Effective Health Care Program

Comparative Effectiveness Review
Number 44

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Attention Deficit Hyperactivity Disorder:

Effectiveness of Treatment in At-Risk Preschoolers; Long-Term Effectiveness in All Ages; and Variability in Prevalence, Diagnosis, and Treatment

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Attention Deficit Hyperactivity Disorder: Effectiveness of Treatment in At-Risk Preschoolers; Long-Term Effectiveness in All Ages; and Variability in Prevalence, Diagnosis, and Treatment

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. MME2202 290-02-0020

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AHRQ Publication No. 12-EHC003-EF
October 2011

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None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Suggested citation: Charach A, Dashti B, Carson P, Booker L, Lim CG, Lillie E, Yeung E, Ma J, Raina P, Schachar R. Attention Deficit Hyperactivity Disorder: Effectiveness of Treatment in At-Risk Preschoolers; Long-Term Effectiveness in All Ages; and Variability in Prevalence, Diagnosis, and Treatment. Comparative Effectiveness Review No. 44. (Prepared by the McMaster University Evidence-based Practice Center under Contract No. MME2202 290-02-0020.) AHRQ Publication No. 12-EHC003-EF. Rockville, MD: Agency for Healthcare Research and Quality. October 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

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 are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Acknowledgments

The researchers at the Evidence-based Practice Center would like to acknowledge the following people for their contributions.

We are grateful to our Task Order Officer, Steven Fox, for his support and guidance. Members of the Technical Expert Panel were instrumental in the formation of the parameters and goals of this review.

We would also like to thank those who worked so conscientiously retrieving and screening citations, abstracting data, preparing figures, and editing the report: Julianna Beckett, Bryan Cheeseman, Roxanne Cheeseman, Alicia Freeborn, Connie Freeborn, Jeffrey Freeborn, Mary Gauld, Suzanne Johansen, Sara Kaffashian, Dorothy Kendry, Jinhui Ma, Leah Macdonald, Sandra McIsaac, Rachael Morris, Galatea Papageorgiou, Maureen Rice, Robert Stevens, and Ian White. Our thanks to Drs. Michael Boyle and Harry Shannon and Ms. Nancy Santesso for providing assistance along the way.

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Attention Deficit Hyperactivity Disorder: Effectiveness of Treatment in At-Risk Preschoolers; Long-Term Effectiveness in All Ages; and Variability in Prevalence, Diagnosis, and Treatment

Structured Abstract

Objectives. (1) Compare effectiveness and adverse events of interventions (pharmacological, psychosocial, or behavioral, and the combination of pharmacological and psychosocial or behavioral interventions) for preschoolers at high risk for attention deficit hyperactivity disorder (ADHD); (2) compare long-term effectiveness and adverse events of interventions for ADHD among persons of all ages; and (3) describe how identification and treatment for ADHD vary by geography, time period, provider type, and sociodemographic characteristics, compared with endemic prevalence.

Data Sources. MEDLINE®, Cochrane CENTRAL, EMBASE, PsycInfo, and ERIC (Education Resources Information Center) were searched from 1980 to May 31, 2010. Reference lists of included studies and gray literature were searched manually.

Review Methods. Reviewers applied preset criteria to screen all citations. Decisions required agreement between two independent reviewers, with disagreements regarding inclusion or exclusion resolved by a third. The Effective Public Health Practice Project (EPHPP) process was used to evaluate internal validity of publications regarding interventions for preschoolers at high risk of ADHD and long-term outcomes following interventions for ADHD in persons of all ages. Overall strength of the evidence (SOE) was assessed using the GRADE approach, accounting for risk of bias and study design, consistency of results, directness of evidence, and degree of certainty regarding outcomes of interest.

Results. Of included studies, only a subset could be pooled statistically using meta-analytic techniques. For the first objective, we rated as "good" quality eight studies of parent behavior training (PBT) with 424 participants. These demonstrated high SOE for improving child behavior (standardized mean difference [SMD] = −0.68; 95-percent confidence interval [CI], −0.88 to −0.47). A single "good" quality study of methylphenidate (MPH) with 114 preschool children provided low SOE for improving child behavior (SMD = −0.83; 95-percent CI, −1.21 to −0.44). Adverse effects were present for preschool children treated with MPH; adverse effects were not mentioned for PBT.

For the second objective, the majority of studies were open extension trials without continuation of untreated comparison groups. Evidence from the single "good" quality study of MPH demonstrated low SOE for reduction of symptoms, with SMD = −0.54 (95-percent CI, −0.79 to −0.29). Evidence from the single "good" quality study of atomoxetine demonstrated low SOE for reduction of symptoms, with SMD = −0.40 (95-percent CI, −0.61 to −0.18). Evidence from the single "good" quality study of combined psychostimulant medication with behavioral/psychosocial interventions provided low SOE, with SMD = −0.70 (95-percent CI, −0.95 to −0.46). Safety reports for pharmacological interventions derived from observational studies on uncontrolled extensions of clinical trials, as well as from administrative databases,

provided inconclusive evidence for growth, cerebrovascular, and cardiac adverse effects. Evidence that psychostimulant use in childhood improves long-term outcomes was inconclusive.

For the third objective, a discussion of contextual issues and factors relating to underlying prevalence and rates of diagnosis and treatment was included. Population-based data were relatively scarce and lacked uniform methods and settings, which interfered with interpretation. The available evidence suggested that underlying prevalence of ADHD varies less than rates of diagnosis and treatment. Patterns of diagnosis and treatment appeared to be associated with such factors as locale, time period, and patient or provider characteristics.

Conclusions. The SOE for PBT as the first-line intervention for improved behavior among preschoolers at risk for ADHD was high, while the SOE for methylphenidate for improved behavior among preschoolers was low. Evidence regarding long-term outcomes following interventions for ADHD was sparse among persons of all ages, and therefore inconclusive, with one exception. Primary school–age children, mostly boys with ADHD combined type, showed improvements in symptomatic behavior maintained for 12 to 14 months using pharmacological agents, specifically methylphenidate medication management or atomoxetine. Other subgroups, interventions, and long-term outcomes were under-researched. Evidence regarding large-scale patterns of diagnosis and treatment compared with endemic rates of disorder was inconclusive.

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Executive Summary

Background and Clinical Context

Children with attention deficit hyperactivity disorder (ADHD), a condition characterized by inattention, overactivity, and impulsivity, are most frequently identified and treated in primary school. Population studies indicate that 5 percent of children worldwide show impaired levels of attention and hyperactivity. Boys are classified with ADHD approximately twice as frequently as girls, and primary school-age children approximately twice as frequently as adolescents. ADHD symptoms exist on a continuum in the general population and are considered a "disorder" to a greater or lesser degree, depending on the source of identification (e.g., parent or teacher), extent of functional impairment, diagnostic criteria, and the threshold chosen for defining a "case." The developmentally excessive levels of inattention, overactivity, and impulsivity characteristic of ADHD are present from an early age. However, preschoolers with early signs of ADHD may also have co-occurring oppositional noncompliant behaviors, temper tantrums, and aggression that overshadow symptoms of inattention and overactivity and confound the diagnosis. These behaviors may be given the more general label of disruptive behavior disorder (DBD), which includes oppositional defiant disorder (ODD) and conduct disorder (CD), as well as ADHD. If not already identified at an early age, preschool youngsters with ODD frequently meet criteria for ADHD by grade school.

History

Although the condition now classified as ADHD was first described clinically in 1902,[1] few widely available treatments were developed for children with difficulties with attention, hyperactivity, and impulsiveness until the 1950s, when the syndrome was identified as "minimal brain damage" or "hyperkinetic syndrome." At about the same time, methylphenidate (MPH; brand name, Ritalin) was developed to target the condition. The use of pharmacotherapy has increased through the years, along with refinements in understanding and recognition of the condition as a disorder, as reflected by its inclusion into generally accepted classification systems, such as the Diagnostic and Statistical Manual, or DSM (included in DSM-II in 1968), and International Classification of Diseases, or ICD (included in ICD-9 in 1977). The changes in labels over time reflect the contextual understanding of the condition as one of both environmental and biological etiology—from "defects of moral control" in the Edwardian typology, through "minimal brain dysfunction" in the 1960s, to attention deficit hyperactivity disorder with identified subtypes in the 1980s and 1990s. Diagnosis of ADHD and prescriptions for its treatment have grown exponentially, particularly in North America, where the preferred DSM-IV criteria identify greater numbers of children than the ICD-10 diagnosis of "hyperkinetic disorder" used more commonly in Europe. In the 1970s, the psychostimulants were classified as controlled substances due to rising concerns about misuse and abuse, and data collection regarding their use became mandatory. During the same time period, dextroamphetamine (DEX) and MPH were evaluated as effective treatments for children with the syndrome characterized by inattention and hyperactivity.

By the end of the 1960s, approximately 150,000 to 200,000 children were treated with stimulants, which represented 0.002 percent of the U.S. child population at that time.[2] Comparisons over time are difficult, since issues of definitions, informants, and reporting cloud the picture; however, from 1991 to 1999, prescriptions for MPH increased from 4 million to 11

million, and prescriptions for amphetamines from 1.3 million to 6 million.[3] The U.S. National Survey of Child Health (NSCH) provides a 2003 estimate of 4.4 million children who were identified at some point as having ADHD, which represents 7.8 percent of that population, and 2.5 million (56 percent of those identified) were receiving medication for this condition.[4] Within the United States, the estimated prevalence of adult ADHD stands at 4.4 percent.[5] The International Narcotics Control Board, using a denominator of standardized defined daily doses (S-DDDs), reports that the medical use of MPH in the United States has increased from 7.14 S-DDDs per 1,000 inhabitants per day in 2004 to 12.03 S-DDDs per 1,000 inhabitants per day in 2008. Within the same time period, and using the same definitions, MPH consumption increased from 4.22 to 6.12 S-DDDs/day/1,000 inhabitants in Canada and from 1.38 to 3.67 S-DDDs/day/1,000 inhabitants in the United Kingdom.[6] Controversy continues, with ongoing concerns identified about misuse in the community, as well as a mismatch between who is identified and who is treated. The controversy around accurate diagnosis is particularly heightened with documented increases in diagnosis of younger children and associated increases in treatment with psychoactive medications.

Social Burden

Throughout childhood and adolescence, clinically significant ADHD is often associated with concurrent oppositional and aggressive behaviors, and also anxiety, low self-esteem, and learning disabilities. Symptoms are clinically significant when they cause impaired functioning; they generally interfere with academic and behavioral functioning at school, and they may also disrupt family and peer relationships. While ADHD can begin before children enter school, it is most commonly identified and treated in primary school, around ages 7 to 9 years. Over the years, the literature examining interventions has largely focused on the primary school–age group, with the hope that intervening at this stage will diminish the adolescent risks of dropping out of school; initiating substance use, with its associated conduct, mood, and anxiety disorders; and dangerous driving. Preschoolers treated for ADHD most often have co-occurring noncompliant behaviors, temper, and aggression that impair their relationships with family and care providers, and interfere with social and emotional development. The DSM-IV criteria include subtypes: (1) predominantly inattentive, (2) predominantly hyperactive-impulsive, and (3) combined inattentive and hyperactive. In clinical samples, preschoolers are more likely to show the hyperactive-impulsive subtype,[7] while primary school–age children exhibit inattentive and combined subtypes, with somewhat older children and teens showing the predominantly inattentive subtype. Overall, levels of symptoms of overactivity and impulsiveness decrease with age; however, the majority of children with ADHD continue to show impairment, especially poor attention, relative to same-age peers throughout adolescence and into adulthood. The estimate of prevalence of ADHD among adults in the United States is 5.2 percent,[8] while worldwide it is 2.5 percent (95% confidence interval [CI], 2.1 to 3.1).[9]

Scope and Purpose of the Systematic Review

The purpose of this review is to (1) critically examine the effectiveness and adverse events of interventions in preschool children with clinically significant disruptive behavior and therefore at high risk for ADHD; (2) critically examine the comparative long-term effectiveness and adverse events of interventions for ADHD (pharmacological, psychosocial, or behavioral, and the combination of pharmacological and psychosocial or behavioral interventions); and (3) summarize what is known about patterns of identification and treatment for the condition. Factors to be examined include geography, sociodemographics, temporal aspects, and provider

background. This systematic appraisal also identifies gaps in the existing literature that will inform directions for future research. The Key Questions (KQs) are as follows.

KQ1. Among children younger than 6 years of age with ADHD or DBD, what are the effectiveness and adverse event outcomes following treatment?

KQ2. Among people 6 years of age or older with ADHD, what are the effectiveness and adverse event outcomes following 12 months or more of any combination of followup or treatment, including, but not limited to, 12 months or more of continuous treatment?

KQ3. How do (a) underlying prevalence of ADHD and (b) rates of diagnosis (clinical identification) and treatment for ADHD vary by geography, time period, provider type, and sociodemographic characteristics?

Pharmacological Interventions Reported in This Review

We report on the following pharmacological interventions:

Psychostimulants

- Methylphenidate (MPH)
- Dextroamphetamine (DEX)
- Mixed amphetamine salts (MAS)

Selective Norepinephrine reuptake Inhibitor

- Atomoxetine (ATX)

Alpha-2 Agonist

- Guanfacine extended release (GXR)

Nonmedication Interventions Reported in This Review

We report on the following nonmedication interventions:

- **Parent behavior training—**Manualized programs designed to help parents manage a child's problem behavior using rewards and nonpunitive consequences
- **Psychosocial interventions—**Including any one of a number of interventions aimed to assist children and their families through psychological and social therapies (e.g., psychoeducational, parent counseling, and social-skills training)
- **Behavioral interventions—**Manualized programs designed to help adults (parent, teachers, other) using rewards and nonpunitive consequences
- **School-based interventions—**Interventions in which teachers are primary intervenors and where the intervention takes place in a classroom or school setting

Methods

Search Strategy

There is no limit to publication date for studies to be included for KQ1, and the databases were searched from their inception date to May 31, 2010. Studies for KQ2 were limited to

publications from 1997 to 2010 inclusive because the Agency for Healthcare Research and Quality (AHRQ) has already reviewed long-term treatment of ADHD for dates before 1997.[10] For KQ3, publications dated back to 1980 were included.

The following databases were searched for KQ1 and KQ2: MEDLINE®, Cochrane CENTRAL, Embase, PsycInfo, and ERIC (Education Resources Information Center). For KQ3, the Cochrane Library and ERIC database were excluded from the scope of the search because prevalence data were the focus of this question. However, Medline, Embase, and PsycInfo were explored.

Study authors were contacted via email for missing outcome or design data. Reference lists of included papers were screened for possibly relevant papers that had not already been screened. Gray literature, including review data from regulatory agencies such as the Food and Drug Administration, was identified by the AHRQ Scientific Resource Center and searched manually.

Reference lists of studies determined to be eligible at full-text screening were reviewed. Any potentially relevant citations were cross-checked within our citation database, and any references not found within the database were retrieved and screened at full text.

Criteria for Inclusion/Exclusion of Studies in the Review

Target Population

For KQ1, the population includes children younger than 6 years of age with a diagnosis of ADHD or DBD (including ODD and CD) by DSM or ICD criteria. In addition, we included samples in which children showed clinically significant symptoms, defined by referral to treatment or high scores on screening measures.

For KQ2, the population includes people 6 years of age and older who have been diagnosed with ADHD by DSM or ICD criteria and treated for ADHD, or are a control group of people with ADHD.

For KQ3, the population includes people of any age who have been diagnosed with ADHD or treated for ADHD. Because much of the data come from cross-sectional, survey, and medical databases using drug treatments and survey symptom checklists to identify people with ADHD, a DSM or ICD diagnosis is not required for inclusion.

Types of Comparators

We identified and included studies with comparative intervention groups. From a design hierarchy perspective, comparative group designs provide stronger evidence for efficacy and effectiveness than noncomparative designs.

The interventions (either alone or in combination) may be compared with any of the following:

- Placebo
- Same pharmacologic agent of different dose or duration
- Other pharmacologic agent
- Behavioral intervention
- Psychosocial intervention
- Academic intervention
- Any combination of pharmacologic, academic, behavioral, or psychosocial interventions

Outcomes

No limits have been placed on the effectiveness or adverse event outcomes included in this report. Numerical or statistical results of any effectiveness or adverse event outcomes are included. Effect sizes are reported as standardized mean differences (SMDs) whereby the difference in outcome (using continuous measures) between the intervention and comparison groups is divided by the pooled standard deviation to estimate intervention effectiveness. By convention, 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect.[11] The SMD is used as a summary statistic in meta-analysis when the studies use different instruments to measure the same outcome. The data are standardized to a uniform scale before they can be combined. The SMD expresses the size of the intervention effect in each study relative to the variability observed in that study.[12]

Methodology for KQ3

For the prevalence question, we searched the literature and screened the resulting citations up to the full-text examination using systematic review methodology, with question screening and agreement by two raters who used preset inclusion/exclusion criteria for all decisions. All abstracts of the resulting reports were examined, and those that reported data directly addressing prevalence, clinical identification, and treatment of ADHD as specified in KQ3 were selected. The process of external review identified additional references, which were subsequently incorporated into the final document.

Assessment of Methodological Quality of Individual Studies

We interpret methodological quality to include primarily elements of risk of bias (systematic error) related to the design and conduct of the study. We selected the Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies[13] and applied it in KQ1 and KQ2. Studies were reviewed independently by two raters and, where conflicts were unresolved, by a third. No similar tool for evaluating epidemiological and health service studies was used. The process for preparing this report included peer review by experts in the field of inquiry. For KQ3, we included additional studies recommended for inclusion by the reviewers, all of which had been identified in previous steps through the search methodology.

Rating the Body of Evidence

We assessed the overall strength of the body of evidence using the context of the GRADE approach, modified as the Grading System as defined by AHRQ.[14,15] Although we included papers that were not randomized controlled trials, several factors suggested by the GRADE approach may decrease the overall strength of evidence (SOE):

- Study limitations (predominantly risk-of-bias criteria)
- Type of study design (experimental versus observational)
- Consistency of results (degree to which study results for an outcome are similar between studies, that variability is easily explained)
- Directness of the evidence (assessment of whether interventions can be linked directly to the health outcomes)
- Precision (degree of certainty surrounding an effect estimate for a specific outcome)

The ratings were arrived at through discussion among two or more of the investigators. Only papers rated as "good" were included in these analyses, since they represent the best available data at this point in time.

Conclusions

KQ1. Treatment of Preschoolers With Disruptive Behavior Disorders

For the management of preschoolers with disruptive behavior disorders, including children considered to be at risk for ADHD, we found evidence pertaining to two broad categories of treatment: behavioral interventions and psychostimulant medication. We pooled results for eight good-quality studies to evaluate the effect of parent behavior training (PBT) on child disruptive behavior in preschoolers (SMD = -0.68; 95% CI, 0.88 to -0.47). See Figure A. By analogy, we used the single good-quality study of the effectiveness of methylphenidate on child behavior in preschoolers (SMD = -0.83; 95% CI, -1.21 to -0.44). Both interventions appear to be effective. The SOE for use of PBT was judged high due to number of studies and consistency of results. The SOE for methylphenidate was judged low because there is only one good-quality study.

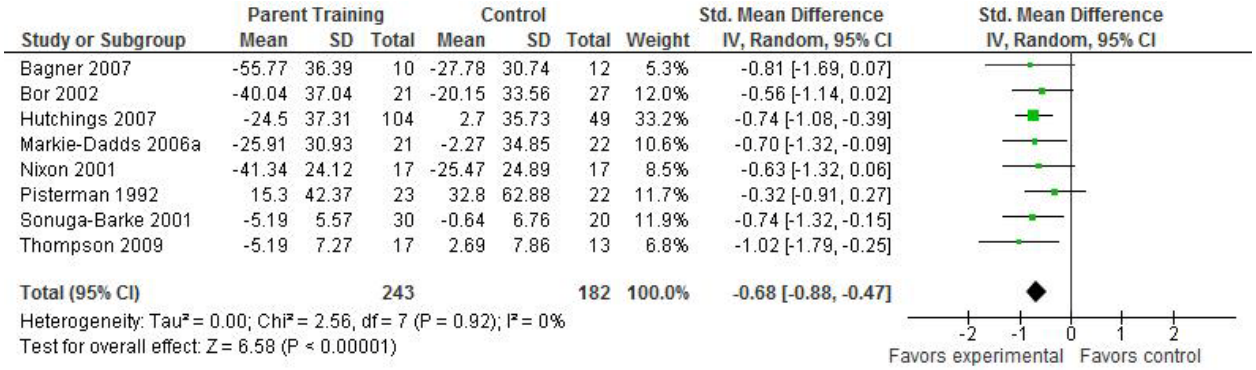
Very few randomized controlled trials (RCTs) offer information about PBT interventions designed specifically for preschoolers with ADHD. There are primarily four standardized programs of behavior training interventions for parents of preschoolers with DBD that have been developed by separate research groups in the past 25 years. While each program has its own specific features, the Triple P (Positive Parenting of Preschoolers program),[16-22] Incredible Years Parenting Program,[23-27] Parent-Child Interaction Therapy,[28-35] and New Forest Parenting Program[36-39] share common therapeutic components and are documented in manuals to ensure intervention integrity when disseminated. These programs are designed to help parents manage their child's problem behavior with more effective discipline strategies using rewards and nonpunitive consequences. An important aspect of each is to promote a positive and caring relationship between parents and their child. Primary outcomes are improved child behavior and improved parenting skills. Each program also includes educational components regarding childhood behavior problems and common developmental issues. Programs may include coaching or consultation to support parents' efforts. The New Forest Parenting Program was specifically designed to address ADHD symptoms.

Twenty-eight RCTs show that PBT is an efficacious treatment for preschoolers with DBD; eight of these studies documented improvement specifically in ADHD symptoms. These meta-analyses confirm that long-term extension (followup) studies for the RCTs of PBT suggest that the benefits are maintained for several years. However, no long-term study (lasting 12 months or more) of PBT alone included untreated comparison groups, and attrition was high, from 24 percent at 18 months to 54 percent at 3 to 6 years, limiting interpretation of the results. A recent study examining PBT with and without school-based teacher or child interventions included a no-treatment control. This study showed maintenance of benefits of PBT at 2 years.[40] Studies do not comment on adverse events related to PBT.

Meta-analyses were performed to evaluate the overall strength of effect of PBT interventions on disruptive behavior, including ADHD, in preschoolers and on parent sense of competence. These meta-analyses confirmed that PBT improves parent-rated child behavior as well as parent-rated confidence in parenting skills. The SMD for PBT on child behavior was not significantly

different, although slightly increased, when three studies with "fair" internal validity were included in the analysis (SMD = -0.76; 95% CI, -0.95 to -0.57).

Figure A. Effect of PBT on preschool child behavior outcomes (eight "good" studies)



Note: Includes RCTs rated as "good" quality (assumes correlation between postscore and prescore of 0.3). *Means* are post/pre differences; *standard mean difference* reflects the difference of these differences.
CI = confidence interval; df = degrees of freedom; IV = ; PBT = parent behavior training; RCT = randomized controlled trial; SD = standard deviation.

Studies:

Bagner DM, Eyberg SM. Parent-child interaction therapy for disruptive behavior in children with mental retardation: a randomized controlled trial. J Clin Child Adolesc Psychol 2007;36(3):418-29.
Bor W, Sanders MR, Markie-Dadds C. The effects of the Triple P-Positive Parenting Program on preschool children with co-occurring disruptive behavior and attentional/hyperactive difficulties. J Abnorm Child Psychol 2002;30(6):571-87.
Hutchings J, Gardner F, Bywater T, et al. Parenting intervention in Sure Start services for children at risk of developing conduct disorder: pragmatic randomised controlled trial. BMJ 2007;334(7595):678.
Markie-Dadds C, Sanders MR. Self-directed Triple P (Positive Parenting Program) for mothers with children at-risk of developing conduct problems. Behav Cogn Psychother 2006;34(3):259-75.
Nixon RDV. Changes in hyperactivity and temperament in behaviourally disturbed preschoolers after parent-child interaction therapy (PCIT). Behav Change 2001;18(3):168-76.
Pisterman S, Firestone P, McGrath P, et al. The role of parent training in treatment of preschoolers with ADDH. Am J Orthopsychiatry 1992;62(3):397-408.
Sonuga-Barke EJ, Daley D, Thompson M, et al. Parent-based therapies for preschool attention-deficit/hyperactivity disorder: a randomized, controlled trial with a community sample. J Am Acad Child Adolesc Psychiatry 2001;40(4):402-8.
Thompson MJJ, Laver-Bradbury C, Ayres M, et al. A small-scale randomized controlled trial of the revised new forest parenting programme for preschoolers with attention deficit hyperactivity disorder. Eur Child Adolesc Psychiatry 2009;18(10):605-16.

Five studies examining combinations of PBT and school or daycare interventions for preschool children at risk for DBD and/or ADHD suggest that adding classroom teacher consultation may be important for children in low socioeconomic status (SES) communities, but not for families with educated parents who live in communities with resources. Three of these five studies followed children for 12 months, while the other two assessed children following completion of the initial kindergarten year and at a 2-year followup. Without reinforcement, benefits of the kindergarten treatment classroom disappeared at 2 years. Direct comparisons of identical interventions offered to families of different SES have not yet been performed.

An additional two studies[41,42] examined PBT with specific teacher behavior training and child training as combination interventions, with children in a no-treatment condition for 8 months (on a wait list) used as the comparison. All behavioral interventions showed benefits relative to no-treatment controls. A dose response to the number of PBT sessions attended by

parents was also identified.[41] These two additional pieces of evidence (that benefits of PBT compared to no treatment are maintained for 8 months or more and that the effect on child behavior improvement is greater when the parent attends more PBT sessions) both enhance the overall SOE for effectiveness of PBT.

Fifteen reports representing 11 investigations of psychostimulant medication use in preschoolers, primarily immediate release MPH, suggest that it is efficacious and safe; however, the evidence comes primarily from short-term trials lasting days to weeks with small samples.[7,43-56] The Preschool ADHD Treatment Study (PATS)[7,51-54] addresses a number of important methodological limitations and clinical concerns, examining the potential additional benefit of optimized dose of immediate release MPH for 4 weeks following a series of 10 PBT sessions. As above, the PATS study suggests that MPH is effective for improving parent-rated child behavior in preschoolers. The SMD for pharmacological intervention was essentially the same when two RCTs[47,48] evaluating MPH that were judged to be of "fair" quality were included with the PATS study in a meta-analysis.

In the intervention studies for preschoolers, adverse events were documented for medication interventions, as described above, but not for PBT or school-based interventions. Careful attention to details regarding adverse events and their impact on medication adherence offers clear information about long-term (up to 10 months) effectiveness and safety in this age group. Parent- and teacher-reported ADHD symptoms improved concurrently with parents' noting increased mood problems.[7] The PATS study offers information about both the potential benefits and limitations of stimulant medication use in very young children. Limitations include the following: preschool children experience more dose-related adverse events than older children, stimulants interfere with rates of growth,[53] and the presence of three or more comorbid conditions and psychosocial adversity are associated with lessened effectiveness of psychostimulant medication following PBT.[52] Only 60 percent of those enrolled in the study entered the open-label medication titration component following PBT. Following medication titration and the RCT phase, approximately 46 percent continued in the 10-month open-label extension phase, suggesting that even under ideal clinical monitoring conditions, concerns about tolerability and parent preferences play an important role in providing optimum care for young children with ADHD. Long-term extension studies following children after PBT are few; however, RCTs comparing PBT, teacher training, child training, and combinations of the above demonstrate that benefits following PBT, and combined parent and teacher training, are present at 1 year postintervention.[41,42] Some, but not all, studies show maintenance of benefits at 2 years; greater improvement and maintenance of improvement is more likely when parents participate in a greater number of PBT sessions. In the studies lasting up to 2 years, some children received nonprotocol co-interventions of medication. To date, no studies have examined the benefits of combining PBT and psychostimulant medication.

Our results using the GRADE approach to assign SOE are summarized in Table A. The SMD for behavior improvement is -0.68 (95% CI, -0.88 to -0.47). The SMD for behavior improvement following MPH intervention in the PATS study is of similar size but greater variability, -0.83 (95% CI, -1.21 to -0.44). There are important differences in the goals of the interventions, as PBT most often targets a range of disruptive behavior whereas the PATS study targeted ADHD behaviors. Both interventions are effective, with no adverse events reported for PBT, while there are adverse effects with MPH. This favors the use of PBT for preschoolers at risk for ADHD due to disruptive behavior. A direct comparison has not yet been done.

KQ2. Long-Term Effectiveness and Safety of Interventions in People Age 6 and Older

Pharmacologic Agents

The body of literature examining long-term effectiveness and safety is most robust among samples of children ages 6–12 years at recruitment, mostly boys with ADHD, combined subtype (ADHD-C), and for studies examining pharmacotherapeutic interventions for the core symptoms of ADHD. Studies evaluating long-term outcomes in children younger than 6 years of age were discussed in the results for KQ1 of this review. This section summarizes details from studies of pharmacologic agents.

The long-term effectiveness and safety of several psychostimulants (e.g., MPH immediate release amphetamine [MPH-IR], OROS MPH [Osmotic-controlled Release Oral delivery System methylphenidate], DEX, MAS, and sequential combinations of psychostimulants), the norepinephrine reuptake inhibitor ATX, and the noradrenergic agonists clonidine and GXR have been examined prospectively in children and adolescents age 6 and over. One cohort describes psychostimulants without distinguishing between MPH and DEX agents,[57,58] while other reports describe amphetamine, MPH-IR, DEX, MAS, and OROS MPH.[58-65] Four reports describe cohorts of participants in trials of the norepinephrine reuptake inhibitor ATX;[66-69] one of these is an extension of clinical trials in adults. Two reports focus on the safety and continued efficacy of the noradrenergic agonist GXR.[70,71] Three additional RCTs compare MPH with the combination of MPH and psychosocial and/or behavioral interventions lasting 14 months to 2 years.[72-77] One of these, the Multimodal Treatment of ADHD Study (the MTA Study), also compared medication management of MPH to psychosocial and behavioral intervention alone and to a community control group. Twelve of 21 clinical trials or extension studies reviewed were funded wholly or in part by industry. The agents examined were all shown to be efficacious for control of inattention, overactivity, and impulsiveness for at least 12 months and up to 3 years, and few serious adverse events were noted, although GXR appears to be less well tolerated than other agents examined. Global ratings of impairment also indicate continued benefit throughout the extension studies for patients still receiving medications. Placebo-controlled discontinuation trials, where patients receiving treatment are allocated to continue or to stop treatment, are few; one trial discontinued treatment with amphetamine after 15 months, another discontinued MPH following 12 months and compared these participants with those in an ongoing psychosocial intervention,[75] and another examined relapse in children receiving ATX for 12 months. Attrition from the trials occurs for a variety of reasons, including adverse events and ineffectiveness. Retention of participants on active treatment at 12 months varies across studies and agents, from a high of 98 percent for MPH-IR to 75 percent for amphetamine, 63 percent for OROS MPH, 58 percent for MAS XR (extended release), 56 percent for ATX, and 43 percent for GXR. In general, those who remain on medication show continued benefit, and few adverse events are reported for them. With a majority of the studies funded by industry, there may be enhanced representations of effectiveness and safety.

Psychostimulants continue to provide control of ADHD symptoms and are well tolerated for months to years at a time. The MTA study clearly demonstrates that MPH improved ADHD symptoms and overall functioning alone or in combination with psychosocial/behavioral interventions for 14 months[74] and up to 24 months.[73,76] In the MTA study, the SMD for improved symptoms following 14 months of medication management is −0.54 (95% CI, −0.79 to −0.29) and is −0.70 (95% CI, −0.95 to −0.46) for 14 months of combined medication and

psychosocial/behavioral interventions. Overall, few available studies make direct comparisons of long-term outcomes of psychostimulants. Barbaresi et al.[59] compare MPH and DEX use in a population-based retrospective cohort of boys and girls followed from birth to late adolescence. The mean duration of treatment for any single agent was 3.5 years ± 3.1 years. The youngest and oldest children in the study showed less benefit and more adverse effects. More boys than girls showed a positive response to DEX. Fewer children experienced adverse events with MPH than with DEX. Concerns about adverse events led to discontinuation of medications for 15 to 20 percent of children age 6 and over using MAS XR.[63,65] Concerns about exacerbation of tics with stimulants appear to be unfounded, although the sample size remains small and may result in type II error.[58,62] Use of psychostimulants slows the rate of growth, and increases blood pressure and heart rate to a small degree.[53,57,62,64,65,78]At a group level, the mean changes are clinically insignificant, although on rare occasions individuals discontinue an agent because of changes in vital signs.[65]

Overall, the benefits and safety of MPH for symptom control and general functioning are clearly documented, primarily for boys ages 7-9 years at initiation with ADHD-C. There are many similarities between MPH immediate release and other preparations of psychostimulants, both in terms of efficacy and in the side effect profile. Therefore, many researchers and clinicians assume all psychostimulants are effective and safe for extended periods of time. The documentation for this assertion is not yet robust.

Atomoxetine is both safe and effective for ADHD symptoms over 12 to 18 months among children and for up to 3 years in adults. Unlike studies of other agents, two studies offer direct comparison with placebo for examination of relapse prevention, offering clear evidence of effectiveness in children and teens.[66,67] Buitelaar et al.[67] demonstrated improved symptoms following 12 months of ATX, with SMD of -0.40 (95%, -0.61 to -0.18). However, teacher-reported outcomes do not document a statistically significant superiority of ATX over placebo after 1 year of treatment, as children randomized to placebo also maintained benefits to some degree following the clinical trial. The study set a high threshold for relapse (i.e., a return to 90 percent of baseline symptom score), and in this context, the vast majority of those on ATX (97.5 percent) as well as those on placebo (88 percent) did not relapse.[67] Discontinuation in children and teens appears to be higher (26 percent) due to ineffectiveness and lower (3 percent) due to adverse events than with other agents, although these are not direct comparisons.[67] These findings are consistent with those from an RCT lasting less than 12 months showing that ATX is less effective than OROS MPH for ADHD symptoms.[79] As with psychostimulants, the group means for blood pressure and heart rate show small but clinically insignificant increases.[68,69] Adler et al. offer the only study of a pharmacologic intervention over an extended time period (3 years) in adults with ADHD.[68] Symptom improvement was maintained for those on ATX, and discontinuation due to adverse events was somewhat higher for adults (11 percent) than for children (3 percent).

An extension study of guanfacine suggests that this agent is also effective in controlling ADHD symptoms for up to 2 years; however, high rates (40 to 60 percent) of somnolence, headache, and fatigue occur when it is used as a monotherapy, especially in the initial 6 to 8 months of treatment.[70] A second study examined concurrent use of psychostimulants and noted improved tolerance to these adverse effects.[71] Changes in vital signs occur, but no clear group trends are noted. Individuals may develop clinically significant hypotension and bradycardia.[70,71] Serious adverse events noted include syncope, and 1 percent of participants developed clinically significant changes on electrocardiogram (ECG), such as asymptomatic bradycardia. As GXR has not been available as long as ATX, conclusions as to its general usefulness are premature.

The clinically significant ECG changes noted in 1 percent of children may warrant increased cardiac monitoring for this agent.

Overall, pharmacologic agents used for controlling the symptoms of inattention, overactivity, and impulsivity of ADHD show maintenance of effectiveness and safety for 12 to 24 months. Following that, attrition from use interferes with the ability to draw conclusions. Along with decreased symptoms, overall functioning is improved, although studies do not control for adjunctive nonpharmacological interventions. A byproduct of the placebo-controlled relapse prevention studies has been the opportunity to collect long-term comparison data suggesting that some children show maintenance of gains on placebo, which may indicate that maturation may also be contributing to benefits seen when young people remain on medications for several years. The majority of children who participate in the trials of newer agents are school-aged boys with ADHD-C and few comorbid conditions.

Psychosocial and Behavioral Interventions, Alone and in Combination With Medication

Investigations comparing psychosocial/behavioral interventions, alone and in combination with psychostimulant medication management, showed that both medication and combined medication/behavioral treatment are more effective in treating ADHD and ODD symptoms than psychosocial or behavioral interventions alone.[72-76] These results apply to children, primarily boys ages 7–9 years of normal intelligence with ADHD-C, especially during the first 2 years of treatment. The combination of psychosocial and behavioral treatment with medication may have a slight advantage during the first 14 months (SMD = -0.70; 95% CI, -0.95 to -0.46), especially for children with multiple comorbidities.[80] However, combined treatment is equivalent to medication alone in controlling ADHD and ODD symptoms for up to 2 years if the child shows an early favorable response to medication.[76]

Longer Term Outcomes

Evaluation of long-term outcomes following interventions for ADHD is complex due to multiple patterns of services used and very few studies available, with only two RCTs of well-characterized clinical samples, both of boys ages 7–9 years with DSM-IV ADHD-C. The best quality data come from the MTA study, with publications about outcomes at 14 months (the length of the initial RCT), 24 months, and 3 years, and a publication regarding 6- and 8-year followup data.[73,74,81,82] The initial RCT compared 14 months of management with MPH-IR to three other interventions: psychosocial and behavioral treatment; the combination of medication management and psychosocial and behavioral treatment; and standard community care. Three years after initiation, the four intervention groups showed comparable outcomes. The majority of ADHD children who received interventions were maintaining improved functioning, although they did not match the functional levels of the non-ADHD comparison group. A small proportion returned to previous levels of poor functioning over time.[83]

In the MTA trial, no clear relationship was identified between duration of medication use and psychiatric or overall functional outcomes at 3 years or beyond.[82,84] In contrast, a few long-term cohort studies lasting 5 years or more suggest that increased duration of medication was associated with improved grade retention and academic achievement, and may also lessen onset of substance use disorders as well as ODD, conduct, anxiety, and depressive disorders.[85-88] These cohort studies provide longer duration of followup into late adolescence and adulthood, but most rely on participant recall to provide information regarding medication use, except for one that used linked administrative, clinical, and educational data to examine a birth cohort.[87] No

prospective studies have been designed to investigate the question of long-term functional outcomes directly.

Very few studies describe long-term outcomes of treatments for ADHD on academic or school-based outcomes. There appear to be long-term academic benefits with medication interventions in some domains (e.g., improved absenteeism and grade retention).[85,86] Combining psychosocial/behavioral and academic skills interventions with medication offers no additional gains over medication alone, at least for children with ADHD without comorbid learning disabilities.[89] The psychosocial/behavioral intervention in the MTA study included a home and school focus on homework that successfully improved homework completion for up to 2 years.[90] Interventions directed at academic skills in classroom-based programs result in academic enhancement in a range of areas, but sustained intervention is required to provide continued academic growth over time.[91,92]

The types of interventions and domains of academic functioning and school outcomes under investigation vary widely across studies, making it difficult to compare results. In addition, few of the studies controlled for child characteristics such as learning disabilities and overall intellectual abilities. Additional aspects to consider are the challenges inherent in examining the multiple co-interventions offered in home, school, and clinic settings over extended lengths of time.

Our results using the GRADE approach to assign SOE are summarized in Table B. The evidence for long-term effectiveness of pharmacologic agents for improving ADHD symptoms is based on a single good study for methylphenidate with SMD = −0.54 (95% CI, −0.79 to −0.29) and a single good study for atomoxetine with SMD = −0.40 (95% CI, −0.61 to −0.18). These studies followed the children for 12 or 14 months and showed benefit with few adverse effects, thereby resulting in low strength of evidence for longer term effectiveness for each of these agents. Similarly, there is a single good study showing benefits for the combination of methylphenidate and psychosocial interventions, with SMD = −0.70 (95% CI, −0.95 to −0.46). Overall there is insufficient information to comment on longer term outcomes for ADHD symptoms following behavior training for children, or for parents, or for academic interventions.

KQ3. Variability in Prevalence, Diagnosis, and Treatment

One worldwide pooled prevalence estimate of ADHD among those 18 years of age or younger is 5.29 percent (95% CI, 5.01 to 5.56), although the percentage use of stimulants in the United States in selected subsets (e.g., Medicaid recipients) exceeds this rate.[93] More boys than girls have ADHD, and children in the age group 5–10 years show the highest prevalence. In addition, some studies suggest children from lower SES demonstrate higher levels of symptoms. Research detailing prevalence in other age groups worldwide is generally lacking, with few studies examining prevalence among preschoolers, adolescents, or adults. Primary sources of variability among studies were diagnostic criteria and informant. Table C summarizes information regarding the underlying prevalence of ADHD, rates of diagnosis and treatment by geography, time period, provider type, and sociodemographic characteristics.

Clinical identification of ADHD and treatment with psychostimulants increased throughout the early 1960s to mid-1990s in North America, and use of ADHD medications of various types has continued to grow.[94-96] Changing patterns of ADHD medication use suggest increases among girls and adolescents. While at much lower rates, medication use (frequently off label) has also increased among preschoolers.[97] Agents prescribed have changed from short-acting preparations of stimulants to long-acting formulations.[98] Disparities occur among those who are identified and

receive medication. Studies in the United States document that more boys than girls, more whites than Hispanics or African Americans, more children living in prosperous than less affluent communities, and more children living in urban than rural centers are dispensed medication.[99-102] Regional variations occur both within and outside the United States. More children in the Midwest and South receive diagnoses and ADHD medications relative to the western United States. More people in the United States receive medications than in Europe and the rest of the world.[98,103] Not surprisingly, the source of data influences these findings. Epidemiological surveys with parents suggest a smaller increase in medication use than is indicated by insurance claims and Medicaid data sources. In addition, Medicaid data sources document that only about half those identified receive medication treatment.[104] Prescription data show that many who fill an initial prescription do not continue using medication for long periods of time, especially among low-income and ethnic minority youths.[105,106] Clinical identification by nonphysicians and nonmedication interventions for ADHD were not captured in the sources of data used. Assessing possible interactions among various factors that appear to affect patterns of diagnosis and treatment (e.g., region by time period by provider type) would be informative but is beyond the scope of this review.

Concerns regarding inaccurate identification of children and youths with ADHD in the community appear to be justified. However, the current review should be seen as preliminary, as the data to answer service use questions are incomplete and primarily reflect services available through the health sector. Some of the increased identification and treatment likely reflect acknowledgment of the disorder in children and youths who were previously undiagnosed and untreated. On the other hand, prescriptions, as captured in databases collected for insurance claims, may reflect physicians' responding to concerns raised by parents and teachers. When lack of clinical certainty exists and the intervention is relatively quick and safe, a doctor may easily respond to a request for help on an individual level with "try this and see if it helps." Studies based on epidemiological surveys rather than health insurance claims suggest a more gradual rise in identification and prescription treatment. Since children and youths with ADHD also can receive interventions at school and through mental health centers, the patterns observed may reflect reliance on physician services by those who lack access to other alternatives. The differential changes over time in ADHD diagnoses and prescription treatments among regions of the United States, or between the United States and Europe, also reflect cultural differences in beliefs and attitudes about the disorder and how it should be treated.

Table A. KQ1: Effectiveness of interventions for ADHD and DBD in children younger than 6 years of age

Intervention	Level of Evidence	Conclusion
Parent Behavior Training	SOE: High SMD: -0.68 (95% CI, -0.88 to -0.47)	Parent behavioral interventions are an efficacious treatment option for preschoolers with DBD and show benefit for ADHD symptoms. These studies support the long-term effectiveness of parent interventions for preschoolers with DBD, including ADHD symptoms, with evidence that benefits are maintained for up to 2 years. There also appears to be a dose-response effect.
Multicomponent Home and School or Daycare-Based Interventions	SOE: Insufficient	Evidence is drawn from few reports. Where there is no socioeconomic burden, multicomponent interventions work as well as a structured parent education program in several domains. Where there is socioeconomic burden, the treatment classroom appears to be the primary beneficial intervention, and this appears to be related to lack of parent engagement and attendance at PBT sessions. Relative benefits of the school-based intervention diminished over 2 years.
Medication (MPH Only)	SOE: Low SMD: -0.83 (95% CI, -1.21 to -0.44)	With evidence drawn primarily from the PATS study, MPH (e.g., short-acting, immediate-release MPH) is both efficacious and generally safe for treatment of ADHD symptoms, but there has been no long-term followup in preschoolers.

Note: ADHD = attention deficit hyperactivity disorder; CI = confidence interval; DBD = disruptive behavior disorder; KQ = Key Question; MPH = methylphenidate; PATS = Preschool ADHD Treatment Study; PBT = parent behavior training; SMD = standardized mean difference; SOE = strength of evidence.

Table B. KQ2: Long-term (>1 year) effectiveness of interventions for ADHD in people 6 years and older

Intervention	Level of Evidence	Conclusion
Medication Treatment	SOE: Low MPH: SMD: -0.54 (95% CI, -0.79 to -0.29) ATX: SMD: -0.40 (95% CI, -0.61 to -0.18)	Very few studies include untreated controls. Studies were largely funded by industry. Psychostimulants continue to provide control of ADHD symptoms and are generally well tolerated for months to years at a time. The evidence for MPH use in the context of careful medication monitoring shows good evidence for benefits for symptoms for 14 months. ATX is effective for ADHD symptoms and well tolerated over 12 months.
	SOE: Insufficient	Only one study of GXR monotherapy is available. It reports reduced ADHD symptoms and global improvement, although less than a fifth of participants completed 12 months. Monitoring of cardiac status may be indicated since approximately 1% of participants showed ECG changes judged clinically significant.
Combined Psychostimulant Medication and Behavioral Treatment	SOE: Low SMD: -0.70 (95% CI, -0.95 to -0.46)	The results from 2 cohorts indicate both medication (MPH) and combined medication and behavioral treatment are effective in treating ADHD plus ODD symptoms in children, primarily boys ages 7-9 years of normal intelligence with combined type of ADHD, especially during the first 2 years of treatment. Several reports from one high-quality study suggest that combined medication and behavioral treatment improves outcomes more than medication alone for some subgroups of children with ADHD combined type and for some outcomes.
Behavioral/ Psychosocial	SOE: Insufficient	There is not enough evidence to draw conclusions for persons 6 years and older with a diagnosis of ADHD.
Parent Behavior Training	SOE: Insufficient	There is not enough evidence to draw conclusions for persons 6 years and older with a diagnosis of ADHD.
Academic Interventions	SOE: Insufficient	One good-quality study and its extension showed that classroom-based programs to enhance academic skills are effective in improving achievement scores in multiple domains, but following discontinuation, the benefits for sustained growth in academic skills are limited to the domain of reading fluency. All other domains show skill maintenance but not continued growth.

Note: ADHD = attention deficit hyperactivity disorder; ATX = atomoxetine; ECG = electrocardiogram; GXR = guanfacine extended release; KQ = Key Question; MPH = methylphenidate; ODD = oppositional defiant disorder; SMD = standardized mean difference; SOE = strength of evidence.

Table C. KQ3: Underlying prevalence of ADHD, rates of diagnosis, and treatment by geography, time period, provider type, and sociodemographic characteristics

Issue	Factor	Conclusion
Prevalence	Geography	Context and cultural overlay influence how ADHD is understood from country to country, and thus how it is treated. Underlying prevalence does not appear to vary much between nations and regions, once differences in methodologies for ascertainment are taken into account
	Time period	Since identified as a clinical entity in 1902 in the context of mandatory education, prevalence of cases identified has increased. Some proportion of this secular trend is due to refinement of the state of knowledge, as well as changes in definition of acceptable informant, uses of screening tests, and changes in classification systems and diagnostic categories over time. In addition, patterns of access and location of service have been used to document prevalence.
	SES	Some studies suggest that those of lower SES have a higher prevalence of ADHD, although those of higher SES are more likely to be treated.
	Sex	Most studies illustrate a sex difference in the prevalence of ADHD (males > females).
	Age	The age group ≈5-10 years appears to experience the highest prevalence. ADHD research detailing prevalence in adults is lacking
Clinical Identification	**Service provider**	**Appreciation of the combined neurodevelopmental and environmental etiologies and magnitude of impairment due to the condition has increased over the past 4 decades.** Providers vary in level of expertise in diagnosis of ADHD, as well as in familiarity with screening instruments and classification systems
	Location	Rates of diagnosis vary considerably due to cultural context, access to health care services, and provider type. Significant regional variations are noted within the United States. Prevalence is reported to average 7.8%, with variability from 5.0% in Colorado to 11.1% in Alabama. In special populations, such as the incarcerated, rates as high as 25.5% have been noted.[107]
	Informant	Parent and teacher observations have been accepted by some researchers in population studies in lieu of clinician diagnosis. The NSCH[4] accepted a positive response from the primary caretaker to the question, *"Has a doctor or health professional ever told you that [child name] has … ADD or ADHD?"* to estimate ADHD prevalence in 2003. Rates of diagnosis vary considerably due to cultural context. Some ethnicities are more likely to seek help or accept the diagnosis than others.
	Sex	Boys are identified as having ADHD more frequently than girls.
	Age	Primary school–age children are identified as having ADHD more frequently than older children. Formerly thought to disappear in adulthood, it is now recognized that ADHD may persist throughout the lifespan.

Table C. KQ3: Underlying prevalence of ADHD, rates of diagnosis, and treatment by geography, time period, provider type, and sociodemographic characteristics (continued)

Issue	Factor	Conclusion
Treatment	Location	Rates of treatment vary considerably due to location and access to providers of health care services, internationally as well as regionally or even within the same community, dependent on provider type and availability, provider remuneration, and insurance status of patient.
	Provider	Family practitioners in many jurisdictions, particularly those with limited access to specialists, report significant pressure from parents and teachers to prescribe stimulant medications.
	Informant	The sociocultural experience of the parent or teacher informant may influence interpretation and reporting of behaviors, willingness and persistence in seeking professional help, and/or the acceptance of treatment. Accuracy and completeness of data influence prevalence estimates, as health insurance and prescription administrative databases suggest greater increase in treatment with medications over time than repeated community surveys do.
	Time	The rate of psychostimulant medication has increased over the past 3 decades. More recent statistics from the International Narcotics Control Board, using a denominator of standardized defined daily doses, reports that medical use of MPH (i.e., Ritalin) in the United States has increased from 7.14 S-DDDs per 1,000 inhabitants per day in 2004 to 12.03 S-DDDs per 1,000 inhabitants per day in 2008.[6]
	SES	Children of lower SES are identified as having ADHD more often than children of higher SES; however, the latter are more likely to receive stimulant medications. Lower SES and minority ethnicity are associated with shorter duration of medication use. Insurance status may influence access to specialist providers in the United States.
	Sex	Only sparse comparative data are available examining rates of treatment by sex once ADHD is diagnosed.
	Age	Medication treatment prevalence is higher for primary school–age children than for adolescents or adults.

Note: ADD = attention deficit disorder; ADHD = attention deficit hyperactivity disorder; KQ = Key Question; MPH = methylphenidate; NSCH = National Survey of Children's Health; S-DDD = standardized defined daily dose; SES = socioeconomic status.

Remaining Issues

Since the AHRQ review of long-term intervention studies for ADHD, published in 1997, researchers have sought opportunities to discover what has happened to the participants in earlier studies and have begun to tackle the challenges of prospective cohort studies. The primary weaknesses reflected in the literature relate to these challenges. Overall, data were difficult to compare due to lack of clarity with regard to uniformity of assessment and reporting, as well as inconsistencies in study design and the development of objective outcomes. For interventions for preschoolers with DBD, a primary challenge is distinguishing the overlying effect of normal maturation from the clinical condition; few extended studies encompass untreated comparison

groups and these studies are of more complex combinations of parent, teacher, and child behavior training interventions. Only recently have investigations of PBT included direct measures of ADHD symptoms and associated functional impairments. Researchers also should describe what, if any, unintended negative consequences occur when families are offered PBT for their preschooler. For example, some parents may respond better to individual rather than group PBT sessions, and some children with comorbid developmental disorders may not respond to standard behavioral interventions. Documenting what works best for whom is an important next step in describing the overall effectiveness of the intervention.

A second important finding follows the suggestive outcome that parents from different SES groups appear to benefit from different approaches. An important subtext is the question of how approaches to PBT could be refined to be acceptable to lower SES families, as well as examining the mix of parent, teacher, and child approaches both at home and at school. Further studies examining a range of child functional outcomes are important as well. Remaining untapped as a source of information is the likelihood that "care as usual" varies in different communities, leading to diverse outcomes in comparison groups.

The lack of research in adolescents and adults with ADHD presents a major gap in the literature. Also, few study participants are girls or come from diverse racial or ethnic groups. Studies have not included subgroup analyses for those with ADHD inattentive subtype, comorbid anxiety, or learning disorders. No clinical studies have been designed to follow children through adolescence and into adulthood, tracking the mix of interventions obtained by participants and their functional outcomes. It will be particularly challenging to coordinate observations regarding academic interventions and outcomes. No prospective studies examining nonmedication interventions have enrolled adolescents or adults identified with ADHD to investigate whether interventions at later stages of development are effective for improving function.

