

Draft Comparative Effectiveness Review

Number XX

Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder (ADHD) 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 systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

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, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

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If you have comments on this systematic review, 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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Structured Abstract

Objectives. Attention deficit hyperactivity disorder (ADHD) is a common pediatric neurobehavioral disorder often treated in the primary care setting. This systematic review provides an update regarding the comparative effectiveness of methods that can be used to establish the diagnosis of ADHD in children and adolescents, comparative effectiveness of pharmacologic and nonpharmacologic treatments, and an evaluation of different monitoring strategies. This review focused on processes and care that could be provided in the primary care setting for individuals from birth through 17 years of age.

Data sources. We searched PubMed[®], Embase[®], PsycINFO[®] and the Cochrane Database of Systematic Reviews for relevant English-language studies published from January 1, 2011 through November 15, 2015.

Review methods. Two investigators screened each abstract and full-text article for inclusion, abstracted the data, and performed quality ratings and evidence grading. Random-effects models were used to compute summary estimates of effects when sufficient data were available for meta-analysis.

Results. A total of 95 articles describing 82 unique studies contributed evidence. Nineteen studies were relevant to diagnosis and issues of being labeled with the diagnosis of ADHD; 63 studies were relevant to treatment, and no studies were identified regarding monitoring. Most of the diagnostic comparative studies (n=14/17) were of fair quality. The variability in tools assessed and their findings resulted in insufficient evidence regarding the comparative diagnostic accuracy of electroencephalograms (EEGs), neuroimaging, or executive function tests to diagnose ADHD. No studies directly assessed the harms of being labeled as having ADHD. Little evidence was identified in this updated search that compared pharmacologic treatment to placebo. However, earlier studies support the benefit of pharmacotherapy to improve ADHD outcomes. Three randomized clinical trials (two fair quality, one poor quality) found that combining methylphenidate with neurofeedback or behavioral therapy was not significantly different than methylphenidate alone. Meta-analysis of four studies of omega-3/6 supplementation did not find benefit in parent ratings of ADHD symptoms. Similarly, meta-analysis of three studies did not find effects of omega-3/6 supplementation in teacher ratings of ADHD symptoms. Across all treatments, little evidence was identified regarding the risk of serious adverse events, including cardiovascular risk. No studies compared different monitoring strategies for children or adolescents diagnosed with ADHD. Factors leading to the low strength of evidence across all key questions and study designs including the heterogeneous population and short duration of follow-up.

Conclusions. This evidence review found insufficient evidence regarding new approaches to the diagnosis of ADHD. Based on the previous evidence review, pharmacotherapy appears to provide the most effective short-term improvement in symptoms. This evidence review did not find additional benefit in adding neurofeedback or behavioral therapy to pharmacotherapy. Omega-3/6 supplementation does not appear to improve ADHD outcomes. The relative benefits and harms of different therapies could not be evaluated. No information was identified regarding the optimal strategy for monitoring after diagnosis. Little is known about the impact of being labeled as having ADHD.

Introduction

This review updates a 2011 EPC report that focused on the effectiveness of ADHD treatment in at-risk preschoolers, the long-term effectiveness of ADHD treatment in all ages, and the variability in ADHD prevalence, diagnosis, and treatment.¹ The previous report focused on (1) primarily pharmacologic treatments for children under 6 years of age with ADHD and a disruptive behavior disorder; (2) long-term comparative safety and effectiveness of a variety of treatment options for children 6 years of age or older with ADHD; and (3) prevalence of ADHD and rates of diagnosis and treatment for ADHD. The authors of that report concluded that there was high SOE in support of the effectiveness of parent behavior training and low SOE in support of MPH for improving the behavior of children aged 6 years or younger. The previous report also concluded that there was sparse evidence at the time regarding long-term outcomes following interventions for ADHD, but that treatment for 12 months or longer with MPH or atomoxetine appeared to be associated with improvements in symptomatic behavior. The current review builds on the previous report and addresses important gaps in knowledge related to the diagnosis of ADHD, concerns about overtreatment and undertreatment, and conflicting literature about the effectiveness of treatment.

Background

Attention deficit hyperactivity disorder (ADHD) is a common neurobehavioral disorder, with about 11% of children ages 4 through 17 having been diagnosed.² In the United States, there are significant geographical variations in the rate of diagnosis and treatment, and the prevalence has increased over time.^{2,3} The most recent Diagnostic and Statistical Manual of Mental Disorders (DSM-5)⁴ has revised the diagnostic criteria for ADHD. To be diagnosed with ADHD, a child or younger adolescent needs to meet 6 out of 9 possible inattentive symptoms (such as failing to give close attention to details or being easily distracted) and/or 6 out of 9 possible hyperactivity/impulsivity symptoms (such as being “on the go” or difficulty waiting their turn). Also, symptoms need to be present for at least 6 months, occur in at least 2 different settings, be present before 12 years of age, and not be better explained by another disorder. For older adolescents and adults, the number of required symptoms per category is reduced to 5 out of 9. ADHD has three presentations: (1) predominantly inattentive, (2) predominantly hyperactive/impulsive, and (3) combined, based on how many symptoms in each diagnostic category an individual meets.

Psychostimulants are effective in reducing distractibility, improving sustained attention, reducing impulsive behaviors, and improving activity level. Nonpharmacologic therapies (e.g., behavioral therapy, psychotherapy, psychosocial interventions, and complementary and alternative medicine interventions), either alone or in combination with medication management, could potentially address core symptoms of ADHD or the long-term impairments that are associated with the disorder.

Despite growing research on treatment for ADHD and awareness of the condition’s course of illness, important questions remain about ADHD diagnosis and management. Ensuring appropriate diagnosis and avoidance of misdiagnosis is a key concern for clinical practice. For treatment, key questions include how to best tailor therapy to individuals based on their characteristics (e.g., age, sex, ADHD symptoms, comorbid conditions, prior and current therapy) and how to efficiently and effectively monitor individuals with ADHD over time.

Population

This systematic review focuses on children through 17 years of age, categorized to reflect broad developmental stages (less than 4 years, 4 through 6 years, 7 through 12 years, and 13 through 17 years). We explored the impact of ADHD and its treatment and monitoring strategies in several subgroups of interest. These include sex because the clinical presentation can vary as can the response to therapy.⁵

Many risk factors have been associated with ADHD, including prenatal factors (e.g., tobacco use, alcohol use, substance abuse), perinatal factors (e.g., low birth weight, prematurity), and early postnatal factors (e.g., lead exposure, social environment).⁶ Also, family history of ADHD and specific genetic conditions (e.g., Fragile X syndrome) can be associated with ADHD. We evaluated these subpopulations by stratifying outcomes based on common these risk factors when available.

Diagnosis

ADHD diagnosis is based on clinician assessment to determine whether the criteria described in the DSM are met. For this review, studies based on the DSM-5 or DSM-IV criteria were included. Rating scales, which can be completed by parents, teachers, and/or patients, are used to evaluate the presence of each of the 18 symptoms as well as the degree of impairment that results from symptoms. 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 comorbid 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 in primary care has been the lack of adequate time and expertise to distinguish ADHD from other conditions that may appear similar (e.g., anxiety, conduct disorders, speech or language delay, other developmental disorders) and to determine whether another condition may better explain ADHD symptoms or is present as a comorbid diagnosis.

Although most previous research has relied on interviews and rating scales for diagnosis, the U.S. Food and Drug Administration (FDA) has recently approved a new device “to aid in the diagnosis of ADHD.”⁷ The Neuropsychiatric Electroencephalograph [EEG]-Based Assessment Aid (NEBA; NEBA Health, Augusta, GA) was approved to provide clinical support for an ADHD diagnosis in patients ages 6-17 years but is not intended to replace the clinical evaluation.⁷ There is significant interest in the use of tests to either supplement or replace the standard methods of diagnosis used in the primary care setting.

Adverse Effects of Diagnosis

Being diagnosed with ADHD can lead to “labeling harms,” which can lead to stigma, reduced self-esteem, or reduced future educational attainment or career opportunities.⁸⁻¹⁰ Misdiagnosis can lead to overdiagnosis or underdiagnosis and can also miss conditions that can be similar in appearance to ADHD (e.g., anxiety, conduct disorders, speech or language delay, other medical disorders/diseases, or other developmental disorders) that may warrant a different course of treatment.

Treatment Strategies

Treatment strategies for ADHD can be divided into pharmacologic and nonpharmacologic therapies. The main categories of pharmacologic therapies include stimulants, selective

norepinephrine reuptake inhibitors, alpha-2 agonists, and antidepressants. Nonpharmacologic therapies include psychosocial interventions, behavioral interventions, school interventions, cognitive training therapies, learning training, biofeedback or neurofeedback, parent behavior training, dietary supplements (e.g., omega-3 fatty acids, vitamins, herbal supplements, probiotics), elimination diets, vision training, and chiropractic treatment. The American Academy of Pediatrics (AAP) recommends stimulant therapy as the first line of therapy.¹¹

Adverse Effects of Treatment

Adverse effects associated with pharmacologic treatment can include changes in appetite, growth suppression,¹² weight decrease, sleep disturbance, gastrointestinal symptoms, elevated blood pressure, increased heart rate, risk of sudden cardiac death, cardiac arrhythmias, conduction abnormalities, tics or other movement disorders, behavior changes, hallucination, aggression, suicide (attempted or completed), and suicidal ideation. Importantly, suicide and suicidal ideation can be both an adverse effect of treatment and an ADHD-related health outcome. Treatment can also lead to personality changes or loss of spontaneity as perceived by the treated individual, family members, or other close acquaintances. Adverse effects of nonpharmacologic treatment depend on the specific intervention.

Individuals who are initially misdiagnosed may be overtreated, and those who have inadequate monitoring may be overtreated or undertreated. Overtreatment leads to risk of treatment with no or little potential benefit. Because many of the pharmacologic treatments are controlled substances, overtreatment could also lead to abuse of a drug to which the treated individual might not otherwise have access.¹³ Although reduction of ADHD symptoms can improve family functioning, the need to provide treatments can potentially also lead to parental stress, and depending on the specific treatment, there may be significant time demands or opportunity costs.

Monitoring Strategies with Intermediate Outcomes

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 to treatments are made when needed. Several instruments are available to monitor treatment response and adverse effects over time, including the Vanderbilt scales, the Conner scales, and the SNAP-IV rating scales.¹⁴⁻¹⁶ Monitoring also includes assessment of any adverse effects of treatment. There are variations in the frequency of monitoring, often based on the age of the child, the specific treatment, duration of treatment, previous symptoms and comorbid conditions, and family and healthcare provider preferences. Rating scale results are intermediate monitoring outcomes associated with the outcomes described below.

Long-Term Outcomes

Outcomes associated with ADHD in childhood are based on measures of performance and/or functional impairment. In childhood, individuals with ADHD are at risk for lower academic performance (e.g., grades, scores on standardized tests), lower rates of graduation from high school, higher rates of grade retention, and higher rates of school suspension. In adulthood, outcomes may include limited workforce participation and/or difficulty maintaining a steady job. Throughout the lifespan, social outcomes associated with ADHD may include problematic peer and family relationships. Individuals with ADHD are also at risk for negative outcomes associated with risk-taking behaviors such as motor vehicle collisions or other accidents as well

as substance use (e.g., higher rates of smoking, more difficulty quitting smoking). Mental health outcomes that are associated with ADHD include higher rates of mood disorders, depression or anxiety, higher likelihood of having self-injurious nonsuicidal behavior, suicide (attempted or completed), suicidal ideation, and risk of mortality. Because these long-term outcomes can be associated with the known course of illness for ADHD, with commonly occurring comorbid conditions or in some cases with ADHD treatment, it can be difficult to fully assess and predict long-term outcomes for individuals with ADHD.

Scope and Key Questions

Scope of This Review

This review focuses on the diagnosis and management of ADHD within the primary care practice setting or other settings in which care can be coordinated by primary care providers (e.g., in partnership with community-based psychologists or psychiatrists). Although treatment of ADHD in childhood and adolescence is the focus, this review also evaluates outcomes in adulthood from treatment that occurs during childhood or adolescence.

Our review updates a 2011 EPC review that focused on the effectiveness of ADHD treatment in at-risk preschoolers, the long-term effectiveness of ADHD treatment in all ages, and the variability in ADHD prevalence, diagnosis, and treatment.¹ The current review builds on this previous report and addresses important gaps in knowledge related to the diagnosis of ADHD, concerns about overtreatment and undertreatment, and conflicting literature about the effectiveness of treatment.

Rationale and Context

DSM-5 Criteria for Diagnosis

The DSM-5 criteria are the gold standard for the diagnosis of ADHD. However, most of the previous studies were developed before the release of these criteria, which were released in 2013. Compared with the DSM-IV, the DSM-5 criteria allow some symptoms to appear prior to 12 years of age compared with 7 years of age, so more adolescents fulfill the criteria. In addition, DSM-5 permits the co-occurrence of autism spectrum disorder with the diagnosis of ADHD, whereas these disorders could not be co-diagnosed in DSM-IV. The DSM-5 criteria emphasize the life-long, chronic nature of ADHD and the need to monitor individuals over time.

Patient Preferences

There are differences in patient and family preferences related to both pharmacologic and nonpharmacologic treatment¹⁷ and potential outcomes. These treatment preferences have been shown to be associated with treatment initiation and choice. Findings from this systematic review are intended to help inform patient and family decisions based on the benefits and harms of specific treatments.

Other Factors

In the period since the 2011 publication of the AAP clinical practice guideline,¹¹ four new medications have become available (methylphenidate transdermal system, lisdexamfetamine, amphetamine sulfate tablets, and dextroamphetamine sulfate tablets), and the DSM-5 has been released, increasing clinical and decisionmaking uncertainty. A separate EPC report on disruptive behavior disorder is nearly complete and was therefore not targeted in this systematic review. However, we do include disruptive behavior specifically related to ADHD.

Cost

Cost assessment was not included in this review.

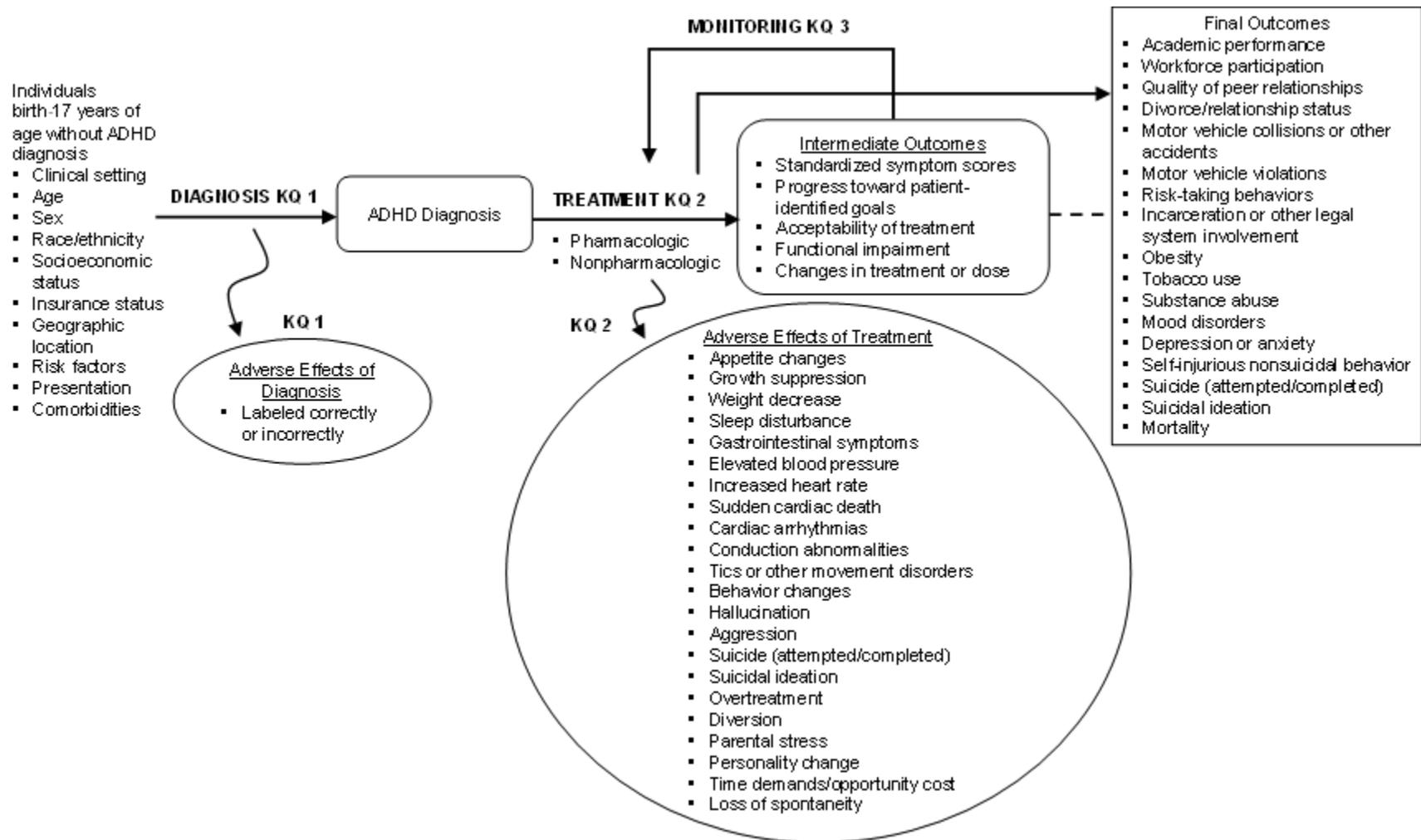
Key Questions

The specific Key Questions (KQs) addressed in this review are listed below, and Figure 1 displays the analytic framework that guided our work.

- KQ 1: 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 executive function approaches 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?
- KQ 2: What are the comparative safety and effectiveness of pharmacologic and/or nonpharmacologic treatments of ADHD in improving outcomes associated with ADHD? How do these outcomes vary by presentation (inattentive, hyperactive/impulsive, and combined) or other comorbid conditions? What is the risk of diversion of pharmacologic treatment?
- KQ 3: What are the comparative safety and effectiveness of different monitoring strategies to evaluate the effectiveness of treatment or changes in ADHD status (e.g., worsening or resolving symptoms)?

The analytic framework presented in Figure 1 illustrates the population, interventions, outcomes, and adverse effects that guided the literature search and synthesis. This figure shows how individuals through 17 years of age without ADHD may be diagnosed and treated for ADHD, and how treatment is associated with a range of potential adverse effects and outcomes. KQ 1 evaluates the comparative accuracy of approaches used to diagnose ADHD, including how the diagnostic accuracy varies by setting, patient subgroup, or other risk factors. KQ 1 also addresses adverse effects of ADHD diagnosis. KQ 2 considers the comparative safety and effectiveness of pharmacologic and nonpharmacologic treatments for ADHD and how the outcomes vary by presentation or other comorbid conditions. KQ 2 also addresses adverse effects of ADHD treatment. KQ 3 considers the comparative safety and effectiveness of different monitoring strategies to evaluate the effectiveness of treatment or changes in ADHD status over time.

Figure 1. Analytic Framework for ADHD



Organization of This Report

The remainder of the review first presents our methods followed by an overview of the results. Each results section describes “Findings in Relationship to What is Known” to provide appropriate context for the reader. We then synthesize the literature and provide summary tables and strength of evidence grades for the outcomes. The discussion section offers our conclusions, summarizes our findings, and provides other information relevant to interpreting this work for clinical practice and future research.

Appendix A contains the exact search strings for the literature searches. Appendix B presents the data elements abstracted from the included studies. Appendix C lists the included studies. Appendix D lists the excluded studies and the reason for exclusion. Appendix E provides a key to the primary and companion studies. Appendix F presents details on the study characteristics of included studies.

Abbreviation List

Table 1 lists the abbreviation and its expansion for terms used in this report.

Table 1. List of Abbreviations

AAP	American Academy of Pediatrics
ADHD	Attention Deficit Hyperactivity Disorder
ADHD-RS	Attention Deficit Hyperactivity Disorder Rating Scale
ADHD RS-IV	Attention Deficit Hyperactivity Disorder Rating Scale 4
AHRQ	Agency for Healthcare Research and Quality
ATTEX	Attention and Executive Function Rating Inventory
ATX	Atomoxetine
AUC	Area under the curve
BASC-2	Behavior Assessment System for Children, Second Edition
BASC-2 BESS	Behavior Assessment System for Children, Second Edition Behavioral and Emotional Screening System
BRIEF	Behavior Rating Inventory of Executive Function
CANTAB	Cambridge Neuropsychological Test Automated Battery
CARE	Coping With ADHD Through Relationships and Education
CBCL	Child Behavior Checklist
CBRS	Comprehensive Behavior Rating Scale
CBT	Cognitive behavioral therapy
CBV	Caudate body volume
CD	Conduct disorder
CDI	Children’s Depression Inventory
CDSR	Cochrane Database of Systematic Reviews
CER	Comparative effectiveness review
CGI	Conners’ Global Index Clinician Global Impressions
CHEXI	Childhood Executive Functioning Inventory
CHIP-CE-PRF	Child and Health Illness Profile-Child Edition, Parent Report Form
CHP-AS	Challenging Horizons Program-After School

CHP-M	Challenging Horizons Program-Mentoring
CI	Confidence interval
CLAS	Child Life and Attention Skills
Conners 3	Conners 3rd Edition
Conners CPT	Conners Continuous Performance Test
CPFT	Continuous Performance Function Test
CPRS	Conners Parent Rating Scale
CPT	Continuous Performance Test
CRS	Conners Rating Scales
CTRS	Conners Teacher Rating Scale
DASS	Depression Anxiety Stress Scale
DB-DOS	Disruptive Behavior-Diagnostic Observation Schedule
DBDRS	Disruptive Behavior Disorder Rating Scale
DBRS	Disruptive Behavior Rating Scale
DBP	Diastolic blood pressure
DEX	Dextroamphetamine
DICA-IV	Diagnostic Interview for Children and Adolescents 4
DISC	Dominance, Inducement, Submission, and Compliance
DISC-IV	Diagnostic Interview Schedule for Children Version IV
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
D-TMP	Dexamethylphenidate
EEG	Electroencephalograph
EHC	Effective Health Care
EIS	Electro-interstitial scans
EPC	Evidence-based Practice Center
FDA	Food and Drug Administration
FSSEE	Family-School Success—Early Elementary
GXR	Guanfacine extended release
ICD-10	10th revision of the International Statistical Classification of Diseases and Related Health Problems
ICTRP	International Clinical Trials Registry Platform
IVA-2 (BrainTrain, Inc)	Integrated Visual and Auditory 2
IVA-AE2 (BrainTrain, Inc)	Integrated Visual and Auditory Advanced Edition 2
IVA-QS (BrainTrain, Inc)	Integrated Visual and Auditory Quick Screening
K-DBDS	Kiddie-Disruptive Behavior Disorder Schedule
K-DISC-IV	Kiddie-Computerized Diagnostic Interview Schedule for Children
KQ	Key question
K-SADS-PL	Kiddie-Sads-Present and Lifetime Version
LDX	Lisdexamfetamine

MAS	Mixed amphetamine salts
MASC	Multidimensional Anxiety Scale for Children
MATH-CPT	Mathematics Continuous Performance Test
Mini KID	Mini International Neuropsychiatric Interview for Children and Adolescents
MPH	Methylphenidate
MTA	Multisite Multimodal Treatment Study of Children with ADHD
NDG	Ningdong granule
NEBA	Neuropsychiatric EEG-Based Assessment AID
NICHQ Vanderbilt Assessment Scale - PARENT NICHQ Vanderbilt Assessment Scale - TEACHER	National Institute for Children’s Health Quality Vanderbilt Assessment Scale— Parent National Institute for Children’s Health Quality Vanderbilt Assessment Scale— Teacher
NSS	Neurological subtle signs
ODD	Oppositional defiant disorder
OROS-MPH	Osmotic release oral system methylphenidate
PACS	Parental account of children’s symptoms
PICOTS	Populations, Interventions, Comparators, Outcomes, Timing, Settings
RCT	Randomized controlled trial
SBP	Systolic blood pressure
SDQ	Strengths and Difficulties Questionnaire
SDSC	Sleep Disturbance Scale for Children
SMD	Standardized mean difference
SNAP-IV	Swanson, Nolan and Pelham Revision
SOE	Strength of evidence
STEPP	Strategies to Enhance Positive Parenting
TEP	Technical expert panel
TOVA	Test of Variables of Attention
WHO	World Health Organization
WIAT	Wechsler Individual Achievement Test
WRAT	Wide Range Achievement Test

Methods

We followed the methods for this comparative effectiveness review provided by the Agency for Healthcare Research and Quality (AHRQ)'s *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter referred to as the Methods Guide) for the Evidence-based Practice Center (EPC) program.¹⁸ We sought feedback regarding the conduct of the work (such as development of search strategies and identifying outcomes of key importance) from the Task Order Officer and the Technical Expert Panel. Certain methods map to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.¹⁹ All methods and analyses were determined *a priori*.

Topic Refinement and Review Protocol

During topic refinement, we engaged in a public process to develop a draft and final protocol for the review. We generated an analytic framework, preliminary key questions (KQs), and preliminary inclusion/exclusion criteria in the form of PICOTS (populations, interventions, comparators, outcomes, timing, settings). Information provided by the topic nominator helped guide our processes. Initially a panel of 9 key informants representing medical professionals with expertise in areas of family medicine, child and adolescent psychiatry, psychology, and pediatrics; payers; Federal agencies; and patients/caregivers gave input on the KQs to be examined; these KQs were posted on AHRQ's Effective Health Care (EHC) website for public comment from June 17, 2015, to July 8, 2015, and were revised to refine the scoping for KQ 1 and KQ 2, clarify the exclusion of pre–post studies, and update the grey literature to be searched. These revisions were made prior to seeing the results of any studies.

We then drafted a protocol for the systematic review and recruited a panel of technical experts to provide high-level content and methodological expertise throughout the development of the review. This panel included medical professional and Federal agency representation similar to that of the key informant group. The finalized protocol is posted on the EHC website (www.effectivehealthcare.ahrq.gov). The PROSPERO registration is CRD42016029134.

Literature Search Strategy

Search Strategy

To identify relevant published literature, we searched MEDLINE[®] (via PubMed), Embase[®], PsycINFO[®], and the Cochrane Database of Systematic Reviews (CDSR), limiting the search to studies conducted in children 17 years of age and younger and published from January 1, 2009, to the present. These databases were selected based on internal expert opinion that they would identify most of the relevant literature on this topic and following prior related systematic reviews. We believe that the evidence published from 2009 forward both represents the current standard of care for the population of interest in this review and allows this report to build on the previous systematic review published in 2011 (which included literature through May 31, 2010).¹

We used a combination of medical subject headings and title and abstract keywords, focusing on terms to describe the relevant population and interventions of interest. Exact search strings used for each KQ are in Appendix A. Where possible, we used existing validated search filters. An experienced search librarian guided all searches. We supplemented the electronic searches with a manual search of citations from a set of key primary and review articles.²⁰⁻⁶³ The reference list for identified pivotal articles was hand-searched and cross-referenced against our

database, and additional relevant manuscripts were retrieved. All citations were imported into an electronic bibliographical database (EndNote® Version X7; Thomson Reuters, Philadelphia, PA).

To identify relevant gray literature, the EPC Scientific Resource Center made requests to drug and device manufacturers for scientific information packets solicited through the AHRQ Effective Health Care website and a notice posted in the Federal Register. We also searched study registries for relevant articles from completed studies. Gray literature databases included ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) search portal, and the National Guidelines Clearinghouse.

As an additional step in identifying adverse effects of interest, we reviewed the known adverse effects of ADHD medications monitored by the FDA to identify further potential adverse effects reported by the FDA.⁶⁴ As a result of that assessment, we added two additional outcomes to consideration for this review: chemical leukoderma and priapism.

Inclusion and Exclusion Criteria

We specified our inclusion and exclusion criteria based on the PICOTS identified in topic refinement. Table 2 specifies inclusion and exclusion criteria.

Table 2. Inclusion and Exclusion Criteria

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Populations	<p>KQ 1: Individuals birth through 17 years of age without the diagnosis of ADHD, divided by subquestion as follows:</p> <ul style="list-style-type: none"> • KQ 1a considers the initial diagnosis of individuals under 7 years of age. • KQ 1b considers the initial diagnosis of individuals through 17 years of age using EEG, imaging, or executive function approaches. • KQs 1c and 1d considers both populations. <p>KQ 2: Individuals birth through 17 years of age with a diagnosis of ADHD</p> <p>KQ 3: Individuals birth through 17 years of age who have previously begun treatment for ADHD</p> <p>Subgroups of interest for KQs 1-3:</p> <ul style="list-style-type: none"> • The general population of children and adolescents: ages less than 4, 4-6, 7-12, and 13-17 years • When data are available, findings are separately evaluated by sex or specific risk factors (prenatal tobacco, alcohol, or substance abuse; prematurity or low birth weight; and family history); ADHD presentation; comorbidity; race/ethnicity; socioeconomic status; insurance status; geographic location 	<p>Individuals 18 years of age or older. Note that studies with individuals greater than 18 years of age are included as long as findings are reported separately for individuals 18 years and under, or if the mean patient age plus the standard deviation is not greater than 21 years of age. Also note that for long-term studies, the age of the individuals may be greater than 18, but these studies are only considered for inclusion if the age at enrollment in the study was 18 years or younger.</p>
Interventions	<p>KQ 1: Any standard ADHD diagnostic strategy, including clinician interview or standardized instrument (e.g., Vanderbilt scales, the Conner scales, and the SNAP-IV rating score) for individuals under 7 years of age. The use of EEG-based systems, imaging, or executive function approaches were evaluated in the diagnosis of ADHD in individuals through 17 years of</p>	<p>KQ 1: Validation studies or diagnosis conducted using a nonvalidated instrument</p> <p>KQ 2: Studies comparing pharmacologic agents approved by the</p>

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	<p>age.</p> <p>KQ 2: Any pharmacologic or nonpharmacologic treatment of ADHD, alone or in combination:</p> <ul style="list-style-type: none"> • Pharmacologic treatments considered are brand name and generic formulations of the following medications^a: <ul style="list-style-type: none"> ○ Psychostimulants <ul style="list-style-type: none"> ▪ Methylphenidate (MPH) ▪ Dexmethylphenidate (D-TMP) ▪ Dextroamphetamine (DEX) ▪ Lisdexamfetamine (LDX) ▪ Mixed amphetamine salts (MAS) ▪ Amphetamine ○ Tricyclic antidepressants <ul style="list-style-type: none"> ▪ *Desipramine ▪ *Nortriptyline ○ Selective norepinephrine reuptake inhibitors <ul style="list-style-type: none"> ▪ Atomoxetine (ATX) ○ Alpha-2 agonists <ul style="list-style-type: none"> ▪ Clonidine ▪ Guanfacine extended release (GXR) ○ Dopamine reuptake inhibitors <ul style="list-style-type: none"> ▪ *Modafinil ▪ *Armodafinil ○ Norepinephrine-dopamine reuptake inhibitors <ul style="list-style-type: none"> ▪ *Bupropion ○ Serotonin-norepinephrine reuptake inhibitors <ul style="list-style-type: none"> ▪ *Duloxetine ○ Serotonin-norepinephrine-dopamine reuptake inhibitors <ul style="list-style-type: none"> ▪ *Venlafaxine ○ Monoamine oxidase type B inhibitors <ul style="list-style-type: none"> ▪ *Selegiline ○ N-methyl-D-aspartate receptor antagonists <ul style="list-style-type: none"> ▪ *Amantadine ▪ *Memantine • Nonpharmacologic therapies considered include psychosocial interventions, behavioral interventions, cognitive behavioral therapy, play therapy, mindfulness-based therapies, school interventions, cognitive training therapies, biofeedback or neurofeedback, parent behavior training, dietary supplements (e.g., omega-3 fatty acids, vitamins, herbal supplements, probiotics), homeopathy, acupuncture, elimination diets, vision training, exercise, and chiropractic treatment. <p>KQ 3: Follow-up visits in primary care with various methods and within times (monthly to annually) for repeat monitoring, independent of treatment.</p>	<p>FDA for the treatment of ADHD that have enrollment of fewer than 100 patients with ADHD, or less than 6 months of follow-up.</p>
Comparators	<p>KQ 1: Confirmation of diagnosis by a specialist (gold standard), including psychologist or psychiatrist or other care provider using a well-validated and reliable process of confirming the diagnosis of ADHD according to the DSM-4 or DSM-5.</p> <p>KQ 2: Specific treatments compared with other</p>	<p>KQ 1: Comparison to diagnosis with a nonvalidated instrument</p>

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	<p>treatments as described above or to no treatment.</p> <p>KQ 3: Follow-up compared with differing durations of follow-up or differing settings of follow-up.</p>	
Outcomes	<p>KQ 1:</p> <ul style="list-style-type: none"> • Accuracy of diagnostic strategy, as measured by: <ul style="list-style-type: none"> ○ Diagnostic concordance of primary care provider with specialist ○ Inter-rater reliability ○ Internal consistency ○ Test-retest ○ Sensitivity ○ Specificity ○ Positive predictive value ○ Negative predictive value ○ False positives ○ False negatives ○ Risk of missed condition that can appear as ADHD (i.e., misdiagnosis) • Labeling is any measure of stigma following diagnosis comparing those with and without ADHD. <p>KQ 2:</p> <ul style="list-style-type: none"> • Intermediate outcomes: <ul style="list-style-type: none"> ○ Changes on standardized symptom scores or progress toward patient-identified goals. Standardized symptom scores include narrow-band focused instruments (Vanderbilt rating scales, ADHD Rating Scale) and broad-band scales (Child Behavior Checklist and Teacher Report Form, Behavior Assessment System for Children, Conners' Rating Scales-Revised) ○ Acceptability of treatment ○ Functional impairment • Final outcomes include: <ul style="list-style-type: none"> ○ 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 interactions with the legal system (juvenile detention, probation, court-mandated interventions, need for residential placement) ○ Obesity ○ Tobacco use ○ Substance abuse ○ Mood disorders ○ Depression or anxiety ○ Self-injurious nonsuicidal behavior ○ Suicide (attempted or completed) ○ Suicidal ideation ○ Mortality • Adverse effects of treatment, including: <ul style="list-style-type: none"> ○ Changes in appetite 	

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	<ul style="list-style-type: none"> ○ Growth suppression ○ Weight decrease ○ Sleep disturbance ○ Gastrointestinal symptoms ○ Elevated blood pressure ○ Increased heart rate ○ Risk of sudden cardiac death ○ Cardiac arrhythmias ○ Conduction abnormalities ○ Tics or other movement disorders ○ Behavior changes ○ Hallucination ○ Aggression ○ Suicide (attempted or completed) ○ Suicidal ideation ○ Overtreatment ○ Diversion of pharmacotherapy ○ Parental stress ○ Personality change ○ Time demands/opportunity cost ○ Loss of spontaneity ○ Chemical leukoderma ○ Priapism <p>KQ 3:</p> <ul style="list-style-type: none"> ● Changes in treatment or dose ● Adverse effects of treatment as described under KQ 2 ● Changes in intermediate outcomes (e.g., standardized symptom scores, progress toward patient-identified goals, functional impairment) as described under KQ 2 	
Timing	<p>KQ 1:</p> <ul style="list-style-type: none"> ● For assessment of diagnostic accuracy: diagnostic follow-up must be within 4 months of the initial evaluation and must be completed before treatment is initiated ● For labeling: any time after the ADHD diagnosis <p>KQs 2 and 3: Any</p>	
Settings	<p>KQ 1: Primary or specialty care settings</p> <p>KQs 2 and 3: Any</p>	None
Study design	<ul style="list-style-type: none"> ● Original data ● Randomized trials, prospective and retrospective observational studies with comparator; for diagnostic accuracy, cross-sectional studies are acceptable if they include patients with diagnostic uncertainty and direct comparison of diagnosis in primary care to diagnosis by a specialist ● Randomized controlled trials with sample size: <ul style="list-style-type: none"> ○ ≥20 subjects for KQs 1 and 3 ○ ≥50 subjects for KQ 2 (or 100 subjects for studies comparing two or more pharmacologic treatments approved by the FDA for the treatment of ADHD) ● Observational studies with sample size: <ul style="list-style-type: none"> ○ ≥20 subjects for KQs 1 and 3 	<p>Editorials, nonsystematic reviews, letters, case series, case reports, abstract-only, pre-post studies</p> <p>Because studies with fewer than 20 subjects are often pilot studies or studies of lower quality, we excluded them from our review.</p>

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	<ul style="list-style-type: none"> ○ ≥50 subjects for KQ 2 (or 100 subjects for studies comparing two or more pharmacologic treatments approved by the FDA for the treatment of ADHD) 	
Publications	<ul style="list-style-type: none"> • English-language only • Published January 1, 2009, to present • Relevant systematic reviews, meta-analyses, or methods articles (used for background only) 	Given the high volume of literature available in English-language publications, the focus of our review on applicability to populations in the United States, and the scope of our current KQs, non-English articles were excluded. ^b

^aPharmacologic treatments listed are FDA-approved for an indication of ADHD with the exception of those marked with an asterisk, which are available within the United States and are FDA-approved but not specifically approved for ADHD.

