Parents were trained ADHD presentation: inattentive: 33.5, hyperactive: 15.2, combined: 50.6 Diagnosis: Confirmation by specialist DSM IV diagnosis confirmed by confirmed by clinical evaluation conducted by a psychologist with child and parent Comorbidity: N/A Female: 26.2% Age mean: N/A Minimum age: 3 Maximum age: 4 Ethnicity: % Hispanic or Latino: 25.6</td>
<td>Intervention: New Forest Parenting Package, 8 weekly 1-to-1.5-hour sessions, home-based intervention which fosters constructive parenting to target ADHD-related dysfunctions in attention and impulse control Control: Wait list Comparator: Parent training Helping the Noncompliant Child, clinic-based parenting intervention for treating noncompliant behavior Follow-up: 24 months</td>
<td>New York Parent Rating Scale - Physical Aggression Subscale, parent, post-tx Comparator group participants, but not intervention group, were rated better than control (p &lt; 0.003) at 6 months. There was no significant difference between intervention and comparator at 2 years. CPRS (Conners Parent Rating Scale) total Intervention and comparator groups significantly improved score compared to control (p &lt; .001); there was no significant difference between intervention and control. Parent treatment satisfaction Treatment satisfaction was equally high for intervention and comparator. P value not reported. There were no adverse effects with either NFPP or HNC.</td>
</tr>
</tbody>
</table>
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chacko, 2009</td>
<td>Author, year;</td>
<td>Multiple publications;</td>
<td>Intervention: Strategies to Enhance Positive Parenting (STEPP), a manualized, 9-week program held for 2.5 hours each week</td>
<td>Inattentive score, Disruptive Behavior Disorders rating scale</td>
</tr>
<tr>
<td>ID: NA RCT</td>
<td>Trial ID;</td>
<td>Site;</td>
<td>Control:</td>
<td>Benefits of the combined parent training groups compared to the waitlist control group were observed on DBD ODD symptoms (p &lt; .009) at treatment end but not follow-up. No significant differences in Disruptive Behavior Disorders Inattentive and Hyperactivity Impairment Rating Scale (IRs)</td>
</tr>
<tr>
<td>Single center</td>
<td>Study design;</td>
<td>Study target;</td>
<td>Comparator: Parent trainingTraditional manualized behavioral parent training program; meets for one 2.5 hour session per week for 9 weeks; sessions included videotapes of parenting errors whereby single mothers identified these errors and then formulated alternative parenting strat</td>
<td>The intervention group was significantly more improved than the control group, while the comparator group was not significantly different from the control group.</td>
</tr>
<tr>
<td>N = 120</td>
<td>ADHD presentation:</td>
<td>Diagnosis: Confirmation by specialist diagnosis was determined through completion of parent and teacher rating scales of DSM IV, completion of semistructured interviews with the parent, and assessment of cross-situational impairment through completion of parent and teacher rating scales (Imp)</td>
<td></td>
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</tr>
<tr>
<td>US</td>
<td>Comorbidity:</td>
<td>% Female:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Setting: Other</td>
<td>N/A</td>
<td>29.3 %</td>
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<tr>
<td></td>
<td>Age mean:</td>
<td>7.85 (2.14)</td>
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</tr>
<tr>
<td></td>
<td>Minimum age:</td>
<td>5</td>
<td></td>
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<tr>
<td></td>
<td>Maximum age:</td>
<td>12</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Ethnicity:</td>
<td>% Hispanic or Latino : 12.7</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>% Black/African American : 21.0</td>
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<tr>
<td></td>
<td></td>
<td>% White : 53.3</td>
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<tr>
<td></td>
<td></td>
<td>% Multiracial : 13.0</td>
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</tr>
<tr>
<td>Study</td>
<td>Population</td>
<td>Comparison</td>
<td>Outcome and results</td>
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</tbody>
</table>
| Churchill, 2018<sup>234</sup>  
ID: N/A  
RCT  
Unclear/Not reported  
N = 174  
US  
Setting: N/A | **Target:** Child 4–18 years old with ADHD; child must live with mother or primary female caregiver; English or Spanish speaking; lack of comorbid intellectual disability, autism, or psychosis  
**Other:** Mother or primary female caregiver of child with ADHD  
**ADHD presentation:** inattentive : 16.7, hyperactive : 23.55, combined : 33.35, combined_other : % unknown (26.4)  
**Diagnosis:** Confirmation by specialist  
Participants with ADHD diagnosis were recruited from Children and Families Program of the Mental Health and Addiction Services Division of Multnomah County Human Services, 10 neighborhood primary care health clinics with Multnomah County Health Department  
**Comorbidity:** N/A  
**Female:** 33.9 %  
**Age mean:** | **Intervention:** In-home nurse visits with families for one year, with variable frequency based on participant family needs, participant families given a resource guide and received a newsletter every 6 months with up-to-date information about ADHD  
**Control:** NA  
**Comparator:** Parent training  
Parenting book on ADHD and same newsletter every 6 months with up-to-date information about ADHD  
**Follow-up:** 18 months | CBCL (Child Behavior Checklist)  
There was no significant difference between groups (p=0.374). |
<table>
<thead>
<tr>
<th>Intervention Study:</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention group mean age (10.6) and SD (3.2). Control group mean age (10.8) and SD (3.4).</td>
</tr>
<tr>
<td></td>
<td>Minimum age: 4</td>
</tr>
<tr>
<td></td>
<td>Maximum age: 18</td>
</tr>
<tr>
<td></td>
<td>Ethnicity:</td>
</tr>
<tr>
<td></td>
<td>% Hispanic or Latino : 8.6</td>
</tr>
<tr>
<td></td>
<td>% Black/African American : 14.35</td>
</tr>
<tr>
<td></td>
<td>% American Indian or Alaska Native : 7.5</td>
</tr>
<tr>
<td></td>
<td>% Asian : 6.95</td>
</tr>
<tr>
<td></td>
<td>% White : 79.35</td>
</tr>
<tr>
<td></td>
<td>Other info on race or ethnicity:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention; Control; Comparator; Follow-up</td>
<td>Group interaction effects on receptive vocabulary, expressive vocabulary, character reading, morpho-logical awareness, phonological awareness, listening comprehension, and reading interest were significant (p &lt; .001) in favor of the DR groups over the control reading group. Sibling DR was significantly superior to parent DR regarding expressive vocabulary, character reading, morpho-logical awareness, and reading interest (p &lt; .001 for all) but inferior regarding improvement in listening comprehension (p &lt; .001).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parent education</th>
<th>Dong, 2022</th>
</tr>
</thead>
<tbody>
<tr>
<td>ID:</td>
<td>RCT Multicenter</td>
</tr>
<tr>
<td>N = 850</td>
<td>China Setting: Other</td>
</tr>
<tr>
<td>Target: Kindergarteners with ADHD, with sibling in Grade 7 or 8.</td>
<td></td>
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<tr>
<td>Other: Parents or siblings participated, but did not provide outcome data.</td>
<td></td>
</tr>
<tr>
<td>ADHD presentation: N/A</td>
<td></td>
</tr>
<tr>
<td>Diagnosis: Confirmation by specialist</td>
<td></td>
</tr>
<tr>
<td>Diagnosed by licensed clinical psychologists per DSM</td>
<td></td>
</tr>
<tr>
<td>Comorbidity: N/A</td>
<td></td>
</tr>
<tr>
<td>Female: 50.3 %</td>
<td></td>
</tr>
<tr>
<td>Age mean: 5.35 (0.20)</td>
<td></td>
</tr>
<tr>
<td>Minimum age:</td>
<td></td>
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<tr>
<td>Maximum age:</td>
<td></td>
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<tr>
<td>Ethnicity:</td>
<td></td>
</tr>
<tr>
<td>% Asian : 100</td>
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<tr>
<td>Intervention: Dialogic reading with parent 25 minutes twice per week for 12 weeks; a shared book reading approach where parent engages in dialog with the child through interactive question and answer communication while reading picture books together</td>
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</tr>
<tr>
<td>Control: Attention-matched control</td>
<td>Reading same books with parent 25 minutes twice per week for 12 weeks, but without dialogic reading</td>
</tr>
<tr>
<td>Comparator: Other</td>
<td>Dialogic reading with older sibling 25 minutes twice per week for 12 weeks; a shared book reading approach where parent engages in dialog with the child through interactive question</td>
</tr>
</tbody>
</table>
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose, 2017233</td>
<td>University of Cologne, Shire, 20121097</td>
<td>Other info on race or ethnicity:</td>
<td>and answer communication while reading picture books together</td>
<td>Follow-up: 12 weeks</td>
</tr>
<tr>
<td></td>
<td>ID: NCT01660425 RCT Single center N = 103 Germany Setting: Other</td>
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<tr>
<td></td>
<td>Target: Children aged 6 to 12 with ADHD taking methylphenidate for at least 2 months and had to show functional impairment in at least 1 of the domains of the Weiss Functional Impairment Rating Scale – Parent Report</td>
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<td></td>
<td>Other: Parents were the intervention target and provided some outcome data</td>
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<td></td>
<td>ADHD presentation: N/A</td>
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<td></td>
<td>Diagnosis: Confirmation by specialist Diagnosis by psychologist or psychiatrist required.</td>
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<tr>
<td></td>
<td>Comorbidity: N/A</td>
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<tr>
<td></td>
<td>Female: 18.5 %</td>
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<tr>
<td></td>
<td>Age mean: 9.78 (1.60) Minimum age: 6 Maximum age: 12</td>
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<tr>
<td></td>
<td>Ethnicity: Other info on race or ethnicity: N/A</td>
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<tr>
<td></td>
<td>Intervention: Year long telephone-assisted self-help program for parents, reading 8 self-help booklets, then parents receive 10 telephone consultations of about 30 min each during the first 6 months and four booster telephone consultations during the second 6-month period; children received also methylphenidate but no specific dose was required</td>
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<tr>
<td></td>
<td>Control: TAU Usual care plus children received methylphenidate, but no specific dosage was required</td>
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<td></td>
<td>Comparator: NA</td>
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<tr>
<td></td>
<td>Follow-up: 12 months</td>
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<tr>
<td></td>
<td>FBB-ADHS (German symptom checklist for ADHD), total score</td>
<td>No difference in German ADHD scale, total score, at follow-up (p = 0.12). Intervention group performed better on German symptom checklist for Oppositional Deviant Disorder at follow-up (p = .03). Weiss Functional Impairment Rating Scale – Parent Report There was no significant difference between groups (p = 0.30).</td>
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</table>
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study</th>
<th>Population</th>
<th>Comparison</th>
<th>Outcome and results</th>
</tr>
</thead>
</table>
| Parent education | Ercan, 2014  
ID: NA  
Clinical trial  
Single center  
N = 120  
Turkey  
Setting: Specialty care | Target: Children diagnosed with ADHD and oppositional defiance disorder or conduct disorder by psychiatrists, other comorbid disorders (i.e., anxiety disorders, mental retardation, or bipolar disorder) not permitted  
Other: Parents, teachers  
ADHD presentation: N/A  
Diagnosis: Confirmation by specialist DSM IV per KSADS-PL  
Comorbidity: ODD  
Female: 31.7 %  
Age mean: 9.07 (1.92)  
Minimum age: 6  
Maximum age: 13  
Ethnicity: Other info on race or ethnicity: N/A | Intervention: Parent-training program plus methylphenidate, optimal methylphenidate dose taken daily for 12 months, parent-training program consisted of 4 consecutive weekly meetings that started at the beginning of the 2nd month and 10 monthly meetings that took place during the remaining 10 months of the treatment with each parent-training group consisted of 10 to 15 members  
Control: Other  
Methylphenidate only, initial dose was 7.5 mg/day for children between 7 and 10 years of age and 10 mg/day for children between 11 and 13, dose was adjusted in response to continuous feedback from the parents, mean (SD) dose throughout the 12-month study  
Comparator: NA  
Follow-up: 12 months | CPRS (Conners’ Parent Rating Scale)  
No significant effect of parent training on CPRS or Conners’ Teacher Rating Scale.  
Hyperactivity-impulsivity scale, T-DSM-IV-S, parent rating  
No significant effect of group on T-DSM-IV-S Hyperactivity / Impulsivity - Parent (p = .60), T-DSM-IV-S Attention - Parent (p = .89), T-DSM-IV-S OD - Parent (p = .39), or T-DSM-IV-S CD - Parent (p = .39). No significant effect of group on T-DSM-IV-S |
| Parent education | Ferrin, 2014  
ID: N/A  
RCT  
Single center  
N = 81  
Spain  
Setting: Other | Target: Diagnosis of ADHD any subtype according to the DSM-IV; the diagnosis was confirmed by clinical interview with a child psychiatrist, supplemented with structured interview using the validated Spanish version of the semi-structured clinical interview of the Schedule for Affective | Intervention: Psychoeducation program composed of 5 successive groups of 8–10 families who received 12-week 90 min weekly sessions  
Control: NA  
Comparator: Parent trainingParent counselling and support intervention, ADHD Index, CPRS-R (Conners’ Parent Rating Scale Revised 27-items), parent | There was no significant difference between groups.  
Strengths and Difficulties Questionnaire (SDQ), parent  
There was no statistically significant interaction effect of time by group. |
<table>
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<tr>
<th>Intervention</th>
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<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Disorders and Schizophrenia for school age children (KSADS-PL); either sex; consenting and legal capable parents’ age greater than or equal to 18 years; clinical ADHD symptoms stabilization for at least 1 month before entering the study</td>
<td>Interventions; Control; Comparator; Follow-up</td>
<td>5 successive groups of 8–10 families who received 12-week 90 min weekly sessions, families were reunited and encouraged to comment on their thoughts and share their experiences in a nondirective, nonthreatening manner</td>
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<td></td>
<td>Other: ADHD presentation: N/A Diagnosis: Confirmation by specialist KSADS-PL Comorbidity: N/A Female: 20 % Age mean: Intervention 11.25(2.96), control 9.94(3.04) Minimum age: 5 Maximum age: 18 Ethnicity: Other info on race or ethnicity: N/A</td>
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<td></td>
<td>Target: Participants age 3 to 19 with diagnosis of ADHD, parents’ age greater than or equal to 18 years, and stabilizing medication for 1 month prior to baseline assessment. Participant should not have severe learning disabilities (IQ &lt; 70), autistic spectrum disorder as primary diagnosis, any clinically significant or unstable</td>
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<tr>
<td>Parent education: Ferrin, 2020</td>
<td>Intervention: Psychoeducation with 5 successive groups of 7-10 families who received six sessions of 2 hr at weekly intervals, a handout was delivered and parents were assigned some short additional homework to prepare for the next session</td>
<td>CGI-I (Clinical Global Impression Scale global improvement) change, clinician rating Interventions showed a significant effect on the clinical global impression compared to control (p=.038) ADHD Index, Conners’ Parent Rating Scale: Short Form (CPRS-R:S) Mean differences in scores showed statistically significant differences between the</td>
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<td>Control: TAU</td>
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<tr>
<td></td>
<td>Other: ADHD presentation: N/A Diagnosis: Confirmation by specialist KSADS-PL Comorbidity: N/A Female: 20 % Age mean: Intervention 11.25(2.96), control 9.94(3.04) Minimum age: 5 Maximum age: 18 Ethnicity: Other info on race or ethnicity: N/A</td>
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<tr>
<td></td>
<td>Control: TAU</td>
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<td></td>
<td>Other: ADHD presentation: N/A Diagnosis: Confirmation by specialist KSADS-PL Comorbidity: N/A Female: 20 % Age mean: Intervention 11.25(2.96), control 9.94(3.04) Minimum age: 5 Maximum age: 18 Ethnicity: Other info on race or ethnicity: N/A</td>
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<tr>
<td></td>
<td>Target: Participants age 3 to 19 with diagnosis of ADHD, parents’ age greater than or equal to 18 years, and stabilizing medication for 1 month prior to baseline assessment. Participant should not have severe learning disabilities (IQ &lt; 70), autistic spectrum disorder as primary diagnosis, any clinically significant or unstable</td>
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<td>Parent education: Ferrin, 2020</td>
<td>Intervention: Psychoeducation with 5 successive groups of 7-10 families who received six sessions of 2 hr at weekly intervals, a handout was delivered and parents were assigned some short additional homework to prepare for the next session</td>
<td>CGI-I (Clinical Global Impression Scale global improvement) change, clinician rating Interventions showed a significant effect on the clinical global impression compared to control (p=.038) ADHD Index, Conners’ Parent Rating Scale: Short Form (CPRS-R:S) Mean differences in scores showed statistically significant differences between the</td>
<td></td>
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<tr>
<td></td>
<td>Control: TAU</td>
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</tbody>
</table>
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>medical or psychiatric condition, and children whose families had received any similar school-based individual and/or group treatments at any point in time Other: Parents of children with ADHD ADHD presentation: N/A Diagnosis: Confirmation by specialist DSM-IV Comorbidity: N/A Female: 13 % Age mean: Intervention 10.86 (3.04), control 10.56 (3.20) Minimum age: 5 Maximum age: 18 Ethnicity: % Black/African American : 10.14% % White : 50.7% % Multiracial : 24.6 Other info on race or ethnicity:</td>
<td>Treatment as usual group, families continued routine medical care as usual with their clinicians; they were offered the opportunity to join the psychoeducation group once their collaboration with the study had ended; control participants received monthly Comparator: NA Follow-up: 6 months</td>
<td>two groups for the cognitive/inattention and the hyperactive/impulsive subdomains. Strengths and Difficulties Questionnaire, teacher rating There were no statistically significant effects for time or an interaction between time and treatment condition (p=0.67). There were no statistically significant differences in parental stress across groups (p=0.521).</td>
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</tbody>
</table>