An important strength of research in the past decade is evidence for effective and safe medications for children, youths, and adults with ADHD. There are several documented pharmacological agents that control symptoms for 1 to 2 years. The choices help to optimize effectiveness and tolerability over this time period. Beyond 2 years, benefit appears to be highly variable. Evidence now suggests that some children experience mild decrements in their growth rate while on psychostimulants. While these are considered of little clinical significance, it is not clear if these changes may also represent potential nutritional or developmental concerns that are not yet recognized.

An opportunity and a challenge for this review was integrating information from clinical trials research with the broad picture provided by newly emerging research using a variety of large-scale databases reflecting community access to health services and use of pharmacological agents. Some of the administrative data sources were useful to explore rare but potentially serious adverse events following use of ADHD medications. On this topic, health administrative data suggest that neither cardiac events among those aged 20 years and younger nor cerebrovascular accidents in adults are more frequent among those using medications for ADHD than for persons in the general population. However, further examination using appropriate data sources (e.g., case control studies) is warranted, as adult users of psychostimulants or ATX may be at increased risk of transient ischemic attacks.

Our final question focused on the match between community prevalence of ADHD and rates of identification and treatment of the disorder. The complex issues of mental health service delivery are superimposed on the underlying sociocultural mix of beliefs about ADHD as a

health disorder and attitudes toward use of medication. While recognized as the standard for effectiveness research, clinical trials are nonetheless limited to relying on volunteer participants who are then carefully selected as pure examples of a condition and provided with a carefully controlled intervention. Epidemiological survey methods offer information on risk and protective factors in large populations but still rely on volunteers to provide information, and in that way underrepresent marginalized or transient segments of the population. The way diagnoses and interventions are actually used in day-to-day clinical practice in the community is rarely so precise or carefully controlled.

In the past two decades, increased technological advances have allowed research using existing administrative data to represent clinical practice. Insurance claims and prescription databases have become important complementary sources of health services information to investigate questions about ADHD identification and treatment in actual practice. The key limitations in this body of literature are the use of data collected for the purpose of justifying health services, the lack of quality control regarding reliability and validity of measures, and the selective nature of clinical services captured, almost exclusively pharmacological interventions. On the other hand, the size and representativeness of the sample populations offer compensatory advantages and strongly suggest that many children and youths are diagnosed who then receive suboptimal care. There appears to be little research documenting nonpharmacological interventions or educational services use for those with ADHD, which reflects a lack of infrastructure for linkage among data sources across health, education, and specialty care systems. Better synchronization of information across these complementary domains would promote population-based research and improved services delivery for ADHD.

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Introduction

Historical Background

Children with Attention Deficit Hyperactivity Disorder (ADHD), a condition characterized by inattention, overactivity, and impulsivity, are most frequently identified and treated in primary school. Population studies indicate that five percent of children worldwide show impaired levels of attention, as well as hyperactivity. Boys are classified with ADHD approximately twice as frequently as girls and primary school age children approximately twice as frequently as adolescents. ADHD symptoms exist on a continuum in the general population, and are considered as a 'disorder' to a greater or lesser degree depending on the source of identification, (e.g., parent or teacher), perception of extent of functional impairment, diagnostic criteria, and the threshold chosen for defining a 'case.' The developmentally excessive levels of inattention, overactivity, and impulsivity characteristic of ADHD are present from an early age. However, preschoolers with early signs of ADHD may also have co-occurring oppositional noncompliant behaviors, temper tantrums, and aggression that overshadow symptoms of inattention and overactivity and confound the diagnosis. These behaviors may be given the more general label of a Disruptive Behavior Disorder (DBD), which include Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) as well as ADHD. If not already identified by an early age, preschool youngsters with ODD frequently meet criteria for ADHD by grade school.

Key Question 3 will address issues which influence our understanding of prevalence; at this point we include a brief, necessarily truncated, history, with a somewhat expanded timeline of relevant events in Table 14.

Although anecdotally and in stories characters with ADHD-like behaviors are described much earlier, the first clinical description of the syndrome was presented by Sir George Frederick Still in 1902.[1] In a series of lectures subsequently published in The Lancet, he describes children, more often boys than girls, who display 'an abnormal capacity for sustained attention causing school failure, even in the absence of intellectual retardation'. He provides virtually a textbook description of ADHD children: his assessment and interpretations perhaps influenced and obscured slightly with other conditions now categorized separately and, in keeping with the understanding of the times, attributed to "defects of moral control." He presents his observations of these children under different social conditions and environments, and enlarges on the limitations and impairments they experience as a result.

Since, discoveries usually occur in a larger social context, however, it cannot be coincidence that this constellation of behaviors was thrown into sharp relief within a generation of the passing of The Educational Act (1876), which mandated elementary education for all children. It is in the context of this structured environment that even today, for many children, attentional difficulties are defined.[2]

Observing that the sequelae in some survivors of the Spanish influenza epidemic included agitation, in 1922, Tredgold postulated the source of what we now term ADHD as neurologically based and called it 'minimal brain damage,' although in fact only a few children displayed this post-influenza reaction. However, this theory set the stage for interpreting ADHD as a neurological condition for the next half century, until subsequent scientific discoveries, classification models, and social events nudged theoretical constructs toward some combination of genetic, biological, social, and evolutionary explanations.[2,108]

Helping these young patients was another matter, and it was not until Charles Bradley identified *d*,l-amphetamine in 1932 and discovered it worked 'paradoxically' for some among the inpatient children under his care, did doctors have an effective treatment strategy. The impact of this development has been such that once an apparently effective pharmacological solution appeared, widespread dependence on it as a model for treatment has persisted, even though 50 years later, in 1980, Rapoport observed that the calming and focusing effects of stimulants were apparent in both normal and ADHD children and that age, rather than susceptibility, was likely the defining feature of the drug effect.[3] Parallel to these pharmacological developments, creation of diagnostic categories, psychometric instruments, and definitions were proceeding, both deriving from and shaping our understanding of this heterogenous disorder.[109,110] The controversy around accurate diagnosis is particularly heightened with documented increases in diagnosis of younger children and associated increases in treatment with psychoactive medications.

From an estimated 150,000 to 200,000 children in the United States treated with stimulants at the end of the 1960s, as of 2005, current estimates stand at 4.4 million children diagnosed with ADHD, of whom 56 percent or 2.5 million receive medication.[4] Prescription sales data have been available for psychostimulant drugs since 1971, when they were recategorized as Schedule II controlled substances with mandatory reporting requirements. Despite its status as a controlled substance, there is still cause for concern since methylphenidate (MPH) appears so widely available beyond the normal range of medical access points (e.g., through internet sources, as well as with increased use as a 'study aid' on campuses[111,112]) and the evidence of mismatch between who gets diagnosed and who gets prescribed. Eisenberg[3] cites the Great Smoky Mountain studies by Angold[113] and Costello,[114] which find a definite diagnosis prevalence of ADHD as 0.9 percent in the population (as measured by interviews with parents), and rates of psychostimulant treatment more than double that, with many of those using medication meeting partial but not full diagnostic criteria. Other studies do not find such strong evidence of a mismatch, as reported by Goldman[115] and Schachar et al.[116]

We close this synopsis of the history of ADHD with reference to another influential school related legislation, the 2005 introduction and passage of the Child Medication Safety Act (House of Representatives (H.R.) 1790) which was 'enacted to protect children and parents from being coerced into administering a controlled substance or psychotropic drug in order to attend school, and for other purposes, …'[117] The introduction of this legislation may introduce limits on the role of institutions in decisions about children with ADHD, so that parents maintain authority over decisions in regard to medication for their child. However, the controversy also points to the need for further development of a range of alternative strategies for families who prefer no medication.

Clinical Context

Children with ADHD, characterized by inattention, overactivity, and impulsivity, are most frequently identified and treated in primary school. Population studies identify that approximately 5 percent of children worldwide show impaired levels of attention, as well as hyperactivity.[93] Boys are classified with ADHD approximately twice as frequently as girls, and younger children approximately twice as frequently as adolescents. ADHD symptoms exist on a continuum in the general population, and are considered as a 'disorder' to a greater or lesser degree depending on the source of identification (e.g., parent or teacher), including extent of functional impairment, diagnostic criteria, and the threshold chosen for defining a 'case.'[93] As

alluded to in the preceding section, the cultural and situational context are also influential in case identification, largely through the responses of parents and teachers who answer the questions about symptoms and impaired functioning. Therefore, formal diagnostic criteria such as the DSM-IV include presence of impairment across settings, for example both at home and at school. There is increasing interest in identifying and treating very young children, those in preschool, in order to ameliorate the burden on child and family as early as possible and thereby diminish the later development of social and academic repercussions.

The Social Burden Associated With Attention Deficit Hyperactivity Disorder (ADHD)

Clinically significant ADHD is often associated with concurrent oppositional and aggressive behaviors, anxiety, low self-esteem, and learning disabilities. Symptoms generally interfere with academic and behavioral functioning at school, and may also disrupt family and peer relationships. ADHD begins before children enter school although it is most commonly identified and treated in primary school, at age 7 to 9 years.[118] In the preschool age group, ADHD is characterized not only by impairment in attention span, excessive impulsivity, and overactivity, but also is frequently accompanied by additional disruptive behavior symptoms, including severe temper tantrums, demanding, uncooperative behavior, and aggressiveness.[119] While levels of symptoms decrease with age, the majority of children with ADHD continue to show impairment relative to same-age peers throughout adolescence and into adulthood. Estimates of prevalence of ADHD among adults worldwide is 2.5 percent.[9]

Interventions for ADHD

Interventions for ADHD include a range of medication and nonmedication options. Many children, teens, and families receive nonspecific psychosocial support, counseling, and advice, as well as academic tutoring and coaching, both in school and out. Complementary and alternative medicine options, including dietary supplements, are also available. Few of these interventions have been systematically evaluated, and fewer still have been examined for their long-term effectiveness. One area of careful study has been the efficacy of pharmacological agents on the core symptoms of ADHD and more recently on several aspects of overall functional impairment. This research has often, but not always, been supported by industry.

Nonpharmacological interventions, especially behavior training with parents and teachers, have been studied most extensively for treatment of DBD, primarily ODD and CD. These conditions often co-occur with ADHD, especially hyperactive impulsive subtype, and in community practice can be hard to distinguish from one another. The well known Multimodal Treatment Study of ADHD (MTA Study) funded by the U.S. National Institutes of Mental Health (NIMH) remains the best source of information regarding the comparative effectiveness of pharmacological versus non pharmacological interventions for ADHD over an extended period of time. The MTA study is discussed at length later in this report (pp. 74–76). Following the initial results, published in 1999,[74] behavioral interventions for children age 6 and up generally targeted ODD and CD symptoms with MPH and other psychostimulants used for core symptoms of ADHD, inattention, impulsivity, distractibility, and overactivity.

Pharmacological Interventions

Multiple short-term studies document that psychostimulant medications, either MPH, dextroamphetamine (DEX), or mixed amphetamine salts (MAS), effectively decrease the core symptoms of ADHD and associated impairment.[10] A review of the mechanisms of action of pharmacological interventions for ADHD is beyond the scope of this report. Some preparations last only a few hours, with symptoms returning as the medication wears off. Many families choose to use medication primarily on school days, and these medications have primarily been studied in school-aged children and youth aged 6 years and older. Psychostimulants, most commonly MPH and DEX, are generally safe and well tolerated. Common side effects include poor appetite, insomnia, headaches, stomachaches, and increased blood pressure and heart rate. Prolonged use may result in a decreased rate of growth, generally considered clinically insignificant.[118] Concerns have been raised from postmarketing surveillance suggesting a rare incidence of sudden death, perhaps associated with pre-existing cardiac defects, however, the rate does not appear to exceed that of the base rate of sudden death in the population.[118] As noted earlier, approximately 2.5 million children in the United States, ages 4 to 17 years with a diagnosis of Attention Deficit Disorder (ADD) or ADHD, currently take medication.[4]

Several extended release preparations of psychostimulants have been developed in recent years aimed at improved adherence and symptom control throughout the day as well as decreased abuse potential.[120] Non-stimulants (e.g., alpha adrenergic agents and atomoxetine (ATX)) have also been developed and found to be helpful in controlling symptoms with few adverse events.[121] However, in general, the benefits of medications wear off when they are discontinued. Since ADHD is a chronic disorder, many children, teens, and adults stay on medications for years at a time. Given the possibility of cumulative effects over time, a review of evidence regarding benefits and risks of prolonged medication use for ADHD is indicated.

Nonpharmacological Interventions

In the area of nonpharmacologic interventions, behavior training has been found to be helpful, primarily for disruptive behaviors that frequently coincide with ADHD.[122] Since ADHD may begin before school age, using the precedent of older children, increasing numbers of preschoolers are being identified and treated, sometimes with medications. However, the most commonly used psychostimulant, MPH, does not yet have government regulatory approval for use in children less than 6 years of age, while MAS has been granted approval by the FDA in the United States for children under 6 years, but older than 3 years of age.[123] Recent reviews of treatments for preschoolers with ADHD emphasize the use of parenting interventions prior to medication based on general clinical consensus.[124] Indeed, the Preschool ADHD Treatment Study (PATS), funded by the U.S. National Institute for Mental Health (NIMH), included parent behavior training (PBT) as the first phase for all children recruited into the study prior to randomization for the purpose of evaluating efficacy and safety of psychostimulant medication.[125] While the few studies available suggest stimulant medications are effective for the core symptoms of inattention, hyperactivity, and impulsiveness in very young children, psychostimulants also appear to cause more adverse events in preschool children than in older children.[54] Beyond the PATS, little information exists to document effectiveness of either medication or non-medication interventions specifically for ADHD in this age group. Part of the difficulty has been lack of clarity regarding reliability and validity of diagnostic criteria and therefore lack of widespread application of the ADHD diagnosis for children under 6 years.[119]

To address this information gap we will examine interventions for preschoolers with DBD, which include ADHD behaviors. Research has accumulated regarding PBT for preschoolers with disruptive behavior in the past decade, but many of the studies do not recruit based on an ADHD diagnosis, but rather based on clinically significant disruptive behavior. However, ADHD in preschoolers is commonly identified in the context of comorbid oppositional and aggressive behavior.[126] A review of these studies will provide useful information about parenting interventions in preschoolers at very high risk of ADHD, especially those with defiant and aggressive behaviors. Other interventions and combinations of interventions for preschoolers with DBD including ADHD will also be reviewed.

Long-Term Outcomes

Children with ADHD are at risk for poor adolescent outcomes including decreased high school completion, early substance use, increased driving infractions, early parenthood, increased contact with the law, and the onset of concurrent psychiatric disorders. Both retrospective studies and prospective longitudinal studies over long time periods face challenges in documenting outcomes and controlling for recall bias. Comparisons of treated versus untreated individuals can be hard to interpret as both known and unknown factors play a role over the developmental spectrum from preschool to young adulthood. The natural history of those with ADHD, in comparison to those not meeting the diagnostic criteria for ADHD, remains poorly documented as standardized diagnostic criteria and methods of investigation have been in existence a relatively short time. Not knowing the natural history of the disorder complicates interpretation of treatment extension studies. Despite these limitations, it is timely to examine the current literature to see what has been accomplished and to consider directions for future research. Outcomes of interest for these studies include: persistence of ADHD, new onset psychiatric and substance use disorders, as well as educational, occupational, and social functioning outcomes.

Prevalence and Variations in Management

Over the past several decades, rates of identification and treatment for people with ADHD have increased as documented by population-based studies using health administrative databases.[94,95,127] In some cases, small-area variation in prescriptions has been linked to specific physicians, suggesting that increases in identification may be linked with changes in practice patterns rather than an increase in the underlying endemic prevalence of the disorder.[128,129] In fact, the underlying prevalence of the disorder in children appears to have been relatively stable since the 1980s, to the extent that it has been measured using identical research methods.[130] In the past 10 years, increases in identification and treatment have occurred primarily among girls and older children consistent with changes in clinical guidelines.[95,131] Increases in off-label prescription of psychotropic medications for very young children have also been noted, presumably for preschoolers identified at high risk for ADHD because of disruptive behavior.[97]

Scope and Purpose of the Systematic Review

The purpose of this review is to: (i) critically examine the effectiveness and adverse events of interventions in preschool children with clinically significant disruptive behavior (that is, meeting clinical thresholds on standardized symptom scales and/or clinically diagnosed with disruptive behavior disorders or ADHD), and therefore at high risk for ADHD; (ii) critically

examine the comparative long-term effectiveness and adverse events of interventions for ADHD (pharmacological, psychosocial, or behavioral, and the combination of pharmacological and psychosocial or behavioral interventions); and (iii) summarize what is known about patterns of identification and treatment for the condition. Factors to be examined include geography, sociodemographics, temporal aspects, and provider background. This systematic appraisal will also identify gaps in the existing literature that will inform directions for future research.

This review follows the 1999 publication of a systematic review of ADHD sponsored by the AHRQ.[10] That review examined subjects of any age and all lengths of treatment and followup. The current review is focusing attention on both the treatment of preschoolers, which has become of greater interest to parents and physicians since 1999, and on the long-term outcomes of treatment of any type for ADHD for any age. The previous report looked at only RCTs, while this review will include other study designs in order to capture more long-term outcomes and more adverse events.

The key questions are as follows:

Key Question 1. Among children less than 6 years of age with Attention Deficit Hyperactivity Disorder or Disruptive Behavior Disorder, what are the effectiveness and adverse event outcomes following treatment?

Key Question 2. Among people 6 years of age or older with Attention Deficit Hyperactivity Disorder, what are the effectiveness and adverse event outcomes following 12 months or more of any combination of followup or treatment, including, but not limited to, 12 months or more of continuous treatment?

Key Question 3. How do: (a) underlying prevalence of ADHD, and (b) rates of diagnosis (clinical identification) and treatment for ADHD vary by geography, time period, provider type, and sociodemographic characteristics?

Methods

Topic Development

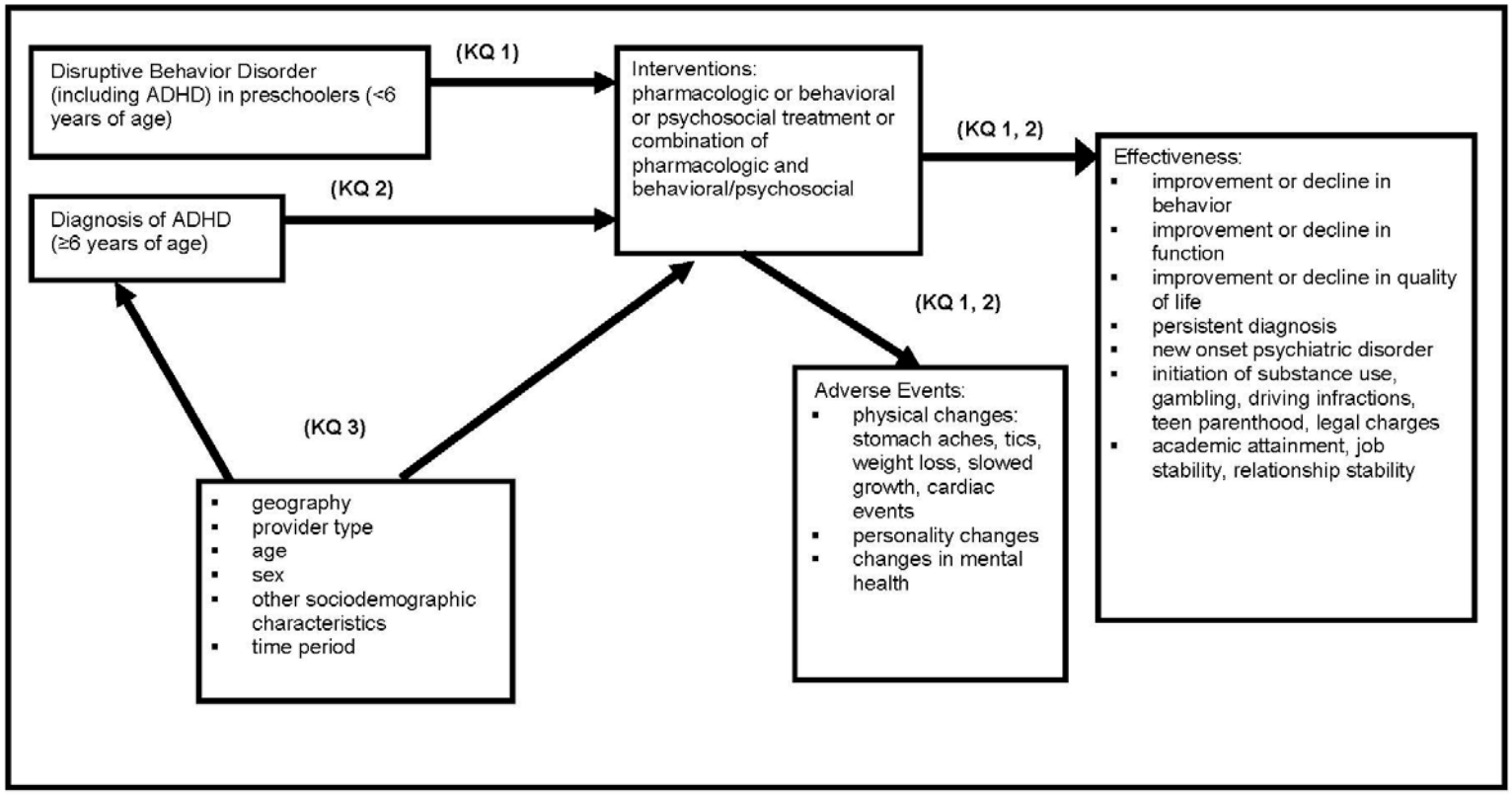
The topic of this report and preliminary key questions (KQs) were developed through a process involving the public, the Scientific Resource Center for the Effective Health Care program of the Agency for Healthcare Research and Quality (AHRQ) (www.effectivehealthcare.ahrq.gov/aboutUS/contract.cfm), and various stakeholder groups. Study, patient, intervention, eligibility criteria, and outcomes, were refined and agreed upon through discussions between the McMaster University Evidence-based Practice Center, the Technical Expert Panel (TEP) members, the AHRQ Task Order Officer (TOO), and comments received from the public posting of the key questions and protocol document.

Analytic Framework

Following consultation with key informants, the AHRQ TOO, and our investigative team, we developed our key research questions. Figure 1 shows a flow diagram indicating the relationship between research questions in this Comparative Effectiveness Review (CER).

This framework depicts the key questions as described in the PICO table, Table 1, (population, intervention, comparison, and outcomes). The figure illustrates how geography, age, provider type, and sociodemographic characteristics may influence the diagnosis and the treatment of Attention Deficit Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD), and Conduct Disorder (CD). Treatment results in measurable outcomes, showing improvement or decline in behavior, function or quality of life. Indicators of long-term outcomes are new onset psychiatric disorder, initiation of substance use, gambling, driving infractions, teen parenthood, legal charges, academic attainment, job stability, relationship stability, physical health, and changes in mental health.

Figure 1. Analytic framework: ADHD in preschoolers and long-term effects of ADHD pharmacotherapy



Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; KQ = key question

Table 1. PICO table for ADHD review

Question	Question 1	Question 2	Question 3
Population	• Children <6 years of age AND • Diagnosed with ADHD or at risk for ADHD or diagnosed with DBD (including ODD and CD by DSM)	• ≥6 years of age (subjects <6 years are described in Question 1) • Diagnosed with ADHD by the DSM or ICD criteria that was in use at the time of the study or of the publication	• No age limit for population • Diagnosed with or treated for ADHD
Intervention	• Any pharmaceutical treatment • Any psychosocial, behavioral, or PBT treatment or combination treatment • Not including alternative treatments (e.g., diet, massage)	• Any pharmaceutical treatment • Any psychosocial, behavioral, or PBT treatment or combination treatment • Not including alternative treatments	• Any pharmaceutical treatment • Not including alternative treatments
Comparator/ Design	• Comparative studies (RCT, cohort, case/control) • Any drug, psychosocial, or behavioral treatment or combination treatment compared against placebo or any other of the above treatments • Not case series or case reports	• Comparative studies (RCT, cohort, case/control) • Any drug, psychosocial, or behavioral treatment or combination treatment compared against placebo or any other of the above treatments • Not case series or case reports AND • Combination of followup and treatment time is equal to or greater than 12 months	• Descriptive statistics
Outcomes	• Numerical or statistical results of any effectiveness or adverse event outcomes	• Numerical or statistical results of any effectiveness or adverse event outcomes	• Prevalence of ADHD diagnosis or treatment, analyzed by geography, time period, provider type, socio-demographic characteristics (i.e., age, sex, family status, race/ethnicity, health insurance coverage)

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder, CD = Conduct Disorder, DSM = Diagnostic and Statistical Manual of Mental Disorders, ICD = International Classification of Diseases, ODD = Oppositional Defiant Disorder, PBT = parent behavior training; RCT = Randomized Controlled Trial

Methodology for Prevalence and Variations in Management Question

For the prevalence question (KQ3), we searched the literature and screened the resulting citations right up to the full text examination using systematic review methodology, which includes preset inclusion/exclusion criteria screening questions and agreement by two raters for all decisions. All abstracts of the resulting reports were examined and those selected which reported data that directly addressed prevalence, clinical identification, and treatment of ADHD as specified in KQ3. The process of external review identified additional references subsequently incorporated into the final document.

Search Strategy

For KQ1, the databases were searched from their inception date to the 31st of May, 2010. Studies were limited for KQ2 to include any publication from 1997 to the 31st of May, 2010 inclusive because long-term treatment of ADHD has already been reviewed by AHRQ for dates before 1997.[10] For KQ3, publications dated back to 1980 were included.

The following databases were searched for KQ1 and KQ2: MEDLINE, Cochrane CENTRAL, EMBASE, PsycInfo, and ERIC (Education Resources Information Center). For KQ3, the Cochrane Library and ERIC Database were not searched because clinical trials were not the target of this review. Strategies used combinations of controlled vocabulary (medical subject headings) and text words. The complete search strings used can be found in Appendix A. Searches were performed on December 1, 2009 and the update performed on May 31, 2010.

Reference lists of eligible studies at full text screening were reviewed. Any potentially relevant citations were cross-checked within our citation database and any references not found within the database were retrieved and screened at full text.

Study Selection

Criteria for Inclusion or Exclusion of Studies in the Review

Target Population

For KQ1, the population includes children less than 6 years of age with a diagnosis of ADHD or DBD (including ODD and CD) by Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria. In addition, samples where children showed clinically significant symptoms were included, defined by referral to treatment or high scores on screening measures.

For KQ2, the population includes subjects of greater or equal to age 6 years who have been treated for ADHD or are a control group of ADHD subjects, diagnosed with ADHD by DSM or ICD criteria.

For KQ3, the population includes subjects of any age who have been diagnosed with ADHD or treated for ADHD. Because much of this data would come from cross-sectional, survey, and medical databases using drug treatments and survey symptom checklists to identify ADHD subjects, subjects did not require a DSM or ICD diagnosis for inclusion.

Sample Size

There are no restrictions for study sample size.

Study Design and Publication Types

Inclusion

Full text reports of clinical trials and comparative observational studies were included for KQ1 and KQ2. For KQ3, we also included cross-sectional reports.

Eligible designs include:

- Experimental studies with comparator groups (randomized and quasi-randomized trials)
- Open label extensions following randomized controlled trials (RCTs)
- Observational studies with comparator groups (retrospective and prospective cohort, and case control)
- For KQ3 only, noncomparative cross-sectional studies

Exclusion

Letters, editorials, commentaries, reviews, meta-analysis, abstracts, proceedings, case reports, case series, qualitative studies, and theses were excluded.

Non-English publications were excluded for this review.

Definition of Terms

ADHD, ODD, and CD will be as defined by the version of DSM or ICD current at the time of the study or of the publication.

Further Search Methods

Study authors were contacted via email for missing outcome or design data. Reference lists of included papers were screened for possibly relevant papers that had not already been screened. Grey literature was identified by the AHRQ Scientific Resource Center and included:

- FDA—Medical Reviews and Statistical Reviews
- Health Canada—Drug Monographs
- Authorized Medicines for EU - Scientific Discussions
- ClinicalTrials.gov
- Current Controlled Trials (U.K.)
- Clinical Study Results (PhRMA)
- WHO Clinical Trials (International)
- CSA Conference Papers Index
- Scopus - limited to conference papers

Standardized forms were developed in DistillerSR (Evidence Partners Inc., Ottawa, Ontario, Canada) and Microsoft Excel for the purposes of this systematic review.

Types of Comparators

We identified and included studies with comparative intervention groups. From a design hierarchy perspective, comparative group designs provide stronger evidence for efficacy and effectiveness than non-comparative designs.

The interventions (either alone or in combination) may be compared to any of the following:

- Placebo
- Same pharmacologic agent of different dose or duration
- Other pharmacologic agent
- Behavioral intervention
- Psychosocial intervention
- Academic intervention
- Any combination of pharmacologic, academic, behavioral, or psychosocial intervention

Reports studying any drug for treatment of ADHD were included in this review if the other inclusion criteria were met.

Pharmacological Interventions Reported in This Review

Psychostimulants

- Methylphenidate (MPH)
- Dextroamphetamine (DEX)
- Mixed Amphetamine Salts (MAS)

Selective Norepinephrine Reuptake Inhibitor

- Atomoxetine (ATX)

Alpha-2 Agonist

- Guanfacine extended release (GXR)

Non-Medication Interventions Reported in This Review

- **Parent behavior training—**manualized programs designed to help parents manage child's problem behavior using rewards and non-punitive consequences
- **Psychosocial interventions—**include any one of a number of interventions aimed to assist child and family through psychological and social therapies (e.g., psychoeducational, parent counseling and social skills training
- **Behavioral interventions—**manualized programs designed to help adults (parent, teachers, other) using rewards and non-punitive consequences
- **School-based interventions—**interventions in which teachers are primary intervenors and where the intervention takes place in a classroom or school setting

Outcomes

No limits have been placed on the effectiveness or adverse event outcomes included in this report. The primary focus for outcome in this report is identification of improvement in child

behavior. Numerical or statistical results of any effectiveness or adverse event outcomes are included.

Data Extraction

Relevant fields of information were taken from individual studies by trained data extractors using standardized forms and a reference guide. Key study elements were reviewed by a second person (study investigator) with respect to study outcomes, seminal population characteristics, and characteristics of the intervention. Disagreements were resolved by consensus.

Abstracted data includes study characteristics (e.g., first author, country of research origin, study design, sample size, clinical indications, and study duration or length of followup). Details of the patient population include age, gender, racial composition, socioeconomic status (SES) (e.g., income, education), and comorbidities (e.g., psychiatric and medical disorders). Details of the study intervention include type of intervention (e.g., pharmacological and non-pharmacological) and the comparators, dosage of intervention, duration of followup (from immediately post treatment to long term), and characteristics of treatment providers. Characteristics of the outcomes include the type of instrument or scale, type of effect measure (e.g., endpoint or change score, measure of variance, standard deviation, standard error, etc.), and definition of treatment response.

All forms and guides used in the screening and data extraction process are provided in Appendix B.

Peer Review

Prior to finalization of the report, the AHRQ submitted a draft to seven peer reviewers and their comments were implemented after consideration by the research team. The report was also made available on the AHRQ website for public review; public reviewers' comments were also implemented after consideration by the research team. In situations where the research team decided not to revise the content of the report based on a reviewer's comments, a written explanation of the reason(s) for choosing not to revise have been submitted to the AHRQ.

Assessment of Methodological Quality of Individual Studies

We interpret methodological quality to include primarily elements of risk of bias (systematic error) related to the design and conduct of the study. We have selected the Effective Public Health Practice Project, Quality Assessment Tool for Quantitative Studies Risk of Bias (EPHPP) (see Appendix B)[13] and used this in KQ1 and 2, where each paper was rated independently by two raters and conflicts resolved by a third. No similar tool for evaluating epidemiological and health service studies was used. The process for preparing this report included peer review by experts in the field of inquiry. For KQ3, we included additional studies recommended for inclusion by the reviewers, all of which had been identified in previous steps through the search methodology.

The tool, which measures internal validity, contains eight sections that include evaluation of the domains of selection bias, study design, confounders, blinding, data collection methods, withdrawals and dropouts, intervention integrity, and analyses. A global rating of "good," "fair," or "poor" for each report results from agreement by two raters on the combination of all of these items. Ratings result from a combination of the quality of the study design, execution, and reporting. A "good" paper will have mostly strong ratings in each section with possibly a

moderate rating in one or two of the eight sections. A "fair" paper will have mostly moderate ratings for the eight domains, or it will have a split between weak, moderate, and strong ratings. A "poor" paper could have one or two strong domains, but has three or more weak domains in the rating.

Rating the Body of Evidence

We assessed the overall strength of the body of the evidence using the context of the GRADE approach, modified as the Grading System as defined by AHRQ.[14,15] Although we included papers that were not RCTs, there are several factors suggested by the GRADE approach that may decrease the overall strength of the evidence (SOE):

- Study limitations (predominately risk of bias)
- Type of study design (experimental versus observational)
- Consistency of results (degree to which study results for an outcome are similar between studies, and variability is easily explained)
- Directness of the evidence (assesses whether interventions can be linked directly to the health outcomes)
- Precision (degree of certainty surrounding an effect estimate for a specific outcome)

The ratings were arrived at through discussion among two or more of the investigators. Only papers rated as "good" were included in these analyses since they represent the best available data at this point in time. See Appendix D.

No limits have been placed on the effectiveness or adverse event outcomes included in this report. Numerical or statistical results of any effectiveness or adverse event outcomes are included. Effect Sizes are reported as Standardized Mean Differences (SMD) whereby the difference in outcome (using continuous measures) between the intervention and comparison groups is divided by the pooled standard deviation to estimate intervention effectiveness. By convention, 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect.[11] The SMD is used as a summary statistic in meta-analysis when the studies use different instruments the measure the same outcome. The data are standardized to a uniform scale before they can be combined. The SMD expresses the size of the intervention effect in each study relative to variability observed in that study.[12]

Data Synthesis

Qualitative Synthesis

For each trial, information on population characteristics (e.g., history of treatment(s), age of first diagnosis, etc.), study outcomes, sample size, settings, funding sources, treatments (type, dose, duration, and provider), methodological limitations, statistical analyses, and any important confounders were summarized in text and summary tables.

Quantitative Synthesis

The decision to pool individual study results was based on clinical judgment with regards to comparability of study populations, treatments, and outcome measures. Aspects considered were: methodological quality (e.g., high-risk of bias vs. low-risk of bias), clinical diversity (e.g., study population gender, disease severity), treatment characteristics (e.g., type of intervention), and

outcome characteristics (e.g., long-term followup vs. short-term followup, different measuring scales, different definitions of dichotomous outcomes). The extent of heterogeneity was explored through subgroup and sensitivity analyses.

Subgroup and Sensitivity Analysis

Key patient-specific or intervention-specific factors that may affect the treatment effect were explored. Clinical heterogeneity was assessed by considering any potential differences in participants among the trials (e.g., age, gender, diagnoses, disease severity, definition of response). Methodological heterogeneity was explored by evaluating where studies failed to meet the criteria.

To maximize the similarities among studies that could potentially be combined for meta-analyses, we further stratified where possible studies based on: (1) behavior disorder (ADHD, ODD, CD), and (2) age categories (preschool, child, adolescent, adult). There are several patient characteristics that we further explored for potential subgroup and sensitivity analysis and these include the following: (1) disease severity and ADHD subtype, (2) gender, and (3) comorbidities related to other psychological disorders. Trial specific factors include: (1) duration or dose of intervention, (2) type of treatment provider, and (3) method of defining response.

Results

Figure 2 details the flow of studies and the final subset for review of KQ1 and KQ2. The search for reports for the treatment questions addressing preschool children and addressing long-term treatment or outcomes, yielded 36,888 unique citations. During two levels of title and abstract screening, 35,541 articles were excluded. A total of 1,347 citations proceeded to full text screening. After the final eligibility screening, 129 publications were eligible for data extraction.

Figure 2. Flow of studies through review (KQ1 and KQ2)

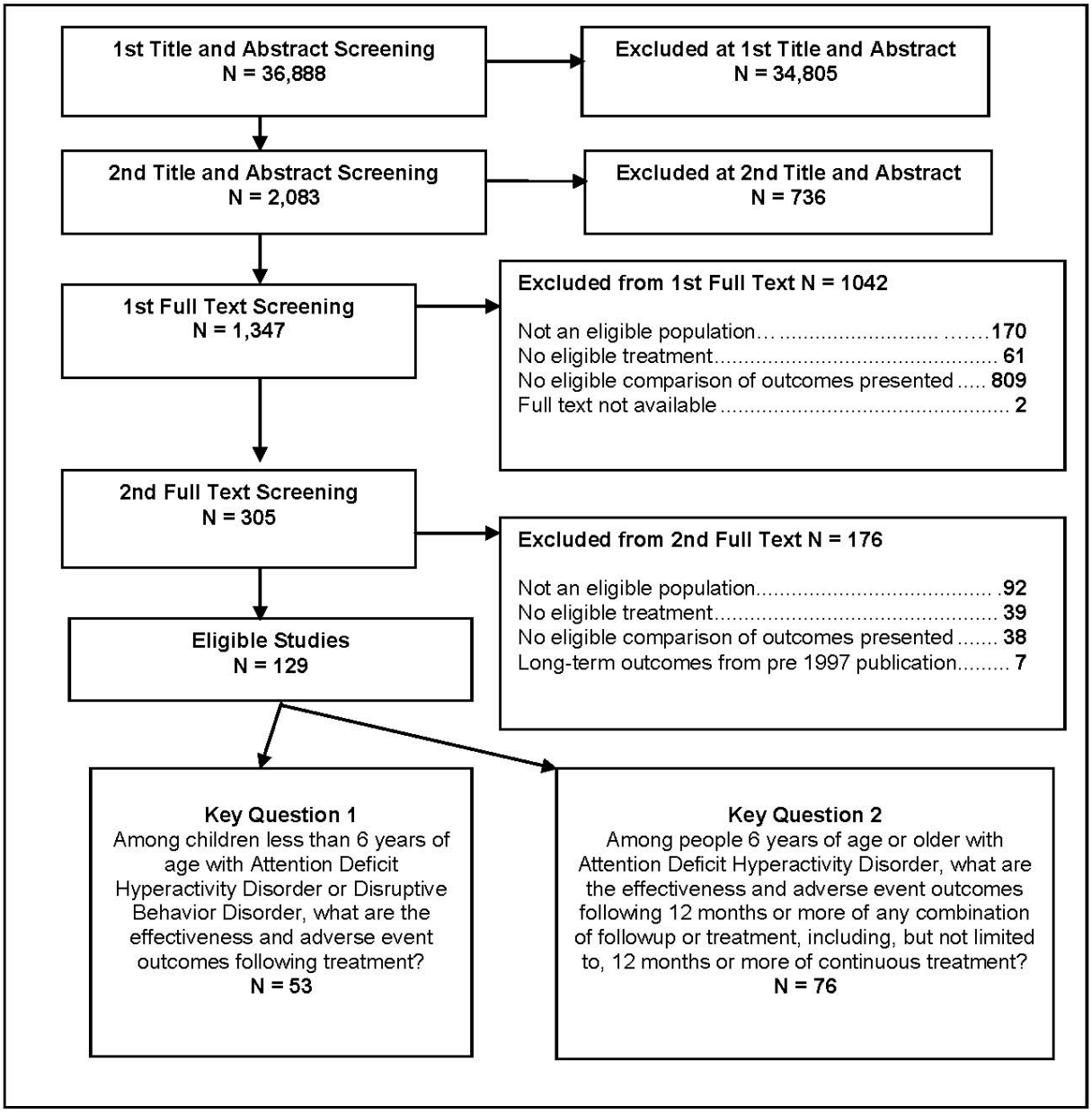
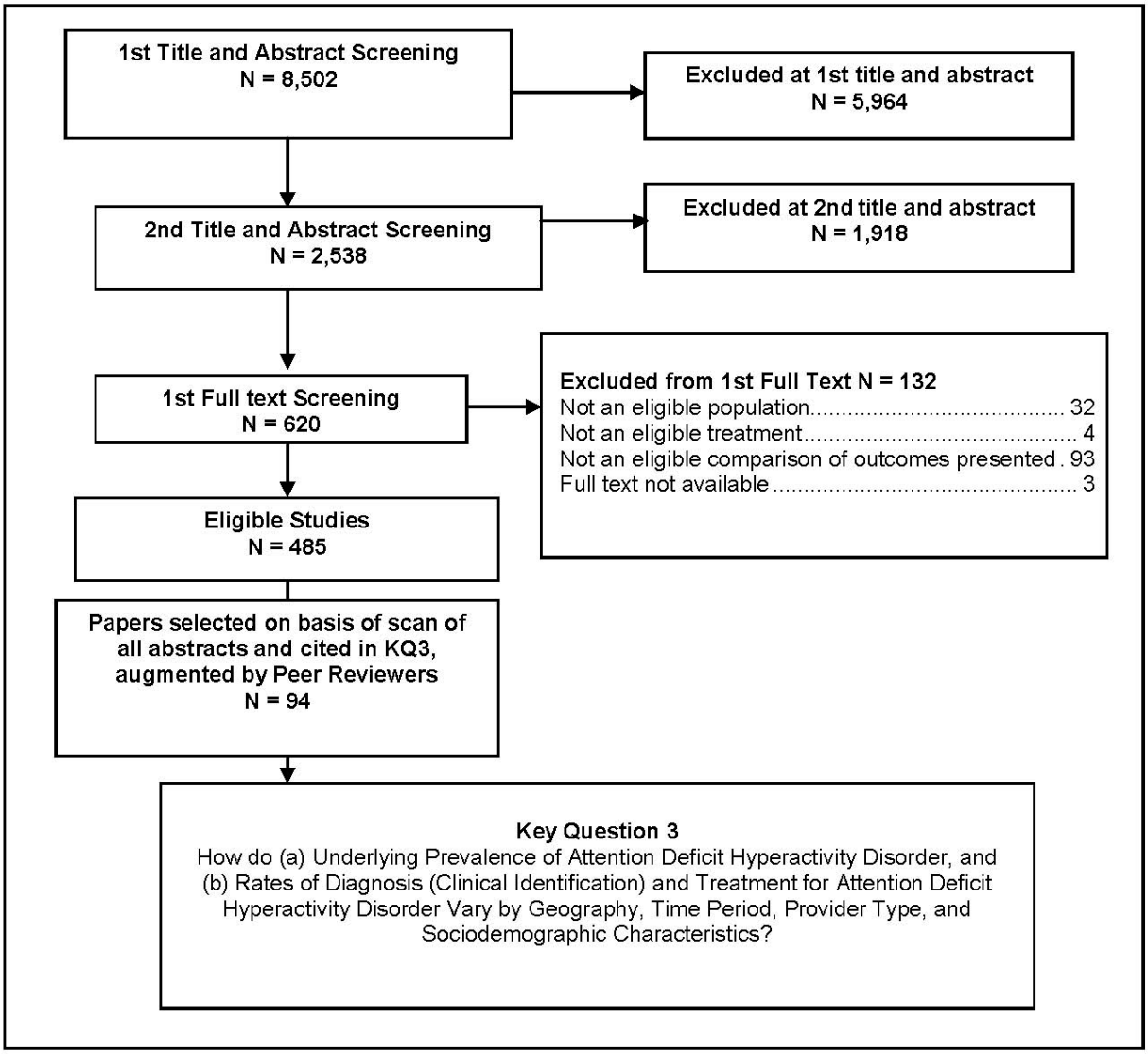


Figure 3 outlines the flow of studies and the final subset for review of KQ3. A separate search was performed for prevalence reports (KQ3). The initial yield of papers was 8,502 of which 5,964 were excluded at the title and abstract screening level 1, with an additional 1,918 excluded at level 2. Of the remaining 620 papers, an additional 132 were excluded at full text screening. Having applied the methodology of systematic review to reduce the volume of papers, the authors then addressed KQ3 using data from 94 of the 485 reports selected as a result of a scan of abstracts and then augmented with other supporting methodological and epidemiological studies which informed discussion of issues surrounding estimates of prevalence.

Figure 3. KQ 3. Flow of studies through review for prevalence question



Key Question 1. Among children less than 6 years of age with Attention Deficit Hyperactivity Disorder or Disruptive Behavior Disorder, what are the effectiveness and adverse event outcomes following treatment?

Introduction

The systematic search results for comparative clinical trials of psychosocial, behavioral, or pharmacologic interventions for preschoolers with Disruptive Behavior Disorders (DBD) are organized by type of intervention. The first section describes parent behavior training (PBT), with a summary of efficacy trials addressing child disruptive behavior problems and parents' sense of competence. Three of these trials investigated PBT specifically for preschoolers identified with Attention Deficit Hyperactivity Disorder (ADHD) symptoms. Ten studies measured hyperactivity/impulsivity among other behavior symptoms. The next section summarizes studies investigating long-term extensions following the clinical trials of PBT. The third and fourth sections report on studies designed to address symptoms of ADHD in preschoolers, as well as other disruptive behavior and school readiness. The third section examines interventions that combine PBT and school or daycare components. The last group of studies examines pharmacological agents, specifically trials of psychostimulants.

Parent Behavior Training Interventions for Preschoolers With Disruptive Behavior Disorders

There are primarily four manualized programs of behavior training interventions for parents of preschoolers with DBD that have been developed by separate research groups in the past 25 years. While each program has its own specific features, the Triple P (Positive Parenting of Preschoolers program),[16-22] Incredible Years Parenting Program (IYPP),[23-27] Parent-Child Interaction Therapy (PCIT),[28-35] and the New Forest Parenting Program (NFPP)[36-39] share common therapeutic components and are manualized to ensure intervention integrity with dissemination. These programs are designed to help parents manage their child's problem behavior with more effective discipline strategies using rewards and non-punitive consequences. An important aspect of each is to promote a positive and caring relationship between parents and their child. Primary outcomes are improved child behavior and improved parenting skills. Each program also includes educational components regarding childhood behavior problems and common developmental issues, and may include coaching or consultation to support the parents' efforts.

Thirty-one reports of controlled trials of parenting interventions met criteria for review;[17-39,132-138] of these, 28 met criteria for "good" or "fair" internal validity and will be the basis of this discussion. Additionally, the 8 studies which met criteria for "good" internal validity were used in the general meta-analysis highlighted in the Strength of Evidence Tables (see Table 21). Tables 2 and 3 provide information on the characteristics of the 31 reports. Most of the studies were randomized controlled trials (RCTs). Most studies examined parent-reported child symptom behavior scores, self-reported parenting skills, and sometimes researcher-rated observations of parent-child interactions. The Eyberg Child Behavior Inventory (ECBI) was the most frequently used child behavior measure, with subscales for frequency and intensity of child disruptive behaviors. Several parenting scales were used, most frequently the Parent Sense of Competence scale (PSOC). Almost all studies compared groups of treatment intervention

completers to wait list controls, while one study compared two different interventions,[132] and two studies compared variants of an intervention without a treatment control group.[20,138]

Eight of the trials conducted examined PCIT.[28-35] Two studies evaluated the efficacy of PCIT for preschoolers with symptoms of ADHD.[30,31] Results from these studies show that PCIT is efficacious in reducing oppositional symptoms and increasing compliance. In addition, both studies reported a reduction in ADHD symptoms posttreatment. Six additional studies evaluated PCIT in oppositional or aggressive preschoolers and found similar results.[28,29,32-35] At postintervention, parents who received treatment reported fewer and less intense child externalizing symptoms, in addition to decreased parenting stress and increased internal locus of control.

Seven studies evaluated the Triple P program or its precursors.[16-22] Four studies examined self-directed variants,[16-18,21] while two studies examined enhanced and standard variants of the program.[19,22] In general, results from these studies show that compared to wait list controls, parents who completed the intervention reported fewer and less intense child behavior problems, less frequent use of dysfunctional discipline strategies, and increased sense of competence in their own parenting skills at post-intervention followup. Bor, et al.,[19] did not find the enhanced intervention, which included adjunctive components addressing partner support and coping skills, to be superior to the standard Triple P intervention on any of their outcome measures.

Five of the trials examined the efficacy of the IYPP compared to wait list control.[23-27] Results from these studies showed reductions in problem behaviors and clinically significant gains in families that completed the intervention. In addition, one of these studies reported a significant decrease in inattention and hyperactivity symptoms even when controlling for postintervention changes in child deviant behavior.[24] Another trial examined the efficacy of Supportive Expressive Therapy – Parent Child (SET-PC), a psychodynamic psychotherapy, as compared to the IYPP.[132] Results show that both interventions were efficacious in reducing externalizing behaviors and increasing parents' psychological functioning, as well as positive interactions between parent and child.

Four of the studies examined the efficacy of the New Forest Parenting Program (NFPP), specifically designed for preschoolers with ADHD.[36-39] Results from two studies showed a reduction in ADHD symptoms postintervention,[36,39] while reductions in oppositional symptoms were less marked.[39] One study, in which PBT was delivered by nonspecialist nurses as part of routine primary care, did not result in any change of ADHD symptoms postintervention.[37]

Three reports on two RCTs by Pisterman, et al.,[135-137] reported support for the efficacy of group parent-mediated behavioral intervention to reduce noncompliant behavior in preschoolers and to reduce parent stress and improve parenting competence.

One RCT evaluated the efficacy of the Help Encourage Affect Regulation (HEAR) for aggressive preschoolers.[134]

A final RCT evaluated a PBT program offered either to individual families in a clinic setting or to groups of parents in a community location.[133] Results showed that parents enrolled in a group and community-based program reported greater improvements of behavior problems at home compared to an individual, clinic-based program and wait list control. Moreover, the community/group program was found to be much more cost-effective than the individual/clinic program.

In summary, these studies show that parent behavioral interventions are an efficacious treatment option for preschoolers with DBD. Compared to wait list controls, children show reduced number and intensity of problem behaviors and clinically significant changes

postintervention. In five out of six studies where ADHD symptoms are a focus of treatment, these also improve. Moreover, parents report an increased sense of competence and show improved parenting strategies. Self-directed, group, and individual variants of parenting interventions are generally equally effective, though group therapy may be more cost-effective when compared to individual therapy.