^bIt is the opinion of the investigators that the resources required to translate non-English articles would not be justified by the low potential likelihood of identifying relevant data unavailable from English-language sources.

Abbreviations: ADHD = attention deficit hyperactivity disorder; ATX = atomoxetine; DEX = dextroamphetamine; DSM = *Diagnostic and Statistical Manual of Mental Disorders*; D-TMP = dexamethylphenidate; EEG = electroencephalograph; GXR = guanfacine extended release; KQ = key question; LDX=lisdexamfetamine; MAS = mixed amphetamine salts; MPH = methylphenidate; PICOTS = Populations, Interventions, Comparators, Outcomes, Timing, Settings; RCT = randomized controlled trial

Study Selection

For citations retrieved from MEDLINE, Embase, PsycINFO, and CDSR, two reviewers used the prespecified inclusion/exclusion criteria to review titles and abstracts for potential relevance to the research questions. Articles included by either reviewer underwent full-text screening. At the full-text screening stage, two independent reviewers were required to agree on a final inclusion/exclusion decision. Disagreements were resolved by a third expert member of the team. Articles meeting eligibility criteria were included for data abstraction. At random intervals during screening, quality checks by senior team members were made to ensure that screening and abstraction were consistent with inclusion/exclusion criteria and abstraction guidelines. All results were tracked using the DistillerSR data synthesis software program (Evidence Partners Inc., Manotick, ON, Canada).

Appendix C provides a list of all articles included for data abstraction. Appendix D provides a list of articles excluded at the full-text screening stage, with reasons for exclusion.

Data Extraction

The research team created abstraction forms that were programmed into DistillerSR software to collect the data required to evaluate the specified eligibility criteria for inclusion in this review, as well as demographic and other data needed for determining outcomes (intermediate, final, and adverse events outcomes). Particular attention was given to describing the details of the treatment (e.g., pharmacotherapy dosing, methods of behavioral interventions), patient characteristics (e.g., ADHD presentation, comorbidities, age), and study design (e.g., RCT versus observational) that may be related to outcomes. Comparators were described carefully because treatment standards may have changed during the period covered by the review. The safety outcomes were framed to help identify adverse events, including those from drug therapies and those resulting from misdiagnosis and labeling.

All data abstraction form templates were pilot-tested with a sample of included articles to ensure that all relevant data elements were captured and that there was consistency and reproducibility between abstractors. Forms were revised as necessary before full abstraction of all included articles. Final abstracted data will be uploaded to AHRQ’s Systematic Review Data Repository.⁶⁵

Based on clinical and methodological expertise, a pair of researchers abstracted data from each of the eligible articles, with one researcher abstracting the data and the second over-reading the article and the accompanying abstraction to check for accuracy and completeness. Disagreements were resolved by consensus or by obtaining a third reviewer’s opinion if consensus was not reached. To avoid duplication of patient cohorts, we linked related studies.

Quality Assessment of Individual Studies

We assessed the methodological quality, or risk of bias, for each individual study based on the Cochrane Risk of Bias⁶⁶ tool for randomized studies and the Newcastle-Ottawa Scale⁶⁷ for observational studies. We supplemented these tools with additional assessment questions, such as use of appropriate analysis, based on recommendations in the AHRQ’s Methods Guide.¹⁸ We rated each study as being of good, fair, or poor quality based on its adherence to well-accepted standard methodologies. Table 3 defines these quality ratings, which are presented in the results tables in the Results section as well as the strength of evidence tables in the Discussion section of the report.

Table 3. Definition of Quality Assessment Ratings

Rating	Definition
Good (low risk of bias)	These studies had the least bias, and the results were considered valid. These studies adhered to the commonly held concepts of high quality, including the following: a clear description of the population, setting, approaches, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytical methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.
Fair	These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems.
Poor (high risk of bias)	These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

The grading was outcome-specific such that a given study that analyzed its primary outcome well but did an incomplete analysis of a secondary outcome was assigned a different quality grade for each of the two outcomes. Studies of different designs were graded within the context of their respective design. Thus, RCTs were graded as good, fair, or poor, and observational studies were separately graded as good, fair, or poor.

Data Synthesis

We began by summarizing key features of the included studies for each KQ. To the degree that data were available, we abstracted information on study design; patient characteristics; clinical settings; interventions; and intermediate, final, and adverse event outcomes. We ordered

our findings by treatment or diagnostic comparison and then within these comparisons by outcome with long-term final outcomes emphasized.

We reviewed and highlighted studies using a hierarchy-of-evidence approach. The best evidence available was the focus of our synthesis for each key question. If high quality evidence was not available, we described any lower quality evidence we were able to identify, but we underscored the issues that made it lower quality and the uncertainties in our findings. We assessed and stated whether the inclusion of lower quality studies would change any of our conclusions and performed sensitivity analyses excluding this evidence where appropriate.

We then determined the feasibility of completing quantitative syntheses (i.e., meta-analyses). Feasibility was dependent on the volume of relevant literature (we required 3 appropriate studies to consider meta-analysis), conceptual homogeneity of the studies, and completeness of the reporting of results. When a meta-analysis was appropriate, we used random-effects models to synthesize the available evidence quantitatively. We tested for heterogeneity using graphical displays and test statistics (Q and I^2 statistics), while recognizing that the ability of statistical methods to detect heterogeneity may be limited. We presented summary estimates, standard errors, and confidence intervals. We anticipated that intervention effects may be heterogeneous. We hypothesized that the methodological quality of individual studies, study type, the characteristics of the comparator, and patients' underlying clinical presentation were associated with the intervention effects. When there were sufficient studies, we performed subgroup analyses and/or meta-regression analyses to examine these hypotheses. We performed quantitative and qualitative syntheses separately by study type and discussed their consistency qualitatively.

Strength of the Body of Evidence

We assessed the strength of evidence using the approach described in AHRQ's Methods Guide.^{18,68} We graded the strength of evidence for each outcome assessed; thus, the strength of evidence for two separate outcomes in a given study may be graded differently. These grades are presented in the strength of evidence tables in the Discussion section of the report. In brief, the approach requires assessment of five domains: study limitations (previously named risk of bias), consistency, directness, precision, and reporting bias, which includes publication bias, outcome reporting, and analysis reporting bias. Additional domains were used when appropriate (most relevant to observational studies) and included coherence, dose-response association, impact of plausible residual confounders, and strength of association (magnitude of effect). These domains were considered qualitatively, and a summary rating of high, moderate, or low strength of evidence was assigned for each outcome after discussion by two reviewers. In some cases, high, moderate, or low ratings were impossible or imprudent to make, for example, when no evidence is available or when evidence on the outcome was too weak, sparse, or inconsistent to permit any conclusion to be drawn. In these situations, a grade of "insufficient" was assigned. Table 4 defines the four-level grading scale.

Table 4. Definition of Strength of Evidence Grades

Rating	Definition
High	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.
Moderate	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.
Low	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.
Insufficient	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.

Applicability

We assessed applicability across our KQs using the method described in AHRQ’s Methods Guide.^{18,69} In brief, this method uses the PICOTS format as a way to organize information relevant to applicability. The most important issue with respect to applicability is whether the outcomes are different across studies that recruit different populations (e.g., age groups, ADHD presentations, exclusions for comorbidities) or use different methods to implement the interventions of interest; that is, important characteristics are those that affect baseline (control group) rates of events, intervention group rates of events, or both. We used a checklist to guide assessment of the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population in comparison with the target population, characteristics of the intervention used in comparison with care models currently in use, the possibility of diagnostic tool or treatment intervention learning curves, and clinical relevance and timing of the outcome measures (Appendix B). We summarized issues of applicability qualitatively.

Peer Review and Public Commentary

This draft report will be posted on the AHRQ EHC website for 4 weeks to elicit public comment. Experts in the fields of pediatrics and child development, child psychiatry and psychology, pharmacology, and public health have been invited to provide external peer review of this draft report; AHRQ and an associate editor will also provide comments. The authors will address all reviewer comments, revising the text as appropriate, and document the responses in a disposition of comments report that will be made available 3 months after the Agency posts the final systematic review on the EHC website.

Results

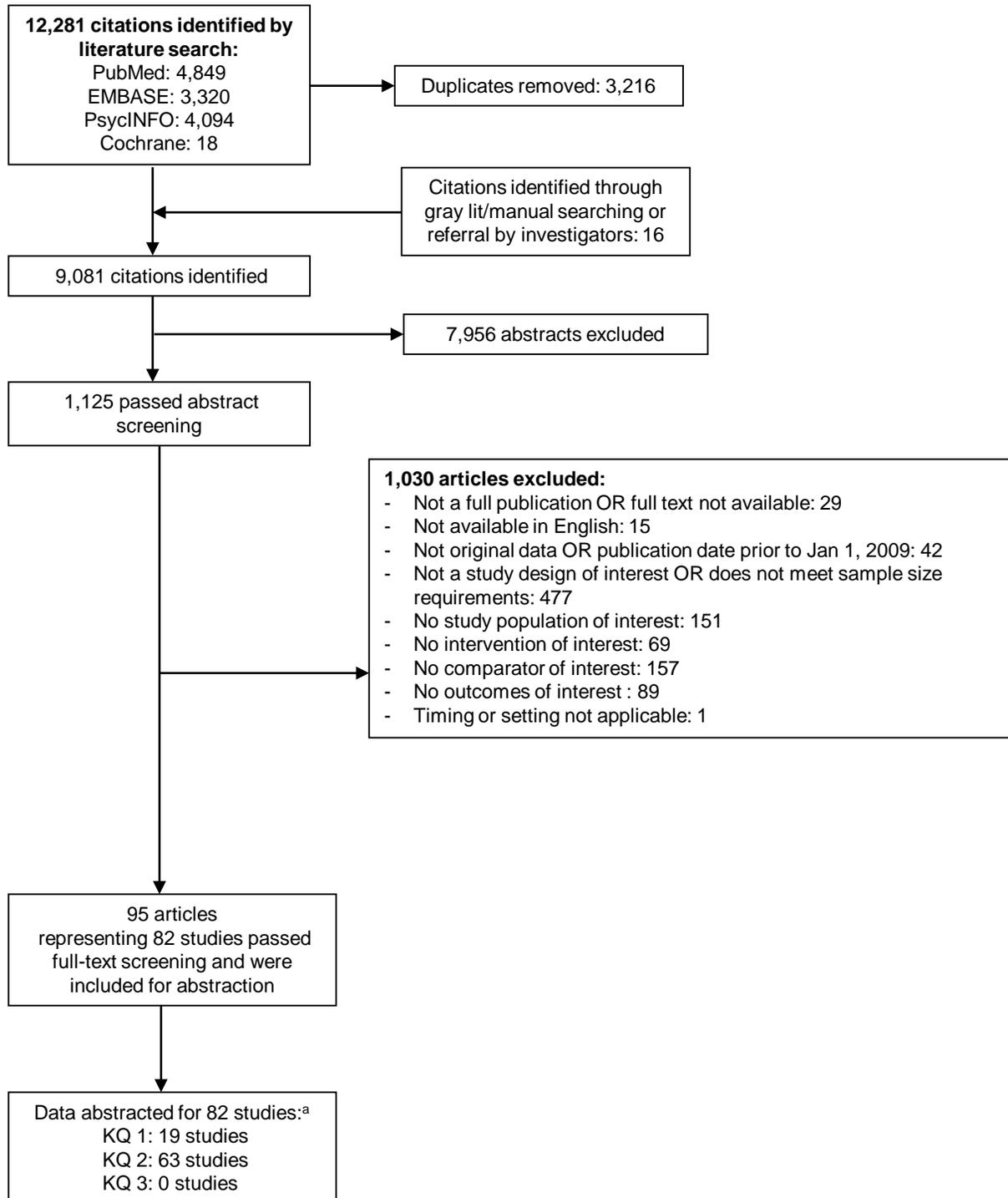
In what follows, we begin by describing the results of our literature searches. We then provide a brief overview description of the included studies. The remainder of the chapter is organized by key question (KQ). Under each of the three KQs, we begin by listing the key points of the findings, followed by a brief description of included studies, a detailed synthesis of the evidence, and a final discussion of the results in “Findings in Relationship to What is Known” to provide context for the reader. Within KQ 2, the detailed syntheses are organized first by treatment comparison and then by outcome. We conducted quantitative syntheses where possible, as described in the Methods chapter. For a list of the abbreviations, please refer to the Introduction.

Results of Literature Searches

Figure 2 depicts the flow of articles through the literature search and screening process. Searches of PubMed[®], Embase[®], PsycINFO[®], and the Cochrane Database of Systematic Reviews yielded 9,065 unique citations. Manual searching of gray literature databases and bibliographies of key articles or referral by investigators identified 16 additional citations, for a total of 9,081 citations. After applying inclusion/exclusion criteria at the title-and-abstract level, 1,125 full-text articles were retrieved and screened. Of these, 1,030 were excluded at the full-text screening stage, leaving 95 articles for data abstraction. These 95 articles described 82 unique studies. The relationship of studies to the review questions is as follows: 19 studies relevant to KQ 1, 63 studies relevant to KQ 2, 0 studies relevant to KQ 3.

Appendix C provides a detailed listing of included articles. Appendix D provides a complete list of articles excluded at the full-text screening stage, with reasons for exclusion. Appendix E provides a “study key” table listing the primary and companion publications for the 82 included studies.

Figure 2. Literature Flow Diagram



Description of Included Studies: Overview

Overall, we included 95 articles representing 82 studies: 19 studies were relevant to KQ 1, 63 studies to KQ 2, and 0 studies to KQ 3. Studies were conducted wholly or partly in continental Europe or the UK (33 studies, 40%), the United States or Canada (21 studies, 26%), the Middle East (11 studies, 13%), Asia (9 studies, 11%), Latin America (2 studies, 3%), Australia/New Zealand (3 studies, 4%), both in the United States and UK/Europe (1 study, 1%), both in UK/Europe and Australia/NZ (1 study, 1%), and location not reported (1 study, 1%). Further details on the studies included for each KQ are provided in the relevant results sections below and in Appendix F.

We searched the ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) study registries as a mechanism for ascertaining publication bias by identifying studies that have been completed but are as yet unpublished. We acknowledge that this is not an exhaustive strategy, as several other registries also exist with differing geographical focus and varying degrees of overlap in their trial listings; however, in the opinion of the investigators, the widely used, U.S.-based ClinicalTrials.gov registry and the WHO ICTRP registry provided the most relevant information to the populations and interventions of interest in this review. Our search yielded 337 records of completed trials in the ClinicalTrials.gov registry and 195 non-NCT records of completed trials in the WHO ICTRP registry for screening. Manual review identified 79 of the records from ClinicalTrials.gov and 75 of the records from WHO ICTRP as potentially relevant to this review (154 records in total). Of those 154 records, we were not able to identify publications for 79 studies that had expected completion dates prior to our search. Of the 65 studies for which we could identify publications, all were considered potentially relevant to KQ 2. However, all publications had been previously identified in our PubMed, Embase, PsycINFO, and the Cochrane Database of Systematic Reviews searches. No novel publications were identified from our clinical trial registry searches.

Key Question 1. ADHD Diagnosis

KQ 1 examines the comparative diagnostic accuracy of approaches that can be used in the primary care practice setting or specialty clinic to initially diagnose ADHD. KQ 1a focuses on the comparative diagnostic accuracy of approaches for diagnosing ADHD among individuals younger than 7 years of age. KQ 1b examines the comparative diagnostic accuracy of EEG, imaging, or executive function approaches that can be used to diagnose ADHD among individuals aged 7 through 17. KQ 1c focuses on how the comparative diagnostic accuracy of these approaches varies by clinical setting or patient subgroup including age, sex, or other risk factors associated with ADHD. KQ 1d examines the adverse effects associated with being labeled correctly or incorrectly as having ADHD.

Description of Included Studies

For KQ 1, we identified 20 articles⁷⁰⁻⁸⁹ representing 19 studies, 17 of which examined the comparative diagnostic accuracy of approaches used to diagnose ADHD, and 2 of which evaluated adverse effects of being labeled with ADHD. One study was described in more than one publication; Appendix E provides a key to primary and companion articles.

All 17 studies examining diagnostic accuracy were observational in design and represented a total of 4,105 enrolled patients. In 10 of the 17 studies, the gold standard used for identifying ADHD was based on DSM-IV diagnostic criteria using tools such as the ADHD-Rating Scale (2

studies), Conners Teacher Rating Scale (2 studies), K-DBDS (1 study), K-SADS-PL (1 study), Disc-IV (2 studies), DICA-IV (1 study), and a structured checklist (1 study). The other 7 studies did not report the specific ratings scales performed, but included a mixture of parent/teacher scales, clinical evaluations, and various DSM-IV criteria checklists. The diagnosis was confirmed by a specialist in 13 studies. In 6 studies it was not clear who validated the diagnosis. Four studies assessed diagnostic accuracy in a sample population aged 6 years and younger. Five studies focused on how the approaches varied by patient subgroups including age (1 study), sex (1 study), and ADHD subtype (3 studies). Two studies examined the adverse effects associated with being labeled correctly or incorrectly as having ADHD.

Eighteen studies were conducted at a single center and 1 at multiple centers.⁷⁵ Five studies were conducted in a primary care setting^{72-74,86,88} and 11 in a specialty practice.^{70,71,76-78,80,82,84-86,88} Three were conducted in a community setting,^{74,75,86} 5 in a school setting,^{73,75,83,85,87} and 2 in unclear or unknown locations.^{79,81} Two studies were conducted in Asia,^{70,72} 1 in Australia/NZ,⁸⁰ 1 in Canada,⁸⁷ 1 in Latin America,⁸³ 3 in the Middle East,^{76,78,82} 1 in the United States,⁸⁸ and 10 in UK/ Europe.^{71,73-75,77,79,81,84-86}

Four studies reported government funding,^{70,74,80,88} and 2 reported nongovernment, nonindustry funding.^{83,85} Multiple studies reported a combination of funding sources; specifically, 2 studies reported a combination of government and nongovernment funding,^{71,79} and 1 study reported a combination of government and industry funding.⁷⁵ Ten studies did not report the funding source, or it was unclear.^{72,73,76-78,81,82,84,86,87}

Of the 19 studies relevant to KQ 1, 3 were rated as good quality,^{85,87,88} 14 as fair quality,^{70,72-78,80-84,86} and 2 as poor quality.^{71,79} Details of the study characteristics of the included studies are in Appendix F.

Key Points

- Limited studies demonstrated variable and inconsistent findings for diagnostic accuracy for all diagnostics tools (SOE = insufficient)
- Insufficient evidence was found regarding labelling or stigma of children with ADHD

Detailed Synthesis—Diagnosis

Diagnostic Comparative Studies

Across the 17 diagnostic comparative studies, 14 different assessment tools were evaluated, including electroencephalography (EEG), integrated visual and auditory computerized performance test (IVA-CPT), continuous performance function tests (CPFT), event-related potentials (ERP), magnetic resonance imaging (MRI) of caudate body volume (CBV), Test of Variable of Attention (TOVA), Cambridge Neuropsychological Testing Automated Battery (CANTAB), Attention and Executive Function Rating Inventory (ATTEX), Childhood Executive Function Inventory (CHEXI), electro interstitial scans (EIS), Disruptive Behavior-Diagnostic Observation Schedule (DB-DOS), neurological subtle signs (NSS), Kiddie-Disruptive Behavior Disorder Schedule (K-DBDS), and Strengths and Difficulties Questionnaire (SDQ). The diagnostic accuracy of the tools was measured primarily by receiver operator characteristics (ROC) for overall accuracy and area under the curve (AUC) from which sensitivity, specificity, false positives, and false negatives could be derived as shown in Table 5 below. The heterogeneity in methods and outcomes of these studies prevented quantitative meta-analysis.

Among the imaging studies, EEG was variable in its accuracy, ranging from 46% to 87% in four studies.^{70,72,74,77} ERP evaluations yielded consistently higher accuracy scores when conducted independently (91%, the highest imaging accuracy⁸³) and in combination with EEG (73%⁷⁵). MRI scans of CBV also had accuracy scores of 84%.⁸⁴ IVA-CPT had 75% to 82% based on outcomes assessed with commission errors and 68% to 85% based on outcomes assessed with omission errors.^{70,72,77} Other CPTs, such as the TOVA, demonstrated limitations in their ability to correctly identify non-ADHD patients.^{76,78,82} Among the executive function tests, ATEXI⁸⁵ and CHEXI⁸⁶ performed better with overall accuracy rates of 91% to 93%, respectively, than the CANTAB,⁷⁶ which had low specificity. Biometric devices such as EIS and Actigraphy had high sensitivity (80% to 97%) and specificity (84% to 98%).^{79,81} Additional approaches to diagnosing ADHD with promising clinical utility included neurological examinations for subtle signs of abnormal functioning (overall accuracy 84%), observational assessments of disruptive behaviors (92% AUC, 87% sensitivity, 79% specificity), and interviews using the K-DBDS (98% AUC, 77% sensitivity, 98% specificity).^{73,80,89}

Few studies examined whether there are differences in accuracy based on age,⁸⁰ sex,⁸⁵ and ADHD presentation.^{71,73,85} Also, there were no studies that compared how approaches to diagnosing ADHD differed by clinical settings. Collectively, a variety of approaches were tested in primary care and specialty clinics. Approaches in primary care clinics (5 studies) included imaging, computerized function tests, executive function tests, and standardized questionnaires. Similarly, studies conducted in specialty clinics (11 studies) investigated these same approaches as well as biometric tools and observational assessments.

Table 5. Diagnostic Accuracy of Included Studies

	Overall Accuracy	AUC	Sensitivity	Specificity	False +	False –
EEG and Imaging studies						
Fair quality (Gonzalez, 2013 ⁷⁴) 43 subjects aged 7-17 (22 ADHD, 21 non-ADHD) 1. EEG IM generalized 2. EEG IM beta band	86.7% 74.4%		81.80% 63.60%	90.50% 90.50%		
Fair quality (Liechti, 2013 ⁷⁵) 62 subjects aged 7-17 (32 ADHD, 30 non-ADHD) 1. EEG + event-related potentials – including all stepwise variables	72.6%		71.9%	73.3%		
Fair quality (Castro-Cabrera, 2010 ⁸³) 46 subjects aged 7-17 (23 ADHD, 23 non-ADHD) 1. Event-related potentials – best combination of features	91.3%	94%	96%	87%		
Fair quality (Soliva, 2010 ⁸⁴) Subgroup = ADHD subtypes 78 subjects aged 7-17 (39 ADHD, 39 non-ADHD) 1. MRI of caudate body volume	84%		60.0%	95.0%		
EEG, Imaging, and CPT studies						
Fair quality (Kim, 2015 ⁷⁰) 97 subjects aged 7-17 (53 ADHD, 44 non-ADHD) 1. EEG theta-phase gamma-amplitude coupling 2. EEG delta wave 3. EEG theta/beta ratio 4. IVA CPT commission error 5. IVA CPT omission error	71.1% 63.3% 58.7% 75.3% 68.1%		60% 56% 49% 66% 58%	23% 27% 30% 18% 27%		
Fair quality (Kim, 2015 ⁷²) 157 subjects aged 7-17 (85 ADHD, 72 non-ADHD) 1. EEG delta wave 2. EEG theta wave 3. EEG theta/beta ratio 4. IVA CPT commission error 5. IVA CPT omission error	60.8% 56.4% 45.7% 82.1% 78.6%		60.1% 48.2% 47.1% 68.1% 64.7%	43.0% 40.5% 49.4% 9.54% 13.7%		

	Overall Accuracy	AUC	Sensitivity	Specificity	False +	False –
Fair quality (Ogrim, 2012 ⁷⁷) 101 subjects aged 7-17 (62 ADHD, 39 non-ADHD) 1. EEG theta 2. EEG theta/beta ratio 3. Visual CPT omission error	63% 58% 85%					
CPT studies						
Fair quality (Zelnik, 2012 ⁷⁸) 230 subjects aged 7-17 (179 ADHD, 51 non-ADHD) 1. TOVA (Test of Variables of Attention)			91.1%	21.6%	80.3% (78.4%)	40.7% (8.9%)
Fair quality (Berger, 2010 ⁸²) 58 subjects aged 7-17 (45 ADHD, 13 non-ADHD) 1. Continuous performance functions tests (CPT) 2. TOVA 3. Conners CPT 4. TOVA + Conners CPT	94.8% – – –		100% 75% 52% 64%			– 25% 36% 46%
CPT and executive function studies						
Fair quality (Bloch, 2012 ⁷⁶) 34 subjects aged 7-17 (27 ADHD, 7 non-ADHD) 1. Cambridge Neuropsychological Testing Automated Battery 2. TOVA			57%-71% 63%	7%-22% 85%	94%	37%
Executive function studies						
Good quality (Klenberg, 2010 ⁸⁵) Subgroups = sex & ADHD subtype 916 subjects aged 7-17 (215 ADHD, 701 non-ADHD) 1. Attention and Executive Function Rating Inventory	91% (boys) 93% (girls)	87% subtype	85% (boys) 83% (girls) 81% (subtype)	84% (boys) 85% (girls) 76% (subtype)		
Fair quality (Thorell, 2010 ⁸⁶) 52 subjects aged 7-17 (22 ADHD, 30 non-ADHD) 1. Childhood Executive Function Inventory – Parent rating inhibition subscale	93.3%		93.3%	93.3%		

	Overall Accuracy	AUC	Sensitivity	Specificity	False +	False –
Biometric devices						
Fair quality (Caudal, 2011 ⁸¹) 112 subjects aged 7-17 (52 ADHD, 60 non-ADHD) 1. Electro-interstitial scans			80%	98%		
Poor quality (Martin-Martinez, 2012 ⁷⁹) 63 subjects aged 6 and under (31 ADHD, 32 non-ADHD) 1. Actigraphy-PCA1 [Px00(15 min, D) + Pz22 (1 min, FR) + Py01 (15 min, AA)]	90.48%	94.96%	96.77%	84.38%		
Observational assessment Studies						
Fair quality (Ferrin, 2012 ⁸⁰) Subgroup = age 1185 subjects aged 7-17 (1055 ADHD, 130 non-ADHD) 1. Neurological subtle signs	84%	90.3% (<13 year) 77.9% (≥13 year)				
Fair quality (Bunte, 2013 ⁸⁹) 178 subjects aged 6 and under (120 ADHD, 58 non-ADHD) 1. Disruptive Behavior – Diagnostic Observation Schedule		92%	87%	79%		
Standardized questionnaire studies						
Poor quality (Carballo, 2014 ⁷¹) Subgroup = ADHD subtypes 523 subjects aged 6 and under (283 ADHD, 240 non-ADHD) 1. Strengths and Difficulties Questionnaire			38.3% (ADHD) 84% (ADHD-C) 25% (ADHD-I) 77.8% (ADHD-HI)	66.70% (ADHD) 60.00% (ADHD-C) 75.00% (ADHD-I) 66.70% (ADHD-HI)		
Fair quality (Bunte, 2013 ⁷³) Subgroup = ADHD subtypes 168 subjects aged 6 and under (110 ADHD HI, 58 non-ADHD) 1. Kiddie-Disruptive Behavior Disorder Schedule – specific coding method		98% (ADHD-HI)	77% (ADHD-HI)	98% (ADHD-HI)		

Abbreviations: ADHD=attention deficit hyperactivity disorder; ADHD-C=ADHD combined type; ADHD-HI=ADHD hyperactive/impulsive type; ADHD-I=ADHD inattentive type; AUC=area under the curve; CPT=continuous performance test; EEG=electroencephalogram; IVA=integrated visual and auditory; MRI=magnetic resonance imaging; TOVA=test of variables of attention

ADHD Labeling/Stigma Studies

Only two studies evaluated the adverse effects associated with being labeled correctly or incorrectly as having ADHD.^{87,88} These good-quality studies did not address the negative experiences or outcomes of the children with ADHD but rather teachers' reactions and parents' concerns regarding ADHD labels for affected youth.

Strength of Evidence—Diagnosis

Tables 6 and 7 summarize the strength of evidence for the KQ 1 findings.