| Parent education | Geissler, 2020; Jans, 2015; Jans, 2015; Jaite, 2019; Hautmann, 2018; ID: CCT-ISRCTN73911400 RCT | Target: Diagnosed with ADHD; not currently receiving psychopharmacotherapy; or their medication had been stable for at least 4 weeks prior to baseline assessment Other: | Intervention: 12 weeks weekly group psychotherapy plus methylphenidate, then 12-week individualized parent-child training program comprised a structured and modular behavioral psychotherapy program for children with methylphenidate medication and ADHD symptoms, Schedule for Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) | Home Situations Questionnaire (HSQ), externalizing problem behavior in the family There were no differences between groups (p=0.62). |
### Intervention

<table>
<thead>
<tr>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multicenter N = 144 Germany Setting: Specialty care</td>
<td>ADHD presentation: combined : 52, combined_other : 52% children / 66% mothers Diagnosis: Confirmation by specialist DSM-IV specially trained expert clinicians at each study centre’s Department of Child and Adolescent Psychiatry European Child &amp; Adolescent Psychiatry (assessment and treatment of children; PCT) or Department of Psychiatry (assessment and treatment of Comorbidity: N/A Female: 26.5% Age mean: Mean age 9.4 Minimum age: Maximum age: Ethnicity: Other info on race or ethnicity: N/A</td>
<td>group psychotherapy (1 appointment/4 week), then 6 months of maintenance of all previous interventions</td>
<td>No statistically significant difference between groups (p=0.35) Strength and Difficulties Questionnaire global score There was no significant difference between groups (p=0.54) No difference in Strengths and Difficulties Questionnaires rated by teachers (p=0.73).</td>
</tr>
<tr>
<td>Hornstra, 2021 N = 92 Netherlands Setting: Mixed</td>
<td>Target: Participants have a Diagnostic and Statistical Manual of Mental Disorders-5, have an IQ &gt; 70, and do not use psychotropic medications. Other: Parents of ADHD children ADHD presentation: inattentive : 26, hyperactive : 11, hyperactive_other :</td>
<td>Intervention: Antecedent-based condition: parents were provided with information about executive functioning deficits in children with ADHD, parents practiced techniques through guided role-play or visualization and after that potential barriers to implementation of the plan were discussed, intervention</td>
<td>Daily Rated Problem Behaviors Compared to the control group, the intervention and comparator groups had significantly improved scores. SWAN (The Strengths and Weaknesses of ADHD symptoms and Normal behavior rating scale) Compared to the control group, the intervention and comparator groups had</td>
</tr>
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</table>
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent education</td>
<td>Lange, 2018&lt;sup&gt;175&lt;/sup&gt; University of Aarhus, 2012&lt;sup&gt;193&lt;/sup&gt; ID: NCT01684644 RCT Multicenter N = 164 Denmark Setting: Specialty care</td>
<td>hyperactive/impulsive, combined: 63 Diagnosis: Confirmation by specialist DSM-V Comorbidity: N/A Female: 30% Age mean: N/A Minimum age: 4 Maximum age: 12 Ethnicity: % White: 97 Other info on race or ethnicity:</td>
<td>plan consisted of antecedent-based techniques only (i.e., defining rules, giving clear instructions, anticipating misbehaviors, and providing structure in time and space), two sessions of two hours each provided in two consecutive weeks.</td>
<td>significantly improved scores for hyperactivity-impulsivity symptoms. For symptoms of inattention, only the intervention group had significantly improved scores compared to the control.</td>
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<td>Control: Wait list Comparator: Parent training Consequent-based parent education, parents learned how consequences can affect behavior, and how and which consequent-based techniques can be used to change behaviors (e.g., by ignoring unwanted behaviors and praising every attempt to show the appropriate behaviors).</td>
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<td>Follow-up: 4 months</td>
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<tr>
<td>Parent education</td>
<td>Plan consisted of antecedent-based techniques only (i.e., defining rules, giving clear instructions, anticipating misbehaviors, and providing structure in time and space), two sessions of two hours each provided in two consecutive weeks.</td>
<td>Parent training Consequent-based parent education, parents learned how consequences can affect behavior, and how and which consequent-based techniques can be used to change behaviors (e.g., by ignoring unwanted behaviors and praising every attempt to show the appropriate behaviors).</td>
<td>Directly observed ADHD behaviors during solo play “index of attention/engagement” using the Child Solo Play instrument. No significant difference. ADHD-RS-IV (ADHD Rating Scale) symptom severity, parent ratings. After treatment, the parent training program was superior to treatment as usual on parent-rated ADHD symptoms (p=0.009; effect size d=0.30).</td>
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</table>


<sup>193</sup> ADHD diagnosis supported by the Development and Well-Being Assessment (DAWBA); Danish as a first language spoken at home; IQ greater than or equal to 70; no autism spectrum disorder diagnosis; not in receipt of pharmacologic or psychosocial treatment for ADHD; no severe parental psychiatric disorder; no severe social adversity in the home
# Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Target</th>
<th>Population</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parent education</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Diagnosed with ADHD, only taking methylphenidate for 6 months prior to study, with a fixed dose of drug in the last 30 days prior to start of study - with at least one sleeping issue and children needed to have no physical or mental comorbidities</td>
<td>Other: Parents and teachers of children with ADHD ADHD presentation: N/A Diagnosis: Confirmation by specialist ADHD diagnosis was made by specialist child and adolescent psychiatrists based on results from all clinical assessments and Development and Well-Being Assessment profiles, which were conducted by trained raters. Development and Well-Being Assessment design Comorbidity: N/A Female: 27% Age mean: 57% of children were aged 3-5; 43% of children were aged 6-7 Minimum age: 3 Maximum age: 7 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Intervention: Behavioral parental training on sleep problems, including information, sleep hygiene and nutrition health, control of environmental stimuli, cognitive behavioral therapy strategies, conducted in 2 groups of 14 parents per week in week 1, 3, and 5 of the Intervention group experienced a significantly greater improvement in total sleep scores compared to the control group (p = 0.03). Also the intervention group had a significantly greater decline in total sleep problem compared to the control group (p = 0.01).</td>
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</table>

<table>
<thead>
<tr>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
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<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
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</table>

Parent education: Mehri, 2020<sup>2</sup>, Department of Research and Technology, 2013<sup>14</sup> ID: IRCT2013042112990N1 RCT

Intervention: Behavioral parental training on sleep problems, including information, sleep hygiene and nutrition health, control of environmental stimuli, cognitive behavioral therapy strategies, conducted in 2 groups of 14 parents per week in week 1, 3, and 5 of the Intervention group experienced a significantly greater improvement in total sleep scores compared to the control group (p = 0.03). Also the intervention group had a significantly greater decline in total sleep problem compared to the control group (p = 0.01).
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
</table>
| Parent education | Schorr-Sapir, 2021<sup>50</sup>  
ID: N/A  
RCT Unclear/Not reported  
N = 101  
Israel  
Setting: Mixed | Target: Children aged 5-13 years with primary DSM-5 ADHD diagnosis and scores above 55 on the Conners' Scale for ADHD; con changes medication during the study; no psychotic symptoms and no concurrent psychotherapy  
Other: Parents of children with ADHD that are fluent and have no Hebrew no psychotic symptoms  
ADHD presentation: N/A  
Diagnosis: Confirmation by specialist  
Children have primary DSM-5 ADHD diagnosis.  
Comorbidity: N/A  
Female: 21 % | Intervention: Nonviolent resistance parent training with clinical psychologist, 12 sessions (one session involving the parents and members of the school staff was conducted in the child’s school); two weekly telephone conversations with undergraduate student; special emphasis was given to psychoeducation on ADHD, parental emotion regulation and self-control, and the development of a collaborative relationship with the school  
Control: Wait list  
Waiting period is 12 weeks, given nothing during waiting period | Conners’ Rating Scale - ADHD index, parent There was a reduction in ADHD core symptoms by the end of treatment, but these gains were not maintained at follow-up (p = 0.63). |
| Parent education | Other: ADHD presentation: N/A  
Diagnosis: Confirmation by specialist diagnosed by psychiatrist based on DSM-IV criteria  
Comorbidity: Sleep  
Female: 14.3 %  
Age mean: 8.50 (1.79)  
Minimum age: 6  
Maximum age: 12  
Ethnicity: Other info on race or ethnicity: N/A | study; participants also received methylphenidate treatment  
Control: Other  
Methylphenidate treatment only  
Comparator: NA  
Follow-up: 2 months | | |
### Appendix C. Evidence Tables

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<tr>
<th>Intervention Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
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<tr>
<td></td>
<td></td>
<td>Intervention; Control; Comparator; Follow-up</td>
<td></td>
</tr>
<tr>
<td><strong>Parent education</strong></td>
<td><strong>Age mean:</strong> 8.8 (1.77)</td>
<td><strong>Comparator:</strong> NA</td>
<td><strong>Child Behavior Checklist (CBCL) - Aggressive Behavior Subscale, parent and teacher score composite</strong>&lt;br&gt;There were no significant differences between treatment and comparator groups. Intervention group had greater score improvement than comparator for Child Behavior Checklist (CBCL) - Withdrawn / Depressed Subscale, parent and teacher score composite</td>
</tr>
<tr>
<td>Smit, 2021[^33]</td>
<td><strong>Minimum age:</strong> 5</td>
<td><strong>Follow-up:</strong> 4 months</td>
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<tr>
<td>Mikami, 2020[^34]</td>
<td><strong>Maximum age:</strong> 13</td>
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<tr>
<td>ID: NA</td>
<td><strong>Ethnicity:</strong> Other info on race or ethnicity:</td>
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<td>RCT</td>
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<tr>
<td>Multicenter</td>
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<td>N = 172</td>
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<td>Canada</td>
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<td>Setting: Specialty care</td>
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<tr>
<td><strong>Target:</strong> Children aged 6 to 11 with ADHD who children scored ≥3 on parent or teacher reports on the Strengths and Difficulties Questionnaire Peer Problems subscale.</td>
<td><strong>Intervention:</strong> Parental Friendship Coaching: behavioral parent training where parents learn to be friendship coaches by teaching their children friendship skills and facilitating opportunities for children to make real-life friends; weekly, 90-min sessions for parents over 10 weeks</td>
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<tr>
<td><strong>Diagnosis:</strong> Confirmation by specialist DSM V diagnosis required. Children required to have ≥6 symptoms of inattention and/or hyperactivity/impulsivity endorsed by either the parent on the K-SADS (Kiddie-Schedule for Affective Disorders and Schizophrenia) or the teacher on the CSI (Child Sympt</td>
<td><strong>Control:</strong> NA</td>
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<tr>
<td><strong>Comorbidity:</strong> N/A</td>
<td><strong>Comparator:</strong> Parent trainingPsychoeducation and social support (Coping with ADHD through Relationships and Education), weekly, 90-min sessions for parents over 10 weeks</td>
<td></td>
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<tr>
<td><strong>Female:</strong> 30 %</td>
<td><strong>Follow-up:</strong> 8 months</td>
<td></td>
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<tr>
<td><strong>Age mean:</strong> 8.54 (1.55)</td>
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<tr>
<td><strong>Minimum age:</strong> 6</td>
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<tr>
<td><strong>Maximum age:</strong> 11</td>
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</tbody>
</table>
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
</table>
|              | Sonuga-Barke, 2001[^1][^9] ID: N/A RCT Single center N = 78 UK Setting: Community | **Target:** Children had to be born between January 1992 and September 1993, and the parents had to take the Parental Account of Childhood Symptoms examination to determine if the child needed a further clinical evaluation  
**Other:** Parents  
**ADHD presentation:** N/A  
**Diagnosis:** Confirmation by specialist  
They followed the American Psychiatric Association, DSM-IV standard.  
**Comorbidity:** N/A  
**Female:** 38.5%  
**Age mean:** All age 3  
**Minimum age:** 3  
**Maximum age:** 3  
**Ethnicity:** Other info on race or ethnicity: N/A | **Intervention:** Parent Training group received coaching in child management techniques, eight 1-hour weekly sessions  
**Control:** Wait list  
**Comparator:** Parent trainingParent counseling and support, non-directive support and counseling for parent of children with ADHD  
**Follow-up:** 3.75 months | Observation of ADHD behavior during 10 minute play with multipurpose toy  
Significant effects seen for the intervention in direct observation measures (p<.05).  
Parental Account of Childhood Symptoms (PACS) to assess core symptoms of ADHD, parent  
Recovery (Jacobson & Truax criteria)  
Significant effects were seen for the intervention (p<0.001). |

[^1]: Reference number  
[^9]: Reference number
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
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<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
</table>
| Parent education | Sonuga-Barke, 2004 | **Target:** Three year old children with ADHD  
**Other:** Parents receiving training and providing outcome measures  
**ADHD presentation:** N/A  
**Diagnosis:** Confirmation by specialist  
Children met cut-offs on the Werry-Weiss-Peters Activity Scale and the Parental Account of Childhood Symptoms Structured Clinical Interview and their parents reported significant clinical impairment.  
**Comorbidity:** N/A  
**Female:** %  
Not reported  
**Age mean:** 3 years old at time of enrollment  
**Minimum age:** 3  
**Maximum age:** 3  
**Ethnicity:** Other info on race or ethnicity: N/A | **Intervention:** Parent training of mothers, conducted in home with 1 hour per week for 8 weeks  
**Control:** Wait list  
**Comparator:** NA  
**Follow-up:** 3.75 months | BCL (Behaviour checklist)  
Difference in Behavior Checklist not significant between intervention and control.  
AD/HD score PACS (Parental Account of Childhood Symptoms)  
No difference in follow-up ADHD symptoms between intervention and control groups. |
| Parent education | Sonuga-Barke, 2018 | **Target:** Children were included if parent and/or caregiver aged 18 years or over; (iii) screened positive for ADHD symptoms (score ≥ 20) on the Werry-Weiss-Peters Activity Rating Scale (WWP) [18] and; (iv) were given an ADHD research diagnosis of any sub-type based on the parent DISC-IV-ADHD Scale | **Intervention:** New Forest Parenting Programme parent training intervention delivered at home for 12 weeks of 1.5 hour sessions  
**Control:** TAU  
Standard patterns of preschool ADHD care available in the parents' region; in two regions, there was SNAP-IV (Swanson Nolan and Pelham - IV - Parent)  
Small, non-significant, benefits of NFPP over TAU were seen for parent-rated SNAP-IV, ADHD combined symptoms [− 0.189 95% CI (− 0.380, 0.003), p = 0.053]. |
### Appendix C. Evidence Tables