Table 2. KQ1. Characteristics of parenting interventions

Study	Intervention	Length of Intervention Primary/ Followup	Characteristics of Intervention								
			Mode of delivery			Location of delivery			Adjunctive components		
			Group	Individual	Self-directed	Home	Community	Clinic	Direct intervention with child	Parent mental health	Marital conflict
Bagner, 2007[28]	PCIT	4m/0		✓				✓		✓	
Bor, 2002[19]	Triple-P	15wk/1y		✓		✓	✓	✓		✓	✓
Bywater, 2009[26]	IYPP	12wk/ 18m	✓				✓				
Connell, 1997[17]	SDBI pre-Triple P	10wk/4m			✓	✓				✓	
Cummings, 2008[132]	SET-PC/IYPP	14wk/1y	✓	✓				✓		✓	
Cunningham, 1995[133]	CBPT	8wk/6m	✓	✓			✓	✓			
Dadds, 1992[22]	CMT vs. CMT + AST pre-Triple P	8wk/6m	✓	✓		✓		✓		✓	
Eyberg, 1995[34]	PCIT	12wk/		✓				✓	✓	✓	
Funderburk, 1998[33]	PCIT	12wk/18m		✓				✓	✓	✓	
Hood, 2003[29]	PCIT	12wk/6y		✓				✓		✓	
Hutchings, 2007[25]	IYPP vs. WLC	12wk/6m	✓				✓		✓		
Jones, 2007[24]	IYPP vs. WLC	12wk/6m	✓				✓				
Landy, 2006[134]	HEAR	15wk/0	✓	✓			✓				
Lavigne, 2008[23]	IYPP	12wk/1y	✓				✓				
Markie-Dadds, 2006[18]	Triple P	17wk/6m			✓	✓					
Markie-Dadds, 2006[16]	Triple P	12wk/6m			✓	✓					
Matos, 2009[30]	PCIT	12w/3.5m		✓		✓			✓	✓	
Nixon, 2003[32]	PCIT	12wk/6m		✓		✓			✓	✓	
Nixon, 2001[31]	PCIT	12wk/6m		✓		✓			✓	✓	

Table 2. KQ1. Characteristics of parenting interventions (continued)

Study	Intervention	Length of Intervention Primary/ Followup	Characteristics of Intervention								
			Mode of delivery			Location of delivery			Adjunctive components		
			Group	Individual	Self-directed	Home	Community	Clinic	Direct intervention with child	Parent mental health	Marital conflict
Pisterman, 1989[135]	PBT	12wk/3m	✓	✓				✓			
Pisterman, 1992[136]	PBT	12wk/3m	✓	✓				✓			
Pisterman, 1992[137]	PBT	12wk/3m	✓	✓				✓			
Sanders, 1985[20]	Triple-P	7wk/3m		✓		✓	✓				
Sanders, 2007[21]	Triple-P	15wk/3y		✓	✓	✓	✓	✓		✓	✓
Shuhmann, 1998[35]	PCIT	12wk/4m		✓		✓			✓	✓	
Sonuga-Barke, 2001[36]	NFPP	2m/15w		✓		✓			✓		
Sonuga-Barke, 2002[38]	NFPP	2m/15w		✓		✓			✓		
Sonuga-Barke, 2004[37]	NFPP	8wk/5wk		✓		✓			✓		
Thompson, 2009[39]	NFPP	8wk/9wk		✓		✓			✓	✓	
Weeks, 1997[138]	NFPP	8wk/0		✓		✓			✓	✓	
Williford, 2008[27]	IYPP	10wk/1y	✓				✓				

Abbreviations: AST = Ally Support Training; CBPT = community-based parent behavior training; CMT = Child Management Training; HEAR = Helping Encourage Affect Regulation; IYPP = Incredible Years Parenting Program; m = month; MPH = methylphenidate; NFPP = New Forest Parenting Program; PBT = parent behavior training; PCIT = Parent Child Intervention Therapy; SDBI = self-directed behavioral intervention; SET-PC = Supportive Expressive Therapy – Parent Child; wk = week; Triple P = positive parenting of preschoolers; WLC = Wait List Control; y = year

Table 3. KQ1. RCTs of parenting interventions

Study	Quality	N Mean Age (SD) % Male	Interventions compared	Results	
				Child behavior	Parent competence
Bagner, D 2007[28]	Good	N = 30 Mean age: 54m Male: 77%	PCIT vs. WLC	Developmentally delayed children showed significantly improved compliance compared to nontreated controls	Significant improvement in positive communication ITT, F(1,29) = 5.79, p = 0.023, d = 0.67
Bor, W 2002[19]	Good	N = 87 Mean age: 41m Male: 68%	Triple P vs. EBFI vs. WLC	Behavior improved under both enhanced and standard Triple P interventions ECBI-I p <0.01 ECBI-P p <0.001	No change in negative parenting style, both enhanced and standard program effected change to an equally significant degree; neither intervention reduced inattentive behavior from post to followup PS p <0.001 PSOC p <0.001 Child behavior improvement F(8,82) = 3.17, p = 0.004
Bywater, T 2009[26]	Good	N = 116 Mean age: 53m Male: 58%	IYPP vs. WLC	Significant reduction in antisocial and hyperactive behavior and increased self control ECBI-I p <0.001 ECBI-P p <0.001 Conners p <0.001	Improved measures of perceived parenting stress and positive communication ITT effect size of intervention 0.95 (95% CI, 0.82 to 1.37) Only 18% of children in intervention group above behavior cut-off did not show some improvement at 3months post
Connell, S 1997[17]	Fair	N = 24 Mean age: 49m Male: 43%	Triple P self directed vs. WLC	Reduction in disruptive behavior F(1,22) = 30.67; p = 0.0005 ECBI- P p <0.00 ECBI-I p <0.00	Self-directed Triple P with telephone contact effectively reduced disruptive behavior
Cummings, JG 2008[132]	Good	N = 54 Mean age: NR Male: 61%	IYPP vs. SET-PC	Both interventions show significantly improved cooperation and enthusiasm ECBI-I p <0.070 Reduction shown in BSI F(1, 26) = 8.14, p = 0.008	SET-PC essentially equivalent in outcome to IYPP and IYPP is more cost-effective and does not require same intensity of intervention leader training
Cunningham, CE 1995133	Good	N = 150 Mean age: 54m Male: 51%	CBPT	Significant improvements in child behavior CBCL-E p <0.001 Decrease in negative child behaviors F(92,192) = 8.91, p <0.001	Significant group improvement over clinic/individual, post and followup points; Sense of Competence more improved in clinic/individuals than in group intervention; immigrant, ESL, and parents of severely behavior disordered children more likely to enroll in community groups; Community Tx groups more than 6 times more cost-effective than clinic and individual groups

Table 3. KQ1. RCTs of parenting interventions (continued)

Study	Quality	N Mean Age (SD) % Male	Interventions compared	Results	
				Child behavior	Parent competence
Dadds, M 1992[22]	Fair	N = 22 Mean age: 55m Male: 68%	CMT vs. CMT with support person (ally) (pre-Triple P)	Children showed improved behavior under both conditions: CMT, F(4,16) = 96.13, p <0.001 and CMT with Ally, F(4,16) = 50.63, p <0.001	Mothers' perceived support system best predictor of response to treatment conditions
Eyberg, SM 1995[34] Primary study related to Shuhmann (1998)[35] Hood, (2003)[29]	Fair	N = 50 Mean age: 64m Male: 80%	PCIT vs. WLC	ECBI-I p <0. 01 ECBI-P p <0.00 Disruptive behavior reduced Post-Tx classroom observations do not differ between referred children and classroom peers	Initial data on short-term effect on parenting locus of control PLOC p <0.02
Funderburk, BW 1998[33]	Good	N = 84 Mean age: 54m Male: 100%	PCIT vs. WLC	Significant improvement in social competence between post-treatment and followup (maturational); Strong generalization of PCIT at 12m; 18m, ECBI-I, F(3,5) = 6.66, p = 0.03 ECBI-P, F(3,4) = 11.81, p = 0.02	Home behavior stays within normal limits at 18m, so slide in classroom likely due to classroom demands
Hood, K 2003[29]	Good	N = 64 Mean age: 59.5m Male: 81%	PCIT vs. WLC	ECBI-I, F(2, 44) = 35.69, p <0.0001 ECBI-P, F(2, 44) = 38.68, p <0.0001 Improved behavior in reported by parents and observed in classroom	Parent report more positive interaction with children; less parent stress; increased locus of control; parents were more tolerant of child's behavior immediately postintervention than at 3 to 6 years postintervention
Hutchings, J 2007[25] See Table 4: 2007[24] , Bywater T, 2009[26] , Jones K, 2008[139]	Good	N = 116 Mean age: 53m Male: 58%	IYPP vs. WLC	Significant reduction in antisocial and hyperactive behavior and increased self control ECBI-I p <0.001 ECBI-P p <0.001 Conners p <0.001	Improved measures of perceived parenting stress and positive communication Behavioral effect size 0.63 (95% CI, 2.0 to 6.9)
Jones, K 2007[24] See Hutchings, 2007[25]	Good	N = 79 Mean age: 46m Male: 68%	IYPP vs. WLC	Using clinical cutoff criteria, 58% of Tx group compared with 33% of WLC had followup scores below the level of clinical concern Connors p <0.013 DPICS-CD p >0.004	mean difference of 9.6 (3.7 to 15.5, p <0.002) between groups at follow-up for positive parenting behaviors; effect size of 0.57

Table 3. KQ1. RCTs of parenting interventions (continued)

Study	Quality	N Mean Age (SD) % Male	Interventions compared	Results	
				Child behavior	Parent competence
Lavigne, JV 2008[23]	Good	N = 117 Mean age: 54m Male: 53%	IYPP vs. MIT	Significant behavior improvement with intervention across all 3 conditions including bibliotherapy (MIT) over time F(2, 305.94) = 25.52, p = 0.001 ECBI-I p <0.002 ECBI-P p <0.001	Dose effect – little effect of therapist led intervention over bibliotherapy unless parents attended significant proportion of sessions PSI p <0.01 PLOC p <0.02
Markie-Dadds, C 2006a[18]	Fair	N = 63 Mean age: 43m Male: 63%	Triple P vs. SD vs. WTC	Both SD and EBFI ECBI-I p <0.01 ECBI-P p <0.01 Children showed lower levels of disruptive behavior F(4,34) = 3.39, p = 0.019	Improved at posttreatment but some evidence of relapse effect in parenting at followup. At followup, mothers report decline in perceived self efficacy PSOC-S p <0.001 PSOC-E p <0.05
Markie-Dadds, C 2006b[16]	Good	N = 41 Mean age: 47m Male: 76%	ESD vs. SD vs. WLC	ECBI-I p <0.001 ECBI-P p <0.001 Children in Enhanced Triple P showed significantly lower levels of disruptive behavior than standard program, although both interventions demonstrated significant improvement over WLC, F(4,30) = 10.41, p = 0.0001	ESD SD PDR-T p <0.01 NS Mothers in Enhanced Triple-P report higher levels of perceived parenting efficacy than mothers in standard Triple P condition
Matos, M 2009[30]	Fair	N = 32 Mean age: NR Male: NR	PCIT vs. WLC	Highly significant reduction in ADHD and oppositional behaviors F = 32.73; p <0.000 ECBI-I p <0.000 ECBI-P p <0.000	PPI p <0.000 Increased use of positive parenting practices
Nixon, RD 2001[31]	Good	N = 34 Mean age: 47m Male: 82%	PCIT vs. WLC	Reduced hyperactivity and improved behavioral flexibility; by 6m, intervention group comparable to normal social validation controls; ADHD symptom severity reduced F(1, 30) = 5.42, p <0.05	Results from PSI NR

Table 3. KQ1. RCTs of parenting interventions (continued)

Study	Quality	N Mean Age (SD) % Male	Interventions compared	Results	
				Child behavior	Parent competence
Nixon, RD 2003[32] Related to Nixon 2004[140] see Table 4	Fair	N = 54 Mean age: 47m Male: 70%	PCIT vs. ABB PCIT	Initially standard PCIT intervention superior but at 6m followup the result of the Standard and the Abbreviated programs become similar ST ABB ECBI-I-MR p <0.001 p <0.001 CBCL-E NS NS Independent observations of reduced child non-compliant behavior F(5,39) = 7.25; p <0.001	Shorter PCIT intervention works as well as standard intervention; Mother report significantly less stress in the abbreviated program; blinded observations of parenting interaction show increased in positive communication ST ABB PSI NS p <0.05 PSOC p <0.05 p <0.05 PLOC p <0.001 p <0.01 P- p <0.01 NS P + p <0.001 p <0.001
Pisterman, S 1989[135]	Good	N = 50 Mean age: 49m Male: 81%	PBT vs. WLC	Positive Tx effect on child compliance p <0.001	Positive Tx effect on parental style of interaction and management skills; effects maintained at 3m followup
Pisterman, S 1992[137]	Fair	N = 57 Mean age: 47m Male: 91%	PBT vs. WLC	Significantly increased child compliance F(2,86) = 11.05, p <0.05	Parents observed to have increased quality and frequency of positive parenting communication; improved parental compliance-management skills
Pisterman, S 1992[136]	Good	N = 91 Mean age: 50m Male: 86%	PBT vs. WLC	Lack of concordance between measures of observed vs. reported child behavior, however PBT showed impact on child behavior and compliance F(6,168) = 3.90, p <0.01	Group PBT had positive impact on parenting stress and parental sense of competence, independent of actual improvements in observed child and parent behavior
Sanders, MR 2007[21]	Good	N = 139 Mean age: 85m Male: 68%	Triple P vs. EBFI vs. SD vs. WLC	ECBI-F p <0.01 Enhanced, Standard and Self-directed all showed maintenance of Txd gains; Changes in disruptive behavior maintained or further improved Sustained improvement at 1 and 3yr followup; (F= 2.72, p = 0.01)	PSOC p <0.05
Schumann, EM 1998[35] Related to Eyberg (1995)[34] and Hood, (2003)[29]	Good	N = 64 Mean age: 60m Male: 81%	PCIT vs. WLC	ECBI-I p <0.01 ECBI-P p <0.01 Improved behavior both reported by parents and observed in classroom F(1,38) = 36.18, p <0.01	Allocation by family so both available parents could participate Parent report more positive interaction with children; less parent stress; increased locus of control; maternal perception of child behavior more positive than paternal perception

Table 3. KQ1. RCTs of parenting interventions (continued)

Study	Quality	N Mean Age (SD) % Male	Interventions compared	Results	
				Child behavior	Parent competence
Sonuga-Barke, EJ 2001[36]	Good	N = 78 Mean age: 36m Male: 62.9%	PBT (preNFPP) vs. PCS vs. WLC	PBT effect size usually found in range associated with stimulant medications F(2,74) = 11.64; p <0.0001; Clinically significant improvement in child behavior under PBT condition; little or no effect with PCS	PBT had more effect on measures of parent satisfaction than PCS
Sonuga-Barke, EJ 2002[38]	Good	N = 83 Mean age: 36m Male: NR	PBT (preNFPP) vs. WLC	Intervention related to high levels of improvement in child behavior unless mother also has ADHD, F(2,80) = 8.32, p <0.005	High levels of maternal ADHD limit behavioral improvement in child
Sonuga-Barke, EJ 2004[37]	Good	N = 89 Mean age: 36m Male: NR	PBT vs. WLC	PBT did not significantly improve ADHD symptoms when delivered by specialist vs. non-specialist visitors F = 0.26 (95% CI, -0.24 to -0.68)	Maternal well-being decreased in PBT and WLC conditions; Change between groups 0.22 (95% CI, -0.23 to 0.67); difference may be due to specialist vs. non-specialist health visitors
Thompson, MJJ 2009[39]	Good	N = 41 Mean age: 52m Male: 100%	NFPP vs. TAU	Large effect size (>1) of intervention of ADHD symptoms on the PACS Chi-squared(1) = 7.025; p = 0.008 Impact of intervention on ODD is less pronounced Calculated on small N	No significant improvement in measures of maternal mental health
Williford, AP 2008[27]	Good	N = 96 Mean age: 53m Male: 72%	IYPP vs. NT	Intervention decreased child disruptive behavior in the classroom Chi-square(1, N = 76) = 7.04, p = 0.008	Positive impact on parenting behavior, but no difference in caregiver report of perceived changes of child behavior between intervention and control groups; teachers in consultation model and parents in intervention model report significantly improved behavior (at least 1SD decrease in at least one measure of disruptive behavior)

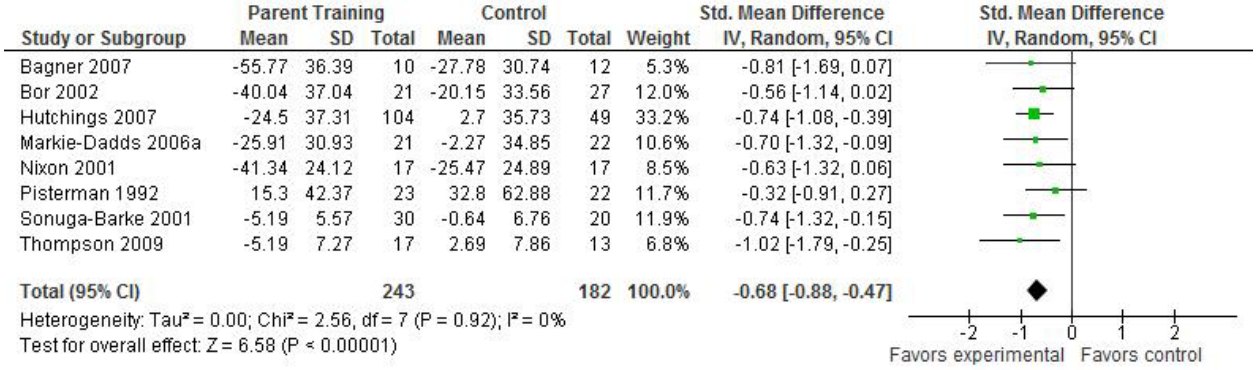
Note: table reports effect size for studies included in quality assessment of data

Abbreviations: ABB = Abbreviated PCIT delivery; ADHD = Attention Deficit Hyperactivity Disorder; BSI = Brief Symptom Inventory; CBCL-A = child behavior checklist-attention; CBCL-E = child behavior checklist-externalizing; CBPT = community-based parent behavior training; CI = confidence interval; CMT = Child Management Training; DPICS = Dyadic Parent-Child Interaction Coding Scheme – Child Deviance; EBFI = enhanced behavioral family intervention; ECBI-I = Eyberg Child Behavior Inventory; ECBI-F = Eyberg Child Behavior Inventory - function; ECBI-I = Eyberg Child Behavior Inventory - Intensity; ECBI-I-MR = Eyberg Child Behavior Inventory – Intensity-Mother Report; ECBI-P = Eyberg Child Behavior Inventory - Problem; ESD = enhanced self directed Triple P; ESL = English as a second language; HEAR = Helping Encourage Affect Regulation; ITT = Intention to Treat analysis; IYPP = Incredible Years Parenting Program; m = months; MIT = minimal intervention therapy; N = sample size; NFPP = New Forest Parenting Program; NR = not reported; NS = not significant; ODD = oppositional defiant disorder; PBT = parent behavior training; PCIT = Parent-Child Integration Therapy; PCS = Parent counseling and support; PS = parent stress; PS-T = parenting style, Total; PSI = parent stress index; PLOC = parental locus of control; PSOC = parenting sense of competence; PSOC-E = parenting sense of competence-satisfaction; PSOC-E = parenting sense of competence-efficacy; PPI = Parenting Practices Inventory; SD = standard deviation; SET-PC = Supportive Expressive Therapy-Parent Child; ST = standard; TAU = treatment as usual; Tx = treatment; WLC = Wait List Control; y = year

Meta-Analysis of Parent Behavior Training for Disruptive Behavior Disorder in Preschoolers

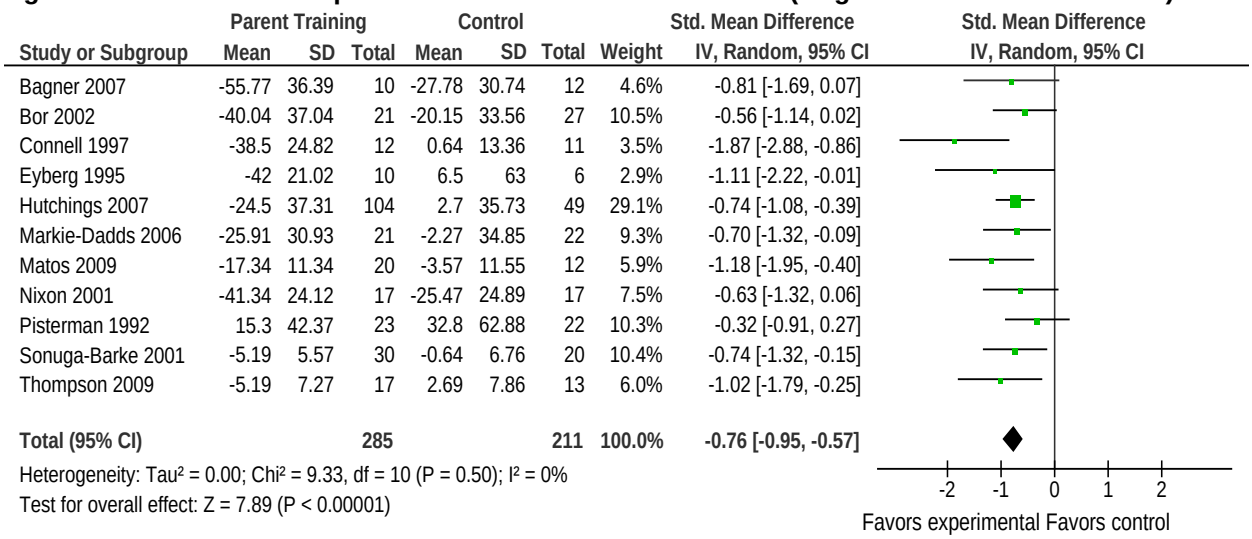
We performed meta-analyses in order to document the degree of benefit following PBT for DBD in preschoolers. We compared all studies with both "fair" and "good" internal validity, presenting the forest plots both with and without the studies rated as "fair." The standardized mean difference(SMD) for each study represents the measured change in parent-rated child behavior between intervention and control groups. The studies used differing measures of child disruptive behavior, including reports of ADHD symptoms. Sensitivity analysis was done based on different assumptions on the correlation between baseline and outcome values for individual children, using 0.0, 0.3 and 0.5. A random effects model was used for the meta-analyses. Similar results were obtained in the sense of significant overall treatment effect. In all cases, heterogeneity was within acceptable limits. Figure 4 shows the forest plot using the eight "good" studies, using a correlation factor of 0.3. Figure 5 is a forest plot that uses both studies rated as "good" and as "fair." These summaries indicate that PBT improves parent rated child behavior in preschoolers.

Figure 4. Effect of PBT on preschool child behavior outcomes (8 "good" studies)*



*includes RCTs rated as "good" quality (assumes correlation between post- and prescore of 0.3)
Note: *means* are post/pre differences; *Std. Mean Difference* reflects difference of these differences

Figure 5. Effect of PBT on preschool child behavior outcomes (8 "good" and 3 "fair" studies)*



*includes RCTs rated as "good" and "fair" quality (assumes correlation between post- and prescore of 0.3)
Note: *means* are post/pre differences; *Std. Mean Difference* reflects difference of these differences

These meta-analyses confirm the efficacy of PBT interventions for preschool DBD, including ADHD. There is a high degree of consistency across studies despite the fact that samples were from different countries, different studies used different instruments, and there are differences among the interventions. It should be noted that only those participants who completed the interventions were included in the treatment groups for the purpose of analysis (not an intention-to-treat analysis). In addition, studies were not blinded. Both are factors that lead to higher estimates of effectiveness.

Long-Term Extensions of Controlled Trials of Parenting Interventions

This section describes results from the extension studies investigating maintenance of behavior benefits for preschoolers following PBT (see Table 4). Eight cohorts of preschoolers were followed for greater than 12 months after enrolment in a clinical trial examining parent interventions for DBD. Long-term effects were examined across 9 studies[19,21,26,27,29,33,139-141] and ranged from 1 to 6 years after treatment. Most studies examined parent-report and clinician observation of maintenance of treatment gains; one study examined maintenance of treatment effects in the school environment.[33] No extension study included untreated comparison groups, and attrition over the followup period ranged from 24 percent at 18 months[26] to 54 percent at 3 to 6 years,[21,29] limiting interpretation of the results. In general, these extension studies suggest that post-treatment gains, including improvements in ADHD symptoms, are maintained over time. A recent study examining PBT with and without school-based teacher or child interventions did include a no-treatment control. This study showed maintenance of benefits of PBT at two years.[40] Studies do not comment on adverse events related to PBT.

In summary, parenting interventions are effective in reducing child DBD and improving parenting skills. The benefits appear to be maintained following completion of the treatment, but appropriate comparison groups are not available

Table 4. KQ1. Long-term extensions of clinical trials of parenting interventions

Study	Quality	Attrition from study (dropouts/ randomized)	Program Length of RCT/ Followup	Results	
				Child behavior	Parent competence
Bor, 2002[19] Also included in Table 2 and Table 3	Good	28% (24/87)	Triple P vs. EBFI 15w/ 1y	Behavior improved under both Enhanced and Standard Triple P interventions ECBI-I p <0.01 ECBI-P p <0.001	No change in negative parenting style, Both enhanced and standard program effected change to an equally significant degree; neither intervention reduced inattentive behavior from post to followup PS p <0.001 PSOC p <0.001
Bywater, 2009[26] See Hutchings, 2007[25] Table 2 and Jones 2007[24] and Jones 2008[139]	Good	24% (25/104)	IYPP 12w/12m and 18m followup	Significant improvement in child behavior maintained at 18m post Tx	Significant improvement in parenting behaviors; improvement reported in levels of perceived parental stress and depression measures
Funderburk, 1998[33] See also Table 2, Table 3 and Table 5	Good	NR (NR/84)	PCIT 12w/12m and 18m	Significant improvement in social competence between post Tx and followup (maturational?); Strong generalization of PCIT at 12m; less so at 18m, with shifts toward pretreatment levels	Home behavior stays within normal limits at 18m, so slide in classroom likely due to classroom demands
Hood, 2003[29] Related to Eyberg. 1995 and Schumann, 1998[35] see Table 2	Fair	54% (27/50)	PCIT 12w/6y	75% of children maintained behavioral improvement and made continuing gains	Long-term effects on improved parenting self efficacy
Jones, 2008[139] See Hutchings, 2007[25]	Good	44 % (35/79)	IYPP 12w/18m	Positive effect of IYPP on all aspects of measured child behavior	Significant improvement in + ve parenting behavior;
Nixon, 2004[140] Related to Nixon 2003[32] see Table 3	Fair	41% (38/92)	PCIT vs. ABB PCIT 12w/1y	Tx gains in both standard and abbreviated PCIT are maintained at 1 and 2 y followup	Positive changes in parenting style and communication maintained

Table 4. KQ1. Long-term extensions of clinical trials of parenting interventions (continued)

Study	Quality	Attrition from study (dropouts/ randomized)	Program Length of RCT/ Followup	Results	
				Child behavior	Parent competence
Sanders, 2007[21] Also included in Table 2 and Table 3	Good	54 % (166/305)	Triple P vs. EBFI vs. SD 15w/3y	ECBI-F p <0.01 Enhanced, Standard and Self-directed all showed maintenance of Txd gains; Changes in disruptive behavior maintained or further improved	Sustained improvement at 1 and 3y followup; PSOC p <0.05
Shelton, 2000[141] Extension of Barkley, 2000[142] , see Table 3, and Table 5	Fair	NR (NR/151)	BKLY 10m/2y	Early intervention in class may not produce enduring effects once Tx withdrawn; improvement may be due to maturation effect; Only small proportion of disruptive children may be truly at risk for psychiatric disorder	No benefits to parenting program post 1y, however there were significant limitations in the parenting arm of study
Williford, 2008[27] Also in Table 2 and Table 3 as RCT and Table 5 as mixed nonpharmacological intervention	Good	7% (7/103)	IYPP 10w/ 1 yr	Intervention decreased child DBD in the classroom	Positive impact on parenting behavior, but no difference in caregiver report of perceived changes of child behavior between intervention and control groups; teachers in consultation model and parents in intervention model report significantly improved behavior (at least 1SD decrease in at least one measure of disruptive behavior)

Abbreviations: ABB = Abbreviated PCIT delivery; BKLY = Barkley intervention; DBD = Disruptive Behavior Disorder; EBFI = enhanced behavioral family intervention; ECBI-F = Eyberg Child Behavior Inventory - function; ECBI-I = Eyberg Child Behavior Inventory - Intensity; ECBI-P = Eyberg Child Behavior Inventory - Problem; IYPP = Incredible Years Parenting Program; m = months; NR = not reported; PCIT = Parent-Child Integration Therapy; PS = parent stress; PSOC = parenting sense of competence; RCT = randomized controlled trial; SD = standard deviation; Triple P = positive parenting of preschoolers; Tx = treatment; vs. = versus; w = week; y = year

Effectiveness of Combinations of Parent Behavior Training and School- or Daycare-Based Interventions for Preschool Children With Disruptive Behavior Disorder or ADHD

Seven articles examining multiple component psychosocial and/or behavioral interventions for Disruptive Behavior Disorder (DBD) in preschool children met criteria for review.[27,40,42,122,141-143] This group of studies did not include a focus on pharmacological interventions, but primarily examined combinations of PBT and school- or daycare-based interventions. Of these, four met quality criteria for "good" internal validity,[27,40,122,143] and three met criteria for "fair" internal validity (see Table 5).[42,141,142]

Five of these studies[27,122,141-143] included a specific focus on effectiveness of interventions for children with ADHD symptoms. A sixth study included ADHD symptoms as part of two composite child symptoms variables, either rated by parents or by teachers.[40] The seventh study examined children with Oppositional Defiant Disorder (ODD) as the primary concern, however 49.5 percent of them received medication for ADHD between the time of original intervention and 2-year followup assessment.[42] Two studies recruited preschoolers using clinical diagnostic assessments, and examined an intensive multicomponent intervention (MCI) comprised of PBT plus school or daycare consultation for preschool children with ADHD.[122,143] One of these trials compared MCI with diagnostic assessment and community care treatment as usual[143] and the second compared MCI to diagnostic assessment and a standardized parent education program.[122] These trials enrolled children from primarily middle class, educated families, with three percent on social assistance. Three studies in this group recruited children using high ADHD and DBD symptom ratings on screening measures obtained when parents enrolled children for kindergarten and examined combined PBT and teacher training versus no treatment.[27,141,142] Barkley, et al.,[142] examined a 1-year intervention which included PBT and a specialized treatment classroom, alone and in combination, compared to a no treatment control group for preschoolers with high levels of parent reported ADHD and other DBD symptoms. Adjustments to group assignments due to feasibility issues interfered with randomization. These children were drawn from low to middle socioeconomic status (SES), predominately European-American families, 39 percent of whom received social assistance. This sample was followed long-term by Shelton, et al.,[141] who evaluated these children 2 years postintervention in comparison to a community control. Williford, et al.,[27] compared teacher consultation and PBT versus services as usual for preschoolers in Head Start programs.[27] These children were from predominantly low SES African-American families whose preschoolers had high levels of ADHD and ODD behaviors on screening measures. The sixth study, Hanisch, et al.,[40] examined PBT and teacher training versus waitlist control among German kindergarten children of parents with low education levels over a 10-week intervention, reporting ADHD symptoms as part of a composite behavior measure. Overall, these studies of combined PBT and teacher or classroom interventions for children with ADHD or ADHD and DBD symptoms discovered that parent participation in groups for behavior training could be modest even when transportation and babysitting were provided and sessions occurred at convenient times. In this way, outcomes for these PBT interventions will differ systematically from those in the RCTs described earlier, where PBT intervention outcomes were measured for children whose parents completed the intervention.

The seventh study included in this section, Reid, et al.,[42] was a 2-year follow up of 159 children ages 4 to 7 (mean age 5.8 years) who participated in an Incredible Years Training program comparing several treatment components alone and in combination. Children were randomly assigned to receive PBT only, teacher training (TT) only, child training (CT) only, PBT + TT, CT + TT, PBT + CT, PBT + TT + CT, or wait list control for 8 to 9 months and then received treatment. Of the 133 families who received treatment initially, 121 (91%) completed 2-year posttreatment assessments. Attendance at sessions was high (90 to 95%), and at the second year assessment almost half of the children were receiving medication, two important differences from other studies discussed in this section.

Two studies investigated the effectiveness of a multicomponent intervention (MCI) for preschoolers with ADHD who generally came from families from a middle income background.[122,143] Overall, children in the MCI group did not improve significantly more than children whose parents were enrolled in the parent education (PE) program[122] or who received community treatment as usual.[143] Parents in the MCI group attended a mean of 37 percent of 20 group behavior training sessions and 60 percent of families received a home behavior plan, while school plans were developed for 82 percent of children. Parents in the PE group attended 30 percent of 20 sessions, but received no additional services by protocol.[122] Child behavior, social skills, and school readiness improved significantly over 12 months in both groups. In the study where the comparison intervention was community treatment as usual, approximately 20 percent received stimulant medication at some point during the intervention.[143] These studies suggest that additional resources for home-based behavior plans, or classroom/daycare-based behavior plans, do not provide substantially increased benefit for preschool children with ADHD, beyond that provided by diagnostic assessment and well-organized parent education programs, or community treatment as usual for children in families of middle income. These studies had few children from low SES background. There were no nontreatment comparison groups in these studies.

In contrast, Barkley, et al.,[142] showed that at the end of a school year-long intervention, classroom interventions demonstrated significant positive impact on teacher-reported disruptive behavior and social skills outcomes, compared to PBT alone and to a no-treatment comparison. In the PBT groups, 68 percent of parents attended less than 5 of 14 sessions. Ten children (six% of the sample) received medication, and half were in the classroom interventions, half not. The classroom program included behavior training to improve classroom compliance, social skills training, and self control training, along with an emphasis on early academic skills. Their first grade teachers were provided with information about the children and general suggestions about management, and offered additional consultations over the next three months, but only 10 percent of teachers accepted. Two years later, however, Shelton, et al.,[141] found that children who had received the classroom intervention no longer showed improved behavior relative to those who did not receive a classroom intervention (controlling for initial behavior scores), suggesting that the benefits derived from the classroom intervention were not maintained 2 years later. The study did not examine the 2-year maintenance effects of PBT.

Williford, et al.,[27] examined school consultation and PBT compared with services as usual, in preschoolers from low SES, primarily African-American families enrolled in Head Start programs. The group receiving combined school and home intervention showed improved child behavior and social skills reported by both teachers and parents; in addition, both teachers and parents showed improved child management skills. The majority of parents (65%) did not attend more than 50 percent of the sessions, but those who did reported increased parenting skills.

The recent German study, by Hanisch, et al.,[40] examined dose effect for a number of PBT sessions attended in an intervention that offered combined PBT and teacher behavior training for children with ADHD and/or DBD. In a generally low SES sample, approximately 20 percent of parents attended no sessions despite expressed willingness to do so prior to the study. Intention to treat analysis showed improved child behavior and improved parenting strategies with effect size in the range of 0.25 to 0.30. For those families where parents attended five or more PBT sessions, children showed greater improvement in behavior at school than those children whose parents did not attend PBT, with an effect size of 0.39.

Summary and Limitations

Very few studies offer information about the benefits of psychosocial/behavioral interventions for preschoolers with DBD who also have ADHD or who are at risk for ADHD. The seven studies reviewed examine the question of efficacy or effectiveness in offering PBT combined with school or daycare-based interventions for the combination of ADHD, oppositional and aggressive symptoms and, in some studies, school readiness in children, as well as measures of parenting among parents. The outcome measures examined and the methods of analysis vary widely from study to study, as do the interventions to some extent, precluding meta-analysis. Descriptive comparison of these studies suggests that SES may be an important determinant of outcome. Direct SES comparisons within a single study, utilizing proper control groups, would provide the best information to answer these questions.

One study offers observations that enhance the findings reported earlier regarding PBT because they provide a no-treatment wait list comparison group demonstrating superiority of treatment conditions, including PBT, over a school year, upon a 10-week intervention.[41] In addition, Hanisch, et al.,[40] show a dose response of additional improvements to five or more sessions of PBT, as not all parents attended all sessions. Predictors regarding full attendance were not addressed. The issue of attendance is important, as studies described above supporting effectiveness of parent behavior programs report results for those children whose parents completed the intervention.

Table 5. KQ1. Summary of studies comparing nonpharmacological combination treatment modalities for preschoolers with ADHD or with DBD

Study	Study Design Quality Rating	ADHD DBD	N Mean age (SD) % Male SES	Interventions compared					Length of Intervention Primary/ Followup	Results: Effectiveness	Comments Other details
				PBT Behavioral	Teacher Consult	Classroom	CC/ Parent Edu	None			
Barkley, 2000[142] Followup Shelton, 2000[141]	RCT Fair	DBD	N = 158 Age: 4.8y Male: 40% low to middle SES	✓			✓		10w/24m	Early intervention results in significant improvement in DBD which may not endure once Tx withdrawn CBCL-At p = 0.008 CBCL-A p = 0.002 No improvement in academic skills	No benefit in PBT program after training phase; only a small proportion of disruptive children may be truly at risk for future psychiatric disorder
Hanisch, 2010[40]	RCT Good	At risk of DBD	N = 155 Age: 4.2y Male: 73% low SES	✓				✓	10w/8w	Parent report and teacher report = less disruptive child behavior after treatment	Low compliance reported
Kern, 2007[122]	Prospective cohort Good	Risk ADHD	N = 135 Age: 4y Male: 78.5% Mixed population SES	✓			✓		12m/12m	Significant decrease in problem behaviors (ADHD & aggression) in both groups; Statistically significant improvement in behavior, social and preacademic skills in both conditions	No difference between modalities may be due to dose effect of MCI intervention, i.e.: only 1/2 Tx group received all 3 parts of MCI
McGoey, 2005[143]	RCT Good	Risk ADHD	N = 57 Age: 4.0y Male: 85.9% Primarily middle class			✓	✓		12w/12m	Small positive effects social control school and home Moderate increase in + ve parenting	Child compliance not increased over control group

Table 5. KQ1. Summary of studies comparing nonpharmacological combination treatment modalities for preschoolers with ADHD or with DBD (continued)

Study	Study Design Quality Rating	ADHD DBD	N Mean age (SD) % Male SES	Interventions compared					Length of Intervention Primary/ Followup	Results: Effectiveness	Comments Other details
				PBT Behavioral	Teacher Consult	Classroom	CC/ Parent Edu	None			
Reid, 2003[42]	RCT Fair	ODD	N = 159 Age: 5.9y Male: 90% Predominantly lower SES	✓	✓	✓		✓	6m/24m	75% functioning in the normal range at 2y followup 25% classified as treatment nonresponders Teacher training added significantly to long-term school outcomes Baseline maternal parenting and posttreatment marital discord were associated with poor treatment response at home	Parenting behavior predicted 2y outcome and child behavior did not
Shelton, 2000[141] Followup to Barkley, 2000[142]	Followup to RCT Fair	DBD	N = 158 Age: 4.8y Male: 66.5% Predominantly lower SES	✓			✓		10w (Barkley)/ 24m	CBCL-T p = 0.001 Despite ongoing signs of risk in DB children, significant improvement with maturity – some so that at followup they had no sign of DB.	Small proportion of DB truly at-risk; subsequent service utilization not affected by early intervention
Williford, 2008[27]	Prospective cohort Good	At risk for ADHD/ ODD	N = 96 Age: 4.5y Male: 70% Predominantly lower SES	✓	✓	✓			4m (IYPP)/ 12m	Intervention decreased child DBD in the classroom	Effective BMT prevents escalation of DBD Teachers in consult model & parents in PBT model report significantly improved behavior (at least 1 SD decrease in at least one measure of DBD)

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; BMT = Behavior Management Therapy; CBCL-A = Child Behavior Checklist-Aggression; CBCL-At = Child Behavior Checklist-Attention; CBCL-T = Child Behavior Checklist-Thought; CC/Parent Edu = Community care and parent education; DB = disruptive behavior; DBD = Disruptive Behavior Disorder; IYPP = Incredible Years Parenting Program; m = month; MCI = Multi-component Intervention; ODD = Oppositional Defiant Disorder; PBT = parent behavior training; RCT = randomized controlled trial; SD = standard deviation; SES = socioeconomic status; Tx = treatment; w = week; y = year

Efficacy and Safety of Psychostimulant Interventions for Preschool Children With ADHD

This section reviews pharmacologic interventions for preschoolers with documented ADHD (Table 6). Fifteen articles representing 11 studies examined efficacy of psychostimulants, primarily immediate release MPH, prescribed two or three times daily in preschool children with documented ADHD.[7,43-56] The largest randomized clinical trial, the Preschool ADHD Treatment Study (PATS) was rated as a "good" study and is described in detail below.[7,51-54] There was one additional "good" study[55] and the remaining nine studies were rated "fair" in internal validity. Except for the PATS, samples were generally small. Study participants were primarily boys from middle SES families, with ADHD Combined type (ADHD-C), or hyperactive impulsive type. Two studies examined children with ADHD and developmental disabilities or pervasive developmental disorders.[46,48] Clinical trials were generally of short duration, lasting days to weeks. Almost all of the studies investigated immediate release MPH, in comparison to placebo.[44-48,50,55,56] One study compared the most effective and well-tolerated dose of either MPH or mixed amphetamine salts (MAS) to placebo.[49] All studies noted clinically significant symptomatic improvements on psychostimulant medication. Those studies which compared adverse events of medication or placebo, noted that behaviors attributed to side effects were present in subjects on placebo as well.[46,47,49] For those children who participated in fixed dose titrations, adverse events were more common and of greater intensity at high rather than low dose.[47] Poor appetite, social withdrawal, lack of alertness, stomach ache, irritability, and rebound were noted as increased when on stimulants relative to placebo.[46,49]

One study compared combinations of medication and parent intervention. Heriot, et al.,[43] randomized 26 preschool children with ADHD to four conditions: a single dose of 0.3mg/kg 2 times daily (b.i.d.), immediate release MPH or placebo in combination with PBT or parent support. Only 12 children (46%), ages 3 to 5, and their parents completed the study. Descriptive comparison of individual pre-post analyses indicated that children in active treatment conditions showed improvement relative to those in nonactive treatments. All children in the combination active MPH plus active PBT condition showed symptomatic improvement in at least one domain, whereas only one child showed improvement in one domain in the non-active interventions condition. Some individual children receiving only one active treatment also benefited. This study suggests efficacy for both MPH and for PBT, with the combination addressing a wider range of needs for a greater number of children. However, the sample is too small to draw conclusions, and most of the participants did not complete the protocol.

Preschool ADHD Treatment Study

The multisite National Institute of Mental Health (NIMH) funded PATS, which offers high quality evidence about efficacy, safety, and effectiveness of immediate release MPH, 3 times daily (t.i.d.), for preschool children 3 to 5 years of age.[7,51-54] The study included several stages, and ensured that parents of ADHD children received 10 weeks of PBT prior to the initiation of medication. The sample were 76 percent boys, 63 percent Caucasian, and 76 percent two parent families, of which 97 percent had completed high school. Only 165 children of the 303 enrolled (54%) actually entered the randomized double blind crossover titration trial. Two phases preceded randomization: 10 PBT sessions and a preliminary open-label medication safety lead-in phase. However, overall characteristics of the sample remained essentially the same.

Of the 303 participants who consented and enrolled, 279 entered PBT, and 261 completed the 10 sessions. Following this, 34 (11% of original sample) declined further participation or did not want to use medication. Eighteen families (6%) were satisfied with their child's improvement, and another 19 children (6%) showed significant improvement. Of the remaining children, 183 enrolled in the open-label safety lead-in phase. One hundred sixty five who tolerated the open-label safety lead-in phase were randomized into the double blind titration trial. The investigation of MPH efficacy consisted of a randomized 5-week double blind crossover titration trial including four different MPH doses (1.25mg, 2.5mg, 5.0mg, 7.5mg) and placebo, given t.i.d. to identify best dose. Best dose was determined from parent and teacher reports of symptom ratings and side effects during the cross-over titration trial. One hundred fourteen children entered and 77 completed the next phase, a four-week double blind RCT comparing best dose to placebo. And finally, 140 entered the 10-month open-label maintenance phase. Between each phase families could opt to discontinue the study or move on to another phase. For example, 61 families opted to move to the open-label maintenance phase prior to completing the 4-week RCT parallel phase.

Eleven of 183 children (6%) enrolled in the open-label lead-in phase had moderate to severe adverse events and were not eligible to enter the titration phase. An additional 21 of 183 (11.5%) children did not tolerate the highest dose, 7.5mg t.i.d., and received a second week at 5.0mg t.i.d. during the titration trial.[7] These numbers suggest that a substantial proportion of preschool children experience moderate to severe adverse events with doses of MPH within recommended range of doses. Five additional children did not tolerate the crossover titration or parallel phases, while 12 were placebo responders and 7 were MPH nonresponders. Forty children experienced behavioral deterioration during the parallel RCT.

The PATS study offers good evidence for the efficacy of MPH in improving core ADHD symptoms using several different measures. Symptom improvement was noted during the crossover titration phase comparing placebo with low dose and high dose conditions for MPH (low dose mean optimal dose 0.7 $\pm$ 0.4mg/kg/day, and high dose mean optimal total dose of 14.2 $\pm$ 8.1mg/kg/day).[7] During the 4-week parallel phase, functional outcomes included small positive effect for teacher- but not parent-rated ADHD symptoms and social competence on MPH, no improvement in parental stress, and moderate worsening of parent-rated child mood on MPH; clinicians, on the other hand, rated children as improved with a strong effect size.[51] These findings were contrary to expectations. In addition, children noted to have more comorbid conditions at baseline were less likely to benefit from the MPH intervention. Those 15 (9% of 165) who had 3 or 4 comorbid conditions were also more likely to have family adversity.[52]

It is hard to know what to make of the fact that parent ratings and clinicians ratings do not agree about effectiveness of MPH treatment during the 4-week parallel trial. Parent ratings showed little benefit and some functional worsening for children on best dose MPH compared to those on placebo, while clinician's global impressions documented improvement. One explanation could be that the parent- and teacher-rated symptom measures reported in this phase of the study are designed to be used as population screening measures and therefore are not sufficiently sensitive to change over time.

Adverse Events

The PATS study provides the best quality evidence regarding adverse events in preschoolers using MPH.[54] In the study, adverse event recordings included spontaneous reports by parents to a physician's general inquiry about their child's health, as well as parent and teacher reports on

research forms. Adverse events were recorded whether or not they could be attributed to the use of MPH. Moderate severity of adverse events was defined as causing some functional impairment and/or requiring medical attention or intervention (e.g., over-the-counter medication for headache). Severe adverse events prevented functioning in a major area of daily life and/or presented a serious medical threat. A serious adverse event had to meet the U.S. Food and Drug Administration (FDA) definition (requiring hospitalization or leading to persistent incapacity).

Physicians also monitored vital signs, height, and weight. Tachycardia was defined as a resting heart rate >120 beats/minute twice at the same visit. Hypertension was defined as blood pressure (BP) above 95th percentile for age and gender on two readings at the same visit. If such a reading was noted then the child's BP was measured again within 7-14 days. If the BP remained elevated then an adverse event for hypertension was noted. Only severe ratings are reported in the article, defined as having a BP >20mmHg above the limit.

Results show that emotionality/irritability was the most common reason for families to discontinue MPH use in the early stages of medication use. Of the 21 children who discontinued the study because of adverse events, nine discontinued because of emotionality/irritability.[54] These observations are concordant with functional outcomes reported above for the parallel phase where parents indicated worsening in child mood in the MPH group.[51] Early termination from medication was also related to symptomatic behaviors such as increased talking, restlessness, and "spaciness," suggesting that poor efficacy may also interfere with adherence. Other adverse events, such as sleep difficulties and appetite loss, were tolerated, and were not associated with termination of the MPH trial.[54]

While emotional adverse events were reported most frequently during the double blind titration trial, they did not occur more frequently for children while on MPH in any of the dose conditions compared with placebo. By contrast, trouble sleeping, appetite loss, being dull/listless/tired, stomach ache, social withdrawal, and buccal/lingual movements were reported more frequently by parents while children were on MPH than on placebo.[54] Changes in vital signs, BP, and pulse occurred in similar frequencies in both active treatment and placebo groups. Eight children exceeded the norms for BP on a single visit; none exceeded the norms on a second visit. Cardiovascular adverse events were therefore of no clinical significance during the titration trial.[54]

Overall, the study evaluating safety and tolerability of MPH for preschoolers in the PATS confirms that physiological adverse events are common for young children with ADHD (spontaneously reported by 30% of parents), but serious clinically significant adverse events attributable to MPH are rare.[54] Eleven percent of children who started medication discontinued treatment due to adverse events.

Growth rates were impacted by the use of MPH.[53] While the children enrolled were significantly larger than average for their age at baseline, they also showed significant reductions in rate of growth over the period of the study. On average, the children were 2.0 cm taller and 1.8kg heavier than peers at baseline. For those who remained on MPH, the annual growth rate was 22 percent (1.4cm/yr) less than expected for height and 55 percent (1.3kg/yr) less than expected for weight.[53]

Please refer to the section following Table 7 for further discussion of adverse events related to pharmacological treatments.

The PATS study provides useful information about adherence to medication in this age group. While the main message of the PATS is that MPH is generally safe for young children, a secondary message is that parents remain uncertain about using stimulant medications for

preschoolers. Even in this select group of families willing to participate in research, 34 of 261 (13%) who completed the 10 session PBT declined further participation or did not want medications, while an additional 18 (7%) were satisfied with the child's improvement; a further 19 children (7%) showed significant improvement in ADHD symptoms following PBT. Only 183 of the original 303 (60%) children entered the open-label safety lead-in trial and 140 (46%) entered the maintenance phase following the trial. Of these only 95/303 (31%) completed the 10 months, although some may have discontinued the trial in order to switch to long-acting MPH.[54]

The primary study examining long-term outcomes for preschool children using stimulant medication for ADHD is the PATS study, summarized above, which reported on the 10-month outcomes following an open-label continuation trial.[7,53,54] In one additional study, Cohen[56] followed 24 preschoolers with hyperactive symptoms for a year following a trial of MPH. Where preschool children remain on medication they appear to maintain symptom benefits, but lack of control for maturational effects interferes with drawing conclusions. Many families withdraw from continued use. Ninety-five of 183 (52%) of those in the PATS who tried medication completed the open-label phase and not all of these experienced adverse events, as adverse events accounted for 11 percent of those who discontinued (21 out of 183).

Table 6. KQ1. Summary of studies reporting interventions with pharmacological agents for preschoolers with ADHD

Study	Study design Quality rating	N Mean age (SD) % Male Length of study	Interventions compared				Results		Comments Duration of intervention or followup
			MPH	MAS	PBT	Placebo	Effectiveness	Safety	
Abikoff H 2007[51] (PATS)	RCT Good	N = 114 Age: 4.4y Male:80% 20w	✓			✓	Secondary outcomes Functional measures: PR and TR SWAN symptom scores did not show improvement on MPH CGI improved PR depression worsened TR social competence improved CGI Effect Size 0.73	One subject dropped out for drug related AE	Families participated in 10 PBT sessions prior to RCT; Best dose of MPH compared with placebo over 4 weeks
Ghuman J 2007[52] (PATS)	RCT Good	N = 165 Age:4.7y Male: 74% 5w	✓			✓	High comorbidity subgroup showed no improvement with increased MPH dose response compared to significant response in Moderate, Low or No comorbidity groups	AE not reported	5w 14 variables examined, # of co-morbid disorders served as moderator of MPH response; Children in High comorbidity subgroup had more family adversity than compared to No, Low, or Moderate comorbidity
Greenhill L 2006[7] (PATS)	RCT Good	N = 165 Age: 4.8y Male: 74% 70 w	✓			✓	ADHD symptoms showed significant decreases on MPH at 2.5mg, 5mg, and 7.5mg three times daily doses but not for 1.25mg daily, compared with placebo	92% tolerated MPH on open safety lead-in phase. AE: Appetite, sleep, stomach ache, social withdrawal, lethargy; Less common tachycardia, high blood pressure; possible seizure	70w protocol Titration trial – significant reductions on symptom scales, although effect size (0.4-0.8) smaller than for school-age children

Table 6. KQ1. Summary of studies reporting interventions with pharmacological agents for preschoolers with ADHD (continued)

Study	Study design Quality rating	Sample N Mean age (SD) % Male Length of study	Interventions compared				Results		Comments Duration of intervention or followup
			MPH	MAS	PBT	Placebo	Effectiveness	Safety	
Swanson J 2006[53] (PATS)	Exten-sion of RCT Good	N = 140 Age: 4.4y Male: 74% 15 m	✓			✓		Evaluation of growth rates over one year of MPH use ADHD children started out larger and heavier than norms, and while growth slowed on MPH regimen, they still were larger and heavier than norm at end of one year	1 year followup
Wigal T 2006[54] (PATS)	RCT Good	N = 183 Age: 4.8y Male: 74% 14 m	✓		✓	✓	Significantly increased ADHD behaviors related to withdrawal suggest lack of drug efficacy ADHD-B p >0.0001	Serious and severe adverse events LDp HDp P-TS <0.005 <0.0001 Occurrence of AE increased between lower and high dose conditions 30% of parents spontaneously report moderate to severe symptoms after baseline	1 wk open label lead-in, 5wk RCT, 5wk parallel phase, 10m open label maintenance 11% discontinued due to AE Preschooler AE similar to ADHD symptoms
Barkley R 1984[45]	RCT Fair	N = 60 Age: NR Male: 100% 1m	✓			✓	Greater drug effects in task period over play period	#SE p <0.05 LD and HD both produced greater number of AE	5w Only HD MPH improved child compliance
Barkley R 1988[44]	RCT Fair	N = 27 Age: 46.8m (+ /-6.7) Male: 70% 1m	✓			✓	Increased positive parent/child interactions	Mothers reported more AE during medication phase than placebo phase (p<0.10) but there was no difference in severity between drug and placebo phases	4w intervention Interpreted as supporting + ve effects on parent/child interactions

Table 6. KQ1. Summary of studies reporting interventions with pharmacological agents for preschoolers with ADHD (continued)

Study	Study design Quality rating	Sample N Mean age (SD) % Male Length of study	Interventions compared				Results		Comments Duration of intervention or followup
			MPH	MAS	PBT	Placebo	Effectiveness	Safety	
Cohen N 1981[56]	CCT Fair	N = 24 Age: range 4 to 6 years Male: 88% 15m	✓		✓	✓	PR child behavior improved at 1 year but their ratings in clinic were not significantly better	At 1-year followup, unmedicated children showed significant drop in verbal IQ while children on meds did not	No evidence that any one treatment more effective than any other; may be a function of maturation
Firestone P 1998[55] Same population as Musten[47]	Cross-over Fair	N = 31 Age: 4.8y Male: 87% 1m	✓			✓	NR	Higher dosage of stimulant medication related to intensified frequency and magnitude of AE	Younger children may display different behaviors than school-age while on stimulant medications; behaviors may have been associated with the condition rather than side effects
Ghuman J 2009[48]	Cross-over Fair	N = 14 Age: 4.8y Male: 93% 5w	✓			✓	Improved behavior reported by parents and observed in clinic	Buccal-lingual movements significantly increased in Tx group	Response to MPH more subtle and variable than among older and/or typically developing children
Handen B 1999[46]	RCT Fair	N = 11 Age: range 4.0 to 5.1y Male: 82% 5 w	✓			✓	Significant improvement on TR of hyperactivity and inattention as well as activity levels and compliance	Nearly half the children experienced significant AE: withdrawal, crying, irritability	Developmentally delayed children with ADHD respond to MPH, however may be more susceptible to adverse drug side effects

Table 6. KQ1. Summary of studies reporting interventions with pharmacological agents for preschoolers with ADHD (continued)

Study	Study design Quality rating	Sample N Mean age (SD) % Male Length of study	Interventions compared				Results		Comments Duration of intervention or followup
			MPH	MAS	PBT	Placebo	Effectiveness	Safety	
Heriot S 2007[43]	RCT Fair	N = 16 Age: 4.8y Male: 81% 3 m	✓		✓	✓	Most clinically significant results in MPH + PBT where 4/4 improved in two or more domains. In PBT only and in MPH only, 3 /4 improved in one or more domains. In placebo and parent support 1/ 4 improved in one domain	AE not reported	MPH prescribed at 0.3 mg /kg twice daily
Musten L 1997[47] Same population as Firestone[55]	Cross-over Fair	N = 31 Age: 4.8y Male: 83% 1 m	✓			✓	Dosage effects not uniformly evident; positive effects on cognitive measures	Increased AE and increased severity with higher doses	MPH improves functioning of preschool children similar to school-age children; no evidence that ODD was contraindication
Schleifer M 1975[50]	RCT Fair	N = 26 Age: 4.1y Male: NR 6 w	✓			✓	H-scores p <0.01 FI p <0.0001 Ref p <0.01	Mother reports of sadness, irritability, poor appetite, difficulty getting to sleep	3w intervention H in this population a heterogenous phenomenon
Short E 2004[49]	Cohort Fair	N = 28 Age: 5.3y Male: 85% 1m	✓	✓		✓	Improvement in behavior with either MPH or MAS	Titrated to best dose, there were minimal differences between number or severity of AE on active medication or placebo	4w intervention Comparing best dose and placebo. Best dose of either MPH twice daily or MAS once daily identified by a preliminary trial

Notes: PATS studies listed first; table reports effect size for studies included in quality assessment of data

Abbreviations: ADHD-B = Attention-Deficit Hyperactivity Disorder-Behavioral; AE = Adverse Events; CGI = Clinical Global Impressions; FI = field independence; H = Hyperactivity; HD = High Dose; IQ = intelligence quotient; LD = Low dose; m = months; MAS = Mixed amphetamine salts; MPH = methylphenidate; NR = not reported; ODD = Oppositional Defiant Disorder; PATS = Preschoolers with Attention Deficit/Hyperactivity Disorder; PBT = Parent behavior training; PR = parent rating; P-TS = Parent-Trouble sleeping; RCT = randomized controlled trial; Ref = Reflectivity impulsivity; SD = Standard deviation; SE = side effects; TR = teacher rating; Tx = treatment; w = weeks; y = year

Summary and Limitations

There are several short-term studies, most with small sample size examining psychostimulant use in preschoolers. Of these, only one small study compares medication directly with PBT and the combination of medication and PBT.[43] The medication dose it examines is low compared with doses suggested by other studies. The sample size was very small, perhaps due to attrition (16/26 children completing interventions), precluding the usual statistical analysis for controlled trials examining efficacy. The second trial, the PATS study, offered careful analysis of psychostimulants following 10 sessions of PBT, a format consistent with clinical consensus for treatment of ADHD in preschoolers. It confers information about parent preferences, documents the small proportion of children with ADHD benefiting from a series of 10 PBT groups, and the additional benefits (as well as adverse events) posed by MPH use in preschool children with ADHD. It examines functional as well as symptomatic outcomes, with information from several informants. The study shows that for children with no comorbid conditions, or with only one, MPH is very effective, similar to its effectiveness in samples of older children. As informative as this study is, it deserves replication in other samples, especially in light of the finding that presence of three or more comorbid conditions and psychosocial adversity decreases the effectiveness of psychostimulant medication.