Table 6. Strength of Evidence for Major Outcomes—Diagnosis

Outcome	No. Studies/ Design (N Patients)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Diagnostic Tools							
EEG and Imaging	4 Obs (229 patients)	Medium	Direct	Inconsistent	Imprecise	None	EEG demonstrated variability in four studies. ERP evaluations yielded consistently higher accuracy scores than EEGs when conducted independently and in combination with EEG. MRI scans of cerebral blood volume had similar accuracy scores to ERPs. ^{74,75,83,84}
Insufficient							
EEG, Imaging, and CPT	3 Obs (355 patients)	Medium	Direct	Inconsistent	Imprecise	None	EEG demonstrated variability in four studies. ERP evaluations yielded consistently higher accuracy scores than EEGs when conducted independently and in combination with EEG. MRI scans of cerebral blood volume had similar accuracy scores to ERPs. ^{70,72,77}
Insufficient							
CPT	2 Obs (288 patients)	Medium	Direct	Inconsistent	Imprecise	None	For CPT, those with integrated visual and auditory components or those combined with continuous performance testing performed better than basic CPTs such as the TOVA. ^{78,82}
Insufficient							
CPT and executive function	1 Obs (34 patients)	Medium	Direct	NA	Imprecise	None	For CPT, those with integrated visual and auditory components or those combined with continuous performance testing performed better than basic CPTs such as the TOVA. ⁷⁶
Insufficient							
Executive function	2 Obs (961 patients)	Medium	Direct	Consistent	Precise	None	Among executive function tests, ATTEX and CHEXI performed better than the CANTAB. ^{85,86}
Insufficient							
Biometric Devices	2 Obs (175 patients)	Medium	Direct	Inconsistent	Imprecise	None	Biometric devices for EIS and actigraphy demonstrated high sensitivity and specificity. ^{79,81}
Insufficient							
Observational assessment	2 Obs (1,436 patients)	Medium	Direct	Inconsistent	Imprecise	None	Additional approaches with promising clinical utility included neurological examinations for subtle signs of abnormal functioning, observational assessments of disruptive behaviors, and interviews using the K-DBDS. ^{80,89}
Insufficient							
Standardized questionnaire	2 Obs (774 patients)	Medium	Direct	Inconsistent	Imprecise	None	Additional approaches with promising clinical utility included neurological examinations for subtle signs of abnormal functioning, observational assessments of disruptive behaviors, and interviews using the K-DBDS. ^{71,73}
Insufficient							

Abbreviations: ADHD=attention deficit hyperactivity disorder; ATTEX=Attention and Executive Function Rating Inventory; CANTAB=Cambridge Neuropsychological Testing Automated Battery; CHEXI= Childhood Executive Function Inventory; CPT=continuous performance test; EEG=electroencephalogram; EIS= Electro-interstitial scans;

ERP=event-related potentials; K-DBDS= Kiddie-Disruptive Behavior Disorder Schedule; MRI=magnetic resonance imaging; Obs=observational; SDQ=Strengths and Difficulties Questionnaire; TOVA=test of variables of attention

Table 7. Strength of Evidence for Major Outcomes—Labeling/Stigma

Outcome	No. Studies/ Design	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Major outcomes							
Labeling/Stigma Insufficient	2 Obs (104 patients)	Low	Indirect	Consistent	Imprecise	None	Two good-quality studies did not address the negative experiences or outcomes of the children with ADHD but rather teachers' reactions and parents' concerns regarding ADHD labels for affected youth. ^{87,88}

Abbreviations: ADHD=attention deficit hyperactivity disorder; Obs=Observational

Key Question 2. ADHD Treatment

KQ 2 examines the comparative safety and effectiveness of pharmacologic and nonpharmacologic treatments for improving outcomes associated with ADHD. KQ 2 also evaluates how these outcomes vary by presentation (inattentive, hyperactive/impulsive, and combined) or other comorbid conditions, and assesses the risk of diversion of pharmacologic treatment.

Description of Included Studies

For KQ 2, we identified 75 articles⁹⁰⁻¹⁶⁴ representing 63 studies that examined the comparative safety and effectiveness of pharmacologic and nonpharmacologic treatments for the treatment of ADHD. Eleven studies were described in more than one publication; Appendix E provides a key to primary and companion articles.

Of the 63 included studies, 11 were observational, representing a total of 37,099 enrolled patients.^{90,91,114,115,127,134,137,140,141,145,162} The 52 remaining studies were RCTs, representing a total of 6,990 enrolled patients. Twenty-seven studies were conducted in multiple centers,^{90,91,94-97,99,103,105,108,120,125,130,131,134,135,137,139,142,146-149,151,154,156,161,162} 32 were conducted in a single center,^{92,93,102,104,106,107,110,111,113,115-118,121,123,127-129,132,136,138,140,141,143,144,150,157-160,163,164} and 4 did not report the study site or it was unclear.^{101,114,124,145} Seven studies were conducted in Asia,^{124,135,141,157,158,160,164} 2 in Australia/New Zealand,^{97,125} 1 in Latin America,¹⁰⁷ 8 in the Middle East,^{93,117,118,132,143,144,147,159} 23 in the UK/Europe,^{91,92,94,95,99,101,104,106,110,111,114,121,123,127,130,134,137,139,142,151,154,162,163} 19 in the United States,^{90,96,102,105,108,113,115,116,120,128,129,136,138,140,145,148-150,156,161} 1 in both UK/Europe and United States,¹⁰³ 1 in both UK/Europe and Australia/NZ,¹³¹ and 1 where location was unclear.¹⁴⁶

Thirty studies reported government funding,^{92,96,97,102,104-106,108,110,113,114,116,118,120,121,123-125,129,130,134,135,137,138,145,148,149,151,156,162,163,165-167,169-171,173-175,177-179,181,183,185,187,189,191,193,195,197,199,201,203,205,207,209,211,213,215,217,219,221,223,225,227,229,231,233,235,237,239,241,243,245,247,249,251,253,255,257,259,261,263,265,267,269,271,273,275,277,279,281,283,285,287,289,291,293,295,297,299,301,303,305,307,309,311,313,315,317,319,321,323,325,327,329,331,333,335,337,339,341,343,345,347,349,351,353,355,357,359,361,363,365,367,369,371,373,375,377,379,381,383,385,387,389,391,393,395,397,399,401,403,405,407,409,411,413,415,417,419,421,423,425,427,429,431,433,435,437,439,441,443,445,447,449,451,453,455,457,459,461,463,465,467,469,471,473,475,477,479,481,483,485,487,489,491,493,495,497,499,501,503,505,507,509,511,513,515,517,519,521,523,525,527,529,531,533,535,537,539,541,543,545,547,549,551,553,555,557,559,561,563,565,567,569,571,573,575,577,579,581,583,585,587,589,591,593,595,597,599,601,603,605,607,609,611,613,615,617,619,621,623,625,627,629,631,633,635,637,639,641,643,645,647,649,651,653,655,657,659,661,663,665,667,669,671,673,675,677,679,681,683,685,687,689,691,693,695,697,699,701,703,705,707,709,711,713,715,717,719,721,723,725,727,729,731,733,735,737,739,741,743,745,747,749,751,753,755,757,759,761,763,765,767,769,771,773,775,777,779,781,783,785,787,789,791,793,795,797,799,801,803,805,807,809,811,813,815,817,819,821,823,825,827,829,831,833,835,837,839,841,843,845,847,849,851,853,855,857,859,861,863,865,867,869,871,873,875,877,879,881,883,885,887,889,891,893,895,897,899,901,903,905,907,909,911,913,915,917,919,921,923,925,927,929,931,933,935,937,939,941,943,945,947,949,951,953,955,957,959,961,963,965,967,969,971,973,975,977,979,981,983,985,987,989,991,993,995,997,999,1001,1003,1005,1007,1009,1011,1013,1015,1017,1019,1021,1023,1025,1027,1029,1031,1033,1035,1037,1039,1041,1043,1045,1047,1049,1051,1053,1055,1057,1059,1061,1063,1065,1067,1069,1071,1073,1075,1077,1079,1081,1083,1085,1087,1089,1091,1093,1095,1097,1099,1101,1103,1105,1107,1109,1111,1113,1115,1117,1119,1121,1123,1125,1127,1129,1131,1133,1135,1137,1139,1141,1143,1145,1147,1149,1151,1153,1155,1157,1159,1161,1163,1165,1167,1169,1171,1173,1175,1177,1179,1181,1183,1185,1187,1189,1191,1193,1195,1197,1199,1201,1203,1205,1207,1209,1211,1213,1215,1217,1219,1221,1223,1225,1227,1229,1231,1233,1235,1237,1239,1241,1243,1245,1247,1249,1251,1253,1255,1257,1259,1261,1263,1265,1267,1269,1271,1273,1275,1277,1279,1281,1283,1285,1287,1289,1291,1293,1295,1297,1299,1301,1303,1305,1307,1309,1311,1313,1315,1317,1319,1321,1323,1325,1327,1329,1331,1333,1335,1337,1339,1341,1343,1345,1347,1349,1351,1353,1355,1357,1359,1361,1363,1365,1367,1369,1371,1373,1375,1377,1379,1381,1383,1385,1387,1389,1391,1393,1395,1397,1399,1401,1403,1405,1407,1409,1411,1413,1415,1417,1419,1421,1423,1425,1427,1429,1431,1433,1435,1437,1439,1441,1443,1445,1447,1449,1451,1453,1455,1457,1459,1461,1463,1465,1467,1469,1471,1473,1475,1477,1479,1481,1483,1485,1487,1489,1491,1493,1495,1497,1499,1501,1503,1505,1507,1509,1511,1513,1515,1517,1519,1521,1523,1525,1527,1529,1531,1533,1535,1537,1539,1541,1543,1545,1547,1549,1551,1553,1555,1557,1559,1561,1563,1565,1567,1569,1571,1573,1575,1577,1579,1581,1583,1585,1587,1589,1591,1593,1595,1597,1599,1601,1603,1605,1607,1609,1611,1613,1615,1617,1619,1621,1623,1625,1627,1629,1631,1633,1635,1637,1639,1641,1643,1645,1647,1649,1651,1653,1655,1657,1659,1661,1663,1665,1667,1669,1671,1673,1675,1677,1679,1681,1683,1685,1687,1689,1691,1693,1695,1697,1699,1701,1703,1705,1707,1709,1711,1713,1715,1717,1719,1721,1723,1725,1727,1729,1731,1733,1735,1737,1739,1741,1743,1745,1747,1749,1751,1753,1755,1757,1759,1761,1763,1765,1767,1769,1771,1773,1775,1777,1779,1781,1783,1785,1787,1789,1791,1793,1795,1797,1799,1801,1803,1805,1807,1809,1811,1813,1815,1817,1819,1821,1823,1825,1827,1829,1831,1833,1835,1837,1839,1841,1843,1845,1847,1849,1851,1853,1855,1857,1859,1861,1863,1865,1867,1869,1871,1873,1875,1877,1879,1881,1883,1885,1887,1889,1891,1893,1895,1897,1899,1901,1903,1905,1907,1909,1911,1913,1915,1917,1919,1921,1923,1925,1927,1929,1931,1933,1935,1937,1939,1941,1943,1945,1947,1949,1951,1953,1955,1957,1959,1961,1963,1965,1967,1969,1971,1973,1975,1977,1979,1981,1983,1985,1987,1989,1991,1993,1995,1997,1999,2001,2003,2005,2007,2009,2011,2013,2015,2017,2019,2021,2023,2025,2027,2029,2031,2033,2035,2037,2039,2041,2043,2045,2047,2049,2051,2053,2055,2057,2059,2061,2063,2065,2067,2069,2071,2073,2075,2077,2079,2081,2083,2085,2087,2089,2091,2093,2095,2097,2099,2101,2103,2105,2107,2109,2111,2113,2115,2117,2119,2121,2123,2125,2127,2129,2131,2133,2135,2137,2139,2141,2143,2145,2147,2149,2151,2153,2155,2157,2159,2161,2163,2165,2167,2169,2171,2173,2175,2177,2179,2181,2183,2185,2187,2189,2191,2193,2195,2197,2199,2201,2203,2205,2207,2209,2211,2213,2215,2217,2219,2221,2223,2225,2227,2229,2231,2233,2235,2237,2239,2241,2243,2245,2247,2249,2251,2253,2255,2257,2259,2261,2263,2265,2267,2269,2271,2273,2275,2277,2279,2281,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4283,4285,4287,4289,4291,4293,4295,4297,4299,4301,4303,4305,4307,4309,4311,4313,4315,4317,4319,4321,4323,4325,4327,4329,4331,4333,4335,4337,4339,4341,4343,4345,4347,4349,4351,4353,4355,4357,4359,4361,4363,4365,4367,4369,4371,4373,4375,4377,4379,4381,4383,4385,4387,4389,4391,4393,4395,4397,4399,4401,4403,4405,4407,4409,4411,4413,4415,4417,4419,4421,4423,4425,4427,4429,4431,4433,4435,4437,4439,4441,4443,4445,4447,4449,4451,4453,4455,4457,4459,4461,4463,4465,4467,4469,4471,4473,4475,4477,4479,4481,4483,4485,4487,4489,4491,4493,4495,4497,4499,4501,4503,4505,4507,4509,4511,4513,4515,4517,4519,4521,4523,4525,4527,4529,4531,4533,4535,4537,4539,4541,4543,4545,4547,4549,4551,4553,4555,4557,4559,4561,4563,4565,4567,4569,4571,4573,4575,4577,4579,4581,4583,4585,4587,4589,4591,4593,4595,4597,4599,4601,4603,4605,4607,4609,4611,4613,4615,4617,4619,4621,4623,4625,4627,4629,4631,4633,4635,4637,4639,4641,4643,4645,4647,4649,4651,4653,4655,4657,4659,4661,4663,4665,4667,4669,4671,4673,4675,4677,4679,4681,4683,4685,4687,4689,4691,4693,4695,4697,4699,4701,4703,4705,4707,4709,4711,4713,4715,4717,4719,4721,4723,4725,4727,4729,4731,4733,4735,4737,4739,4741,4743,4745,4747,4749,4751,4753,4755,4757,4759,4761,4763,4765,4767,4769,4771,4773,4775,4777,4779,4781,4783,4785,4787,4789,4791,4793,4795,4797,4799,4801,4803,4805,4807,4809,48}

Findings in Relationship to What is Already Known

In the 2011 report,¹ 13 short-term studies compared MPH with placebo (one also compared MAS with placebo) in children under 6 years of age; 9 longer term studies compared pharmacologic agents (4 MPH, 2 ATX, 1 AMP or MAS, and 2 any stimulant) with placebo. The studies in children under 6 years of age were relatively small and thus most of the conclusions are based on a single larger RCT of good quality, the Preschool ADHD Treatment Study (PATS),¹⁶⁵ indicating that for children without comorbidities, MPH was very effective. However, the SOE was insufficient.

In people 6 years of age and older, the 2011 report did not focus on comparative efficacy or safety of pharmacologic drugs compared with placebo. Therefore, no definitive conclusions were made in that report for any ADHD drug compared with placebo.

This updated systematic review—although focused on assessing the comparative efficacy and safety of FDA approved ADHD medications versus placebo—was likewise unable to make definitive conclusions given the small number of studies during the current time period and the limited quality of those studies.

Detailed Synthesis—Pharmacologic Versus Placebo/Usual Care

For this comparison, we identified six articles^{103,115,131,148,149,161} representing five studies that compared an FDA-approved medication for ADHD with placebo or usual care. The study with two publications was the NIMH Collaborative Multisite Multimodal Treatment Study of Children with ADHD (MTA) in which one publication reported academic performance, psychiatric outcomes, and antisocial behavior between treatment arms at 8 years following the 14 months of active treatment,¹⁴⁸ and the other reported blood pressure and heart rate by initial treatment group assignments over 10 years.¹⁴⁹ Three of the five studies were conducted exclusively in the United States,^{115,148,161} one was conducted in the United States and Europe,¹⁰³ and one was conducted in Europe, Australia, New Zealand, Israel, and South Africa.¹³¹

One study was rated poor quality¹⁰³ and the remaining rated fair quality. All but one¹¹⁵ were multicenter studies, and all of the multicenter studies were classified as RCTs; however, one study randomized subjects to treatment following an initial RCT (withdrawal) to either continue lisdexamfetamine or placebo and assessed effects in the “withdrawal period,”¹⁰³ and one study reported results long after the RCT treatment periods.^{148,149}

Placebo was the comparator in all of the studies except the single-site observational study¹¹⁵ and the MTA study.¹⁴⁸ In the single-site observational study, there were 4 study arms—two arms with ADHD medications (one given as part of a clinical trial and the other a historical group given ADHD medications by their physician), one arm not given ADHD medications by their physician, and one arm of patients without ADHD. For this section of the review, only the comparisons between medication and nonmedication arms are reported.

In the MTA study, there were also 4 treatment arms—medication management, behavioral management, combination of medications and behavior management, and community care (usual care). For this section, only the comparison between the medication arm and community care arm are reported. There were only two treatment arms in all of the RCTs with placebo comparators except for one study in which there were three doses of lisdexamfetamine compared with placebo.¹⁶¹

ADHD Symptom Scores

One fair-quality study presented results of ADHD symptom scores in children with active pharmacologic treatment versus placebo.¹⁶¹ Three doses of lisdexamfetamine were compared with placebo. Although no statistical comparisons were made, there was a much smaller proportion of patients receiving placebo when compared with any dose of lisdexamfetamine that had achieved symptomatic remission at 1 month, defined as an ADHD-RS IV score ≤ 18 (23.6% placebo, 62.3% lisdexamfetamine 30 mg/day, 67.6% lisdexamfetamine 50 mg/day, and 71.2% lisdexamfetamine 70 mg/day).

Alcohol Use

One fair-quality study focused on assessing youth self-reported alcohol use using the Drug Use Screen Inventory in children aged 12 to 17 who were mostly male.¹¹⁵ The study groups for this observational study conducted in the United States were clinical trial participants receiving open label methylphenidate, nonclinical trial youth receiving methylphenidate or amphetamine per their primary care provider, nonclinical trial youth not receiving any ADHD medications, and youth without ADHD. A lower proportion of clinical trial participants reported alcohol use in the preceding year (10%) than nonclinical trial youth receiving methylphenidate or amphetamine (33%, $p=0.008$ compared with clinical trial participants) or nonclinical trial youth not receiving any ADHD medications (35%, $p=0.002$ compared with clinical trial participants). However, it is not clear whether the clinical trial participation or the more rigorous screening for the clinical trial created a selection bias.

Sexual Development

One fair-quality study focused on sexual development in children initially aged 6 to 15 years who were randomized to atomoxetine versus placebo.¹³¹ Among 394 patients who were mostly male, no statistically significant differences were seen in median age of puberty (12.6 in atomoxetine group and 12.3 in placebo group, $p=0.88$) or frequency of onset of puberty (26% in atomoxetine group and 26.9% in placebo group $p=0.88$). However, the mean height change was higher in the placebo group (3.2 inches in atomoxetine group and 4.22 in placebo group, $p=0.01$).

Peer Relationships

One poor-quality study reported results of the quality of peer relationships on the CHIP-CE PRF subdomain for peer relationships at the end of a 6-week period in which one group had their lisdexamfetamine continued and the other group was switched to placebo.¹⁰³ The effect size was 0.434 ($P<0.001$) for the lisdexamfetamine group versus placebo, indicating better peer relationships in the lisdexamfetamine group than placebo.

Risk Avoidance

One poor-quality study reported results of risk avoidance on the CHIP-CE PRF subdomain risk avoidance at the end of a 6-week period in which one group had their lisdexamfetamine continued and the other group was switched to placebo.¹⁰³ The effect size was 0.613 ($P<0.01$) for the lisdexamfetamine group versus placebo, indicating greater risk avoidance in the lisdexamfetamine group than placebo.

Academic Performance

The four-arm MTA study reported results of academic performance at 8 years, finding no statistically significant treatment effects identified for reading, math, or GPA at 8 years.¹⁴⁸

Antisocial Behavior, Accidents, and Psychiatric Illness

The four-arm MTA study found no statistically significant treatment effects on incarceration, aggression, or motor vehicle accidents at 8 years.¹⁴⁸ There was a statistically significant treatment effect with anxiety at 8 years (14.9% medication management, 16.7% behavioral management, 18.3% combination, and 19.7% placebo; p value for treatment effect=0.0217).

Adverse Effects

In one study, selected adverse effects of atomoxetine versus placebo were reported.¹³¹ There was a higher rate of increased appetite (7.1% vs 1.4%, p=0.006) and gastrointestinal symptoms (8.2% vs. 2.7%, p=0.046) in patients receiving atomoxetine versus placebo.

Strength of Evidence—Pharmacologic Versus Placebo/Usual Care

Table 8 summarizes the strength of evidence for comparisons between pharmacologic and placebo/usual care treatments.

Table 8. Strength of Evidence for Major Outcomes—Comparisons Between Pharmacologic and Placebo/Usual Care Treatments

Outcome	No. Studies/ Design (N Patients)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Major outcomes							
Academic performance	1 RCT (436)	Medium	Direct	NA	Imprecise	Unclear	Eight years after completion of assigned treatments no statistically significant differences were identified in reading, math or GPA between those who received medications versus usual care. ¹⁴⁸ Note “medication” management here used a stepped approach and therefore it was unclear which specific medication was used for specific patients.
Insufficient							
Aggression	1 RCT (436)	Medium	Direct	NA	Imprecise	Unclear	Eight years after completion of assigned treatments no statistically significant differences were identified in aggression between those who received medications versus usual or community care. ¹⁴⁸ Note “medication” management here used a stepped approach and therefore it was unclear which specific medication was used for specific patients.
Insufficient							
Changes in appetite	1 RCT (394)	Medium	Direct	NA	Imprecise	None	A statistically higher rate of increased appetite was seen in patients taking atomoxetine versus placebo. ¹³¹
Insufficient							
Changes in standardized symptom scores	1 RCT (285)	Medium	Direct	NA	Imprecise	None	A smaller proportion of patients receiving placebo as compared to any of three doses of lisdexamfetamine achieved symptomatic remission at 1 month. ¹⁶¹
Insufficient							
Depression or anxiety	1 RCT (436)	Medium	Direct	NA	Imprecise	Unclear	Eight years after completion of assigned treatments no statistically significant higher rate of anxiety in the usual or community care groups than medication group. ¹⁴⁸ Note “medication” management here used a stepped approach and therefore it was unclear which specific medication was used for specific patients.
Insufficient							
Elevated blood pressure	1 RCT (493)	Medium	Direct	NA	Imprecise	Unclear	Eight years after completion of assigned treatments no statistically significant treatment group effects were found. ¹⁴⁸
Insufficient							
Gastrointestinal symptoms	1 RCT (394)	Medium	Direct	NA	Imprecise	None	A statistically higher rate of GI symptoms was seen in patients taking atomoxetine versus placebo. ¹³¹
Insufficient							
Growth	1 RCT (394)	Medium	Direct	NA	Imprecise	None	There was a statistically significantly change in height in

Outcome	No. Studies/ Design (N Patients)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
suppression							the placebo group compared to the atomoxetine group but no statistically significant differences in median age of puberty or frequency of onset of puberty. ¹³¹
Insufficient							
Incarceration	1 RCT (436)	Medium	Direct	NA	Imprecise	Unclear	Eight years after completion of assigned treatments no statistically significant differences were identified in incarceration between those who received medications versus usual care. ¹⁴⁸ Note “medication” management here used a stepped approach and therefore it was unclear which specific medication was used for specific patients.
Insufficient							
Increased heart rate	1 RCT (507)	Medium	Direct	NA	Imprecise	Unclear	Eight years after completion of assigned treatments no statistically significant treatment group effects were found. ¹⁴⁸
Insufficient							
Motor vehicle collisions	1 RCT (436)	Medium	Direct	NA	Imprecise	Unclear	Eight years after completion of assigned treatments no statistically significant differences were identified in motor vehicle accidents between those who received medications versus usual care. ¹⁴⁸ Note “medication” management here used a stepped approach and therefore it was unclear which specific medication was used for specific patients.
Insufficient							
Quality of peer relationships	1 RCT (Unclear)	High	Direct	NA	Imprecise	Unclear	Statistically significantly better peer relationships were seen in patients who continued lisdexamfetamine as compared to patients who were switched to placebo for 6 weeks. ¹⁰³
Insufficient							
Risk-taking behaviors	1 RCT (Unclear)	High	Direct	NA	Imprecise	Unclear	Statistically significantly greater risk avoidance was seen in patients who continued lisdexamfetamine as compared to patients who were switched to placebo for 6 weeks. ¹⁰³
Insufficient							
Substance abuse	1 Obs (211)	Medium	Direct	NA	Imprecise	None	Youth enrolled in a clinical trial and receiving methylphenidate reported a statistically significantly lower alcohol use than youth who were not in clinical trial and not receiving any ADHD medications. ¹¹⁵
Insufficient							

Abbreviations: ADHD=attention deficit hyperactivity disorder; NA=not applicable; Obs=observational; RCT=randomized controlled trial; SOE=strength of evidence

Key Points for Pharmacologic Versus Pharmacologic

- Based on evidence from 3 observational studies, the proportion of patients reporting GI effects was slightly higher for atomoxetine than MPH (SOE = low)
- Little additional evidence has been generated for comparing safety and efficacy of select FDA-approved medications for treatment of ADHD and strength of evidence was insufficient for all other outcomes

Findings in Relationship to What is Already Known

The 2011 report¹ included comparisons of pharmacologic agents (MPH, DEX, MAS, ATX, and extended release guanfacine) in children under 6 years of age with ADHD or disruptive behavior disorder as part of Key Question 1 and in people 6 years of age and older (including adults) with ADHD in Key Question 2. In that systematic review, there were relatively few studies that directly compared pharmacologic agents relative to the number of studies that compared medications to placebo, nonpharmacologic assessment, and noncomparative studies. In children under 6 years of age, no studies directly compared pharmacologic agents. Our review did not specifically focus on this population of patients; however, children as young as 3 years of age were included in studies reported on adverse events associated with pharmacologic agents in comparative assessments.

In people aged 6 years and older, there were 9 comparative studies of pharmacologic agents in the 2011 report; however that report was focused on ascertaining only longer-term efficacy and safety. One study compared efficacy in people receiving MPH compared with pemoline;¹⁶⁶ but pemoline is not a pharmacologic agent of interest in this updated review as it has been removed from the US market. One other study compared extended-release guanfacine monotherapy with extended release guanfacine plus either amphetamine or MPH.¹⁴⁶ That study is also included in this updated review. Three studies assessed adverse events between ATX and unspecified stimulants,¹⁶⁷ between MPH and DEX,¹⁶⁸ and between MPH and MAS.¹⁴⁵ The remaining four studies compared growth in patients receiving MPH versus MAS,¹⁶⁹ DEX versus MPH,¹⁷⁰ AMP versus MPH,¹⁷¹ and MPH versus DEX.¹⁷² Because of the small number of comparative studies of pharmacologic agents, no specific conclusions were made regarding the comparative efficacy or safety of the included pharmacologic agents.

This updated systematic review provides results from a larger number of studies comparing FDA-approved pharmacologic agents, especially comparisons of atomoxetine and methylphenidate; however, the SOE for efficacy or safety remains insufficient.

Detailed Synthesis—Pharmacologic Versus Pharmacologic

For this comparison, we identified nine studies.^{90,91,114,134,137,145,146,159,162} Of these, seven were multisite studies,^{90,91,114,134,137,146,162} one was a single site,¹⁵⁹ and one did not report the number of sites.¹⁴⁵ Only one study was an RCT.¹⁵⁹ Among the eight observational studies, four analyzed data from the Italian National ADHD Registry—three from a whole region^{91,114,162} and one from selected sites in a specific region.¹³⁴ Government funding was reported for five studies,^{114,134,137,145,162} industry funding for two studies,^{90,146} and unknown funding for two studies.^{91,159}

Treatments compared in six of the studies were atomoxetine versus methylphenidate.^{91,114,134,145,159,162} One study compared extended-release guanfacine monotherapy with extended release guanfacine plus either amphetamine or methylphenidate,¹⁴⁶ one assessed atomoxetine monotherapy compared with atomoxetine combined with any other ADHD medication,⁹⁰ and one was a survey collecting patient-reported adverse events from any ADHD medication.¹³⁷

Of the nine studies, two reported results using one of the selected ADHD symptom scores, the Connor Rating Scale-Parent¹⁵⁹ and the ADHD Rating Scale.¹⁴⁶ One study reported results from one of the selected functional impairment tests, the Clinical Global Impression.⁹⁰ Of the nine studies, seven only reported adverse events of interest for this systematic review.^{91,114,134,137,145,146,162}

ADHD Symptom Scores

Two studies reported results of ADHD symptom scores.^{146,159} One study was an RCT conducted in a single site in Turkey in which children between the ages of 7 and 16 were randomly assigned to receive atomoxetine (59 evaluable) or osmotic release oral system methylphenidate (OROS-MPH) (61 evaluable).¹⁵⁹ The Conners Comprehensive Behavior Rating Scale-Teacher was used to assess and compare changes on the hyperactive, inattentive, and behavior subscales from baseline to 6 months and to compare the proportion of children achieving at least a 40% reduction in the hyperactive, inattentive, and behavior subscales at 6 months. There were no statistically significant differences between the children taking atomoxetine and those taking OROS-MPH in any of these measures. This study was rated as fair quality.

The second study was an observational study enrolling children from two prior RCTs conducted in the United States evaluating extended-release guanfacine (one of which permitted use of amphetamine or methylphenidate with the extended-release guanfacine).¹⁴⁶ In this observational extension study, children aged 6 to 17 at initiation received one of four doses of extended-release guanfacine monotherapy (n=206) or any dose of extended-release guanfacine in combination with amphetamine or methylphenidate as the combination group (n=53). The ADHD Rating Scale was used to assess ADHD symptoms at various time points. The change in score within each treatment arm (monotherapy or combination therapy) from baseline to last assessment (time varied up to 24 months) was determined, but treatment arms were not compared. There was a statistically significant decrease in mean score in each arm; -20.1 (± 13.5) for monotherapy and -16.1 (± 11) for combination therapy (both p < 0.001). This study was rated as poor quality.

Functional Impairment Scores

Only one study presented results using a selected functional impairment tool.⁹⁰ This study was an industry-funded, observational study conducted in two U.S. sites. Chart-abstracted data were used to compare least-square means of the Clinical Global Impressions Scale assessed at least 50 days after the start of pharmacologic therapy in children aged 6 to 17 receiving atomoxetine monotherapy (n=37) compared with children receiving atomoxetine combination therapy (combined with any other ADHD medication) (n=34). The statistical model was adjusted using propensity scores. No statistically significant difference in least-square mean Clinical Global Impressions Score was found between the treatment groups (p=0.4072). This study was rated as poor quality.

Adverse Events

Seven studies presented adverse events from ADHD pharmacologic therapies.^{91,114,134,137,145,146,162} One fair-quality study presented results from a single survey of the parents of 578 children aged 3 to 16 conducted in the UK to ascertain recalled adverse drug reactions to any ADHD medication.¹³⁷ Among 200 completed surveys, 80% were from children taking methylphenidate alone or in combination. Because the number of patients exposed to each drug or drug combination was not reported, it is difficult to draw any conclusions from these results.

Five studies reporting adverse effects were observational studies comparing atomoxetine with methylphenidate.^{91,114,134,145,162} Four of these used data from the Italian National ADHD Registry—three in whole^{91,114,162} and one from selected sites in a specific region.¹³⁴ Thus, it is not possible to determine the total number of unique patients, as patients may have been included in more than one study. Of these four studies, one poor-quality study focused on ECG, blood pressure, and heart rate changes only.¹¹⁴ In this study, there was a higher risk of having at least one altered ECG (RBBB, sinus bradycardia, sinus tachycardia, increased QTc, and/or AV block) at 6 months (RR 1.29; 95% CI 0.52 to 3.21) and 12 months (RR 2.41; 95% CI 1.04 to 5.60) in patients receiving methylphenidate versus atomoxetine, although the increased risk at 6 months was not statistically significant. Systolic blood pressure, diastolic blood pressure, and heart rate were not compared by treatment arms but rather by changes at 6, 12, and 24 months. The only statistically significant change in patients taking methylphenidate was an increase in heart rate at 6 months. The only statistically significant changes in patients taking atomoxetine were an increase in heart rate at 6 and 12 months and an increase in diastolic blood pressure at 6 months.