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<tr>
<th>Intervention</th>
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<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent education</td>
<td>Tiwawatpakorn, 2021</td>
<td>Interventions: Parental training + Routine Clinical care (PT + RCC): routine clinical care included psychoeducation, problem-oriented counseling, prescription of standard medications, and child evaluation, visits were scheduled every 3–6 months and took 15–30 minutes for each visit, parenting training consisting of six 120-minute weekly sessions consisting of general knowledge about ADHD and quality time, functional behavioral analysis, effective communication, positive and negative reinforcement, punishment, and time and school management</td>
<td>VADPRS (Vanderbilt ADHD Diagnostic Parent Rating Scale) subscales The scores of inattention, hyperactivity/impulsivity, and oppositional-defiant behavior showed a noticeable reduction in both groups; no significant interactions were found between time and treatment arm (P &gt; 0.05) indicating that the improvement in score Treatment arm was not associated with changes in parenting style.</td>
<td>little provision for preschool ADHD while in one region provision might include parenting education and training Comparator: Parent training Incredible Years, developmentally based interventions, delivered weekly for 12 weeks, sessions were 2-2.5 hours long Follow-up: 6 months</td>
</tr>
</tbody>
</table>

| Other: Parent and/or caregiver aged 18 years or over ADHD presentation: N/A Diagnosis: Confirmation by specialist Werry-Weiss-Peters Activity Rating Scale and DISC-IV-ADHD Scale Comorbidity: N/A Female: 27 % Age mean: 42.7 (6.75) Minimum age: 3 Maximum age: 5 Ethnicity: Other info on race or ethnicity: N/A | | |

| Target: Participants diagnosed with ADHD by a developmental behavioral pediatrician or child and adolescent psychiatrist, receiving stable medication for at least 3 months, and living with their primary caregivers for at least 5 days a week. Other: Parents ADHD presentation: inattentive_other: Intervention: 1.7 (0.6); Control: 1.6 (0.6), hyperactive_other: 1.8 (0.6); Control: 1.6 (0.8) Diagnosis: Confirmation by specialist | | |
## Appendix C. Evidence Tables

| Intervention | Study:  
Author, year;  
Multiple publications;  
Trial ID;  
Study design;  
Sites;  
Study size;  
Location  
Setting | Population:  
Setting;  
Study target;  
ADHD presentation;  
Diagnosis;  
Comorbidity;  
% Female;  
Age mean;  
Minimum age;  
Maximum age;  
Ethnicity | Comparison:  
Intervention;  
Control;  
Comparator;  
Follow-up | Outcome and results |
|---|---|---|---|
| **Physical exercise**  
Durgut, 2020  
University, Bezmialem Vakif, University, Medipol, 2018  
ID: NCT03469180  
RCT  
Single center  
N = 30  
Turkey  
Setting: Specialty care | Vanderbilt ADHD Diagnostic Parent Rating Scale (VADPRS)  
Comorbidity: N/A  
Female: 18 %  
Age mean: 8.3 (1.1)  
Minimum age:  
Maximum age:  
Ethnicity:  
Other info on race or ethnicity:  
Target: Treatment naive children with ADHD. Exclusions: history of chronic and severe systemic disease or a seizure-like neurological disorder or vision, speech and hearing problems; any contraindications for physical activity; comorbid conditions such as autism spectrum disorders or intellectual disability.  
Other: Teachers and parent provided some outcome data  
ADHD presentation: inattentive: 16.7, hyperactive: 3.3, combined: 80.0  
Diagnosis: Confirmation by specialist diagnosed by psychiatrists via DSM V  
Comorbidity: N/A | Control: Other  
Routine clinical care only: psychoeducation, problem-oriented counseling, prescription of standard medications, and child evaluation, visits were scheduled every 3–6 months and took 15–30 minutes for each visit  
Comparator: NA  
Follow-up: 2 months | CPRS-R/L (Conners’ Parent Rating Scale-Revised/Long Form)  
Intervention group had more improvement in CPRS-R/L-total (parent report) but did not reach statistical significance (p = .055). Intervention group had significantly more improvement in CTRS-R/L-total (teacher report) p = .041.  
No difference between groups in Behavior Rating Inventory of Executive Function (BRIEF) - Parent report (p = 0.816) at follow-up. Intervention groups scored significantly better on BRIEF- teacher report (p = 0.023). |
### Appendix C. Evidence Tables

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<td><strong>Intervention</strong> Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Comparison: Intervention; Control; Comparator; Follow-up</td>
<td><strong>Outcome and results</strong></td>
</tr>
</tbody>
</table>
| Kadri, 2019 University of Genova, 2018 ID: NCT03678844 RCT Single center N = 40 Tunisia Setting: Other | Female: 20 %  
Age mean: 8.13 (1.19)  
Minimum age: 7  
Maximum age: 11  
Ethnicity: Other info on race or ethnicity: N/A | **Intervention:** Taekwondo exercises practiced for 50-minutes twice weekly for a year and a half, 10-minute general warm-up before each session and 10-minute recovery after each session  
**Control:** Other Engaged in physical activities, including athletics, handball and gymnastic, during two sessions of physical education per week at school.  
**Comparator:** NA  
Follow-up: 18 months | Processing speed measured using total time in seconds to complete the Ruff’s test 2 and 7. Total speed of intervention group mean (240.3). Total speed of intervention group SD (19.7). Total speed of control group mean (288.1). Total speed of control group SD (12.5). |
| **Physical exercise**  
Kadri, 2019 University of Genova, 2018 ID: NCT03678844 RCT Single center N = 40 Tunisia Setting: Other | Target: Young Tunisian patients with ADHD. No consumption of any diet supplements or drugs; no history of chronic disease, bronchospasm or atopy; not being color blind or vision-impaired. Other: ADHD presentation: N/A Diagnosis: No Participants with ADHD were recruited from Tunis and Sidi Bouzid mental centers, but DSM criteria not mentioned. Comorbidity: N/A Female: 10 % Age mean: Intervention group mean age (14.5) and SD (3.5). Control group mean age (14.2) and SD (3.0) Minimum age: Maximum age: Ethnicity: Other info on race or ethnicity: | **Intervention:** Taekwondo exercises practiced for 50-minutes twice weekly for a year and a half, 10-minute general warm-up before each session and 10-minute recovery after each session  
**Control:** Other Engaged in physical activities, including athletics, handball and gymnastic, during two sessions of physical education per week at school.  
**Comparator:** NA  
Follow-up: 18 months | Processing speed measured using total time in seconds to complete the Ruff’s test 2 and 7. Total speed of intervention group mean (240.3). Total speed of intervention group SD (19.7). Total speed of control group mean (288.1). Total speed of control group SD (12.5). |
## Physical exercise

### Liang, 2022<sup>187</sup>
ID: RCT  
Single center  
N = 80  
China  
Setting: Specialty care

**Population:**  
**Target:** Children with ADHD without comorbid psych disorders  
**Other:** None  
**ADHD presentation:** inattentive: 51.25, hyperactive: 16.25, combined: 32.5  
**Diagnosis:** Confirmation by specialist  
DSM 5 by psychiatrist using K-SADS-PL  
**Comorbidity:** N/A  
**Female:** 22.6%  
**Age mean:** 8.46 (1.5)  
**Minimum age:** 6  
**Maximum age:** 12  
**Ethnicity:** % Asian: 100  
Other info on race or ethnicity: 

**Comparison:**  
**Intervention:** 12-week combined aerobic-and neurocognitive-exercise, 3 sessions per week, 60-minutes per session  
**Control:** Wait list  
**Comparator:** NA  
**Follow-up:** 3 months

**Outcome and results:**  
Intervention group decreased reaction time as measured by Arrow Flanker Task for Inhibitory Control, compared to wait list group. Intervention group also increased working memory as measured by the Tower of London task, compared to wait list group. Intervention group also improved cognitive flexibility measured by the Trail Making Test for Cognitive Function compared to the wait list group. Sleep quality also improved significantly. However, the significant differences in all measures disappeared 1 month after intervention ended.

### Ludyga, 2022<sup>197</sup>
ID: DRKS00020125  
RCT  
Multicenter  
N = 63  
Multiple countries  
Setting: Other

**Population:**  
**Target:** Right-handed children with ADHD undergoing pharmacotherapy with methylphenidate or dexamphetamine for at least three months (to reduce inter-individual variations in symptom severity)  
**Other:**  
**ADHD presentation:** N/A  
**Diagnosis:** Confirmation by specialist  
DSM-5

**Comparison:**  
**Intervention:** Two weekly 60-min sessions of judo training in a group setting supervised by one or two instructors, per week, for 3 months  
**Control:** Wait list  
**Comparator:** NA  
**Follow-up:** 3 months

**Outcome and results:**  
No group difference in Movement Assessment Battery for Children-2 (MABC-2) at 3 months. Intervention group performed better on a Change Detection Task (p = 0.003).
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications;</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provider</td>
<td>Elmaadawi, 2022</td>
<td>Comorbidity: N/A</td>
<td>Intervention: Pharmacogenetic testing to enable genomically assisted prescribing (GAP).</td>
<td>Clinical Global Impression Scale-, Improvement Component (CGI-I) Significantly more improvement in intervention group.</td>
</tr>
<tr>
<td>Provider</td>
<td>Enns, 2017</td>
<td>Target: Children and adolescents with ADHD</td>
<td>Intervention: ADHD intervention service, participants and their families receive a range of services that can include assessment, treatment, and consultative services</td>
<td>Adjusted rate ratios (95% CI) for health and social services use outcomes for intervention (n =485) and control (n = 1884):</td>
</tr>
</tbody>
</table>
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<tr>
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<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 2369 Canada Setting: Community</td>
<td>ADHD presentation: N/A Diagnosis: Confirmation by specialist Manitoba Population Research Data Repository Comorbidity: N/A Female: 15.37 % Age mean: 16% of the intervention cohort were 6 years old or younger, 13% were 13 years old or older; 17% of the control cohort were 6 years old or younger, 10% were 13 years old or older Minimum age: 5 Maximum age: 17 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>(e.g. individual therapy, parent support, group therapy, education, and medication management) from multiple providers; the typical participation length in the program ranges from 3-6 months, but can extend further based on participant needs Control: No intervention No contact with the ADHD Service matched on age, sex, year of ADHD diagnosis, and income quintile; matches were identified separately in urban and rural income quintiles Comparator: NA Follow-up: 24 months</td>
<td>Hospital admissions (rate of): 1.29 (0.68 to 2.46) (p = 0.43) Visits to emergency department (rate of): all 1.03 (0.75 to 1.41) (p = 0.87), injury-related 1.00 (0.68 to 1.46) (p =1.00) Medication use (proportion of participants who were dispensed 1 or more medications): 1.21 (1.08 to 1.36) (p &lt; 0.01) Medication adherence (proportion of participants who have a medication possession ratio of at least 0.8): 1.42 (1.03 to 1.96) (p &lt; 0.05) Children with child welfare contact: 1.34 (0.54 to 3.35) (p = 0.53) Children in age-appropriate grade: 1.33 (1.09 to 1.63) (p &lt; 0.01).</td>
<td></td>
</tr>
<tr>
<td>Epstein, 2007 ID: NA Cluster RCT Multicenter N = 377 US Setting: Primary Care</td>
<td>Target: Children from participating practices who met DSM-IV criteria for ADHD, stimulant-naive, attending 1st - 5th grade Other: Pediatricians and associated healthcare professionals (27 men, 25 women) from 12 practices ADHD presentation: N/A Diagnosis: Confirmation by specialist Conners Rating Scale</td>
<td>Intervention: Collaborative consultation services: pediatricians were encouraged to and assisted in using titration trials to determine optimal dosages, taught to prescribe 4 different weekly dosages of methylphenidate hydrochloride during a titration trial (placebo, 18 mg, 36 mg, 54 mg) and the order of weekly dosages was blinded but standardized across all patients (week 1, 18 mg; week 2, placebo; week 3, 36 mg; week 4, 54 mg)</td>
<td>DSM-IV symptomatology, Conners Parent Rating Scale Children in the intervention group demonstrated a 27% reduction in DSM-IV symptomatology compared with an 18% reduction in the control group (p=.008).</td>
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<th>Outcome and results</th>
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</table>
| Provider | Epstein, 2016<sup>558</sup>  
Childrens Hospital  
Medical Center,  
Cincinnati, 2010<sup>1692</sup>  
ID: NCT01143701  
Cluster RCT  
Multicenter  
N = 577  
US  
Setting: Primary Care | **Comorbidity:** N/A  
**Female:** 36.3 %  
**Age mean:** 7.8 (1.5)  
**Minimum age:** 6  
**Maximum age:** 10  
**Ethnicity:**  
% Hispanic or Latino: .68  
% Black/African American: 16.4  
% American Indian or Alaska Native: .68  
% White: 79.5  
% Multiracial: .68  
Other info on race or ethnicity: | **Control:** TAU  
Patients in control group received treatment as usual alone, practices assigned to control group do not have access to consultative services  
**Comparator:** NA  
**Follow-up:** 12 months |
| **Target:** Patients in grades 1 through 5, presenting for ADHD evaluation, and were ADHD medication naive  
**Other:** Pediatric practices with ≥2 physicians, uses an electronic billing system, office has Internet access, must not have co-located mental health care  
**ADHD presentation:** N/A  
**Diagnosis:** Confirmation by specialist DSM-IV by research staff  
**Comorbidity:** N/A  
**Female:** 29.5 %  
**Age mean:** 7.8 (1.4)  
**Minimum age:** | **Intervention:** Four training sessions for providers, office flow modification, guided quality improvement, and an ADHD Internet portal to assist with treatment monitoring  
**Control:** No intervention  
Control practices  
**Comparator:** NA  
**Follow-up:** 12 months |
| | ADHD symptoms parent ratings  
Intent-to-treat analyses examining outcomes of all children assessed for ADHD were not significant (P=0.08) but among the 373 children prescribed ADHD medication, there was a significant intervention effect (P=0.04) indicating greater reductions in parent ADHD treatment care around medication was significantly better at intervention practices compared with control practices. |
## Appendix C. Evidence Tables