Key Question 2. Among people 6 years of age or older with Attention Deficit Hyperactivity Disorder, what are the effectiveness and adverse event outcomes following 12 months or more of any combination of followup or treatment, including, but not limited to, 12 months or more of continuous treatment?

Studies examining the long-term effectiveness and safety of pharmacologic interventions are an important focus of this review. With the advent of new technologies and formulations of psychostimulants and the development of non-stimulant agents for use in ADHD, industry-sponsored research has provided several high quality extension studies following participants in clinical trials. As well, researchers have used chart reviews and examinations of clinical database information to learn about the naturalistic patterns and long-term outcomes of stimulant use for children with ADHD.

Long-Term Effectiveness and Safety of Psychostimulants, Atomoxetine, and Guanfacine Extended Release Interventions for ADHD

In all, we found 18 studies representing 16 cohorts, 14 in children and two in adults, that offer details about long-term treatment effectiveness and safety of pharmacologic interventions.[57-71,144-146] (Table 7). Seven reports representing six studies were rated as "good"[58,61-63,66,67,146] while nine reports[57,59,60,64,65,68-71] were of "fair" internal validity and two[144,145] were assessed as weak by the quality assessment tool. Only studies rated as having "good" and "fair" internal validity are discussed in this section.

Of these, two cohorts describe psychostimulants without distinguishing between MPH and dextroamphetamine (DEX) agents,[57,58,146] while other reports describe amphetamine, MPH immediate release, DEX, MAS, and OROS MPH.[58-65] Four reports describe cohorts of

participants in trials of the norepinephrine reuptake inhibitor atomoxetine (ATX); one of these is an extension of clinical trials in adults.[66-69] Three additional RCTs compare MPH with the combination of MPH and psychosocial and/or behavioral interventions lasting 14 months to 2 years. One of these, the Multimodal Treatment of ADHD Study (the MTA study) also compared medication management of MPH to psychosocial and behavioral intervention alone and to a community control group.[72-77] Two reports focus on the safety and continued efficacy of the noradrenergic agonist guanfacine extended release (GXR).[70,71] Overall, the pharmacologic agents found to be efficacious and safe in shorter length trials provide continued maintenance of ADHD symptomatic improvement for at least 12 months. Few serious adverse events are noted, although GXR appears to be less well tolerated than other agents examined. Global ratings of impairment also indicate continued benefit. Placebo-controlled discontinuation trials are few; one trial discontinued treatment with amphetamine after 15 months,[61] another discontinued MPH following 12 months and compared these with ongoing psychosocial intervention,[75] and a third examined relapse in children receiving ATX for 12 months.[67] These trials suggest that many, but not all, individuals continue to benefit from medication.

Most participants are children between 6 and 12 years of age at recruitment, primarily boys with ADHD-C. The more recent trials recruit few children with comorbid conditions except ODD. Attrition over time occurs for a variety of reasons, including adverse events and ineffectiveness. Retention of participants on active treatment at 12 months varies across studies and agents, from a high of 98 percent for immediate release MPH,[58] 75 percent for amphetamines,[61] 63 percent for OROS MPH,[60] 58 percent MAS XR,[63] 56 percent for ATX,[67] and 43 percent for GXR.[71] In general, those who remain on medications show continued benefit and report few adverse events. Over half of these studies were funded all or in part by industry, possibly leading to enhanced representations of effectiveness and safety.[147]

The following sections are organized by the agent under investigation.

Psychostimulants

Barbaresi, et al.,[59] was a population-based birth cohort study with details from school records as well as medical records. They identified 379 children with "research identified ADHD," of which 295 received stimulant treatment, 66 percent treated with MPH and 30 percent treated with DEX. The children were followed until a median age of 17.6 years for those who received stimulants, and a median age 18.6 for those who did not. The pattern of use was marked by interruptions and changes of stimulant type, with a median of three treatment episodes (defined as initiating or changing dose, or changing agent) per child. Boys were 1.8 times (95% CI, 1.1 to 3.1, $p = 0.025$) more likely to receive stimulants than girls. The median age of onset for the start of treatment was 9.8 years; those with ADHD inattentive type (ADHD-I) were slightly older at 12.7 years, and children with ADHD-C were 9.2 years of age. The median duration of treatment was 33.8 months, somewhat less for those with ADHD-I (19.1 months) than for those with ADHD-C (40.6 months). Nearly three-fourths of treatment episodes with either MPH or DEX resulted in a favorable response; boys were more likely than girls to experience a positive response with DEX (OR 3.4, 95% CI, 1.5 to 7.54, $p = 0.002$). However, DSM-IV subtype (i.e., ADHD-C or ADHD-I) was not differentially associated with a favorable response to either MPH or DEX. Eight percent of episodes were associated with a documented side effect; DEX was more likely than MPH to be associated with a side effect (OR 1.8, 95% CI, 1.1 to 3.0, $p = 0.034$). More side effects were noted among younger children and older adolescents.

Charach, et al.,[57] followed 91 children who had been participants in a 12 month RCT of MPH and parent groups (see also Law and Schachar[58]). They were seen annually in a naturalistic followup. They noted that patterns of adherence varied considerably, with some children continuing to use medications, some discontinuing, and some using intermittently over 5 years. High baseline symptom scores were associated with longer adherence to psychostimulant medication (any type) and greater treatment response. However, children with high levels of symptoms remained symptomatic at year five, despite stimulant treatment. Children receiving medication also showed high levels of clinically significant side effects, compared to children off medication. The most common side effect was loss of appetite.

Gillberg, et al.,[61] examined amphetamine response in 62 children 6 to 11 years old with ADHD, 10 percent of whom had pervasive developmental disorder, and 16 percent of whom had mild developmental delay (IQ 51 to 72). The study was initiated with single blind amphetamine treatment where all children improved in Conners parent and teacher ratings, followed by a 12-month double blind placebo randomized discontinuation trial of amphetamine. The primary outcome measured was time to discontinuation of double blind treatment; 71 percent of those randomized to placebo and 29 percent of those randomized to amphetamine stopped treatment or went on to open-label treatment ($p < 0.001$). A final single blind discontinuation of amphetamine to placebo at month 15 for those still on amphetamine led to some statistically insignificant deterioration in teacher symptom scores but not parent scores. Other changes over time included improved IQ for children treated with amphetamine for 9 months or more compared with children treated with placebo for 6 months. Adverse events discussed included poor sleep, which occurred less frequently on single blind amphetamine than at baseline, and 33 of 59 children reported poor appetite following 3 months of single blind amphetamine. Abdominal pain and tics occurred at baseline and in both amphetamine and placebo conditions. Tics were also noted for children at baseline and on amphetamine and on placebo. Of greater concern, hallucinations were noted for four children, three on amphetamine and one on placebo; dose reduction or discontinuation remedied the hallucinations quickly. Weight gain on amphetamine was less than expected over 15 months, while height was not clearly affected.

Three studies specifically addressed the question of worsening of tics with psychostimulants, examining the development of tics while on active treatment and on placebo. Gadow, et al.,[62] examined tics in 34 children, ages 6 to 12 years, with ADHD and chronic multiple tic disorder. There was no statistically significant worsening of tics, and there was a maintenance of benefit for ADHD symptoms over 2 years. Nolan, et al.,[146] discontinued psychostimulant treatment after long-term use by 19 children with ADHD and chronic multiple tic disorders. Abrupt withdrawal neither improved nor worsened tics. Law and Schachar[58] examined 91 children with ADHD but without diagnosable tic disorder at baseline. Nearly 20 percent of the children on active treatment and 17 percent of those on placebo developed clinically significant tics (risk ratio (RR) 1.17, 95% CI, 0.31 to 4.40) while deterioration of tics occurred for 33 percent of those with pre-existing mild tics on both active and placebo interventions (RR 1.0, 95% CI, 0.4 to 1.85). Therefore it appears that tics do not worsen on psychostimulants. All reports concluded by noting that for individual children dose adjustment or discontinuation may be required as some children may be individually susceptible to this adverse event.

Hoare, et al.,[60] examined OROS MPH in 105 children, who had been stabilized on immediate release (IR) MPH. Following a 3-week open trial of once daily MPH at doses of 18mg, 36mg, or 54mg, 88 percent of families wished to enter the 12-month extension trial and 63 percent completed it. Effectiveness was rated higher among children aged 10 to 16 years, those taking

either 36mg or 54mg daily, and for children with ADHD-I. Of the participants who discontinued use, 24 percent were for lack of efficacy and 12 percent for adverse events (insomnia (N = 4), abdominal pain (N = 2), and other (N = 2)). Four children (4%) experienced serious adverse events. Adverse events reported in more than 5 percent of children were headache (9.5%) and tics (7.6%), and were not dose related.

McGough, et al.,[63] examined once daily mixed amphetamine salts extended release (MAS XR) in 568 children, 6 to 12 years of age, 78 percent male, and 92 percent with ADHD-C, who had previously participated in one of two randomized placebo controlled trials without experiencing clinically relevant adverse events. The participants started the 24-month extension trial as one of three subgroups based on their previous trial, those on MAS XR, placebo, or no active treatment. All started a 12-month extension at 10mg MAS XR daily for 1 week, followed by weekly titration in 10mg increments as required, to a maximum dose of 30mg daily. Participants had an option to remain in the study for an additional 12 months, for a total of a 24-month extension. For those who were on no active treatment or on placebo, the parent report Conners global index scores improved by >30 percent following the initiation of the extension trial and this improvement was maintained over 24 months. The symptom scores were similar to those of the group who had remained on active treatment between the RCT and extension study. Fifty-eight percent of children remained on MAS XR for at least 12 months and 48 percent for 24 months. The majority of children received 20mg daily. Adverse events caused 15 percent of children to withdraw. The adverse events most commonly associated with subsequent treatment withdrawal were weight loss (N = 27), decreased appetite (N = 22), insomnia (N = 11), depression (N = 7), and emotional lability (N = 4). Serious adverse events were reported in 18 children (3%). Adverse events were more frequent with increasing dose; of those reported in the first 6 months at rates of more than 5 percent were loss of appetite (37%), headache (27%), insomnia (26%), abdominal pain (18%), nervousness (17%), weight loss (17%), and emotional lability (14%). Mean blood pressure measures increased by 3.5mm Hg, diastolic blood pressure by 3.5mm Hg, and mean pulse rate by 3.4 beats per minute.

Two studies, Findling, et al.,[64] and Weisler, et al.,[65] examined cardiovascular adverse events of MAS XR in 24-month open-label extension studies of clinical trials. In 568 children[64] ages 6 to 12 and taking 10 to 30mg MAS XR daily and in adults[65] taking 20 to 60mg daily, modest increases in blood pressure and pulse rate, and small changes in QT intervals on ECG were noted, all findings judged to be of minimal clinical significance. Four children discontinued due to cardiac events, one for tachycardia, two for intermittent chest pain (one child with premature ventricular contractions, and the other with sinus bradycardia), and one for hypertension.[64] Seven adults were withdrawn from the study because of cardiovascular adverse events, two because of palpitations and/or tachycardia and five because of hypertension.[65]

Summary of Psychostimulant Reports

Psychostimulants continue to provide control of ADHD symptoms and are well tolerated for months to years at a time. MPH improved ADHD symptoms and overall functioning alone or in combination with psychosocial/behavioral interventions for 14 months[74] and up to 24 months.[73,76] Concerns about exacerbation of tics with stimulants appear to be unfounded, although sample sizes remain small and may result in type II error. Some of the research summarizes information based on short-acting formulations of psychostimulants, requiring multiple doses daily. For instance, Barbaresi, et al.,[59] reports that MPH is better tolerated than DEX. However, direct comparison of once-daily agents, such as OROS MPH and MAS XR is

difficult, as Hoare, et al.,[60] included adolescents and those with ADHD inattentive type, whereas the McGough, et al.,[63] study sample had more than 90 percent with ADHD-C. Comparison might suggest that OROS MPH is better tolerated than MAS XR, but both studies had 15 percent of participants withdraw because of adverse events. Also, the methods for collecting adverse events may have been more sensitive in McGough, et al.,[63] as they were collected by both spontaneous reports and by investigator inquiry. It is also possible that participants in the Hoare, et al.,[60] study were offered relatively less efficacious doses, thereby diminishing the likelihood of adverse events. Currently, in the United States, MAS is approved for use in children 3 years of age and above, while in Canada it is approved for children 6 years and older.

Effectiveness or tolerability of psychostimulants based on sample characteristics, such as sex, age, DSM-IV subtype or comorbid disorders, show few differences. Barbaresi, et al.,[59] found that DEX may be somewhat less well tolerated than MPH, that boys are more likely to show a positive response to DEX than girls, and that young children and adolescents tolerate stimulants less well than children in the middle of the age group examined. Overall, the benefits and safety of MPH for symptom control and general functioning are clearly documented, primarily for boys, ages 7 to 9 years at initiation with ADHD-C. The similarities between MPH immediate release as examined and other preparations of psychostimulants are many, both in terms of efficacy and side effect profile. Therefore, many researchers and clinicians assume that all psychostimulants are effective and safe for extended periods of time. The documentation for this assertion is not yet robust and there continue to be too few studies of long-term outcomes of psychostimulants to make direct comparisons of effectiveness and tolerability among them.

Atomoxetine (ATX)

ATX is a non-stimulant agent, a norepinephrine reuptake inhibitor that is approved for use in the treatment of ADHD. Two studies report on a double blind placebo controlled relapse prevention trial following a 12-week open-label titration trial.[66,67] Six hundred and four children, ages 6 to 15 years, 90 percent boys and 74 percent ADHD-C, discontinued any previous medications prior to entering the titration trial. ATX was titrated up to 1.2mg/kg per day in twice daily doses, with further increases to 1.8mg/kg/day if indicated. Four hundred and sixteen patients whose symptoms decreased by more than 25 percent from baseline entered a 9-month randomized relapse prevention trial and after 12 months, 292 on ATX were re-randomized into a second double blind 6-month relapse prevention trial. Michelson et al[66] examined the outcomes following the initial 12 months on ATX and noted that fewer children relapsed in the active treatment group (21%) than placebo group (37%), $p < 0.001$. There were no significant treatment interactions with diagnostic subtype, treatment history, age, or site. Discontinuation due to adverse events occurred in nine out of 292 participants (3%) in the ATX group, and one of 124 participants (0.8%) in the placebo group. Adverse events reported by more than 5 percent of participants and statistically different between ATX and placebo groups include gastroenteritis and pharyngitis for ATX and weight gain for placebo. Both weight gain and height gain were slower in the ATX group. There were no clinically meaningful differences in laboratory values, vital signs, or cardiac QT intervals. Adverse events were similar to those reported during acute trials, specifically increases in heart rate and blood pressure.

Buitelaar, et al.,[67] examined relapse rates during the second relapse prevention trial begun at 12 months and also showed that fewer in the ATX group (2.5%) relapsed than in the placebo group (12%) with RR for relapse 5.6 (95% CI, 1.2 to 25.6). Comparison of the two relapse prevention trials suggests that the relapse rate on placebo following a full year of active

treatment was lower than the relapse rate on placebo following 12 weeks of treatment. The rates of adverse events were similar between ATX and placebo conditions for those who remained in the trial after 12 months of treatment.

Adler, et al.,[68] reported on 385 (72%) of 536 adults with ADHD (mean age 42 years, 64% men) who entered an open-label continuation trial (up to 97 weeks) of ATX following initial 10-week RCTs. They had discontinued ATX following the trials, or remained on placebo, and therefore were symptomatic at initiation of the open-label trial. ADHD symptoms showed improvement of 33 percent on rating scales for total ADHD symptoms during the initial phase of the open-label extension; similar improvements occurred for total disability scores. Adverse events were similar to those noted in acute trials, primarily the expected noradrenergic effects, and included increased heart rate (mean change 5.1 beats per minute) increased systolic and diastolic blood pressure (mean change <2.0mm Hg) and mean decrease in weight of 1.3kg. Discontinuation due to adverse events was 11 percent. No clinically relevant changes in laboratory measures or QTc intervals on EKG were noted. Adverse events noted $\geq$10 percent were dry mouth (24%), headache (21%), insomnia (18%), erectile dysfunction (16%), nausea (15%), and constipation (14%).

Wernicke, et al.,[69] reported on cardiovascular effects of ATX noted in an open-label 12-month extension trial following clinical trials for 169 children and adolescents. Initial doses varied from 0.5mg/kg to 2mg/kg/day in divided doses. For children, mean pulse rate and blood pressure increased during the initial few weeks and blood pressure increased over the first few months with increasing dose. Vital signs tended to stabilize at slightly higher levels over time, and subside upon discontinuation of ATX. Mean increases were small and not clinically meaningful. Likewise, no clinically significant changes were noted in ECG.

Summary of Atomoxetine Reports

ATX appears to be effective for continued control of ADHD symptoms and is well tolerated over 12 months. The research examining its use considers global functional assessments as well as ADHD symptom change. The measured threshold for effectiveness was a decrease in ADHD symptoms of more than 25 percent from baseline, and threshold for relapse was considered a return to more than 90 percent of baseline and increase in clinician rated CGI score of two or more points above the score following initial treatment trial. Relative to studies of other agents, these trials offer direct comparison with placebo for examination of relapse prevention, offering strong evidence of ongoing effectiveness and safety in children and teens for up to 18 months, although the thresholds may appear to be set to enhance measured effectiveness. Adler, et al.,[68] offer a study of pharmacologic intervention over an extended time period in adults with ADHD.

Guanfacine Extended Release (GXR)

GXR is a nonstimulant noradrenergic agonist with selective effects on cortical alpha 2A adrenoreceptors. Similar to clonidine (another alpha 2 adrenoreceptor agonist which has been shown to be effective in improving some but not all domains for children with ADHD), guanfacine immediate release has been shown to be effective in reducing symptoms in ADHD in short-term RCTs. Two industry-sponsored studies examine long-term safety and efficacy of extended release formulations (GXR) in open-label extension studies of earlier clinical trials.[70,71] These multisite studies were similar, enrolling children ages 6 to 17 years, approximately 75 percent boys, and 73 percent ADHD-C. Biederman, et al.,[70] enrolled 240 (70%) of participants in previous trials, and administered GXR in 2 to 4mg doses daily. Sallee, et al.,[71] studied a sample

of 259 children given 1 to 4mg GXR daily, 53 of whom received co-administered psychostimulants. Results were similar in both studies. Reductions in ADHD symptom scores from the baseline of the preceding trial, and improvement in parent-rated global impressions were maintained throughout the extension studies; 57 percent and 60 percent were very much improved or much improved from baseline.

Eighty two percent (N = 198) of participants withdrew from the Biederman, et al., study by 12 months.[70] Of these, 52 (22%) withdrew for adverse events and 25 (10%) for lack of efficacy; the most common reason for discontinuation was withdrawal of consent by 67 participants (34%). Somnolence, weight increase, and fatigue were the most common adverse events for discontinuation, with somnolence or sedation, but not fatigue, appearing dose–related. Reports of somnolence, sedation, and fatigue diminished over time, with 40 percent of participants reporting these symptoms at month one, and about 10 percent of those remaining in the trial at month eight reporting these adverse events. Of 11 serious adverse events reported, three were considered possibly or probably related to the study drug: one event of orthostatic hypotension and two events of syncope. Adverse events reported by more than 10 percent of participants were somnolence (30%), headache (26%), fatigue (14%), sedation (13%), cough (12%), abdominal pain (11%), upper respiratory infection (10%), and pharyngitis (10%). Mild reductions in blood pressure and pulse rates were common and returned to baseline upon tapering GXR. Three children had abnormal ECGs judged clinically significant, two with bradycardia and one had junctional escape complexes. Overall hypotension was reported in seven (3%) children, and bradycardia in five (2%). Two children were discontinued due to treatment emergent abnormal ECGs, worsening of a sinus arrhythmia and asymptomatic bradycardia of 46 bpm, two discontinued for hypotension and two for orthostatic hypotension, one discontinued for syncope, all of which were resolved on discontinuation. There were no changes in clinical laboratory analyses and no unexpected changes in height or weight noted.

Sallee, et al.,[71] report 77 percent (N = 202) of children withdrew from the study prior to 24 months, 82 percent of those in the monotherapy GXR group and 57 percent of those in the group co-adminstered stimulants, suggesting the combination of GXR and psychostimulants was better tolerated than GXR alone. Overall, 10 percent stopped for lack of efficacy and 12 percent for adverse events. Adverse events reported in $\geq$10 percent of monotherapy group were somnolence (38%), headache (25%), upper respiratory infection (16%), nasopharyngitis (14%), fatigue (15%), abdominal pain (12%), and sedation (12%). In the GXR plus stimulants group, no somnolence, fatigue, or sedation were noted. Adverse events that occurred included headache (23%), upper respiratory infection (25%), nasopharyngitis (15%), abdominal pain (15%), pharyngitis (11%), decreased appetite (13%), and irritability (13%). As in Biederman, et al.,[70] reports of somnolence, sedation, and fatigue decreased over time, from 35 percent early in the extension trial to below 15 percent among those who remained in the trial over 7 months. Patterns in vital signs suggested no clear trends in blood pressure or pulse. Heart rates less than 50 bpm were noted in 15 children (6% of the sample) and rates $\geq$100 were noted in nine (3%). While 28 children (14%) had new abnormal ECGs at end point, only two were considered clinically significant. One of these showed atrioventricular block, and was noted to have shown intraventricular delay on baseline ECGs; this child subsequently discontinued treatment. The other clinically significant finding was a child who showed significant but asymptomatic bradycardia in month three, at 45 bpm. This child had a baseline pulse rate of 63 bpm and an end of study rate of 76 bpm. For the entire sample, weight and height gains were as expected with only six children (2.3%) showing weight gain possibly related to the medication.

In summary, the extension trials of GXR suggest it is an effective treatment for ADHD and that it is reasonably well tolerated. However, it does not appear to be as well accepted a treatment for long-term treatment of ADHD in children as either psychostimulants or ATX. Unlike the reports discussed in earlier sections, the published reports for GXR did not identify how many children were in the original clinical trials from which the extension studies recruited participants. Eighty-two percent of recruited participants on GXR monotherapy discontinued prior to 12 months and 18 percent completed 12 months, compared to 58 percent of children on MAS XR,[63] 63 percent of children on OROS MPH,[60] and 56 percent who entered the next phase of research following 12 months on ATX.[67] While parents report benefit with GXR, in reduced ADHD symptoms and global improvement for a substantial number of children and teens with ADHD, high rates of somnolence, headache, and fatigue likely interfere with its use. Tolerance appears to be improved with concurrent administration of psychostimulants.[71] The profile of adverse cardiovascular events with GXR suggests monitoring of cardiac status may be indicated, as there are reports of significant bradycardia, junctional escape complexes, and intraventricular delay.[70] ECG changes judged clinically significant occurred in one percent of participants. Three percent of participants (seven of 198) discontinued because of cardiovascular events in the GXR trial, compared with less than one percent of participants (four of 568) in the MAS XR trial, and 0 participants (of 169) in the ATX trial.

Table 7. KQ2. Summary of studies reporting interventions with pharmacological agents

Study	Study Design Quality Rating	N Mean Age (SD) % Male Population	Interventions compared	Length of Followup	Results	
					Effectiveness	Safety
Psychostimulants						
Andriola, M 2000[145]	Retrospective cohort Weak	N = 500 Age (range): 7y (4 to 18) Male: 70%	MPH vs. pemoline*	12m	Improvement MPH <pemoline d/c'd re: ineffective MPH 32%, pemoline 10%	d/c'd re: AE: pemoline 22%, MPH 5%
Barbaresi, W 2006[59]	Retrospective cohort Fair	N = 379 Age: 10.4y (3.6) Male: 78%	MPH, DEX, levo + DEEX, pemoline*; converted to MPH equivalent units	Birth to mean age 17.2y Tx duration 3.5y (+ /- 3.1y)	73.1% favorable response to stim treatment positive response to stim less likely for very young and for older adolescents positive response to DEX boys>girls	AE DEX (10.0%) >MPH (6.1%) No increase in AEs with higher doses of MPH or DEX; AEs more common for very young and for older adolescents
Charach, A 2004[57] See also Law[58]	RCT, systematic f/u Good	N = 91 Age: 8.4y (1.6) Male: 81%	MPH vs. placebo, then On vs. Off stim meds	12m RCT, followed by 4y systematic f/u	children with high levels of BL symptoms showed most response to stim, remained on them longest, but remained symptomatic at 5 years	Most common AE was loss of appetite across all time points
Findling, R 2005[64] See also McGough J 2005[63]	OLE of CT Fair	N = 568 Age: 8.7y (1.8) Male: 78%	10 to 30mg MAS XR daily	24m	No assessment of ADHD symptoms presented	small increase in BP, not clinically significant no apparent dose response 34 TE ECG abnormalities, none clinically significant

Table 7. KQ2. Summary of studies reporting interventions with pharmacological agents (continued)

Study	Study Design Quality Rating	Sample N Age y (SD) %Male Population	Interventions compared	Followup duration	Results	
					Effectiveness	Safety
Gadow, K 1999[62]	OLE of CT Good	N = 34 Age: 8.8y (1.9) Male: 91% tic disorder	MPH	24m	Behavior improved	NS worsening of tics NS change wght & hght %ile Increased BP at 24m
Gillberg, C 1997[61]	Single- and double-blind relapse prevention trial Good	N = 62 Age: 9y (1.6) Male: 84% Comorbidities = PDD & low IQ	Amphetamine vs. placebo	12m relapse prevention trial following 3 m active Tx, Placebo withdrawal followup after 15 months	Symptoms improved >40%; 29% on amph vs. 71% on placebo d/c'd trial Tx, following placebo withdrawal after month 15, parent report no deterioration, teacher report mild deterioration WISC-R improved CPT changes primarily among older children (9 to 11y)	No increase in tic frequency or severity relative to placebo Hallucinations in 4 subjects (3 amph & 1 placebo)
Hoare, P 2006[60]	OLE of CT Fair	N = 89 Age: 6 to 16y Male: NR Typically developing	OROS MPH Stable dose levels; 18 vs. 36 vs. 54mg	12m	Satisfaction 49% to 69% (GAS); Efficacy 49% to 71% (GAA); >effect in pts older, higher dose, & ADHD-I	12% d/c'd re: AE 4 SAEs: 2 depression/suicidal 1 delusions 1 severe aggression
Law, S 1999[58] see also Charach[57]	RCT Good	N = 91 Age: 8.4y (1.6) Male: 81% ADHD + tics	MPH vs. placebo in subjects	12m	2% on MPH vs. 60% on placebo switched to other arm of trial	No sig. change in tic frequency between subjects on MPH or placebo
McGough, J 2005[63] See also Findling[64]	OLE of CT Good	N = 568 Age: 8.7y (1.8) Male: 78% Typically developing	MAS XR vs. no Tx or placebo prior to OLE	24m	Symptom improvement maintained with LT Tx; No Tx or placebo prior showed 30% decrease in subjects 1% d/c'd re: ineffective	15% d/c'd re: AE; Increased AE with higher dose 2 SAEs: convulsions

Table 7. KQ2. Summary of studies reporting interventions with pharmacological agents (continued)

Study	Study Design Quality Rating	Sample N Age y (SD) %Male Population	Interventions compared	Followup duration	Results	
					Effectiveness	Safety
Nolan, EE 2010[146]	RCT Good	N = 19 Age: 12.3y (0.3) Male: 95% ADHD + tic	MPH or DEX vs. placebo	1y	Tx with stimulants maintenance dose was associated with behavioral improvement in ADHD	Abrupt withdrawal of stimulants after long-term maintenance therapy does not worsen tic frequency or severity
Smith, BH 1998[144]	Retrospective cohort Weak	N = 16 Children: Age: 10.2y (1.5) Adolesc: Age:12y (0.8) Male: 100% Typically developing	MPH + STP vs. STP + placebo	Mode 3y Range 1 to 4y (time elapsed from childhood to adolescence)	MPH Effect size (children) >MPH Effect size (adolesc)	none discussed
Weisler, R 2005[65]	OLE of CT Fair	N = 223 Age:29.8y (11.5) Male: 59% Typically developing	MAS XR	24m	NR no assessment of ADHD symptoms presented	21% d/c'd re: AE 7 adults w/d due to cardiovascular AE - 2 palpitations and /or tachycardia - 5 with hypertension small mean increase in BP, HR, not clinically significant
Atomoxetine (ATX)						
Adler, L 2005[68]	OLE of CT Fair	N = 385 Age: 42.4y (11.2) Male: 56% Typically developing	ATX	14wk CT, followed by up to 97wks OLE	Symp improv >30% maintained over time Impairment improved Disability improved	10.9% d/c'd re: AE

Table 7. KQ2. Summary of studies reporting interventions with pharmacological agents (continued)

Study	Study Design Quality Rating	Sample N Age y (SD) %Male Population	Interventions compared	Followup duration	Results	
					Effectiveness	Safety
Buitelaar, J 2007[67] See also Michelson[66]	DB relapse prevention Good	N = 416 Age: 6 to 15y Male: 90% Typically developing	ATX vs. Placebo	6m relapse prevention trial following 1yr active Tx	Relapse prevention ATX >placebo ATX relapse 2.5 % Placebo relapse 12.2 %	No AE observed growth normal in ATX group
Michelson, D 2004[66] See also Buitelaar[67]	DB relapse prevention trial Good	N = 416 Age:10.6y (2.3) Male: 89% Typically developing	ATX vs. Placebo	12wk OL Tx, followed by 9m DB relapse prevention trial	ATX: 22.3% relapse placebo: 37.9% relapse	AE: Gastroenteritis and pharyngitis ATX >placebo slowed growth with ATX compared to placebo
Wernicke, J 2003[69]	OLE of CT Fair	N = 169 Age:10.7y (2.2) Male: 73% Typically developing	ATX vs. Placebo	minimum 1yr Tx	NR no assessment of ADHD symptoms presented	mean increases to BP, HR were small and not clinically significant no evidence of increase in QT interval with increased dose of ATX, after correcting for HR
Guanfacine Extended Release (GXR)						
Biederman, J 2008[70]	OLE of CT Fair	N = 240 Age:10.5y (2.6) Male: 77% Typically developing	GXR	24m	Symp improvement maintained to 12 m; Parent rated impairment 58.6% improved	d/c'd re: adverse event 22%; Headache, fatigue, somnolence & sedation most common, 7 subjects d/c'd due to CV AEs 3 TE abnormal ECGs, clinically significant (2 bradycardia, 1 junctional escape complex) 3 SAEs: 2 syncope, 1 orthostatic hypotension

Table 7. KQ2. Summary of studies reporting interventions with pharmacological agents (continued)

Study	Study Design Quality Rating	Sample N Age y (SD) %Male Population	Interventions compared	Followup duration	Results	
					Effectiveness	Safety
Sallee, F 2009[71]	OLE of CT Fair	N = 262 Age:10y (2.6) Male: 73% Typically developing	GXR vs. GXR + stim	24m	Symp improv maintained to 24m; CHQ improv maintained D/c'd re: ineffective 13% GXR monotherapy 2% GXR + stim	d/c'd re AE: 13.6% GXR monotherapy 5.7% GXR + stim co-therapy 28 TE abnormal ECGs; 2 clinically significant (1 bradycardia, 1 intraventricular delay) 9 SAEs: 5 syncope

Note: table reports effect size for studies included in quality assessment of data

*removed from market in 2005 due to risk of liver toxicity

Abbreviations: %ile = percentile; ADHD-I: Attention Deficit Hyperactivity Disorder – Inattentive; AE-adverse events; amph = amphetamine; ATX = Atomoxetine; BL -baseline; BP = blood pressure; CGI-IS = Clinical Global Impressions-Impairment scale; CHQ = child health questionnaire; CP = Classroom performance; CPT = Conners parent total score; CT = Clinical Trial; CV = cerebrovascular; d/c'd = discontinued; DEX = dextamphetamine; diff = difference; DR = dose related; ECG- electrocardiogram; extended release; f/u = followup; freq = frequency; GAA = Global Assessment of Adequacy; GAS = Global Assessment Satisfaction; GXR = Guanfacine extended release; hght = height; IR MPH = methylphenidate; levo = levoamphetamine; LT = long-term; MAS XR = mixed amphetamine salts; MPH = methylphenidate; NS = no(t) statistical significance; OLE = Open Label Extension; OROS; PDD = pervasive development disorder; QT interval = measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle; RCR = retrospective chart review; RCT = randomized controlled trial; SAEs = Serious Adverse Events; stim = stimulant; STP = summer treatment program; Symp Improv = symptom improvement; TE = treatment emergent; Tx = treatment; vs = versus; w/d = withdrawal; WISC-R = Weschler Intelligence Scale for Children – Revised; wght = weight; y = year

Adverse Events: Cardiovascular Events, Cerebrovascular Events, and Rates of Growth

Due to the special interest in literature about adverse events for persons using medication for ADHD, two areas of inquiry required adjustments in inclusion criteria for this review: articles about potentially life-threatening events and articles about changes in growth rates. Research about life-threatening events requires large population-based samples; however, it is noteworthy that we found no case-control studies of these rare events. Therefore, for the review of life-threatening events, we included population-based cohort studies of people with ADHD. Three studies were identified, two about cardiac safety[148,149] and one regarding cerebrovascular events.[150] Recent studies examining growth rates for children using medication have often used age- and gender-adjusted population norms for comparison (see Tables 8 and 9).

Cardiac events: population-based studies. Two recent studies examine population rates of cardiac events among children and youth, ages 3 to 20, with recent diagnoses of ADHD, and compared those using stimulant medications to those no longer using stimulants.[148,149] Rates of hospital admission for cardiac reasons are similar to rates in the general population. Rates of emergency department use for cardiac reasons were 20 percent higher for those with ADHD who use stimulant medication compared to those who do not.[148] Rates were comparable among those using MPH and amphetamines. Use of concurrent bronchodilators, antidepressants, or antipsychotics, ages 15 to 20 years, and a history of cardiac problems were associated with increased use of the emergency department (ED).[149]

Cerebrovascular events: population-based study. Holick, et al.,[150] used a health insurance database to examine adults with ADHD who initiated either psychostimulant medications or ATX and compared rates of cerebrovascular accidents (CVAs) or Transient Ischemic Attacks (TIAs). These groups were matched to each other using propensity scores and compared with a contemporaneous general population control, age and sex matched to the treatment groups. The groups were followed for a mean of 1.5 years, during which time 44 CVAs and 21 TIAs were confirmed among the three cohorts using medical record data. There was no difference in the rate of incidents between the ATX or stimulant treated groups. However, the combined ADHD medication cohort exhibited a higher hazard ratio (HR) (3.44, 95% CI, 1.13 to 10.60) for TIAs compared with the general population after adjusting for baseline risk factors. A similar pattern was not observed for CVAs. These results do not support an increased risk of CVA events for users of ATX over psychostimulants. However, users of ADHD medications may be at higher risk of TIAs than the general population.

Table 8. KQ2. Medication and adverse events—long-term effectiveness and safety

Study Quality Rating	Med	General Adverse Event	Nervous System	Psych/Behav	Gastrointestinal	Respiratory	Cardiovascular
Psychostimulants							
Andriola M 2000[145] Weak	MPH vs. PEM	NR	Headache MPH = 8% PEM = 7% Hyperactivity: MPH = 4% PEM = 2% Sluggishness: MPH = 4% PEM = 0% Tics: 4% both groups	Insom: MPH = 4% PEM = 23% Irrit: MPH = 18% PEM = 12%	Anorexia: MPH = 29% PEM = 4% GI distress: MPH = 3% PEM = 0%	NR	NR
Barbaresi W 2006[59] Fair	MPH, MPH equiv units	Fatigue = 14.2%	Headache = 26.3% Somnol = 30.4% Sed = 13.3%	NR	Upper abd pain = 10.8%	URTI = 10.4% Cough = 12.1% Pharyn = 10.4%	NR
Charach A 2004[57] Fair	MPH	Clinically SAE were present for 5 years, most commonly loss of appetite and thus growth	NR	NR	NR	NR	NR
Findling R 200564 Fair	MAS XR vs. placebo	NR	NR	NR	NR	NR	Changes in BP pulse or ECG not clinically significant Long-term Tx changes in mean BP and pulse not clinically significant
Gadow K 199962 Good	MPH	No evidence of clinically significant adverse drug effects on growth	No change in motor tics or vocal tics during 2y maintenance therapy	NR	NR	NR	No evidence adverse drug effects on cardiovascular function after 2 years - small changes in SBP (+ 6mmHG) and DBP (-3mmHg) compared with placebo

Table 8. KQ2. Medication and adverse events—long-term effectiveness and safety (continued)

Study Quality Rating	Med	General Adverse event	Nervous System	Psych/Behav	Gastrointestinal	Respiratory	Cardio-Vascular
Gillberg C 1997[61] Good	AMPH vs. placebo	Weight gain less than expected Height not clearly affected Insomnia second most common AE	No change in tics	Hallucinations: 3 in amph, 1 in placebo	Anorexia most common AE	NR	NR
Hoare P 2006[60] Fair	OROS MPH	Anorexia = 12% Insomnia = 3.8%	Headache = 9.5% Tics = 7.6%	Impulsive behavior = 3.8% SAEs: depression/ suicidal 2, delusions 1, severe aggression 1	Abd pain = 3.8%	NR	NR
Holick C 2009[150] Fair	ATX vs. stim	NR	TIAs may be more frequent than population rate for both groups using medications for ADHD TIAs (N = 21/66) ADHD meds vs. general population: adj HR 3.44 (95%CI 1.13 to 10.60) CVA (N = 44/66) ADHD meds vs. general population: adj HR 0.71 (95%CI 0.34 to 1.47)	NR	NR	NR	NR
Law S 1999[58] Good	MPH vs. placebo	NR	clinically significant tics develop MPH = 19.6% Placebo = 16.7% No difference in tics after 12m	NR	NR	NR	NR

Table 8. KQ2. Medication and adverse events—long-term effectiveness and safety (continued)

Study Quality Rating	Med	General Adverse event	Nervous System	Psych/Behav	Gastrointestinal	Respiratory	Cardio-Vascular
Leibson C 2006[151] Weak	Stim vs. no stim	ED visits (not stratified by AE): Mean ED visits ± SD: Tx = 0.6 ± 0.56 noTx = 0.076 ± 0.78 Mdn ED visits: Tx = 0.47 no Tx = 0.52 focus: medical costs & service utilization	NR	NR	NR	NR	NR
McGough J 2005[63] Good	MAS XR	6m Anorexia = 37% >18m Anorexia = 3.5%	6m headache = 27% >18m Headache = 18% 6m Twitching = 5% SAEs: convulsions 2	6m abnormal thinking = 4.4% Depression = 5% Emotional = 14% Nervousness = 17%	6m abd pain = 18% >18m abd pain = 7%	NR	NR
Weisler R 2005[65] Fair	MAS XR	66% withdrew before 24m 48 of 166 withdrew due to identified AEs	NR	NR	NR	NR	small mean increases in DBP, SBP, and pulse rate not clinically significant AE: HBP 5/223 (2.24%) Tachy/palpit 2/223 (0.90%)

Table 8. KQ2. Medication and adverse events—long-term effectiveness and safety (continued)

Study Quality Rating	Med	General Adverse event	Nervous System	Psych/Behav	Gastrointestinal	Respiratory	Cardio-Vascular
Winterstein A 2009[149] Good	MPH vs. MAS	NR	NR	NR	NR	NR	456 Ss visited ED with cardiac events Current users: 276/456 (60.5%) adj HR 1.01(95%CI 0.80 to 1.28) Past users: 170/456 (37.3%) adj HR 0.95 (95%CI 0.73 to 1.25)
Winterstein A 2007[148] Good	Stim vs. NT	NR	NR	NR	NR	NR	Syncope = 33.7% CarddysR = 32.6% Palpit = 15.7% HBP = 14.7%
Guanfacine Extended Release (GXR)							
Biederman J 2008[70] Fair	GXR	Fatigue = 14.2% Lethargy = 5.8% Pyrexia = 8.3%	Dizzy = 7.1% Headache = 26.3% Sedation = 13.3% Somnol = 30.4% Insomnia = 5.0%	Irrit = 5.4%	Abd pain = 10.8% Nausea = 5.8% Vomiting = 8.3% Diarrhea = 5.0%	URTI = 10.4% Cough = 12.1% Nasal cong = 6.3% N/pharyn = 7.9% Pharyn = 10.4%	change from baseline: Systolic BP - 0.8 Diastolic BP - 0.4 Pulse Rate - 1.9
Sallee F 2009[71] Weak	GXR	Fatigue = 15.0%	Headache = 24.8% Sedation = 12.6% Somnol = 37.9%	All active groups showed 50% improvement from baseline	Abd pain = 12.1%	URTI = 16.0% N/pharyn = 14.1%	Hypotension = 5% No QRS interval >/ = 120mins
	GXR + stim	AEs between monotherapy and combined therapy generally similar	Headache = 22.6%	Irrit = 13.2%	Abd pain = 15.1% Decr app = 13.2%	URTI = 24.5% Pharyn = 11.3%	Modest changes in pulse and BP No serious ECG abnormality reported, but 15 patients had bradycardia

Table 8. KQ2. Medication and adverse events—long-term effectiveness and safety (continued)

Study Quality Rating	Med	General Adverse event	Nervous System	Psych/Behav	Gastrointestinal	Respiratory	Cardio-Vascular
Atomoxetine (ATX)							
Adler L 2005[68] Fair	ATX	Dry mouth = 24% Erectile dysfunction = 16%	Headache = 21% Insomnia = 18 %	Irrit = 8.1%	Nausea = 15% Constipation = 14%	URTI = 8.4%	Small mean increases in BP and pulse rate QTc no change, not clin. sig.
Buitelaar J 2007[67] Good	ATX vs. placebo	Overall AE in Tx group: 9/292 (3.1%)	Headache: Tx = 10.1% Placebo = 8.6%	Lower relapse rate in intervention group	NR	N/pharyn; Tx = 7.6% Placebo = 8.6%	NR
Michelson, D 2004[66] Good	ATX vs. Placebo	Weight loss, slowed growth	NR	NR	Gastroenteritis >5%	Pharyn >5%	no difference in QT intervals between groups

Table 8. KQ2. Medication and adverse events—long-term effectiveness and safety (continued)

Study Quality Rating	Med	General Adverse event	Nervous System	Psych/Behav	Gastrointestinal	Respiratory	Cardio-Vascular
Wernicke J 2003[69] Fair	ATX vs. placebo	NR	NR	NR	NR	NR	Mean changes at end-point (pulse – units in beats; SBP and DBP – units in mm Hg) Children: Pulse: Tx = + 7.8, Placebo = + 1.5 p <0.001 SBP: Tx = + 2.8 Placebo = + 1.2 p = 0.148 DBP: Tx = + 2.1 Placebo = -0.5 p = 0.002 Adults: Pulse: Tx = + 5.3 Placebo = -0.3 p <0.001 SBP: Tx = + 2.9 Placebo = 0.0 p = 0.002 DBP: Tx = + 1.8 Placebo = + 0.5 p = 0.083 Palpitations: Tx = 3.7% Placebo = 0.8% p = 0.037 ATX is associated with mild but persistent increase in heart rate and blood pressure

Abbreviations: + ve = positive; abd pain = abdominal pain; abn = abnormalities; adj = adjusted; AE = adverse event; ADHD-I: Attention Deficit Hyperactivity Disorder – Inattentive; AMPH = amphetamine; ATX = Atomoxatine; Behav = Behavioral; BP = blood pressure; CarddysR = Cardiac dysrhythmia; CHQ = child health questionnaire; CI = confidence interval; Cong = congestion; CVA = cerebrovascular; DBP = diastolic blood pressure; Decr app = decreased appetite; Diz = dizziness; ECG = electrocardiogram; ED = Emergency Department; GXR = Guanfacine Extended Release; HBP = hypertension; HR = hazard ratio; incr app = increased appetite; inf = infection; insom = insomnia; int = interval; irrit = irritability; LT = long-term; MAS XR = mixed amphetamine salts Extended Release; Mdn = Median; Med = Medication; MPH = methylphenidate; N/pharyn = nasopharyngitis; NS = not significant; NT = no treatment; palpit = palpitations; PEM = pemoline; pharyn = pharyngitis; Psych = Psychiatric; QRS interval = time for depolarization of the ventricles; QTc = QT interval corrected; RCT = randomized controlled trial; SAE = serious adverse event; SBP = systolic blood pressure; sed = sedation; sig = significant; somnol = somnolence; stim = stimulant; Tachy = tachycardia; TIA = transient ischemic attack; Tx = treatment; URTI = upper respiratory tract infection; vs. = versus

Rates of growth. Studies examining the effects of psychostimulant treatment on growth rates for children with ADHD are listed in Table 9. Of these, six compared the height and weight to population norms by converting to age and sex population norms using z scores.[152-157] Two studies compare adult or adolescent height to parent or sibling height or community control groups.[154,158] Two studies compare growth rates to both population norms and community controls.[53,78] Overall, the studies rated as "good" and "fair" identify somewhat diminished rates of growth, for both weight and height in children receiving MPH, DEX, or MAS. Two well designed clinical trials of psychostimulants, the PATS and the MTA study, both examined the question of growth in children with ADHD who received, and those who did not receive, psychostimulants. The PATS study[53] is described in the MPH section of KQ1, and the MTA study[78] in the combined interventions section of KQ2. Both studies document decreased growth rates for children receiving MPH over 12 months to 3 years.[53,78] These studies note that clinical samples of children with ADHD are taller and heavier than the average for their sex and age. The research overall suggests that there may be an association with cumulative dose.[152] Some, but not all studies suggest that catch up weight gain may occur when children take breaks from medication.

Spencer, et al.,[159] examined growth in 61 children who had received ATX for 5 years. Both weight and height showed diminished rates of growth at the 12- to 15-month time points relative to population norms, but returned to baseline z scores over time.

In summary, medications used for ADHD appear to have a small but distinct dose–related impact on rates of growth for children with ADHD. Limitations in the studies include small sample size, many use population norms as comparison, and relatively short duration of studies, which interfere with clarification regarding final adult height following years of medication use.

Table 9. KQ2. Summary of studies reporting on medication and growth rate

Study	Study Design Quality Rating	N Mean Age (SD) % Male	Intervention compared	Length of Followup	Results
Charach A 2006[152]	Systematic followup to RCT Good	N = 79 Age: 8.3y (1.5) Male: 81%	MPH or other stim	5y	Long-term use of high doses of stim during a period of 1 to 5 years to have measurable effects on the rate of growth in school-age children with ADHD
Faraone S 2007[153]	OLL Fair	N = 127 Age: 6 to 12y Male: NR%	MPH TD	37m	Adverse event: small but sig delays in growth (hgt, wght, and BMI) Wght & BMI dose dependent Stim naïve and heavier/taller children most likely experience growth deficit Effect on growth strongest year 1 and less over time
Kramer J 2000[158]	Multi-sample longitudinal Weak	N = 97 Age: 8.2y Male: 100%	MPH	Tx: 36m (at 4-12y) Followup NR~22y	Stim pts at final stature similar in avg. hgt/wght to family, community, or non-stim controls Some adverse events with nausea and vomiting + higher doses of MPH associated with adult growth decrements
Pliszka S 2006[157]	Cohort Fair	MPH N = 113 Age: 8.5y (2.1) Male: 83.2% MAS N = 66 Age: 9.0y (2.3) Male: 77.2%	MPH vs. MAS	Tx: 2.6y (min = 1y) Followup: 3y	Effect on height MPH = MAS Effect on weight MAS >MPH
Poulton A 2003[154]	Retrospective review Fair	N = 51 Age: 7.2y (1.8) Male: 86%	DEX vs. MPH	Tx: 6-42m Followup: median 23m	Stim associated with decrease in hgt & wght trajectory during first 6 to 30 months of administration, with characteristic growth curve

Table 9. KQ2. Summary of studies reporting on medication and growth rate (continued)

Study	Study Design Quality Rating	Sample N Mean Age y (SD), %Male	Intervention compared	Followup duration	Results
Spencer T 2006[159]	5 y OLL Fair	N = 1,312 Age: 11.0y (2.5) Male: 77%	ATX LT	Tx: 5y Followup: 5y	ATX Tx to 5 years- little or no long-term effect on growth and final stature for most patients; persistent decreases from expected may occur in some Pts larger than average before Tx
Sund A 2002[155]	Retrospective cohort Fair	N = 91 Age: 3 to 13y Male: 100%	AMPH vs. MPH	Tx: 1y to 5y Followup: annually to 5y	Extended AMPH or MPH – no impact on growth. Some Pts show wght loss during the 1st year of Tx, more pronounced with AMPH. Among pts with reduced weight gain, most >mean wght prior to Tx
Swanson J 2006[53] PATS	Extension of RCT Fair	N = 140 Age: 4.4y Male: 74%	Stim vs. none	Followup: 1y	Annual growth rates were 20.3% less than expected for height
Swanson J 2007[78] MTA	RCT Good	N = 370 Age: 7 to 9.9y Male: 80%	Stim vs. none	Followup: 3y	Medicated group showed growth of 2.0cm and 2.7kg less than the non-medicated group with no evidence of rebound within 3 y
Zachor D 2004[156]	Retrospective chart-review Fair	N = 81 Age: 8.5y Male: 72%	MPH vs. DEX vs. Adderall	Tx: 3y Followup: 3m, 6m, 12m, 24m, 36m	Pre-pubertal children and those with AE appetite suppression more subject to slowed growth No long-term impact on height Diff stim meds had similar growth impact.