The other three studies using the Italian National ADHD Registry and comparing atomoxetine with methylphenidate reported on numerous adverse events (Table 9). In one of these, after controlling for presence of comorbid psychiatric conditions, there was a statistically higher incidence rate ratio for gastrointestinal side effects (4.56; 95% CI 2 to 10.43), cardiovascular side effects (3.43; 95% CI 1.21 to 9.76), and neuropsychiatric side effects (2.54; 95% CI 1.34 to 4.74) for atomoxetine versus methylphenidate.⁹¹ In another, there was a statistically significant greater risk of adverse reactions to atomoxetine versus methylphenidate (RR 3.57; 95% CI 1.92 to 6.64).¹⁶² These studies were rated as fair to good quality.

Table 9. Adverse Events Reported in Italian National ADHD Registry

Reported Adverse Event of Interest	Atomoxetine (%)	Methylphenidate (%)
Cortese, 2015⁹¹	N=753	N=1350
GI effects	1.3	0.4
Eating disorders	1.5	0.7
Suicidal Ideation	0.7	0
Sleep disorders	0.4	.07
Mood disorders	0.5	0.07
Tachycardia	0.5	0.1
Didoni, 2011¹³⁴	N=96	N=34
Decreased appetite	16	15
Irritability	9	0
Tachycardia	8	0
Unstable mood	7	0
Insomnia	3	3
Tics	2	3
Abdominal pain	3	0
Dyspepsia	3	0
Pane, 2010¹⁶²	N=781	N=643
Suicidal ideation	0.4	0
ECG abnormality	1	0.9
Tics	0	0.2
Decreased appetite	0.3	0.3
GI disease	0.9	0
Increased blood pressure	0.1	0.2

Abbreviations: ECG = electrocardiogram; GI=gastrointestinal

The fifth observational study presenting adverse effects of atomoxetine versus MPH was U.S.-government funded and used Medicaid claims data of individuals aged 13 to 20 to compare emergency department visits for cardiac causes among past and current users of atomoxetine and MPH.¹⁴⁵ No statistically significant differences between MPH and atomoxetine were found for current users (adjusted HR 1.01; 95% CI 0.8 to 1.28) or past users (adjusted HR 0.95; 95% CI 0.73 to 1.25). This study was rated as fair quality. The last study reporting adverse effects was a poor-quality RCT comparing extended-release guanfacine monotherapy versus combination therapy with amphetamine or MPH.¹³⁷

The rates of selected adverse events are presented in Table 10.

Table 10. Rates of Adverse Events

Selected Adverse Event	Monotherapy N=206	Combination Therapy N=53
Somnolence	38%	–
Headache	25%	23%
Fatigue	15%	–
Upper abdominal pain	12%	15%
Syncope	2%	0%

Strength of Evidence—Pharmacologic Versus Pharmacologic

Table 11 summarizes the strength of evidence for comparisons of pharmacologic therapies.

Table 11. Strength of Evidence for Major Outcomes—Comparisons of Pharmacologic Treatments

Outcome	No. Studies/ Design (N Patients)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Major outcomes							
Changes in standardized symptom scores	2 RCTs and 1 Obs (448)	High	Direct	Inconsistent	Imprecise	Unclear	Two RCTs reported changes in symptom score. ^{146,159} No statistically significant differences in ADHD symptom scores were seen with MPH versus atomoxetine in one RCT. Statistically significant improvements in ADHD symptom scores occurred from baseline to last follow-up (up to 24 months) in patients receiving guanfacine XR monotherapy and guanfacine XR with amphetamine or MPH but changes between groups were not compared. No statistically significant difference in functional impairment scores were found in an observational study comparing atomoxetine monotherapy to atomoxetine combined with other ADHD medications. ⁹⁰
Insufficient							
Acceptability of treatment-Discontinuation Rate	1 Obs (130)	Medium	Direct	NA	Imprecise	None	29% discontinued MPH and 26% discontinued atomoxetine within 12 months of observation. ¹³⁴
Insufficient							
Behavior changes	1 Obs (130)	Medium	Direct	NA	Imprecise	None	Number of patients with irritability, unstable mood, and psychosis were reported. No patients in the MPH group had reports of these changes but 9, 7, and 4, patients respectively had reports of these changes. ¹³⁴
Insufficient							
Cardiac arrhythmias	1 Obs (750)	High	Direct	Consistent	Imprecise	None	Statistically significant greater relative risk of having at least 1 ECG change at 12 months with MPH versus atomoxetine but no difference at 6 months. No significant difference in risk of ED visit for any cardiovascular cause between current or past users of MPH and atomoxetine. ^{114,145}
Insufficient	1 Obs (28,285 person years)						
Changes in appetite	3 Obs (1,966)	Medium	Direct	Inconsistent	Imprecise	None	Three observational studies reported changes in appetite outcomes. Percentage of patients with decreased appetite were similar in two studies comparing MPH and atomoxetine and percentage of patients with eating disorders was
Insufficient							

Outcome	No. Studies/ Design (N Patients)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Conduction abnormalities	1 Obs (1,424)	Medium	Direct	NA	Imprecise	None	slightly higher with atomoxetine versus MPH in a third study. ^{91,134,162} Rates of ECG abnormalities were similar in patients receiving MPH and atomoxetine (both 1%). ¹⁶²
Insufficient							
Elevated blood pressure	2 Obs (2,175)	High	Direct	Consistent	Imprecise	None	No statistically significant differences in elevated blood pressure were seen between MPH and atomoxetine. ^{114,162}
Insufficient							
Gastrointestinal symptoms	3 Obs (1,966)	Medium	Direct	Consistent	Imprecise	None	The proportion of patients reporting GI effects or disease was small in all 3 studies and slightly higher for atomoxetine than MPH. ^{91,134,162}
Low							
Increased heart rate	3 Obs (930)	Low	Direct	Consistent	Imprecise	None	Three studies reported outcomes relating to heart rate. ^{91,114,134} Two studies reported slightly higher proportions of patients with tachycardia who received atomoxetine versus MPH. The third study elevations in heart rate from baseline at 6 months for MPH and at 6 and 12 months for atomoxetine.
Insufficient							
Sleep disturbance	1 Obs (130)	Medium	Direct	NA	Imprecise	None	The proportion with sleep disturbances was slightly higher with atomoxetine versus MPH. ¹³⁴
Insufficient							
Suicide ideation	1 Obs (1424)	Medium	Direct	Consistent	Imprecise	None	The number of patients reporting suicidal ideation was slightly higher with atomoxetine versus MPH. ^{91,162}
Insufficient							
Tics or other movement disorders	2 Obs (1554)	Medium	Direct	Consistent	Imprecise	None	The number of patients with tics was slightly higher with MPH than atomoxetine. ^{134,162}
Insufficient							

Abbreviations: ECG=electrocardiogram; MPH=methylphenidate; NA=not applicable; Obs=observational; RCT=randomized controlled trial; SOE=strength of evidence; XR=extended release

Key Points for Pharmacologic Versus Nonpharmacologic

- Three small randomized clinical trials (two good quality, one fair quality) compared MPH with the supplements ginkgo biloba, ningdong granule, or omega-3/6 fatty acids. All three studies found a greater number of participants with decreased appetite and sleep disturbances when on MPH compared to supplementation (SOE = low)
- Evidence was insufficient for all other outcomes.

Findings in Relationship to What is Already Known

Previous reviews have examined the relationship between pharmacologic and nonpharmacologic treatments comparing omega-3/6 with placebo.^{173,174} Our summary findings directly comparing MPH with the supplements of ginkgo biloba, ningdong granule, or omega-3/6 fatty acids have not been reported in previous reviews. We found low SOE that ginkgo biloba, ningdong granule, or omega-3/6 supplements produced greater improvements compared to MPH on the ADHD Rating Scale. Several limitations existed among this literature including overall study quality, small sample sizes, and measuring only short-term outcomes.

The 2011 report¹ found that the evidence on long-term outcomes of MPH treatment was sparse and inconclusive. One exception to this was the study by Molina et al.¹⁴⁸ (also included in this updated review) that showed reduced ADHD symptoms in a mostly male sample with ADHD combined type following 14 to 24 months of MPH treatment. Our update evaluates one additional study, observational in design, by Zhang et al.¹⁴¹ that specifically looked at the long-term outcomes of height and weight from MPH use. Findings from that study indicate small but significant reductions in height and weight among the MPH groups compared with non-ADHD participants.

The 2011 report¹ also reported on adverse effects of pharmacologic interventions. The findings from that report were determined to be inconclusive due to information from observational studies and uncontrolled extensions to clinical trials. However, that review did not examine adverse effects of pharmacologic treatments when compared with supplements (i.e., ginkgo biloba, ningdong granule, and omega-3/6). Generally, a higher proportion of adverse effects was reported with MPH or combination of supplements and MPH compared with supplement. The most common side effects for supplements were dyspepsia with omega-3/6 and increased appetite with ningdong granule. Our findings comparing MPH with these supplements are likewise limited due to small sample sizes, overall quality of the studies, and assessment of short-term outcomes.

The effectiveness of omega-3/6 for the treatment of ADHD symptoms was not included in the 2011 report. However, a 2011 systematic review by Bloch and Qawasmi¹⁷³ included a meta-analysis comparing omega-3 fatty acid supplementation with placebo. These relational findings are discussed under the Nonpharmacologic versus Nonpharmacologic/Placebo comparison in this report.

Detailed Synthesis—Pharmacologic Versus Nonpharmacologic

For this KQ 2 comparison, we identified 8 studies, 6 RCTs^{107,121,135,144,148,163} and 2 observational studies,^{115,141} published between 2009 and 2015 that met our inclusion criteria. There was a total of 1,250 participants with a mean age ranging from 7.42 to 15.5, and the majority were male (65% to 85.3%). Country sites varied, with the majority conducted in the

United States (n=2), UK (n=2), or Asia (n=2). Half the studies (n=4) were government-sponsored research, most were single site (n=6), and the majority of studies recruited participants from specialty clinics (n=6). Study characteristics are in Table 12.

Of the 6 RCTs, MPH was the primary pharmaceutical intervention. Three trials were 3-arm studies comparing MPH alone or in combination with a nonpharmacologic intervention. The dosage of MPH was clinically adjusted according to tolerability and efficacy, ranging from 0.3 mg/kg per day to 1.5 mg/kg per day. Comparators in the trials included supplements (n=3; ginkgo biloba, omega-3/6, and ningdong), neurofeedback (n=2), behavioral therapy (n=1), or a combination of behavioral therapy, education, and physical activity (n=1). The duration of studies ranged from 6 weeks to 8 years.

The two observational studies evaluated longer term outcomes. Methylphenidate was the pharmaceutical in both studies, with doses of 0.3 to 0.6 mg/kg per day¹⁴¹ and up to 1.5 mg/kg per day.¹¹⁵ One study¹¹⁵ compared study participants in the treatment group with a naturalistic sample as a control. The goal of that study was to determine if the 24-month use of MPH affected the risk of alcohol and illicit drug outcomes. The other study¹⁴¹ also examined long-term (2-4 years) use of MPH and the risk of height and weight gaps or growth deficits.

Outcome Measures

The selected outcome measures varied considerably across the 8 included studies (Table 12). Change in the ADHD rating scale for parent (n=3) and teacher (n=2) was the most commonly used outcome measure. Behavioral changes and academic performance were also commonly measured outcomes.

Table 12. Characteristics of Included Studies

Characteristic	Value
Study design	
RCTs	6
Observational	2
Combined number of patients; range of % males	1,250; 65.0% to 85.3%
Range of mean ages, years	7.42 to 15.5
Study years	2009-2015
Length of intervention / follow-up period	6 weeks to 8 years
Countries	
Asia	2
UK	2
Middle East	1
South America	1
USA	2
Funding source	
Government	4
Industry	2
Nongovernment, nonindustry	1
Unclear	1
Study Sites	
Single site	6
Multisite	2
Setting	
Specialty clinic	6
Primary clinic	1
Academic setting	1

Characteristic	Value
Comparisons*	
Supplements	3
Neurofeedback	2
Behavioral therapy	1
Physical exercise, education, behavioral modification	1
No treatment or non-ADHD participants (observational studies)	2
Pharmaceutical intervention and dosage	
Methylphenidate	8
0.3-1 mg/kg/day	7
1.5 mg/kg/day	1
Timing of last outcome assessment	
Short-term: ≤3 months	4
Long-term: 6+ months	4
Change in standardized scale outcomes	
ADHD Rating Scale–Parent	3
ADHD Rating Scale–Teacher	2
Barkley Rating Scale	1
Clinician Global Impression–Clinician	1
Clinician Global Impression–Parent	1
Visual and Auditory Continuous Performance	1
Other outcomes	
Behavior changes (sadness, aggression, irritability, anxiety, depression)	6
Academic performance	3
Incarceration	2
Motor vehicle collision	1
Substance abuse	1
Adverse effects of treatment	
Height and weight change	2
Gastrointestinal symptoms (nausea, dyspepsia, stomach pain)	2
Sleep disturbances (insomnia, hypersomnia, trouble falling asleep)	3
Changes in appetite (suppression, decreased, increased)	3

Abbreviations: ADHD=attention deficit hyperactivity disorder

We identified three RCTs (2 good quality, 1 fair quality) comparing MPH with a supplement of ginkgo biloba,¹⁴⁴ ningdong granule,¹³⁵ or omega-3/6 fatty acid.¹⁰⁷ Sample sizes were small, consisting of 50 to 90 participants, with one 3-arm trial comparing the combination of MPH plus omega-3/6. Changes in the ADHD Rating Scale were the primary outcome for all three trials. Findings indicate that ginkgo biloba was less effective while ningdong granule and omega-3/6 had effects similar to MPH.

Three RCTs (2 fair quality, 1 poor quality) compared MPH with neurofeedback or¹⁶³ behavioral therapy,^{148,163} and a 3-arm trial combined MPH with neurofeedback.¹²¹ Sample sizes were small in two of the trials (n=57 and 91) and large (n=579) in the 8-year follow-up study.^{148,163} The primary outcome measures varied among the trials. Findings from these trials indicate that neurofeedback or behavioral therapy are similar in effect to MPH with no differences in outcomes between them.

Two observational studies (1 fair quality,¹¹⁵ 1 poor¹⁴¹), both moderate in size (n=115 and n=149), examined the long-term (2-8 years) effects of MPH on alcohol or drug use and height or weight changes. Findings from these two studies indicate small significant reductions in height and weight among the MPH groups and higher rates of alcohol or drug use during the past year. Both studies compared ADHD participants with non-ADHD participants.

Table 13 summarizes the findings across the 8 studies.

Table 13. Findings on Pharmacologic Versus Nonpharmacologic Interventions for ADHD

Study Quality	# Participants Type of ADHD Diagnosis Criteria Age range in years % Male	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison
Academic performance						
Molina, 2009 ¹⁴⁸ Fair	N=579 Combined Type DSM-IV 7.0-9.9 years 80% Male	Medication management	Behavioral training (parent group, parent individual, classroom (student), and teacher sessions) Combination: Medication management and Behavioral training Usual care	8 years	WIAT reading Mean = 96.1 (SD = 14.2) P = .8541 WIAT math = 91.5 (SD = 14.8) P = .5156 GPA = 2.79 (SD = .57) P = .3354	WIAT reading Mean = 96.2 (SD = 13.2) WIAT math = 96 (SD = 17) GPA = 2.83 (SD = .56) WIAT reading Mean = 94.7 (SD = 14.5) WIAT math = 94.7 (SD = 17.4) GPA = 2.7 (SD = 0.56) WIAT reading Mean = 95.6 (SD = 13.4) WIAT math = 95.7 (SD = 15.9) GPA = 2.71 (SD = 0.59)
Aggression						
Molina, 2009 ¹⁴⁸ Fair	N=579 Combined Type DSM-IV 7.0-9.9 years 80% Male	Medication management	Behavioral training (parent group, parent individual, classroom (student), and teacher sessions) Combination: Medication management and Behavioral training Usual care	8 years	Aggression conduct parent measure rated 1 (never) to 4 (often) Mean = 1.17 (SD = .22) P = .4511	Aggression conduct parent measure rated 1 (never) to 4 (often) Mean = 1.13 (SD = .17) Aggression conduct parent measure rated 1 (never) to 4 (often) Mean = 1.15 (SD = .24) Aggression conduct parent measure rated 1 (never) to 4 (often) Mean = 1.15 (SD = .23)
Behavior changes						
Barragan, 2014 ¹⁰⁷ Poor	N=90 Any subtype DSM-IV-TR 6-12 years 67.0% Male	MPH (maximum 1 mg/kg/day)	Omega-3/6 fatty acid supplementation (6 capsules/day) MPH (maximum 1 mg/kg/day and	1 year	Irritability by the end of the study period (clinical assessment) % patients with outcome = 23.33	Irritability by the end of the study period (clinical assessment) % patients with outcome = 0 Irritability by the end of the study period % patients with outcome = 0

Study Quality	# Participants Type of ADHD Diagnosis Criteria Age range in years % Male	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison
			omega-3/6 fatty acid supplementation (6 capsules/day)			
Li, 2011 ¹³⁵ Good	N=72 NR DSM-IV 6-13 years 65.3% Male	MPH 1 mg/kg/day	Ningdong granule (a traditional Chinese medicine preparation)	8 weeks	Anxiety # patients with outcome = 5	Anxiety # patients with outcome = 1
Changes in appetite						
Barragan, 2014 ¹⁰⁷ Poor	N=90 Any subtype DSM-IV-TR 6-12 years 67.0% Male	MPH (maximum 1 mg/kg/day)	Omega-3/6 fatty acid supplementation (6 capsules/day) MPH (maximum 1 mg/kg/day and omega-3/6 fatty acid supplementation (6 capsules/day)	1 year	Appetite suppression by the end of the study period % patients with outcome = 70	Appetite suppression by the end of the study period % patients with outcome = 33.3 Appetite suppression by the end of the study period % patients with outcome = 6.7
Li, 2011 ¹³⁵ Good	N=72 NR DSM-IV 6-13 years 65.3% Male	MPH 1 mg/kg/day	Ningdong granule (a traditional Chinese medicine preparation)	8 weeks	Decreased appetite # patients with outcome = 13 Increased appetite # patients with outcome = 4	Decreased appetite # patients with outcome = 1 Increased appetite # patients with outcome = 5
Salehi, 2010 ¹⁴⁴ Good	N=50 Combined Type DSM-IV-TR 6-14 years 78% Male	MPH (up to 30 mg/day)	Ginkgo biloba	6 weeks	Decreased appetite # patients with outcome = 5	Decreased appetite # patients with outcome = 19
Changes in standardized symptom scores						
Barragan, 2014 ¹⁰⁷ Poor	N=90 Any subtype DSM-IV-TR 6-12 years 67.0% Male	MPH (maximum 1 mg/kg/day)	Omega-3/6 fatty acid supplementation (6 capsules/day)	1 year	ADHD-RS total score – 6 month Mean = 25.43 (SD = 4.84) ADHD-RS inattention – 6 months Mean = 11.73 (SD = 1.78) ADHD- RS hyperactivity – 6 months	ADHD-RS total score – 6 month Mean = 28.17 (SD = 7.92) ADHD-RS inattention – 6 months Mean = 12.33 (SD = 2.83) ADHD- RS hyperactivity – 6 months

Study Quality	# Participants Type of ADHD Diagnosis Criteria Age range in years % Male	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison
			MPH (maximum 1 mg/kg/day and omega-3/6 fatty acid supplementation (6 capsules/day)		Mean = 13.7 (SD = 3.71) ADHD- RS – total – 12 month Mean = 25.83 (SD = 4.67) ADHD-RS inattention – 12 month Mean = 12.03 (SD = 1.71) ADHD-RS hyperactive – 12 month Mean = 13.8 (SD = 3.68) CGI-severity – parents- 6 months Mean = 4 (SD = 0.98) CGI- clinician – 6 months Mean = 4 (SD = 1.08) CGI – Parent – 12 month Mean = 4.1 (SD = 1.06) CGI- clinician – 12 month Mean = 4.1 (SD = 1.06)	Mean = 15.83 (SD = 5.78) ADHD- RS – total – 12 month Mean = 27.77 (SD = 7.84) ADHD-RS inattention – 12 month Mean = 12.17 (SD = 2.7) ADHD-RS hyperactive – 12 month Mean = 15.6 (SD = 5.68) CGI-severity – parents- 6 months Mean = 3.97 (SD = 1.33) CGI- clinician – 6 months Mean = 4.1 (SD = 1.32) CGI – Parent – 12 month Mean = 3.7 (SD = 1.51) CGI- clinician – 12 month Mean = 3.7 (SD = 1.51) ADHD-RS total score – 6 month Mean = 25.5 (SD = 5.01) ADHD-RS inattention – 6 months Mean = 11.7 (SD = 2.17) ADHD- RS hyperactivity – 6 months Mean = 13.8 (SD = 3.28) ADHD- RS – total – 12 month Mean = 24.33 (SD = 5.09) ADHD-RS inattention – 12 month Mean = 11.3 (SD = 1.95) ADHD-RS hyperactive – 12 month Mean = 13.03 (SD = 3.44) CGI-severity – parents- 6 months Mean = 3.23 (SD = 0.866) CGI- clinician – 6 months

Study Quality	# Participants Type of ADHD Diagnosis Criteria Age range in years % Male	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison
						Mean = 3.23 (SD = 0.86) CGI – Parent – 12 month Mean = 3.63 (SD = 0.85) CGI- clinician – 12 month Mean = 3.63 (SD = 0.85)
Duric 2012 ¹²¹ Poor	N=91 Attention and Hyperactive ICD-10 Diagnosis Criteria 6-18 years 80% Male	MPH (dose not reported) MPH + Neurofeedback	Neurofeedback	10 weeks	Total: Barkley Rating Scale for parent's Mean w/in group change = 7.9 95% CI = 4.5-11.4	Total: Barkley Rating Scale for parent's Mean w/in group change = 8.6 95% CI = 5.0-12.2
Li, 2011 ¹³⁵ Good	N=72 NR DSM-IV 6-13 years 65.3% Male	MPH 1 mg/kg/day	Ningdong granule (a traditional Chinese medicine preparation)	8 weeks	ADHD-RS parent Mean w/in group change = 13.3 (SD = 3.2)	ADHD-RS parent Mean w/in group change = 14.1 (SD = 2.9)
Salehi, 2010 ¹⁴⁴ Good	N=50 Combined Type DSM-IV-TR 6-14 years 78% Male	MPH (up to 30 mg/day)	Ginkgo biloba	6 weeks	Parent ADHD Rating Scale-IV Mean = 26 (13,38) P < .01 Teacher ADHD Rating Scale-IV Mean = 25 (15,35) p < .001	Parent ADHD Rating Scale-IV Mean = 16 (5, 27) Teacher ADHD Rating Scale-IV Mean = 11 (4, 20)
Morena-Garcia, 2015 ¹⁶³ Fair	N=57 Combined, Inattentive and Hyperactive/Impulsive DSM-V 7-14 years 77.2% Male	Standard Pharmacological Treatment	Neurofeedback Behavioral treatment	20 weeks	Integrated Visual and Auditory Continuous Performance Test (IVA/CPT) – Full Scale Attention Mean = 2.1 (SD = 16.88)	Integrated Visual and Auditory Continuous Performance Test (IVA/CPT) – Full Scale Attention Mean = -28.57 (SD = 11.67) Integrated Visual and Auditory Continuous Performance Test (IVA/CPT) – Full Scale Attention Mean = -3.88 (SD = 16.24)
Chemical leukoderma						
Li, 2011 ¹³⁵ Good	N=72 NR DSM-IV 6-13 years 65.3% Male	MPH 1 mg/kg/day	Ningdong granule (a traditional Chinese medicine preparation)	8 weeks	ADHD-RS Teacher Mean w/in group change = 12.3 (SD = 3.1)	ADHD-RS Teacher Mean w/in group change = 13.9 (SD = 2.3) P = NS

Study Quality	# Participants Type of ADHD Diagnosis Criteria Age range in years % Male	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison
Depression or anxiety						
Salehi, 2010 ¹⁴⁴ Good	N=50 Combined Type DSM-IV-TR 6-14 years 78% Male	MPH (up to 30 mg/day)	Ginkgo biloba	6 weeks	Sadness # patients with outcome = 2 P value NS Anxiety # patients with outcome = 7 P value NS	Sadness # patients with outcome = 7 Anxiety # patients with outcome = 9
Molina, 2009 ¹⁴⁸ Fair	N=579 Combined Type DSM-IV 7.0-9.9 years 80% Male	Medication management	Behavioral training (parent group, parent individual, classroom (student), and teacher sessions) Combination: Medication management and Behavioral training Usual care	8 years	Depression (CDI) Mean = 5.78 (SD = 7.84) Anxiety (MASC) Mean = 77.7 (SD = 14.9)	Depression (CDI) Mean = 7.84 (SD = 7.24) Anxiety (MASC) Mean = 82.8 (SD = 16.7) Depression (CDI) Mean = 8 (SD = 7.66) Anxiety (MASC) Mean = 84.1 (SD = 18.3) Depression (CDI) Mean = 7.19 (SD = 7.73) Anxiety (MASC) Mean = 85.8 (SD = 19.7)
Elevated blood pressure						
Molina, 2009 ¹⁴⁸ Fair	N=579 Combined Type DSM-IV 7.0-9.9 years 80% Male	Medication management	Behavioral training (parent group, parent individual, classroom (student), and teacher sessions) Combination: Medication management and Behavioral training Usual care	8 years	SBP at 14 months Mean = 102.4 (SD = 9.7) DBP at 14 months Mean = 67.6 (SD = 9.6)	SBP at 14 months Mean = 103.2 (SD = 10.3) DBP at 14 months Mean = 68.9 (SD = 9.1) SBP at 14 months Mean = 102.6 (SD = 10.2) DBP at 14 months Mean = 66.5 (SD = 10.4) SBP at 14 months Mean = 104.1 (SD = 10.6) DBP at 14 months Mean = 67.8 (SD = 8.8)

Study Quality	# Participants Type of ADHD Diagnosis Criteria Age range in years % Male	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison
Gastrointestinal symptoms						
Barragan, 2014 ¹⁰⁷ Poor	N=90 Any subtype DSM-IV-TR 6-12 years 67.0% Male	MPH (maximum 1 mg/kg/day)	Omega-3/6 fatty acid supplementation (6 capsules/day) MPH (maximum 1 mg/kg/day and omega-3/6 fatty acid supplementation (6 capsules/day)	1 year	Dyspepsia by the end of the study period % patients with outcome = 0	Dyspepsia by the end of the study period % patients with outcome = 0 Dyspepsia by the end of the study period % patients with outcome = 40
Li, 2011 ¹³⁵ Good	N=72 NR DSM-IV 6-13 years 65.3% Male	MPH 1 mg/kg/day	Ningdong granule (a traditional Chinese medicine preparation)	8 weeks	Nausea # patients with outcome = 16 Stomach pain # patients with outcome = 12	Nausea # patients with outcome = 2 Stomach pain # patients with outcome = 2
Growth suppression						
3659 Zhang et al (2010) Poor	N=149 Combined, Inattentive and Hyperactive/Impulsive DSM-IV 6-12.5 years 85.1%	MPH 10-20 mg/day	No MPH	2-4 years	Gap to mean height, in cm, before vs. after treatment within-group change in gap to mean height cm = -1.86 (SD = .82)	Gap to mean height, in cm, before vs. after treatment within-group change in gap to mean height cm = -0.26 (SD = 0.51)
Incarceration						
Molina, 2009 ¹⁴⁸ Fair	N=579 Combined Type DSM-IV 7.0-9.9 years 80% Male	Medication management	Behavioral training (parent group, parent individual, classroom (student), and teacher sessions) Combination: Medication management and Behavioral training Usual care	8 years	Arrested once % patients with outcome = 22.4 P = .735 Arrested 2 or more times % patients with outcome = 10.3 P = .735	Arrested once % patients with outcome = 17.4 Arrested 2 or more times % patients with outcome = 7.8 Arrested once % patients with outcome = 18.9 Arrested 2 or more times % patients with outcome = 5.7 Arrested once % patients with outcome = 22.9 Arrested 2 or more times % patients with outcome = 7.8

Study Quality	# Participants Type of ADHD Diagnosis Criteria Age range in years % Male	Intervention	Comparison	Follow-up Times	Findings-Intervention	Findings-Comparison
Increased heart rate						
Molina, 2009 ¹⁴⁸ Fair	N=579 Combined Type DSM-IV 7.0-9.9 years 80% Male	Medication management	Behavioral training (parent group, parent individual, classroom (student), and teacher sessions) Combination: Medication management and Behavioral training Usual care	14 months	Heart rate at 14 months Mean = 84.2 (SD = 12.4) Incidence of Tachycardia at 14 months % patients with outcome = .8	Heart rate at 14 months Mean = 79.1 (SD = 12) Incidence of Tachycardia at 14 months % patients with outcome = .8 Heart rate at 14 months Mean = 84.6 (SD = 12.2) Incidence of Tachycardia at 14 months % patients with outcome = 2.2 Heart rate at 14 months Mean = 78.9 (SD = 12.9) Incidence of Tachycardia at 14 months % patients with outcome = 2.5
Motor vehicle collisions						
Molina, 2009 ¹⁴⁸ Fair	N=579 Combined Type DSM-IV 7.0-9.9 years 80% Male	Medication management	Behavioral training (parent group, parent individual, classroom (student), and teacher sessions) Combination: Medication management and Behavioral training Usual care	8 years	Accidents, citations, ticket % patients with outcome = 28.6	Accidents, citations, ticket % patients with outcome = 19.7 Accidents, citations, ticket % patients with outcome = 19 Accidents, citations, ticket % patients with outcome = 21.5
Sleep disturbance						
Barragan, 2014 ¹⁰⁷ Poor	N=90 Any subtype DSM-IV-TR 6-12 years 67.0% Male	MPH (maximum 1 mg/kg/day)	Omega-3/6 fatty acid supplementation (6 capsules/day) MPH (maximum 1 mg/kg/day and omega-3/6 fatty acid supplementation (6	1 year	Insomnia by the end of the study period % patients with outcome = 20	Insomnia by the end of the study period % patients with outcome = 0 Insomnia by the end of the study period % patients with outcome = 0

Study Quality	# Participants Type of ADHD Diagnosis Criteria Age range in years % Male	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison
			capsules/day)			
Li, 2011 ¹³⁵ Good	N=72 NR DSM-IV 6-13 years 65.3% Male	MPH 1 mg/kg/day	Ningdong granule (a traditional Chinese medicine preparation)	8 weeks	Trouble falling asleep # patients with outcome = 9 Hypersomnia # patients with outcome = 0	Trouble falling asleep # patients with outcome = 1 Hypersomnia # patients with outcome = 6
Salehi, 2010 ¹⁴⁴ Good	N=50 Combined Type DSM-IV-TR 6-14 years 78% Male	MPH (up to 30 mg/day)	Ginkgo biloba	6 weeks	Insomnia # patients with outcome = 3	Insomnia # patients with outcome = 12
Substance abuse						
Hammerness, 2010 ¹¹⁵ Fair	N=115 NR DSM-IV 12-17 years 73.5% Male	MPH	Naturalistic Non-ADHD Control	2 years	Rates of alcohol use in past year # patients with outcome = 12	Rates of alcohol use in past year # patients with outcome = 6 rates of alcohol use in past year # patients with outcome = 9
Weight decrease						
Salehi, 2010 ¹⁴⁴ Good	N=50 Combined Type DSM-IV-TR 6-14 years 78% Male	MPH (up to 30 mg/day)	Ginkgo biloba	6 weeks	Weight loss # patients with outcome = 3	Weight loss # patients with outcome = 8

Abbreviations: CDI=Children’s Depression Inventory; DSM=Diagnostic and Statistical Manual of Mental Disorders; MASC=Multidimensional Anxiety Scale for Children; MPH=methylphenidate; WIAT=Wechsler Individual Achievement Test

Adverse Effects of Supplementation

Adverse effects were identified in three of the included studies.^{107,135,144} Changes in gastrointestinal symptoms (nausea, dyspepsia, stomach pain), sleep disturbances (insomnia, hypersomnia, trouble falling asleep), and changes in appetite (suppression, decreased, increased) were measured. A higher proportion of participants experienced adverse effects when assigned to the MPH or combined group with MPH. A high proportion (40%) of subjects reported dyspepsia when receiving omega-3/6 supplements, and a higher proportion (13.9%) of those receiving ningdong granule supplementation reported increased appetite compared with MPH. Table 14 summarizes the proportion of participants with adverse effects.