<table>
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<tr>
<th>Intervention</th>
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<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Intervention; Control; Comparator; Follow-up</td>
<td>ADHD symptoms VPRS (Vanderbilt Parent Rating Scale)</td>
</tr>
<tr>
<td></td>
<td>Guevara, 2021&lt;sup&gt;30b&lt;/sup&gt; Childrens Hospital of Philadelphia, 2016&lt;sup&gt;304&lt;/sup&gt; ID: NCT02716324 RCT Multicenter N = 303 US Setting: Primary Care</td>
<td>Target: Received care at a participating practice, had an ADHD diagnosis code (International Classification of Diseases, Ninth Revision [ICD-9] code 314) recorded at an ambulatory visit in the past year Other: ADHD presentation: Diagnosis: Confirmation by specialist International Classification of Diseases, Ninth Revision Comorbidity: N/A Female: 31% Age mean: 8.5 Minimum age: 5 Maximum age: 12 Ethnicity: % Hispanic or Latino : 5 % Black/African American : 45.9 % White : 26.4 Other info on race or ethnicity: Other : 9.2</td>
<td>Intervention: Portal combined with an ADHD care manager to enhance communication and promote greater shared decision-making; designed to (1) collect and share patient and family treatment preferences and goals with a clinician; (2) trend ADHD symptoms, performance impairment ratings, medication side effects, treatment receipt, and medication side effects by using electronically submitted parent and teacher reports; (3) provide a repository of ADHD educational materials; and (4) support information sharing between parents and teachers. ADHD care managers were bachelor’s-trained individuals who were responsible for communicating information and facilitating coordination of care Control: Other Electronic Health Record portal alone Comparator: NA Follow-up: 9 months</td>
<td>In multivariate models, VPRS scores decreased over time (Adjusted b 5 .015; 95% confidence interval 0.023 to 0.07) in both groups, but there were no intervention-by-time effects (Adjusted b 5 .000; 95% confidence interval 0.011 to 0.012) between groups. There were no adverse effects from either intervention identified, and interactions of intervention by race or income were not significant, suggesting no heterogeneity of treatment effects.</td>
</tr>
</tbody>
</table>
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### Intervention

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<tbody>
<tr>
<td>Kolko, 2020</td>
<td>University of Pittsburgh, 2008; ID: NCT00600470 Cluster RCT Multicenter N = 411 US Setting: Primary Care</td>
</tr>
<tr>
<td>Lavigne, 2011</td>
<td>Childrens Hospital of Chicago, 2005; ID: NCT00179894 Cluster RCT Multicenter N = 270 US</td>
</tr>
</tbody>
</table>

### Population:

<table>
<thead>
<tr>
<th>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
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<tbody>
<tr>
<td>Target: Children aged 5 to 12 years diagnosed with ADHD based on the DSM-IV criteria. Other: Parents ADHD presentation: N/A Diagnosis: Confirmation by specialist At intake, parents and children participated in a diagnostic/clinical interview based on the DSM-IV criteria to identify formal diagnoses. Comorbidity: N/A Female: 31% Age mean: 8.0 (1.9) Minimum age: 5 Maximum age: 12 Ethnicity: % White: 70 Other info on race or ethnicity: N/A: No other race info reported outside of White</td>
</tr>
<tr>
<td>Target: Participants must have a diagnosis of ADHD according to DSM-IV criteria, IQ &gt;= 70. Exclude: comorbidity of ASD, Tourette, other major health conditions; have taken ADHD medications in the past 2 months, or taking medications incompatible with stimulants (did not specify)</td>
</tr>
</tbody>
</table>

### Comparison:

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<tr>
<th>Intervention; Control; Comparator; Follow-up</th>
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</thead>
<tbody>
<tr>
<td>Intervention: Collaborative care, care manager delivered content modules which taught behavioral strategies to manage ADHD with caregivers and ADHD &quot;survival skills&quot; with participants in 3 to 4 1-hr sessions</td>
</tr>
<tr>
<td>Control: NA Comparator: ProviderEnhanced usual care; families received a referral to a mental health provider and could receive services for ADHD from their primary care provider and/or a community mental health provider Follow-up: 6 months</td>
</tr>
</tbody>
</table>

### Outcome and results

| ADHD symptoms measured using Vanderbilt ADHD Diagnostic Parent Rating Scale (VADPRS). Change from baseline to follow-up for intervention group compared to comparator group slope (~3.31), significant (p=.02). |
| Children in both specialized care and treatment-as-usual groups improved on the ADHD Rating Scales and SNAP-IV, and there were no group differences in improvement rates. There were no differences on the Barkley adverse effects scale between groups at 4, 9, or 12 months. |
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</tr>
</thead>
<tbody>
<tr>
<td>Setting: Specialty care</td>
<td>Other: Physicians from 24 Chicago-area pediatric practices</td>
<td>ADHD presentation: inattentive: 41.2, hyperactive: 9.8, combined: 49.0</td>
<td></td>
<td>office/office practices for the first 3 patients per physician to ensure that staff understood program use</td>
</tr>
<tr>
<td></td>
<td>Diagnosis: Confirmation by specialist Diagnostic Interview Schedule for Children IV-Parent</td>
<td>Comorbidity: N/A</td>
<td>Control: Other Pediatricians in treatment as usual group provided treatment per their usual procedure</td>
<td>Comparator: NA</td>
</tr>
<tr>
<td></td>
<td>Female: 23.0%</td>
<td>Age mean: Specialized care SC: 8.25 (SD = 1.38, n = 138), treatment as usual TAU: 8.19 (SD = 1.62, n = 133)</td>
<td>Follow-up: 12 months</td>
<td></td>
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<tr>
<td></td>
<td>Minimum age: Maximum age: Ethnicity:</td>
<td>% Hispanic or Latino: 12.2 % Black/African American: 2.5 % White: 81.5 Other info on race or ethnicity:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Provider</td>
<td>Myers, 2015; Rockhill, 2016; Myers, 2013; Vander Stoep, 2017; Rockhill, 2020; Seattle Childrens Hospital, 2009</td>
<td>Target: Children aged 5 through 12 with ADHD in rural underserved communities, 75% had at least one comorbidity (oppositional defiant behavior 40%)</td>
<td>Intervention: Telehealth intervention combining pharmacotherapy and caregiver behavior training; 6 sessions, 3-4 weeks apart over 22 weeks</td>
<td>Vanderbilt ADHD Parent Rating Scale Number meeting parent-reported diagnostic criteria in Inattention subscale of the Vanderbilt Attention-Deficit/Hyperactivity Disorder (ADHD) Rating Scale, 25 weeks The percent of participants with at least 50% reduction in ADHD symptoms was significantly higher in the intervention group (p = 0.000). Lower proportions of children in the</td>
</tr>
</tbody>
</table>
## Appendix C. Evidence Tables

<table>
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<tr>
<th>Study</th>
<th>Population</th>
<th>Comparison</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT Multicenter N = 223 US Setting: Other</td>
<td>ADHD presentation: N/A : Percentages above do not add to 100 because they are not mutually exclusive (caregiver ratings, not clinician diagnosed) Diagnosis: Confirmation by specialist Children scoring &gt;= 65 on the Child Behavior Checklist (CBCL) ADHD diagnostic subscale online were eligible. Clinician then confirmed in person via DSM-IV criteria Comorbidity: N/A Female: 26 % Age mean: 9.25 (2.0) Minimum age: 5 Maximum age: 12 Ethnicity: % Hispanic or Latino : 13.0 % Black/African American : 0.9 % American Indian or Alaska Native : 2.7 % Asian : 0.9 % Native Hawaiian or Pacific Islander : 1.8 % White : 80.7 Other info on race or ethnicity:</td>
<td>Intervention; Control; Comparator; Follow-up</td>
<td>intervention arm met diagnostic criteria on the VADRS-Caregiver: inattention, hy Columbia Impairment Scale-Parent Version (CIS-P) Children assigned to the intervention improved significantly more than children in the comparator group (p&lt;0.001).</td>
</tr>
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<tbody>
<tr>
<td><strong>Provider</strong></td>
<td><strong>Target:</strong> Children receiving ongoing treatment for ADHD, prescribed ADHD medication, parents and children proficient in English&lt;br&gt;<strong>Other:</strong> Clinicians providing ADHD care&lt;br&gt;<strong>ADHD presentation:</strong> N/A&lt;br&gt;<strong>Diagnosis:</strong> Confirmation by specialist Neurology department clinician&lt;br&gt;<strong>Comorbidity:</strong> N/A&lt;br&gt;<strong>Female:</strong> 24.3 %&lt;br&gt;<strong>Age mean:</strong> 11&lt;br&gt;<strong>Intervention 9.85 (3.21), control 11.09 (3.24)</strong>&lt;br&gt;<strong>Minimum age:</strong>&lt;br&gt;<strong>Maximum age:</strong>&lt;br&gt;<strong>Ethnicity:</strong> % Hispanic or Latino : 5.8 % White : 78.4 % Other : 406&lt;br&gt;<strong>Other info on race or ethnicity:</strong></td>
<td><strong>Intervention:</strong> Trigger algorithm and alert resolution process, web-based platform that enables clinicians to administer online clinical questionnaires to parents and teachers to monitor patients remotely between visits, data collected for 13 months&lt;br&gt;<strong>Control:</strong> No intervention&lt;br&gt;<strong>Comparator:</strong> NA&lt;br&gt;<strong>Follow-up:</strong> 15 months</td>
<td>CGI-S scores&lt;br&gt;Alert group patients had lower scores than non-alert group patients indicating worse global functioning.&lt;br&gt;Vanderbilt scores&lt;br&gt;Alert group patients had higher Vanderbilt scores at time 2 than the non-alert group indicating a worse ADHD severity (p&lt;0.001).</td>
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<tr>
<td><strong>Intervention</strong></td>
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<td>Oppenheimer, 2019&lt;sup&gt;674&lt;/sup&gt; Boston Childrens Hospital, 2014&lt;sup&gt;678&lt;/sup&gt; ID: NCT02097355 Cluster RCT Multicenter N = 518 US Setting: Specialty care</td>
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<tr>
<td>Abikoff, 2013&lt;sup&gt;713&lt;/sup&gt; ID: N/A RCT Multicenter N = 158 US Setting: Other</td>
<td><strong>Target:</strong> Children in 3rd through 5th grade with ADHD and organizational deficits&lt;br&gt;<strong>Other:</strong> Parents received training and provided some outcome data&lt;br&gt;<strong>ADHD presentation:</strong> inattentive : 55.7, hyperactive : 0, combined : 44.3</td>
<td><strong>Intervention:</strong> Organizational skills training; session time is spent working with the child, with parents joining during the last 10 minutes; 20 hour long in-clinic sessions held twice-a-week after school&lt;br&gt;<strong>Control:</strong> Wait list&lt;br&gt;<strong>Follow-up:</strong></td>
<td>Clinical Global Impression-Improvement (CGI-I)&lt;br&gt;Responder rates were significantly better for OST (85.3%) and PATHKO (86.9%) than waitlist (0%), overall p&lt;0.0001.&lt;br&gt;Children's Organizational Skills Scale, parent&lt;br&gt;The intervention group performed better than the comparator group (p &lt; 0.02).</td>
</tr>
<tr>
<td>Intervention</td>
<td>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Comparison: Intervention; Control; Comparator; Follow-up</td>
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<tr>
<td>Boyer, 2016</td>
<td>Boyer, 2015</td>
<td>Diagnosis: Confirmation by specialist DSM IV diagnosis confirmed by clinical evaluation required Comorbidity: Other: Organizational deficits Female: 35.4 % Age mean: 9.04 (0.82) Minimum age: 7 Maximum age: 11 Ethnicity: % Hispanic or Latino: 13.9 % Black/African American: 14.6 % White: 69.6 Other info on race or ethnicity:</td>
<td>Comparator: Other Performance-based intervention that precluded skills, training motivates children by training teachers and parents to establish specific, individualized goals for children on written charts completed daily and to prompt, monitor, and praise/reward children Follow-up: 24 months</td>
</tr>
<tr>
<td>Psychological or behavioral</td>
<td>Target: Adolescents with a prior DSM-IV-TR diagnosis of ADHD by a child psychiatrist or certified psychologist, (2) a confirmed ADHD diagnosis on the ADHD sections of the diagnostic interview schedule for children for DSM-IV parent version (DISCIV). Exclusions: (1) the adolescents themselves or their parents received alternative non-pharmacological treatment between pre- and post-assessment aimed at the participating adolescent. When the adolescent or parents did receive alternative treatment, they could only</td>
<td>Intervention: Plan my life: an cognitive behavioral treatment consisting of eight adolescent sessions and two parental sessions of 45–60 min, one session per week Control: NA Comparator: Behavioral Solution-focused treatment, consisting of eight individual adolescent sessions and two parental sessions (between adolescent session 2 and 3, and between adolescent session 5 and 6) of 45–60 min. At every session the adolescent discussed a problem he/she Follow-up: 3 months</td>
<td>ADHD-RS (ADHD-Rating Scale), parent-rated Marginally significant differences were found in favor of the intervention. At 12 months there no significant differences. Overall impairment, parental report There was a significant time x treatment effect. Executive function, teacher rated, significantly improved over time. At 1 year, no differences between groups. Attendance Intervention group showed significantly higher attendance rates than comparator (p = .03).</td>
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</table>
### Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
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<td>participate if they stopped this treatment until post-test had taken place, (2) autism spectrum disorder, (3) predominant addiction, depression with suicidal ideations, acute familial crisis or CD. Because these disorders bring forward risks for participants themselves or others, it was unethical to discourage additional treatment, (4) they received pharmacological treatment with Atomoxetine. <strong>Other:</strong> ADHD presentation: inattentive : 70, hyperactive : 5, combined : 25 Diagnosis: Confirmation by specialist DSM-IV Comorbidity: N/A Female: 26 % Age mean: Intervention 14.4(1.2), control 14.4(1.3) Minimum age: 12 Maximum age: 17 Ethnicity: Other info on race or ethnicity: N/A</td>
<td></td>
<td>At 1 year, no differences in effect on depression, anxiety, parent-adolescent conflict, or neurological tasks.</td>
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<td><strong>Appendix C. Evidence Tables</strong></td>
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<td><strong>Intervention</strong></td>
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<td><strong>Study:</strong></td>
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<tr>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td><strong>Population:</strong></td>
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<tr>
<td><strong>Target:</strong> Unmedicated children aged 5 through 13 with ADHD</td>
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<td><strong>Other:</strong> Parents of the children</td>
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<tr>
<td><strong>ADHD presentation:</strong> N/A</td>
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<tr>
<td><strong>Diagnosis:</strong> Confirmation by specialist</td>
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<td><strong>DSM-IV diagnosis required. A Ph.D.-level clinician conducted interview with parents and reviewed symptom rating and impairment scales (DBD-RS)</strong></td>
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<tr>
<td><strong>Comorbidity:</strong> N/A</td>
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<tr>
<td><strong>Female:</strong> 16 %</td>
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<tr>
<td><strong>Age mean:</strong> 9.3 (2.0)</td>
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<td><strong>Minimum age:</strong> 5</td>
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<td><strong>Maximum age:</strong> 13</td>
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<tr>
<td><strong>Ethnicity:</strong></td>
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<tr>
<td>% Hispanic or Latino : Not reported</td>
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<tr>
<td>% Black/African American : 13</td>
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<tr>
<td>% Asian : Not reported</td>
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<tr>
<td>% White : 79</td>
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<tr>
<td>Other info on race or ethnicity:</td>
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<tr>
<td><strong>Comparison:</strong> Intervention; Control; Comparator; Follow-up</td>
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<tr>
<td><strong>Outcome and results</strong></td>
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<tr>
<td>Intervention: Behavioral consultation with school and home components (high or low intensity); school: 3 initial teacher visits to set up Daily Report Card with home-based rewards, bank of 3 additional consultation visits throughout year; home: 1 initial home visit to establish a homebased Daily Report Card, bank of 3 additional consultation visits throughout year, option to attend monthly group parent training booster sessions</td>
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<tr>
<td>Control: No intervention</td>
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<tr>
<td>Comparator: NA</td>
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<tr>
<td>Follow-up: 9 months</td>
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<td>Inattention/Overactivity, Conners Score, parent report</td>
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<tr>
<td>No difference in teacher or parent reported Conners Score, Oppositional/Defiant subscale or Inattention/ Overactivity subscale between children receiving or not receiving the behavioral consultation.</td>
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<tr>
<td>Children who received the intervention were about half as likely those who did not to initiate medication use each week at school or home and used lower doses when medicated at school, 63% of the control group was medicated at home at endpoint compared to 26% of the intervention group (p &lt; .01).</td>
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<thead>
<tr>
<th><strong>Psychological or behavioral</strong></th>
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<tbody>
<tr>
<td><strong>Intervention:</strong> Supporting the Effective Entry to the Roadway (STEER), 8-week parent-teen intervention of weekly sessions divided into two 45-minute meetings with the first half including individual parent and teen meetings that occur in parallel and the second half including a joint activity. Adjunct to</td>
</tr>
<tr>
<td><strong>Comparison:</strong> Treatment satisfaction</td>
</tr>
<tr>
<td><strong>Outcome and results</strong></td>
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<tr>
<td>No difference between groups.</td>
</tr>
<tr>
<td>Compared to the driver education practice program, the teens in the supporting the effective entry to the roadway group reported lower levels of risky driving behavior at the six-month (p=0.03) but not the 12-month follow-up</td>
</tr>
</tbody>
</table>
### Appendix C. Evidence Tables