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; assoc = associated; AE = adverse event; ATX LT = atomoxetine long term; avg = average; BMI = body mass index; btwn = between; def = deficits; DEX = dexidrine; exp = experience; f/u = followup; Hgt = height; m = month; MAS = mixed amphetamine salts; MAS XR = mixed amphetamine salts extended release; MPH = methylphenidate; MPH TD = methylphenidate trans-dermal system; NR = not reported; OLL = open label longitudinal; pts = patients; rel = relationship; RCT = randomized controlled trial; sig = significant; stim = stimulant; Tx = treatment; wght = weight; y = year

Medication Versus Combination

Medication Plus Behavioral/Psychosocial Interventions. A total of 26 papers which compared medication management against multi-modal treatment (combined medication plus psychosocial/behavioral interventions) were identified (see Table 10). There were two large multicentre RCTs conducted in North America which had "good" internal validity: National Institute of Mental Health's Multimodal Treatment Study of ADHD (MTA) study, with 14-month intervention and 8-year followup, for which 19 papers are included in this review,[72-74,78,80-84,160-169] and the second study led by Abikoff, Hechtman, and Klein, with 2-year intervention, of which we include 5 papers.[75,76,89,170,171] There was a small 6-month intervention RCT with 18-month followup in a Chinese population, which had "fair" internal validity.[77] Another small study compared MPH, EEG biofeedback, and parenting style in a 1-year multimodal outpatient program that included MPH, parent counseling, and academic support at school. EEG biofeedback therapy was provided for 51 of the 100 subjects.[172] These RCTs involved predominantly male children ages 7 to 9 with ADHD-C who have an IQ above 80.

There were 22 papers with "good" internal validity as rated by our assessment tool[72-78,80-83,89,160,161,161,163-168,170,171] and two papers with "fair" rating.[84,169] The following organizes the discussion by focusing on each study in turn, in order of its overall quality.

MTA study. The MTA study compared medication management, intensive behavioral treatment (PBT, child-focused treatment, and a school-based intervention), combined medication management and intensive behavioral treatment, and usual community care. The mean age of the participants at study entry was 8.5 years. The medication strategy in the MTA study was intensive and involved a systematic effort to fully suppress ADHD symptoms using MPH in divided doses.[166] Children receiving combined treatment ended maintenance on a lower dose (31.1 $\pm$ 11.7mg/day) than the medication only group (38.1 $\pm$ 14.2mg/day). Two-thirds of the children in the community care group received medication, mainly MPH (mean dose 18.7mg/day); their visit duration and frequency were shorter than the MTA-medicated subjects (30 min. vs. 18 min. and 8.8 vs. 2.3 visits/year respectively).[164]

Primary outcomes analyzed included parent- and teacher-rated ADHD and ODD symptoms, comorbid conditions, reading achievement scores, social skills and functional impairment.[74] Children in the combined treatment and medication groups showed significantly greater improvement in ADHD symptoms than the behavioral treatment and community care groups. Combined treatment was superior to behavioral treatment and/or community care in improving oppositional/aggressive symptoms, internalizing symptoms, teacher-rated social skills, parent-child relations, and reading achievement. Conners, et al.,[72] utilized a single composite measure of treatment outcome by combining standardized parent and teacher measures, covering internal problems, external problems, and social skills, and found combination therapy to be significantly better than all other treatments, with effect sizes ranging from small (0.28) versus medication, moderate (0.58) versus behavioral treatment, to moderately large (0.70) versus community care. Medication management was significantly superior to behavioral treatment and community care, with small effect sizes (0.26 and 0.35 respectively). Behavioral treatment and community care were comparable. Swanson, et al.,[165] utilized a categorical outcome based on the average rating by the parent and teacher of ADHD and ODD symptoms on the Swanson, Nolan, and Pelham, version IV (SNAP-IV) scale. The analysis gave the MTA medication algorithm a large effect size (0.59), with combined treatment incrementally superior to medication (effect size of 0.26).

Across all treatment groups, rates of Conduct Disorder and anxiety disorders were reduced, and rates of mood and learning disorders remained the same at 14 months, with no difference between the treatment groups.[168]

The MTA 24-month outcome reported persisting superiority for both combined and medication groups, but with reduced effect size for both ADHD and ODD symptoms.[73] The greater deterioration for the combination and medication groups compared to the behavioral and community care groups from the 14- to 24-month time points was related to patients stopping medication in the two former groups and starting medication in the latter two groups.[160] By 3 years, Jensen, et al.,[81] did not find any significant difference between treatment groups although each treatment group showed substantial improvements from baseline. There was significant reduction in rates of ODD/CD, anxiety, and depressive disorders, but no effect of treatment assignment was seen. Medication use declined for medication and combined treatment groups from >90 percent over the first 14 months to 71 percent, increased from 14 percent to 45 percent for the behavioral treatment group, and remained stable at 62 percent for the community care group. By 8 years, Molina, et al.,[82] found that among those followed up (70.1% of original cohort), 32.5 percent of those who were medicated at 14 months were medicated in the past year. There were also no significant differences in medication use among the four treatment groups. They found no significant differences in the primary outcomes or additional outcomes including grades earned in school, arrests, psychiatric hospitalizations, and other clinically relevant outcomes between treatment groups. Overall, the ADHD symptom trajectories noted in the first 3 years appeared to continue in similar patterns through 6 and at 8 years.

Additional post-hoc analyses of the study's 14-month results are discussed here. Jensen, et al.,[80] reported that children with ADHD and a single comorbidity of anxiety disorders responded equally well to medication management and psychosocial/behavioral interventions for 14 months. Children with ADHD-only or ADHD with ODD/CD responded better to medication and combined treatment, while children with multiple comorbid disorders (anxiety *and* ODD/CD) responded optimally to combined treatment. Wells, et al.,[161] found that all three MTA treatments decreased self-reported negative parenting more than community care treatment, with no significant effect of treatment on positive parenting. Using more objective measurement by assessing parent-child interactions in a laboratory setting for 89.9 percent of the families in the MTA study, Wells, et al.,[162] found significantly greater improvements in parents' use of proactive parenting strategies in the combined treatment group than the community care group (Cohen's d = 0.49) and the medication management group (Cohen's d = 0.38). Hinshaw, et al.,[163] found that reductions in negative and ineffective parenting practices at home could be related to improved teacher-reported outcomes in the combination group. Arnold, et al.,[167] analyzed ethnicity as a moderator and found that combined treatment produced better outcome than medication management (effect size = 0.36) for the pooled minorities, but not for Caucasians. Hoza, et al,[169] found that all groups remained significantly impaired on peer-assessed outcomes with no significant difference between treatment groups. Despite the use of an objective outcome, the study's validity was affected by the 'drop out' of half of the original cohort.

A series of analyses using the 36-month data were conducted. It was hypothesized that the loss of relative superiority of the combined treatment and medication management groups could be due to selective treatment of the most severe cases, but Swanson, et al.,[78] did not find evidence for this self-selection hypothesis. This analysis found decreased growth rates when initiating treatment in stimulant-naive children; this may be present for up to 3 years of treatment and accumulate to result in a difference of about 2.0cm in height and 2.0kg in weight. Molina, et

al.,[83] could not establish a clear benefit of medication treatment on subsequent delinquency and recommended re-evaluation at older ages. When controlled for baseline delinquency, the psychosocial/behavioral treatment group had a lower rate of substance use at 24 months. The published results at 36 months suggested that this benefit no longer held.[83] While Molina has presented a different analysis adjusting for developmental stage, and showing continued benefit of psychosocial/behavior intervention for delaying substance use, this has not been published. Between 24 and 36 months, medication use was a marker for deterioration, and Swanson, et al.,[84] did not find evidence that "self-selection," the hypothesis that families with more impaired children are more likely to use medication, accounted for this.

Multimodal Study. The study by Abikoff, et al.,[72,73] Hechtman, et al.,[75,76,89,170,171] and Klein, et al.,[171] randomized 103 children with ADHD ages 7 to 9 years who were free of conduct and learning disorders, and who had responded to short-term MPH, to receive MPH alone, MPH plus multimodal psychosocial treatment (PBT, behavior management training, family therapy, and child social skills training), or MPH plus attention control treatment (parental support and education) over a 2-year period. They reported that all subjects 'relapsed' when they received placebo substitution at the end of 1 year, suggesting that combination therapy did not attenuate symptom relapse following medication discontinuation.[75] Significant improvement occurred across all treatments and continued over 2 years, and combination therapy was not superior.[89] There were no differences among treatment groups for rates of diagnoses of persistent ADHD, ODD, CD, or psychosocial functioning at 24 months.[76] In stimulant-responsive children with ADHD, the authors concluded that there is no support for adding an ambitious long-term psychosocial intervention to improve ADHD and ODD symptoms. There was also no difference in the social functioning variables examined between groups, which led the authors to conclude that there is no support for clinic-based social skills training as part of a long-term psychosocial intervention to improve social behavior. These conclusions may not apply for young children who do not show an early favorable response to stimulant treatment or who have comorbidities, especially conduct problems. Hechtman, et al.,[170] examined the impact of treatment on parental practices. Psychosocial treatment did not enhance parenting practices, as rated by parents and children. Significant improvement in mothers' negative parenting occurred across all treatments and was maintained.

Other studies. The smaller study of So, et al.,[77] involved 90 ethnic Chinese children, 7 to 10 years old, randomized to receive either MPH or MPH with behavioral treatment for 6 months. The mean dose of medication was 13.6 to 16.8mg/day. Although the combined treatment group improved significantly more than the medication management group in ADHD symptoms at the end of the six month treatment period, there was no difference at 12 or 18 months. However, ODD symptoms improved significantly more in the combined group at 12 and 18 months; there was no noticeable improvement in the medication management group in terms of ODD symptoms. Over 18 months, there was faster rate of improvement in ADHD and ODD symptoms in the combined group, and all gains made were sustained in both groups. However, the study is limited by the relatively small sample size, high dropout rate in the medication-only group, and more significant ODD symptoms among those remaining in the trial.

The EEG biofeedback study of Monastra, et al.,[172] reported post-treatment assessments with and without MPH. Significant improvement was noted on the Test of Variables of Attention and the Attention Deficit Disorders Evaluation Scale when participants were tested while using

MPH. However, only those who had received EEG biofeedback sustained these gains when tested without MPH.

Table 10. KQ2. Summary of long-term controlled studies comparing different treatment modalities for children/adolescents with ADHD

Study	Study design Quality rating	N Mean Age (SD) %Male	Interventions compared					Length of Intervention Primary/ Followup	Outcome measures	Results†
			Med	Behav	Comb	CC	No med			
Arnold LE 2003[167]	RCT (MTA) Good	N = 579 Age: 7 to 9.9y Male: 80%	√	√	√	√		Intervention 14m Followup 14m	Ethnicity effects on attendance, o/c, acceptance & compliance, sensitivity & response ADHD meds; SES & informant explanations of ethnic effects	Caucasian <African-American & Latino on some symptoms (Sig), Response to Tx – NS differences after controlling for SES, Ethnic minority families cooperated with and benefited significantly from Comb Tx >Med for minority families
Conners C 2001[72]	RCT (MTA) Good	N = 579 Age: 7 to 9y Male: 80%	√	√	√	√		Intervention 14m Followup 14m	Analyses of multiple measures of MTA outcomes	Comb>MedMgt, Behav, CC; MedMgt>CC
Hechtman L 2005168	RCT (MTA) Good	N = 576 Age: 7 to 9y Male: 80%	√	√	√	√		Intervention 14m Followup 14m	Prevalence of other Dx (ODD, CD, anxiety, depression, MD, LD)	Sig decreases at 14m in Dx of ODD, CD, & Anx, not LD or MD CC group developed sig >new ODD and retained more baseline ODD than Comb or Med NS differences for specific other conditions. Only the Comb sig >CC in reducing disorders and impairment at 14m in Ss with multiple conditions at baseline Well-titrated and monitored stimulant medication can decrease ODD and possibly prevent future CD
Hinshaw S 2000163	RCT (MTA) Good	N = 579 Age: 7 to 9.9y Male: 80%	√	√	√	√		Intervention 14m Followup 14m	parenting vs. teacher-reported outcomes	Reduced Neg /Ineffective discipline mediated better school social skills Comb Med + behave Tx >CC only for reductions in –ve parenting Comb Tx → reduced negative/ ineffective discipline associated with reduced disruptive class behavior

Table 10. KQ2. Summary of long-term controlled studies comparing different treatment modalities for children/adolescents with ADHD (continued)

Study	Study design Quality rating	N Mean Age (SD) % Male	Interventions compared					Length of Intervention Primary/ Followup	Outcome measures	Results†
			Med	Behav	Comb	CC	No med			
Hoza B 2010[169]	RCT (MTA) Fair	N = 285 Age: 7 to 9.9y Male: 80%	√	√	√	√		Intervention 14m Followup 14m	Peer-assessed sociometric procedures Tx comparisons: Med + Comb vs. Behav + CC; Med vs. Comb; Behav vs. CC	limited evidence on peer-assessed outcomes favoring Tx with Meds
Jensen P 2000[80]	RCT (MTA) Good	N = 579 Age: 8.2 (SD NR) Male: 80%	√	√	√	√		Intervention 14m Followup 14m	Tx effects of ID and ED comorbid disorders with ADHD Outcomes assessed by head-to-head comparison of singly comorbid groups; CD + ANX examines diff benefits of specific Txs on comorbid groups, and by effect size	Children with ADHD and anxiety, but no ODD/CD were likely to respond equally well to MTA behavioral and medication Tx Children with ADHD only or ADHD and ODD/CD (but no anxiety) respond best to medication (with or without behavior Tx) Children with multiple comorbid disorders respond optimally to Comb Tx
Jensen P 2001[164]	RCT (MTA) Good	N = 579 Age: 7 to 9.9y Male: 80%	√	√	√	√		Intervention 14m Followup 14m	LT Tx: MedMgt, Behav, Comb Optimal Tx vs. CC TAU Relative Tx efficacy & drug action Behavioral health impact	Comb and MedMgt >Behav and CC interventions for ADHD symptoms. Comb Tx>single Tx (Med, Behav) and CC for other function domains (social skills, academics, parent-child relations, ODD, anxiety) Parent attitudes and practices appeared to mediate improved response to Behav and Comb Tx
Jensen P 2007[81]	RCT (MTA) Good	N = 579 Age: 7 to 9.9y Male: 80%	√	√	√	√		Intervention 14m Followup 36m	3yr followup of MTA	earlier advantage of 14m MTA MED algorithm was no longer apparent; regardless of Tx; but all groups improved from baseline

Table 10. KQ2. Summary of long-term controlled studies comparing different treatment modalities for children/adolescents with ADHD (continued)

Study	Study design Quality rating	N Mean Age (SD) % Male	Interventions compared					Length of Intervention Primary/ Followup	Outcome measures	Results†
			Med	Behav	Comb	CC	No med			
Molina, 2009[82]	RCT (MTA) Good	N = 579 Age: 7 to 9.9y Male: 80%	√	√	√	√		Intervention 4w titration 13m maint Followup 84m	ADHD and ODD symptoms, delinquent behavior, global functioning, depression, academic competence, social skills, driving infractions	No difference between treatment groups for all outcomes 3 year symptom trajectory predicted 8 year outcome
Molina B 2007[83]	RCT (MTA) Good	N = 579 Age: 7 to 9.9y Male: 80%	√	√	√	√	√	Intervention 14m Followup 36m	Prevalence of delinquency and substance abuse and prediction based on Tx and self-selected prescribed meds	MTA >rates of delinquency & substance use. Intensive Behavior less 24 m substance use than other MTA Ss By 24 and 36 months, more days of prescribed meds assoc with more serious delinquency but not substance use
MTA Cooperative Group, 1999[74]	RCT (MTA) Good	N = 579 Age: 7 to 9.9y Male: 80%	√	√	√	√		Intervention 14m Followup 14m	ADHD sympt; Agg/ODD, Internalizing, social skills, parent-child relations, acad achievement SMD = -0.54 (95% CI, -0.79 to -0.29)	Comb Tx and MedMgt Tx appear to significantly improve behavior more than Behav or CC Comb vs. Med Tx ->NS
MTA Cooperative Group, 2004[160]	RCT (MTA) Good	N = 579 Age: 7 to 9.9y Male: 80%	√	√	√	√		Intervention 14m Followup 24m	ADHD; ODD; social skills, IQ, acad, growth, negative/ineffective parental discipline	Comb and MedMgt >Behav and CC Comb vs. MedMgt: NS Behav vs. CC: NS stim associated with maintained effectiveness but continued mild growth suppression
MTA Cooperative Group, 2004[73]	RCT (MTA) Good	N = 540 Age: 8.4 (0.8) Male: 80%	√	√	√	√		Intervention 14m Followup 24m	ADHD and ODD symptoms, acad, social skills, negative/ineffective discipline	Med >Behavior and CC (SIG) for ADHD and ODD symptoms at 24m, but less than 14m Comb >Med and Behavior >CC NS

Table 10. KQ2. Summary of long-term controlled studies comparing different treatment modalities for children/adolescents with ADHD (continued)

Study	Study design Quality rating	N Mean Age (SD) % Male	Interventions compared					Length of Intervention Primary/ Followup	Outcome measures	Results†
			Med	Behav	Comb	CC	No med			
Swanson J 2001[165]	RCT (MTA) Good	N = 576 Age: 7 to 9y Male: 80%	√	√	√	√		Intervention 14m Followup 14m	EoT status -averaged P & T ratings of ADHD and ODD (SNAP-IV) and low symptom-severity as clinical cutoff to form COM	Summary SNAP-IV scores increased precision of measures by 30%. *Group differences in success (Comb = 68%; Med = 56%; Behav = 34%; CC = 25%) confirmed large effect Med and MMT p <0.05 Confirms primary findings and clarify clinical decisions re: MMT & UMT with meds
Swanson J 2007[78]	RCT (MTA) Good	N = 370 Age: 7 to 9.9y Male: 80%	√				√	Intervention 36m Followup 36m	Physical growth as function of Stim meds	Stimulant-naïve children with ADHD-C larger before Tx but decreased growth rate after Tx; asymptotes within 3y without evidence of growth rebound
Swanson J 2007[84]	RCT (MTA) Fair	N = 579 Age:7 to 9.9y Male:80%	√	√	√	√		Intervention 14m Followup 36m	Propensity score analyses of 5 sub-groups; char and sev ADHD	All propensity subgroups showed initial advantage of medication gone by 36m assessment
Vitiello B 2001[166]	RCT (MTA) Good	N = 198 Age: 7 to 9y Male: 80%	√					Intervention 4w titration 13m maint Followup 14m	Optimal drug dosing	Initial titration dose of MPH in the general range did not prevent need for subsequent adjustments
Wells K 2000[161]	RCT (MTA) Good	N = 579 Age: 8.5(SD not reported) Male: 80%	√	√	√	√		Intervention 14m Followup 14m	Parenting behav, family stress	negative parenting Behav alone, Med alone, and Comb >CC →Sig

Table 10. KQ2. Summary of long-term controlled studies comparing different treatment modalities for children/adolescents with ADHD (continued)

Study	Study design Quality rating	N Mean Age (SD) % Male	Interventions compared					Length of Intervention Primary/ Followup	Outcome measures	Results†
			Med	Behav	Comb	CC	No med			
Wells K 2006[162]	RCT (MTA) Good	N = 579 Age: 7 to 9.9y Male: 80%	√	√	√	√		Intervention 14m Followup 14m	Constructive parenting Child negativity	Parenting; Comb >MedMgt or CC sig Treatment effects on child behaviors were NS
Abikoff H 2004[76]	RCT Good	N = 103 Age: 7 to 11y Male: 93%	√	√	√			N/A as per design/24m	Social functioning	young ADHD - no support for SST as part of a long-term psychosocial intervention Significant benefits from MPH stable over 2 years.
Abikoff H 2004[75]	RCT Good	N = 103 Age: 7 to 11y Male: 93%	√	√	√			N/A as per design/24m	Symptomatic improvement	long-term psychosocial intervention to improve ADHD, ODD symptoms NS benefits of MPH stable over 2 y
Hechtman L 2004[89]	RCT Good	N = 103 Age: 7 to 11y Male: 93%	√	√	√			Intervention N/A as per design Followup 24m	Rx, Rx + behav, Rx + psychosocial	Sig improvement occurred across all treatments maintained over 2 y
Hechtman L 2004[170]	RCT Good	N = 103 Age:7 to 11y Male: 93%	√	√	√			Intervention N/A as per design Followup 24m	Parenting	Psychosocial led to better knowledge but not better practice; improvement in mothers' negative parenting maintained
Klein R 2004[171]	RCT Good	N = 103 Age: 7 to 11y Male: 93%	√	√	√			Intervention N/A as per design Followup 24m	Augment effects of meds, not replace them	Successful delivery of comprehensive 2yr psychosocial program

Table 10. KQ2. Summary of long-term controlled studies comparing different treatment modalities for children/adolescents with ADHD (continued)

Study	Study design Quality rating	N Mean Age (SD) % Male	Interventions compared					Length of Intervention Primary/ Followup	Outcome measures	Results†
			Med	Behav	Comb	CC	No med			
Monastra 2002[172]	Prospective cohort Fair	N = 100 Age: 6 to 19y Male%: 83	√	√	√			Intervention 12m Followup 12m	Symptom Scale Cognitive scale	Stimulants improved cognitive and behavioral measures of attention. Parenting style exerted a sig moderating effect on behavioral symptoms at home but not at school
So C 2008[77]	RCT Good	N = 86 Age: 7 to 10y Male: 90%	√	√				Intervention 6m Followup 12m	Rx and Rx + BT for Chinese children	added benefits of Beh + Med Chinese ADHD children with Tx by regular medical and paramedical staff

Notes: MTA studies listed first; table reports effect size for studies included in quality assessment of data
†Only statistically significant results are reported.
Abbreviations: –ve = negative; acad = academic; ADHD = Attention Deficit Hyperactivity Disorder; agg = Aggression; anx = Anxiety; assoc = associated; behav = behavior; BT = Behavioral treatment; CC = Community Care; CD = Conduct Disorder; char = characteristics; COM = categorical outcome measure; comb = combined Stimulant + Behavioral treatments; Dx = diagnoses; ED = externalizing disorders; EoT = End of Treatment; f/u = followup; ID = internalizing disorders; LD = learning disorder; LT = Long Term; m = month(s); maint = maintenance; MD = Mood disorder; Med = Stimulant medication treatment; MedMgt = Medical Management; MMT = multi-modal treatment; MTA = Multimodal Treatment of Children with ADHD; N/A = not applicable; neg = negative; No med = No Stimulant medication treatment; NR = not reported; NS = no(t) statistically significant; o/c = outcome; ODD = oppositional defiant disorder; P = Parent; RCT = randomized controlled trial; Rx = prescription; SES = socio-economic status; sev = severity; SMD = Standardized Mean Difference; SNAP-IV = Swanson, Nolan, and Pelham - version IV; Ss = subjects; sst = social skills training; Sympt = symptoms; TAU = Treatment as usual; T = Teacher; Tx = treatment; UMT = unimodal treatment; y = year

Summary

Overall, the results from these three cohorts indicate both medication and combined medication and behavioral treatment are effective in treating ADHD plus ODD symptoms in children, primarily boys ages 7 to 9 years of normal intelligence with combined type of ADHD, especially during the first 2 years of treatment. Overall, secondary analyses of the MTA study suggests that combined therapy may have a slight advantage over medication management during the first 14 months (effect size 0.26 to 0.28),[72,165] especially for children with multiple co-morbidities.[80] However, if the child is free of conduct and learning problems and shows an early favorable response to stimulant medication, then medication alone is equivalent to combined treatment in controlling ADHD and ODD symptoms for the first 2 years.[75,76] The MTA study also suggests that these two strategies are superior to psychosocial/behavioral treatment alone or community care during the first 2 years,[73,74,160,169] with the exception that children with ADHD and anxiety disorder as their single comorbidity benefit equally from medication management and behavioral interventions for 14 months.[80] It appears that psychosocial/behavioral treatment reduces the risk for substance use for 10 months following intervention, 24 months after baseline. Initial analyses suggest that this protective effect disappears by 22 months,[83] while subsequent analysis adjusting for age, suggests that benefit is maintained through 22 months post-intervention (3 years after baseline). These results have not appeared in a peer-reviewed publication, although formally presented (Molina, October 2010). No treatment strategy is clearly superior in reducing other comorbid psychiatric disorders at 14 months or 3 years.[81,168] The trajectories for outcomes identified at the 3-year assessment point are generally maintained at 6 and 8 years with the majority of youth (including those in community care), maintaining benefit relative to baseline, but not improving to the degree of a nonclinical comparison group of children not referred for assessment or treatment. A small proportion (14% of cases) of youth deteriorated by the 3-year assessment after formal interventions ceased.[83] Continuity of care following the end of a research study has not been investigated as a potential factor contributing to deterioration. Clearly, participants accessed a complex mix of interventions after following the protocol treatments[82,83]

Combining medication with behavioral/psychosocial treatment reduces the dose of psychostimulant medication required to maintain behavioral effects and may retain patients in treatment, at least among Chinese families.[77] In So's study involving Asian children, the overall mean daily dose of stimulant medication was less than half that used in the MTA study, although cultural and genetic factors may contribute to this observation.[77] From Abikoff's 2004 study, it may be more cost-effective to treat stimulant-responsive children free of learning and conduct problems with medication alone.[75,76] Treatment with medication, intensive behavioral treatment, or a combination of the two can reduce negative parenting, but combined treatment may be the most effective in improving positive parenting.[89,161-163,170]

Behavioral/Psychosocial Treatment Compared With No Treatment

The literature describing behavioral treatments commonly focuses on these interventions for outcomes of disruptive behavior, not ADHD symptoms, even though these are commonly comorbid conditions. Therefore, few long-term extension studies lasting 12 or more months are available. One paper investigated a behavioral/psychosocial treatment program for parents of children with ADHD. The efficacy of a 9-week parent stress management training program for reducing parenting stress and improving parenting style was compared to a wait list control

group, and they were followed up at one year. The study by Treacy, et al.,[173] of "fair" internal validity, involved 63 parents from 42 families with at least one child (ages 6 to 15 years) diagnosed with DSM-IV ADHD. They were randomized to either the intervention group or control wait list for 9 weeks. The controls received similar intervention thereafter, and all participants were followed up for one year. The intervention was more effective for mothers than fathers, who reported less stress and less negative parenting. These improvements were maintained at one-year followup.

Long-Term Academic Achievement and School Outcomes Following Interventions for ADHD

While children with ADHD have impairments in many areas of functioning, a common primary focus of concern is academic achievement. This section describes 13 studies reporting on academic achievement outcomes, broadly defined as improvements in standardized test scores and report card grades, and decreases in absenteeism and grade retention following interventions for ADHD (see Table 11). The majority of studies reporting on academic functioning included academic measures as one of several secondary outcomes. Academic outcomes following medication intervention were examined in four studies with "fair" and "good" quality ratings.[61,85,86,174] There were five reports looking at academic effects of multimodal interventions in two cohorts; these are reported in publications describing the randomized clinical trials with "good" internal validity.[74,89] Four publications of "good" quality describe extensions of the MTA study, reporting on assessments at different time points up to 8 years of followup.[73,81,82,90] Three reports on two cohorts examined academic achievement as the primary outcome following classroom-based interventions. These studies were rated as having "fair" internal validity.[91,92,175] Overall results indicate that there are improvements in academic functioning with medication, especially in reading skills. There is no added benefit with combining behavioral or psychosocial components to the medication interventions. In contrast, classroom-based programs to enhance academic skills are effective in improving achievement scores in multiple domains, but the benefits are sustained only as long as the intervention is implemented.

Following are the results of the studies reporting on academic outcomes, organized by the type of intervention.

Medication Interventions

The medication interventions were primarily psychostimulants. Powers, et al.,[174] followed a group of 90 ADHD children for the average duration of 9 years and the average duration of receiving psychostimulants was 5 years. They found that adolescents diagnosed with ADHD at childhood who had received stimulants for at least 1 year, compared to those who had not, had higher scores on three measures of academic achievement, word reading, pseudo-word reading, and numerical operations. They also showed higher secondary school grade point average (GPA). However, the medicated group did not reach the level of academic function of their non-ADHD peers. The study provides evidence of a modest positive effect of stimulant medication on long-term academic function. In spite of controlling for IQ, the participants were not matched on comorbidity of learning disability, potentially interfering with the conclusions.

Barbaresi, et al.,[85] also investigated the benefits of long-term stimulant medication use on academic outcomes in a retrospective birth cohort, including 370 ADHD children. The mean duration of treatment for cases that had a history of receiving medication was nearly 3 years. The participants were followed to a median age of 18 years. There was no difference with regard to

mental retardation and learning disability between the two groups. Overall, the authors found a positive correlation between cumulative stimulant dose and last documented achievement skills at a median age of almost 13 years. School absenteeism was significantly lower in the treatment group; any treatment and duration of treatment with stimulants were both negatively associated with the percentage of days absent. Stimulant-treated children were nearly two times less likely to be held back a grade. In contrast, one area of academic skills, the average reading score at the time of the last assessment, was similar between the cases that were treated and those not treated. Biederman, et al., 2009[86] followed 140 boys with ADHD, 6 to 17 years of age at diagnosis, 73 percent had received stimulants, with a mean duration of treatment of 6 years. Those using medication were less likely to repeat a grade.

Other studies reporting on academic outcomes[61,86] found that children treated with stimulants experienced improvements in measured IQ and less grade retention.

In summary, it seems that extended use of psychostimulant medications may enhance some dimensions of academic functioning. However, the outcomes reported are diverse and suggest that more investigation of this question is required.

Combination Interventions

MTA studies are described comprehensively earlier in this report. Following is the description of MTA results in academic and school performance. At the 14-month endpoint of the RCT, combined treatment was superior to intensive behavioral treatment and community care in improving reading achievement. At the 24-month assessment, nine months following discontinuation of the interventions, the differential between groups was no longer present.[73,160] At the 36-month assessment, the intention to treat analysis of the study also showed no significant difference between the treatment groups on reading achievement scores, similar to the other symptomatic and functional outcomes reported.[81] However, all treatment groups showed substantial improvement from baseline in all domains, although the relative effect size for reading achievement was small compared to other areas (reading 0.1 to 0.2, ADHD symptoms 1.6 to 1.7, functional impairment 0.9 to 1, and social skills 0.8-0.9). After 8 years, intention to treat analyses again showed that originally randomized treatment groups did not differ significantly on academic assessments and grades earned at school.[82] Looking at the trajectory of symptoms, impairment and academic achievement, there was convergence of treatment groups from 36 months to 8 years and maintenance of improved overall functioning relative to the baseline, with a somewhat different pattern for mathematics achievement. Examination of math achievement showed a positive association between past year medication use and improved scores at 36 months, 6 years, and 8 years. In contrast, past year medication use was associated with worse hyperactivity impulsivity, ODD symptoms, and functional impairment. Past year medication use was interpreted by the authors as suggesting continued rather than new onset use, and therefore may represent longer duration of use.

The other study reporting academic outcomes following extended use of combination psychostimulants and multimodal psychosocial intervention was a 24-month RCT, described earlier in this report.[89] It included 103 participants, ages 7 to 9 years, with ADHD (excluding those with documented learning disabilities or CDs), who received either MPH alone, MPH combined with multimodal psychosocial and academic remediation treatment, or MPH combined with an attention control intervention. Significant improvement in academic functioning was observed with all three interventions at 24 months. There was no advantage on any measure of academic performance with the combination treatment over MPH alone.

In summary, the results of studies investigating combined medication and psychosocial/behavioral interventions indicate improvement from baseline in academic outcomes, with no difference in effect between combined interventions and medication alone. Results from the MTA study suggest that there may be different outcome trajectories for reading and mathematics achievement.

Classroom-Based Interventions

The study by Evans, et al.,[175] is a controlled clinical trial of the Challenging Horizon Program and consultation (CHP-C) versus a community care control group over the intervention period of 3 years and a followup after 6 years. CHP-C was an intervention targeting academic skills such as assignment tracking, note taking, and organization skills in addition to social skills training, conversation skills, and problem solving. The beneficial results of treatment on ADHD symptoms were few during the first year of intervention but emerged after 2.5 years. However, neither teacher nor parent rating of academic functioning showed any significant academic benefit. Similarly, no long-term effect was found in student GPA.

The study by Jitendra, et al.,[91] consisted of a 15-month RCT of the Intensive Data-based Academic Intervention (IDAI) versus the Traditional Data-based Academic Intervention (TDAI). Volpe, et al.,[92] reported the results of this study after a 1-year followup. The assessments at 3, 12, and 15 months of the intervention indicated that both consultation groups demonstrated improvement in reading and mathematics skills on curriculum-based measurement (CBM) and in report card grades, although grades improved more for reading than for mathematics. The followup study at 1 year after discontinuation of interventions revealed that while students in both groups maintained the previous achievements, continued growth in skills was significant only for reading fluency.

While there are few comparative classroom-based intervention studies lasting 12 months or more, information from the ones available is mixed. Some programs are clearly beneficial and lead to improvement in academic skills for children with ADHD, but only as long as they continue to receive them.

Summary

The review of the academic outcomes with long-term followup of treatment interventions revealed benefits with medication interventions in some limited domains, such as very specific skills related to reading and arithmetic. Combining psycho-behavioral and academic skills interventions with medication offers no additional gains over and above that of medication alone for children with ADHD without comorbid learning disabilities. The psychosocial/behavioral intervention in the MTA study included a home and school focus on homework which successfully improved homework completion for up to two years.[90] Interventions for academic skills in classroom-based programs enhance both academic achievement and grades, but continued improvement in academic skills and functioning over time.

Table 11. KQ2. Summary of studies reporting academic outcomes

Study	Study Design Quality rating	N Mean Age (SD) % Male	Interventions compared	Length of Intervention Treatment/ Followup	Results
Jensen 2007[81]	RCT (MTA) QR: Good	N = 485 Age: range 7 to 9y Male: 80%	MedMgt vs. beh vs. comb vs. CC	Tx:14m F/u: 36m	No difference in originally randomized groups
Langberg, 2010[90]	RCT (MTA) QR: Good	N = 540 Age: 8.4y (0.8) Male: 80%	MedMgt vs. beh vs. comb vs. CC	Tx: 14 m F/u: additional 10m	Homework completion improved
Molina 2009[82]	RCT (MTA) QR: Good	N = 436 Tx; 170 control Age:8.5y (0.8) range 7 to 9.9y Male: NR	MedMgt vs. beh vs. comb vs. CC	Tx: 14m F/u:24m, 36m, 6y, 8y	No difference in originally randomized groups
MTA Cooperative Group, 1999[74]	RCT (MTA) QR: Good	N = 579 Age: 8.5y (0.8) Male: 80%	MedMgt vs. comb vs. beh. vs. CC	Tx: 14 m F/u: additional 10m	Combination Tx superior to beh Tx and CC in improving reading achievement on standardized tests
MTA Cooperative Group, 2004[73]	Open label extension of RCT (MTA) QR: Good	N = 540 Age: 8.4y (0.8) Male: 80%	MedMgt vs. beh vs. comb vs. CC	Tx: 14 m F/u: additional 10m	No significant effect on academic achievement on standardized tests
Barbaresi 2007[85]	Retrospective, population-based cohort QR: Fair	N = 370 Age: Median at last f/u 18.4y Male: 75%	Stim vs. no Tx	Mean Tx duration = 2.8y F/u: 13y	Tx with Stim: Decreased rates of absenteeism Modest positive correlation between stim and last reading score Decrease in rate of dx substance abuse
Biederman 2009[86]	10yr Prospective cohort followup QR: good	N = 140 Age: range 6 to 17y Male:100%	Stim vs. no Tx	Mean Tx duration:6y (SD: 4.7) F/u: 10y	Less grade repetition in those treated with stim

Table 11. KQ2. Summary of studies reporting academic interventions (continued)

Study	Study Design Quality rating	N Mean Age (SD) % Male	Interventions compared	Length of Intervention Treatment/ Followup	Results
Evans 2007[175]	Controlled clinical trial QR: Fair	N = 79 Age: 11.93y (0.72) range 10 to 14y Male: 77%	CHP-C vs. control	Tx: 3 school years F/u: every 6m over 3y	Significant benefit with ADHD symptoms and social functioning No effect on academic achievement
Gilberg 1997[61]	RCT QR: Good	N = 62, Age: 9y (1.6) Male: 84%	Amphetamine vs. placebo	Tx:15m F/u: 18m	IQ score improvement
Hechtman 2004[89]	RCT QR: Good	N = 103 Age: range 7 to 9y Male: NR	MPH vs. MPH + MPT vs. MPH + ACT	Tx: 2y F/u: 6, 12, 18, 24m	Improvement with Achievement on standardized tests and homework behavior across all treatments; maintained over 2 years No advantage of combination Tx over the others
Jitendra 2007[91] Followup study: Volpe 2009[92]	RCT QR: fair	N = 167 Age: 8.7y (1.23) Male: 76%	TDAI vs. IDAI	Jitendra: Tx: 15m over 2 school years F/u: 15m Volpe: Tx: none F/u: 1y after no treatment	Jitendra: Positive growth with academic performance and report card, more prominent for reading than math No difference for rate of growth between two Volpe: Continued growth in reading fluency Maintenance of performance in other academic areas No difference between the two groups
Powers 2008[174]	Prospective longitudinal QR: Fair	N = 80 Age: 9.11y (1.22) Male: 88%	Stim medicated vs. un-medicated vs. normal controls	Mean Tx duration: 30.4m F/u: 9.13y (SD 1.5)	Academic achievement (WIAT, GPA): Stim Ss >Control ($p < 0.05$). nonADHD >Control Stim pts with ADHD may benefit from long-term adolescent academic performance

Abbreviations: ACT = attention control treatment; ADHD = Attention Deficit Hyperactivity Disorder; beh = behavioral intervention; CC = Community Care; CCR = controlled clinical trial; CHP-C = Challenging Horizons Program-training and consultation model; comb = combination; dx = diagnosis; f/u = followup; GPA = grade point average; IDAI = intensive data-based academic intervention; MedMgt = Medical Management; MPH = methylphenidate; MPT = multimodal psychosocial treatment; MTA = multimodal treatment study; pts = patients; QR = quality rating; RCT = randomized control trial; SD = standard deviation; Ss = subjects; Stim = stimulant; TDAI = Treatment data-based academic intervention; Tx = treatment; WIAT = Wechsler Individual Achievement Test; y = year

Long-Term Studies (5 or More Years) Examining Stimulant Medication Treatment

The studies reviewed in this section examine outcomes which were five or more years after initiation of the intervention (see Table 12). All the studies identified compared those who had been treated with stimulant medication against those who had not. The 6 to 8 year outcome of the MTA study, which compared medication, behavioral, and multimodal interventions, has been discussed in an earlier section.[82]

There were 15 papers identified. Two studies were rated with "good" internal validity,[82,176] nine studies had "fair" internal validity,[57,86-88,177-181] and four were weak,[151,182-184] according to the quality assessment tool used. Twelve papers[57,86-88,151,176-182] reported on prospective followup studies of one or more cohorts of ADHD youth, while two were retrospective studies.[183,184] As these papers reported on a variety of outcomes, they are summarized according to the outcomes studied. Only studies meeting criteria for at least "fair" internal validity are discussed below.

Psychiatric Disorders

Biederman, et al.[86] conducted a 10-year prospective cohort followup study involving 140 Caucasian male children with ADHD, ages 6 to 17 years at baseline, which controlled for parental psychopathology. Out of the 112 participants assessed, 73 percent had lifetime treatment with stimulant medication, starting at a mean age of 8.8 years for a mean duration of 6 years. Those who were treated with stimulants were significantly less likely to subsequently develop ODD, CD, depressive, and anxiety disorders, and were less likely to repeat a grade.[86] There was no significant difference for Bipolar Disorder between groups.

Substance Use Disorders

Katusic, et al.,[87] reported on 379 research-identified ADHD children from a birth cohort (74.9% boys) and followed them up for a mean duration of 17 years. While 295 received stimulant medication (alone or in combination, median average daily dose of 21.4 MPH-equivalent units, median duration 34 months, median age at treatment 10 years), 84 did not receive treatment. The study found stimulant treatment to be associated with reduced risk for later substance abuse among boys, but not among girls. Mannuzza, et al.,[88] followed 176 MPH-treated Caucasian male children, ages 6 to 12 years, with DSM-II hyperkinetic reaction but without CD, into adulthood (mean age 25 years, retention rate 85%), and overall found no association between use of stimulants and substance use outcomes. However the early-treated subjects (age 6 to 7 years) had lower lifetime rates of substance use disorders compared with those treated at older age. Age at stimulant treatment initiation was also significantly and positively related to the later development of antisocial personality disorder, but was unrelated to mood and anxiety disorders. The study by Biederman, et al.,[86] which was described at the beginning of this section, also examined substance use disorders as an outcome. The analysis of 56 medicated and 19 non-medicated boys who were over the age of 15 (54% of original cohort of ADHD children) at the 4-year followup, revealed that those who were medicated were at a at lower risk for substance use disorders.[179,182] However, when they reassessed 112 young men (80%) after 10 years (mean age at followup was 22 years), they found no associations between stimulant treatment (including age and duration of treatment) and alcohol, drug, or nicotine use disorders.[179] The report by Wilens, et al.,[181] on the 5-year outcomes of the same cohort of girls as

previously studied by Biederman, et al.,[185] assessed 114 (mean age at followup 16 years, 95% Caucasian, 67% treated with stimulants) of the original 140 English-speaking females ages 6 to 18 years with ADHD. They found stimulant treatment to reduce the risk of development of any substance use disorder and cigarette smoking, even after controlling for CD. Huss, et al.,[180] performed a multi-site retrospective study on a nonrandomized cohort of 215 ADHD children. One hundred and six received treatment with short-acting MPH (mean duration of treatment was 2.3 years) while 109 did not. The medicated group was significantly delayed in their age of onset of regular smoking, by a time period of approximately 2 years. Monuteaux, et al.,[176] followed up on 99 subjects (70% male, 80% Caucasian, with a mean age of13 years) with ADHD involved in an initial year-long placebo-controlled RCT of bupropion treatment (mean dose 3.2mg/kg at week 52) for up to 6.5 years (the mean duration of followup was12 months). Twenty-nine study subjects received concurrent stimulant treatment (mean maximum dose 1.0mg/kg). They found bupropion not to be effective in the prevention of smoking, but stimulant treatment was associated with statistically significant lower risk of smoking initiation ($p = 0.03$) as well as a lower risk of continued smoking (hazard ratio (HR) = 0.3, $p = 0.02$).

Several of the above studies suggest that stimulant treatment may protect against early onset of adolescent substance use, however, most of the studies were cohorts where families self-select into treatment conditions rather than being randomized. Therefore, the apparent benefits of stimulant treatment may result from other nonspecific protective factors associated with this choice. For example, the level of detail reported in most studies did not include potential co-interventions such as PBT, or school interventions.

Other Functional Outcomes

In their 30-year prospective longitudinal study, Satterfield, et al.,[178] followed 179 Caucasian patients diagnosed as ‘hyperactive’ between ages 6 to 12 years, whom they reported would have met DSM-IV-TR criteria for ADHD (78% had parent-reported conduct problems), and studied their official arrest records later in adulthood. There was no statistically significant difference in the criminality rates studied between those who had received drug treatment only (N = 103) and those who had received combined treatment (the behavioral component included PBT, individual or group therapy for the child, family therapy, and educational therapy). Even the ‘most-treated’ subgroup, who received 2 to 3 years of combined treatment, did not differ in the rate of arrest from those who received medication management only. The rates of anti-social behavior were no greater in ADHD individuals without concomitant conduct problems as children (7.8%) than in the community control group (8.0%).[178]

Treatment-Adherent Versus Treatment-Non-Adherent Groups

Charach, et al.,[57] followed up 79 of 91 participants (81% males with no comorbid anxiety or mood disorder) of a 12-month randomized controlled trial comparing MPH and parent groups. Those who were adherent to medication showed better teacher-reported outcomes at years two and five, but by year five, only 16 treatment-adherent and 14 nontreatment-adherent patients remained. For those who continued to use medication, stimulants continued to be effective with few side effects. The study sample size was small and adherents tended to have more severe baseline ADHD symptoms. Youth who no longer found medications effective or who experienced adverse effects may have discontinued.

Summary

The outcomes and time frames varied across studies. Except for Biederman[179] and the Wilens[181] group, which studied an exclusively female cohort, all others studied an exclusively or predominantly male sample. Stimulant medication might protect against psychiatric disorders (e.g., ODD, CD, depression, or anxiety disorder) in the long-term (at 10 years). Some studies suggest that stimulant medication reduces substance use disorders in late adolescence,[87,181] while another reported no benefit by young adulthood.[179] Two studies suggested stimulant medication may protect against nicotine use.[176,181] Treatment with stimulant medication, especially at an earlier age, may delay onset of smoking and reduce substance use disorder.[88,177,180] However, these benefits may disappear by adulthood.[88,179]

Satterfield found no clear effect of childhood intervention on arrest rates in adulthood.[178]

Table 12. KQ2. Summary of controlled studies reporting very long-term (>5 years) outcomes of ADHD treatment

Study	Study design Quality rating	N Mean Age (SD) % Male	Interventions compared					Length of Intervention Primary/ Followup (SD)	Outcome Measures	Results†
			Med	Behav	Comb	CC	No med			
Biederman J 2008[179]	10 year cohort prospective followup Fair	N = 140 Age: 6 to >18y Male: 100%	√				√	1y/10y	Substance use disorders	No statistically significant associations between stimulant treatment and alcohol, drug or nicotine use disorders
Biederman J 2009[86]	Cohort prospective Fair	N = 140 Age: 6 to 17y Male: 100%	√				√	6y(4.7)/10y	Psychiatric disorders	Med <No med
Biederman J 1999[182]	Cohort prospective Weak	N = 75 Age: 17.2 (2.1) Male: 100%	√				√	4.4y(2.7)/4y	Substance use	Medicated <un-medicated
Charach A 2004[57]	Uncontrolled extension of clinical trial Fair	N = 79 Age: 8.09 (1.38) Male: 81%	√				√	1y/5y	Symptoms Adverse events	Stim improve ADHD symptoms for up to 5 years, but adverse events persist.
Daviss W 2008[184]	Cohort retrospective Weak	N = 75 Age: 6 to 18y Male: 57.4%	√					N/A per design/ >5y	Depression	Pharmacotherapy may reduce risk of later depression

Table 12. KQ2. Summary of controlled studies reporting very long-term (>3 years) outcomes of ADHD treatment (continued)

Study	Study design Quality rating	N Mean Age (SD) % Male	Interventions compared					Length of Intervention Primary/ Followup (SD)	Outcome Measures	Results†
			Med	Behav	Comb	CC	No med			
Goksoyr P 2008[183]	Retrospective Weak	N = 104 Age: 6 to 18y Male: 69.6%	√				√	N/A per design/ >5y	Substance abuse; criminality	Tx contributes to increased social and psychological functioning
Huss M 2008[180]	Cohort retrospective Fair	N = 215 Age: 6 to 18y Male: 90%	√				√	N/A per design/ >12y	Nicotine use	No effect of medication on frequency of use, or continuous use of nicotine, but MPH had minor benefit for delaying age of onset
Katusic S 2005[87]	Cohort retrospective Fair	N = 379 Age at baseline: birth, Age at last followup: median 18.2 Male: 75%	√				√	Any Tx during childhood/ 17.2y	Substance abuse	Substance Abuse: Med <no med
Lambert N 2005[177]	Prospective longitudinal Fair	N = 492 Age at baseline:5 to 11y Male: 78%	√				√	N/A per design/ To age 26y	Substance abuse	Stimulant Tx for >1y resulted in 2.9 times more likely to become a daily smoker in adulthood, while Tx for <1y resulted in 4.0 times likelihood of becoming a daily smoker Stimulant Tx was associated with greater likelihood of use of amphetamines
Leibson C 2006[151]	Prospective cohort analytic Weak	N = 313 Age at baseline: 5y Age at outcome: 7.7 (1.9) Male: 75%	√				√	14 days to 11.8 years/ To age 18y	ED visits, medical cost	The number of ED visits per year and the ED costs per year were lower during periods they were on stimulants compared with periods they were off stimulants. Total medical costs, were significantly higher during periods on versus off stimulants.
Mannuzza S 2008[88]	Cohort prospective Fair	N = 176 Age: <6 to >18y Male: 100%	√				√	1yr/12y	Substance abuse	Significant positive relationship between age at treatment initiation and nonalcohol substance use disorder

Table 12. KQ2. Summary of controlled studies reporting very long-term (>3 years) outcomes of ADHD treatment (continued)

Study	Study design Quality rating	N Mean Age (SD) % Male	Interventions compared					Length of Intervention Primary/ Followup (SD)	Outcome Measures	Results†
			Med	Behav	Comb	CC	No med			
Molina B 2009[82]	Prospective followup to RCT (MTA) Good	N = Age at 6 y f/u: 14.9 (1.0) Age at 8 y f/u: 16.8 (1.0) Male: 78%	√	√	√	√		14m/8y	Symptom ratings, antisocial behavior, other mental health disorders, academic, social functioning	The originally randomized treatment groups did not differ significantly on repeated measures or newly analyzed variables (e.g., grades earned in school, arrests, psychiatric hospitalizations, other clinically relevant outcomes)
Monuteaux M 2007[176]	Prospective cohort Good	N = 99 Age: <6 to 18y Male: 70%	√				√	1y/to age 18y	Adverse event & Substance use	No change Medicated < non-medicated
Satterfield J 2007[178]	Cohort retrospective Fair	N = 279 Age: 6 to >18y Male: 100%	√		√			30y	Criminality	no change in occurrence of criminality in patients with ADHD w/o CD after 3y of MMT
Wilens T 2008[181]	Cohort prospective Fair	N = 114 Age: 10 to 24y Male: 0%	√				√	1yr/5y	Smoking and substance use disorders	Med reduces risk & delays onset of smoking

†Only statistically significant results are reported.

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; behav = behavioral treatment; Comb = stimulant + behavioral treatments; CC = Community care; CD = Conduct Disorder; ED = Emergency Department; Med = Stimulant medication treatment; MMT = multimodal treatment; MPH = methylphenidate; N/A = not applicable; no med = no stimulant medication treatment; RCT = randomized control trial; SD = standard deviation; Tx = treatment; w/o = without; y = year

Key Question 3. How do (a) underlying prevalence of Attention Deficit Hyperactivity Disorder, and (b) rates of diagnosis (clinical identification) and treatment for Attention Deficit Hyperactivity Disorder vary by geography, time period, provider type, and sociodemographic characteristics?

The introduction to Key Question 3 (KQ3) underlines the complexity of addressing issues of ADHD prevalence in the population, compared with prevalence of clinical identification and of treatment. The literature obtained to address the issues was largely based on epidemiological surveys and administrative data sources in the United States. From this body of research, it appears that clinical identification in the United States exceeds estimates of population prevalence worldwide. As a corollary, ADHD medication use is higher than expected for per capita GDP. Variability exists among regions of the United States, with lower rates of identification and medication treatment in the West than in other regions. More boys than girls, and more Caucasians than African-Americans or Hispanics receive diagnoses and treatments. Rates of identification and treatment have increased over the past 20 years, especially among girls and adolescents. While rates of medication use are small compared with school age children, they have been increasing among preschoolers and adults as well. Service provider characteristics and access to insurance are important health systems factors which play influential roles in the receipt of treatment.

Some important limitations were imposed on the review process for KQ3. While the literature was searched using the methodology of a systematic review, selection of papers for inclusion was not subject to the same constraints dictated by the methodology, since it was included as a context piece and choices were made as to which of the over 440 included reports appeared most pertinent to the question asked. With the assistance of peer reviewer feedback, other relevant papers were identified and added to this section.

Underlying Prevalence

As will be evident from Tables 13 through 20, within the ranges of prevalence reported worldwide, from different regions, and even from different studies in the same region, there are nearly as many estimates as published studies.[93] The thrust of KQ3 is to identify the background or "endemic" rate of ADHD and compare it with rates of clinical identification and subsequent treatment. The question implies that there is a "true" rate of disorder but, as indicated earlier in this report, and discussed more fully below, historical, cultural, and contextual factors affect the definition of ADHD. Moving into the clinical context, characteristic traits or symptoms alone do not confer the status of disorder, but poor functioning in a particular context, causing distress and concern for the individual and family, is important. Below are comments about methodological and contextual aspects of ADHD that influence the interpretation of results.