Table 14. Summary of Adverse Effects

Adverse Effect	Findings
<i>Physical</i>	
Weight loss ¹⁴⁴	12.0% (n=3) receiving ginkgo biloba and 32.0% (n=8) receiving MPH
<i>Gastrointestinal</i>	
Nausea ^{107,135}	5.6% (n=2) receiving NDG and 44.4% (n=16) receiving MPH 20%(n=6) receiving MPH alone
Dyspepsia ¹⁰⁷	40% (n=9) receiving omega-3/6 alone after 1 month of treatment
Stomach pain ^{135,144}	5.6% (n=2) receiving NDG and 33.3% (n=12) receiving MPH 12.0% (n=3) receiving ginkgo biloba and 20.0% (n=5) receiving MPH
<i>Sleep</i>	
Insomnia ^{107,144}	20% (n=6) receiving MPH alone 12.0% (n=3) receiving ginkgo biloba and 48.0% (n=12) receiving MPH
Hypersomnia ¹³⁵	16.7% (n=5) receiving NDG and 0 receiving MPH
Trouble falling asleep ¹³⁵	2.8% (n=1) receiving NDG and 13.9% (n=5) receiving MPH
<i>Appetite</i>	
Suppression ¹⁰⁷	70% (n=21) receiving MPH alone, 6.7% (n=2) receiving omega-3/6 alone, and 33.3% (n=10) receiving combined
Decreased ^{135,144}	2.8% (n=1) receiving NDG and 36.1% (n=13) receiving MPH 20.0% (n=5) receiving ginkgo biloba and 76.0% (n=19) receiving MPH
Increased ¹³⁵	13.9% (n=5) receiving NDG and 11.1% (n=4) receiving MPH

Abbreviations: MPH=methylphenidate, NDG=ningdong granule

Strength of Evidence—Pharmacologic Versus Nonpharmacologic

Table 15 summarizes the strength of evidence for pharmacologic versus nonpharmacologic treatments.

Table 15. Strength of Evidence for Major Outcomes—Comparisons Between Pharmacologic and Nonpharmacologic Treatments

Outcome	No. Studies/ Design (N Patients)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Major outcomes							
Academic performance	1 RCT (436)	Medium	Direct	NA	Imprecise	Unclear	Eight years after completion of assigned treatments no statistically significant differences were identified in aggression between those who received the MPH medications versus behavioral therapy or the combination of medication and behavioral therapy. ¹⁴⁸
Insufficient							
Aggression	1 RCT (436)	Medium	Direct	NA	Imprecise	Unclear	Eight years after completion of assigned treatments no statistically significant differences were identified in aggression between those who received the MPH medication versus behavioral therapy or the combination of medication and behavioral therapy. ¹⁴⁸
Insufficient							
Behavior changes	2 RCTs (162)	Medium	Direct	Inconsistent	Imprecise	None	Percentage of patients with anxiety were significantly (p<0.05) greater in proportion one supplement (ningdong granule) compared to MPH medication and no reports of increased irritability were noted in the omega-3/6 when compared to MPH medication. ^{107,135}
Insufficient							
Changes in appetite	3 RCT (212)	Medium	Direct	Consistent	Imprecise	None	All three studies found the MPH medication group to have a significantly greater number of participants with decreased appetite when compared to supplementation by ningdong, omega-3/6 or Gingko Biloba. ^{107,135,144}
Low							
Changes in standardized symptom scores	5 RCTs (356)	Medium	Direct	Inconsistent	Imprecise	Unclear	Five RCTs reported changes in symptom scores. ^{107,121,135,144,163} One study reports a significant change in standardized symptom scores favoring MPH medication compared to supplementation of ginkgo biloba. In two studies, no significant differences between groups supplemented by omega-3/6 alone or in combination with MPH medication or Ningdong granule and MPH medication was identified by standardized symptom scores. In two studies, no significant differences were found between MPH medication and either neurofeedback or behavioral therapy groups on changes in standardized symptom scores.
Insufficient							
Depression or anxiety	2 RCTs (486)	Medium	Direct	Consistent	Imprecise	Unclear	In both studies no statistically significant difference in anxiety between the MPH medication and behavioral treatment or supplementation groups. ^{144,148}
Insufficient							
Elevated blood pressure	1 RCT (493)	Medium	Direct	NA	Imprecise	Unclear	Eight years after completion of assigned treatments no statistically significant treatment group effects were found between those who received MPH medication versus

Outcome	No. Studies/ Design (N Patients)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Insufficient							behavioral therapy or the combination of medication and behavioral therapy. ¹⁴⁸
Gastro- intestinal symptoms	2 RCTs (162)	Medium	Direct	Inconsistent	Imprecise	None	One study reports a higher proportion of participants with gastrointestinal symptoms in the supplement group (omega-3/6) compared to MPH medication. The other study reports a higher proportion of participants with gastrointestinal symptoms in the MPH medication group compared to the supplement (ningdong granule). ^{107,135}
Insufficient							
Growth suppression	1 Obs (175)	Medium	Direct	NA	Imprecise	None	Two to four-year follow-up of MPH versus control participants found a small significant deceleration of height velocity from long term MPH medication use; related to the duration of treatment. No significant influence of long term MPH medication on weight or body mass index values. ¹⁴¹
Insufficient							
Incarceration	1 RCT (436)	Medium	Direct	NA	Imprecise	Unclear	Eight years after completion of assigned treatments no statistically significant difference was identified in incarceration between those who received MPH medication versus behavioral therapy or the combination of medication and behavioral therapy. ¹⁴⁸
Insufficient							
Increased heart rate	1 RCT (507)	Medium	Direct	NA	Imprecise	Unclear	Eight years after completion of assigned treatments no statistically significant treatment group effects were found between those who received MPH medication versus behavioral therapy or the combination of medication and behavioral therapy. ¹⁴⁸
Insufficient							
Motor vehicle collisions	1 RCT (436)	Medium	Direct	NA	Imprecise	Unclear	Eight years after completion of assigned treatments no statistically significant differences were identified in motor vehicle accidents between those who received MPH medication versus behavioral therapy or the combination of medication and behavioral therapy. ¹⁴⁸
Insufficient							
Sleep disturbance	3 RCT (212)	Medium	Direct	Consistent	Imprecise	None	Three RCTs ^{107,135,144} reported sleep disturbance outcomes. In two of the trials a significantly greater proportion of sleep disturbances were found in the MPH medication group compared to supplementation by ningdong granule or ginkgo biloba. The other trial reports a higher proportion of sleep disturbances in the MPH medication group (67.0%) compared to 0% in the omega-3/6 group.
Low							
Substance abuse	1 Obs (115)	Medium	Direct	NA	Imprecise	None	Significantly lower rates of alcohol and drug use in the previous year among the MPH medication group compared to non-ADHD controls. ¹¹⁵
Insufficient							
Weight decrease	1 RCT (50)	Medium	Direct	NA	Imprecise	None	No significant difference in weight decrease between

Outcome	No. Studies/ Design (N Patients)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Insufficient							MPH medication and supplementation use of ginkgo biloba. ¹⁴⁴

Abbreviations: MPH=methylphenidate NA=not applicable; Obs=observational; RCT=randomized controlled trial; SOE=strength of evidence

Key Points for Nonpharmacologic Versus Nonpharmacologic/Placebo

- There is insufficient evidence to evaluate the effectiveness of neurofeedback in reducing ADHD symptoms.
- Nine RCTs evaluated cognitive training strategies for changes in standardized symptom scores. Studies provide some evidence that computer-based Cogmed cognitive training program may reduce ADHD symptoms but the evidence is inconsistent between studies and not demonstrated at all follow-up assessment times (SOE = low)
- Two RCTs evaluated cognitive behavioral therapy and found improvement in ADHD symptoms (SOE = low)
- Two RCTs found no differences in academic performance associated with child or parent training (SOE = low)
- Evidence from eight RCTs demonstrated improvements in ADHD symptoms associated with child or parent training (SOE = moderate)
- Evidence from 8 RCTs demonstrated no differences from omega-3 fatty acid supplementation on ADHD symptoms (SOE = moderate)

Categories of Interventions for this Comparison

We organized the comparison of nonpharmacologic versus nonpharmacologic/placebo treatments into the following 7 intervention categories:

1. Neurofeedback
2. Cognitive training
3. Cognitive behavioral therapy (CBT)
4. Child or parent training or behavioral intervention
5. Dietary supplementation with omega-3/6 fatty acids
6. Herbal or dietary approaches
7. Other approaches

Findings in Relationship to What is Already Known

Of the 7 intervention categories, only 2 had data for findings in relationship to what is already known—child or parent training or behavioral intervention and other approaches. These findings are described in their corresponding section below.

Detailed Synthesis—Overview

For this KQ 2 comparison, we identified 56 articles^{92-102,104-106,108-113,116-120,123-130,132,133,136,138-140,142,143,147-158,160,163,164} representing 45 studies that met our inclusion criteria. All but two studies were RCTs. Of the 43 RCTs, 25 were rated as high quality,^{93-95,97,101,102,105,106,108,110,111,113,120,123-125,130,132,139,142,150,151,154,157,160} 17 as fair quality,^{92,96,99,104,116,118,128,129,136,138,143,147,148,156,158,163,164} and 1 as poor quality.¹¹⁷ The two observational studies were rated as fair quality.^{127,140}

Of these, 16 were multisite studies, 27 were single-site studies, and 2 did not report the number of sites. Fourteen studies included patients in the United States, 17 were conducted in Europe, and 14 included patients from the Middle East, Asia, Australia, or New Zealand. Government funding supported 25 studies, industry supported 3 studies, nongovernment and

nonindustry funding supported 7 studies. External funding was either not provided or not reported for 15 studies.

The 45 studies reported 48 comparisons of a nonpharmacologic therapy with either another nonpharmacologic therapy or no therapy (e.g., a placebo intervention, usual care, or a waitlist control). Of the 7 intervention categories, 4 evaluated neurofeedback; 9, cognitive training; 2, CBT; 10, child or parent training or behavioral intervention; 9, dietary supplementation with omega-3/6 fatty acids; 5, herbal or dietary approaches; and 8, other approaches. Details of these comparisons are reported below, organized by intervention category.

Detailed Synthesis—Neurofeedback

Neurofeedback is a computer-aided type of nonpharmacologic treatment for ADHD that is based on biofeedback principles. Treatment typically involves patients using a computer monitor that shows brainwave activity through EEG. In the neurofeedback process, patients are trained to adjust their attention and thereby their brainwave activity. Three good-quality^{101,108,151} and 1 fair-quality¹⁶³ studies representing 353 patients evaluated neurofeedback. Findings are summarized by outcome and described in Table 16.

Acceptability of Treatment

Only one study examined parent-rated motivation of children to participate in treatment and the effectiveness of treatment, finding no difference between neurofeedback and the attention skills control condition.¹⁵¹

Changes in Standardized Symptom Scores

One study found a statistically significant decrease in ADHD symptoms using a standard scale comparing neurofeedback with an attention skills control condition.¹⁵¹ A second study found no difference between neurofeedback and cognitive training, but did find significant improvements in ADHD symptoms according to parent and teacher reporting for neurofeedback compared with control.¹⁰⁸ A third study compared neurofeedback with standard pharmacologic treatment and a behavioral treatment and found that the group treated with neurofeedback showed greater improvement in a continuous performance test score when compared with each of the other groups.¹⁶³ Finally, a fourth study did not find any significant changes between children receiving neurofeedback versus those receiving treatment as usual.¹⁰¹

Adverse Effects of Neurofeedback

No adverse effects from neurofeedback were reported.

Table 16. Findings on Neurofeedback Interventions for ADHD

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Acceptability of treatment						
Gevensleben 102 Good RCT	Neuro-feedback training	Attention skills training	2 months	Effectiveness of treatment Mean = 3.19 (SD = .82) Parent rated motivation of their children to participate in treatment Mean = .64 (SD = .77)	Effectiveness of treatment Mean = 3.13 (SD = .90) Parent rated motivation of their children to participate in treatment Mean = .56 (SD = 1.13)	p=.77 p = .71
Changes in standardized symptom scores						
Bink, 2015 ¹⁰¹ 90 Good RCT	Neuro-feedback plus treatment as usual	Treatment as usual	0 months baseline 6 months	ADHD-RS Inattention Mean=4.4 (SD=2.49) ADHD-RS Hyperactivity/inattention Mean=3.44 (SD=2.12) Youth Self Report Total score Mean=48.5 (SD=22.01) CBCL Total score Mean=60.81 (SD=28.57)	ADHD-RS Inattention Mean=5.27 (SD=2.16) ADHD-RS Hyperactivity/inattention Mean=3.27 (SD=2.01) Youth Self Report Total score Mean=52.58 (SD=18.89) CBCL Total score Mean=63.77 (SD=27)	NS
Gevensleben, 2009 ¹⁵¹ 102 Good RCT	Neuro-feedback training	Attention skills training	2 months	German ADHD rating scale Mean within group change = -.39 (SD = .37)	German ADHD rating scale Mean within group change = -.1 (SD = .44)	p<.005
Moreno-Garcia, 2015 ¹⁶³ 57 Fair	Neuro-feedback	Standard Pharmacological Treatment	NR	Integrated Visual and Auditory Continuous Performance Test – Full Scale Attention Mean = 2.1 (SD = 16.88)	Integrated Visual and Auditory Continuous Performance Test – Full Scale Attention Mean = 28.57 (SD = 11.67)	p =.002

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
RCT		Behavioral Treatment			Changes in standardized symptom scores Integrated Visual and Auditory Continuous Performance Test – Full Scale Attention Mean = 3.88 (SD = 16.24)	p =.013
Steiner, 2014 ¹⁰⁸ 104 Good RCT	Neuro- feedback	Cognitive training		Conner 3 Parent Inattention Within-group effect size = -0.8 Conners 3 Parent Executive Functioning Within-group effect size = -0.49 Conners 3 Parent Global Index Within-group effect size = -0.37 Conners 3 Teacher Inattention Within-group effect size = -0.25	Conner 3 Parent Inattention Within-group effect size = -0.46 Conners 3 Parent Executive Functioning Within-group effect size -0.12 Conners 3 Parent Global Index Within-group effect size = -0.09 Conners 3 Teacher Inattention Within-group effect size = -0.24 Conner 3 Parent Inattention Within-group effect size = -0.15 Conners 3 Parent Executive Functioning Within-group effect size = -0.09 Conners 3 Parent Global Index Within-group effect size = -0.05 Conners 3 Teacher Inattention Within-group effect size =0	p<.05 p<.001 p<.001 p<.001

Abbreviations: ADHD=attention deficit hyperactivity disorder; CBCL=Child Behavior Checklist; RS=rating scale; SD=standard deviation

Strength of Evidence—Neurofeedback

Table 17 summarizes the strength of evidence for neurofeedback.

Table 17. Strength of Evidence for Major Outcomes—Neurofeedback

Outcome	No. Studies/ Design (N Patients)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Major outcomes							
Acceptability of treatment	1 RCT (102)	Low	Direct	NA	Imprecise	None	No difference between neurofeedback and the attention skills control condition. ¹⁵¹
Insufficient							
Changes in standardized symptom scores	4 RCTs (353)	Low	Direct	Inconsistent	Imprecise	Unclear	Four RCTs reported changes in symptom scores. ^{101,108,151,163} Three of the 4 studies demonstrated improvement in standardized symptoms scores compared with an inactive control, a behavioral intervention, and standard pharmacologic treatment. 1 study found no difference relative to cognitive training, and 1 study found no difference compared with usual care.
Insufficient							

Abbreviations: NA=not applicable; Obs=observational; RCT=randomized controlled trial; SOE=strength of evidence

Detailed Synthesis—Cognitive Training

Six good-quality^{94,106,108,111,113,151} and 3 fair-quality^{92,116,140} studies representing 768 patients evaluated cognitive training interventions. All but one study involved computer-based cognitive training programs, and of those five used a specific brand of intervention (Cogmed). Findings are summarized by outcome and described in Table 18. Meta analysis was not possible given heterogeneity in outcomes and time frames.

Academic Performance

A single, good-quality RCT found no significant treatment effects in improvement Wide Range Achievement Test 4 Progress Monitoring Version (WRAT) scores compared with a low-level (placebo) working memory training program that was identical to active intervention with respect to the types of training games utilized and the number of training trials per session, but for which difficulty level was not adjusted according to each user's performance parameters.¹¹³

Acceptability of Treatment

A single study examined parent-rated motivation of children to participate in treatment and the effectiveness of treatment, finding no difference between cognitive training and neurofeedback.¹⁵¹

Behavior Changes

A good-quality RCT found no significant between-group differences in scores on the Disruptive Behavior Disorder Rating Scale (DBDRS) compared with a partially-active-condition where inhibition and cognitive-flexibility were trained and the WM-training task was presented in placebo-mode, or to a full placebo-condition.⁹⁴

Changes in Standardized Symptom Scores

Of studies examining the Cogmed cognitive training programs,^{92,106,111,113,140} three^{106,111,113} found no significant changes on standard ADHD scales compared with low-level working memory games or a waitlist control. Two studies found a significant improvement on standardized scales.^{92,140} Of those, one compared the Cogmed intervention with a waitlist control, and at 4 months the treatment group had significantly better scores on parent report on the ADHD Index, Conners Cognitive Problems/Inattention, Conners Hyperactivity Parent, and BRIEF Metacognition Index.¹⁴⁰ No teacher measures showed any significant changes. In the other study, there was improvement at 2 and 6 months on the parent rated BRIEF Metacognition Index, and at 2 months (but not 6 months) on the BRIEF parent-rated behavioral index.⁹²

Three other studies examined computer-based cognitive training programs.^{94,108,151} One compared the Braingame program to a computer game that did not have any cognitive training characteristics, finding no significant effect of this type of training.⁹⁴ The other two were studies comparing neurofeedback with computer-based cognitive training.^{108,151} There was no difference between cognitive training and control in one,¹⁰⁸ but neurofeedback was found to be superior to both. The other directly compared the two interventions and found neurofeedback superior to cognitive attention skills training on a standardized ADHD scale.¹⁵¹

One study evaluated a cognitive training program that did not involve a computer program, finding a significant difference between the intervention and a waitlist control at 12 weeks on parent and child reported measures of ADHD symptoms.¹¹⁶

Adverse Effects of Cognitive Training

No adverse effects from cognitive training were reported.

Table 18. Findings on Cognitive Training Interventions for ADHD

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Academic performance						
Chacko, 2014 ¹¹³ 85 Good RCT	Cogmed working memory training with difficulty titrated to a user's ability	“Placebo” Cogmed working memory training with difficulty <u>not</u> titrated to a user's ability	3 weeks post	WRAT-4 – word reading WRAT-4 Sentence completion WRAT-4 Math computation WRAT-4 Spelling		Treatment effect = - 2.72 (SE = 5.5) p = - .5 Treatment effect = 5.6 (SE = 4.7) p = .23 Treatment effect = 5.22 (SE = 5.21) p = .31 Treatment effect = 1.28 (SE = 6.17) p = .83
Acceptability of treatment						
Gevensleben, 2009 ¹⁵¹ 102 Good RCT	Neurofeedback training	Attention skills training	2 months	Effectiveness of treatment Mean = 3.19 (SD = .82) Parent-rated motivation of their children to participate in treatment Mean = .64 (SD = .77)	Effectiveness of treatment Mean = 3.13 (SD = .90) Parent-rated motivation of their children to participate in treatment Mean = .56 (SD = 1.13)	P=.77 P=.71
Behavior changes						
Dovis, 2015 ⁹⁴ 89 Good RCT	Braingame Brian (computerized, home-based executive functioning training)	Braingame Brian in training mode and the working memory task in placebo mode	3 months	Parent DBDRS Inattention Mean=12.9 (SD=4.1) P-DBDRS Hyperactivity/Impulsivity Mean = 12.6 (SD = 6.4) Teacher DBDRS Inattention Mean = 12.2 (SD = 5.8) Teacher DBDRS Hyperactivity/Impulsivity	Parent DBDRS Inattention Mean = 14.6 (SD = 5.3) P-DBDRS Hyperactivity/Impulsivity Mean = 13 (SD = 5.1) Teacher DBDRS Inattention Mean = 13.3 (SD = 6.6) Teacher DBDRS Hyperactivity/Impulsivity	NS NS NS NS

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
		All tasks in training mode (overall easier)		Mean = 9.3 (SD = 4.9)	Mean = 11.5 (SD = 7) Parent DBDRS Inattention Mean = 14.1 (SD = 4.7) P-DBDRS Hyperactivity/Impulsivity Mean = 12.5 (SD = 5.7) Teacher DBDRS Inattention Mean = 11.3 (SD = 5.1) Teacher DBDRS Hyperactivity/Impulsivity Mean = 6 (SD = 9.1)	NS NS NS NS
Changes in standardized symptom scores						
Chacko, 2014 ¹¹³ 85 Good RCT	Cogmed working memory training with difficulty titrated to a user's ability	"Placebo" Cogmed working memory training with difficulty <u>not</u> titrated to a user's ability	3 weeks post	Parent Disruptive Behavior Disorder Rating Scale – Inattention symptoms Parent Disruptive Behavior Disorder Rating Scale – Hyperactive symptoms Teacher Disruptive Behavior Disorder Rating Scale – Inattention symptoms Teacher Disruptive Behavior Disorder Rating Scale – Hyperactive		Treatment effect = 1.98 (SE = 1.17) p = .2 Treatment effect = 1.88 (SE = 1.15) p = .2 Treatment effect = 1.84 (SE = 1.49) p = .22 Treatment effect = 1.94 (SE = 1.54) p = .21
Egeland, 2013 ¹¹¹ 75 Good RCT	Cogmed RoboMemo program	Waitlist control	8 months	ADHD-RS Total Score Teacher Mean=20.1 (SD=9.8) ADHD-RS Parent Mean=27 (SD=11.5)	ADHD-RS Total Score Teacher Mean=22.6 (SD=12.3) ADHD-RS Parent Mean=28.1 (SD=11)	NS NS

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Gevensleben, 2009 ¹⁵¹ 102 Good RCT	Neurofeedback Training	Attention skills training	1 month	German ADHD rating scale (FBB-HKS) Mean w/in group change = -.39 (SD = .37)	German ADHD rating scale (FBB-HKS) Mean w/in group change = -.1 (SD = .44)	P<.005
Steiner, 2014 ¹⁰⁸ 104 Good RCT	Neurofeedback	Cognitive training Waitlist control	5 months	Conner 3 Parent Inattention Within-group effect size = -0.8 Conners 3 Parent Executive Functioning Within-group effect size = -0.49 Conners 3 Parent Global Index Within-group effect size = -0.37 Conners 3 Teacher Inattention Within-group effect size = -0.25	Conner 3 Parent Inattention Within-group effect size = -0.46 Conners 3 Parent Executive Functioning Within-group effect size -0.12 Conners 3 Parent Global Index Within-group effect size = -0.09 Conners 3 Teacher Inattention Within-group effect size = 0.24 Conner 3 Parent Inattention Within-group effect size = -0.15 Conners 3 Parent Executive Functioning Within-group effect size = -0.09 Conners 3 Parent Global Index Within-group effect size = -0.05 Conners 3 Teacher Inattention Within-group effect size =0	p<.05 NS p<.05 p<.05 p<.001 p<.001 p<.001 NS
van Dongen-Boomsma, 2014 ¹⁰⁶ 51 Good RCT	Cogmed training program	Cogmed training program without adjustment for patient skill level (control group)	5 weeks	ADHD-RS Total Investigator Score Mean=32.4 (SE=5.7) ADHD-RS Teacher Mean=27.5 (SE=10.1)	ADHD-RS Total Investigator Score Mean=30.3 (SE=7.4) ADHD-RS Teacher Mean=25.5 (SE=7.7)	NS NS
Beck, 2010 ¹⁴⁰ 52 Fair Obs	Computer-based working memory intervention	Waitlist control	Baseline	ADHD Index Parent Mean = 71.7 (SD = 8.82) Conners Cognitive Problems/Inattention Parent Mean = 67.96 (SD = 9.55) Conners Hyperactivity Parent Mean = 68.37 (SD = 15.98) Conners Oppositional Parent	ADHD Index Parent Mean = 69.92 (SD = 7.86) Conners Cognitive Problems/Inattention Parent Mean = 65.38 (SD = 9.22) Conners Hyperactivity Parent Mean = 65.7 (SD = 16.5) Conners Oppositional Parent	

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
			4 months	<p>Mean = 60 (SD = 13.34)</p> <p>Conners ADHD Index Teacher # patients with outcome = 60.78 (SD = 14.96)</p> <p>Conners Cognitive Problems/Inattention Teacher Mean = 60.89 (SD = 10.58)</p> <p>Conners Hyperactivity Teacher Mean = 59.59 (SD = 15.17)</p> <p>Conners Oppositional Teacher Mean = 56.52 (SD = 8.93)</p> <p>BRIEF Metacognition Index Parent Mean = 72.96 (SD = 8.06)</p> <p>BRIEF Metacognition Index Teacher Mean = 67.96 (SD = 18.67)</p> <p>ADHD Index Parent Mean = 62.78 (SD = 9.35)</p> <p>Conners Cognitive Problems/Inattention Parent Mean = 59.89 (SD = 9.15)</p> <p>Conners Hyperactivity Parent Mean = 59.59 (SD = 14.89)</p> <p>Conners Oppositional Parent Mean = 53.96 (SD = 9.67)</p> <p>Conners ADHD Index Teacher # patients with outcome = 56.38 (SD = 13.28)</p> <p>Conners Cognitive Problems/Inattention Teacher Mean = 57.5(SD = 7.91)</p> <p>Conners Hyperactivity Teacher Mean = 56.31 (SD = 13.47)</p> <p>Conners Oppositional Teacher Mean = 52.35 (SD = 10.12)</p> <p>BRIEF Metacognition Index Parent Mean = 64.19 (SD = 9.24)</p>	<p>Mean = 59.79 (SD = 12.17)</p> <p>Conners ADHD Index Teacher # patients with outcome = 58.4 (SD = 11.4)</p> <p>Conners Cognitive Problems/Inattention Teacher Mean = 56.24 (SD = 11.05)</p> <p>Conners Hyperactivity Teacher Mean = 55.36 (SD = 13.2)</p> <p>Conners Oppositional Teacher Mean = 52.92 (SD = 8.93)</p> <p>BRIEF Metacognition Index Parent Mean = 71.38 (SD = 7.73)</p> <p>BRIEF Metacognition Index Teacher Mean = 60.2 (SD = 13.04)</p> <p>ADHD Index Parent Mean = 67.33 (SD = 7.33)</p> <p>Conners Cognitive Problems/Inattention Parent Mean = 64.75 (SD = 10.22)</p> <p>Conners Hyperactivity Parent Mean = 62.75 (SD = 13.73)</p> <p>Conners Oppositional Parent Mean = 57.5 (SD = 10.59)</p> <p>Conners ADHD Index Teacher # patients with outcome = 56.52 (SD = 10.25)</p> <p>Conners Cognitive Problems/Inattention Teacher Mean = 55.56 (SD = 10.26)</p> <p>Conners Hyperactivity Teacher Mean = 55.64 (SD = 11.14)</p> <p>Conners Oppositional Teacher Mean = 50.58 (SD = 8.71)</p> <p>BRIEF Metacognition Index Parent Mean = 69.61 (SD = 7.19)</p>	<p>P=.01</p> <p>P<.01</p> <p>P=.04</p> <p>P=.10</p> <p>P=.43</p> <p>P=.23</p> <p>P=.25</p> <p>P=.59</p> <p>P=.01</p>

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
				BRIEF Metacognition Index Teacher Mean = 64.85 (SD = 16.35)	BRIEF Metacognition Index Teacher Mean = 60.79 (SD = 12.76)	P=.22
Tamm, 2013 ¹¹⁶ 105 Fair RCT	Pay Attention! Program (attention training)	Waitlist control	12 weeks	SNAP-IV Parent Inattention Mean=1.42 (SD=.5) SNAP-IV Parent Hyperactivity/Impulsivity Mean=.93 (SD=.6) Child SNAP-IV Inattention Mean=1.84 (SD=.5) SNAP-IV Child Hyperactivity/Impulsivity Mean=1.27 (SD=.6)	SNAP-IV Parent Inattention Mean=2.15 (SD=.5) SNAP-IV Parent Hyperactivity/Impulsivity Mean=1.3 (SD=.7) Child SNAP-IV Inattention Mean=2.39 (SD=.5) SNAP-IV Child Hyperactivity/Impulsivity Mean=1.51 (SD=.7)	P<.001 P=.007 P<.001 P=.003
Van der Donk, 2015 ⁹² 105 Fair RCT	Cogmed Working Memory Training	Paying Attention in Class (experimental, combined working memory and compensatory training)	6 weeks 6 months	CBCL Attention Problems Scale CBCL Externalizing Problems Scale	CBCL Attention Problems Scale CBCL Externalizing Problems Scale	NR NR

Abbreviations: ADHD=attention deficit hyperactivity disorder; BRIEF=Behavior Rating Inventory of Executive Function; CBCL= Child Behavior Checklist; DBDRS=Disruptive Behavior Disorder Rating Scale; SNAP=Swanson, Nolan and Pelham Revision

Strength of Evidence—Cognitive Training

Table 19 summarizes the strength of evidence for cognitive training.

Table 19. Strength of Evidence for Major Outcomes—Cognitive Training

Outcome	No. Studies/ Design (N Patients)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Major outcomes							
Academic performance	1 RCT (85)	Low	Direct	NA	Imprecise	None	1 good-quality RCT found no significant treatment effects in WRAT scores compared with a control intervention. ¹¹³
Insufficient							
Acceptability of treatment	1 RCT (102)	Low	Direct	NA	Imprecise	None	1 good-quality RCT found no significant treatment effects in parent-rated motivation of children to participate in treatment compared with attention skills training. ¹⁵¹
Insufficient							
Behavior changes	1 RCT (89)	Low	Direct	NA	Imprecise	None	1 good-quality RCT found no significant between-group treatment effects in DBRS or DBDRS scores compared with a control intervention. ⁹⁴
Insufficient							
Changes in standardized symptom scores	9 RCTs (768)	Medium	Direct	Inconsistent	Imprecise	None	Nine RCTs reported changes in symptom scores. ^{92,94,106,108,111,113,116,140,151} 2 fair-quality RCTs (out of a total of 5) that evaluated the Cogmed cognitive training program demonstrated a significant improvement in standardized scale scores at some, but not all, of the follow-up assessment times. A good-quality RCTs found no treatment effect associated with the Braingame program compared with no intervention, and 2 good-quality RCTs that compared computer-based cognitive training programs to neurofeedback found either no treatment effect or superiority of neurofeedback relative to cognitive training. 1 fair-quality RCT demonstrated a reduction in ADHD symptoms associated with cognitive training relative to no intervention.

Abbreviations: DBDRS=Disruptive Behavior Disorder Rating Scale; DBRS=Disruptive Behavior Rating Scale; NA=not applicable; Obs=observational; RCT=randomized controlled trial; SOE=strength of evidence

Detailed Synthesis—Cognitive Behavioral Therapy

One good-quality⁹⁵ and 1 fair-quality⁹⁹ study representing 278 patients evaluated CBT. Findings are summarized by outcome and described in Table 20.

Changes in Standardized Symptom Scores

Both studies found a statistically significant improvement in ADHD symptom scores for the CBT program as opposed to the control condition after the initial treatment. One fair-quality study⁹⁹ followed patients through 12 months and found the CBT condition maintained superiority in terms of ADHD scale scores. In addition, this study found that there was a greater improvement in the CBCL conduct disorder/oppositional defiant disorder subscale both immediately after treatment and at 12 months.

Depression or Anxiety

The fair-quality study⁹⁹ examined changes in the depression anxiety scale scores and found that the CBT group had greater improvement in depression and anxiety scores as opposed to the control group at 3 months and that the depression score improvements were maintained at 12 months.

Adverse Effects of CBT

No adverse effects from CBT were reported.