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<tbody>
<tr>
<td></td>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>ADHD symptoms and DSM scale on the Child Behavior Checklist and Teacher Report Form</td>
<td>drivers ed program which control group also received.</td>
<td>(p = 0.07); there was also no significant differences for observed positive parenting.</td>
</tr>
<tr>
<td></td>
<td>Multiple publications</td>
<td>Comorbidity: N/A</td>
<td>Control: Attention-matched control Driver education driver practice program, 10-week diver education course with 30 hours of classroom instruction and 10 45-minute individual driving lessons</td>
<td>Control: TAU</td>
</tr>
<tr>
<td></td>
<td>Murdoch Childrens Research Institute (Australia), 2014&lt;sup&gt;[1]&lt;/sup&gt;</td>
<td>Female: 27.4 % 26.7 and 28.1% girls</td>
<td>Comparator: NA</td>
<td>Target: Met full DSM-5 diagnostic criteria for ADHD – that is at least six of nine symptoms of inattention and/or hyperactivity were rated as 'often' or 'very often' present on the ADHD Rating Scale IV, and the symptoms had been present for at least 6 months, and were associated with cross-situational impairment (e.g. at home and school); had a moderate to severe parent-rated sleep problem; and met the International Classification of Sleep Disorders – 3rd edition criteria for chronic insomnia</td>
</tr>
<tr>
<td>Psychological or behavioral</td>
<td>Hiscock, 2019&lt;sup&gt;[2]&lt;/sup&gt; Murdoch Childrens Research Institute (Australia), 2014&lt;sup&gt;[3]&lt;/sup&gt; ID: ISRCTN50834814 RCT Multicenter N = 361 Australia Setting: Other</td>
<td>Target: Two face-to-face sessions with the parent and child approximately 2 weeks apart, each session 3.5 hours, parents completed a sleep diary, the second consultation and followup telephone call were used to review the sleep diary, reinforce suggested strategies, and troubleshoot any problems; clinician provided information about normal sleep, sleep cycles, and sleep hygiene strategies, and formulated a behavioral sleep management plan</td>
<td>Intervention: Two face-to-face sessions with the parent and child approximately 2 weeks apart, each session 3.5 hours, parents completed a sleep diary, the second consultation and followup telephone call were used to review the sleep diary, reinforce suggested strategies, and troubleshoot any problems; clinician provided information about normal sleep, sleep cycles, and sleep hygiene strategies, and formulated a behavioral sleep management plan</td>
<td>Children’s Sleep Habits Questionnaire. Proportion of children with moderate to severe sleep problems was lower in the intervention (28.0%, 35.8%) compared with usual care group (55.4%, 60.1%) at 3 months as reported by primary caregiver.</td>
</tr>
</tbody>
</table>

<sup>[1]</sup> Murdoch Childrens Research Institute (Australia), 2014
<sup>[2]</sup> Hiscock, 2019
<sup>[3]</sup> ID: ISRCTN50834814 RCT Multicenter N = 361 Australia Setting: Other
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<th>Intervention</th>
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<tr>
<td>N/A</td>
<td>disordered delayed sleep phase disorder, or had sleep-related anxiety Other: Pediatricians ADHD presentation: Diagnosis: Confirmation by specialist DSM-5 diagnostic criteria for ADHD Comorbidity: Sleep Female: 25.1 % Age mean: 9.6 (1.7) Minimum age: 5 Maximum age: 13 Ethnicity: Other info on race or ethnicity</td>
<td>Families in the control group could access care as usual from their pediatrician, which does not typically include assessment and management of child sleep problems Comparator: NA Follow-up: 6 months</td>
<td>National Youth Survey Self-Report Delinquency Scale, Delinquency Among adolescents who engaged in any delinquency, CASH-AA + MIP clients showed greater declines in delinquent acts than CASH-AA Only clients. Inattentive/Disorganized and Hyperactive/Impulsive subscale, Mini-International Neuropsychiatric Interview (MINI) There was a significant association between intervention group and fewer inattentive symptoms (self report) in a quadratic equation controlling for age, race, sex, and baseline substance use. Effects on self-reported hyperactive symptoms were not sign</td>
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<td>Hogue, 2020</td>
<td>Hogue, 2020\textsuperscript{125} National Center on Addiction and Substance Abuse at Columbia University, 2015\textsuperscript{1080} ID: NCT02420990 Cluster RCT Multicenter N = 145 US Setting: Specialty care</td>
<td>Target: Adolescents with ADHD, 77% met criteria for more than one disorder, 42% were on ADHD medication Other: Parents involved with intervention ADHD presentation: N/A Diagnosis: Confirmation by specialist Yes, however only 77% of the sample met full diagnostic criteria for ADHD based on researcher administered interviews; per the study eligibility criteria, the remaining 23% were enrolled</td>
<td>Intervention: Changing Academic Support in the Home for Adolescents with ADHD, a 3-module protocol that utilizes family and individual sessions to improve school performance, flexible protocol that do not prescribe a fixed number of sessions or intervention sequences, one year of observation Control: NA Comparator: Medication + behavioralMedication program is a family-based protocol designed to integrate medication services into behavioral treatment planning for adolescents with ADHD; contains 5</td>
<td>N/A</td>
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<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
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<tr>
<td>Psychological or behavioral</td>
<td>Huang, 2015(^{11}) ID: N/A Clinical trial Single center N = 97 Taiwan Setting: N/A</td>
<td>Target: Boys and girls with ADHD in grades 1 though 4; children with autism and mental retardation were excluded Other: Parents and teachers provided outcome data ADHD presentation: inattentive : 19.6,combined : 80.4 Diagnosis: Confirmation by specialist DSM-IV-TR Comorbidity: N/A Female: 17.5 % Age mean: 8.4 (0.9) Minimum age: 7 Maximum age: 10</td>
<td>Intervention: Social skill training combined with parent training, 7 consecutive 8-week behavioral-based group sessions, 80-minute group sessions during consecutive weeks teaching social skill modules using didactic instructions, modeling, role-play activities, behavior rehearsal, homework was assigned for each week Control: No intervention Recruited from referral as a control group, motivated for group therapy but could not find a mutually available time Comparator: NA Follow-up: 4 months</td>
<td>Change in Delinquent Behavior, Child Behavior Check List (CBCL) No statistically significant group effect (p=0.38). Inattention scale SNAP-IV (Swanson, Nolan, and Pelham, version IV) change, parent There was no significant difference between groups on parent SNAP IV inattention (p=.41) or hyperactive/impulsivity (p = .13) scales. Significant effect of intervention on oppositional scale (p = .04). No significant effect of group on any teacher SNAP I Teacher version of modified social skill rating system (SSRS): intervention group improved more on Active Participation scale (p = .03) but not on Cooperative Behavior, Self Assertion, Self Control or Conflict Coping</td>
</tr>
</tbody>
</table>

<p>| | based on already being treated for ADHD Comorbidity: N/A Female: 28 % Age mean: 14.8 (1.95) Minimum age: 12 Maximum age: 18 Ethnicity: % Hispanic or Latino : 37 % Black/African American : 15 % White : 42 % Multiracial : 6 Other info on race or ethnicity: modular tasks: ADHD Assessment &amp; Medication Consult, ADHD Psychoeducation &amp; Client Acceptance Follow-up: 12 months | School functioning Association with grades, academic self-efficacy, problems with homework, and time spent on homework were not statistically significant in models controlling for age, sex, race, and baseline substance abuse. |</p>
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<td><strong>Study:</strong> Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td><strong>Comparison:</strong> Intervention; Control; Comparator; Follow-up</td>
<td><em>Impulsivity/ hyperactivity scale, Conners parent symptom questionnaire</em>&lt;br&gt;Significant effect of intervention (p &lt; .001).&lt;br&gt;Intervention effect on hyperactivity index was also significant (p &lt; .001).&lt;br&gt;Significant effect of intervention on full-scale attention quotient (FAQ; p &lt; .001) and full-scale response control quotient (FRCQ, p = 0.014) from integrated visual and auditory comprehensive continuous performance tests.</td>
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<td><strong>Ethnicity:</strong> Other info on race or ethnicity: N/A</td>
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<td>Huang, 2021&lt;sup&gt;139&lt;/sup&gt; Fujian Maternity and Child Health Hospital, 2022&lt;sup&gt;79&lt;/sup&gt; ID: ChiCTR2100049863 RCT Single center N = 201 China Setting: Other</td>
<td><strong>Target:</strong> Treatment naive children with ADHD. Exclusion: IQ &lt;75, history of seizures, psc co-morbidities.&lt;br&gt;<strong>Other:</strong> Parents provided some outcome information &lt;br&gt;<strong>ADHD presentation:</strong> inattentive : 62.7, hyperactive : 13.9, combined : 23.4 &lt;br&gt;<strong>Diagnosis:</strong> Confirmation by specialist 2 independent providers used DSM V &lt;br&gt;<strong>Comorbidity:</strong> N/A &lt;br&gt;<strong>Female:</strong> 29.4 % &lt;br&gt;<strong>Age mean:</strong> 5.6 (0.65) Preschool &lt;br&gt;<strong>Minimum age:</strong> &lt;br&gt;<strong>Maximum age:</strong> &lt;br&gt;<strong>Ethnicity:</strong> % Asian : 100 Other info on race or ethnicity:</td>
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<td><strong>Intervention:</strong> Behavioral intervention group included parental training (1 hour weekly sessions), behavioral therapy, attention training (twice per day), relief therapy and game therapy, plus conventional therapy (biofeedback and a health education booklet), intervention lasted for 1 year</td>
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<td>Intervention</td>
<td>Study</td>
<td>Population</td>
<td>Comparison</td>
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<tr>
<td>Psychological or behavioral</td>
<td>Kareem, 2021</td>
<td>Target: Children recently diagnosed with ADHD</td>
<td>Intervention: Attention training intervention consisted of 12 sessions from 30 to 45 min with 5 children with their parents, 1 session per week</td>
</tr>
<tr>
<td>Psychological or behavioral</td>
<td>Li, 2022</td>
<td>Target: Children with ADHD without co-morbid serious psychiatric disorders or medical conditions</td>
<td>Intervention: Theme building block games, with 2 to 3 children per group, once a week for 8 weeks - the scheme provides an interactive environment for children to promote their psychological and behavioral development - the research instructor gives specific instructions (e.g., we are going to build a castle today)</td>
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<td>Intervention</td>
<td>Study:</td>
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<tr>
<td>Psychological or behavioral</td>
<td>McGrath, 2011 RCT</td>
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<tr>
<td></td>
<td>ID: NA</td>
<td>Female: 47.8 %</td>
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<td></td>
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<td>Age mean: 5.01 (0.36)</td>
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<td></td>
<td></td>
<td>Minimum age: 3</td>
<td>Follow-up: 2 months</td>
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<td></td>
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<td>Maximum age: 7</td>
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<td></td>
<td></td>
<td>Ethnicity:</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>% Asian: 100</td>
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<td></td>
<td></td>
<td>Other info on race or ethnicity:</td>
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<tr>
<td></td>
<td></td>
<td>ADHD presentation: N/A</td>
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<td></td>
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<td>Diagnosis: Confirmation by specialist DSM-IV, K-SADS-PL</td>
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<td></td>
<td></td>
<td>Comorbidity: N/A</td>
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<tr>
<td></td>
<td></td>
<td>Female: 25 %</td>
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<tr>
<td></td>
<td></td>
<td>Age mean: 8.89 (1.92)</td>
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<td></td>
<td></td>
<td>Minimum age: 8</td>
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<td></td>
<td></td>
<td>Maximum age: 12</td>
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<td></td>
<td>Intervention: The Strongest Families intervention based on evidence and skill-focused learning, anxiety program consisted of 11 sessions and the behavior programs had 12 sessions, weekly coach session calls were on average 40 minutes, 1 year of follow-up</td>
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<tr>
<td></td>
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<td>Control: No intervention</td>
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<td></td>
<td></td>
<td>Control participants received one call from the coach to review the randomization placement results and to inform the parent that the next contact from study staff would be at the 120-day follow-up time point to collect assessment data only</td>
<td>Comparator: NA</td>
</tr>
<tr>
<td></td>
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<td>Follow-up: 12 months</td>
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Appendix C. Evidence Tables
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<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological or behavioral</td>
<td>Meyer, 2021 Uppsala County Council, 2016 ID: ISRCTN17366720 RCT Multicenter N = 184 Sweden Setting: Specialty care</td>
<td>Target: Adolescents with ADHD; exclusion: severe depression, suicidality, psychosis, or bipolar disorder without stable meds, mental retardation, autism, current substance abuse. Other: Parents reported some outcomes. ADHD presentation: inattentive : 25.6, combined : 70.7, N/A : Unspecified: 3.7 Diagnosis: Confirmation by specialist DSM V per Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) Comorbidity: N/A Female: 63.9 % 65.8% (SSTG) and 62% (Control) females (all with ADHD) Age mean: SSTG 16.46 (0.88), control 16.71 (0.94) Minimum age: 15</td>
<td>Intervention: Age-adapted structured skills training group program based on a manualized dialectical behavioral therapy (DBT) consisting of 14 weekly 2-hour sessions where each session focused on a specific theme; the program includes elements of DBT, psychoeducation and strategies for managing difficulties related to ADHD. Control: NA Comparator: OtherManual-based psychoeducational group program of three 2-hour sessions focusing on psychoeducation about ADHD, including information about ADHD symptomatology, strengths and challenges with ADHD, sleep and diet; the participants also received a book descri</td>
<td>ASRS-A (ADHD Self-Report Scale for Adolescents) - Self-rating No group effect on patient or parent reported symptoms on ADSR. Child Sheehan Disability Scale (CSDS), adolescent report No difference in effect on patient or parent report. No significant group differences regarding acceptability. No difference in effect on Quality of Life or Impact of ADHD Symptoms (IAS) on well-being. No difference in effect on Hospital Anxiety and Depression Scale (HADS).</td>
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### Appendix C. Evidence Tables