Methodological Considerations

Additional complexity for identification of community prevalence is introduced by methodological issues regarding identification of the population at risk, individual cases within that population, measurement reliability and validity, and quality of data sources. Once a definition of disorder is chosen (e.g., using specific diagnostic criteria), operationalizing the definition for use in large population-based studies raises issues. The symptoms used for characterizing ADHD, as well as quality of day-to-day functioning, are generally understood to

exist on a continuum within a community; the question then becomes how to choose a threshold on that continuum that maximizes accuracy. The choice of measure, its reliability, validity, and the source of informant, are all important. Frequently, the cost, feasibility, and measurement burden on informants influence choice of measures, as well as methods of data collection (e.g., epidemiological survey or use of pre-existing administrative data). Study designs used to answer KQ1 and KQ2, (RCTs and observational cohorts) use volunteer participants and have rigorous diagnostic and intervention specificity. The studies compiled for KQ3 are descriptive and use research designs geared for large community populations. Strengths include generalizability of information to large segments of a community population, while weaknesses include a loss of detailed descriptions of individual cases. Administrative data provide important information about trends in actual clinical practice. Since the data are collected for nonresearch purposes (e.g., insurance claims to justify use of intervention, prescription records of tablets bought), reliability and validity of case identification and characterization of treatment received is comparatively weak. Relative strengths and weaknesses of study designs are described in Table 13.

Table 13. KQ3. Study design and application to ADHD research

Design	Strengths	Weaknesses
Randomized Control Trial	• Clear case definition • Reproducibility of intervention • Experimental Design	• Necessarily smaller study population • Participants willing to be in research likely to be higher SES, more knowledgeable, and adherent to health care • Shorter study period so long-term impact of pharmacological treatment may not be evident • Expensive • Requires clear case definition which may not reflect “real world” and may be difficult with ADHD, especially among children under the age of 6 years • Results not readily generalized to the ‘real world’ for several of the reasons above
Observational	• Impact of condition or treatment over the lifespan • Increased variability in participants, therefore improved generalizability • Intervention more typical of usual practice • More cost-effective than experimental designs	• High rate of loss to long-term followup (this can be addressed by newer statistical designs, e.g., survival analyses) • Lack of certainty that sample participants who receive intervention and those who do not have similar prognosis, although can be addressed by statistical control methods • Requires clear case definition which may not reflect “real world” and may be difficult with ADHD, especially among children under the age of 6 years • Increased likelihood of false positive results
Administrative Database	• Very large population possible • Data is already collected/accessible • Evidence of “real world health service activity”, (i.e., who provides which services, where and to whom) • Comparatively inexpensive	• Loose case definition • Coding error unlikely to be identified • Missing values not easily recovered • Treatment data may be used for identification of the disorder (tautology) • Must use variables collected for administrative purposes (very different than health research purposes) as proxy for diagnosis, treatment, and health outcomes

Table 13. KQ3. Study design and application to ADHD research (continued)

Epidemiological Survey	• Large sample • Represents whole population • Clear case definition using standardized measures • Survey with direct patient/family input • Measures designed to capture variables of interest • Measures generally reliable; valid compared with administrative data bases • Few coding errors • Many variables obtained at the same time, providing good opportunity to identify determinants of health	• Volunteer participants, may not be representative of those who do not live in a stable residence or own a telephone • If longitudinal study design, likely to be attrition and require statistical adjustment • Measures are usually shortened from clinical measures to lessen measurement burden • Expensive • Difficult to implement

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; SES = socioeconomic status

Definition of ADHD

While there are many, one of the key challenges which obscures definition of ADHD cases and therefore contributes to the difficulty of defining its prevalence, is the difficulty identifying children and adults in a population who display the representative behaviors in the middle range of possibility. The nature of the condition is defined by the context of a situation – with other people, in families, in classrooms, and in play yards. Patients at either end of the spectrum, those having the true condition and those who clearly do not, are quite readily identified; however, there is a large population in the centre for whom the picture is less clear. Rather, the condition is a matter of degree with no startlingly clear boundaries and is often understood as a continuous variable rather than a categorical one. In common with other medical disorders, the use of diagnostic criteria imposes a categorical paradigm, which is subsequently used for decisionmaking regarding recommendations for treatment within the individual clinician-patient relationship, or for describing population health needs.[186]

Criteria for International Comparison

The history of the identification and inclusion of ADHD and related disorders in disease classifications is also instructive in this regard (see Table 14). Since introduction of Hyperkinesis Syndrome of Childhood in DSM-II (1968) and ICD-9 (1977) and Attention Deficit Disorder (ADD) to the DSM-III (1980), subcategories have burgeoned with variants and subtypes further parsed with each release of updates to the classification systems. This process highlights two additional issues which affect prevalence estimates as well as diagnosis of individuals, the evolution of criteria and how these influence who is diagnosed with the condition over time, and how these criteria are interpreted and operationalized in real life situations rather than within the rigorous setting of research.[187] Different prevalence rates have been derived for the same population when the results from questionnaires based on the diagnostic criteria of DSM-III-R and DSM-IV are analysed.[188]

Table 14. Timeline of identification of ADHD and development of treatment—derived from Eisenberg[3] and Mayes[2]

Year	Country	Nosology/Diagnosis	Social and Economic factors
1876	U.K.		*The Educational Act* passed, mandating elementary education for all children, and thus, a structured environment against which childhood ADHD is often identified
1902	U.K.	Sir G.F. Still[1] describes distinctive constellation of behaviors in children who cannot focus and fail school despite intelligence. He describes their behavior under various conditions, occurring more often among boys than girls, frequently apparent by early school years, generally showing little relationship to child training and home environment, and commonly sharing a poor prognosis	
1922	U.K	Tredgold observes agitated behaviors among Spanish Influenza Epidemic (1919) survivors and hypothesizes relationship to *encephalitic lethargica*, referring to the condition as "minimal brain damage"	
1932	U.S.		Bradley identifies *d,* l-amphetamine and observes its "paradoxical" calming and focusing effect on children who were psychiatric inpatients
1952	U.S.	DSM-1 released; no mention of hyperkinetic syndrome	
1950s	U.S. U.K.	"minimal brain damage" "hyperkinetic reaction of childhood" (DSM-II)	Research studies on children using antipsychotic drugs such as chlorpromazine (i.e., Largactil, Thorazine)
1955	Switzerland		Geigy develops MPH (i.e., "Ritalin")
1957	U.S. Switzerland		Dextroamphetamine included in pharmacotherapy as the only effective treatment for ADHD/ADD, although no evidence about efficacy is available since no clinical trials are performed Geigy releases "Ritalin" to the market; and states that their experience with it is too limited to make a valid statement as to its usefulness
1958	U.S.		NIMH Pharmacological branch sponsor first ever conference on use of psychoactive drugs in treatment of children
1961	U.S.		"Ritalin" approved for use in children
Mid 60s	U.S.	Questions about link between brain 'damage' and hyperactivity; new phrase coined "Minimal Brain Dysfunction" hedging between old terminology and new discoveries	

Table 14. Timeline of identification of ADHD and development of treatment—derived from Eisenberg[3] and Mayes[2] (continued)

Year	Country	Nosology/Diagnosis	Social and Economic Factors
1965	WHO	ICD-8 309 – Behavior disorders in childhood	
1967	WHO	Inclusion of hyperkinesis as syndrome in WHO Seminar on Diagnosis and Classification in Child Psychiatry	
1968	U.S.	DSM-II released, includes “hyperkinetic reaction of childhood”	NIMH requests longer term studies (i.e., >8 weeks) on effects of stimulant drugs on children
End 60s	U.S.	Estimated 150,000 to 200,000 children treated with stimulants (0.002% of child population at that time)	
1970	U.K.	Rutter’s Isle of Wight study; first well designed epidemiological ascertainment of prevalence of hyperkinesis which found 2 cases among 2199 children between ages 10 and 11 (i.e., 0.9%)	
1971	U.N. and U.S.	U.N. Convention on Psychotropic Substances: Substances in Schedule II	Congressional hearing which changed classification of stimulant drugs to controlled substances and making data collection mandatory Wender’s book released which notes familial nature of ADHD, pointing way to genetic studies Eisenberg and Conners receive NIMH grants to study MPH
1975	U.S.		Popular Feingold diet published Characterisation in the media of medication for hyperactive children as ‘chemical straitjacket’, as reflection of the social period
1977	WHO	ICD-9 314 - Hyperkinetic syndrome of childhood	

Table 14. Timeline of identification of ADHD and development of treatment—derived from Eisenberg[3] and Mayes[2] (continued)

Year	Country	Nosology/Diagnosis	Social and Economic Factors
1979	U.S.	ICD-9-CM **314 Hyperkinetic syndrome of childhood** *Excludes: hyperkinesis as symptom of underlying disorder? code the underlying disorder* **314.0 Attention deficit disorder (ADD)** Adult Child **314.00 Without mention of hyperactivity** Predominantly inattentive type **314.01 With hyperactivity** Combined type Overactivity NOS Predominantly hyperactive/impulsive type Simple disturbance of attention with overactivity **314.1 Hyperkinesis with developmental delay** Developmental disorder of hyperkinesis Use additional code to identify any associated neurological disorder **314.2 Hyperkinetic Conduct Disorder** Hyperkinetic Conduct Disorder without developmental delay *Excludes hyperkinesis with significant delays in specific skills (314.1)* **314.8 Other specified manifestations of hyperkinetic syndrome** **314.9 Unspecified hyperkinetic syndrome** Hyperkinetic reaction of childhood or adolescence NOS Hyperkinetic syndrome NOS	
1978	U.S.		Therapeutic response to drugs taken as confirmation of Dx Rapoport observes that both normal children and ADHD children respond to stimulant medications with greater focus; age may be the operative factor in its effectiveness, not 'disorder'
1980	U.S.	DSM-III released; includes "Attention Deficit/Hyperactivity (ADHD) Disorder"	
1987	U.S.	MPH use ("defined daily doses") = ~60 million	
1991	U.S.	MPH prescriptions = 4 million Amphetamine prescriptions = 1.3 million	

Table 14. Timeline of identification of ADHD and development of treatment—derived from Eisenberg[3] and Mayes[2] (continued)

Year	Country	Nosology/Diagnosis	Social and Economic Factors
1992	WHO	ICD-10 Mental and behavioral disorders (F00-F99) **Behavioral and emotional disorders with onset usually occurring in childhood and adolescence** (F90-F98) F90 – Hyperkinetic disorders Excludes anxiety disorders (F41.-) mood [affective] disorders (F30-F39) pervasive developmental disorders (F84.-) schizophrenia (F20.-) **F90.0 Disturbance of activity and attention** Attention deficit: · disorder with hyperactivity · hyperactivity disorder · syndrome with hyperactivity Excludes: hyperkinetic disorder associated with Conduct Disorder (F90.1) **F90.1 Hyperkinetic Conduct Disorder** Hyperkinetic disorder associated with Conduct Disorder **F90.8 Other hyperkinetic disorders** **F90.9 Hyperkinetic disorder, unspecified** Hyperkinetic reaction of childhood or adolescence NOS Hyperkinetic syndrome NOS **F91 Conduct disorders** **Excludes:** mood [affective] (F30-F39) pervasive developmental disorders (F84.-) schizophrenia (F20.-) when associated with: · emotional disorders (F92.-) · hyperkinetic disorders (F90.1) **F91.0 Conduct disorder confined to the family context** **F91.1 Unsocialized Conduct Disorder** Conduct disorder, solitary aggressive type Unsocialized aggressive disorder **F91.2 Socialized Conduct Disorder** Conduct disorder, group type Group delinquency Offences in the context of gang membership Stealing in company with others Truancy from school **F91.3 Oppositional defiant disorder** **F91.8 Other Conduct Disorders** **F91.9 Conduct disorder, unspecified**	

Table 14. Timeline of identification of ADHD and development of treatment—derived from Eisenberg[3] and Mayes[2] (continued)

Year	Country	Nosology/Diagnosis	Social and Economic Factors
		Childhood: · behavioral disorder NOS · Conduct Disorder NOS	
1993	U.K.	Methylphenidate released to general availability in the U.K.[189]	
1994	U.S.	DSM-IV released with amplified ADHD subtypes **Attention-deficit and Disruptive Behavior Disorders** Attention-Deficit Hyperactivity Disorder 314.01 Combined subtype 314.01 Predominantly hyperactive-impulsive subtype 314.00 Predominantly inattentive subtype 314.9 Attention-Deficit Hyperactivity Disorder NOS Conduct disorder 312.81 Childhood onset 312.82 Adolescent onset 312.89 Unspecified onset 313.81 Oppositional Defiant Disorder 312.9 Disruptive Behavior Disorder NOS	
1999	U.S.	MPH use ("defined daily doses") = ~360million MPH prescriptions =~11 million/amphetamine =~6 million	
2000/ 2003	U.S.	Great Smoky Mountain studies[113,114] report unequivocal prevalence of 0.9% among children between 9 and 16 (2.2% at age 9 declining to 0.3% at age 16) but rate of stimulant treatment more than twice rate of unequivocal diagnosis, and majority of children treated did not meet ADHD criteria; serious mismatch between need and provision; others[115,116] do not find the potential for mismatch so clear cut.	
2003	U.S.	NSCH[4] survey of children 4 to 17: Diagnosed (see below): 4.4 million Medication for ADHD: 2.5 million (56%) Estimated prevalence based on parent report of response to the NSCH survey question "Has a doctor or health professional ever told you that [child name] has ….ADD or ADHD?" Prevalence reports average 7.8% with variability from 5.0% in Colorado to 11.1% in Alabama	Lexchin[147] among others identifies company sponsored studies more than four times likely to have outcomes that favor sponsor than neutrally sponsored research

Table 14. Timeline of identification of ADHD and development of treatment—derived from Eisenberg[3] and Mayes[2] (continued)

Year	Country	Nosology/Diagnosis	Social and Economic Factors
2005	U.S.		Child Medication Safety Act (H.R.1790) to protect children and parents from being coerced into administering a controlled substance or psychotropic drug in order to attend school, and for other purposes, as amended

Abbreviations: ADD = Attention-Deficit Disorder; ADHD = Attention-Deficit Hyperactivity Disorder; CM = Clinical Modification; DSM = Diagnostic and Statistical manual; Dx = diagnosis; F = subsection of ICD codes; H.R. = House of Representatives; ICD = International Classification of Disease; MPH = methylphenidate; NIMH = National Institutes of Mental Health; NOS = not otherwise specified; NSCH = National Survey of Child Health; U.K. = United Kingdom; U.N. = United Nations; U.S. = United States; WHO = World Health Organization

ADHD has only recently been recognized as persisting among the adult population,[190,191] although it is not yet differentiated from formal classification with a childhood disorder. The work on estimating prevalence of ADHD in adult populations is further obscured since, as a result of lack of diagnosis in childhood, retrospective self-report measures are often accepted as a best available proxy for diagnosis of ADHD.[192,193]

Lower rates of background prevalence are generally cited in Europe and there may be more than one explanation or factor contributing to this discrepancy. The DSM criteria, the use of which is favored in the United States, are generally cited as being more inclusive, such that higher rates are consistently cited in regions where studies use these; in Europe, however, the ICD codes are used preferentially and these are generally agreed to require more stringent interpretation of criteria, resulting in much lower reported rates of ADHD.[109,110,194] Santosh, et al.,[195] report that only 25 percent of children in the MTA study who were diagnosed as ADHD using DSM criteria would have met criteria for "Hyperkinetic disorder" using the ICD system. Other classification options have also been put forward for consideration, such as the ICF,[196] which introduces considerations of function and impairment into the picture of ADHD, the composite international diagnostic interview (CIDI),[93] another instrument from the WHO which was used as part of their global mental health survey, the Development and Well-being Assessment (DAWBA), used by the United Kingdom for a national statistics study of child psychiatric morbidity[197] and the ADHD Rating Scale,[198] among many others.

Instruments

A vast array of standardized, and not so standardized, measures have been used to assess ADHD children in research and in clinic, and may be applied to situations for which they were not designed so that the resultant data is interpreted in a manner not consistent with their psychometric properties. Even when assessment instruments are validated and applied in a standardized manner, the sheer variety of validity tests makes comparisons difficult. The logistics of finding trained personnel to make rigorous identifications is impractical on a scale large enough to identify the background population prevalence of the disorder and, therefore, clinical research measures have been adjusted to create the simpler and less time-consuming diagnostic screening measures used in epidemiological surveys adminstered by nonprofessionals. How these instruments are collected, interpreted, and applied may be a source of imprecision.[199] Lack of standardization across studies can make comparison difficult.[23] To date, there has been limited monitoring reported in the literature of fidelity of application, even with the most widely used instruments.

Cultural and Ethnic Observations

Cultural expectations and child-rearing practices may also influence background prevalence rates. Harkness, et al.,[200] observes that expectations regarding normal development in infants vary from country to country, as well as beliefs about sleep hygiene, optimal socialization for infants, and different classroom cultures and expectations as to desirability of whether to teach and promote attention and focus, as in the Netherlands - or to 'stimulate,' which is valued in the United States[186,200] Ethnicity may influence the interpretation of behaviors, as well; Gidwani, et al.,[201] find differences in perception and interpretation of hyperactivity in U.S. subpopulations, Stevens[202] in regional rates of identification and service provision, while Mattox and Harder[203] report similar findings in their review of ADHD in diverse populations, from the perspective of social work.

Point of View

Diagnostic measures of childhood ADHD, whether detailed measures or simpler screening instruments, generally rely on parents or teachers to describe symptoms and impairment. More rigorous studies include both parent and teacher informants, since identification of the clinical disorder should be documented as causing impairment across settings. Teacher reports generally correspond only partially with parent reports.[199,204] Similarly, for studies using youth self-report as a key source of information, adolescents and their parents show only partial agreement.[204] The child may act differently in different settings and contexts, but the informants may also hold different expectations for child behavior.

Parental understanding of effective parenting strategies may influence interpretation of normal child behavior,[205] some of which will resolve with maturity;[206,207] Children have a limited repertoire of responses to stress, and can show behaviors which mimic ADHD but which are not. Researchers have observed that family stressors in the forms of poverty,[208] trauma,[209] insurance status,[210-213] disordered sleep,[214] and food insecurity[215] contribute to apparent rates of behavioral problems in children of the affected households.

Teachers may exert significant influence in who gets diagnosed since they may be the first to introduce the idea of ADHD to a family as a potential "diagnosis" for their child, and this identification may be influenced by a myriad of social factors, such as teacher perceptions and understanding of the child, the family, and background.[216-220] Nevertheless, the more subtle influence of halo[221] and rater[222] effects may still be found to influence diagnosis, treatment, and thus expressed prevalence rates. Similarly, the concept of 'a good student' is culture-bound, which makes the correct attribution of behaviors and their interpretation as beyond an accepted norm within a particular classroom very unlikely.[222]

The discrepancy between the reports of parent and teacher informants may also introduce a confounding effect, as noted by Costello, et al.,[223] in the U. S., while Rowland, et al.,[224] further demonstrate that the weight given to the observation of a particular informant influences the classification into a subtype. Discrepancies between parent and teacher assessments have also been identified in Japan.[225]

For estimates of adult ADHD, self-report measures are used. However, aspects of the diagnosis depend on a history of having had ADHD as a child. For this information, both clinicians and researchers depend on retrospective reports from adults about their own behavior as children, and it is therefore open to problems with interpretation.

Underlying Population Prevalence of ADHD Compared With Clinical Identification of ADHD and Subsequent Treatment of ADHD

The section above discussed the methodological pitfalls to examining the background population prevalence of ADHD using epidemiological methods that include diagnostic screening measures. Despite the difficulties noted, the screening measures that include symptom scales and measures of impairment most closely approximate a valid and reliable diagnosis for purposes of accurately assessing population prevalence.[93] In comparison, an additional level of contextual complexity is added when determining the prevalence of diagnosed or clinically identified ADHD. Clinical identification can be impacted by access to clinical services and by service provider and patient characteristics. The most common way this prevalence has been ascertained in the United States is by including items in epidemiological surveys that ask

caregivers, usually mothers, if their child has ever been diagnosed with attention problems or ADHD by a professional.[104,219,226,227] Froehlich, et al.,[104] examined both background population prevalence and parent-reported clinical identification and treatment in a nationally representative U.S population; approximately half the children identified with ADHD via research measures had a prior clinical identification of ADHD, and a third were treated. In contrast, Barbaresi, et al.,[228] examined medical and school records in a population birth cohort in Rochester, Minnesota for documentation of diagnosis. This study of written records noted a continuum of certainty regarding the clinical diagnosis, where definite diagnoses were more likely to result in higher rates of treatment than diagnoses where the record was less certain. Indeed, in the cohort from Rochester, Minnesota, definite diagnoses resulted in 85 percent of children receiving stimulant treatment compared with probable diagnoses resulting in 40 percent of children receiving treatment.[228]

Characteristics of service provider type as well as system of remuneration have been linked to likelihood of both clinical diagnosis and treatment.[2,227,229] These additional sources of potential bias are important in understanding research using administrative databases as sources of information. Recent studies examining trends in identification and prescribing practices using insurance claims and prescription databases offer useful information about geographic and time trends in clinical practice, but pressures to justify treatments shape data reporting and collection. Patient and parent requests also play a role. In a 1999 survey of Canadian physicians drawn from family physicians, developmental and general pediatricians, and child psychiatrists, the top four explanations selected for recent increases in MPH use were "increasing public awareness of ADHD and its treatments," "pressure from parents and teachers to use medications to treat ADHD," "acceptance of medication as a treatment for ADHD," and "few resources for other interventions."[230] Other pressures occur among university age patients. There are societal pressures on university and college campuses to use stimulant medications as "study aids"[231] and likely, motivated students can convincingly feign ADHD symptoms,[232,233] presumably well enough to acquire prescriptions from harried physicians. Despite these examples, however, analysis of prescription trends in administrative databases can provide insights into service access and provision gaps.[127]

Geography, Time Period, Provider Type, and/or Sociodemographic Factors in Studies of Population Prevalence

Of the above-mentioned factors, recent studies from a variety of countries primarily address issues of age, gender, and in some cases, SES and ethnicity/race in the ascertainment of ADHD prevalence. In general, epidemiological survey methods are used and include diagnostic screening measures, using either a parent or teacher informant or questions regarding past identification of the disorder from the parent. The bulk of the literature consists of studies of children with ADHD conducted either in North America or Western Europe, with clear gaps in knowledge on the subject of the prevalence of ADHD among adolescents and adults, and in ethnically distinct regions where it has been scarcely researched. The general pattern of results includes higher rates of the disorder among boys than girls, higher rates among primary school age children than among preschoolers or older adolescents, and higher rates of identification among children from lower SES families.

Children and Youth

Examining recent national surveys, the National Health Interview Survey (NHIS) in 2007 estimated that nearly 4.5 million children in the United States between the ages of 3 to 17 years (7%) had ADHD, with a larger proportion of boys (10%) than girls (4%).[100] The National Health and Nutrition Examination Survey (NHANES) estimated 2.4 million children ages 8 to 15 years, or 8.7 percent (95% CI, 7.3 to 10.1) met DSM-IV criteria for ADHD between 2001 and 2004.[104] Of these, more boys than girls (11. 8% vs. 5.4%) and children in lowest SES group were more likely to meet criteria, as well as those not in minority racial /ethnic groups.[104] In Germany, the KiGGs study (The German Health Interview and Examination Survey for Children and Adolescents), a representative cross-sectional health study of 17,461 individuals ages 3 to 17 years, reported an overall lifetime prevalence of ADHD diagnosis of 4.8 percent (95% CI, 4.4 to 5.3), with a significant gender difference (7.8% for boys, 1.8% for girls).[234] Significant effects of age and SES were also detected; the prevalence of a parent-reported lifetime diagnosis was 1.5 percent for those of preschool age, 5.3 percent in primary school, and 7.1 percent in secondary school, and was 6.4 percent, 5.0 percent, and 3.2 percent for low, medium, and high SES, respectively.[234] Logistic regression results highlighted boys of low SES as having the greatest risk of a diagnosis of ADHD.[234] Another report from Germany, the BELLA mental health module of the KiGGS, generally supported these trends, with the exception of a different age effect: they found a decline in prevalence with increasing age (their sample was comprised of 7-17 year olds).[110] The latter study used different methods to measure ADHD; namely, the German ADHD rating scale (FBB-HKS/ADHS), which is consistent with other DSM-IV scales and assesses functional impairment.[110]

The effects of gender and age (that is, a greater prevalence in boys and a negative association between age and prevalence of ADHD) emerge in many studies, though not all. In a Puerto Rican community sample of children ages 4 to 17 years, the 12-month prevalence using the DISC-IV was 7.5 percent (95% CI, 6.1 to 9.3).[235] The estimate for males was 10.3 percent (95% CI, 8.0 to 13.1) versus 4.7 percent (95% CI, 3.1 to 7.2) for females, with the highest prevalence documented in the 6 to 8 years age group.[235] In a randomly selected sample from school registers in Venezuela (N = 1,535 children ages 4 to 12 years), the total prevalence estimate (DISC-IV-P) was 10 percent (95% CI, 7.9 to 13.0), with a greater prevalence in males (7.6% vs. 2.4% in females).[236] In addition, a larger proportion of ADHD cases were classified as lower SES than medium or high SES.[236] In contrast, in a sample of 300 children ages 6 to 12 years from outpatient pediatric clinics at private hospitals in Buenos Aires, Argentina, 9 percent (95% CI, 6.0 to 12.8) had positive scores on the DuPaul Scale consistent with DSM-III-R ADHD, and no gender differences were found.[237] Similarly, in a study of 774 school children ages 6 to 17 years conducted in Salvador, Brazil using a teacher ADHD scale designed to evaluate ADHD behavioral symptoms in a school setting, 6.7 percent were judged highly likely to have the disorder and no trend with respect to gender was observed.[238]

From other settings for ADHD research, a study of preschoolers in Mumbai (N = 1,250, ages 4 to 6 years) whose Conner's index questionnaire scores (completed by teachers and parents) were positive for ADHD (>15) reported that in total, 12 percent were diagnosed, with a significant difference between boys and girls (19.0% vs. 5.8%, respectively).[239] Having adopted a similar methodological strategy, 12.3 percent (95% CI, 10.3 to 14.2) were given a diagnosis in a randomly selected sample of kindergarten-aged children (N = 1,083) in Mashhad, Iran.[240] Another study conducted in nearby Shiraz, in a random sample of 2,000 school-aged children (7 to 12 years), employing a DSM-IV referenced rating scale of ADHD symptoms (the CSI-4)

completed by parents, found that approximately 10.1 percent obtained screening cut-off scores for probable ADHD, with 13.6 percent in boys vs. 6.5 percent in girls.[241] A gender difference (prevalence ratio of 2:1 across the subtypes of ADHD except hyperactivity/impulsive type which had a ratio of 3.2:1) was also revealed in a study of primary school children ages 6 to 12 years in Nigeria (N = 1,112), assessed by means of rating scales based on DSM-IV ADHD criteria (the Vanderbilt ADHD Teacher Rating Scale (VARTRS) and Vanderbilt ADHD Diagnostic Parent Rating Scale (VADPRS), with an overall estimated prevalence of 8.7 percent.[242]

Other relevant, exploratory studies include the following. Among 7 to 10 year-olds in Yemen sampled from school registers (N = 1,210,), the prevalence of various DSM-IV psychiatric disorders, including ADHD, were examined and were reported to be among the least common disorders at 1.3 percent (95% CI, 0.1 to 2.5), with a significantly higher prevalence among boys than girls.[243] This was determined in 2 phases, using the SDQ as a screener and both the parent and teacher information included in the Development and Well-Being Assessment (DAWBA) to generate diagnoses in screen positive children. A cross-sectional study of patterns of mental health morbidity in children attending the psychiatry clinic of a tertiary care hospital in Karachi, Pakistan (N = 200, up to age 14 years included) stated a prevalence estimate of 17 percent, occurring most frequently in those between the ages of 5 to 10 years.[244] This estimate was ascertained using the P-CHIPS (Child Interview for Psychiatric Syndrome), a structured interview for parents based on DSM-IV criteria.[244] From a high school-based panel study carried out in Taiwan between 1995 to 97 of 1,070 students, ages 13 to 15 years, the weighted 3-month prevalence estimates of DSM-IV ADHD were 7.5 percent (95% CI, 5.1 to 10.0), 6.1 percent (95% CI, 4.6 to 7.5), and 3.3 percent (95% CI, 2.2 to 4.4) among 7th graders, 8th graders, and 9th graders, respectively, with higher odds of the diagnoses in boys than in girls.[245] Cases were identified using the Chinese K-SADS-E along with the teacher report form of the CBCL.[245]

Finally, a recent review of all epidemiological studies on ADHD carried out in Arab countries from 1966 to 2008 in various samples reported that the estimate of ADHD symptoms using rating scales in a school setting ranged from 5.1 to 14.9 percent, whereas estimates of an ADHD diagnosis using structured interviews in children and adolescents ranged from 0.5 percent in the school to 0.9 percent in the community.[246] It was noted, however, that the limited number of studies conducted in the designated countries and their employment of different methodologies rendered the task of comparing the results difficult.[246]

Fewer studies have been conducted in the adolescent age group. Some, but not all, of these agree with the gender and age effects proposed in studies of school-aged children. For instance, in a sample of 4,175 Houston youths ages 11 to 17 years from households enrolled in large health maintenance organizations, the DISC-IV prevalence of ADHD (any type) was 2.1 percent (95% CI, 1.59 to 2.54), with lower odds of ADHD noted in females.[247] However, a study of the prevalence of ADHD symptoms assessed by teacher reports using the SNAP-IV SDQ scales in 536 adolescents (ages 12 to 17 years) in a community in the European north of Russia found that 8.9 percent of boys and 3.6 percent of girls had positive ratings on the six items in either of the ADHD sub-types.[248] The estimate of DSM-IV ADHD in 541 Hong Kong Chinese adolescents (mean age 13.8 years, SD 1.2) from 28 randomly selected high schools was 3.9 percent (95% CI, 2.3 to 5.5).[249]

Worldwide Pooled Estimate of ADHD in Children and Youth

A recent comprehensive systematic review and meta-regression analysis that encompassed studies from many regions estimates the worldwide pooled prevalence of ADHD among those 18

years of age or younger to be 5.3 percent (95% CI, 5.01 to 5.56).[93] Though a significant amount of variability was noted in the comparison of prevalence estimates across world regions, results seemed to indicate that once methodological differences of studies were controlled for, geographic location explained very little of the variability. In fact, after this step, significant differences were only detected between studies carried out in North America, Africa, and the Middle East. The requirement of impairment for the diagnosis, diagnostic criteria used, and source of information (parent or teacher), were the main sources of variability in the pooled prevalence estimate of ADHD. For that reason, a standardized methodological approach has been proposed in order to improve the state of epidemiological research in this domain.[93,250]

ADHD in Adults

Estimates of the prevalence of DSM-IV adult (18 to 44 years) ADHD in the World Health Organization's (WHO) World Mental Health Survey Initiative (comprising of Belgium, Colombia, France, Germany, Italy, Lebanon, Mexico, The Netherlands, Spain, and the United States, N = 11,422) were: 3.4 percent (total sample), with a significantly higher estimate in France (7.3%) and lower in Colombia, Lebanon, Mexico, and Spain: 1.9 percent, 1.8 percent, 1.9 percent, and 1.2 percent, respectively.[8] A study in the United States reported a prevalence of 2.9 percent for 'Narrow' ADHD and 16.4 percent for 'Broad' ADHD in a random sample of 966 adults (>18 years) in the community.[251] As part of a larger telephone survey, respondents were asked about each DSM-IV symptom of ADHD, with a narrow diagnosis constructed to estimate the prevalence of adult ADHD among those who presented strong evidence of ADHD in both childhood and adulthood and a broader diagnosis serving to estimate the screening prevalence, although this strategy comes with the caveats of telephone survey methodology.[251] In terms of sociodemographic correlates, adult ADHD was significantly more prevalent in men and among those with a level of education less than university, though limitations such as imputation and the use of self-report without confirmation were identified.[8] Recently, a meta-regression, perhaps the first of its kind to address these issues, cited a pooled prevalence of adult DSM-IV ADHD of 2.5 percent (95% CI, 2.1 to 3.1), while reporting that the proportion of individuals with ADHD seems to decrease with age.[9] The question of appropriate diagnostic criteria for use with adults was, however, highlighted as a potentially problematic factor in producing epidemiological estimates in this age group.[9] Furthermore, many of the same problems (i.e., methodological and diagnostic differences) that plague ADHD research in children and youth, also appear to be relevant in adult studies.[9]

Brief Summary

- The estimated worldwide pooled prevalence of ADHD among those 18 years of age or younger is 5.29 percent (95% CI, 5.01 to 5.56).[93]
- Little geographic variability was noted, once methodological variability was taken into account.[93]
- ADHD is more common in boys than in girls.
- ADHD is more common in the age-group 5 to 10 years, than in preschoolers or in adolescents or adults.
- ADHD is more common among those from a low SES background.
- ADHD research detailing prevalence in adults is lacking.
- Key limitations: different sample types (e.g., school, community, clinical) are used, along with different informants/instruments to measure ADHD across geographic areas.

How Do Rates of Diagnosis (Clinical Identification) and Treatment of ADHD Vary by Geography, Time Period, Provider Type, and/or Sociodemographic Characteristics?

Much variation remains in the literature concerning the factors of interest on the receipt of a diagnosis and the use of psychotropic medication by individuals with ADHD, with some of the characteristics more commonly investigated than others. Though these factors have not been fully investigated, they appear to play a role in determining these outcomes and therefore, warrant attention.[102] A review of relevant findings follows, organized by geographic region. Details regarding the surveys will also be included to clarify whether the study is based on epidemiological surveys providing parent-reported data about individual children or administrative data providing information about patients through less direct, secondary sources collected for alternative purposes. Overall, the picture that emerges is one of increasing rates of lifetime diagnosis as children enter adolescence, starting as early as preschool years in the United States, with patterns of diagnosis similar to patterns of background population prevalence; that is, more boys than girls, and occurring more frequently among lower SES and non-minority children. However the overlap between clinical identification and underlying prevalence is inexact, with variation in geographic rates, and social, school, and health care system characteristics predicting clinical diagnosis. The picture that emerges regarding treatment for ADHD, most commonly stimulant medication use, varies to some degree from that of clinical diagnosis. Use of educational and health care services is higher among children with ADHD, and most frequent among those from higher SES families. Time trends show clear increases in medication use from the early 1990s to 2005 or later, perhaps due to the increasing size of the pool of individuals identified. Also noted are increasing use of multiple psychotropic medications, often in concert with the assignment of multiple diagnoses. Especially noteworthy are higher rates of diagnosis and medication use among Medicaid supported populations in the United States, a population representing low SES and minority groups. Regional disparity in rates of diagnosis and medication treatment are present, with no statistically significant increases noted in the west relative to other regions of the country. Rates of diagnosis and medication use are higher in the United States than in Europe.

United States

Clinical diagnosis. Regarding the receipt of a clinical diagnosis, it is clear from reports from the National Health and Nutrition Examination Survey (NHANES) that children whose parents report that they have been identified with ADHD overlap with, but are not identical to, those who are identified by DSM-IV diagnostic parent-report measures.[104] For approximately half of those who met criteria for ADHD and had received an ADHD diagnosis, predictors of clinical identification were being male, older in age, and having health insurance. One third of those with a diagnosis were likely to have received consistent treatment in the past year, with higher income a significant predictor.[104] The National Health Interview Survey (NHIS) shows gradual increases in the clinical identification of ADHD between 1997 and 2006, more in girls than in boys, and primarily among adolescents rather than primary school age children, with prevalence of 8.4 percent among children ages 6 to 17 years.[226] Children with ADHD were more likely to use health care and educational services, and use prescription medication. Hispanic children were less likely to have ADHD.[226] Another nationally representative survey of parents, the Medical Expenditure Panel Survey, (MEPS) was used to examine diagnosis and treatment issues for

children between the ages of 3 to 18 years. It found that Hispanic-American as well as African-American children were less likely to receive a diagnosis of ADHD compared to Caucasian children.[210] Furthermore, once given a diagnosis by a physician, African-American children were found to be less likely to ever receive stimulant medication, compared to Caucasian children.[210] Children in the 7 to 12 years age group were most likely to be diagnosed with ADHD and children with ADHD between the ages of 7 to 18 years were more likely to receive at least one stimulant prescription relative to children in the 3 to 6 years age category.[210] In 2000-2002, Caucasian children between the ages of 5 to 17 years were found to be approximately twice as likely to use stimulants as either Hispanic or African-American children.[252] Differences in individual/family characteristics (i.e., health insurance status, access to care) accounted for about 25 percent of the discrepancy between Caucasians and Hispanics in stimulant use, although the same characteristics cannot account for any of the differences between Caucasian and African-American children, with respect to stimulant use.[252] A Centers for Disease Control (CDC) national survey, the 2003 National Survey of Children's Health (NSCH), identified that nearly 8 percent of children ages 4 to 17 years are diagnosed with ADHD nationally, with geographic variation in both clinical identification and medication treatment.[227] Lower rates of identification and medication use occur in the west, and diagnosis rates are higher in the south, with treatment rates higher both in the south and the midwest compared with the west.[227,253] Rates of clinical identification and treatment were associated with characteristics of pediatricians within a state, but not with educational policies.[227] The NSCH survey was repeated in 2007 and rates of ADHD reported by parents increased from 7.8 percent to 9.5 percent, most dramatically among adolescents ages 15 to 17 years, and in all regions but the West.[254] In a study of younger students, the 2002 Early Childhood Longitudinal Study-Kindergarten cohort (ECL-K) sponsored by the U.S. Department of Education, social and school environment factors were identified that influenced rates of ADHD diagnoses.[219] Of the children in grade three at the time of the survey, 5.44 percent had received a previous diagnosis of ADHD. Lower rates of diagnosis were reported among girls, African-American children, Hispanic children, and those living with their biological father. School contextual predictors of diagnosis were having an older teacher, and stricter state-level performance accountability laws, but not larger class sizes; lower rates were associated with Caucasian teachers.[219]

A recent review has suggested that being male, belonging to a family with a high education level, and having a non-Hispanic ethnic background are factors that are most consistently associated with receiving a diagnosis of ADHD.[102] Additionally, the use of stimulants by Caucasian males seems disproportionately higher than the use by African-American and Hispanic children.[102] Another recent review of the ADHD literature with reference to African-American children arrived at these conclusions: although African-American youths have a tendency to be rated by parents and teachers as having more ADHD symptoms than Caucasian youth, they are only two-thirds as likely to have been diagnosed with the disorder by health professionals as their Caucasian counterparts.[101] The authors suggest that that this less frequent receipt of ADHD diagnoses in the former group may be attributable to a lack of information on the part of parents, a lack of access to appropriate health care services, or a lack of willingness to seek out services.[101]

Table 15. KQ3. A sample of summary data for clinical diagnostic prevalence of ADHD among children in the United States

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Barbaresi, W. (2002)[228] Cumulative incidence of ADHD only 7.4%	Rochester, Minnesota	Reflects community which is 95% Caucasian	12 to 19 years All children born between 1976 and 1982 who remained in community after age 5	Definite ADHD Male = 10.8% Female = 3.9% Definite + probable ADHD Male = 13.3% Female = 5.1% Definite + probable + questionable ADHD Male = 21.0% Female = 10.5%	N = 5,718 Population-based birth cohort study	Primarily middle class community with 82% of adults being high school graduates or beyond	ADHD only 7.4% (CI 95% 6.5 to 8.4) ADHD (including definite, probable and questionable cases) = 16.0% (CI 95% 14.7 to 17.3) Different case identification criteria yielded widely differing prevalence estimates
Bloom, B. (2009) NHIS[100] Average = 7.0%	Region Northeast 6.4% Midwest 7.4% South 9.0% West 4.9% MSA of Residence Large 6.8% Small 7.8% Non-urban 7.4%	NR	All children 3-17y	Male: 10.0% Female: 4.0%	Estimates based on question, "Has a doctor or health professional ever told you that (child's name) had (ADHD) or Attention Deficit Disorder (ADD)?"	Health insurance • Private 6.3% • Medicaid/public 9.5% • Other 12.4% • Uninsured 5.9% Poverty status Poor = 8.7% Near poor = 9.2% Not Poor = 6.5%	9% of all children had no health insurance 6% of all children had no usual place of health care

Table 15. KQ3. A sample of summary data for clinical diagnostic prevalence of ADHD among children in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Evans, W. (2010)[207] Children born just after cut-off date (to enter Kindergarten) Dx: 2.1% less likely to be diagnosed with ADHD	National	NR	7 to 17y	Dx: Male: 13% Female: 5%	1997-2006 National Health Interview Survey (NHIS) N = 60,000 households 1996-2006 Medical Expenditure Panel Survey (MEPS) N = 31,641 Nationwide private health insurance company between 2003-2006 N = 22,317	MEPS includes data on uninsured	Final conclusion: in 2006 1.1 million children misdiagnosed with ADHD 800,000 of these treated with stimulant medication Datasets were not pooled, as not considered comparable More specific results of children born within 120, 90 and 30 days of cutoff date also included
Froehlich, T.E. (2007)[104] Dx: 8.7% Of these,47.9% were already diagnosed	National	Dx: African-American: 14.7% Mexican-American: 12.0% Other: 10.8% White, non-Hispanic: 62.5%	Dx: 8 to 11y: 47.5% 12 to 15y: 52.5%	Dx: Male: 51% Female: 49% Rates of meeting DSM-IV criteria: Male: 11.8% Female: 5.4% Girls less likely than boys to have disorder identified (AOR 0.3; 95% CI, 0.1 to 0.8)	National Health and Nutrition Examination Survey N = 3,082	Dx: Poorest more likely than wealthiest to fulfill ADHD criteria (AOR 2.3; 95% CI, 1.4 to 3.9)	3.3% of children did not meet diagnostic criteria but had been treated and were identified by parents as having had a diagnosis of ADHD in the past year

Table 15. KQ3. A sample of summary data for clinical diagnostic prevalence of ADHD among children in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Fulton, B.D. (2009)[227] 7.7%	National Northeast: 7.2% Midwest: 7.8% South: 9.1% West: 5.9%	White: 63.7% Black: 13.7% Hispanic or Latino: 15.5% Other: 7.1%	4 to 17y 4 to 5y: 14.7% 6 to 8y: 20.5% 9 to 13y: 36.6% 14 to 17y: 28.2%	Male: 51.3% Female: 48.7%	2003 National Survey of Children's Health Dx = 69,505 Tx = 5,670 Provider data from Area Resource File	Health Insurance: None: 8.7% Private: 66.8% Public: 24.5% School: Home: 6.7% Public: 79.9% Private: 24.5% Household income (% Fed Property Level): <100: 16.0% 100-199: 22.4% 200-299: 18.1% >300: 43.5% Education (of parents): <High School: 6.6% HS: 25.6% >HS: 67.8%	Some focus on nature of physician (age, practice type, continuing education, etc.) Found no correlation for Dx, but a correlation between a younger doctor (<45y) and medication Specialty was also associated with Dx, but not clear how –

Table 15. KQ3. A sample of summary data for clinical diagnostic prevalence of ADHD among children in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Merikangas, K.R. (2010)[253] Dx: ADHD, all: 8.6% ±0.7 AD: 4.3±0.6 HA: 2.0±0.4 Combined: 2.2±0.2 *With severe Impairment: 7.8±0.7	National	Compared to non-Hispanic White youths, Mexican-American youths had significantly lower rates of 12-month ADHD(HA) X^2 = 28.2, df = 3, p <0.001)	8 to 15y Dx: ADHD, all: 8 to 11y: 9.9% 12 to 15y: 7.4% AD: 8 to 11y: 4.6% 12 to 15y: 4.0% HA: 8 to 11y: 2.8% 12 to 15y: 1.3% Combined: 8 to 11y: 2.4% 12 to 15y: 2.1% *With severe impairment: ADHD, all: 8 to 11y: 9.1% 12 to 15y: 6.7%	Dx: ADHD, all: Male: 11.6% Female: 5.4%6 AD: Male: 5.4% Female: 3.1% HA: Male: 2.8% Female: 1.2%3 Combined: Male: 3.4% Female: 1.1% *With severe impairment: Male: 10.8% Female: 4.7%	National Health and Nutrition Examination Survey N = 3,042	Youths with low Poverty Index Ratio (PIR) were more likely to report any 12m disorder, ADHD and its attentive subtype	Significant association found between ADHD and Conduct Disorder (OR 7.6, 95% CI, 4.0 to 14.7), and ADHD and mood disorders (OR 3.4, 95% CI, 1.8 to 6.4) ADHD(HA) was significantly greater in younger children (X^2 = 3.85, df = 1, p = 0.059)

Table 15. KQ3. A sample of summary data for clinical diagnostic prevalence of ADHD among children in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Pastor, P.N. (2005)[226] ADHD without LD = 4.7% ADHD with LD = 4.9% ADHD + LD (dual diagnosis) = 3.7%	National survey sample	Hispanic less likely than non-Hispanic Black and non-Hispanic White children to have each diagnosis	6 to 17y	Boys more likely than girls to have each of the diagnoses ADHD without LD Male: 6.7% Female: 2.5%	NHIS 2004, 2005 and 2006 N = 23,051 Estimate based on parent response to: "Has a doctor or health professional ever told you that (sample child) has ADHD or ADD?"	Children with medical coverage more likely than uninsured and privately insured children to have ADHD, LD or both	Children in mother only families noted to have higher prevalence of diagnosed ADHD and LD
Roberts, R.E. (2007)[247] 2.1%	Houston, Texas	Drawn from HMOs	11 to 17y	Significantly more boys affected than girls	DISC-IV CGAS (parent report)	Greater odds of mental illness with lower income	NR
Rowland, A.S. (2008)[224] Prevalence NR	Johnson County, North Carolina	Source population: 18% African-American 8% Hispanic Potential cases White: 68% Non-White: 32%	6-11y Potential cases: 5/6y: 7% 7/8y: 39% 9/10y: 39% 11+y: 16%	Potential cases Male: 72% Female: 32%	NIEHS – NTRS Teacher Report of ADHD Symptoms School impairment: VARTRS Modified DISC – parent interview by telephone (ADHD module only) N = 6,139 screened by teachers (Phase 1) N = 1,160 of the eligible 1,819	Results not reported by SES	Subtype distribution differs based on how informant data is used or combined in order to define cases

Table 15. KQ3. A sample of summary data for clinical diagnostic prevalence of ADHD among children in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Sax, L. (2003)[220]	Washington, DC	491 Physicians NR	NR	NR	Anonymous 1-page survey According to physicians, who is most likely to suggest a diagnosis of ADHD to parents? Teachers: 46.4% (95% CI, 44.1 to 48.7) Parents: 30.2% (95% CI, 28.3 to 32) Primary Care Physicians: 11.3% (95% CI, 9.7 to 12.8) School personnel: 6.0% (95% CI, 4.9 to 7.2) Consultants (psychiatrists/psychologists): 3.1% (95% CI, 2.3 to 3.9) Other: 3.0% (95% CI, 2.4-3.6)	NR	Physicians asked to estimate about all patients with ADHD Limitations are admitted, including low response rate (45%)

Table 15. KQ3. A sample of summary data for clinical diagnostic prevalence of ADHD among children in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Schneider, H. (2006)[252] Dx Prevalence: 5.44%	National sample of 9,278 children Regional variation in diagnosis with western USA reports significantly lower instances of ADHD cases	Black (OR 0.0928, 95% CI, 0.0315 to 0.279), Hispanic (OR 0.335, 95% CI, 0.175 to 0.643), and Asian (OR 0.0715, 95% CI, 0.00668 to 0.766) children are much less likely to receive an ADHD diagnosis than White (OR 0.0928, 95% CI, 0.0315 to 0.279) Multi-racial children more likely get ADHD diagnosis than White children (OR 3.06, 95% CI, 1.27 to 7.38)	Birth date in the summer months associated with higher rates of ADHD (OR 3.06, 95% CI, 1.10 to 2.61) May be due to cut-off dates for school admission and summer born children likely to be youngest in their classes	Girls are less likely to receive diagnosis than boys	2002 followup ECLS-K Parent and teacher report Data analyzed through logistic regression Diagnosis of ADHD is less prevalent for children with white teacher, more prevalent among children with an older teacher, and less likely to receive diagnosis if in Catholic or other religious school Stricter accountability for student performance in schools associated with increases in odds of diagnosis by a factor of 1.32 (95% CI, 1.05 to 1.65) for each point on the 4 point accountability scale	Children with diagnosis of ADHD less likely to live with biological father (OR 2.54, 95% CI, 0.869 to 0.17)	Receipt of ADHD diagnosis likely influenced by child's social and school environment as well as exogenous child characteristics Raises concerns that increased pressure for school performance is associated with higher ADHD diagnosis rates may be justified

Table 15. KQ3. A sample of summary data for clinical diagnostic prevalence of ADHD among children in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Stevens, J. (2005)[210] Dx Prevalence: 4.1% (N = 1,061)	National Dx: Northeast: 3.6% Midwest: 4.3% South: 4.8% West: 2.9%	Dx: White-American: 5.1% African-American: 2.1% Hispanic-American: 1.8%	3-18y Dx: 3- to 6y: 1.2% 7 to 12y: 6.4% 13 to 18y: 3.7%	NR	1997-2000 Medical Expenditure Panel Survey (MEPS)	Dx: Insurance: Private: 4.2% Public: 4.7% Uninsured: 2.2%	"Of the four sociodemographic characteristics examined in this study, insurance status was most consistently associated with disparities in ADHD health care." "Significant group differences were obtained for age, ethnicity, and type of insurance ($p < 0.05$) but not for region."
Zarin, DA. (1998)[255] 3.2% of all physician visits by patients 14 and under were ADHD-related (5-fold increase from 1985)	National	NR	0-14y	NR	National Ambulatory Medical Care Survey (NAMCS)	NR	Purpose of paper: psychiatrists account for 12.4% of ADHD-related visits The 5-fold increase could be due to the addition of a checkbox for ADHD

*With severe impairment: defined as ≥2 intermediate or 1 severe rating on the 6 impairment questions regarding personal distress and social (at home or with peers) or academic difficulties

Abbreviations: AD = Attention Deficit; ADHD-C = Attention Deficit Hyperactivity Disorder Combined type; ADHD-HI = Attention Deficit Hyperactivity Disorder – predominantly hyperactive impulsive type; ADHD-I = Attention Deficit Hyperactivity Disorder – Inattentive subtype; AMP = Amphetamine; AOR = Adjusted Odds Ratio; CGAS = Child Global Assessment Scale; CI = confidence interval; DEX = dextroamphetamine; DISC–Parent Module = Diagnostic Inventory for Screening Children; DSM = Diagnostic and Statistical Manual of Mental Disorders; Dx = diagnosis; ECLS–K = Early Childhood Longitudinal Survey – Kindergarten Cohort; ESI = Express Script Inc.; GDP = Gross Domestic Product; HA = hyperactivity; HMOs = Health Maintenance Organizations; ICD = International Classification of Diseases; LD = Learning Disability; MEPS = Medical Expenditure Panel Survey; MPH = methylphenidate; MPH-ER = methylphenidate, extended release; MPH-IR = methylphenidate, immediate release; MSA = metropolitan statistical area; MTPP = Michigan Triplicate Prescription Program; NAMCS = National Ambulatory Medical Care Survey; NCSR = National Comorbidity Survey Replication; NHANES = National Health and Nutrition Examination Survey; NHIS = National Health Interview Survey; NIEHS = National Institutes of Environmental Health Sciences; NR = Not reported; NSCH = National Survey of Children's Health; NTRS = NIEHS Teacher Rating Scale; PEM = pemoline; PR = prevalence ratio; SE = standard error; SSI = Supplemental Security Income; Tx = treatment; VARTRS = Vanderbilt ADHD Diagnostic Teacher Rating Scale; vs = versus; WMH = World Mental Health

Medication treatment. While treatments indicated for ADHD include both pharmacological and nonpharmacological interventions, studies examining treatment patterns have primarily focused on the use of psychotropic medications, both because medical care and pharmacy data sources have become available and because concerns exist about the rate of increase of medication use in recent years (see Table 16).