Table 20. Findings on Cognitive Behavioral Therapy Interventions for ADHD

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Changes in standardized symptom scores						
Vidal, 2015 ⁹⁵ 119 Good RCT	CBT	Usual care	12 weeks	ADHD-RS Adolescent Inattention Mean 10.14 (0.51) ADHD-RS Adolescent Impulsivity Mean 8.29 (0.7) ADHD-RS Parents Inattention 11.31 (0.58) ADHD RS Parents Impulsivity Mean 7.72 (0.77) CGI-S Self Report Mean 2.9 (0.12) CGI-S Clinician 2.86 (0.07)	ADHD-RS Adolescent Inattention Mean 14.47 (0.5) ADHD-RS Adolescent Impulsivity Mean 11.72 (0.7) ADHD-RS Parents Inattention Mean 16.99 (0.6) ADHD RS Parents Impulsivity Mean 11.56 (0.78) CGI-S Self Report Mean 3.35 (0.12) CGI-S Clinician 3.4 (0.07)	ES=8.57 (p<.001) ES=4.9 (p<.001) ES=9.62 (p<.001) ES=4.95 (p<.001) ES=3.75 (p<.001) ES=7.71 (p<.001)
Boyer, 2015 ⁹⁹ 159 Fair RCT	CBT with an aim to improve planning skills	Solution-focused CBT without an aim to improve planning skills	3 months	ADHD symptom scale – combined inattentive and Hyperactivity/Impulsivity Mean = 18.66 (9.64) Disruptive Behavior Disorders – summarized ODD/CD subscales Mean = 5.84 (5.49)	ADHD symptom scale – combined inattentive and Hyperactivity/Impulsivity Mean = 19.99 (9.69) Disruptive Behavior Disorders – summarized ODD/CD subscales Mean = 5.99 (5.78)	
			12 months	ADHD symptom scale – combined inattentive and Hyperactivity/Impulsivity Mean = 18.41 (9.76) Disruptive Behavior Disorders – summarized ODD/CD subscales Mean = 4.74 (4.30)	ADHD symptom scale – combined inattentive and Hyperactivity/Impulsivity Mean = 20.02 (8.21) Disruptive Behavior Disorders – summarized ODD/CD subscales Mean = 4.55 (3.80)	p < .001 p < .001
Depression or anxiety						
Boyer, 2015 ⁹⁹ 159 Fair RCT	CBT with an aim to improve planning skills	Solution-focused CBT without an aim to improve planning skills	3 months	Child Depression Inventory Mean = 8.92 (6.82) Screen for Child Anxiety Related Emotional Disorders Mean = 20.49 (16.17)	Child Depression Inventory Mean = 9.21 (5.57) Screen for Child Anxiety Related Emotional Disorders Mean = 19.54 (18.17)	

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
			12 months	Child Depression Inventory Mean = 7.68 (5.10) Screen for Child Anxiety Related Emotional Disorders Mean = 18.86 (14.39)	Child Depression Inventory Mean = 8.48 (4.65) Screen for Child Anxiety Related Emotional Disorders Mean = 18.53 (16.17)	p < .001 p < .001

Abbreviation: CBT=cognitive behavioral therapy; CGI-S=Clinical Global Impression-Severity; ODD/CD=Oppositional defiant disorder/conduct disorder

Strength of Evidence—Cognitive Behavioral Therapy

Table 21 summarizes the strength of evidence for CBT.

Table 21. Strength of Evidence for Major Outcomes—Cognitive Behavioral Therapy

Outcome	No. Studies/ Design (N Patients)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Major outcomes							
Changes in standardized symptom scores	2 RCTs (278)	Low	Direct	Consistent	Imprecise	Suspect	A good-quality and a fair-quality RCT found statistically significant improvement in ADHD symptom associated with CBT relative to usual care or a limited CBT intervention. ^{95,99}
Low							
Depression or anxiety	1 RCT (159)	Medium	Direct	NA	Imprecise	Suspect	A fair-quality RCT demonstrated improvement in CDI and the Screen for Child Anxiety Related Emotional Disorders scores associated with CBT relative to usual care. ⁹⁹
Insufficient							

Abbreviations: ADHD=attention deficit hyperactivity disorder; CBT=cognitive behavioral therapy; CDI=Children’s Depression Inventory; NA=not applicable; Obs=observational; RCT=randomized controlled trial; SOE=strength of evidence

Detailed Synthesis—Child or Parent Training or Behavioral Interventions

Eight good-quality RCTs,^{97,105,110,120,123,130,150,157} 1 fair-quality RCT,¹⁵⁸ and 1 fair-quality observational study¹²⁷ representing 1,278 patients evaluated child or parent training or behavioral interventions. These included a range of different types of non-CBT behavioral interventions including organizational skills, social skills, attention skills, positive parenting, psychoeducational, sleep hygiene/behavioral, or parent or teacher behavioral training interventions. Findings are summarized by outcome and described in Table 22. Note that the interventions were mixed in terms of their strategies: some were interventions which helped parents learn how to cope with their own emotions, most strategies focused on how parents could manage specific behaviors from their children with ADHD.

Findings in Relationship to What is Already Known

The 2011 report¹ identified 31 studies that evaluated parent behavior training for preschoolers with disruptive behavior disorders. Of these, three RCTs included only preschoolers who exhibited ADHD symptoms but who were not necessarily formally diagnosed with ADHD.¹⁷⁵⁻¹⁷⁷ All three RCTs demonstrated significant improvement in the preschoolers' behavior or symptoms relative to usual care only. In contrast, this updated review provides results from 9 RCTs and 1 observational study that evaluated the effectiveness of either parent or child behavior training on outcomes among children with a wider age range who had been formally diagnosed with ADHD. The findings of these 10 studies are summarized below.

Academic Performance

The two RCTs of child-focused interventions that evaluated academic performance outcomes found no change compared with the control condition. One of these trials evaluated organizational skills training¹²⁰ and the other evaluated social skills training.¹²³

Acceptability of Treatment

The single RCT that assessed the outcome of acceptability of treatment found that parent satisfaction with process was superior with the behavioral intervention compared to the control group.¹⁵⁰

Changes in Standardized Symptom Scores

Two studies examined psychoeducational programs for parents.^{110,157} Both found significant improvement on some standard measures of ADHD symptoms. One study that examined children 6 to 16 years of age compared psychoeducation with a general counseling control and found significant improvement in overall ADHD scores for the intervention group compared with control.¹⁵⁷ Another study comparing psychoeducation with a control in children 5 to 18 years of age found significantly better ADHD scores on a standard scale at 12 weeks for overall symptoms and attention, and at 12 months there was significant difference only on inattention/cognition standard scores.¹¹⁰

Other parenting interventions included a positive parenting program that did not find a strong effect on ADHD symptoms, but did find a significant effect on overall impairment rating compared to a behavioral parenting program and an even greater effect compared to a waitlist control.¹⁵⁰ There was a significant improvement in ADHD symptoms when comparing the

positive parenting program to the waitlist control. Another parenting intervention that evaluated sleep hygiene and behavioral training for parents found improvements at 6 months in all parent-reported ADHD scores, but no difference between controls on teacher reported scores.⁹⁷ Another parent study compared children on MPH who received MPH alone or medication plus parent training; this study found no significant difference between groups.¹²⁷

A combined behavioral training intervention for parents and teachers found no changes in ADHD scores at 10 weeks as reported by parents or teachers, but at 3 months postintervention did find improvement in parent reported ADHD scale scores, but not on teacher report.¹³⁰ Another combined intervention study compared a combination of parent group and child group interventions with parent intervention alone or community care in general.¹⁰⁵ This study found improvement on symptoms of the combined groups, compared to both comparison conditions at 3 months. At approximately 6 months the improvements in parent reported ADHD symptoms were maintained. In terms of functional impairment there was no difference at 3 months between groups, while at 6 months the parent-reported, but not teacher-rated, functional impairment was improved in the intervention as compared to the parent group alone or the community control. Another study examined social skills for children with a parallel parent group and found significant changes on the CBCL attention problem subscale as compared to a control condition including treatment as usual.¹⁵⁸

In summary, of the eight studies that included a parent intervention component, six showed improvement in some standard measure of ADHD symptoms, often on parent report. One of the two studies that did not show improvement on ADHD symptoms did show improvement on functional impairment.

Depression or Anxiety

No differences in depression and anxiety were found in an RCT that evaluated sleep hygiene counseling for parents combined with behavior therapy.⁹⁷

Functional Impairment

A good-quality RCT found that Child Life and Attention Skills Treatment was associated with improved parent and teacher CGI scores relative to parent training alone or no intervention.¹⁰⁵

Sleep Disturbance

Sleep habits at 6 months were improved among patients randomized to an intervention that combined sleep hygiene counseling for parents and behavior therapy.⁹⁷

Workforce Participation

A single RCT found that an intervention that combined sleep hygiene counseling for parents and behavior therapy found that the intervention as associated with fewer days late for work and fewer missed days of work.⁹⁷

Adverse Effects of Child or Parent Training or Behavioral Interventions

No adverse effects of these behavioral treatments were examined.

Table 22. Findings on Child or Parent Training or Behavioral Interventions for ADHD

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Academic performance						
Abikoff, 2013 ²⁰ 180 Good RCT	Organizational skills	Performance- based intervention precluding skill Waitlist	12 weeks	Academic Performance Rating Scale Mean=pre: 53.45; post: 62.16 (SD=pre: 10.34; post: 10.52) Academic Proficiency Scale Mean=pre: 16.39; post: 18.55 (SD=pre: 4.27; post: 4.26)	Academic Performance Rating Scale Mean=pre: 54.45; post: 63.96 (SD=pre: 11.12; post: 11.90) Academic Proficiency Scale Mean=pre: 17.08; post: 18.35 (SD=pre: 3.54; post: 3.89) Academic Performance Rating Scale Mean=pre: 54.06 ; post: 54.53 (SD=pre: 8.58; post: 9.74) Academic Proficiency Scale Mean=pre: 16.05 ; post: 16.63 (SD= pre: 3.22; post: 3.30)	NS NS
Storebo, 2012 ²³ 56 Good RCT	Social skills group + medication management	Medication management (usual care)	3 months 6 months	Conners CBRS Academic Score Mean=20.13 (SD=15.15) Conners CBRS Academic Score Mean=21.04 (SD 11.98); Between group MD: -0.48 (95% CI=-7.254 to 6.293)	Conners CBRS Academic Score Mean=17.88 (SD=10.11) Conners CBRS Academic Score Mean=21.52 (SD 12.56)	NS NS
Acceptability of treatment						
Chacko, 2009 ¹⁵⁰ 120 Good RCT	STEPP	BPT program Waitlist	2.07 months	Parent Treatment Attitude Inventory- Satisfaction with Process Mean = 16.36 (SD = 2.03)	Parent Treatment Attitude Inventory- Satisfaction with Process Mean = 14.12 (SD = 2.09)	 P<0.01
Changes in standardized symptom scores						
Bai, 2015 ¹⁵⁷ 89 Good RCT	A psycho- education program based on the theory of planned behavior	General clinical counseling	3 months	ADHD-RS-IV Mean=33.7 (SD=5.4) (Baseline mean=49.9, SD 11.5)	ADHD-RS-IV Mean=45.1 (SD=7.9) (Baseline mean=48.1, SD 8.1)	 P=.008

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value	
Chacko, 2009 ¹⁵⁰ 120 Good RCT	STEPP	BPT program	2.07 months	Disruptive Behavior Disorder scale-Inattentive Mean = 1.78 (SD = .63)	Disruptive Behavior Disorder scale-Inattentive Mean = 1.67 (SD = .74)	NR	
				Disruptive Behavior Disorder-Hyperactive/Impulsive: Mean = 1.69 (SD = .57)	Disruptive Behavior Disorder-Hyperactive/Impulsive: Mean = 1.59 (SD = .70)	NR	
				Impairment Rating Scale (IRS)-Overall Mean = 3.31 (SD 1.41)	Impairment Rating Scale (IRS)-Overall Mean = 4.11 (SD 1.67)	P<.01	
		Waitlist			Treatment Attitude Inventory- Satisfaction with Outcome Mean = 24.18 (SD = 3.02)	Treatment Attitude Inventory- Satisfaction with Outcome Mean = 20.20 (SD = 2.35)	NR
					Disruptive Behavior Disorder scale-Inattentive Mean = 1.72 (SD = .65)	Disruptive Behavior Disorder scale-Inattentive Mean = 1.72 (SD = .65)	NR
					Disruptive Behavior Disorder-Hyperactive/Impulsive: Mean = 1.72 (SD = .56)	Disruptive Behavior Disorder-Hyperactive/Impulsive: Mean = 1.72 (SD = .56)	NR
				Impairment Rating Scale (IRS)- Overall Mean = 4.65 (SD 1.30)	NR		
Ferrin, 2014 ¹¹⁰ 81 Good RCT	Psycho-educational program	Control	12 weeks	CPRS inattention -12 weeks Mean = 7.95 (SD = 3.84) p = .001	CPRS inattention -12 weeks Mean = 11 (SD = 3.28)	P=0.001	
				CPRS hyperactivity/impulsivity -12 weeks Mean = 6.74 (SD = 4.84)	CPRS hyperactivity/impulsivity -12 weeks Mean = 8.45 (SD = 4)	NS	
			12 months	Conners parent rating scale – index Mean = 18.6 (SD = 8.66)	Conners parent rating scale – index Mean = 21.16 (SD = 7.08)	NS	
				Conners parent rating scale – opposition subscale Mean = 5.2 (SD = 4.06)	Conners parent rating scale – opposition subscale Mean = 5.63 (SD = 3.86)	NS	
				Conners parent rating scale- inattention/cognition Mean = 8.26 (SD = 4.3) p = .032	Conners parent rating scale- inattention/cognition Mean = 10.41 (SD = 3.62)	P=0.0032	
				Conners parent rating scale – hyperactivity/impulsivity Mean = 7.4 (SD = 4.84)	Conners parent rating scale – hyperactivity/impulsivity Mean = 8.47 (SD = 3.82)	NS	
				CPRS index -12 weeks Mean = 16.8 (SD = 7.18) p = .001	CPRS index -12 weeks Mean = 22.44 (SD = 6.13)	P=0.001	
				CPRS opposition -12 weeks	CPRS opposition -12 weeks	NS	

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
				Mean = 4.95 (SD = 3.79)	Mean = 6.18 (SD = 3.87)	
Hiscock, 2015 ⁹⁷ 244 Good RCT	Sleep hygiene practices and standardized behavioral strategies	Children in the control group received usual clinical care	6 Months	ADHD rating scale IV-total symptoms (parent report) Mean = 28.4 (SD = 10.8) ADHD Rating Scale IV – Parent Report (Inattentive) Mean = 15.1 (SD = 6.0) ADHD Rating Scale IV – Parent Report (Hyperactivity/Impulsivity) Mean = 13.3 (SD = 6.0) ADHD rating scale IV Total Score (Teacher Report) Mean = 20.6 (SD = 11.6) ADHD Rating Scale IV: Teacher Report (Inattentive) Mean = 14.1 (SD = 6.9) ADHD Rating Scale IV: Teachers Report (Hyperactivity/Impulsivity) Mean = 8.4 (SD = 6.2)	ADHD rating scale IV-total symptoms (parent report) Mean = 33.8 (SD = 9.5) ADHD Rating Scale IV – Parent Report (Inattentive) Mean = 18.2 (SD = 4.8) ADHD Rating Scale IV – Parent Report (Hyperactivity/Impulsivity) Mean = 15.6 (SD = 5.8) ADHD rating scale IV Total Score (Teacher Report) Mean = 25.1 (SD = 12.6) ADHD Rating Scale IV: Teacher Report (Inattentive) Mean = 12.3 (SD = 6.9) ADHD Rating Scale IV: Teachers Report (Hyperactivity/Impulsivity) Mean = 10.9 (SD = 7.1)	P=0.004 P=0.001 P=0.04 P=0.31 P=0.59 P=0.19
Ostberg, 2012 ¹³⁰ 92 Good RCT	Barkley based Parent + Teacher behavioral intervention	Waitlist	10 weeks 3 months	ADHD-C Parent Mean = 9.1 (SD = 4.5) ADHD-C Teacher Mean = 7.7 (SD = 6.3) ADHD-C Parent Mean = 7.7 (SD = 4.7) ADHD-C Teacher Mean = 7.7 (SD = 5.7)	ADHD-C Parent Mean = 9.8 (SD = 6) ADHD-C Teacher Mean = 9.4 (SD = 6.3) ADHD-C Parent Mean = 10.1 (SD = 5.3) ADHD-C Teacher Mean = 9.4 (SD = 5.4)	NS NS P<.05 NS
Pfiffner, 2014 ¹⁰⁵ 199 Good RCT	Child Life and Attention Skills Treatment	Parent group component only Evaluation and community care	10-13 weeks	Parent Child Symptom Inventory Mean=2.2 (SE=0.3) Child Symptom Inventory Mean=2.99 (SE=0.3)	Parent Child Symptom Inventory Mean=3.2 (SE=0.3) Child Symptom Inventory Mean=4.2 (SE=0.3) Parent Child Symptom Inventory Mean=4.1 (SE=0.4) Child Symptom Inventory Mean=5 (SE=0.4)	P=.001 P<0.001 NR NR NR

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
		Parent group component only	5-7 months	Parent Child symptom inventory Mean=2.2 (SE=0.3)	Parent Child Symptom Inventory Mean=3.2 (SE=0.3)	NR
		Evaluation and community care		Child symptom inventory Mean=3.7 (SE=0.4)	Child Symptom Inventory Mean=4.2 (SE=0.4)	P<0.001
					Parent Child Symptom Inventory Mean=4.1 (SE=0.4)	P=0.396
					Child Symptom Inventory Mean=4.2 (SE=0.4)	NR
Ercan, 2014 ¹²⁷ 120 Fair Obs	MPH+11 months of parent training	MPH (Usual care)	12 months	CPRS Mean w/in group change = 7.91 (SD = 6.9)	CPRS Mean w/in group change = 10.07 (SD = 5.74)	NS
				CTRS–teacher Mean = 29.69 (SD = 15.03)	CTRS–teacher Mean = 35.27 (SD = 13.47)	
Huang, 2015 ¹⁵⁸ 97 Fair RCT	Behavioral-based social skill training for patients and parallel parent group sessions	Group therapy for motivation and treatment per usual care, such as medication and counseling at the outpatient department	6 months	Change in Child Behavioral Checklist Withdrawn Subscale Mean= -.84 (SD=2.3)	Change in Child Behavioral Checklist Withdrawn Subscale Mean= -.28 (SD=1.6)	P=0.84
				Change in CBCL Somatic Complaints Subscale Mean within group change= -.14 (SD=2.7)	Change in CBCL Somatic Complaints Subscale Mean within group change= -1.42 (SD=3.7)	P=0.14
				CBCL Change Anxious/Depressed Subscale Mean within group change= -2.19 (SD=4)	CBCL Change Anxious/Depressed Subscale Mean within group change= -.89 (SD=3.7)	P=0.79
				CBCL Change Social Problems Subscale Mean within group change= -1.4 (SD=2.3)	CBCL Change Social Problems Subscale Mean within group change= -.92 (SD=2.2)	P=0.57
				CBCL Change Thought Problems Subscale Mean within group change= -1.02 (SD=2.8)	CBCL Change Thought Problems Subscale Mean within group change= -1.06 (SD=2.1)	P=0.60
				CBCL Change Attention Problems Subscale Mean within group change= -1.26 (SD=2.8)	CBCL Change Attention Problems Subscale Mean within group change= -1.772 (SD=3.2)	P=0.04
				CBCL Change Delinquent Behavior Subscale Mean within group change= -.76 (SD=2.2)	CBCL Change Delinquent Behavior Subscale Mean within group change= -.6 (SD=1.9)	P=0.91
				CBCL Change Aggressive Behavior Subscale Mean within group change= -4 (SD=7.1)	CBCL Change Aggressive Behavior Subscale Mean within group change= -2.37 (SD=5.9)	P=0.94

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Depression or anxiety						
Hiscock, 2015 ⁹⁷ 244 Good RCT	Sleep hygiene practices and standardized behavioral strategies	Children in the control group received usual clinical care	6 Months	Depression or anxiety-Depression Anxiety Stress Scale Mean = 31.3 (SD = 23.6) Depression or anxiety-Parent mental health with the Depression Anxiety Stress Scale – Total score	Depression or anxiety-Depression Anxiety Stress Scale Mean = 33.9 (SD = 28.5)	P=0.55
Functional impairment						
Pfiffner, 2014 ¹⁰⁵ 199 Good RCT	Child Life and Attention Skills Treatment	Parent group component only	10-13 weeks	Parent CGI Mean=6 (SE=0.7) Teacher CGI Severity Mean=5.8 (SE=0.8)	Parent CGI Mean=5.8 (SE=0.9) Teacher CGI Severity Mean=5.2 (SE=1)	P=0.0 P=0.0
		Evaluation and community care			Parent CGI Mean=5 (SE=1) Teacher CGI Severity Mean=5 (SE=1.1)	NR NR
		Parent group component only	5-7 months	Parent CGI Mean=6 (SE=1) Teacher CGI-Severity Mean=3.4 (SE=0.2)	Parent CGI Mean=5.8 (SE=1) Teacher CGI-Severity Mean=3.5 (SE=0.2)	P=0.001 P=0.775
		Evaluation and community care			Parent CGI Mean=5.3 (SE=0.23) Teacher CGI Severity Mean=3.6 (SE=0.2)	NR NR
Sleep disturbance						
Hiscock, 2015 ⁹⁷ 244 Good RCT	Sleep hygiene practices and standardized behavioral strategies	Children in the control group received usual clinical care	6 Months	Sleep disturbance-Child Sleep Habits Questionnaire (CSHQ) Total Score Mean 53.2 (7.5)	Sleep disturbance-Child Sleep Habits Questionnaire (CSHQ) Total Score, Mean = 55.9 (8.8)	P<0.001
Workforce participation						
Hiscock, 2015 ⁹⁷ 244 Good	Sleep hygiene practices and standardized behavioral	Children in the control group received usual clinical care	3 months	Workforce participation-Days late for work Workforce participation-Missed days of work		P=0.02 P=0.03 (both non-

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
RCT	strategies					parametric tests)

Abbreviations: ADHD=attention deficit hyperactivity disorder; CBCL=Child Behavior Checklist; CBRS=Comprehensive Behavior Rating Scale; CGI= Clinician Global Impressions; DASS=Depression Anxiety Stress Scale; NR=not reported; STEPP=Strategies to Enhance Positive Parenting; RCT=randomized controlled trial

Strength of Evidence—Child or Parent Training/Behavioral

Table 23 summarizes the strength of evidence for child or parent training or behavioral interventions.

Table 23. Strength of Evidence for Major Outcomes—Child or Parent Training or Behavioral

Outcome	No. Studies/ Design (N Patients)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Major outcomes							
Academic performance	2 RCTs (356)	Low	Direct	Consistent	Imprecise	None	2 good-quality RCTs found no differences in academic performance associated with organizational skills or social skills training relative to no intervention. ^{120,123}
Low							
Acceptability of treatment	1 RCT (120)	Low	Direct	NA	Imprecise	None	1 good-quality RCT demonstrated improvement in the Parent Treatment Attitude Inventory—Satisfaction with Process score associated with the STEPP program relative to a behavioral intervention or usual care. ¹⁵⁰
Insufficient							
Changes in standardized symptom scores	8 RCTs (1,042)	Low	Direct	Consistent	Imprecise	None	Of 6 good-quality and 2 fair-quality RCTs, ^{97,105,110,127,130,150,157,158} only 1 fair-quality study did not demonstrate a significant improvement in ADHD symptoms associated with child or parent training or sleep hygiene.
Moderate							
Depression or anxiety	1 RCT (244)	Low	Direct	NA	Imprecise	None	1 good-quality RCT did not find a significant treatment effect as measured by the DASS associated with sleep hygiene compared with no intervention. ⁹⁷
Insufficient							
Functional impairment	1 RCT (199)	Low	Direct	NA	Imprecise	None	1 good-quality RCT found that Child Life and Attention Skills Treatment was associated with improved Parent and Teacher CGI scores relative to parent training alone or no intervention. ¹⁰⁵
Insufficient							

Abbreviations: NA=not applicable; Obs=observational; RCT=randomized controlled trial; SOE=strength of evidence

Detailed Synthesis—Omega-3/6 Fatty Acid Supplementation

We identified five good-quality,^{124,125,132,142,154} two fair-quality,^{104,147} and one poor-quality studies¹¹⁷ representing 1,080 patients evaluated essential fatty acid supplementation. Seven of these trials compared essential fatty acid supplementation with placebo. Of these, the active intervention was omega-3 alone in four trials,^{104,117,132,142} omega-6 alone in 1 trial,¹⁴⁷ and a combination of omega-3 and omega-6 in 2 trials.¹⁵⁴ Treatment duration ranged between 7-weeks and 6-months. The enrolled children ranged between 6 years to 18 years of age and the range of included male children was 59.4% to 77.3% across the trials. Children were included in the trials if they met DSM-IV ADHD criteria in 6 of the 7 trials. Inclusion of ADHD subtypes varied with a mixed grouping of ADHD subtypes included in 3 of the trials, a specific oppositional sub-type in one trial and three trials did not specify an ADHD sub-type of included children. Two of the 7 trials^{104,124} measured outcomes of ADHD symptoms with scales that were not part of our inclusion criteria and were excluded from the meta-analysis. The remaining 5 trials measured ADHD symptoms with the Conners Scale (full or abbreviated version) or the ADHD Rating Scale. Findings are summarized below by outcome and described in Table 24.

Findings in Relationship to What is Already Known

The effectiveness of omega-3/6 for the treatment of ADHD symptoms was not included in the 2011 report.¹ However, a systematic review and meta-analysis comparing omega-3 fatty acid supplementation with placebo was conducted in 2011 by Bloch and Qawasmi.¹⁷³ Using only PubMed, they searched from database inception to December 2010. Their findings, using fixed-effects meta-analysis, indicated a small significant effect (SMD 0.31, 95% CI 0.16 to 0.47) on ADHD symptoms with omega-3 use associated with improved symptoms. Due to an overlap in search dates, our review includes 3 of the 10 studies that were also included in the Bloch and Qawasmi review. Our inclusion and exclusion criteria differed from that review as we excluded studies where the sample size was less than 50 participants.¹⁷⁸ Our review also conducted a separate meta-analysis for teacher- and parent-reported ADHD symptoms whereas the Bloch and Qawasmi review included only the parent- or teacher-reported ADHD symptoms depending on the number of completed ADHD subscales. Our meta-analysis used random-effects models and corrected the standard errors for a small sample meta-analysis using the Knapp-Hartung method, both techniques that create a more conservative confidence interval.¹⁷⁹ As such, due to differences in search dates, inclusion/exclusion criteria and analytical approaches, differences in pooled estimates between the two reviews would be expected. However, the overall strength of effect for the parent reports of ADHD symptoms in our meta-analysis is similar to the strength of effect in the Bloch and Qawasmi review.

Academic Performance

A good-quality RCT found that a higher proportion of patients who received omega-3/6 fatty acid supplementation reported improvement in academic performance compared to patients in the placebo arm.¹²⁴

Behavior Changes

A good-quality RCT did not find a difference in the proportion of patients who were prone to crying or who talked less after supplementation with omega-3 fatty acids, relative to placebo.¹³³

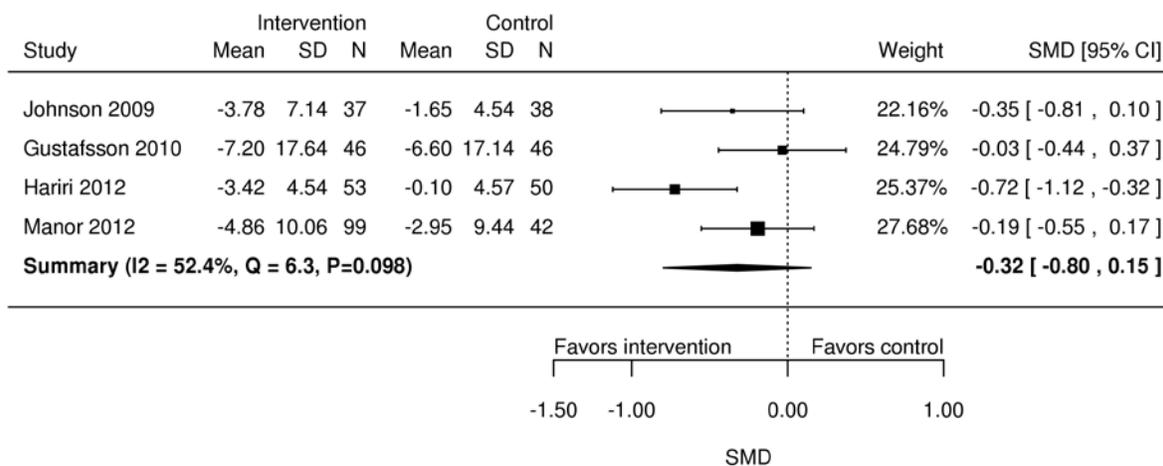
Changes in Standardized Symptom Scores

We conducted meta-analyses of 4 eligible RCTs that reported parent ratings of ADHD total symptoms and 3 eligible RCTs that reported teacher ratings of ADHD total symptoms.

Parent Ratings of ADHD Total Symptoms

We summarized four RCTs, with random-effects meta-analysis, examining omega-3/6 supplementation versus placebo with the outcome of parent-rated total ADHD symptoms.^{117,132,142,154} Effects were consistent and studies demonstrated moderate heterogeneity; however, no statistical evidence was found that omega-3/6 was superior to placebo with the outcome of parent rating of ADHD total symptoms (n=411, SMD -0.32, 95% CI -0.80 to 0.15, $I^2=52.4%$, $Q=6.3$, $p=0.098$) (Figure 3). The two trials that we excluded from the meta-analysis both found no significant differences between omega-3/6 and placebo for parent rating of total ADHD symptoms.^{104,124}

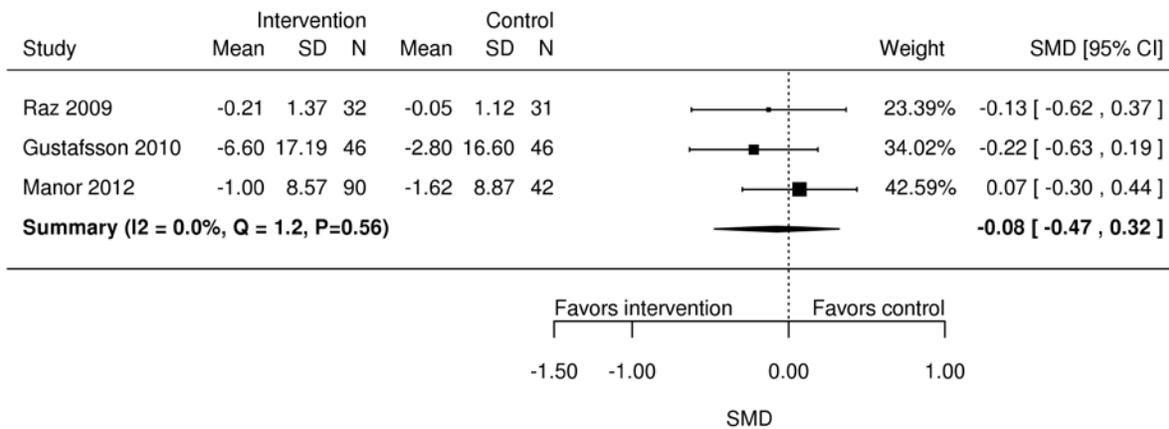
Figure 3. Meta-analysis for Effects of Omega-3/6 Supplementation Compared With Placebo—Parent Ratings



Teacher Ratings of ADHD Total Symptoms

We summarized three RCTs, with random effects meta-analysis, examining omega-3/6 versus placebo with the outcome of teacher rated total ADHD symptoms.^{132,142,147} Effects were fairly consistent and studies were homogeneous; however, we found no statistical evidence that omega-3/6 was superior to placebo with the outcome of teacher rated total ADHD symptoms (n=287, SMD -0.08, 95% CI -0.47 to 0.32, $I^2=0.0%$; $Q=1.2$, $p=0.56$) (Figure 4). The one RCTs excluded in this meta-analysis¹⁰⁴ also found no significant difference between omega-3 and placebo for teacher rating total ADHD symptoms.

Figure 4. Meta-analysis for Effects of Omega-3/6 Supplementation Compared With Placebo—Teacher Ratings



Functional Impairment

A good-quality RCT found no difference in Clinical Global Impression scores associated with omega-3 fatty acid supplementation compared with placebo.¹⁵⁴

Adverse Effects of Omega-3 Fatty Acid Supplementation

A single RCT reported the incidence of adverse effects associated with omega-3 fatty acid supplementation compared with placebo.¹³² This trial did not report statistically significant between-group differences for any of the following adverse effects: chemical leukoderma; elevated blood pressure; sleep disturbance; tics or other movement disorders; gastrointestinal symptoms; growth suppression; increased heart rate; personality change; or weight decrease.