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<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Comparison: Intervention; Control; Comparator; Follow-up</td>
<td>Classroom rule violations The behavior management intervention exhibited significantly fewer classroom rule violations per hour than the comparator of medication intervention (incidence rate ratio 0.66, p&lt;0.01). ADHD, Disruptive Behavior Disorders Rating Scale No difference between groups (effect size - 0.01). Social Skills Total Score SSRS, parent There was no significant difference between groups for the Social Skills Total Score. 67% of the children who began treatment with behavioral interventions required additional treatment by the end of the school year compared with 47% of the children who began the school year receiving a low dose of medication (OR 2.23). Survival analyses indicated a significant group difference (p &lt; 0.01).</td>
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<td>Pelham, 2016&lt;sup&gt;52&lt;/sup&gt;</td>
<td>Maximum age: 18</td>
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<td>ID: N/A</td>
<td>Ethnicity: Other info on race or ethnicity: N/A</td>
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<tr>
<td>Crossover trial</td>
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<td>Single center</td>
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<td>N = 152</td>
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<td>US</td>
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<td>Setting: Mixed</td>
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<tr>
<td>Psychological or behavioral</td>
<td>Target: Children with ADHD, between the ages of 5 and 12, were included with clinically diagnosed ADHD. Children should not have (1) Full-Scale IQ below 70; (b) history of seizures or other neurological problems; (c) history of other medical problems ; (d) childhood history or concurrent diagnosis of pervasive developmental disorder, schizophrenia or other psychotic disorders, sexual disorder, organic mental disorder, or eating disorder; (e) lack of functional impairment; and (f) placement in special education classrooms. Other: Parents, teachers ADHD presentation: inattentive_other : mean score: Medication First: 7.6 (1.9); Behavioral First: 8.1 (1.5),hyperactive_other : mean score Hyperactivity/Impulsivity: Medication First: 7.1 (2.2); Behavioral First: 6.8 (2.1)</td>
<td>Intervention: Behavioral first intervention, social skills training sessions for children, parent training (8 group sessions), and brief teacher consultation to establish a daily report card, report cards were sent home each day and parents provided rewards for good performance, monthly parent-training booster session for 8 weeks, case manager communicated with teacher monthly for one school year Control: NA Comparator: MedicationMedication first intervention, extended-release methylphenidate (equivalent to .15 mg/kg/dose bid)</td>
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<td>Follow-up: 4 months</td>
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<tr>
<td>Intervention</td>
<td>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Comparison: Intervention; Control; Comparator; Follow-up</td>
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<tr>
<td>Pfiffner, 2014; Tran, 2018; Haack, 2017; Rooney, 2018; Adalio, 2018</td>
<td>Diagnosis: Confirmation by specialist DSM-IV by clinicians Comorbidity: N/A Female: 24 % Age mean: Medication first 8.3 (2), behavioral first 8.5 (1.8) Minimum age: 5 Maximum age: 12 Ethnicity: % Black/African American: 12.3 % White: 80.1 Other info on race or ethnicity:</td>
<td></td>
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</tr>
<tr>
<td>Psychological or behavioral</td>
<td>Target: Children with ADHD-inattentive type and IQ &gt; 80, living with at least one parent for the past year, attending school (grades 2 - 5) full time in a regular classroom, ability to participate in our groups on the days scheduled, school proximity within 45 minutes of study site to allow for the clinician to conduct school meetings, and teacher consent to participate in a school-based treatment Other: Parents received training and provided some outcomes ADHD presentation: inattentive: 100</td>
<td>Intervention: Child Life and Attention Skills (CLAS) program included three manualized coordinated components: (a) ten 90-minute parent group meetings, along with up to six 30-minute family meetings (parent, child, and therapist); (b) ten 90-minute child group meetings; and (c) teacher consultation, which included one 30-minute orientation meeting involving the teacher and therapist and up to five subsequent 30-minute meetings with the parent, child, teacher, and therapist and booster sessions, treatment occurred over a 10- to 13-week period</td>
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### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
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<th>Comparison:</th>
<th>Outcome and results</th>
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</thead>
<tbody>
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<td></td>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Diagnosis: Confirmation by specialist DSM-IV diagnosis confirmed by the KSADS-PL by clinician Comorbidity: N/A Female: 42 % Age mean: 8.6 (1.2) Minimum age: 7 Maximum age: 11 Ethnicity: % Hispanic or Latino : 17 % Black/African American : 5.0 % Asian : 8.0 % White : 54.0 % Multiracial : 17.0 Other info on race or ethnicity:</td>
<td>Control: TAU Treatment as usual did not receive either study intervention; families received a written diagnostic report based on the assessment conducted at baseline, a list of community treatment providers, but no specific treatment recommendations; families were Comparator: Behavioral Parent-focused treatment included parent training teaching parent skills but did not receive specific training in how to work with teachers and were not informed about the child skills taught in the CLAS condition; families received the same number of par</td>
<td>Teachers did not report differences across groups regarding overall impairment. Parent and teacher satisfaction Parent and teacher satisfaction with CLAS was very high; &gt;95% of parents rated the child and parent skills taught as useful or very useful, 94% of teacher rated the classroom challenge as helpful or very helpful. Parent satisfaction with the comparator in</td>
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<td></td>
<td>Power, 2012 [49]</td>
<td>Target: Children meeting criteria for ADHD, Combined Type or ADHD, Inattentive Type who are enrolled in school and scored at or above 0.75 of a standard deviation above the mean on the Homework Problem Checklist; children scoring at or above an estimated IQ of 75 on the 2-subtest version of the Wechsler Abbreviated Scale of Intelligence Other: Parents, teachers ADHD presentation: inattentive: 51.8, combined: 48.3</td>
<td>Intervention: Family-School Success over the course of 12 weekly sessions, which included 6 group sessions (90 minutes each), 4 individualized family sessions (60 minutes each), and 2 school-based consultations (45 minutes each) Control: NA Comparator: Behavioral Coping with ADHD through Relationships and Education (CARE) included 11 group sessions and 1 family-school meeting, which were held on consecutive weeks. The initial</td>
<td>SNAP-P (Swanson, Nolan, and Pelham Questionnaire), parent-report There was no intervention effect on ADHD and ODD symptoms, as assessed by parent and teacher ratings on the SNAP-IV. parent-rated Treatment Acceptability Questionnaire (TAQ) Tx acceptance significantly higher for intervention (p = .006). Academic Performance Rating Scale (APRS) Group had no effect on improvement.</td>
</tr>
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<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychological or behavioral</strong></td>
<td>Qian, 2021\textsuperscript{[474]}; Zili Fan, 2016\textsuperscript{[1156]}; ID: NCT02656758</td>
<td><strong>Diagnosis:</strong> Confirmation by specialist Parent-report on the Schedule for Affective Disorders and Schizophrenia for School Age Children - DSM IV by clinician <strong>Comorbidity:</strong> Learning disability: homework problems, N/A <strong>Female:</strong> 32% <strong>Age mean:</strong> Grade level (M and SD) 3.5 (1.2) <strong>Minimum age:</strong> 7 <strong>Maximum age:</strong> 10 <strong>Ethnicity:</strong> % Hispanic or Latino: 7.1 % Black/African American: 22.2 % Asian: 2.0 % White: 72.4 % Multiracial: 3.5 Other info on race or ethnicity: session was conducted on a Saturday for 3 hours and subsequent meetings were 75 minutes</td>
<td><strong>Follow-up:</strong> 3 months</td>
<td>ADHD-RS-IV (ADHD Rating Scale IV) scores intervention group improved more (group x time p = 0.004). Same for inattention (p = 0.007) and hyperactivity (p = 0.020) subscales. WEISS Function Impairment Scale-Parent report, total There was no significant difference between groups.</td>
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<th>Outcome and results</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>emergent psychiatric condition that needed immediate medication</td>
<td>12-week waitlist, after which group received intervention</td>
<td>Behavior Rating Scales of Executive Function (BRIEF): no effect of group on any subscales.</td>
</tr>
<tr>
<td></td>
<td>Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Other: Parents</td>
<td>Comparator: NA</td>
<td></td>
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<tr>
<td></td>
<td>ADHD presentation: inattentive : 51.43, hyperactive : 4.29, combined : 44.29</td>
<td>Diagnosis: Confirmation by specialist</td>
<td>Follow-up: 3 months</td>
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<td></td>
<td>DSM-IV criteria based on parent ratings of the ADHD-rating scale-IV and was then confirmed by a semi-structured interview conducted by experienced pediatric psychiatrists using the clinical diagnostic interview scale.</td>
<td>Comorbidity: N/A</td>
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<td></td>
<td>Gender: 23 %</td>
<td>Female: 23 %</td>
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<td></td>
<td>Age mean: 9.24 (1.04)</td>
<td>Age mean: 9.24 (1.04)</td>
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<td>Minimum age: 6</td>
<td>Minimum age: 6</td>
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<td>Maximum age: 12</td>
<td>Maximum age: 12</td>
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<td>Ethnicity: Other info on race or ethnicity:</td>
<td>Ethnicity: Other info on race or ethnicity:</td>
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<tr>
<td>Psychological or behavioral</td>
<td>Schuck, 2018&lt;sup&gt;110&lt;/sup&gt; Schuck, 2018&lt;sup&gt;195&lt;/sup&gt;</td>
<td>Target: Children with ADHD Combined Type</td>
<td>Intervention: Canine assisted psychosocial intervention, 12 weekly 2-hour sessions</td>
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<tr>
<td></td>
<td>ID: NA RCT Single center N = 88 US</td>
<td>Other: Parents</td>
<td>Control: Other Psychosocial intervention without canine assisted intervention; parents participated in 12 weekly 2-hour sessions of group Behavioral Parent Training emphasizing positive</td>
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<td></td>
<td>ADHD presentation: combined : 100</td>
<td>ADHD presentation: combined : 100</td>
<td>Social Skills Improvement System (SSIS) Problem Behaviors scale A significant interaction of group by time (p =.002) was found at treatment completion for problem behaviors. ADHD-RS-IV (Attention-Deficit/Hyperactivity Disorder Rating Scale, 4th Edition) total score, parent report</td>
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<td></td>
<td>Diagnosis: Confirmation by specialist DSM-IV confirmed by Kaufman-Schedule for Affective Disorders</td>
<td>Diagnosis: Confirmation by specialist DSM-IV confirmed by Kaufman-Schedule for Affective Disorders</td>
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<th>Population:</th>
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</thead>
<tbody>
<tr>
<td><strong>Setting:</strong> Community</td>
<td><strong>and Schizophrenia for School-Age Children: Present and Lifetime Version (K-SADS-PL)</strong></td>
<td><strong>Comorbidity:</strong> N/A</td>
<td><strong>Comparator:</strong> NA</td>
<td>Ratings were significantly lower in the intervention group than control group but the difference was borderline significant (p = 0.06).</td>
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<td></td>
<td><strong>Female:</strong> 28.5 %</td>
<td><strong>Age mean:</strong> 7.65 (0.75)</td>
<td><strong>Follow-up:</strong> 3 months</td>
<td>Self esteem was measured by the Self-Perception Profile for Children and children's self-perceptions in the domains of behavioral conduct, social, and scholastic competence, were significantly increased from baseline to post-treatment in intervention group (p = .021, p = .008, and p = .011) while the control group did not experience significant increases.</td>
</tr>
<tr>
<td></td>
<td><strong>Minimum age:</strong> 7</td>
<td><strong>Maximum age:</strong> 9</td>
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<td>There no adverse events across seven cohorts of treatment</td>
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<td></td>
<td><strong>Ethnicity:</strong></td>
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<tr>
<td></td>
<td>% Hispanic or Latino : 29.5</td>
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<td></td>
<td>% Black/African American : 1.5</td>
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<tr>
<td></td>
<td>% Asian : 12.5</td>
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<td></td>
<td>% Native Hawaiian or Pacific Islander : 1.5</td>
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<td></td>
<td>% White : 62</td>
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<td>% Multiracial : 20.5</td>
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<td>Other info on race or ethnicity:</td>
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<tr>
<td><strong>Target:</strong> Children with ADHD and behavioral sleep disorder or experiencing significant bedtime anxiety leading to insomnia, and parents needed to rate as moderate/severe sleep problem</td>
<td><strong>Other:</strong> Parents</td>
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<td></td>
<td><strong>ADHD presentation:</strong> N/A</td>
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<tr>
<td></td>
<td><strong>Diagnosis:</strong> Confirmation by specialist</td>
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<td><strong>DSM-IV</strong></td>
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<td></td>
<td><strong>Comorbidity:</strong> Sleep</td>
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<td></td>
<td><strong>Female:</strong> 14.7 %</td>
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<tr>
<td><strong>Intervention:</strong> Family intervention, 2 face to face, fortnightly consultations about sleep with a trained clinician; clinician assessed the child’s sleep problem, elicited parent goals for sleep management, provided information about normal sleep, sleep cycles, and sleep hygiene strategies, and formulated a behavioral sleep management plan tailored to the child’s sleep problem; parents were asked to complete a sleep diary; the second consultation and a follow-up telephone call were used to review the sleep diary,</td>
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<td><strong>ADHD-RS-IV (ADHD rating scale IV), total score,</strong> parent</td>
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<td>intervention group improved more on parent rating (p = .001) but not teacher rating (p = .91).</td>
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<td><strong>Daily Parent Rating of Evening and Morning Behavior (DPREMB)</strong></td>
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<th>Outcome and results</th>
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<tbody>
<tr>
<td></td>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Age mean: 10.1 (2.0) Minimum age: 5 Maximum age: 12 Ethnicity: Other info on race or ethnicity: N/A</td>
<td>Intervention; Control; Comparator; Follow-up</td>
<td>The intervention group improved more than control group (p = .001). Child sleep habits questionnaire—total score: Intervention group improved more than control (p &lt; .02).</td>
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<tr>
<td></td>
<td>Sibley, 2016</td>
<td>ADHD presentation: inattentive: 39.1, combined: 60.9</td>
<td>Control: TAU Families allocated to ‘usual care’ accessed care from their child’s pediatrician, which does not usually involve the assessment and treatment of sleep problems Comparator: NA</td>
<td>Disruptive behavior, parent report Group by time effects were nonsignificant (p=0.343). ADHD Symptom Severity, Disruptive Behavior Disorder Rating Scale (DBD), parent report The intervention group improved compared to the control group (p &lt; .001). Cumulative GPA There were no significant differences between intervention and comparator group (p=0.265).</td>
</tr>
<tr>
<td></td>
<td>ID: NA RCT Multicenter N = 128 US Setting: School</td>
<td>Diagnosis: Confirmation by specialist Phone screen containing the DSM-IV-TR ADHD symptoms and questions about impairment was administered to the primary caretaker. Then in person parent structured interview (Computerized-Diagnostic Interview Schedule for Children) and symptom assessment Concomorbidity: N/A</td>
<td>Intervention: Supporting Teens’ Academic Needs Daily (STAND) consists of ten 50-minute manualized family therapy sessions attended by the parent and teen, uses motivational interviewing Control: TAU Treatment as usual, without intervention Comparator: NA</td>
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<tr>
<td></td>
<td>Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td>Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Intervention; Control; Comparator; Follow-up</td>
<td>ADHD symptoms inattention, parent rating No difference in parent reported inattention (p = 0.61) or hyperactivity (p=0.37) scores. No difference in teacher reported inattention (p = 0.07) or hyperactivity (p= 0.50) scores. Organization, time management, and planning impairment, skills applied to homework, school, and chores, parent report There was no difference across groups in either parent (p=0.84) or teacher (p=0.23) reported. Teen treatment satisfaction No significant differences in treatment satisfaction (p = 0.81) or percentage of treatment attended (p=0.16). Grade Point Average (GPA) No difference between groups (p = 0.50).</td>
</tr>
<tr>
<td>Psychological or behavioral</td>
<td>Sibley, 2020&lt;sup&gt;522&lt;/sup&gt; Sibley, 2016&lt;sup&gt;185&lt;/sup&gt; ID: NA RCT Unclear/Not reported N = 123 US Setting: School</td>
<td>Target: Adolescents with ADHD, without any history of autism, intellectual disability or an IQ of less than 70 Other: Parents provided outcome data ADHD presentation: inattentive_other : Dyadic, 49.2% / Parent-Teen Group, 58.3%,combined_other : Dyadic, Parent-Teen 50.8% / Group, 41.7% Diagnosis: Confirmation by specialist DSM 5 via Diagnostic Interview Schedule for Children Comorbidity: N/A Female: 19.6 % Female: Dyadic, 17.5% / Parent-Teen Group, 21.7% Age mean:</td>
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### Appendix C. Evidence Tables