According to a study of regional and national databases in the United States, there was a 2.5-fold increase in the prevalence of MPH treatment for youths ages 5 to 18 years with ADHD during the period 1990 to 95.[94] These increases appear to have been due to the extended duration of medication use, as well as to more girls and adolescents receiving treatment; in addition, public attitudes had improved regarding pharmacotherapy.[94] Another study, also using a national data source of office visits (the NAMCS: National Ambulatory Medical Care Survey), confirmed the trend of an increase in the prevalence of both the diagnosis of ADHD and the prescription of stimulant medication for its treatment during the same time period and in the same age group.[95] Analysis of a more recent wave of data (1995 to 2000) from the same source, demonstrated that an ADHD diagnosis and/or stimulant prescription was less likely to be recorded during visits by Hispanic American youths compared to visits by Caucasian youths (ages 3 to 18 years). However, no differences were found between ethnic groups in terms of the likelihood of being given a prescription once a diagnosis was given.[202] An additional point was that prescriptions were given more frequently to children with ADHD in the south and west areas of the United States versus the northeast.[202] Data from the MEPS showed increased use of stimulants between 1987 and 1996, from approximately one per 100 children to four per 100 children 6 to 12 years old, but suggested that increasing rates in the use of stimulants among children less than 19 years slowed considerably from 1997 to 2002.[96] In 2001 to 2002, use among boys was greater than girls (4.0% vs. 1.7%) and Caucasian greater than African-American or Hispanic children (3.6%, 2.2%, 1.4%), although they noted a trend toward increased use among African-American children. Those without insurance had low usage (0.9%) compared with those with public (3.3%) or private (3.0%) insurance. Geographical regions showed little statistically significant variation in 2002 ranging from higher use in the south, (3.4%), than in the west, (2.2%).[96] Children whose parents reported functional impairment were more likely to use medication (13.9%) than those without (2.7%). Use in preschoolers appeared to have stabilized from 1997 to 2002 at approximately 0.4 percent (1997) and 0.3 percent (2002).[96] In contrast, other data sources suggest that the use of ADHD medications continued to increase during this time period. Data from a large California Health plan identified increases in the prescription of psychostimulants from 1.86 percent of children ages 2 to 18 years in 1996 to 1.93 percent in 2000.[256] Approximately one quarter of those receiving stimulants received a single prescription, suggesting primarily short-term or intermittent use, with more prescriptions written by pediatricians than by psychiatrists.[256] Another study examined time trends in diagnosis and treatment from 1995/96 to 2003/04.[257] Using Medicaid databases, they found increases in both diagnosis of ADHD and treatment with medications among those under the age of 20. Diagnoses of ADHD increased from 3 to 5 percent, and medication use was 5 percent in 2003/04. The most common age to begin medication was 5 to 9 years, more among boys than girls, and more among Caucasians than African-Americans or Hispanics. The largest increase in prevalence was in adolescents ages 15 to 19 years, at 2.5 percent, up from 0.45 percent in 1995/96; persistence of use was variable with only half of new users continuing more than 12 months.[257] More recent pharmacy claims data from 2000 to 2005 suggest that use of ADHD medications increased

among girls and adults, with the overall rate among children up to age 19 at 4.4 percent, and among adults at 0.8 percent in 2005.[258]

In 2001, 2.3 percent of preschoolers ages 2 to 4 years identified in seven state Medicaid databases received one or more prescriptions for psychotropic medications.[97] Two thirds of the prescriptions were for psychostimulants.[97] The overall use of medications for ADHD increased most dramatically in the 1990s, but increases among specific groups and regions appear to be continuing. Rates reported vary based on study methods, participants, and data sources.

An important trend has been an increase in multiple medications, especially for children identified with more than one diagnosis. Data collected between 1993/94 and 1997/98, recorded from visits to doctors offices in the National Ambulatory Medical Care Survey (NAMCS) database, were used to evaluate visits for those under 18 years of age where stimulant medications were prescribed. Authors noted that an increasing proportion of visits also resulted in another psychotropic medication being prescribed, most commonly clonidine or an antidepressant.[259] Data from state Medicaid and State Children's Health Insurance Programs (SCHIP) from 1999 were used to examine medication use among youth less than 20 years of age; 28 to 30 percent of those who received any psychotropic medications received multiple psychotropic medications, primarily stimulants with antidepressants, antipsychotics, or alpha-agonists.[260] The children most likely to receive multiple agents were Caucasian, male, ages 10 to 14 years, disabled, or in foster care.[260] Data from the NAMCS, and the outpatient component of the National Hospital Ambulatory Medical Care Survey (NHAMCS) were used to examine ATX use in 2003/04, following its approval in 2002.[261] Approximately 60 percent of prescriptions for ATX were accompanied by prescriptions of stimulants, with ATX preferred for children ages 10 to 14 years with private insurance.[261]

A final study has used data from the office visit database, NAMCS, to examine use of multiple types of medications among children and teens with mental health disorders.[262] The authors confirm increasing use of co-prescriptions for children and adolescents between 1996 and 2007; a common pairing is ADHD medications and antipsychotic medications.[262]

Geographic variation in the prevalence of stimulant medication use, evaluated using a prescription claim database (restricted to activity in 1999), was observed even after controlling for age and gender—specifically, relative to children living in the western region of the United States, children living in the midwest and south were significantly more likely to use stimulant treatment.[213] Those living in areas with some proximity to urban areas were also found to be more likely to receive stimulant treatment.[213] In support of these findings, the results of a study using National Drug Enforcement Agency Automation of Reports and Consolidated Orders System (ARCOS) data in 2000 looked at variation between counties in terms of their per capita psychostimulant consumption and showed that most variables that were significantly associated with greater per capita use of ADHD medications served as proxies for county affluence (e.g., higher per capita income, lower unemployment).[99] Wide variation in rates of children receiving prescriptions can occur, ranging from 9.6 to 117 per 1000 of 10 and 11 year old boys in 1992, as per Michigan pharmacy data.[129] Pediatricians wrote 59 percent of prescriptions for people under 20 years of age; half of which were written by only 5 percent of those pediatricians.[129]

A final note is how few studies are available regarding interventions that are not pharmacological. In a large county Medicaid program in California, Zima, et al.,[254] identified 530 children with ADHD, ages 5 to 11 years, and followed them to examine services received over 18 months during 2004 to 2006. Children seen in primary care were compared with those seen in specialty care. During the study, 34 to 44 percent of children who showed poor

functioning received no care, more commonly when followed in primary care settings. The majority (80 to 85%) of children seen in primary care received medication and averaged one to two visits per year, with less than half receiving psychosocial services. All children seen in specialty care services received psychosocial services, averaging five visits per month, and less than half received medication. No differences were found between those children who received care and those who did not in a range of functional areas.

Table 16. KQ3. A sample of summary data for treatment prevalence for ADHD among children in the United States

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Barbaresi, W.J. (2002)[228] Cumulative incidence of ADHD only 7.4%	Rochester, Minnesota	Children born between 1976 and 1982 in region Definite ADHD treated with stimulants alone: 72.1% stimulants in combination: 14.4% probable ADHD stimulants alone: 35.7% stimulants in combination: 4.3%, questionable ADHD stimulants alone: 5.9% stimulants in combination: 0.7% or not ADHD stimulants alone: 0.1% stimulants in combination: 0.1%	12 to 19y	Stimulant use data not reported for this criterion	N = 5,718 Population-based birth cohort study		Stimulant medications most likely to have been prescribed for subjects meeting the most stringent research criteria 5.6% in birth cohort treated with stimulants at some time

Table 16. KQ3. A sample of summary data for treatment prevalence for ADHD among children in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Barbaresi, W.J. (2006)[263]	Rochester Minnesota	Children with ADHD-C were treated for longer duration than those with either ADHD–HI or ADHD-I	0 mean of 17.2y of age Mean age at treatment initiation was 9.8y	Males were 1.8 times to be treated than females	N = 370 birth cohort between 1976 and 1982	NR	Likelihood of developing at least one side effect 22.3%
Bhatara, V.S. (2002)[259] Prevalence: NR	National survey of office-based physicians	NR	Patients under age 18y	NR	NAMCS	NR	A stimulant is prescribed during 83% of physician office visits for treatment of ADHD In 10% of these visits, additional psychotropic medications are prescribed Between 1993/94 and 1997/98, proportion of visits where stimulant was prescribed AND also a psychotropic increased from 4.8% to 24.7% Most commonly prescribed concomitant psychotropics were clonidine & antidepressants

Table 16. KQ3. A sample of summary data for treatment prevalence for ADHD among children in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Bhatara, V.S. (2007)[261]	National probability sample of visits to physicians offices and national probability sample of visits to outpatient and EDs	Northeast region less likely to prescribe ATX than doctors in the West No difference in prescription of ATX over other stimulants related to ethnicity	Youth <20y Children 10 to 14y accounted for 60% of ATX use, whereas only 40% of stimulant users	ATX: Male: 76% Female: 24% Stimulant: Male: 76% Female: 24% No difference in prescription of ATX over other stimulants in males vs. females	2003-2004 NAMCS and NHAMCS survey	ATX preferred in pts with private insurance coverage	Only 0.10% of the psychotropic visits involved prescribing both ATX and stimulants in children and adolescents
Brinker, A (2007)[264] % of prescription claim population diagnosed with ADHD who are receiving common stimulants plus ATX Prevalence is per 1,000 covered lives	National	NR	3 to 59y 3 to 9y: 97.7% 10 to 19y: 95.3% 20 to 39y: 86.2% 40 to 59y: 71.9%	NR	IMS Health National Disease and Therapeutic Index (NDTI) N = 43,175 Outpatient prescription claims data	NR	Diagnosis criteria based on codes, no clear diagnosis of ADHD for adults

Table 16. KQ3. A sample of summary data for treatment prevalence for ADHD among children in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Castle, L. (2007)[258] 2005: 4.4% of children Prevalence defined as one or more prescriptions for 'ADHD medications' received during the year	National	NR	Child: 0 to 19y Use was more common among older children, ages 10 to 19y	Male: 6.1% Female: 2.6% Males 2.3x more likely to use medication than females Tx prevalence for females than males	Prescription benefit plans with Medco Health Solutions between 2000-2005	Patients identified for study if eligible for prescription drug benefits	Study done by and for Medco Health Solutions
Chen, C.Y. (2009)[265] Presence of other mental disorders decreased probability of ADHD drug use by 14-54%	More common among children residing in rural areas (81.0%) than urban areas (71.6%) p <0.000	Use if ADHD medications higher among Whites (80.1%) than non-Caucasians (67.6%) p <0.000 Hispanics least likely to receive medication (57.7%) p <0.000	Youth <21y of age Mean age of patients was 8y	Male: 70% Female:	8y of Medicaid claims data	More common among children with Medicaid eligibility due to foster care status (76.8%) or SSI status (73.3%) p <0.000	Youth diagnosed by psychiatrists 42% less likely to received ADHD medications than those diagnosed by primary care physicians

Table 16. KQ3. A sample of summary data for treatment prevalence for ADHD among children in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Comer, J. (2010)[262]	National Ambulatory Medical Care Surveys 1996 to 2007 (office-based physicians)	White youth represent 77.32% of visits, compared to minorities at 22.68% Over sampling period, proportion of Caucasian youth represented in survey dropped slightly (p = 0.07)	6 to 17y	Males more likely to be in treatment (males = 61.9% vs females = 38.1%) and this ratio stable over sampling period	National Ambulatory Medical Care Surveys 1996 to 2007 Service provision provided by predominantly non-psychiatrist physicians (64%) Caveat: no structured diagnostic interview information attached to survey data so impossible to determine variants in prescription patterns due to changing criteria	Access to office-based physicians Over the sampling period, increased representation of youth covered by private insurance (p <.005) and public insurance (p <.01), while self-pay or other sector remained relatively stable.	Across 12 year period, multi-class psychotropic treatment rose from 14.3% to 20.2% Significant increases in co-prescription of ADHD medications and psychotropics (p <0.001) 49.8% visits for ADHD treatment

Table 16. KQ3. A sample of summary data for treatment prevalence for ADHD among children in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Cox, E.R. (2003)[213] Unadjusted 1-year prevalence of stimulant use for sample 4.3%	U.S.: all 50 states and District of Columbia Compared to those living in the West, children in MidWest and South were 1.6 [99% CI 1.28 to 1.87] and 1.71 [99% CI 1.42 to 2.06] times more likely to have at least 1 stimulant claim Compared to children living in rural areas, mostly rural or urban were 1.2 [99% CI 1.01 to 1.32] and 1.14 [99% CI 1.03 to 1.27] times more likely to have at least 1 stimulant claim	Proportions NR Positive relationship between stimulant use and the percent of the population that is White	Average age 10y (range 5 to 14y) Peak use at age 11	Male: 51% Female: 49% Males 3 times more likely to consume at least 1 stimulant medication than females	Data base of random sample of ESI members 1999 N = 178,800	Eligibility for commercial insurance Children with a deductible as part of their prescription benefit were 16% less likely to have at least 1 stimulant claim Commercially insured children living in more affluent areas are more likely to use stimulant medications than children from lower income area Children living in proximity to urban areas more likely to receive stimulant treatment	Among commercially insured children, geographic variation in the use of stimulant medications exists nationally, even after adjusting for age and gender Children in households of 4 or more children are less likely to consume stimulant medication than families with fewer than 4 children under the age of 18. Negative relationship between family size and prescription use

Table 16. KQ3. A sample of summary data for treatment prevalence for ADHD among children in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
dosReis, S. (2005)[260] As many as 1/3 of children with ADHD also have coexisting mood or anxiety disorder	2 U.S. states	Majority of those enrolled in these two public programs in both states were African-American Relative ratio White to African-American mental health service users 1.5:1	Youth <20y of age with at least one mental health related encounter with the medical system in 1999	Relative ratio male to female mental health service users 1.7:1	12m cross sectional analysis of databases of Medicaid and State Children's Health Insurance Program (SCHIP)	Eligibility for Medicaid of SCHIP Medicaid enrolled children receiving psychotropics tend to be Caucasian, male, disabled, 10 to 14y old and living in foster care Comparison of two Mid-Atlantic states highlights importance of small area variations	Multiple use (polypharmacy) occurred in 1/3 of youth with any psychotropic treatment Majority of combined psychotropic treatment involved stimulant medication Nearly ½ of multiple psychotropic use for 5 to 12m Most common disorders among multiclass use ADHD followed by externalizing or internalizing disorder Additional research needed to investigate switching patterns and effectiveness of combined pharmacotherapy

Table 16. KQ3. A sample of summary data for treatment prevalence for ADHD among children in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Froelich, T. (2007)[104] Tx prevalence: 8.7% (47.9% of whom had a prior diagnosis of ADHD)	National	Dx: African-American: 14.7% Mexican-American: 12.0% Other: 10.8 White, non-Hispanic: 62.5%	8 to 15y	Females were less likely than males to have their disorder identified (AOR 0.3; 95% CI, 0.1 to 0.8)	NHANES Medication history from caregiver report	Less than half of children meeting DSM-IV criteria report receiving either a diagnosis of ADHD or regular medication treatment Poor children most likely to meet criteria for ADHD, but least likely to receive consistent pharmacotherapy Wealthiest children more likely than poorest to receive regular medication treatment (AOR 3.4; 95% CI, 1.3 to 9.1)	Among children meeting DSM-IV ADHD criteria, 32.0% treated consistently with ADHD medications during the past year 3.3% of children did not meet diagnostic criteria but had been treated and had parent diagnosis in past year
Fulton, B.D. (2009)[227] Treatment: 57.4%	National Northeast: 58.2% Midwest: 58.8% South: 59.6% West: 49.3%	White: 63.7% Black: 13.7% Hispanic or Latino: 15.5% Other: 7.1%	4 to 17y Dx: 4 to 5y: 14.7% 6 to 8y: 20.5% 9 to 13y: 36.6% 14 to 17y: 28.2%	Predicted Treatment rate: Male: 74.1% Female: 73.4%	2003 National Survey of Children's Health Tx = 5,670 Provider data from Area Resource File	Health Insurance: None: 8.7% Private: 66.8% Public: 24.5% School: Home: 6.7% Public: 79.9% Private: 24.5% Household income (% Fed Property Level): <100: 16.0% 100-199: 22.4% 200-299: 18.1% >300: 43.5% Education (of parents): <High School: 6.6% HS: 25.6% >HS: 67.8%	Some focus on nature of physician (age, practice type, continuing education, etc.) Found no correlation for Dx, but a correlation between a younger doctor (<45y) and medication Specialty was also associated with Dx, but not clear how

Table 16. KQ3. A sample of summary data for treatment prevalence for ADHD among children in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Habel, L.A. (2005)[256] Percentage enrolled 2 to 18 years olds receiving at least on prescription for stimulant medication 1.9% (CI 1.90 to 1.96)	California When standard-ized to age and gender distribution, the percent of children treated with stimulants varied approxim-ately 9.2 fold (95% CI, 7.6 to 11.0)	NR	2 to 18y	Increase in stimulant treatment among females age 8y and older and among males age 12y and older Treatment prevalence peaked for both males and females at age 10 (5.3% and 1.7%, respectively)	Northern California Kaiser-Permanente Medical Care Program Membership is stated to be demographically similar to underlying population	Eligible for enrollment in this health plan	Annual percentage of continuously enrolled children receiving at least 1 stimulant medication rose 3.8% over 5 year study period 55% of stimulant prescriptions written by physicians in pediatrics 45% by physicians in psychiatry
Marcus, S.C. (2005)[106] To increase duration of treatment; Comparing Extended-Release (ER) to Immediate-Release (IR) MPH (MPH) ER-MPH treatment maintained 37% longer than IR-MPH	California	ER: N = 3,444 MPH-IR: N = 8,093 ER: White: 49.2% Black: 20.8% Hispanic: 24.8% Other: 5.2% MPH-IR: White: 43.8% Black: 23.8% Hispanic: 26.5% Other: 5.9%	6 to 17y ER: 6 to 12y: 62.4% 13 to 17y: 37.6% MPH-IR: 6 to 12y: 74.3% 13 to 17y: 25.7%	ER: Male: 77.5% Female: 22.5% MPH-IR: Male: 78.2% Female: 21.8%	California Medicaid program (2000 to -2003)	NR	Study reviewed age, gender, racial differences, and physician provider type

Table 16. KQ3. A sample of summary data for treatment prevalence for ADHD among children in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Merikangas, K.R. (2010)[253] Of children identified with ADHD, 47.7% were treated	National probability sample	Stratified and weighted representative sample	8 to 15y	Male: 51% Female: 49% Significantly more males than females meet DSM-IV criteria (p <0.001)	NHANES (N = 3,042) DSM-IV NHANES used DISC caregiver module for diagnosis 48% of children received prior diagnosis	Wealthiest more likely than poor children to receive medication Poor children more likely to meet criteria for ADHD yet less likely to receive consistent pharmacotherapy	This survey provides the first estimates of the specific DSM-IV defined mental disorders in the U.S. population of children and adolescents
Olfson, M (2009)[266]	National	NR	6 to 12y	Male: 73% Female: 22% for OROS MPH, mean initial dose was significantly higher for males than for females	Claims data from managed care organizations; PharMetrics database (2000 to 2004)	NR Subscribers to managed care groups	Among children who continue stimulants through first 3 months of treatment, dosing in community tends to be lower than clinical trials, and when titration occurs it is linked to lower initial dosing, clinical monitoring, higher final stimulant doses, and treatment by a psychiatrist
Perwien, A. (2004)[105] Tx Prevalence: Child: 2%	National	NR	Children: 0 to 18y Mean age: 9.9y	Children: Male: 76.3% Overall numbers of females treated increased with age: 0 to 6y: 21.9%	6 United Healthcare-affiliated health maintenance organization plans N = 2,199,203 Children Total: N = 604,538 with diagnosis of ADHD: N = 11,962	NR Qualifies for membership in HMO	Method of inclusion: for children, at least two diagnoses of ADHD

Table 16. KQ3. A sample of summary data for treatment prevalence for ADHD among children in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Rappley, M.D. (1995)[129] 2 month point prevalence of MPH use in this group was 11 per 1000 population	State of Michigan Range of prescription rate across counties varied by more than 10-fold	NR	0 to 19y Male: 1.9% Female: 0.4% Children between 8 to 11y represent 45% of users of MPH Prescriptions written for children aged 1y = 3	84% of those receiving MPH were males Males ages 10 and 11y received more MPH prescriptions than any other age groups (43 per 1,000)	Population-based prescription data set (MTPP) N = 32,608	NR	Primary care physicians wrote 84% of prescriptions Pediatricians wrote 59% of prescriptions for pts <20y of age Half of the prescriptions written by pediatricians were written by 5% of pediatricians in the state.

Table 16. KQ3. A sample of summary data for treatment prevalence for ADHD among children in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Safer, D. (1985)[267] Rate of medication treatment for Hyperactivity 1975 to 1983	Baltimore County, Maryland	NR	5 to 15y 1975 to 1983: 5 to 11y: 2.1 to 3.6% 74% increase 12 to 15y: 0.6 to 1.5% 158% increase Senior HS (added 1983): 0.2% Special Ed 1981 to 1983: 5 to 11y: 18.6 to 22.7% 12 to 15y: 10.6 to 11.4%	1983: 5 to 11y: Female 16% 12 to 15y: Female 10%	Baltimore County Department of Health School Nurse Surveys	NR	Rates of medication treatment for 5-11y (elementary school) was 7-fold the main population in 1981 and 6-fold in 1983; In middle/Junior high school, the rate was 9 and 8 times greater than the main population in 1981 and 1983, respectively
Safer, D.J. (2000)[268] medication for ADHD in school hours (in brackets - reconfigured percentage based on inclusion of 20%	Maryland	Special needs: 13% Typically developing: 1.6% Special education: 8.7%	Elementary (K to 5): 3.7% (4.5%) Middle: (6 to 8): 3.5% (4.3%) High School	Male to female ratio: Elementary: 3.5:1 Middle: NR High: 4.3:1	Maryland Statewide School Survey administered by school nurses. Total N = 816,465 Elementary N = 410664 Middle N = 183,803 High N = 221,998	Race/ethnicity more likely to affect treatment with medication than household income. 2 districts with the lowest in-school rates of treatment had highest percentages of 'African-American public school enrollment'; but they were	The estimate of youths who were given medication for ADHD only at home was based on data from 2 sources, both of which found it to be approximately 20% of the total on medication. The first estimate came from a

Table 16. KQ3. A sample of summary data for treatment prevalence for ADHD among children in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
thought to be treated at home) Total: 2.92% (3.65%)		(% of ethnic population enrolled & treated for ADHD) Elementary school: White: 4.12 Black: 2.01 (ratio W:B = 2:1) Hispanic: 1.2 (ratio W:H = 3.3:1) Middle school: White: 4.3 Black: 1.67 (ratio W:B = 2.6:1) Hispanic: 2.02 (ratio W:H = 2.1:1) High school: White: 1.34 Black: 0.26 (ratio W:B = 5.2:1) Hispanic: 0.43 (ratio W:H = 3.1:1)	(9 to 12): 1.1% (1.3%)			not comparable for household income, 6th highest ranked and 4th lowest, respectively	1997 consumer survey of parents in an ADD support group, and the second came from a 1993 school nurse survey in Baltimore

Table 16. KQ3. A sample of summary data for treatment prevalence for ADHD among children in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Safer, D.J. (1996)[94]					National Prescription Audit of IMS America ARCOS RI Duplicate Prescription Program 1990-1994	Surveys indicate higher treatment prevalence in urban than rural; public than parochial or private schools; children in less affluent areas than those in wealthier areas	ARCOS database recorded 2-fold increase in bulk sales of MPH 1990-1993
1991: 5 to 14y: 2.5%; 5 to 17/18y: 2.1% 1993: 5 to 14y: 3.2%; 5 to 17/18y: 2.6% 1995: 5 to 14y: 4.6%; 5 to 17/18y: 3.7%	Baltimore County, Maryland	N = 98,335 (72% White)	5 to 14y 5 to 17/18y	General Female to Male ratios: 1981: 1:12 1983: 1:10 1985: 1:10 1991: 1:7 1993: 1:6 1995: 1:5	Baltimore County Health Department Biennial Survey of Public School Students receiving medication for ADHD		
1990: 1.9% 1991: 2.1% 1992: 2.9% 1993: 3.4% 1994: 4.7%	Maryland	N = 110,481 (58% African-American)	5 to 14y		Maryland Medicaid		
1992: 5 to 14y: 2.0% 5 to 17/18y: 1.6%	Michigan	N = 32,608	5 to 14y 5 to 17/18y		State of Michigan triplicate prescription study		
1991: 2.6%	New York	N = NR	6 to 12y		New York State Health Department Survey		
1991: 1.1%	Oregon and Washington State	N = 380,000 (91% White)	5 to 14y		NW Kaiser Permanente (Oregon and Washington State)		

Table 16. KQ3. A sample of summary data for treatment prevalence for ADHD among children in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Scheffler, R. (2007)[98] 5 to 8%	U.S. in global context	NR	5 to 19y	NR	IMS Health MIDAS database	USA, Canada, and Australia show higher than expected medication use, whereas Italy, Ireland, Austria, Japan, Sweden, and Finland show less than predicted by per capita GDP	U.S. dominates global spending on ADHD medications , making approximately 92 to 95% of total expenditures, with 22.6% growth rate per year Recommendations include determining long-term impact of pharmacologic treatments and ascertaining economic, professional training and cultural factors that promote optimal prescription and monitoring Use of ADHD medications increased 274% between 1993 and 2003.

Table 16. KQ3. A sample of summary data for treatment prevalence for ADHD among children in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Stevens, S. (2005)[210] Tx Prevalence 74.5% (N = 760)	National Tx: Northeast: 73.7% Midwest: 73.4 South: 76.3% West: 72.4%	 Tx: White American: 76.5% African-American: 60.5% Hispanic American: 68.5%	3 to 18y Tx: 3 to 6y: 51.2% 7 to 12y: 76.8% 13 to 18y: 75.7%	NR	1997 to 2000 Medical Expenditure Panel Survey (MEPS)	Tx(%): Insurance: Private: 77.7 Public: 66.7 Uninsured: 62.1	"Of the four sociodemographic characteristics examined in this study, insurance status was most consistently associated with disparities in ADHD health care." "Significant group differences were obtained for age, ethnicity, and type of insurance ($p<0.05$) but not for region."

Table 16. KQ3. A sample of summary data for treatment prevalence for ADHD among children in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Swanson, J. (2009)[269]	National (compared to data from the U.K.)	NR	Between 1999 and 2001, prescription rates for children between 5 to 14y children 20-fold lower in the U.K. (0.5%) than U.S.(9.3%) Rates of prescription increasing in the 15 to 19, 20 to 24y, and 25y + age groups; may be for treatment purposes or for diversion into nonmedical uses	Male: NR Female: NR	General Practice Database (U.K) U.N. report on supply of stimulant drugs	NR	Combined MPH-AMP estimate grew from 0.42 in 1996 to 1.3 in 2005 in the U.K. while during the same period, in the U.S., grew from 4.7 to 17.8
Varley, C.K. (2001)[270] 7.8% of subjects treated with stimulants developed tics	Seattle, Washington	NR	Children on MPH developing tics much younger than those who did not (mean age 9.9y versus mean age 11.1y (p <0.05)	NR	Retrospective chart review N = 555 subjects	NR	MPH = 8.3% DEX = 6.3% PEM = 7.7% No significant relationship between dosage and tic development

Table 16. KQ3. A sample of summary data for treatment prevalence for ADHD among children in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Visser, S.M. (2007)[271] 7.8% reported ADHD and 4.3% had both diagnosis and were currently taking medication for the disorder	National	White race significantly associated with medication treatment for ADHD	4 to 17y Younger age (9 to 12y) significantly associated with medication treatment for ADHD (64%)	Male: 72% Female: 28% Once identified, males no more than females were likely to be receiving medication	NSCH (2003 data) N = 79,264 Adult most knowledgeable of the target youth provided information on ADHD diagnosis, which was inferred from a positive response to the question “Has a doctor or health professional ever told you that (sample child) had attention deficit hyperactivity disorder (ADHD) or attention deficit disorder (ADD)?”	Health care coverage and recent health care contract were significantly associated with medication treatment for ADHD	Regardless of gender, the presence of psychological difficulties were significantly associated with medication treatment for ADHD Prevalence of ADHD >3 times higher among youth who had ever repeated a grade Future studies should characterize how and when the burden associated with ADHD leads to treatment, support, or services
Winterstein, AG (2008)[257]	‘a Southern state’	Whites more likely to be diagnosed and treated than Hispanics [PR in 2003 to 2004 = 2.65 (95% CI, 2.57 to 2.73)] or Blacks [PR in 2003 to 2004 = 1.81 (95% CI, 1.76 to 1.85)]	Children and youth <20y Distribution of ADHD related drug use by age has shifted towards older children/ youth	1 in 5 Caucasian males between ages 10 and 14 received ADHD medication in Males more likely to be diagnosed and treated than females [PR in 2003 to 2004 = 2.96 (95% CI, 2.37 to 2.52)]	Large Medicaid program administrative database	Medicaid eligible	Only 49.9% of users received drugs after 1 year, with 17.2% continuing for 5y or more Studies needed to analyze determinants of treatment as well as outcome associated with long-term use

Table 16. KQ3. A sample of summary data for treatment prevalence for ADHD among children in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Zima, B.T. (2010)[254] Prevalence: NR	Los Angeles	N = 530 87% minority racial or ethnic background African-American: 23% Latino: 54% Caucasian: 13% Two or more ethnic backgrounds or other ethnic groups: 10% 76% met diagnostic criteria for ADHD–C 63% also met diagnostic criteria for ODD or DBD	5 to 11y (mean 9.9)y	Male: 68% Female: 32%	Longitudinal cohort study of Medicaid database 2004 to 2006	Medicaid eligibility Unmet need for mental health services ranged from 13% to 20%	Stimulant medication prescription refill persistence was poor (31 to 41%) Primary care – 80 to 85% had at least one script filled for stimulant medications Specialty mental health clinics = less than 1/3 children received stimulant medication but all received psychosocial interventions averaging more than 5 visits per month Clinical severity and academic variables did not differ significantly between children who received care in a primary care setting as opposed to specialty mental health

Table 16. KQ3. A sample of summary data for treatment prevalence for ADHD among children in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Zito, J.M. (2008)[103] Prevalence of psychotropic drug use: U.S.: 6.7% Netherlands: 2.9% Germany: 2.0% Anti-depressant and stimulant use >3 times greater in U.S. Antipsychotic prevalence was 1.5-2.2 times greater in U.S. Concomitant drug use in U.S.: 19.2%; more than 2 times greater than Netherlands or Germany	National N = 127,157 (compared to data from: Netherlands N = 110,944 and Germany N = 356,520)	NR	Stimulant drug use: U.S.: 0 to 4y: 0.49% 5 to 9y: 7.29% 10 to 14y: 7.40% 15 to 19y: 1.70% Netherlands: 0 to 4y: 0.05% 5 to 9y: 1.77% 10 to 14y: 2.12% 15 to 19y: 0.71% Germany: 0 to 4y: 0.02% 5 to 9y: 1.09% 10 to 14y: 1.45% 15 to 19y: 0.25%	Stimulant drug use: U.S.: Male: 6.52% Female: 1.94% Netherlands: Male: 1.95% Female: 0.37% Germany: Male: 1.16% Female: 0.24%	U.S.: State Children's Health Insurance Program (SCHIP) of a mid-Atlantic state Netherlands: InterAction database (IADB) Germany: Gmuender ErsatzKasse (GEK)	U.S. data from program that insures children because of low income (high limit is twice federal poverty limit) – age, race, family composition all similar to private insurance, but parental education and employment are moderately lower	

Table 16. KQ3. A sample of summary data for treatment prevalence for ADHD among children in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Zuvekas, S.H. (2006)[96] Prevalence use of stimulants 2.9% (95% CI, 2.5 to 3.3) in 2002 while point prevalence of ADHD reported as ~5% of child population of U.S.	Yearly survey of nationally representa-tive sample of civilian, non-institution-alized U.S. households Higher utilization in the South (3.4%) compared with the West (2.2%, p = 0.05)	Use of stimulant medications higher in White (3.6%) than Black (2.2%) or Hispanic (1.4%) children	Children and youth <19y Use highest among 6 to 12 year olds (4.8%) compared to 13 to 19 year olds (3.2%), and 0.3% among children <6y	Use of stimulant medications higher among males (4.0%) than females (1.7%)	MEPS database 1997 to 2001 Relies on self or parent/guardian report	Family income, type of insurance and living in urban setting did not moderate rate of use Subjects without insurance had lowest utilization (0.9%) than either children with either public (3.3%, p <0.001) or private health insurance coverage (3.0% p <0.001)	Steep increase in stimulant utilization which occurred between 1987 and 1996 subsequently attenuated through to 2002, and remains stable among very young children

Abbreviations: ADHD-C = Attention Deficit Hyperactivity Disorder Combined type; AMP = Amphetamine; AOR = Adjusted Odds Ratio; ATX = atomoxetine; CI = confidence interval; DEX = dextroamphetamine; DISC–Parent Module = Diagnostic Inventory for Screening Children; DSM = Diagnostic and Statistical Manual of Mental Disorders; Dx = diagnosis; ED = emergency department; ER = extended release; ESI = Express Script Inc.; GDP = Gross Domestic Product; GEK = Gmuender ErsatzKasse; HMOs = Health Maintenance Organizations; HS = High School; IADB = InterAction database; IR = immediate release; MEPS = Medical Expenditure Panel Survey; MPH = methylphenidate; MSA = metropolitan statistical area; NAMCS = National Ambulatory Medical Care Survey; NHANES = National Health and Nutrition Examination Survey; NR = Not reported; NSCH = National Survey of Children's Health; PEM = pemoline; PR = prevalence ratio; SCHIP = State Children's Health Insurance Program; SSI = Supplemental Security Income; Tx = treatment; U.N. = United Nations; vs = versus

Provider type. Some information is available about differences between provider type and subsequent prescribing patterns (see Table 17). Children diagnosed by psychiatrists are less likely to receive a prescription within the initial 6 months after diagnosis than those identified by primary care physicians, even after adjustment for comorbid conditions.[265] Presence of comorbid disorders, especially bipolar disorder, schizophrenia, or autism decreased the use of ADHD drug use, but increased the use of other categories of psychotropics, prescribed primarily by psychiatrists and neurologists.[265] Higher rates of prescription of these other psychotropics occur among school-aged males, Caucasians, those in rural areas, and those in foster care.[265] Dose titration is associated with a lower initial dose, a higher maximal dose, 3 or more visits in the first 90 days, increased monitoring, and treatment by a psychiatrist.[266] Overall, it appears that specialists' practice patterns are different from those of primary care physicians in regards to ADHD and its pharmacologic treatment. Those who are seen by psychiatrists are more likely to receive a medication titration trial. Specialists are more likely to prescribe a variety of psychotropic medications for combinations of ADHD and comorbid conditions.

Table 17. KQ3. A sample of summary data for provider type for ADHD in the United States

Study	Geography	Data Source	Socioeconomic Status	Comment
Chen, C.Y. (2009)[265]	More common among children residing in rural areas (81.0%) than urban areas (71.6%) p <0.000	8 years of Medicaid claims data	More common among children with Medicaid eligibility due to foster care status (76.8%) or SSI status (73.3%) p <0.000	Youth diagnosed by psychiatrists 42% less likely to received ADHD medications than those diagnosed by primary care physicians rural areas 81.0% >than urban areas (71.6%) p <0.000
Fulton, B.D. (2009)[227]	National Northeast: 7.2% Midwest: 7.8% South: 9.1% West: 5.9%	2003 National Survey of Children's Health Dx = 69,505 Tx = 5,670 Provider data from Area Resource File	Health Insurance: None: 8.7% Private: 66.8% Public: 24.5% Household income (Fed Property Level): <100: 16.0% 100-199: 22.4% 200-299: 18.1% >300: 43.5% Parent Education <High School: 6.6% HS: 25.6% >HS: 67.8%	Some focus on nature of physician (age, practice type, continuing education, etc.) Found no correlation for Dx, but a correlation between a younger doctor (<45y) and medication Specialty was also associated with Dx
Habel, LA (2005)[256]	California	Northern California Kaiser-Permanente Medical Care Program - not-for-profit integrated health care organization that serves as an umbrella for a federation of for-profit medical groups Membership is demographically similar to underlying population	Eligible for enrollment in this health plan	Annual percentage of continuously enrolled children receiving at least 1 stimulant medication rose 3.8% over 5 year study period 55% of stimulant prescriptions written by physicians in pediatrics, 45% by physicians in psychiatry

Table 17. KQ3. A sample of summary data for provider type for ADHD in the United States (continued)

Study	Geography	Data Source	Socioeconomic Status	Comment
Marcus, S.C. (2005)[106]	California	California Medicaid program (2000 to 2003)	Eligibility for Medicaid program	Across age, gender, racial differences, and physician
Sax, L. (2003)[220]	Washington, DC	Anonymous 1-page survey N = 491 Physicians According to physicians, who is most likely to suggest a diagnosis of ADHD to parents? Teachers: 46.4% (95% CI, 44.1 to 48.7) Parents: 30.2% (95% CI, 28.3 to 32) Primary Care Physicians: 11.3% (95% CI, 9.7 to 12.8) School personnel: 6.0% (95% CI, 4.9 to 7.2) Consultants (psychiatrists/psychologists): 3.1% (95% CI, 2.3 to 3.9) Other: 3.0% (95% CI, 2.4 to 3.6)	NR	Physicians asked to estimate about all patients with ADHD Limitations are admitted, including low response rate (45%)
Zarin, D.A. (1998)[255]	National	National Ambulatory Medical Care Survey (NAMCS)	NR	Purpose of paper: psychiatrists account for 12.4% of ADHD-related visits The 5-fold increase (since 1985) could be due to the addition of a checkbox for ADHD 3.2% of all physician visits by patients 14y and under were ADHD-related

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; Dx = diagnosis; HS = high school; NR = not reported; SSI = Supplemental Security Income

Other issues. Other studies point out medication compliance issues, noting that nearly a third of persons prescribed stimulants did not refill their initial prescription and over 60 percent did not use pills for more than 30 days.[105] Extended-release preparations of MPH were associated with longer duration of use, compared with immediate-release preparations.[106] Increased duration of treatment was associated with use of case management services, but inversely related to a comorbid condition, recent inpatient hospitalization, and managed care.[106] Fewer teens compared with younger children, and fewer minority persons compared with Caucasians took stimulants over an extended duration.[106] Increased examination of the factors impacting duration is needed. Certainly convenience, efficacy, and safety of agents is important for increased duration of use, but the high rate of non-refill following initial prescription suggests a more nuanced approach to the issues of medication adherence is warranted. Increased rates of discontinuation among minority groups and teens suggests that cultural and social factors may affect use.

Discussion of ADHD prevalence and treatment among U.S. adults. The estimated prevalence for adult ADHD stands at 4.4 percent.[109] Overall, levels of symptoms of overactivity and impulsiveness decrease with age; however, the majority of children with ADHD continue to show impairment, especially poor attention, relative to same-age peers throughout adolescence and into adulthood. The estimate of prevalence of ADHD among adults in the United States is 5.2 percent,[8] while worldwide it is 2.5 percent (95% CI, 2.1 to 3.1).[93] The lack of research addressing adolescents and adults with ADHD presents a major gap in the literature. For estimates of adult ADHD, self-report measures are used; however, aspects of the diagnosis depend on a history of having had ADHD as a child. For this information, both clinicians and researchers depend on retrospective reports from adults about their own behavior as children, and it is therefore open to problems with interpretation.

No clinical studies have been designed to follow children through adolescence and into adulthood, tracking the mix of interventions obtained by participants and their functional outcomes, as well as providing sufficient control comparison. No prospective studies examining nonmedication interventions have enrolled adolescents or adults identified with ADHD to investigate whether interventions at later stages of development are effective for improving function. As with estimates of diagnostic prevalence, self-report measures of treatment are often used, which will render coordination of observations regarding academic interventions and outcomes particularly challenging.

Table 18. KQ3. A sample of summary data for clinical diagnostic prevalence of ADHD among adults in the United States

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Castle, L. (2007)[258] 2005 data: 0.8% of adults Prevalence defined as one or more prescriptions for 'ADHD medications' received during the year	National	NR	Adult: over 20y Use was more common among older children, ages 10 to 19y	Adult Male/ Female: 0.8% Tx prevalence increased more rapidly for women than men	Prescription benefit plans with Medco Health Solutions between 2000 to 2005	Patients identified for study if eligible for prescription drug benefits	Study done by and for Medco Health Solutions
Eyestone, L.L. and Howell, R.J. (1994)[107] 25.5% ADHD & 25.5% major depression	Utah Prison	Incarcerated	16 to 69y	Males	Self report and DSM-III-R	NR	10%(p <.001) = dual diagnosis of ADHD & major depression
Fayyad, J. (2007)[8] WMH-NCSR 5.2%	National data as reported in an international study	NR	18 to 44y	both	Probability sample Interview with trained personnel	NR	12m treatment for ADHD

Table 18. KQ3. A sample of summary data for clinical diagnostic prevalence of ADHD among adults in the United States (continued)

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Kessler (2005)[190] 36.3% of adults with current ADHD were retrospectively assessed to have had childhood ADHD	National	N = 3,197 total With current ADHD: n = 346 Diagnosed with adult ADHD: White: 37.8% (OR 1.0) Black: 29.6% (OR 0.7, 0.3-1.7) Hispanic: 28.0% (OR 0.7, 0.2-2.0) Other: 48.6% (OR 1.7, 0.4-7.2)	18-44y Diagnosed with adult ADHD: 18-24y: 39.1% (OR 1.1, 0.5-2.5) 25-34y: 31.9% (OR 0.8, 0.4-1.7) 35-44y: 37.8% (OR 1.0)	Of total population: Male: 64.3% Female: 35.7% Diagnosed with adult ADHD: Male: 39.7% (OR 1.4, 0.7-2.7) Female: 31.5% (OR 1.0)	National Comorbidity Survey-Replication (NCS-R)	NR	Childhood ADHD severity and childhood treatment significantly predicted persistence.
Kessler, R.C. (2006)[5] NCSR study 4.4%	National	Low prevalence among Hispanics and non-Hispanic African-Americans	18 to 44y	Men >Women OR 1.6 (p <0.05) Significantly higher proportion of women than men with adult ADHD had received Tx for mental or substance related problems in 12 months before interview (53.1% vs. 36.5%, p = 0.02), but only 25.2% of treated respondents had received Tx for ADHD (22.8% women and 27.7% men)	Adult ADHD Clinical Diagnosis Scale for screening Clinical reappraisal with DSM-IV interview	NR	NR

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; AMP = Amphetamine; DSM = Diagnostic and Statistical Manual of Mental Disorders; DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders (version 3) revised; NCSR = National Comorbidity Survey Replication; NR = Not reported; OR = odds ratio; Tx = treatment; WMH = World Mental Health; y = year

Table 19. KQ3. A sample of summary data for treatment prevalence of ADHD among adults in the United States

Study Prevalence (%)	Geography	Population Ethnicity	Age	Sex	Data Source	Socioeconomic Status	Comment
Brinker, B. (2007)[264] % of prescription claim population diagnosed with ADHD who are receiving common stimulants plus ATX	National	NR	All patients 3 to 59y Data for Adults only: 20 to 39y: 86.2% 40 to 59y: 71.9%	NR	IMS Health National Disease and Therapeutic Index (NDTI) N = 43,175 Outpatient prescription claims data	NR	Diagnosis criteria based on codes, no clear diagnosis of ADHD for adults Prevalence per 1,000 covered lives
Perwien, A. (2004)[105] Tx Prevalence: Adult: 0.2%	National	NR	Adult: 19 to 65y Mean age: 35.2y	Adult: Male: 60.5% Overall numbers of females increased with age: 35 to 64y: 51%	6 United Healthcare-affiliated health maintenance organization plans N = 2,199,203 Adults Total: N = 1,542,304 with diagnosis of ADHD: N = 2,636	NR	Method of inclusion: adults receiving ADHD medications; Diagnosis is derived from treatment

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; Tx = treatment; N = sample size; NR = not reported

Use of ADHD medications increased globally by almost 300 percent between 1993 and 2003.[98] Like other health care interventions, use of ADHD medications is correlated with per capita Gross Domestic Product (GDP). In 2003, moreover, the United States reported a usage rate approximately four times that expected based on per capita GDP.[98] Use of short-acting preparations of stimulants plateaued between 1997 and 2000, and showed a decrease in use through 2003, while use of long-acting preparations increased.[98] Numerous factors contribute to these observations, including regulatory restrictions, differences in diagnostic systems, and availability of alternative formulations of ADHD medications around the world.

Brief Summary With Focus on Trends in United States

- Rates of ADHD medication use have been increasing globally since the early 1990s. Use of pharmacologic interventions is higher in the U.S than in other areas of the world, nearly 4 times that expected by per capita GDP.
- In the late 1990s, use of short-acting stimulant preparations leveled off in the United States and subsequently decreased while use of long-acting formulations has increased. This pattern may be emerging in other countries. The rate of increase appears to have slowed for primary school age boys, however increasing numbers of girls and adolescents are now treated for ADHD. Geographic variation has been noted, with more affluent areas, access to insurance, and access to specific service providers being contributing factors.
- The western region of the United States consistently has fewer children with diagnoses and undergoing treatment from the 1990s until the current time.
- Ethnicity/race predict receipt of a diagnosis and/or treatment, as well as duration of pharmacological treatment Many persons prescribed medication for ADHD do not continue use beyond 1 month.
- ADHD medications are increasingly combined with other psychotropic medications.
- Specialists prescribe fewer stimulants than primary care physicians when prescribing patterns are controlled for comorbid conditions, they start with lower initial doses and titrate to optimal levels, and they require more frequent visits.

Key Considerations, Clinical Identification, and Treatment

Geography and Time Trends

- Clinical identification and treatment vary considerably by geographic area, between nations and between regions within the United States.
- The U.S. national rate of clinical diagnosis of ADHD is high compared with the pooled worldwide prevalence estimates generated from epidemiological studies.
- Treatment rates reported generally provide rates of medication use for ADHD, without details regarding use of other interventions, reflecting data sources available for research
- Based on parent surveys, rates of medication use appear to be lower than those based on administrative or prescription data.
- Data from epidemiological surveys suggests that many children in the United States with a lifetime diagnosis of ADHD do not take medication.

Age, Sex, SES, and Race/Ethnicity in the United States

- More boys than girls are diagnosed and treated for ADHD.
- Increases over time in the diagnosis and treatment of girls and adolescents have occurred.
- More Caucasian children than African-American or Hispanic children receive medication.
- Direct comparisons between SES is difficult; however, access to insurance plays a role, as families having either public or private health insurance use medication more than those without insurance.
- Parent-reported child impairment is associated with increased use of medication.

Provider characteristics. Although few comparisons among service providers are available, it appears that characteristics of the service provider exert strong influence on interventions received.

Canada

Canadian data from cycles of the National Longitudinal Survey of Children and Youth (NLSCY) showed that among children ages 2 to 11 years, the overall prevalence of MPH use as reported by parents was low (<2% from 1994/95 to 1998/99), noting an increase in use among girls and among those aged 6-11 years.[131] Another study using data from cycles 1 (1994/95) and 2 (1996/97) found that boys were 4.6 times more likely than girls across all age categories to use MPH, with the highest prevalence of use among those ages 7 to 9 years.[272] However, the overall prevalence of use of MPH was also deemed to be relatively low, ranging from 0.09 percent to 3.89 percent in children ages 2 to 11 years in1994/95.[272]

To consider variation by province, a study of patterns of use and prescribing of MPH in youth ages 19 years or less, using linked administrative and health databases in B.C. for the period 1990 to 1996, reported an increase from 1.9 per 1,000 children in 1990 to 11.0 per 1,000 in 1996 as the number of children who had received at least one prescription.[127] MPH use was found to be slightly higher (RR 1.17, 95% CI, 1.14 to 1.21) among individuals in the lowest two socioeconomic quintiles (least privileged) relative to the highest three quintiles (most privileged).[127] Pediatricians and psychiatrists wrote 23 percent and 21 percent of all prescriptions, respectively, whereas General Practitioners (GPs) wrote 56 percent of all prescriptions, while writing only 41 percent of the initial prescriptions.[127] Using computerized administrative records of physician visits and prescriptions, a cohort of 4,787 Manitoba children (up to the age of 19 years) diagnosed with ADHD within a 24-month period (1994 to 1996) or prescribed psychostimulant treatment over a 12-month period (1995 to 1996) was assembled in order to calculate estimates of ADHD diagnosis and use of stimulants at the provincial level.[128] Overall, 1.52 percent of Manitoba children were noted to have received a medical diagnosis of ADHD and 0.89 percent, to have received stimulant medication.[128] Among those who received a diagnosis, 58.6 percent were treated with medication. On average, the peak age to receive a diagnosis and medication was between 7 to 9 years of age, with males much more likely to be both diagnosed and treated with stimulants in each age group.[128] Lastly, these outcomes were found to vary according to physician speciality; children in Manitoba appeared more likely to be diagnosed and treated by a pediatrician than by a GP or psychiatrist.[128]

A recent publication compared patterns of stimulant use by those less than 19 years of age in the provinces of B.C. and Manitoba, using population-based administrative prescription

medication data for the years 1997 to 2003.[273] Important differences were detected: though psychostimulant prescription rates were nearly identical in the two provinces in the late 1990s and increased over the next 6 years, the increase in use in Manitoba was more than threefold the increase observed in B.C. children.[273] Next, in 2003, psychostimulant use in Manitoba was greatest in the 11 to 14 year age group, whereas in B.C., it was highest among 15 to 18 year olds.[273] Use was found to have decreased among children ages 6 to 10 years in B.C. between 1997 and 2003, whereas in Manitoba all three categories (6 to 10, 11 to 14, and 15 to 18 years of age) experienced an increase.[273] A suggested explanation of more discriminate diagnosing and prescribing by B.C. physicians was given for these discrepancies.[273]

Brief Summary

- There was a relatively low prevalence of MPH use in the early 1990s among those <11 years old, with boys receiving treatment more often than girls.
- In B.C, more initial prescriptions for psychostimulants were provided by specialists while the majority of prescriptions were provided by primary care physicians.
- Practice patterns vary from province to province as well as over time. Between 1997 and 2003, there was a much larger increase in treatment of children in Manitoba in contrast to B.C.

Europe

Observing time period trends in the United Kingdom (U.K.), a population-based study conducted to estimate the prevalence of psychotropic drug prescriptions in children and adolescents (<19 years of age) between 1992 and 2001 in primary care settings revealed that stimulant prescriptions (mostly MPH) rose significantly from 0.03 per 1,000 (95% CI, 0.02 to 0.04) in 1992 to 2.9 per 1,000 (2.52 to 3.32) in 2001, a 96-fold increase.[274] Of note, 2.4 percent of stimulant prescriptions were made for children less than 6 years of age and a higher proportion of boys received stimulants than girls.[274] Next, using the same large, population-based database (General Practice Research Database (GPRD), patients were between 15 to 21 years of age at this point and had had a minimum of one stimulant prescription and 1 year of research data available), the prevalence of prescribing averaged across all age groups of ADHD medications was found to have increased eightfold, from 0.26 per 1,000 patients in 1999 to 2.07 per 1,000 in 2006.[275]

In the Netherlands, a large increase in the use of psychostimulants during the years 1996 to 2006 was documented in those less than 19 years old using a pharmacy prescription database.[276] The use of psychostimulants increased in boys overall, irrespective of age, from 4.5 percent (95% CI, 3.8 to 5.3) in 1996 to 31.1 percent (95% CI, 29.8 to 32.5) in 2006 and for girls, from 0.7 percent (95% CI, 0.5 to 1.1) to 8.1 percent (95% CI, 7.4 to 8.8), in the same years, respectively.[276] The group that experienced the largest increase in use was boys ages 10 to 19 years and the male to female prevalence ratio declined from 6.4 in 1996 to 3.8 in 2006.[276] It should be pointed out, however, that the U.K. studies used population-based samples, whereas this one used a pharmacy prescription database made up only of individuals who took pharmaceuticals, which may possibly account for the larger estimates in the latter study.