Table 24. Findings on Omega-3 Fatty Acid Supplementation for ADHD

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Academic performance						
Perera, 2012 ¹²⁴ 98 Good RCT	Omega-3/6 fatty acid supplementation	Placebo	3 months	“Academic Performance” item on 11-item parental report scale (3 point Likert)	“Academic Performance” item on 11-item parental report scale (3 point Likert)	P<.05 (ES=0.8787)
			6 months	“Academic Performance” item on 11-item parental report scale (3 point Likert)	“Academic Performance” item on 11-item parental report scale (3 point Likert)	P<.05 (ES=1.1092)
Behavior changes						
Manor, 2012 ¹³² 200 Good RCT	Phosphatidylserine enriched with omega-3 fatty acids	Placebo	15 weeks	Euphoric % patients with outcome = 38.9	Euphoric % patients with outcome = 34.6	NR
				Anxiety % patients with outcome = 45	Anxiety % patients with outcome = 63.5	NR
				Irritable % patients with outcome = 79.1	Irritable % patients with outcome = 84.6	NR
				Prone Cry % patients with outcome = 62.7	Prone Cry % patients with outcome = 57.7	NR
				Talk Less % patients with outcome = 31.8	Talk Less % patients with outcome = 32.7	NR
				Sad/Unhappy % patients with outcome = 40	Sad/Unhappy % patients with outcome = 34	NR
				Irritability % patients with outcome = 15.31	Irritability % patients with outcome = 11.63	NR
Changes in standardized symptom scores						
Gustafsson, 2010 ¹⁴² 109 Good RCT	Omega-3 fatty acid supplementation (eicosapentaenoic acid 500mg daily)	Placebo	15 weeks	Total Conners Parent Rating Scale score Mean = 43.8 (SD = 18.6)	Total Conners Parent Rating Scale score Mean = 39.4 (SD = 18.4)	NS
				Total Conners Rating Scale score Mean = 43.1 (SD = 18.8)	Total Conners Rating Scale score Mean = 40.7 (SD = 17.9)	NS
Johnson, 2009 ¹⁵⁴ 75 Good RCT	Omega-3/6 fatty acid supplementation (792mg daily)	Placebo	3 months (double-blind phase)	ADHD Rating Scale Mean change = -3.78 (7.14)	ADHD Rating Scale Mean change = -1.65 (4.54)	NS
			6 months (open-label)	ADHD Rating Scale Mean change = -7.82 (8.07)	ADHD Rating Scale Mean change = -5.81 (7.16)	NS

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
			extension: continuous and naïve groups)			
Manor, 2012 ¹³² 200 Good RCT	Phosphatidylserine enriched with omega-3 fatty acids	Placebo	15 weeks (treatment and placebo groups, N=162)	CRS-P PS-Omega-3 continuous (30 weeks) ADHD Index Mean = 64.05 (10.21)	CRS-P Placebo (weeks 1-15) ADHD Index Mean = 65.67 (12.79)	NS
				CRS-T PS-Omega-3 continuous (30 weeks) ADHD Index Mean= 62.35 (10.64)	CRS-T Placebo (weeks 1-15) ADHD Index Mean = 64.44 (10.07)	NS
			30 weeks (open-label extension: continuous and naïve groups, N=147)	CRS-P PS-Omega-3 continuous (30 weeks) ADHD Index Mean Change = -0.95 (7.91)	CRS-P PS-Omega-3 (weeks 15-30) ADHD Index Mean Change = -2.86 (8.51)	NS
				CRS-T PS-Omega-3 continuous (30 weeks) ADHD Index Mean Change = 0 (8.62)	CRS-T PS-Omega-3 (weeks 15-30) ADHD Index Mean Change = -1.72 (6.19)	NS
Milte, 2012 ¹²⁵ 90 Good RCT	Fish oil rich in the omega-3 fatty acid, eicosapentaenoic acid (EPA)	Fish oil rich in the omega-3 fatty acid, docosahexaenoic acid (DHA) Placebo: Linoleic acid (LA)	4 months	Conners Parent Rating Scale ADHD total Mean between-group change (vs. placebo) = 1.56 (1.77)	Conners Parent Rating Scale ADHD total Mean between-group change (vs. placebo) = 1.64 (1.9)	NR EPA vs. placebo p=0.38 DHA vs. placebo p=0.39
Perera, 2012 ¹²⁴ 98 Good RCT	Omega-3/6 fatty acid supplementation	Placebo	6 months	11-item parental report scale (3 point Likert) Mean = 15.46 (SD = 3.65)	11-item parental report scale (3 point Likert) Mean = 20.74 (SD = 2.93)	P<0.01
Raz, 2009 ¹⁴⁷ 78 Fair RCT	Omega-3 fatty acid supplementation	Placebo	1.75 months	Conners-ADHD (Teacher) Mean = 3.64 (1.48)	Conners-ADHD (Teacher) Mean = 3.66 (1.12)	NS
				Conners Mood (Teacher) Mean = 2.76 (1.28)	Conners Mood (Teacher) Mean = 2.74 (1.30)	NS
Widenhorn-Muller, 2014 ¹⁰⁴ 110	Omega-3 fatty acid supplementation (720 mg)	Placebo	4	CBCL total problems Mean = 62.36 (SE = 1.47)	CBCL total problems Mean = 60.15 (SE = 1.38)	P=0.98
				Teacher Report Form--total problems	Teacher Report Form--total problems	P=0.62

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Fair RCT	daily) plus 15 mg vitamin E			Mean = 55.8 (SE = 1.09)	Mean = 56.82 (SE = 1.16)	
Hariri, 2012 ¹¹⁷ 120 Poor RCT	Omega-3 fatty acid supplementation (900 mg daily)	Placebo	8 weeks	Conners Abbreviated Mean = 21.03 (3.98)	Conners Abbreviated Mean = 24.02 (4.22)	P=0.251
Elevated blood pressure						
Manor, 2012 ¹³² 200 Good RCT	Phosphatidylserine enriched with omega-3 fatty acids	Placebo	15 weeks	Systolic Mean = 103.6 (SD = 14.82) Diastolic Mean = 64.66 (SD = 11.39)	Systolic Mean = 100.25 (SD = 12.95) Diastolic Mean = 63.89 (SD = 10.28)	P=0.955 P=0.342
Functional impairment						
Johnson, 2009 ¹⁵⁴ 75 Good RCT	Omega-3/6 fatty acid supplementation (792 mg daily)	Placebo	3 months (double-blind phase) 6 months (open-label extension: continuous and naïve groups)	Clinical Global Impression score Mean change = -0.58 (0.87) Clinical Global Impression score Mean change = -1.24 (1.07)	Clinical Global Impression score Mean change = -0.13 (0.50) Clinical Global Impression score Mean change = -0.93 (0.92)	NS NS
Sleep disturbance						
Manor, 2012 ¹³² 200 Good RCT	Phosphatidylserine enriched with omega-3 fatty acids	Placebo	15 weeks	Insomnia % patients with outcome = 38.2 Severe insomnia % patients with outcome = 2.04 Nightmares % patients with outcome = 29.1	Insomnia % patients with outcome = 53.9 Severe insomnia % patients with outcome = 6.98 Nightmares % patients with outcome = 34.6	NR NR NR
Tics or other movement disorders						
Manor, 2012 ¹³² 200 Good RCT	Phosphatidylserine enriched with omega-3 fatty acids	Placebo	15 weeks	Tics % patients with outcome = 22.7	Tics % patients with outcome = 32.7	NR

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Gastrointestinal symptoms						
Manor, 2012 ¹³² 200 Good RCT	Phosphatidylserine enriched with omega-3 fatty acids	Placebo	15 weeks	Stomachaches % patients with outcome = 39.5 Decreased appetite % patients with outcome = 32.7 Severely decreased appetite % patients with outcome = 4.08	Stomachaches % patients with outcome = 46.2 Decreased appetite % patients with outcome = 32.7 Severely decreased appetite % patients with outcome = 4.65	NR NR NR
Growth suppression						
Manor, 2012 ¹³² 200 Good RCT	Phosphatidylserine enriched with omega-3 fatty acids	Placebo	15 weeks	Height in cm Mean = 135.25 (SD = 13.35)	Height in cm Mean = 136.77 (SD = 12.26)	P=0.196
Increased heart rate						
Manor, 2013 ¹³³ 200 Good RCT	Phosphatidylserine enriched with omega-3 fatty acids	Placebo	15 weeks	Increased Heart Rate Mean = 79.72 (SD = 12.03)	Increased Heart Rate Mean = 81.18 (SD = 13.24)	p=0.825
Personality change						
Manor, 2012 ¹³² 200 Good RCT	Phosphatidylserine enriched with omega-3 fatty acids	Placebo	15 weeks	Uninterested % patients with outcome = 32.7	Uninterested % patients with outcome = 38	NR
Weight decrease						
Manor, 2012 ¹³² 200 Good RCT	Phosphatidylserine enriched with omega-3 fatty acids	Placebo	15 weeks	Weight (kg) Mean = 33.39 (SD = 10.61)	Weight (kg) Mean = 33.06 (SD = 8.42)	P=0.980

Abbreviations: ADHD=attention deficit hyperactivity disorder; CRS-P=Conners Rating Scale-Parent; CRS-T=Conners Rating Scale-Teacher; NR=not reported; SE=standard error; SD=standard deviation; RCT=randomized controlled trial

Strength of Evidence—Omega-3 Supplementation

Table 25 summarizes the strength of evidence for omega-3 supplementation.

Table 25. Strength of Evidence for Major Outcomes—Omega-3 Fatty Acid Supplementation

Outcome	No. Studies/ Design (N Patients)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Major outcomes							
Academic performance	1 RCT (98)	Low	Direct	NA	Imprecise	None	1 good-quality RCT found improvement on an Academic Performance scale associated with omega-3/6 supplementation compared with placebo. ¹²⁴
Insufficient							
Behavior changes	1 RCTs (200)	Low	Direct	NA	Imprecise	None	1 good-quality RCT did not report statistical significance of between-group differences in several specific behavior changes for omega-3 fatty acid supplementation compared with placebo. ¹³²
Insufficient							
Changes in standardized symptom scores	8 RCTs (880)	Low	Direct	Consistent	Precise	None	Two meta-analyses of 4 and 3 good-quality studies respectively found no significant differences between Omega-3/6 and placebo for parent ratings (n=411, SMD -0.32, 95% CI -0.80 to 0.15, I ² =52.4%, Q=6.3, p-value=0.098) or teacher ratings of total ADHD symptoms (n=287, SMD -0.08, 95% CI -0.47 to 0.32, I ² =0.0%; Q=1.2, p=0.56). ^{104,117,124,125,132,142,147,154}
Moderate							
Chemical Leukoderma	1 RCT (200)	Low	Direct	NA	Imprecise	None	1 good-quality RCT did not report statistical significance of between-group differences in CRS-T for omega-3 fatty acid supplementation compared with placebo. ¹³²
Insufficient							
Elevated blood pressure	1 RCT (200)	Low	Direct	NA	Imprecise	None	1 good-quality RCT did not find a difference in mean systolic or diastolic blood pressure associated with omega-3 fatty acid supplementation compared with placebo. ¹³²
Insufficient							
Functional impairment	1 RCT (75)	Low	Direct	NA	Imprecise	None	1 good-quality RCT found no difference in Clinical Global Impression scores associated with omega-3 fatty acid supplementation compared with placebo. ¹⁵⁴
Insufficient							
Sleep disturbance	1 RCT (200)	Low	Direct	NA	Imprecise	None	1 good-quality RCT did not report statistical significance of differences in the proportion of patients reporting insomnia for omega-3 fatty acid supplementation compared with placebo. ¹³²
Insufficient							
Tics or other movement disorders	1 RCT (200)	Low	Direct	NA	Imprecise	None	1 good-quality RCT did not report statistical significance of differences in the proportion of patients reporting tics for omega-3 fatty acid supplementation compared with placebo. ¹³²
Insufficient							
Gastrointestinal symptoms	1 RCT (200)	Low	Direct	NA	Imprecise	None	1 good-quality RCT did not report statistical significance of differences in the proportion of patients reporting

Outcome	No. Studies/ Design (N Patients)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Insufficient							decreased appetite for omega-3 fatty acid supplementation compared with placebo. ^{1,3,2}
Growth suppression	1 RCT (200)	Low	Direct	NA	Imprecise	None	1 good-quality RCT found no difference in change in height of patients after treatment with omega-3 fatty acid supplementation compared with placebo. ^{1,3,2}
Insufficient							
Increased heart rate	1 RCT (200)	Low	Direct	NA	Imprecise	None	1 good-quality RCT found no difference in heart rate after treatment with omega-3 fatty acid supplementation compared with placebo. ^{1,3,2}
Insufficient							
Personality change	1 RCT (200)	Low	Direct	NA	Imprecise	None	1 good-quality RCT did not report statistical significance of differences in the proportion of patients reporting personality changes associated with omega-3 fatty acid supplementation compared with placebo. ^{1,3,2}
Insufficient							
Weight decrease	1 RCT (200)	Low	Direct	NA	Imprecise	None	1 good-quality RCT found no difference in change in weight of patients after treatment with omega-3 fatty acid supplementation compared with placebo. ^{1,3,2}
Insufficient							

Abbreviations: NA=not applicable; Obs=observational; RCT=randomized controlled trial; SOE=strength of evidence

Detailed Synthesis—Herbal Interventions or Dietary Approaches

Three good-quality^{93,139,160} and 2 fair-quality^{138,143} studies representing 424 patients evaluated herbal interventions or dietary approaches. Findings are summarized by outcome and described in Table 26.

Behavior Changes

A single RCT found that ginkgo biloba was associated with improved parent and teacher ADHD-RS-Inattention scores but not ADHD-RS-Hyperactivity scores relative to placebo.⁹³

Changes in Appetite

Two fair-quality RCTs did not report statistical significance of the proportion of patients in each study arm who reported changes in appetite associated with two doses of zinc supplementation compared with placebo, or an herbal preparation compared with placebo.^{138,143}

Changes in Standardized Symptom Scores

Three RCTs reported changes in symptom scores. One demonstrated improvement in ADHD-RS scores associated with an elimination diet relative to a nonrestricted diet.¹⁶⁰ Two other RCTs found that neither Memomet syrup nor zinc supplementation improved ADHD symptoms compared with placebo.^{138,139}

Gastrointestinal Symptoms

Two RCTs did not report statistical significance of the proportion of patients in each study arm who reported stomach aches or other gastrointestinal symptoms associated with two doses of zinc supplementation¹³⁸ or herbal preparation¹⁴³ compared with placebo.

Adverse Effects of Herbal Interventions or Dietary Approaches

An RCT that evaluated two doses of zinc supplementation compared with placebo¹³⁸ did not report statistical significance in the difference in proportion of patients in each study arm who reported changes in appetite, stomach aches or other gastrointestinal symptoms, sleep disturbance, harm to self or others, or stereotypical behaviors. Another RCT found no between-group differences between an herbal preparation and placebo in gastrointestinal symptoms, emotional lability, accidental injury, or sleep disturbance.¹⁴³

Table 26. Findings on Herbal Interventions or Dietary Approaches for ADHD

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Behavior changes						
Shakibaei, 2015 ⁹³ 66 Good RCT	Methylphenidate and Ginkgo Biloba	Methylphenidate and placebo	6 weeks	Parent ADHD Rating Scale IV Inattention Mean = 13.58 (SD = 3.68)	Parent ADHD Rating Scale IV Inattention Mean = 14.34 (SD = 4.03)	P<.001
				Parent ADHD Rating Scale IV Hyperactivity-Impulsivity Mean = 11.54 (SD = 4.42)	Parent ADHD Rating Scale IV Hyperactivity-Impulsivity Mean = 11.37 (SD = 4.11)	P=0.417
				Teacher ADHD Rating Scale IV Inattention Mean = 13.74 (SD = 4.04)	Teacher ADHD Rating Scale IV Inattention Mean = 13.75 (SD = 3.85)	P=0.004
				Teacher ADHD Rating Scale IV Hyperactivity-Impulsivity Mean = 10.93 (SD = 4.06)	Teacher ADHD Rating Scale IV Hyperactivity-Impulsivity Mean = 11.2 (SD = 4.43)	P=0.203
				Children’s Global Assessment Scale (CGAS) Mean w/in group change = 8.92 (SD = 7.37)	CGSA Mean w/in group change = 8.51 (SD = 5.33)	P=0.901
Arnold, 2011 ¹³⁸ 52 Fair RCT	Zinc 15 mg once daily (> 8 weeks with amphetamine in all groups)	Zinc 15mg twice daily	8 weeks	Affective blunting # patients with outcome = 1	Affective blunting # patients with outcome = 0	NR
			>8 weeks	Affective blunting # patients with outcome = 4	Affective blunting # patients with outcome = 0	NR
			8 weeks	Anxiety # patients with outcome = 6	Anxiety # patients with outcome = 2	NR
			>8 weeks	Anxiety # patients with outcome = 9	Anxiety # patients with outcome = 3	NR
			8 weeks	Depression # patients with outcome = 7	Depression # patients with outcome = 2	NR
			>8 weeks	Depression # patients with outcome = 11	Depression # patients with outcome = 4	NR
			8 weeks	Irritability # patients with outcome = 9	Irritability # patients with outcome = 5	NR
			>8 weeks	Irritability # patients with outcome = 9	Irritability # patients with outcome = 6	NR
		Placebo	8 weeks		Affective blunting # patients with outcome = 1	NR

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
			>8 weeks		Affective blunting # patients with outcome = 6	NR
			8 weeks		Anxiety # patients with outcome = 6	NR
			>8 weeks		Anxiety # patients with outcome = 5	NR
			8 weeks		Depression # patients with outcome = 5	NR
			>8 weeks		Depression # patients with outcome = 9	NR
			8 weeks		Irritability # patients with outcome = 10	NR
			>8 weeks		Irritability # patients with outcome = 14	NR
Changes in appetite						
Arnold, 2011 ¹³⁸ 52 Fair RCT	Zinc 15 mg once daily (> 8 weeks with amphetamine in all groups)	Zinc 15mg twice daily Placebo	8 weeks >8 weeks 8 weeks >8 weeks	Changes in appetite # patients with outcome = 3 Changes in appetite # patients with outcome = 15	Changes in appetite # patients with outcome = 4 Changes in appetite # patients with outcome = 8 Changes in appetite # patients with outcome = 4 Changes in appetite # patients with outcome = 17	NR NR NR NR
Katz, 2010 ¹⁴³ 120 Fair RCT	Patented herbal preparation	Placebo	0.5 months	Decreased appetite # patients with outcome = 1	Decreased appetite # patients with outcome = 2	NR
Changes in standardized symptom scores						
Dutta, 2012 ¹⁶⁰ 86 Good RCT	Memomet syrup (Bacopa monniera 125 mg, Convulvulus pleuricaulis 100 mg, Centella	Placebo	4 months	Conners 10-point rating scale (hyperactivity) Mean Percent Change 48%	Conners 10-point rating scale (hyperactivity) Mean Percent Change 29%	Reported as significant in text

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
	asiatica 100 mg)					
Pelsser, 2011 ¹³⁹ 100 Good RCT	Restricted elimination diet	No elimination diet	5 weeks after intervention started	ADHD rating scale--Parental total score Mean between group change = 23.7 95% CI = 18.6, 28.8 ADHD rating scale, teacher total score Mean between group change = 15.3 95% CI = 12.0, 18.6 ADHD rating scale, Parent inattention score Mean between group change = 11.8 95% CI = 9.1, 14.4 ADHD rating scale, parent hyperactivity and impulsivity score Mean between group change = 11.9 95% CI = 9.3, 14.5 ADHD rating scale, Teacher hyperactivity and impulsivity score Mean between group change = 8.5 95% CI = 6.8, 10.3 Abbreviated Conners' scale-Parent Mean between group change = 11.8 95% CI = 9.2, 14.5 Abbreviated Conners' scale-Teacher Mean between group change = 7.5 95% CI = 5.9, 6.2 ADHD Rating Scale "Behaviour scores" Total score Mean = 9.6 (SD = 6.9) ADHD Rating Scale "Behaviour scores" Inattention Mean = 4.1 (SD = 3.9) ADHD Rating Scale Hyperactivity and Impulsivity Mean = 5.3 (SD = 3.9) Abbreviated Conners Scale Mean = 5.9 (SD = 3.7)	ADHD Rating Scale "Behaviour scores" Total score Mean = 46.9 (SD = 5.5) ADHD Rating Scale "Behaviour scores" Inattention Mean= 23.4 (SD = 26.3) ADHD Rating Scale Hyperactivity and Impulsivity Mean = 24.1 (SD = 4.2) Abbreviated Conners Scale Mean = 24 (SD = 3.7)	P<.0001 P<.0001 P<.0001 P<.0001 P<.0001 P<.0001 P<.0001
Arnold, 2011 ¹³⁸	Zinc 15 mg	Zinc 15mg	8 weeks	SNAP parent DSM-IV ADHD symptoms	SNAP parent DSM-IV ADHD symptoms	NR

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
52 Fair RCT	once daily (> 8 weeks with amphetamine in all groups)	twice daily	10 weeks	Mean = 1.92 (SD = 0.54)	Mean = 1.47 (SD = 0.65)	NR
		Placebo		CRS-parent Mean = 1.93 (SD = 0.49)	CRS-parent Mean = 1.62 (SD = 0.73)	
				CRS-Teacher * zinc vs. placebo Mean = 1.90 (0.67)	CRS-Teacher * zinc vs. placebo Mean = 1.71 (SD = 0.79)	
		Zinc 15mg twice daily		SNAP parent DSM-IV ADHD symptoms Mean = 1.61 (SD = 0.52)	SNAP parent DSM-IV ADHD symptoms Mean = 1.26 (0.62)	
				CRS-parent Mean = 1.52 (SD = 0.52)	CRS-parent Mean = 1.21 (SD = 0.75)	
		CRS-Teacher * zinc vs. placebo Mean = 1.23 (SD = 0.58)		CRS-Teacher * zinc vs. placebo Mean = 1.40 (0.81)		
		Placebo	SNAP parent DSM-IV ADHD symptoms Mean = 1.47 (0.51)	SNAP parent DSM-IV ADHD symptoms Mean = 1.24 (0.5)	NR	
		13 weeks	Zinc 15mg twice daily	SNAP parent DSM-IV ADHD symptoms Mean = 1.19 (0.56)	SNAP parent DSM-IV ADHD symptoms Mean = 0.67 (0.38)	NR
			Placebo	CRS-parent Mean = 1.08 (SD = 0.45)	CRS-parent Mean = 0.81 (SD = 0.58)	
				CRS-Teacher * zinc vs. placebo Mean = 0.9 (SD = 0.65)	CRS-Teacher * zinc vs. placebo Mean = 0.63 (0.58)	
			Placebo	SNAP parent DSM-IV ADHD symptoms Mean = 1.01 (SD = 0.38)	SNAP parent DSM-IV ADHD symptoms Mean = 1.01 (SD = 0.38)	

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
		Zinc 15mg twice daily	21 weeks	SNAP parent DSM-IV ADHD symptoms Mean = .99 (SD = 0.52)	CRS-parent Mean = 0.91 (0.43)	NR
		Placebo		CRS-parent Mean = .83 (SD = 0.47)	SNAP parent DSM-IV ADHD symptoms Mean = 0.67 (SD = 0.56)	NR
				CRS-Teacher * zinc vs. placebo Mean = 1.17 (SD = 0.53)	CRS-parent Mean = 0.8 (SD = 0.59)	NR
					CRS-Teacher * zinc vs. placebo Mean = 0.94 (0.69)	
					SNAP parent DSM-IV ADHD symptoms Mean = 0.82 (0.44)	
					CRS-parent Mean = 0.72 (0.52)	
Gastrointestinal symptoms						
Arnold, 2011 ¹³⁸ 52 Fair RCT	Zinc 15 mg once daily	Zinc 15mg twice daily	8 weeks	Stomachaches + other GI # patients with outcome = 11	Stomachaches + other GI # patients with outcome = 4	NR
			>8 weeks	Stomachaches + other GI # patients with outcome = 11	Stomachaches + other GI # patients with outcome = 3	NR
		Placebo	8 weeks		Stomachaches + other GI # patients with outcome = 18	NR
			>8 weeks		Stomachaches + other GI # patients with outcome = 14	NR
Katz, 2010 ¹⁴³ 120 Fair RCT	Patented herbal preparation	Placebo	0.5 months	GI discomfort # patients with outcome = 2	GI discomfort # patients with outcome = 3	NR
Mood disorders						
Katz, 2010 ¹⁴³ 120 Fair RCT	Patented herbal preparation	Placebo	0.5 months	Emotional lability # patients with outcome = 2	Emotional lability # patients with outcome = 4	NR
Motor vehicle collisions						
Katz, 2010 ¹⁴³ 120 Fair	Patented herbal preparation	Placebo	0.5 months	Accidental injury # patients with outcome = 1	Accidental injury # patients with outcome = 2	NR

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
RCT						
Sleep disturbance						
Arnold, 2011 ¹³⁸ 52 Fair RCT	Zinc 15 mg once daily	Zinc 15mg twice daily	8 weeks	Sleep # patients with outcome = 0	Sleep # patients with outcome = 1	NR
			>8 weeks	Sleep # patients with outcome = 8	Sleep # patients with outcome = 6	NR
			8 weeks		Sleep # patients with outcome = 4	NR
			>8 weeks		Sleep # patients with outcome = 16	NR
Katz, 2010 ¹⁴³ 120 Fair RCT	Patented herbal preparation	Placebo	0.5 months	Sleep disturbance # patients with outcome = 1	Sleep disturbance # patients with outcome = 4	NR
Suicide ideation						
Arnold, 2011 ¹³⁸ 52 Fair RCT	Zinc 15 mg once daily	Zinc 15mg twice daily	8 weeks	Harm to self or others # patients with outcome = 1	Harm to self or others # patients with outcome = 0	NR
			>8 weeks	Harm to self or others # patients with outcome = 1	Harm to self or others # patients with outcome = 0	NR
			8 weeks		Harm to self or others # patients with outcome = 0	NR
			>8 weeks		Harm to self or others # patients with outcome = 0	NR
Tics or other movement disorders						
Arnold, 2011 ¹³⁸ 52 Fair RCT	Zinc 15 mg once daily	Zinc 15mg twice daily	8 weeks	Stereotypical behaviors # patients with outcome = 3	Stereotypical behaviors # patients with outcome = 1	NR
			>8 weeks	Stereotypical behaviors # patients with outcome = 7	Stereotypical behaviors # patients with outcome = 2	NR
			8 weeks		Stereotypical behaviors # patients with outcome = 5	NR
			>8 weeks		Stereotypical behaviors # patients with outcome = 9	NR

Abbreviations: ADHD=attention deficit hyperactivity disorder; CRS=Conners Rating Scale; SNAP=Swanson, Nolan and Pelham Revision

Strength of Evidence—Herbal Interventions or Dietary Approaches

Table 27 summarizes the strength of evidence for herbal interventions or dietary approaches.

Table 27. Strength of Evidence for Major Outcomes—Herbal Interventions or Dietary Approaches

Outcome	No. Studies/ Design (N Patients)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Major outcomes							
Behavior changes	1 RCT (66)	Low	Direct	NA	Imprecise	None	1 good-quality RCT found that Ginkgo biloba was associated with improved parent and teacher ADHD-RS-Inattention scores but not ADHD-RS-Hyperactivity scores relative to placebo. ⁹³
Insufficient							
Changes in appetite	2 RCTs (172)	Medium	Direct	NA	Imprecise	None	2 fair-quality RCTs did not report statistical significance of proportion of patients in each study arm who reported changes in appetite associated with 2 doses of zinc supplementation relative to placebo, or an herbal preparation vs. placebo. ^{138,143}
Insufficient							
Changes in standardized symptom scores	3 RCTs (238)	Low	Direct	Inconsistent	Imprecise	None	Three studies reported changes in symptom scores. ^{138,139,160} 1 good-quality RCT demonstrated improvement in ADHD-RS scores associated with an elimination diet relative to a non-restricted diet. 1 good-quality and 1 fair-quality study did not find a reduction in ADHD symptoms relative to placebo for either Memomet syrup or zinc supplementation.
Low							
Gastrointestinal symptoms	2 RCTs (172)	Medium	Direct	Inconsistent	Imprecise	None	2 fair-quality RCTs did not report statistical significance of proportion of patients in each study arm who reported stomach aches or other gastrointestinal symptoms associated with 2 doses of zinc supplementation relative to placebo, or an herbal preparation vs. placebo. ^{138,143}
Insufficient							
Mood disorders	1 RCT (120)	Medium	Direct	NA	Imprecise	None	1 fair-quality RCT did not report statistical significance of proportion of patients in each study arm who reported emotional lability associated with an herbal preparation relative to placebo. ¹⁴³
Insufficient							
Motor vehicle collisions	1 RCT (120)	Medium	Direct	NA	Imprecise	None	1 fair-quality RCT did not report statistical significance of proportion of patients in each study arm who reported accidental injury associated with an herbal preparation relative to placebo. ¹⁴³
Insufficient							
Sleep disturbance	2 RCTs (172)	Medium	Direct	Inconsistent	Imprecise	None	2 fair-quality RCTs did not report statistical significance of proportion of patients in each study arm who reported stomach aches or other gastrointestinal symptoms associated with 2 doses of zinc supplementation relative to placebo, or an herbal preparation vs. placebo. ^{138,143}
Insufficient							
Suicide ideation	1 RCT (52)	Medium	Direct	NA	Imprecise	None	1 fair-quality RCT did not report statistical significance of proportion of patients in each study arm who reported harm to self or others associated with 2 doses of zinc supplementation relative to placebo. ¹³⁸
Insufficient							

Outcome	No. Studies/ Design (N Patients)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Tics or other movement disorders	1 RCT (52)	Medium	Direct	NA	Imprecise	None	1 fair-quality RCT did not report statistical significance of proportion of patients in each study arm who stereotypical behaviors associated with 2 doses of zinc supplementation relative to placebo. ¹³⁸
Insufficient							
Abbreviations: NA=not applicable; Obs=observational; RCT=randomized controlled trial; SOE=strength of evidence							

Detailed Synthesis—Other Approaches

One good-quality¹⁰² and 7 fair-quality studies^{96,118,128,129,136,156,164} representing 1,193 enrolled patients evaluated other approaches. These studies looked at a range of programs including community programs and programs that addressed mentoring and parent supports,¹⁵⁶ multisystemic intervention at school and with parents,^{128,129} in-home family training intervention,¹⁰² a general parenting program,¹³⁶ using melatonin as an adjunct treatment, and a homeopathic intervention. This diverse range of interventions share some features with other interventions with several having parent components,^{102,128,129,136,156} but each were different from typical parent focused interventions in that there were other major components or they were generic parenting programs. Findings are summarized by outcome and described in Table 28.

Findings in Relationship to What is Already Known

The 2011 report¹ identified 7 studies that examined multiple component psychosocial and/or behavioral interventions for preschool children with disruptive behavior disorder. Of these, three RCTs included only preschoolers who exhibited ADHD symptoms but who were not necessarily formally diagnosed with ADHD.¹⁸⁰⁻¹⁸⁴ All five of these RCTs demonstrated significant improvement in the preschoolers' behavior or symptoms relative to their comparison groups, most of which were usual care only. In contrast, this updated review provides results from two RCTs that examined a multiple component intervention for children with ADHD that included both school and parent components.^{128,129} Findings of these two studies are summarized below.

Changes in Standardized Symptom Scores

Of the programs that involved parents, those that examined academic achievement^{128,129,156} found no improvement in academic performance. There was no improvement in functional impairment in the one study that examined this.¹⁵⁶ In terms of attentional systems, the New Forest Parenting Package¹⁰² found improved ADHD symptoms on parent ADHD symptoms, but not per teacher report compared to the control condition, while the Incredible Years program¹³⁶ found no change on attention symptoms per parent report.

The melatonin adjunct study found no significant differences on side effect profile or symptoms.¹¹⁸ The study comparing homeopathy with placebo did not find improvement at 6 weeks, but did find change in symptom scores at 12 weeks per parent report. The last study looked more at care delivery mode with telemedicine showing improved symptoms by parent and teacher report on most measures.