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<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
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<td>Dyadic 13.63 (1.49), Parent-teen group 13.59 (1.78)</td>
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<td>Number of disciplinary incidents No difference in number of disciplinary incidents (p = 0.063).</td>
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<td>Inattention, DSM score, parent report No difference in parent rated inattention score (p = .162), teacher rated inattention score (p = .6340, parent rated hyperactivity score (p = .272), or teacher rated hyperactivity score (p = .801).</td>
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<td>Satisfaction with treatment No group differences in adolescent satisfaction.</td>
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<td>Ethnicity: Other: Dyadic, 85.7% / Parent-Teen Group, 85% Other: Dyadic, 4.8% / Parent-Teen Group, 5% Other: Dyadic, 7.9% / Parent-Teen Group, 8.3% Other info on race or ethnicity:</td>
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<td>Grade Point Average (GPA) No difference (p = .904).</td>
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## Appendix C. Evidence Tables

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<tr>
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<tr>
<td><strong>Study:</strong> Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</td>
<td><strong>Population:</strong> Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td><strong>Comparison:</strong> Intervention; Control; Comparator; Follow-up</td>
<td><strong>Outcome and results</strong></td>
</tr>
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<td>Oppositional behavior scale, Conners Parent Rating Scale (CPRS) No difference between groups. Hyperactivity-impulsivity, SWAN (Strengths and Weaknesses of ADHD symptoms and Normal behaviour) parent-rated Parent-rated hyperactivity-impulsivity group differences were larger and significant in favor of intervention group (p&lt;.05). Difference in parent-rated inattentiveness not significant. No differences in teacher reported hyperactivity-impulsivity or inatte</td>
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<td>No difference in parent-rated self-control deficits measured using 75-item Behaviour Rating Inventory of Executive Function-Adult Version (BRIEF). No CAU- or MBI-related Serious Adverse Events were spontaneously reported by the participants or mindfulness teachers.</td>
</tr>
</tbody>
</table>
| **Study:** Siebelink, 2021; Karakter Kinder en Jeugdpsychiatrie, 2017; Siebelink, 2018 | **Population:** Maximum age: 17 Ethnicity: % Hispanic or Latino : 81.7 % Black/African American : 13.3 % White : 4.7 % Multiracial : 0.7 Other info on race or ethnicity: | |}

<p>| <strong>Target:</strong> Dutch-speaking children and adolescents with ADHD; could use ADHD medication if stable dose was reached two weeks prior to study. No current psychosis, bipolar illness, active suicidality, untreated post-traumatic stress disorder or substance use disorder; no intelligence quotient &lt;80. <strong>Other:</strong> Parents <strong>ADHD presentation:</strong> N/A <strong>Diagnosis:</strong> Confirmation by specialist DSM-4 or DSM-5 confirmed with a structured interview conducted by trained researchers <strong>Comorbidity:</strong> N/A <strong>Female:</strong> 30 % <strong>Age mean:</strong> Intervention 11.0 (1.8), control 11.4 (1.8) <strong>Minimum age:</strong> 8 <strong>Maximum age:</strong> 16 <strong>Ethnicity:</strong> Family mindfulness-based intervention, 8 weekly 90-minute group sessions, followed by a booster session 8 weeks later, homework of approximately 30–45 min/day for parents and 15 min/day for children, also received care-as-usual <strong>Control:</strong> TAU Care-as-usual only <strong>Comparator:</strong> NA <strong>Follow-up:</strong> 8 months |</p>
<table>
<thead>
<tr>
<th><strong>Study</strong>: Storebo, 2012&lt;sup&gt;552&lt;/sup&gt;</th>
<th><strong>Population</strong>: ADHD diagnosis according to DSM, 8-12 years, parents willing to partake, without schizophrenia or autism, no violent and criminal children, with an IQ of 80 or above, without having previously taken medication for ADHD</th>
<th><strong>Comparison</strong>: Intervention; Control; Comparator; Follow-up</th>
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<tr>
<td><strong>Target</strong>: ADHD diagnosis according to DSM, 8-12 years, parents willing to partake, without schizophrenia or autism, no violent and criminal children, with an IQ of 80 or above, without having previously taken medication for ADHD</td>
<td><strong>Other:</strong> ADHD presentation: inattentive: 29.1, hyperactive: 3.9, combined: 58</td>
<td><strong>Outcome and results</strong></td>
</tr>
<tr>
<td><strong>Diagnosis</strong>: Confirmation by specialist DSM-IV by psychologists from the Clinic</td>
<td><strong>Comorbidity</strong>: N/A</td>
<td><strong>Hyperactivity-impulsivity subindex Conner’s 3rd Edition Rating Scale</strong></td>
</tr>
<tr>
<td><strong>Female</strong>: 30%</td>
<td><strong>Female</strong>: 30%</td>
<td>Social skills training plus parental training did not show any significant benefit for children with attention deficit hyperactivity disorder when compared with standard treatment.</td>
</tr>
<tr>
<td><strong>Age mean</strong>: 10.4 (1.31)</td>
<td><strong>Minimum age</strong>: 8</td>
<td>Academic performance based on Conners-3 and CBRS No difference between groups.</td>
</tr>
<tr>
<td><strong>Maximum age</strong>: 12</td>
<td><strong>Maximum age</strong>: 12</td>
<td>Participants with adverse events No adverse events were observed.</td>
</tr>
<tr>
<td><strong>Ethnicity</strong>: Other info on race or ethnicity: N/A</td>
<td><strong>Ethnicity</strong>: Other info on race or ethnicity: N/A</td>
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</tbody>
</table>
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<th>Intervention</th>
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<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
</table>
| Psychological or behavioral | Valero, 2021<sup>151</sup>  
ID: NA  
RCT  
Unclear/Not reported  
N = 30  
Spain  
Setting: Community | Target: Children aged 9 through 14 with ADHD  
Other: Parents also received mindfulness training  
ADHD presentation: inattentive: 30, hyperactive: 13, combined: 57  
Diagnosis: Confirmation by specialist  
Diagnosis had to be performed by a specialist—psychologist, neuro-pediatrician, or psychiatrist—at least 2 years prior to participation. ADHD confirmed by parent version of Conners—3rd Edition  
Comorbidity: N/A  
Female: 23.3%  
Age mean: 10.6 (1.69)  
Minimum age: 9  
Maximum age: 14  
Ethnicity: Other info on race or ethnicity: N/A | Intervention: Mindfulness training, 8 sessions over an 8-week period, children’s sessions were 1 hour long, parent sessions were 1.5 hours  
Control: Wait list  
Comparator: NA  
Follow-up: 6 months | and atomoxetine was considered in patients where  
Comparator: NA  
Follow-up: 6 months |

Conners—3rd Edition, aggressive behavior scale  
Intervention group had less aggression at follow-up (p = .045).  
Inattention score, Conner’s Version 3, parent report  
At follow-up, intervention group showed less inattention compared to the wait-list group (p = .0324). There was no difference in hyperactivity/impulsivity score p = (.103).  
Conners Version 3, parent report, executive function, intervention group had better executive function (p = .002).
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<th>Outcome and results</th>
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<tbody>
<tr>
<td>Psychological or behavioral</td>
<td>Wilkes-Gillan, 2016&lt;sup&gt;63&lt;/sup&gt; Barnes, 2017&lt;sup&gt;63&lt;/sup&gt; ID: ACTRN1261400973617 Crossover trial Single center N = 31 Australia Setting: Mixed</td>
<td><strong>Target:</strong> Children with ADHD with co-morbid difficulties (i.e., language difficulties, conduct disorder); exclusion: other major developmental disorders (i.e., intellectual disability, autism spectrum disorder) <strong>Other:</strong> Parents, plus a &quot;typical&quot; friend of each child <strong>ADHD presentation:</strong> inattentive: 38, hyperactive: 3, combined: 59 <strong>Diagnosis:</strong> Confirmation by specialist DSM-IV by pediatrician or psychiatrist <strong>Comorbidity:</strong> Learning disability <strong>Female:</strong> 13 % <strong>Age mean:</strong> 8.4 (1.6) <strong>Minimum age:</strong> 5 <strong>Maximum age:</strong> 11 <strong>Ethnicity:</strong> Other info on race or ethnicity: N/A</td>
<td><strong>Intervention:</strong> 1-hour play-based intervention sessions for 10 weeks <strong>Control:</strong> Wait list No treatment for 10 weeks, after which the group crossed over to the 10-week play-based intervention. Outcomes reported pre-crossover. <strong>Comparator:</strong> NA <strong>Follow-up:</strong> 2.5 months</td>
<td>The change in play scores for the intervention-first group was significantly greater than the change in the control-first group during their 10 week wait period (p &lt; .001). One year follow up did not have adequate power.</td>
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<td>Teacher, school environment</td>
<td>Breaux, 2018&lt;sup&gt;171&lt;/sup&gt; Langberg, 2018&lt;sup&gt;806&lt;/sup&gt;, Smith, 2020&lt;sup&gt;1065&lt;/sup&gt; ID: N/A RCT Multicenter N = 222</td>
<td><strong>Target:</strong> Children met full DSM–IV–TR diagnostic criteria for ADHD based on the Parent Children’s Interview for Psychiatric Syndromes or combined with teacher ratings on the National Institute for Children’s Health Quality Vanderbilt ADHD Rating Scale; intelligence quotient of 80 or more</td>
<td><strong>Intervention:</strong> Completing Homework by Improving Efficiency and Focus (CHIEF) is contingency management-based treatment, 16 sessions delivered during the school day, first 10 sessions occurred twice weekly and final six sessions occurred once per week, completed over 11-weeks, also included two 1-</td>
<td>Grade Point Average (GPA) Adolescent involvement, parent involvement and other therapeutic processes led to an increase in GPA posttreatment.</td>
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### Appendix C. Evidence Tables

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<tr>
<td>Teacher, school</td>
<td>Corkum, 2019; Dalhousie University, 2012</td>
<td>Target: Children attending Grades 1 to 6; enrolled in an English classroom, or teacher was able to complete the program in English; previously diagnosed with ADHD</td>
<td>Intervention: Teachers given weekly online sessions for 6 weeks, session covered a different topic related to education, treatment, support and additional interventions</td>
<td>ADHD Index Conners 3-T Significant improvements based on teacher (but not parent) reports of core ADHD symptoms. Impairment ratings score, teacher</td>
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## Appendix C. Evidence Tables

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<th>Intervention Study:</th>
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<th>Comparison:</th>
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<tbody>
<tr>
<td>Author, year;</td>
<td>Setting;</td>
<td>Intervention;</td>
<td>Significant improvement associated with the intervention.</td>
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<tr>
<td>Multiple publications;</td>
<td>Study target;</td>
<td>Control;</td>
<td>Teacher intervention satisfaction (content presented was easy to understand) Rated 5.28 90.84) on a 6-point scale</td>
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<tr>
<td>Trial ID;</td>
<td>ADHD presentation;</td>
<td>Comparator;</td>
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<tr>
<td>Study design;</td>
<td>Diagnosis;</td>
<td>Follow-up</td>
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<tr>
<td>Sites;</td>
<td>Comorbidity;</td>
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<tr>
<td>Study size;</td>
<td>% Female;</td>
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<tr>
<td>Location Setting</td>
<td>Age mean;</td>
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<td>RCT Multicenter</td>
<td>by health care provider who was certified to make mental health diagnoses; on a stable dose of medication for ADHD or was taking no medication, with no plan to start or change medications for the duration of the study; no Individualized Program Plan due to significant physical, behavioral, communication, or intellectual difficulties; no significant co-occurring mental health problems aside from ADHD; no moderate or severe intellectual impairment; no previous involvement with the Teacher Help for ADHD program Other: Teachers of students with ADHD ADHD presentation: N/A Diagnosis: No doesn’t indicate confirmation, but does indicate that participants were previously diagnosed by a certified health care provider Comorbidity: N/A Female: 12 % Age mean: 8.83 (1.72) Minimum age: 6 Maximum age: 12 Ethnicity: % White : 90</td>
<td>Control: Wait list Waitlist group did not receive any intervention but were free to access usual care. Waitlist lasted 12 weeks Comparator: NA Follow-up: 6 months</td>
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### Intervention

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<tr>
<td>Other info on race or ethnicity: Other : 10% non-caucasian</td>
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<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
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<tr>
<td>Intervention: Multi-component training interventions: individual coaching sessions for 15–20 min twice per week throughout the academic year, at least monthly collaborative problem-solving between the teen and coach, ten 90-min evening group sessions at their school offered separately for adolescents and parents</td>
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<tr>
<td>Control: TAU</td>
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<td>Comparator: NA</td>
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<td>Follow-up: 6 months</td>
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<tbody>
<tr>
<td>Tardiness frequency</td>
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<td>There was no statistically significant Group (p=0.75) or Time (p=0.96) effect for school tardiness.</td>
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<td>Adolescent Academic Problems Checklist Total</td>
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<tr>
<td>The intervention group had significantly fewer academic problems compared to the comparator group (p&lt;0.01).</td>
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<td>Children's Organization Skills Scale Task Planning showed steeper negative slopes (i.e., more improvement over time) for intervention participants than those in the community care condition.</td>
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<tr>
<td>Evans, 2016&lt;sup&gt;262&lt;/sup&gt; Langberg, 2016&lt;sup&gt;361&lt;/sup&gt;; Schultz, 2017&lt;sup&gt;996&lt;/sup&gt; ID: N/A RCT Multicenter N = 326 US Setting: School</td>
<td>% White : 74 Other info on race or ethnicity: Other : Other 4.8%</td>
<td>Intervention: Challenging Horizons Program–after school version (CHP-AS): 2 days per week for 2 hr 15 min per day for 9 months <strong>Control:</strong> TAU Community care condition received a list of available resources in their community at the start of the school year; resource lists were developed in collaboration with school staff to include locally available child and family psychosocial and pharmacolog <strong>Comparator:</strong> Teacher, school environment Challenging Horizons Program–mentoring version provided by a teacher or other staff member in their school (mentor); mentor participation was voluntary, and mentors received a small stipend ($100) for participation. Mentors agreed to meet weekly with thei</td>
<td>Inattention and hyperactivity/impulsivity scale, Disruptive Behavior Disorders (DBD) Rating Scale Challenging Horizons Program after school version is associated with moderate effect size improvements in ADHD symptoms of inattention but not hyperactive/impulsive symptoms. IRS (Impairment Rating Scale), relation with peers scale, teacher There were no significant differences between groups. Classroom Performance Survey (CPS), Academic factor, teacher There were no significant differences between groups. Intervention group performed better than mentoring group (p = .0011) and better than community care (p = 0007). Similar results for COSS materials management scale (p=.0430 vs mentoring, p=0 .0010 vs community care).</td>
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<tr>
<td><strong>Target:</strong> Children had to attend one of the participating schools, met full DSM–IV–TR diagnostic criteria for either ADHD–Predominantly Inattentive Type or ADHD–Combined Type ADHD based on the Parent Children’s Interview for Psychiatric Syndromes or combined with teacher ratings on the Disruptive Behavior Disorders Rating Scale, demonstrated impairment based on parent or teacher report on the Impairment Rating Scale, and demonstrated an IQ of 80 or above, and did not meet diagnostic criteria for a pervasive developmental disorder or bipolar disorder, psychosis, or obsessive–compulsive disorder <strong>Other:</strong> Parents and teachers provided data <strong>ADHD presentation:</strong> combined : 49 <strong>Diagnosis:</strong> Confirmation by specialist DSM-IV <strong>Comorbidity:</strong> N/A</td>
<td>Follow-up: 18 months</td>
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<tbody>
<tr>
<td><strong>Intervention</strong>&lt;br&gt;<strong>Target:</strong> Participants with ADHD and not meeting the criteria for severe comorbid disorders (e.g., psychotic episode)&lt;br&gt;<strong>Other:</strong>&lt;br&gt;<strong>ADHD presentation:</strong> Confirmation by specialist DSM-IV-TR by administered by a clinical psychologist under supervision of a board-certified child and adolescent psychotherapist&lt;br&gt;<strong>Comorbidity:</strong> N/A&lt;br&gt;<strong>Female:</strong> 15 %&lt;br&gt;<strong>Age mean:</strong> 13.99 (1.44)&lt;br&gt;<strong>Minimum age:</strong> 12&lt;br&gt;<strong>Maximum age:</strong> 17&lt;br&gt;<strong>Ethnicity:</strong>&lt;br&gt;<strong>Female:</strong> 29 %&lt;br&gt;<strong>Age mean:</strong> 12.1 (1.0)&lt;br&gt;6th grade to 8th grade&lt;br&gt;<strong>Minimum age:</strong>&lt;br&gt;<strong>Maximum age:</strong>&lt;br&gt;<strong>Ethnicity:</strong>&lt;br&gt;% Hispanic or Latino : 3&lt;br&gt;% Black/African American : 12&lt;br&gt;% White : 70&lt;br&gt;% Multiracial : 8&lt;br&gt;Other info on race or ethnicity:</td>
<td><strong>Intervention:</strong> Learning Skills Training for Adolescents With ADHD, a manualized, multimodal intervention combining an adolescent-direct training approach (maximum of 20 sessions of 60 mins each) with a behavioral training component in methods of contingency management for parents and teachers (3 sessions of 90 mins each)&lt;br&gt;<strong>Control:</strong> Wait list&lt;br&gt;Waiting list controls were invited twice for data collection with an average interval of 5.76 (SD ! 1.65) months in between and expected to start intervention after post-measurement, which was offered for ethical reasons.</td>
<td>Inattention, FBB-HKS (Fremdbeurteilungsbogen für Hyperkinetische Störungen), parent report&lt;br&gt;The training significantly reduced ADHS symptoms and parent- and teacher-rated internalizing problems and increased teacher rated academic enablers compared to waiting list controls.</td>
<td></td>
</tr>
</tbody>
</table>