Table 28. Findings on Other Approaches for ADHD

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Academic performance						
Evans, 2016 ¹⁵⁶ 326 Fair RCT	Challenging Horizons Program—after school version	Challenging Horizons Program—mentoring version Community Care	12 months	GPA Mean = 2.3	GPA Mean = 2.1 GPA Mean = 2.1	P= 0.146
Mautone, 2012 ¹²⁹ 61 Fair RCT	Family-School Success—Early Elementary	Coping with ADHD through Relationships and Education	12 weeks 2 months post-12 weeks	Academic Competence Evaluation Scales score Mean = 3.38 (SD = 0.57) ACES score Mean = 3.39 (SD = 0.48)	Academic Competence Evaluation Scales score Mean = 3.11 (SD = 0.5) ACES score Mean = 3.25 (SD = 0.66)	NR NR
Power, 2012 ¹²⁸ 199 Fair RCT	Family School Success Therapy	Coping With ADHD Through Relationships and Education	3 months 3-month follow-up	Academic Performance Rating Scale Mean = 3.32 (SD = 0.65) Mean = 3.51 (SD = 0.64)	Academic Performance Rating Scale Mean = 3.2 (SD = 0.68) Mean = 3.36 (SD = 0.76)	NS NS
Behavior changes						
Abikoff, 2015 ¹⁰² 164 Good RCT	New Forest Parenting Package	Helping the noncompliant child	6.8 months	Behavior changes-Connors Parent Rating Scale Revised Scale-Revised - Total Mean = 68.01 (SD = 11.69) Behavior changes-Connors Parent Rating Scale Revised Scale-Revised - Inattention Mean = 65.60 (SD 13.53) Behavior changes-Connors Parent Rating Scale Revised Scale-Revised - Hyperactivity Mean = 68.08 (SD 10.69) Behavior changes-Connors Teachers Rating Scale Revised Scale-Revised - Total Mean = 64.27 (SD = 12.27) Behavior changes-Connors Teacher Rating Scale Revised Scale-Revised - Inattention Mean = 61.39 (SD = 13.58) Behavior changes-Connors Teacher Rating	Behavior changes-Connors Parent Rating Scale Revised Scale-Revised - Total Mean = 63.44 (SD = 10.13) Behavior changes-Connors Parent Rating Scale Revised Scale-Revised - Inattention Mean = 61.74 (SD 10.04) Behavior changes-Connors Parent Rating Scale Revised Scale-Revised - Hyperactivity Mean = 63.39 (SD 10.24) Behavior changes-Connors Teachers Rating Scale Revised Scale-Revised - Total Mean = 62.06 (SD = 11.39) Behavior changes-Connors Teacher Rating Scale Revised Scale-Revised - Inattention Mean = 60.48 (SD = 11.79) Behavior changes-Connors Teacher Rating	NS NS NS NS

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
		Control		Scale Revised Scale-Revised - Hyperactivity Mean = 64.25 (SD = 11.64)	Scale Revised Scale-Revised - Hyperactivity Mean = 62.01 (SD = 12.06) Behavior changes-Conners Parent Rating Scale Revised Scale-Revised - Total Mean = 76.44 (SD = 9.84) Behavior changes-Conners Parent Rating Scale Revised Scale-Revised - Inattention Mean = 75.31 (SD 10.38) Behavior changes-Conners Parent Rating Scale Revised Scale-Revised - Hyperactivity Mean = 74.45 (SD 10.67) Behavior changes-Conners Teachers Rating Scale Revised Scale-Revised - Total Mean = 70.65 (SD = 11.22) Behavior changes-Conners Parent Rating Scale Revised Scale-Revised - Inattention Mean = 68.22 (SD = 11.81) Behavior changes-Conners Parent Rating Scale Revised Scale-Revised - Hyperactivity Mean = 70.26 (SD = 11.98)	NS P=.001 P=.001 P=.001 NS NS NS
Mohammadi, 2012 ¹¹⁸ 60 Fair RCT	MPH + melatonin	MPH + placebo	8 weeks	Irritability # patients with outcome = 16 Sadness # patients with outcome = 10	Irritability # patients with outcome = 10 Sadness # patients with outcome = 2	NR NR
Myers, 2015 ⁹⁶ 223 Fair RCT	Telemedicine	Usual Care + Consult	25 weeks	Behavior changes-Vanderbilt caregiver, meeting criteria for inattention Behavior changes-Vanderbilt caregiver, meeting criteria for hyperactivity Behavior changes-Vanderbilt caregiver, meeting criteria for Combined Behavior changes-Vanderbilt teacher, meeting criteria for inattention		P<.001 P=.02 P=.005 NS

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
				Behavior changes-Vanderbilt teacher, meeting criteria for hyperactivity		P=.02
				Behavior changes-Vanderbilt teacher, meeting criteria for combined		P=.045
Oberai, 2013 ¹⁶⁴ 61 Fair RCT	Homeopathy	Placebo	6 weeks	CPRS-R Oppositional Mean = 56.4 (SD = 7)	CPRS-R Oppositional Mean = 63.2 (SD = 8.3)	NR
				CPRS-R Cognition Problems Mean = 56.6 (SD = 7.4)	CPRS-R Cognition Problems Mean = 67.4 (SD = 5.4)	NR
				CPRS-R Hyperactivity Mean = 63.7 (SD = 9.8)	CPRS-R Hyperactivity Mean = 78.3 (SD = 7.9)	NR
				CPRS-R ADHD Index Mean = 58.2 (SD = 7.3)	CPRS-R ADHD Index Mean = 68.3 (SD = 4.6)	NR
				CGI-SS Mean = 2.9 (SD = 0.7)	CGI-SS Mean = 3.8 (SD = 0.6)	NR
			12 weeks	CPRS-R Oppositional Mean = 49.5 (9.5)	CPRS-R Oppositional Mean = 66.2 (7.6)	P=.0001
				CPRS-R Cognition Problems Mean = 50.7 (7.7)	CPRS-R Cognition Problems Mean = 66.6 (6.2)	P=.0001
				CPRS-R Hyperactivity Mean = 55.6 (11.9)	CPRS-R Hyperactivity Mean = 78.2 (6.9)	P=.0001
				CPRS-R ADHD Index Mean = 51.8 (9.1)	CPRS-R ADHD Index Mean = 68.4 (5)	P=.0001
				Clinical Global Impression Severity Scale Mean = 2.5 (0.7)	Clinical Global Impression Severity Scale Mean = 4 (0.6)	P=.0001
Changes in appetite						
Mohammadi, 2012 ¹¹⁸ 60	MPH + melatonin	MPH + placebo	8 weeks	Appetite score Mean = 13.26	Appetite score Mean = 12.33	P=0.755

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Fair RCT				Loss of appetite # patients with outcome = 14	Loss of appetite # patients with outcome = 11	
Changes in standardized symptom scores						
Mohammadi, 2012 ¹¹⁸ 60 Fair RCT	MPH + melatonin	MPH + placebo	8 weeks	ADHD RS attention score Mean = 11.11 ADHD-RS Hyperactivity score Mean = 11.62	ADHD RS attention score Mean = 11.29 ADHD-RS Hyperactivity score Mean = 10.96	P= 0.974 P= 0.720
Webster-Stratton, 2011 ¹³⁶ 99 Fair RCT	Incredible Years Program	Waitlist	5 months	CBCL-mother Attention problems Mean = 65.8 (SD = 7) CBCL Father – Attention problems Mean = 64.8 (SD = 8.6)	CBCL-mother Attention problems Mean = 68.8 (SD = 9.6) CBCL Father – Attention problems Mean = 65.8 (SD = 10)	NS NS
Functional impairment						
Evans, 2016 ¹⁵⁶ 326 Fair RCT	Challenging Horizons Program–after school version	Challenging Horizons Program–mentoring version Community Care	6 months post-treatment	Impairment Rating Scale- Parent report; relation to children Mean = 1.76 (SD = 1.89) Impairment Rating Scale- Teacher report; Relation with peers Mean = 1.93 (SD = 1.91)	Impairment Rating Scale- Parent report; relation to children Mean = 1.67 (SD = 1.78) Impairment Rating Scale- Teacher report; Relation with peers Mean = 1.97 (SD = 1.83) Impairment Rating Scale- Parent report; relation to children Mean = 1.8 (SD = 1.69) Impairment Rating Scale- Teacher report; Relation with peers Mean = 1.72 (SD = 1.94)	NR NS NS
Gastrointestinal symptoms						
Mohammadi, 2012 ¹¹⁸ 60 Fair RCT	MPH + melatonin	MPH + placebo	8 weeks	Stomachache # patients with outcome = 9 Nausea and vomiting # patients with outcome = 3	Stomachache # patients with outcome = 5 Nausea and vomiting # patients with outcome = 3	NR NR
Sleep disturbance						
Mohammadi, 2012 ¹¹⁸ 60 Fair RCT	MPH + melatonin	MPH + placebo	8 weeks	Mean sleep latency (min) Mean = 17.96 Total sleep (hour) Mean = 8.51	Mean sleep latency (min) Mean = 26.37 Total sleep (hour) Mean = 8.27	P=0.267 P= 0.197

Study N Quality Design	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
				SDSC sleep score Mean = 41.3 Insomnia # patients with outcome = 8 Sleepiness # patients with outcome = 4	SDSC sleep score Mean = 45.5 Insomnia # patients with outcome = 8 Sleepiness # patients with outcome = 4	P= 0.528 NR NR
Tics or other movement disorders						
Mohammadi, 2012 ¹¹⁸ 60 Fair RCT	MPH + melatonin	MPH + placebo	8 weeks	Dyskinesias # patients with outcome = 0 Tics # patients with outcome = 1	Dyskinesias # patients with outcome = 2 Tics # patients with outcome = 1	NR NR
Weight decrease						
Mohammadi, 2012 ¹¹⁸ 60 Fair RCT	MPH + melatonin	MPH + placebo	8 weeks	Weight loss # patients with outcome = 9	Weight loss # patients with outcome = 9	NR

Abbreviations: ADHD=attention deficit hyperactivity disorder; CBCL=Child Behavior Checklist; CPRS=Conners Parent Rating Scale; GPA=grade point average; SDSC=Sleep Disturbance Scale for Children

Strength of Evidence—Other Approaches

Table 29 summarizes the strength of evidence for approaches.

Table 29. Strength of Evidence for Major Outcomes—Other Approaches

Outcome	No. Studies/ Design (N Patients)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Major outcomes							
Academic performance	3 RCTs (586)	Medium	Direct	Consistent	Imprecise	None	Neither the Challenging Horizons Program—After School version nor the Family School Success—Early Elementary interventions were not found to improve academic performance in 3 fair-quality RCTs. ^{128,129,156}
Low							
Behavior changes	4 RCTs (508)	Medium	Direct	Consistent	Imprecise	Suspect	Each of 1 good-quality and 3 fair-quality RCTs ^{96,102,118,164} found some positive behavior changes associated with the New Forest Parenting Package, melatonin, a telemedicine intervention, or homeopathy relative to placebo or no intervention.
Insufficient							
Changes in appetite	1 RCT (60)	Medium	Direct	NA	Imprecise	None	1 fair-quality RCT did not differ in the proportion of patients who reported loss of appetite when comparing MPH plus melatonin to MPH plus placebo melatonin. ¹¹⁸
Insufficient							
Changes in standardized symptom scores	2 RCTs (159)	Medium	Direct	Consistent	Imprecise	None	2 fair-quality studies did not find a reduction in ADHD symptoms relative to placebo or no intervention for melatonin or the Incredible Years Program. ^{118,136}
Insufficient							
Functional impairment	1 RCT (326)	Medium	Direct	NA	Imprecise	None	1 fair-quality study did not find a difference in functional impairment between the after school version and the mentoring version of the Challenging Horizons Program. ¹⁵⁶
Insufficient							
Gastrointestinal symptoms	1 RCT (60)	Medium	Direct	NA	Imprecise	None	1 fair-quality RCT did not find a difference in the proportion of patients who reported stomach ache or nausea and vomiting between MPH plus melatonin compared with MPH plus placebo. ¹¹⁸
Insufficient							
Sleep disturbance	1 RCTs (60)	Medium	Direct	NA	Imprecise	None	1 fair-quality RCT did not find a difference in sleep latency, total hours of sleep, SDSC sleep score, or the proportion of patients who reported insomnia or sleepiness between MPH plus melatonin compared with MPH plus placebo. ¹¹⁸
Insufficient							
Tics or other movement disorders	1 RCT (60)	Medium	Direct	NA	Imprecise	None	1 fair-quality RCT did not find a difference in the proportion of patients who reported dyskinesia between MPH plus melatonin compared with MPH plus placebo. ¹¹⁸
Insufficient							
Weight decrease	2 RCTs (60)	Medium	Direct	NA	Imprecise	None	1 fair-quality RCT did not find a difference in the

Outcome	No. Studies/ Design (N Patients)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Insufficient							proportion of patients who reported weight loss between MPH plus melatonin compared with MPH plus placebo. ¹¹⁸

Abbreviations: NA=not applicable; Obs=observational; RCT=randomized controlled trial; SOE=strength of evidence

Key Question 3. ADHD Monitoring

KQ 3 examines the comparative safety and effectiveness of different monitoring strategies to evaluate the effectiveness of treatment or changes in ADHD status (e.g., worsening or resolving symptoms). We did not identify any studies that met criteria for inclusion for KQ 3.

Discussion

Key Findings and Strength of Evidence

In this comparative effectiveness review (CER), we reviewed 19 studies involving 4,105 patients that evaluated ADHD diagnostic strategies for children and adolescents that could be used in the primary care setting and evaluated the impact of being labeled as having ADHD (Key Question [KQ] 1) and 63 studies involving 37,099 patients to evaluate the comparative effectiveness of different pharmacologic and nonpharmacologic therapies for ADHD (KQ 2). Because of variations in “usual care” often used as the comparator, detailed descriptions of the comparator were made and considered in the evaluation of the available evidence. We hoped to evaluate the comparative effectiveness of different follow-up strategies for children and adolescents with ADHD (KQ 3). However, no study was identified that met the criteria for inclusion.

KQ 1. ADHD Diagnosis

Our review focused on evidence evaluating diagnosis in children under 6 years of age or for older children (up to 17 years of age) using novel diagnostic techniques including imaging and EEG. We found studies addressing a wide range of instruments to assist with the diagnosis of ADHD, including the use of biometric testing, EEGs, imaging (e.g., MRI), computerized continuous performance tests (CPTs), observation, and standardized questionnaires. No studies were rated as good quality. Each study addressed validity but not reliability of using these instruments for diagnostic purposes. Although the studies included both children and adolescents, there were insufficient data to evaluate the comparative effectiveness by age.

Standardized questionnaires are typically used to establish ADHD in the primary care setting; however, our review found one study, rated as poor quality, that did not support the use of one such tool, the Strengths and Difficulty Questionnaire, and we found a fair-quality study of another tool, the Kiddie-Disruptive Behavior Disorder Schedule, which found high specificity but only moderate sensitivity. Seven studies explored the use of imaging in the diagnosis of ADHD; these studies did not support the use of imaging scans to diagnose ADHD. Although data from 6 studies did not support the use of CPTs alone to diagnose ADHD, a fair-quality pilot study suggests that CPTs combined with other tests such as TOVA can improve the validity of diagnosis. Insufficient evidence is available to evaluate the use of biometric devices. Limited data from 2 studies suggest that standardized observation may aid in the diagnosis of ADHD.

Limited information was found regarding the harm of being labeled with ADHD. Only two cross-sectional studies were evaluated, and they only assessed the perspective of parents and teachers. Neither study directly assessed the experience of children or adolescents with ADHD. Therefore, no conclusions could be drawn regarding the impact of ADHD diagnosis.

KQ 2. ADHD Treatment

ADHD treatment options include pharmacologic and nonpharmacologic therapies. For each approach, there is a wide variety of specific treatments. In clinical practice, different treatments are often combined on the basis of perceived needs of individual patients.

Atomoxetine and MPH were the most common drugs evaluated in the studies included in this review (evaluated in 8 studies). Insufficient evidence was available to determine which drug is

more effective or whether the side-effect profiles are different. There was also little evidence regarding serious cardiovascular risk with use of these medications.

Nonpharmacologic therapies such as cognitive training, cognitive behavioral therapy, and neurofeedback appear to reduce the symptoms of ADHD based on included studies. In terms of strategies targeting parent behavior training, it is unclear as to whether parents are truly more effective or just feel more effective in dealing with behavior symptoms from ADHD resulting in changes in standardized symptom scores. That is, it may be that the ADHD symptoms are improving in response to the parent parenting differently and helping the child learn how to control symptoms, or it may be that parents feel more efficacious. Limited data suggest that there is no benefit in adding neurofeedback to treatment with MPH. Skills training for children or parents does not appear to improve academic performance.

The most well-studied nutritional therapy is dietary supplementation with omega-3/6 fatty acids. However, based on meta-analysis, there was no impact of omega-3/6 supplements on parent or teacher rating scales of ADHD symptoms. Combining omega-3/6 supplements with MPH could increase minor side effects such as dyspepsia.

Table 30 summarizes the strength of evidence (SOE) findings for KQ 2, which were graded as either low, moderate, or high.

Table 30. Summary Strength of Evidence for Major Outcomes for KQ 2

Outcome	No. Studies/ Design	Findings
SOE Grade (N Patients) Findings		
Pharmacologic vs. Placebo Treatments		
NA		
Pharmacologic vs. Pharmacologic Treatments		
Gastrointestinal symptoms	3 Obs (1,966)	The proportion of patients reporting GI effects or disease was small in all 3 studies and slightly higher for atomoxetine than MPH. ^{91,134,162}
Low		
Pharmacologic vs. Nonpharmacologic Treatments		
Changes in appetite	3 RCTs (212)	All three studies found the MPH medication group to have a significantly greater number of participants with decreased appetite when compared to supplementation by ningdong, omega-3/6 or ginkgo biloba. ^{107,135,144}
Low		
Sleep disturbance	3 RCTs (212)	Three RCTs ^{107,135,144} reported sleep disturbance outcomes. In two of the trials a significantly greater proportion of sleep disturbances were found in the MPH medication group compared to supplementation by Ningdong granule or Ginkgo Biloba. The other trial reports a higher proportion of sleep disturbances in the MPH medication group (67.0%) compared to 0% in the omega-3/6 group.
Low		
Nonpharmacologic vs. Nonpharmacologic or Other Treatments		
Neurofeedback		
NA		
Cognitive Training		

Outcome	No. Studies/ Design	Findings
Changes in standardized symptom scores	9 RCTs (768)	Nine RCTs reported changes in symptom scores. ^{92,94,106,108,111,113,116,140,151} 2 fair-quality RCTs (out of a total of 5) that evaluated the Cogmed cognitive training program demonstrated a significant improvement in standardized scale scores at some, but not all, of the follow-up assessment times. A good-quality RCTs found no treatment effect associated with the Braingame program compared with no intervention, and 2 good-quality RCTs that compared computer-based cognitive training programs to neurofeedback found either no treatment effect or superiority of neurofeedback relative to cognitive training. 1 fair-quality RCT demonstrated a reduction in ADHD symptoms associated with cognitive training relative to no intervention.
Low		
Cognitive Behavioral Therapy		
Changes in standardized symptoms scores	2 RCTs (278)	A good-quality and a fair-quality RCT found statistically significant improvement in ADHD symptom associated with CBT relative to usual care or a limited CBT intervention. ^{95,99}
Low		
Child or Parent Training or Behavioral		
Changes in standardized symptom scores	8 RCTs (1042)	Of 6 good-quality and 2 fair-quality RCTs, ^{97,105,110,127,130,150,157,158} only 1 fair-quality study did not demonstrate a significant improvement in ADHD symptoms associated with child or parent training or sleep hygiene.
Moderate		
Academic performance	2 RCTs (356)	2 good-quality RCTs found no differences in academic performance associated with organizational skills or social skills training relative to no intervention. ^{120,123}
Low		
Omega-3 Supplementation		
Changes in standardized symptom scores	8 RCTs (880)	Two meta-analyses of 4 and 3 good-quality studies respectively found no significant differences between omega-3/6 and placebo for parent ratings (n=411, SMD -0.32, 95% CI -0.80 to 0.15, I ² =52.4%, Q=6.3, p-value=0.098) or teacher ratings of total ADHD symptoms (n=287, SMD -0.08, 95% CI -0.47 to 0.32, I ² =0.0%; Q=1.2, p=0.56). ^{104,117,124,125,132,142,147,154}
Moderate		
Herbal Interventions or Dietary Approaches		
Changes in standardized symptom scores	2 RCTs (172)	Three studies reported changes in symptom scores. ^{138,139,160} 1 good-quality RCT demonstrated improvement in ADHD-RS scores associated with an elimination diet relative to a non-restricted diet. 1 good-quality and 1 fair-quality study did not find a reduction in ADHD symptoms relative to placebo for either Memomet syrup or zinc supplementation.
Low		
Other Approaches		
Academic performance	3 RCTs (586)	Neither the Challenging Horizons Program—After School version nor the Family School Success—Early Elementary interventions were not found to improve academic performance in 3 fair-quality RCTs. ^{128,129,156}
Low		

Findings in Relationship to What is Already Known

Our report extends a previous systematic review sponsored by AHRQ, published in 2011, on the diagnosis and treatment of children with ADHD. The previous report focused on (1) primarily pharmacologic treatments for children under 6 years of age with ADHD and a disruptive behavior disorder; (2) long-term comparative safety and effectiveness of a variety of treatment options for children 6 years of age or older with ADHD; and (3) prevalence of ADHD and rates of diagnosis and treatment for ADHD. The authors of that report concluded that there

was high SOE in support of the effectiveness of parent behavior training and low SOE in support of MPH for improving the behavior of children aged 6 years or younger. The previous report also concluded that there was sparse evidence at the time regarding long-term outcomes following interventions for ADHD, but that treatment for 12 months or longer with MPH or atomoxetine appeared to be associated with improvements in symptomatic behavior.

This current report updates and expands on the prior work by identifying and summarizing evidence from clinical trials published since 2009. In this report, we examine a wider range of both nonpharmacologic and pharmacologic treatment options than those examined in the prior report, and we examine both short-term and long-term interventions for all age groups from early childhood through adolescence.

Since publication of the AAP clinical practice guideline, there has been significant interest in the use of objective tests that could overcome the inherent limitations in the use of behavioral rating scales. Our systematic review could not find sufficient evidence to recommend that such tests now be incorporated into care. The AAP guideline also recognized the potential harm of labeling an individual with ADHD, but our review did not identify studies that would allow an estimate of this potential harm.

The AAP clinical practice guideline recommends behavioral therapy for children 4 through 5 years of age as the first line of therapy, with consideration of MPH if such interventions fail. In contrast, FDA-approved medications are the first line of therapy for older children, followed by behavioral interventions. A recent Cochrane review of randomized controlled trials for the treatment of ADHD found that although MPH might improve ADHD symptoms, the level of certainty was low because most trials were underpowered, of low quality, and had short duration of follow-up.¹⁸⁵ That review included studies of children and adolescents 18 years and younger with ADHD according to DSM 3, 4, or 5 published by March 2015. Another systematic review supported the use of MPH, atomoxetine, and extended-release guanfacine to improve ADHD symptoms in adolescents.¹⁸⁶ That review only included studies of subjects 12 to 18 years of age published from 1999 through January 2016. As with the Cochrane review,¹⁸⁵ limitations in study quality were identified.

Our systematic review was not able to provide further guidance regarding the comparative effectiveness of FDA-approved medications. None of the supplements for ADHD therapy appear to be effective. The behavioral interventions included in this systematic review were of limited effectiveness. However, insufficient data were available to determine whether there is a subgroup of children and adolescents with ADHD (e.g., based on age or other characteristics) for whom these therapies might be more effective.

No existing systematic reviews or guidelines address the frequency that children or adolescents receiving care for ADHD should receive follow-up in the primary care practice setting or what approach should be used for monitoring after treatment is begun. Unfortunately, our systematic review also found no information to inform this question.

Applicability

The accuracy of diagnostic tests and the effects of interventions for ADHD as determined in clinical studies do not always translate well to usual practice, where patient characteristics, clinical training, and resources may differ from study conditions in key ways. In addition, the availability of ADHD interventions studied in our review may differ from those easily available to patients within the United States.

For our analysis of diagnostic tools, study participants were generally adequately described. The main issue affecting applicability was the source of patients, who were selected from specialty clinics. This might affect the reported test characteristics (e.g., sensitivity and specificity). In general, given the scarcity of evidence we were not able to separately consider the role of age, ADHD subtype, or prior therapy. Most studies of diagnostic tools are performed outside of the primary care practice setting, further limiting applicability to children seen in the primary care setting. The studies of labeling have low applicability because they did not address specific patients or were surveys based on hypothetical children labeled with having ADHD.

The treatment studies we evaluated have moderate applicability due to significant heterogeneity regarding the duration of therapy, the study population, and the follow-up period. However, there was consistency in findings related to pharmacotherapy.

We were unable to find any studies that met the inclusion criteria regarding follow-up after treatment initiation (KQ 3).

Table 31 shows potential issues with applicability for studies included for KQ 1. Table 32 shows similar information for studies included in KQ 2 and is broken down by type of intervention.

Table 31. Potential Issues With Applicability of Included Studies for Key Question 1

Issue	N=19 Studies
Population (P)	
Narrow eligibility criteria and exclusion of those with comorbidities	2
More complex patients than typical of the community	1
Run-in period with high exclusion rate for non-adherence or side effects	0
DSM-4/5 diagnosis unclear	0
Intervention (I)	
Diagnostic tools used differently than as recommended or commonly used in practice	0
Dosing not reflective of current practice	0
Co-interventions that are likely to modify the effectiveness of therapy	0
Highly selected intervention team or level of training/proficiency not widely available	1
Follow-up not reflective of current practice	0
Co-intervention that are likely to modify monitoring strategies	0
Comparator (C)	
Diagnostic tools used differently than as recommended or commonly used in practice	0
Comparator unclear	0
Inadequate comparison therapy or use of a substandard alternative therapy	0
Outcomes (O)	
Composite outcomes that mix outcomes of different significance	0
Short-term follow-up	0
Surrogate outcomes	0
Setting (S)	
Level of care different from that in the community	8

Table 32. Potential Issues With Applicability of Included Studies for Key Question 2

Issue	N=64 Studies				
	Pharm vs. Pharm N=11	Pharm vs. Nonpharm N=7	Pharm vs. Placebo N=5	Nonpharm vs. Nonpharm N=13	Nonpharm vs. Placebo N=35
Population (P)					
Narrow eligibility criteria and exclusion of those with comorbidities	0	0	1	2	1

Issue	N=64 Studies				
	Pharm vs. Pharm N=11	Pharm vs. Nonpharm N=7	Pharm vs. Placebo N=5	Nonpharm vs. Nonpharm N=13	Nonpharm vs. Placebo N=35
More complex patients than typical of the community	0	0	0	0	0
Run-in period with high exclusion rate for non-adherence or side effects	0	0	0	0	0
DSM-4/5 diagnosis unclear	1	0	0	0	1
Intervention (I)					
Diagnostic tools used differently than as recommended or commonly used in practice	0	0	0	0	0
Dosing not reflective of current practice	0	0	0	0	0
Co-interventions that are likely to modify the effectiveness of therapy	1	2	1	0	4
Highly selected intervention team or level of training/proficiency not widely available	1	1	1	1	5
Follow-up not reflective of current practice	0	0	0	0	1
Co-intervention that are likely to modify monitoring strategies	0	0	0	0	0
Comparator (C)					
Diagnostic tools used differently than as recommended or commonly used in practice	0	0	0	0	1
Comparator unclear	2	1	0	0	0
Inadequate comparison therapy or use of a substandard alternative therapy	1	0	0	1	3
Outcomes (O)					
Composite outcomes that mix outcomes of different significance	0	0	0	0	0
Short-term follow-up	0	2	0	3	10
Surrogate outcomes	0	0	0	0	0
Setting (S)					
Level of care different from that in the community	1	1	1	2	4

Abbreviations: Pharm=pharmacologic; Nonpharm=nonpharmacologic

Implications for Clinical and Policy Decisionmaking

The lack of strong evidence for objective tests for the diagnosis of ADHD suggests that behavior rating scales should continue to be used as the primary strategy for diagnosing the condition. The findings also suggest that FDA-approved ADHD medications should be the primary treatment approach. However, insufficient data were available to determine whether they should be the first line of therapy for children under 6 years of age. There appears to be a low risk of serious adverse effects associated with MPH. Insufficient evidence is available to support behavioral therapies, either alone or in combination with medication therapy. There is a lack of supportive data for other complementary therapies. Although regular follow-up is recommended for children and adolescents with ADHD, no evidence was found about the comparative benefits and harms of different approaches.

Limitations of the Systematic Review Process

Our findings have limitations related to the literature and our approach. Important limitations of the literature include (1) population heterogeneity; (2) short follow-up periods; (3) small sample sizes; (4) studies conducted outside of primary care; (5) variability in outcomes to assess efficacy and tolerability; and (6) inconsistent reporting of comparative statistical analyses.

Our review methods also have limitations. The time period of this systematic review led to the exclusion of earlier larger studies. Our study was limited to English-language publications. Note that during the protocol development phase of our review we made two scoping revisions in consultation with our technical expert panel (TEP). Specifically the review focused on:

- KQ 1: Diagnostic methods in children aged 6 or under or which compared novel diagnostic methods (e.g., imaging or EEG)
- KQ 2: Studies comparing two or more pharmacologic treatments approved by the FDA for the treatment of ADHD needed include 100 or more patients with ADHD and have a follow-up period of 6 months or longer. Criteria was less stringent for studies assessing nonpharmacologic treatments or pharmacologic treatments not indicated by the FDA for the treatment of ADHD. Data for these interventions was limited to studies including 50 or more patients with ADHD, with no specific requirement for length of follow-up.

This change in scope was performed in consultation with the nominating partner and the TEP in order to focus the systematic review on the areas of the greatest uncertainty and potential impact.

Research Recommendations

ADHD is a common health problem that can be associated with significant impairment over the life span. The current evidence base has several significant gaps regarding diagnosis, treatment, and follow-up in the primary care setting. We did not identify any ongoing studies through trial registries that would help resolve the gap. Here we describe opportunities for future research organized by the three key questions.

KQ 1 ADHD Diagnosis Research Gaps

Significant gaps related to KQ 1 include the lack of studies conducted in primary care and the lack of studies that prospectively evaluate the harm of labeling.

- Validity and reliability of behavior scales in direct comparison to new strategies for diagnosis:
 - Studies should include a typical population of children and adolescents in primary care seeking initial diagnosis.
 - The tools should be performed in the primary care setting.
 - Confirmation should be based on DSM-5 criteria by an expert within a short period of time to evaluate in the primary care setting. The expert should be blinded to the results in primary care.
 - Receiver operator characteristic (ROC) curves should be generated to evaluate the validity of diagnosis using different cut-offs for the behavior scales and consider the impact of combining behavior scales with other diagnostic strategies.
 - Results should be stratified by age group and ADHD subtype.

- Reliability (test-retest reliability, inter-observer reliability, and intra-observer reliability) should be evaluated.
- Harms of labeling: These can be assessed in a longitudinal cohort of patients diagnosed with ADHD as part of an overall study to evaluate the effectiveness of interventions (see KQ 2).

KQ 2 ADHD Treatment Research Gaps

Significant gaps related to KQ 2 include the lack of studies conducted in primary care and the short duration of follow-up.

- Effectiveness of treatment:
 - Typical care would be better informed by a pragmatic randomized trial that includes the typical spectrum of patients seen in primary care.
 - Three-arm studies, using pharmacologic, nonpharmacologic treatments (e.g., behavioral interventions), and a combination of approaches are needed. In a pragmatic trial, therapy could be escalated or combined, based on the responsiveness to treatment.
 - Studies should include a wide range of outcomes, including behavior rating scales, school functioning, risk-taking behaviors, growth and development, comorbid psychiatric disorders, and the typical adverse events monitored in drug trials.
 - Studies should have a meaningful duration. Ideally, those enrolled in a pragmatic trial would be followed for multiple years.
 - Studies should include the full spectrum of children and adolescents seeking care in the primary care setting.
 - Follow-up monitoring should be evaluated, as described for KQ 3.

KQ 3 ADHD Monitoring Research Gaps

Monitoring individuals with ADHD is a central to assuring optimal treatment outcomes. It allows for modification of the treatment plan based on assessment of adherence, changes in symptoms, the presence of comorbidity, the effectiveness of therapy, and the presence of any treatment-related harms. Factors that should be considered are time intervals, setting (e.g., primary care vs. specialty care), and the type of information to be evaluated. In addition, the role of technology should be considered. For example, the use of technology (e.g., web-based tools or smartphone applications) could allow the collection of a wide array of data and decrease the need for in-clinic evaluations. Telemedicine might enable health care providers to communicate with the patient, family, and teachers.

- Monitoring treatment:
 - Within a pragmatic trial, different strategies for monitoring could be embedded.
 - Strategies should include the use of technology versus traditional in-person evaluations.
 - The frequency of monitoring should be a function of the ADHD symptoms and the intervention.

Conclusions

Behavior rating scales are valid for use in the diagnosis of ADHD. The additional benefit of new strategies for diagnosing ADHD (e.g., imaging, EEG) is unclear. Little is known about the

harm of labeling. For ADHD treatment, FDA-approved drugs are most likely to be effective and appear to be associated with a low risk of adverse events. The additional benefit of behavior therapies or complementary medications is unclear. Insufficient data are available to determine whether there are variations in effectiveness by age, sex, or presenting ADHD symptoms. No data were identified to determine the optimal strategy for monitoring children and adolescents with ADHD.

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