| Study: Schramm, 2016<sup>109</sup><br>ID: NA<br>RCT<br>Single center<br>N = 113<br>Germany<br>Setting: Specialty care | | |

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<table>
<thead>
<tr>
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<tr>
<td>Shen, 2021&lt;sup&gt;317&lt;/sup&gt; School of Public Health, 2018&lt;sup&gt;94&lt;/sup&gt; ID: ChiCTR1800014945 RCT Multicenter N = 232 China Setting: School</td>
<td>Other info on race or ethnicity: N/A: Germans</td>
<td>Comparator: Other Progressive muscle relaxation training, adolescents met in groups of 4-5 twice-weekly for 12–15 sessions (60 mins) and were trained by 2 BA-level students followed by playtime; the students did not mention or talk about ADHD or related problems with the a</td>
<td>Follow-up: 48 months</td>
</tr>
<tr>
<td><strong>Target:</strong> Children meeting the diagnosis of ADHD according to DSM-5, being between 6-12 years old; parents agree to use treatment, can read and write the Chinese language, and signed the informed consent <strong>Other:</strong> ADHD presentation: inattentive: 35.3, hyperactive: 25.4, combined: 27.2, N/A: control and intervention <strong>Diagnosis:</strong> Confirmation by specialist Inclusion criterion to meet the diagnosis of the ADHD according to the DSM5 <strong>Comorbidity:</strong> Female: 12.5% 75.4 <strong>Age mean:</strong> 0.2 (0.48)</td>
<td><strong>Intervention:</strong> Multimodal treatment for teachers and parents in the intervention group, 2 teacher training meetings (1 2-hr session and 1 30-min session), 2 group parent trainings sessions (4.5-hrs) and 2 individualized family therapy sessions (2hrs), conducted over 16 weeks, participants also received stimulant medication prescribed by their pediatricians <strong>Control:</strong> TAU Children in the control group were treated with stimulant medication prescribed by their pediatricians referring to the clinical practice guidelines for ADHD children published by the American Academy of Pediatrics <strong>Comparator:</strong> NA</td>
<td>SNAP-IV (Swanson Nolan and Pelham’s 4th scale) The intervention group demonstrated significant improvements compared to that in the control group (p &lt; 0.05). Treatment Acceptability Questionnaire (TAQ) scale 64.8% of the parents in the intervention group indicated that this treatment would help their children. Academic Performance Questionnaire (APQ) change There was no significant time by group effect (p &gt; 0.05). Parental stress measured with the PSI improved in both groups. There were no serious adverse events and adverse events reported.</td>
<td></td>
</tr>
</tbody>
</table>
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
<th>Population: Setting; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</th>
<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teacher, school environment</td>
<td>Sibley, 2018[^19] Sibley, 2020[^34]; Sibley, 2019[^12] ID: NA RCT Single center N = 325 US Setting: School</td>
<td><strong>Target:</strong> Rising&quot; 6th &amp; 9th graders with ADHD referred from Miami-Dade schools; DSM IV diagnosis required; students must display significant academic impairment (at least a 3 on a 0–6 teacher Impairment Rating Scale); Students with autism spectrum disorder were excluded <strong>Other:</strong> Parents and teachers provided data <strong>ADHD presentation:</strong> N/A <strong>Diagnosis:</strong> Confirmation by specialist ADHD diagnosis was confirmed through a combination of parent structured interview (Computerized-Diagnostic Interview Schedule for Children; Shaffer, Fisher, Lucas, Dulcan, &amp; Schwab-Stone, 2000) and parent and teacher symptom and impairment ratings. Clinic <strong>Comorbidity:</strong> N/A <strong>Female:</strong> 25.8 % <strong>Age mean:</strong></td>
<td><strong>Intervention:</strong> 8-week intensive summer program from 8:00 a.m. to 5:00 p.m. on weekdays (45 hr per week), alternated between 30- and 50-min small- and large-group modules, parent training 8-week once per week for 1.5 hours <strong>Control:</strong> No intervention <strong>Comparator:</strong> Teacher, school environment8-week organization skills group 1.5 hr per week; also parent training 8-weeks, once per week for 1.5 hours <strong>Follow-up:</strong> 12 months</td>
<td>School Disciplinary Incidents There were no significant Group × Time interaction effects for school disciplinary incidents. Hyperactivity/Impulsivity scale, Disruptive Behavior Disorder Rating Scale, teacher report There were no significant Group by Time interaction effects between the two groups. Satisfaction with treatment Both groups reported high overall satisfaction that did not significantly differ between groups. Grade Point Average (GPA), 9th Grade Ninth-grade intervention youth showed smaller reductions in GPA over time than ninth-grade control youth. There were no GPA effects for sixth graders.</td>
</tr>
</tbody>
</table>

[^19]: Sibley, 2018[^19] Sibley, 2020[^34]; Sibley, 2019[^12] ID: NA RCT Single center N = 325 US Setting: School | **Minimum age:** 6 **Maximum age:** 12 **Ethnicity:** Other : Chinese Other info on race or ethnicity: | **Follow-up:** 4 months |
## Appendix C. Evidence Tables

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<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
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<td>Intervention; Study target; ADHD presentation; Diagnosis; Comorbidity; % Female; Age mean; Minimum age; Maximum age; Ethnicity</td>
<td>Intervention; Control; Comparator; Follow-up</td>
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<tr>
<td>Tamm, 2017</td>
<td>Rising 6th &amp; 9th graders</td>
<td>Inattention scale, SNAP-IV, parent rating</td>
<td>The medication plus parent training group (p&lt;.012) and combined (p&lt;.001) treatment groups were rated as significantly less inattentive than the reading treatment alone group, but did not significantly differ from one another (p=.058). The medication plus parent training group had higher phonemic decoding scores than the medication plus parent training group but did not differ from one another (p 0.65). There were not significant differences between groups on word reading at follow-up.</td>
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<td>ID: NA RCT Multicenter</td>
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<tr>
<td></td>
<td>% Hispanic or Latino : 72.7</td>
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<tr>
<td></td>
<td>% Black/African American : 17.4</td>
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<td>Target:</td>
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<tr>
<td>Children in grades 2–5 with ADHD and word reading/decoding deficits</td>
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<td>Other: Parents</td>
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<tr>
<td>ADHD presentation: combined : 54.6,N/A : sample included also inattentive and hyperactive presentations</td>
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<td>Diagnosis: Confirmation by specialist</td>
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<tr>
<td>Comorbidity: Learning disability : Word-level reading difficulties or disabilities</td>
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<tr>
<td>Female: 38.9 %</td>
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<td>Age mean: 8.8 (1.3)</td>
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<tr>
<td>Grades 2 through 5</td>
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<td>Minimum age:</td>
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<tr>
<td>% Hispanic or Latino : 12.0</td>
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<td>% Black/African American : 72.2</td>
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<td>% Multiracial : 6.5</td>
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<tr>
<td>Intervention: Reading training by teachers plus medication plus parent training; 9 parent group sessions, each 1.5 hours, over 10 weeks, low dose extended release methylphenidate, atomoxetine or extended release guanfacine could be used if MPH not tolerated, reading treatment provided by teachers to one or two students at a time for 45 minutes, four days per week for 16 weeks</td>
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<td>Control: Other</td>
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<tr>
<td>Parent training plus medication; parent training in behavior management, 9 group sessions conducted by clinical psychologists, each 1.5 hours, over 10 weeks; medication: open label, typically beginning with low dose extended release methylphenidate;</td>
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<tr>
<td>Comparator: Teacher, school environmentReading training alone; reading treatment was provided by</td>
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</table>
## Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Study:</th>
<th>Population:</th>
<th>Comparison:</th>
<th>Outcome and results</th>
</tr>
</thead>
</table>
| Volpe, 2009; Jitendra, 2007 | **Target:** Children in grades 1 through 4 with ADHD who were experiencing achievement problems in either math or reading. **Other:** Teachers conducted intervention  
**ADHD presentation:** combined : 65.0,N/A : sample included inattentive and hyperactive presentations  
**Diagnosis:** Confirmation by specialist Parent and teacher ratings on the ADHD Rating Scale IV and NIMH diagnostic interview scale for children IV  
**Comorbidity:** Learning disability : Problems with either math or reading  
**Female:** 24.0%  
**Age mean:** 8.7 (1.23)  
**Minimum age:**  
**Maximum age:**  
**Ethnicity:** | **Intervention:** Intensive data-based academic intervention involves ongoing feedback to teachers from consultants, individual interventions are selected based on functional and academic assessment data for 15 months  
**Control:** NA  
**Comparator:** Teacher, school environmentTraditional data-based academic intervention, design of intervention based on teacher choice  
**Follow-up:** 27 months | **Follow-up:** 5 months  
**teachers to 1-2 students at a time for 45 minutes, 4 days per week for 16 weeks; training targeted phonics, word identification, spelling, reading fluency, and comprehension**  
Woodcock-Johnson III tests of achievement, standardized math fluency score  
No differences between groups on Woodcock-Johnson tests of achievement, Curriculum based measurement (CBM) scores, Academic Competency Evaluation Scale (ACES), or Report Card grades |
### Appendix C. Evidence Tables

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Study: Author, year; Multiple publications; Trial ID; Study design; Sites; Study size; Location Setting</th>
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<th>Comparison: Intervention; Control; Comparator; Follow-up</th>
<th>Outcome and results</th>
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<td>Zheng, 2020&lt;sup&gt;28&lt;/sup&gt; ID: N/A Cluster RCT Multicenter N = 219 China Setting: School</td>
<td>% Hispanic or Latino : 26.9 % Black/African American : 11.4 % White : 58.0 Other info on race or ethnicity:</td>
<td></td>
<td>SNAP-IV (Chinese Version Swanson Nolan and Pelham, Version IV) Difference of SNAP-IV score changes between the two groups was statistically significant (p=0.009)</td>
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<tr>
<td></td>
<td>Target: Children aged 6-11 diagnosed with ADHD according to DSM-5, Intelligence Quotient ≥70, and no prior ADHD medication use; no comorbidity with autism spectrum disorder, schizophrenia, epilepsy, head injury, or verified neurological disorder, and sensory retardation (hearing/vision problems) Other: Parents or primary caregivers of children with ADHD that can read and write the Chinese language; teachers ADHD presentation: N/A Diagnosis: Confirmation by specialist Participants were diagnosed with ADHD according to DSM-5 Comorbidity: N/A Female: 15.2 % Age mean: Intervention group mean age (7.93) and SD (1.38). Control group mean age (7.21) and SD (1.22). Minimum age: 6</td>
<td>Intervention: Teacher training was 4-weekly 2-hour sessions, consisting of: (1) knowledge about ADHD; (2) behavioral strategies to manage conduct problems; (3) classroom behavior management; (4) teaching how to use scaffolding to promote the development of self-regulation in children with ADHD. Parent training was 4-weekly 2-hour sessions, consisting of: (1) knowledge about ADHD; (2) medication; (3) teaching behavioral strategies; (4) teaching to combine procedures and behavior management techniques. Medication given to children was either methylphenidate or atomoxetine. Control: Other Methylphenidate or atomoxetine alone Comparator: NA Follow-up: 6 months</td>
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## Appendix C. Evidence Tables

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<th>Intervention</th>
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## Appendix D. Critical Appraisal and Applicability Tables

### Table D.1. Critical appraisal for included studies, KQ1

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Patient selection</th>
<th>Index test</th>
<th>Reference standard</th>
<th>Flow timing</th>
<th>Overall RoB</th>
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### Appendix D. Critical Appraisal and Applicability Tables

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<th>Author, year</th>
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<th>Index test</th>
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Appendix D. Critical Appraisal and Applicability Tables

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### Table D.2. Applicability for included studies, KQ1

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### Appendix D. Critical Appraisal and Applicability Tables

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## Appendix D. Critical Appraisal and Applicability Tables

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## Appendix D. Critical Appraisal and Applicability Tables

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## Appendix D. Critical Appraisal and Applicability Tables

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### Appendix D. Critical Appraisal and Applicability Tables

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### Appendix D. Critical Appraisal and Applicability Tables

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<tr>
<th>Author, year</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Setting</th>
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## Appendix D. Critical Appraisal and Applicability Tables

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### Appendix D. Critical Appraisal and Applicability Tables

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### Appendix D. Critical Appraisal and Applicability Tables

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<th>Comparator</th>
<th>Outcome</th>
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## Table D.5. Critical appraisal for included studies, KQ3

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## Table D.6. Applicability for included studies, KQ3

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Appendix E. Expert Guidance and Review

Stakeholder Input in Formulating the Research Protocol

Stakeholders, participated in a virtual workshop by PCORI in November 2021 to discuss the draft KQs and PICOTs. Details on the virtual workshop, including a list of participants, can be found at https://www.pcori.org/events/2021/pcori-stakeholder-webinar-adhd-children-and-adolescents.

Stakeholders in the workshop represented different viewpoints which included patients, patient advocates, clinicians, guideline developers and researches.

During the virtual workshop, stakeholders provided input and guidance on the KQs and PICOTs. Based upon the from the workshop, the protocol was developed by the EPC and the KQs were modified with guidance from PCORI and AHRQ.

Stakeholders did not do analysis of any kind or contribute to the writing of this draft report. They will be given the opportunity to review the report through the peer or public review mechanisms.
Appendix F. PCORI Checklist

To be added for the final report