Notable differences in the prevalence of psychotropic medication used in youth 0 to 19 years of age emerged in a cross-national comparison between Germany, the Netherlands, and the United States, using administrative claims data for the year 2000 for insured enrollees in selected large health insurance systems from the three nations.[103] The annual prevalence of stimulant

medication use in youth was significantly greater in the United States in 2000 (4.29%) than in either Germany or the Netherlands (0.71% and 1.18%, respectively). Keeping provider type factors in mind, GPs prescribe most of the psychotropic drugs in Western Europe whereas in the United States, pediatricians tend to fulfill that role.[103] Diagnostic criteria for the disorder and cultural norms regarding child rearing differ. The variety of psychostimulant agents prescribed was greater in the United States. These factors, taken together, may account for differences in prescribing practices.[103]

Australia

Between the years 1988 and 1993 in Western Australia and New South Wales, a significant increase in the use of stimulants for ADHD in youths up to the age of 16 years was noted, which may have been related to practice patterns.[277] In contrast, an analysis of new psychostimulant prescriptions in south Australia during the period 1990 to 2000 for approximately 5,000 youths up to the age of 18 years observed that despite a significant rise in prescriptions up to the year 1995, the rate then declined.[278] At the end of the year 2000, the rate of children and adolescents on stimulant medication for ADHD was 11.3 per 1,000 (1.1%) of the population ages 2 to 17 years in New South Wales.[279] In terms of sociodemographic profile, the rate of treatment was highest among 10-year olds (19.9 per 1,000 aged 10 years) and the majority of those receiving stimulant treatments were male.[279] An examination of treatment with psychostimulants for ADHD in children ages 3 to 17 years during the year 2004 in the Western Australia region using whole population-based administrative pharmacy data, concluded that the prevalence of treatment with stimulants for this cohort was 2.4 percent, with age-specific prevalence as high as 3.5 percent.[280] The male to female ratio of stimulant treatment was 4 to 1.[280] Prevalence increased rapidly from ages 3 to 8 years, remained high until a peak at 14 years and declined rapidly thereafter, signifying that children between the ages of 8 to 14 years have the highest levels of treatment. Most children (89.3%) received their prescriptions from pediatricians.[280]

Israel

A longitudinal, population-based investigation of MPH use for the treatment of ADHD among children up to the age of 18 years in Israel from 1998-2004 found a rapidly increasing rate of MPH use among Israeli children during this time frame, with the increase being more pronounced in girls.[281] The overall 1-year prevalence estimate of MPH use in the whole group increased from 0.7 percent in 1998 to 2.5 percent in 2004.[281]

Table 20. KQ3. A sample of summary prevalence information by region and subgroup

Study	Prevalence	Sex	Population and Age	SES	Rural / Urban	Diagnostic / Screening Instrument
Globally						
Fayyad, J. et al., (2007)[8]	3.4%	Male: OR 1.5 vs. Female: OR 1.0 p <0.05	18 to 44y	Greater prevalence among adults with less than university level education	NR	WMH ESEMeD
Simon, V. et al., (2009)[9]	2.5%	gender proportions were neither balanced nor representative of larger populations	Adults (proportion of population with ADHD appears to decrease with age)	NR	NR	DSM-IV
Polanczyk, G. et al., (2007)[93]	5.3%	NR	NR	NR	NR	Variability results primarily from methodological differences
Europe						
Belgium (2007)[8]	4.1%	NR	18 to 44y	NR	NR	WMH ESEMeD
France (2007)[8]	7.3%	NR	18 to 44y	NR	NR	WMH ESEMeD
Germany (2008)110,234	4.8%	Male: 7.8 % Female: 1.8%	Preschool: 1.5y Primary: 5.3y Secondary: 7.1y Possible decline in prevalence with age	Preschool: 6.4y Primary: 5.0y Secondary: 3.2y Boys of low SES at greatest risk of Dx	NR	FBB-HKS/ADHS
Germany (2007)8	3.1%	NR	18 to 44y	NR	NR	WMH ESEMeD
Italy (2007)8	2.8%	NR	18 to 44y	NR	NR	WMH ESEMeD

Table 20. KQ3. A sample of summary prevalence information by region and subgroup (continued)

Region / Country	Prevalence	Sex	Population and Age	SES	Rural / Urban	Diagnostic / Screening Instrument
Netherlands (2007)[8]	5.0%	NR	18 to 44y	NR	NR	WMH ESEMeD
Spain (2007)[8]	1.2%	NR	18 to 44y	NR	NR	WMH ESEMeD
Russia (2008)[248]	6.3%	Male: 8.9% Female: 3.6%	12 to 17y	NR	NR	SNAP-IV; SDQ; teacher report
Sweden (1996)[282]	4.0%	NS	6 to 7y	NR	Children born in southern rural Sweden in 1986/87	Parent and teacher interview using rating scale and parent interview
Other North American						
Canada (1989)[283]	5.8%	Male: 9.0% Female: 3.3% ADHD more common in girls and adolescents than previously thought	4 to 16y	NR	No significant differences by rural/urban status	SDI, with parents, teachers and subject informants
Quebec, Canada (1999)[204]	8.9% teachers 5.0% parents 3.3% subjects	NS	4 to 16y	NR	NR	Interview
Puerto Rico (2007)[235]	7.5%	Male: 10.3% Female: 4.7%	Highest prevalence in 6 to 8y age group	Association for ADHD and community population who live in poverty (OR 2.20, 95% CI, 1.29 to 3.76) while among those living in low income (the clinic-based association OR 1.45, 95% CI, 1.02 to 2.09)	NR	DISC-IV
Mexico (2007)[8,284]	1.9%, 5.4%	NR	18 to 44y	NR	NR	WMH, M-NCS, MINI-Plus
South America						
Colombia (2007)[8]	1.9%	NR	Adults	NR	NR	NSMH
Venezuela (2008)[236,236]	10.0%	Male: 7.6% Female: 2.4%	4 to 12y	More ADHD Dx in lower than in medium and high SES	Urban	DISC-IV-P (parent report)

Table 20. KQ3. A sample of summary prevalence information by region and subgroup (continued)

Region / Country	Prevalence	Sex	Population and Age	SES	Rural / Urban	Diagnostic / Screening Instrument
Salvador, Brazil (2007)[238]	6.7%	No differences noted by sex	6 to 17y	NR	Urban	DAH
Buenos Aires, Argentina (2007)[237]	9.0%	No differences noted by sex	6-12y	Pediatric outpatient in private hospitals	Urban	ADHD Rating Scale –IV
Middle East						
Lebanon (2007)[8]	1.8%	NR	18 to 44y	NR	NR	WMH LEBANON
Mashhad, Iran (2007)[240]	12.3%	Male: 18.1% Female: 6.2%	Kindergarten age	NR	Urban	K-SADS-PL
Shiraz, Iran (2008)[241]	10.1%	Male: 13.6% Female: 6.5%	7 to 12y	NR	Urban	CSI-4
Yemen (2008)[243]	1.3%	Male: 2.1% Female: 0.5%	7 to 10y	NR	No significant urban/rural differences	DAWBA-P; DAWBA-T; SDQ
Algeria, Bahrain, Egypt, Gaza, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Palestine, Qatar, Saudi Arabia, Sudan, Syria, Tunisia, United Arab Emirates (UAE), and Yemen (2009)[246]	0.5 to 0.9 % community vs 5.1 to 14.9 % school	Various	Various	Various	Various	Structured interview in community vs. Rating scales in school system Various instruments
Africa						
Nigeria (2007)[242]	8.7%	Male: 11.0% Female 5.1%	Ages 6 to 12y	Various	Semi-urban community	VADPRS; VARTRS
Asia						
Mumbai, India (2009)[239]	12.2%	Male: 19.0% Female: 5.8%	Ages 4 to 6y	NR	Urban	Connors + SADS + DSM-IV-based interview

Table 20. KQ3. A sample of summary prevalence information by region and subgroup (continued)

Region / Country	Prevalence	Sex	Population and Age	SES	Rural / Urban	Diagnostic / Screening Instrument
Karachi Pakistan (2009)[244]	17.0%	Ratio of 3.1 Male to 1 Female	Primarily among children ages 5 to 10y	NR	NR	P-CHIPS
Taiwan, China (2005)[245]	7.5%	Greater likelihood of diagnosis in males than females	7.5 % 7th grade 6.1 % 8th grade 3.3 % 9th grade	SES is higher in urban areas in Taiwan	Prevalence is higher in rural than in urban youth	Chinese K-SADS-E + CBCL
Hong Kong, China (2008)[249]	3.9%	Male: 5.7% Female 3.2%	Mean age 13.8y	NR	NR	DSM - IV
Western Australia (2001)[285]	Symptoms = 7.5% Functional impairment = 6.8%	Tx 4 times more prevalent in males than in females	Children age 6 to 17	NR	NR	Interview and rating scale Informant = parents
Australia (1999)[286]	2.4%parent & teacher 9.9% parent 8.8% teacher	Male to female ratio is 5 to 1	Children age 5 to 11	47.4% male	NR	Limited agreement between parent and teacher information
New Zealand (1993)[287]	3.9% (parent report) 2.8% (subject report)	Male: 5.7% Female: 2.7%	Ages 13 to 15y	NR	Cohort of children born in 1977 in Christchurch urban region	Assessed by interview of parent and of subject using DSM-IIIR criteria

Abbreviations: CBCL = Child Behavior Check List; CSI – Child Symptom Inventory; DAH = Da escala de transtorno de déficit de atenção e hiperatividade; DAWBA = P or T – Development and Well-Being Assessment Parent or Teacher Report; DISC = Diagnostic Interview Schedule for Children-Expressive; DISC-IV-P = Diagnostic Interview Schedule for Children Version IV–Prevalence; Dx = Diagnosis; ESEMeD = European Study of the Epidemiology of Mental Disorders; FBB-HKS/ADHS = Fremdbeurteilungsbogen für Hyperkinetische Störungen/ Aufmerksamkeitsdefizit /Hyperaktivitätsstörungen; K-SADS-E = Kiddie-Schedule for Affective Disorders and Schizophrenia- Epidemiologic Version; K-SADS-PL = Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime; LEBANON = Lebanese Evaluation of the Burden of Ailments and Needs of the Nation; MINI-Plus = Mini-International Neuropsychiatric Interview-Plus; NS = not specified; NSMH = National Survey of Mental Health; P-CHIPS = Child Interview for Psychiatric Syndrome – Parent version; SDI = Survey Diagnostic Instrument; SDQ = Strengths and Difficulties Questionnaire; SES = Socio-economic Status; SNAP-IV = Swanson, Nolan and Pelham (SNAP) Questionnaire – 4th revision; VADPRS = Vanderbilt ADHD Diagnostic Parent Rating Scale; VARTRS = Vanderbilt ADHD Diagnostic Teacher Rating Scale; WMH = World Mental Health

Discussion

Summary of the Evidence

This systematic review examined three questions regarding the effectiveness and safety of interventions for persons with Attention Deficit Hyperactivity Disorder (ADHD). We investigated safety and efficacy of interventions for preschool children with Disruptive Behavior Disorders (DBD) (which includes Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD), as well as ADHD), including those at high risk for ADHD. The SOE for effectiveness of interventions to improve disruptive behavior, including ADHD, in preschoolers is summarized in Table 21. We investigated long-term effectiveness of interventions, with a special focus on the safety of pharmacologic interventions for persons of all ages with ADHD. The SOE for longer term effectiveness for interventions to improve ADHD symptoms is summarized in Table 22.Finally, we report on variability in prevalence, clinical identification, and treatment for ADHD in the United States and elsewhere.

Overall, we found that the most information about long-term outcomes applies to boys ages 7 to 9 years at intervention. Preschoolers with diagnosed ADHD, girls, teenagers, and adults have rarely been the focus of intervention research. In general, safe and effective interventions have been identified. Parent behavior training for preschoolers is efficacious and benefits appear to last, although many parents drop out of treatment. Medications can be efficacious in preschoolers, but are not as well tolerated as in children over 6 years of age, or in adults. In addition, parents show decreasing adherence to medication use for their children over 12 months despite effectiveness. For children over 6 years of age, teenagers, and adults, medications remain the most thoroughly researched interventions, with most studies sponsored by industry. In addition to psychostimulant medications, two additional pharmacologic agents, atomoxetine (ATX) and guanfacine extended release (GXR), have been studied and appear effective and safe for one or more years at a time, with differing adverse event profiles. Classroom teacher-based interventions can improve academic and classroom behavior outcomes for both preschoolers and primary school children, but difficulties re-emerge 1 to 2 years following discontinuation of the intervention. For some subgroups of children, additional benefit may derive from combined medication and behavioral interventions, but not for all. There remains a lack of clarity about how long treatment may be required, of what type, and for whom. For some, incremental improvement accrues with continued intervention over years; for others, medication interventions can be discontinued without symptom relapse. However, these observations are difficult to evaluate due to the absence of information regarding specific subgroups receiving treatment and details regarding co-interventions.

A survey of the research in community samples suggests that clinical identification and treatment of ADHD has increased, especially since the early 1990s, and varies widely geographically. Prevalence estimates for the underlying or background rate of ADHD in school age children vary primarily due to method of measurement, definition of disorder, and informant. Fewer prevalence studies are available addressing older adolescents and adults.. Information regarding clinical identification and treatment for large-scale populations has been gathered through epidemiologic surveys with parents, through studies using administrative claims databases where providers document diagnoses and treatments recommended for insurance claims, and through prescription databases examining the use of medications. Alternative or

additional educational or psychosocial interventions are not represented. The data sources shape what research questions can be answered.

Rating the Body of Evidence

We assessed the overall strength of the body of evidence using the context of the GRADE approach, modified as the Grading System as defined by AHRQ.[14,15] Although we included papers that were not randomized controlled trials (RCTs), there are several factors suggested by the GRADE approach that may decrease the overall strength of the evidence (SOE):

1. Study limitations (predominately risk of bias)
2. Type of study design (experimental versus observational)
3. Consistency of results (degree to which study results for an outcome are similar between studies; variability that is easily explained)
4. Directness of the evidence (assesses whether interventions can be linked directly to the health outcomes)
5. Precision (degree of certainty surrounding an effect estimate for a specific outcome)

The ratings were arrived at through discussion among two or more of the investigators. Only papers rated as "good" were included in these analyses since they represent the best available data at this point in time. See Appendix D.

Table 21. KQ1. Effectiveness of interventions for ADHD and DBD in children <6 years old

Intervention	Level of Evidence	Conclusion
a. Parent behavior training	SOE: High SMD: -0.68 (95% CI, -0.88 to -0.47)	Parent behavioral interventions are an efficacious treatment option for preschoolers with DBD, and show benefit for ADHD symptoms. These studies support the long-term effectiveness of parent interventions for preschoolers with DBD, including ADHD symptoms, with evidence that benefits are maintained for up to 2 years. There also appears to be a dose response effect.
b. Multicomponent home and school or daycare-based interventions	SOE: Insufficient	Evidence is drawn from few reports Where there is no socioeconomic burden, multicomponent interventions work as well as a structured parent education program in several domains. Where there is socioeconomic burden, the treatment classroom appears to be the primary beneficial intervention and appears related to lack of parent engagement and attendance at PBT sessions. Relative benefits of the school-based intervention diminished over 2 years.
c. Medication (MPH only)	SOE: Low SMD: -0.83 (95% CI, -1.21 to -0.44)	With evidence drawn primarily from the PATS study, MPH (e.g., short-acting, immediate release MPH) is both efficacious and generally safe for treatment of ADHD symptoms, but there has been no long-term followup in preschoolers

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; DBD = Disruptive Behavior Disorder; MPH = methylphenidate; PATS = The Preschool ADHD Treatment Study; PBT = parent behavior training; SMD = Standardized Mean Difference; SOE = strength of evidence

Table 22. KQ2. Long-term (>1 year) effectiveness of interventions for ADHD in people 6 years and older

Intervention	Level of Evidence	Conclusion
a. Medication treatment	SOE: Low MPH: SMD: -0.54 (95% CI, -0.79 to -0.29) ATX: SMD = -0.40 (95% CI, -0.61 to -0.18)	Very few studies include untreated controls. Studies largely funded by industry. Psychostimulants continue to provide control of ADHD symptoms and are generally well tolerated for months to years at a time. The evidence for MPH use in the context of careful medication monitoring shows good evidence for benefits for symptoms for 14 months. ATX is effective for ADHD symptoms and well tolerated over 12 months.
	SOE: Insufficient	Only one study of GXR monotherapy is available which reports reduced ADHD symptoms and global improvement, although less than a fifth of participants completed 12 months. Monitoring of cardiac status may be indicated since approximately one percent of participants showed ECG changes judged clinically significant.
b. Combined psychostimulant medication and behavioral treatment	SOE: Low SMD = -0.70 (95% CI, -0.95 to -0.46)	The results from 2 cohorts indicate both medication (MPH) and combined medication and behavioral treatment are effective in treating ADHD plus ODD symptoms in children, primarily boys aged 7-9 years of normal intelligence with combined type of ADHD, especially during the first 2 years of treatment. Several reports from one “good” quality study suggest that combined medication and behavioral treatment improves outcomes more than medication alone for some subgroups of children with ADHD Combined type, and for some outcomes.
c. Behavioral/ psychosocial	SOE: Insufficient	Not enough evidence to draw conclusions for persons 6 years and older and with a diagnosis of ADHD.
d. Parent behavior training	SOE: Insufficient	Not enough evidence to draw conclusions for persons 6 years and older and with a diagnosis of ADHD.
e. Academic interventions	SOE: Insufficient	One “good” study and its extension showed that classroom-based programs to enhance academic skills are effective in improving achievement scores in multiple domains, but following discontinuation, the benefits for sustained growth in academic skills is limited to the domain of reading fluency. All other domains show skill maintenance but not continued growth.

Abbreviations: ADHD = Attention Deficit Hyperactivity Disorder; ATX = atomoxetine; DBD = Disruptive Behavior Disorder; ECG = electrocardiogram; GXR = guanfacine extended release; MPH = methylphenidate; ODD = Oppositional Defiant Disorder; SES = socioeconomic status; SMD = Standardized Mean Difference; SOE = strength of evidence

Key Question 1. Among children less than 6 years of age with Attention Deficit Hyperactivity Disorder or Disruptive Behavior Disorder, what are the effectiveness and adverse event outcomes following treatment?

Twenty-eight “good” or “fair” quality RCTs investigating the effect of parent behavior training (PBT) on a variety of outcomes in preschool children with DBD are available, most comparing interventions to wait list controls (see Tables 2 and 3 for study details). We performed meta-analyses examining effectiveness of PBT for reducing child disruptive behavior, including symptoms of ADHD. The descriptive review of the studies showed that parent behavioral

interventions are an efficacious treatment option for preschoolers with DBD and also improve parents' sense of competence. The meta-analyses indicated that parent-rated child disruptive behaviors improve to a clinically significant degree. Among these RCTs, eight examined measures of ADHD symptoms.[36-39,133,135-137] Seven of the eight studies documented improvements in these symptoms as well. Some studies utilized blinded observations of child and parent interactions and identified improved child compliance and improved parenting strategies. Self-directed, group, and individual variants of parenting interventions are generally equally effective, though group therapy may be more cost-effective when compared to individual therapy. The primary barrier to effectiveness is that parents do not attend or do not complete the recommended numbers of sessions, and this interferes with optimal benefit.

Extension studies suggest that the benefits shown postintervention are maintained.[19,21,26,27,29,33,139-141] However, these studies lack a control group, since most RCTs used wait list controls and the comparison families received the intervention following the prescribed period of waiting. In addition, the extension studies show high levels of attrition. Therefore, the possibility exists that natural maturation or child development would also lead to improvement over extended periods of time.

Seven studies examined interventions combining home- and school- or daycare-based interventions designed specifically for preschoolers or kindergarten children with ADHD or those at high risk for ADHD and DBD.[27,40,42,122,141-143] Two studies examined comprehensive home and school behavior training in comparison to community care or a structured parent education program in a population of children with little socio-economic burden.[122,143] In this population, behavior and school readiness improved following both the multicomponent intervention and the comparison interventions. Few children received medication. In contrast, a combination PBT and teacher consultation program showed definite benefit in comparison to treatment as usual for a low socioeconomic Head Start community.[27] Another study examined a kindergarten treatment classroom intervention in comparison to PBT, combined PBT and treatment classroom, and a no-treatment control. This population included both families on public assistance and those not on public assistance. The treatment classroom appeared to be the primary beneficial intervention, with little additional improvement noted for those in PBT, although parent attendance was poor. Pragmatic issues interfered with randomization potentially biasing outcomes.[141,142] Studies of combined parent and teacher or school-based intervention in less well educated, or low socioeconomic status (SES) families find that parent participation can be modest even when groups occur at convenient times, with transportation and babysitting provided.[27] A dose effect of attendance at sessions has been noted where children of those who attend more sessions show improved child behavior and parents report greater improvement in skills.[40]

There are only a few short-term studies examining psychostimulant use in preschoolers, most with small sample sizes. Of these, only one small study compares medication directly with PBT and the combination of medication and PBT.[43] The medication dose it examines is low compared with doses suggested by other studies. The sample size was very small, perhaps due to attrition (16 of 26 children completing interventions), precluding the usual statistical analysis for controlled trials examining efficacy. There is one RCT with a more robust sample size (N = 165) that offers the best evidence of both efficacy and safety, the preschool ADHD Treatment Study (PATS). Following clinical consensus, all 303 families with children eligible for the study initially participated in a 10-session PBT program. The next phase was an open-label safety lead-in phase followed by a 5-week multiple dose randomized crossover titration trial to examine dose

effects, including adverse events. After identifying the child's best dose, a 4-week parallel RCT compared best dose to placebo. One hundred and forty children entered a 10-month open label extension study. The research program offered excellent evidence that methylphenidate (MPH) is both efficacious and generally safe for treatment of ADHD symptoms.[7] However, additional analyses identify that children do not improve in all domains, as parents report increases in mood and anxiety symptoms, while clinicians identify global improvement and teachers note improved social skills.[51] Children experience more adverse events than older groups, and many families do not maintain adherence.[54] The most common adverse event resulting in withdrawal from the study was irritability. Growth rates are slowed over 1 year's time,[53] and children with multiple comorbidities do more poorly on medication than those who have a less complicated presentation.[52]

Key Question 2. Among people 6 years of age or older with Attention Deficit Hyperactivity Disorder, what are the effectiveness and adverse event outcomes following 12 months or more of any combination of followup or treatment, including, but not limited to, 12 months or more of continuous treatment?

Among the studies available examining extended outcomes following treatment, many examined pharmacologic agents, and these were primarily industry sponsored. Three studies were placebo-controlled discontinuation studies or relapse-prevention studies.[61,66,67] In general pharmacologic agents continue to control the symptoms of ADHD after 12 months of use, with benefits maintained, although studies did not address the possibility of improved symptoms due to maturation. The different agents demonstrate different safety profiles, such that adverse events may be a primary reason for choosing one agent over another (switching to another formulation of psychostimulant, for example) or to another class of agent. Few serious adverse events are noted, although GXR appears to be less well tolerated than other agents examined. With two-thirds of the studies funded by industry, there may be enhanced representations of effectiveness and safety.[147] The following discussion offers details about effectiveness and safety by specific agent.

Psychostimulants

Psychostimulants continue to provide control of ADHD symptoms and are generally well tolerated for months to years at a time. Concerns about exacerbation of tics with stimulants appear to be unfounded, although sample size in studies of tics remain small and this may result in a type II error. Some of the long-term research summarizes information based on short-acting formulations of psychostimulants, requiring multiple doses daily. The Barbaresi[59] study, for instance, reports that MPH is better tolerated than dextroamphetamine (DEX). However, direct comparison of once-daily agents, for example, OROS MPH and MAS XR is can be difficult. For example, the Hoare, et al.[60] study of OROS MPH included adolescents and those with ADHD inattentive type (ADHD-I), whereas the McGough, et al.[63] study of a MAS XR sample had more than 90 percent of participants with ADHD Combined type (ADHD-C). Comparison could be read as suggestive that OROS MPH is better tolerated than MAS XR, but both studies had 15 percent of participants withdraw because of adverse events. Also the methods for collecting adverse events may have been more sensitive in McGough, et al., as they were collected by both spontaneous reports and by investigator inquiry.[63] It is also possible that the Hoare, et al., study

offered participants relatively less effective dose, thereby diminishing the likelihood of adverse events.[60] The agents have not been compared in the same long-term (over 12 months) trial and therefore, it is not possible to make direct comparisons of effectiveness and safety or tolerability.

Atomoxetine

Long-term extension trials show that ATX is both safe and effective for ADHD symptoms in children and teens over 12 to 18 months. The research examining its use considers global functional assessments as well as ADHD symptom change. In contrast to studies of other agents, the research offers direct comparison with placebo for examination of relapse prevention, offering evidence that benefits are maintained following discontinuation.[66,67,69] An important caveat to these statements appears in Newcorn, et. al.,[79] a study not meeting criteria for this review as the total length of treatment and followup was less than 12 months. This study compared effect sizes for ATX with OROS MPH and documented the psychostimulant as more efficacious than ATX for ADHD symptom control. Adler, et al.,[68] offer the only study of a pharmacologic intervention over an extended time period in adults with ADHD.

Guanfacine Extended Release

Open-label extension trials of GXR show it to be effective and generally safe.[70,71] Parents report benefit in reduced ADHD symptoms and global improvement for a substantial number of children and teens with ADHD. Somnolence, headache, and fatigue appear to interfere with its use, but these adverse events appear to diminish following several months of treatment, although this may be due to discontinuation by those who do not tolerate the agent.[70] Substantially fewer children completed the 12-month extension trial on GXR monotherapy than completed the psychostimulant trials and the ATX trials reviewed, suggesting less overall effectiveness and tolerability. Fewer adverse events are reported and adherence improved with concurrent administration of psychostimulants.[71] These observations may also reflect improved symptom control.

Adverse Events

We examined studies regarding three areas of adverse events that required the use of articles that were not clinical trials comparing two or more interventions. The studies examined growth rates in comparison to standardized norms and rates of hospital and emergency department use for cardiac events and cerebrovascular events, such as cerebrovascular accidents (CVAs) and Transient Ischemic attacks (TIAs). In this review, the safety, tolerability, and adverse events of pharmacological agents is reported within the context of clinical trials, the information appears where the clinical trials of the specific agent are described.

Growth

Medications used for ADHD appear to have a small but distinct dose–related impact on rates of growth for children with ADHD. Limitations in the studies include small sample size, comparison with population norms, and the relatively short duration of studies, which interfere with clarification regarding final adult height following years of medication use. Two well designed clinical trials of psychostimulants, the PATS and the MTA study, both examined the question of growth in children with ADHD who received and those who did not receive psychostimulants. The PATS study[53] is described in the MPH section of KQ1, and the MTA

study[78] in the combined interventions section of KQ2. Both studies document decreased growth rates for children receiving MPH over 12 months to 3 years.[53,78]

Cardiac Events

Rates of hospital admission for cardiac reasons are similar between those with ADHD who use psychostimulants and rates in the general population. Rates of emergency department use were 20 percent higher for those with ADHD who use stimulant medication compared ADHD patients who do not.[148] Rates were comparable among those using MPH and amphetamines. Use of concurrent bronchodilators, antidepressants, or antipsychotics, age 15 to 20 years, and a history of cardiac problems were associated with increased use of emergency departments.[149] ECG changes that were judged to be clinically significant, including reports of significant bradycardia, junctional escape complexes, and intraventricular delay occurred in one percent of participants treated with GXR.

Cerebrovascular Events

Groups prescribed ATX and psychostimulants had similar rates of incidents of CVAs or TIAs. However, the combined ADHD medication cohort exhibited a higher hazard ratio (HR) (3.44, 95% CI, 1.13 to 10.60) for TIAs compared with the general population after adjusting for baseline risk factors. A similar pattern was not observed for CVAs. These results do not support an increased risk of cerebrovascular events for users of ATX over psychostimulants. However, users of ADHD medications may be at higher risk of TIAs than the general population.[150]

Psychostimulant Medication Compared With Combination of Psychostimulant Medication and Psychosocial and/or Behavioral Treatment

The studies examining combined PBT and school or daycare interventions for children with ADHD suggest that adding classroom teacher consultation may be of greater importance for children in low SES communities, rather than for families with educated parents who live in communities with resources.[27,122,143] As a group, these studies offered some information about the benefits of PBT over a full school year, but also documented that many disadvantaged families do not attend PBT sessions even when transportation and babysitting are available.[27] When parents attend, children benefit.[40] One recent German study offered quality evidence about combining teacher behavior training and direct child training with and without PBT.[40] Synergies among some, but not all, aspects of the program were noted, and some benefits lasted a year beyond discontinuation of the intervention program. Additional studies of this type will confirm the best means of offering interventions, as well as which children to target.

Three cohorts were identified that examined stimulant medication and/or combined medication and psychosocial or behavioral treatment. One of these was a study in China,[77] and two were in North America,[73,74,160,171] including the followup cohort extension study of the Multimodal treatment (MTA) study of ADHD, the largest RCT to date examining combinations of interventions.[73] The results from these three cohorts indicate that both psychostimulants and combined psychostimulants and behavioral treatment are effective in treating ADHD plus ODD symptoms in children, and also anxiety, primarily boys ages 7 to 9 years of normal intelligence with combined type of ADHD, especially during the first 2 years of treatment. Overall, the MTA

study suggests that combined therapy may have a slight advantage over medication management during the first 14 months, and a clear advantage over behavior treatment,[72,165] especially for children with multiple comorbidities.[80] However, combined treatment is equivalent to medication alone in controlling ADHD and ODD symptoms for up to 2 years if the child shows an early favorable response to medication.[76] The MTA study also suggests that these two strategies may be superior to psychosocial/behavioral treatment alone or community care during the first 2 years,[73,74,169] although psychosocial/behavioral treatment is equally effective as treatments with psychostimulants for ADHD children with comorbid anxiety disorder during the first 14 months.[80] Combination therapy and medication management are effective in reducing ODD during the first 2 years of treatment,[75] and superior to psychosocial/behavioral treatment and Community Care.[73,74] It appears that psychosocial/behavioral treatment reduces the risk of substance use for 10 months following the intervention, but the effect appears to disappear by 22 months.[83] However a re-analysis of the data adjusting outcome for age, suggested that the reduced risk for substance use following behavioral intervention was maintained at 3 years. These results were formally presented, but not published (Molina, October 2010). No treatment strategy is clearly superior in reducing other comorbid psychiatric disorders at 14 months or 3 years.[81,168]

Combining medication with psychosocial/behavioral treatment may reduce the dose of medication required, improve retention of patients in treatment, and improve positive parenting. So, et al., in a study involving Chinese children, set the mean daily dose of stimulant medication to less than half that used in the MTA study, and many fewer families who were offered medication alone continued in care.[77] However, there may be genetic and cultural differences between samples studied that make direct comparison with children in North America complex. Abikoff 's 2004 study suggests that it may be cost-effective to treat stimulant-responsive children free of learning and conduct problems with medication alone, although families in both groups had frequent contact with clinicians.[76] Treatment with psychostimulants, intensive behavioral treatment or combination of the two can reduce negative parenting, but combined treatment may be the most effective in improving positive parenting.[89,161-163] Too few long-term studies examining combinations of medication management and psychosocial/behavioral interventions are available to clarify what subgroups of children do best with which interventions. For some subgroups, multiple interventions are synergistic, but perhaps not for all. Synergies may result in improved effectiveness due to increased treatment adherence, continuity of care, and proactive approaches to new onset of mental health concerns over extended periods of time.

Using intention to treat analyses, the MTA study suggests a loss of superiority of any individual intervention 2 years after treatment has ended.[160] However, secondary analyses such as mixed effects models, propensity score analysis, and growth mixture model analysis have provided additional findings. These secondary studies document that most children with ADHD receiving any of the interventions generally maintained improvement for up to 8 years, while a small proportion began to worsen after the interventions discontinued. On the other hand, while most of the children experienced improved symptoms and functioning, they did not reach levels of functioning comparable to their nonclinical community peers.[82]

We also examined longitudinal cohort studies that followed children for multiple years following initial treatment. The outcomes and time frames varied extensively across studies. Biederman, et al.,[86] and Wilens, et al.,[181] studied an exclusively female cohort, and all others studied an exclusively or predominantly male sample. Although any conclusions can only be

seen as preliminary, it appears that stimulant medication might protect against psychiatric disorders (e.g., ODD, CD, depression, anxiety disorder) at 10 years. Some studies suggest that stimulant medication reduces substance use disorders in late adolescence or adulthood,[87,88,181] while one paper reported no benefit.[179] Two studies suggested that stimulant medication may protect against nicotine use.[176,181] Treatment with stimulant medication, especially at an early age, may delay the onset of smoking and reduce substance use disorder.[88,177,180] Given the challenges inherent in pursuing long-term outcomes studies, with lack of ability to control for co-interventions and significant life events, such information can only be seen as hypothesis generating.

We found three reports on two cohorts that examined academic achievement as the primary outcome following classroom-based interventions. Other studies reported on academic outcome as one of multiple secondary outcome measures. The review of the academic outcomes with long-term followup of treatment interventions revealed benefits, albeit limited, with medication interventions in some aspects of reading and arithmetical skills.[86,174,288] Combining psychobehavioral and academic skills interventions with medication offers no additional gains than medication alone, at least for children with ADHD without comorbid learning disabilities. Interventions for academic skills in classroom-based programs result in academic enhancement, but the findings support the need for sustained intervention to improve academic functioning over time.[91,92,175]

Key Question 3. How do (a) underlying prevalence of ADHD, and (b) rates of diagnosis (clinical identification) and treatment for ADHD vary by geography, time period, provider type, and sociodemographic characteristics?

According to a recent comprehensive systematic review and metaregression analysis that encompassed studies from all areas of the world, the worldwide pooled prevalence estimate of ADHD among those 18 years of age or younger is 5.29 percent (95% CI, 5.01 to 5.56).[93] A significant amount of variability was noted in the comparison of prevalence estimates across world regions and results seemed to indicate that once methodological differences of studies were controlled for, geographic location explained very little of the variability.[93] In fact, after this step, only significant differences were detected between studies carried out in North America, Africa, and the Middle East.[93] The requirement of impairment for the diagnosis, diagnostic criteria, and source of information were the main sources of variability in the pooled prevalence estimate of ADHD.[93]

Most studies show that more boys than girls have ADHD, and children in the age group 5 to 10 years show the highest prevalence. In addition, some studies suggest that children from lower socioeconomic status (SES) demonstrate higher levels of symptoms. Research detailing prevalence in other age groups worldwide is generally lacking, with few studies examining prevalence among preschoolers, adolescents, or adults. These are age groups where diagnostic consensus is less clear, making the task of identifying cases difficult. There is a general lack of uniform protocol for eliciting information about prevalence, including research choices about informants, measurement instruments, and definition of cases across geographic areas.

Despite the inherent difficulties with case identification on a community-wide basis, information about clinical identification and treatment available through epidemiological surveys, administrative claims, and prescription data converge to document that the

pharmacological use of psychostimulants for ADHD increased throughout the early to mid 1990s, and use of medications for ADHD continues to increase through the 2000s in the United States.[94-96] Changing patterns of ADHD medication use suggest increases among girls and adolescents. While at a much lower rate of use, medication use has also increased among preschoolers and adults. Agents prescribed have changed from short-acting preparations of stimulants to long-acting formulations.[98] Similarly, in Canada and in Europe psychostimulant use for children with ADHD increased throughout the 1990s and early 2000s; however, levels of ADHD medication use are three to four times higher in the United States than in the Netherlands or in Germany.[98,103] In general, more boys than girls are treated and in the United States, more Caucasians than Hispanic or African-Americans have medication dispensed once they are diagnosed.[101,102] There are geographic disparities among service use in the United States as well, with more children in the midwest and south receiving psychostimulants relative to the west, and more children in urban rather than rural centers.[213] In addition, children living in more affluent communities are more likely to receive psychostimulants.[99] Both characteristics of service providers and access to health insurance influence clinical identification and subsequent treatment. Patterns of medication use suggest poor adherence and inconsistent use.[105] Fewer teens than younger children, and fewer Caucasians than persons from minority groups, used medication over an extended period of time.[106]

Limitations

Since the AHRQ review of long-term intervention studies for ADHD, published in 1997, researchers have sought opportunities to discover what has happened to the participants of earlier studies, and begun to tackle the challenges of prospective cohort studies. The primary weaknesses reflected in the literature relate to these challenges. Overall, data were difficult to compare due to lack of clarity with regard to uniformity of assessment and reporting, as well as inconsistencies in study design and the development of objective outcomes.

Preschool Interventions

While the overall evidence for preschool interventions is strongest for PBT for disruptive behavior including ADHD, very few RCTs offer information about PBT interventions designed specifically for preschoolers with ADHD. Despite this, seven of the eight PBT intervention studies documented improvement in ADHD symptoms. We chose to emphasize similarities among manualized PBT programs, although differences are also noted. Further research will be required to document whether the programs as currently running are successful in addressing aspects of functional impairment due to ADHD symptoms. Although short-term trials show the efficacy of PBT, evidence for lasting benefits are less robust. While it appears that PBT benefits may last several years, no extension study included untreated comparison groups, and attrition over the followup period ranged from 24 percent at 18 months[26] to 54 percent at 3 to 6 years,[21,29] limiting interpretation of the results.

Investigations of psychostimulant medication use in preschoolers are generally short-term trials with very small samples. The PATS study addresses a number of important methodological and clinical concerns, examining the potential additional benefit of medication following a series of 10 PBT sessions. Careful attention to details regarding adverse events and the impact of these on medication adherence offers clear information about long-term effectiveness and safety. Interestingly, clinicians documented improved global functioning concurrently with parents noting increased mood problems.[51] While parent and teacher ADHD symptom scales measuring

dysfunction noted improvement, those measuring strengths as well as weaknesses in behavior showed no overall behavioral benefit from the addition of stimulant medication. The PATS study offers information about both the potential benefits and limitations of stimulant medication use in young children. Limitations are: 1) younger children experience more dose related adverse events than older children, 2) stimulants interfere with rates of growth, and 3) not all parents agree with ongoing use following medication titration.[7,53,54] Also, the presence of three or more comorbid conditions interfered with the effectiveness of psychostimulant medication following PBT.[52] Only 54 percent of those initially enrolled in the study opted to enter the medication titration component following PBT, suggesting that parent preferences play an important role in providing optimum care for young children with ADHD.

Future work should examine the appropriate place of PBT as a specific intervention for ADHD in preschoolers. A focus of such studies should include different SES and ethnocultural groups, as well as the presence of comorbid conditions in the children. Adverse events are not discussed in reports of PBT trials or teacher training/classroom intervention trials. Outcomes examined should include global functioning and school readiness as well as behavior symptom counts. Specific attention to the circumstances surrounding parental reluctance to engage in treatment or parent attrition from PBT is warranted as that appears to be a primary barrier to success. Additional awareness and understanding of parent preferences may be especially important in this age group.

Extended Studies

Studies conducted over long periods of time face challenges in controlling for many confounders which may affect the outcomes studied. Several of these longer-term studies either did not enroll representatives from lower SES at risk for psychosocial adversity or those who were less able to be contacted for followup. Some studies did not systematically collect or report important confounders, such as socioeconomic demographics, family psychiatric history, childhood abuse, adherence to treatment, or co-interventions. The retrospective studies face problems with recall and documentation bias, both of which prospective longitudinal studies face as well if the time intervals between data collection are lengthy. An important challenge is the documentation of treatment adherence and co-interventions, both formal and informal, which affect treatment outcomes.

A considerable limitation to evaluating academic outcomes following interventions is that classroom-based or teacher consultation-based interventions are by nature difficult to investigate, as it can be challenging to coordinate cross-sector research and to develop informative comparison interventions that are ethically acceptable. In addition, few of the studies reviewed controlled for learning disabilities and IQ, important confounding factors for academic outcomes in an ADHD population. Additional aspects to consider in future studies will be the challenges inherent in coordinating and tracking the co-interventions offered in school settings along with those offered in health care settings.

The most commonly studied population in the extended interventions studies were children, primarily boys, ages 7 to -9 years, with ADHD-C at the time of documented treatment. It is not clear whether the same intervention outcomes apply to community samples across different geographical regions, cultures, and to both genders, other ADHD subtypes, and different age groups. In addition, for the most rigorous studies, there was no comparison group of children with untreated ADHD, as this would be an ethical challenge. It is therefore difficult to be fully

confident that the improvements seen over time were due to treatment effects rather than subsequent co-interventions, maturation or other unmeasured effects.

A major gap in the available literature is the lack of clinical trials and extensions of clinical trials examining non-pharmacological interventions targeting the functional impairment associated with ADHD symptoms in a variety of sample populations.

Prevalence and Health Services Studies

Determining prevalence of ADHD across all age categories in the population is necessary to understand the burden that the condition poses. From this, we can identify gaps in service and develop responses which will help patients and their families in the shorter-term and allow patients to meet their potential in all areas of their lives, such as maintaining fulfilling relationships and finding success in school and workplace environments. There are several methodological factors that influence the calculation of prevalence estimates – namely, the diagnostic criteria employed, along with the informant type, and the data source.[289] As described by a recent systematic review/metaregression of the worldwide prevalence of ADHD,[93] key methodological differences between studies accounted for much of the variability in the pooled prevalence estimate, highlighting the need for a standardized, methodological approach in order to improve comparability of estimates and epidemiological trends reported over time and in different geographical areas.

To date, the prevalence of ADHD among both adolescents and adults is not well delineated in the literature. Adolescents tend to be subsumed under children, though the burden in this age group may well be different and/or incorrectly approximated by current diagnostic methods. It is also unclear whether the diagnostic criteria are appropriate for use with adults. University-aged individuals with ADHD may be worth examining further, as a special group. Other special populations that warrant further interest include diverse cultural groups and/or ethnic minorities, and other vulnerable groups such as immigrants and families of low SES.

To develop an understanding of who is identified and treated for ADHD in community practice, the types of data used most frequently were epidemiologic surveys and administrative claims and prescription databases. The first type of data is limited to relatively smaller numbers of volunteers, although specific research questions about risk and protective factors can be asked.

The administrative claims database is limited in the sense that it represents only services reimbursed whereas the prescription database takes into account only those who use prescription medication. Nevertheless, each provides a depiction of what happens in community practice, identifying enrollee characteristics as well as clinician diagnosis and treatment plans, or in the case of prescription databases, dispensed medication. Similar to epidemiology studies for prevalence, issues of case identification, informant, quality of interventions, and outcome measures limit interpretations of the results. For the purposes of understanding who is receiving what kind of treatment, a significant shortcoming of the current literature is the lack of information on other forms of treatment for ADHD besides the use of psychostimulants or other medications. This renders the task of capturing all aspects of treatment use difficult. In addition to addressing this gap, more attention should be paid to uncovering whether or not certain groups (e.g., those of lower SES, ethnic minorities, children in foster care, or those living in more isolated or rural areas) are being under-recognized and/or undertreated for ADHD.

Some of the potential vulnerable groups appear to be identified and prescribed medication, if not actually treated, to a greater degree than the norm. Overall, the rates of identification and treatment with ADHD medications is high in the United States relative to other areas globally,

and higher in some regions of the United States than others, raising issues about the possibility that some practitioners are identifying too many children and youth, while others may be identifying too few. Evidence suggests that it is not only characteristics of the patients but also characteristics of the providers that influences rates of diagnosis and medication treatment. Patterns suggest that cultural biases exist suggesting that increased information about patient preferences could improve the match between what interventions are offered and what treatments are accepted. As it currently stands, many sufferers may be identified, but a large proportion of those in need do not utilize the treatments offered, even if they can be accessed.

Conclusions and Recommendations for Future Research

Key Question 1. Treatment in Children <6 Years of Age

The evidence available for interventions in preschoolers with Disruptive Behavior Disorders (DBD) is difficult to interpret given the difficulty in diagnosing children this young, since normal maturational processes moderate behavioral responses; however it supports the use of parent behavior training (PBT) as an effective intervention both for oppositional behaviors and for Attention Deficit Hyperactivity Disorder (ADHD) symptoms where measured, with no adverse events reported. The largest barrier to successful completion of the intervention is parent attrition. Preliminary efforts to examine modes of service delivery to accommodate parent preferences suggest such adjustments do not interfere with its effectiveness as long as the program is delivered as designed. For preschoolers, psychostimulant medications are also generally safe and efficacious for improving behavior and can provide benefits in addition to PBT, although essentially nothing is known about possible long-term effects of treatment of preschool children with these or other psychoactive medications. As well, adverse events, especially irritability and moodiness, can lead to discontinuation over extended periods of time, and the use of these medications for several months to a year impacts growth rate to a small degree. The addition of school-based interventions to PBT appears to be more useful for disadvantaged populations, although benefits diminish following discontinuation of the intervention.

Areas for future research:

- Investigations of parent preferences regarding behavior training are needed to determine if parent completion rates for training can be improved.
- Some studies adjusted the PBT to address ADHD specifically, but other interventions also showed improvement in measured ADHD symptoms without adjustment. Evaluation is required regarding the need for specific adjustments to assist children with ADHD.
- Further investigation is required of the role of psychoeducation interventions in the continuum of ADHD care, as this may be a cost-effective intervention option. One study found that a structured parent education program offered the same benefits as combined PBT and school consultation for middle income families.
- The role of teacher consultation or classroom interventions deserves additional evaluation in the context of across-sector research combining health care and education interventions for preschool children at high risk of ADHD.
- The development of methods to investigate long-term outcomes of preschool interventions including appropriate comparison groups is required.
- The optimal circumstances for adding medication in the treatment for preschool children with ADHD, including which subgroups, for how long, and in conjunction with what additional interventions.
- More research on the effects and effectiveness of medication is needed in the younger age groups who are now receiving treatment in increasing numbers.
- This review did not examine alternative interventions such as dietary manipulations, however, the examination of elimination diets, addition of supplements, and awareness of micronutrients for neurological and behavioral functioning in young children is an

important area of potential research that is garnering attention in Europe. The implications for the use of appetite suppressing medications merits serious study

Key Question 2. Long-Term (>1 Year) Outcomes

The long-term effectiveness and safety of several psychostimulants, atomoxetine (ATX) and guanfacine XR (GXR) have been examined prospectively in children and adolescents over the age of 6 years. All of these agents appear efficacious in properly identified populations for the control of core symptoms of ADHD, such as inattention and overactivity for up to 12 months. Fewer individuals discontinue psychostimulants and ATX than GXR due to adverse events. Placebo-controlled discontinuation trials are few, with one in children receiving an amphetamine, and two others after 1 year and again after 2 years of use in children receiving ATX. These trials suggest that some individuals continue to benefit, and others no longer benefit, following 12, 15 or 24 months of continuous treatment with medication. Longer followup of cohorts would be useful, as they offer information about how likely it is that individuals will continue to derive benefit from the ongoing use of medication.

Ongoing examination of adverse events for persons using medications for ADHD throughout the lifespan is certainly still warranted. Evidence now suggests that some children experience mild growth decrements while on psychostimulants for long periods of time. While these are considered of little clinical significance, it is not clear if these changes may represent potential nutritional or developmental concerns that are not yet recognized. Examination of adverse event profiles in the extension of pharmacology studies suggests that while cardiovascular concerns remain rare, use of GXR may require greater monitoring than psychostimulants or ATX. On a broader scale, health administrative data suggest that neither cardiac events among those 20 years of age and younger, nor cerebrovascular accidents in adults are more frequent among those using medications for ADHD than for persons in the general population. Further examination in appropriate data sources is warranted, however, as adult users of psychostimulants or ATX may be at increased risk of transient ischemic attacks.

Evaluation of long-term outcomes following interventions for ADHD is complex due to the multiple patterns of services used. The best data are available through the 8-year followup of the MTA study.[73,74,81,82] By 3 years after initiation, no single intervention group showed superior benefit, likely due to individuals obtaining a complex range of interventions in the community. The majority of children who received an intervention were maintaining improvements in functioning, although they were not improved enough to match nonclinical comparison groups. A small proportion returned to previous levels of poor functioning over time. There was no clear relationship identified between duration of medication use and outcomes. Other cohort studies suggest that long-term use of medication improves grade retention and academic achievement,[85,86] and may lessen onset of Oppositional Defiant Disorder (ODD), Conduct Disorder (CD), as well as substance use, anxiety, and depressive disorders.

Areas for future research:

- Extension studies of pharmacological agents that include placebo-controlled relapse prevention trials are needed, as these offer information about whether or which individuals may gradually discontinue use of medication.
- Direct head-to-head comparison of psychostimulants and ATX or alpha agonists over extended periods of time are not yet available.

- Pharmacy data show that combinations of stimulants and ATX or alpha agonists occur with some regularity. Examination of the relative safety and effectiveness of combined agents requires systematic study in clinical populations.
- Interventions in subgroups not commonly investigated to this point in time are needed, specifically individuals with primarily inattentive subtype of ADHD, girls, teenagers, university students, and adults. Other groups of interest are those with psychiatric comorbidities, and different racial or ethnic groups, or low socioeconomic circumstances.
- Little specific information is available regarding outcomes for those with comorbid learning disabilities, language impairments, reading, mathematics disorders, or other comorbidities.
- The definition of interventions as "psychosocial and/or behavioral" is highly inclusive and based on the intensive intervention used in the MTA study that included PBT, a summer behavior treatment program for the child, and consultation with the school teacher following the summer intervention. The individual aspects of this program require "unpacking" and matching to the subgroups of ADHD and comorbid conditions, as well as sociodemographic groups that the data suggested would most likely benefit. Evaluation of the separate components of the interventions will optimize the match between what the child needs and what intervention he/she receives.
- Understanding the role of academic interventions or combined medication and academic interventions with an emphasis on long-term academic outcomes is important, as maximizing educational success is often an important long-term treatment goal. Examining the impact of educational interventions in subgroups of ADHD children and teens with identified learning disorders is important.
- The use of standardized outcome measures such as global impairment scales or quality of life scales would be useful to compare study outcomes from different cohorts.
- The use of more objective outcomes, such as reduced criminal or court-related events, fewer days of psychiatric hospitalizations or number of hospitalizations, and improved academic performance would be helpful.
- The challenges of lengthy studies are many, and effective studies must include systematic data collection, retention of participants, and identification of appropriate comparison groups.
- Rigorous observational (cohort) research methods, including registries, require further development through efficient data collection (e.g., from Electronic Medical Records enhanced by collection of reliable information of satisfaction, persistence, and proximal and distal outcomes).
- Properly designed case-control studies may be a feasible approach for identifying rarer and/or longer term outcomes.

Key Question 3. Prevalence and Variations in Diagnosis and Treatment

A systematic review and meta-regression placed the worldwide pooled prevalence estimate of ADHD among those 18 years of age or younger at 5.29 percent,[93] with more boys than girls identified and the highest rates of disorder occurring in the 5 to 10 year age group. Primary sources of variability were identified as methodological rather than geographic, and included differences in the requirements for impairment, diagnostic criteria, and sources of information.

Fewer studies are available that document prevalence in adult, adolescent, or preschool age groups, which likely reflects a lack of clarity regarding current diagnostic criteria in these groups. Information about clinical identification and treatment available through administrative and prescription data and health surveys documents that psychostimulant use for ADHD increased throughout the 1980s and early to mid 1990s in the United States. Nonpharmacologic interventions are not documented in these sources. Disparities are noted, with more boys than girls treated, and more Caucasians than Hispanic or African-Americans receiving medication treatment once diagnosed. Rates of identification and treatment also vary geographically. For direct geographic or time period comparisons to be informative, data sources and methods of identifying cases and documenting interventions should be comparable.

In pursuing this question describing rates of clinical identification and of treatment, we identified that no standardized methods are readily available to compare the quality of the research studies with each other. Existing tools designed for other categories of studies (e.g., clinical trials) are not appropriate for evaluating studies using existing administrative data as some of the underlying assumptions behind the research differ. Population-based data were relatively scarce and lacked uniform methods and settings, which interfered with interpretation. The evidence available suggests that underlying prevalence of ADHD varies less than rates of diagnosis and treatment. Patterns of diagnosis and treatment appeared to be associated with such factors as locale, time period, and patient or provider characteristics.

Areas for future research:

- Prevalence data regarding ADHD in subpopulations of adolescents, and adults should be included. In some areas of the world, information about ADHD prevalence among university students is needed. Other special populations to consider are those with developmental disorders, in foster care, or those who have been incarcerated.
- Standardized methods of data collection, case identification and outcomes measurement in epidemiologic surveys and administrative databases is required.
- There is a need for more research on patterns of service use in order to improve our understanding of health system, educational system, health insurance, provider, family and child factors that influence the distribution, access, and receipt of treatment for ADHD.
- Cross-sector coordination of health services, mental health services, and education databases is especially required in the area of ADHD.
- Development of a method for evaluating and comparing the internal validity of studies using administrative data is an important goal that will improve the methods of research in this area.
- More comprehensive ongoing surveillance and population-based surveys will improve the pertinence and quality of available data.

Implications for Clinical Practice and Policy

The three questions addressed in this review target distinctly different aspects of identification and treatment of ADHD. The specific questions about the clinical effectiveness and safety of preschool interventions, extended interventions, and longer-term outcomes across the lifespan, and variations in diagnosis and treatment all inform the broad picture of evolving management practices concerning ADHD. Increasing reliance on medications to treat large numbers of young children, youth, and adults, with a limited body of rigorous evidence as to efficacy or effectiveness, highlights the need for understanding the implications for individual

patients across their lifespan. The United States leads globally in rates of diagnosis and medication treatment of ADHD, which also shapes this discourse. Sociocultural factors, parent and youth beliefs about ADHD, and attitudes about its treatment, as well as individual experiences with the interventions have a strong impact on patterns of treatment adherence in clinical practice.

There is one primary implication from the review of interventions for preschoolers at risk of ADHD: the first line intervention for young children is evidence-based PBT. Other interventions may also be effective, but further research is required before definitive recommendations can be made. Combinations of teacher and child behavioral training and classroom-based programs are promising, in some subgroups more than others. Stimulant medication for ADHD symptoms also plays a role. Awareness of physiologic adverse effects is important, especially as children show decrements in growth when using the medications. Adverse effects of behavior training have not been identified, although lack of parental engagement appears to be the most important barrier to receiving care.

A review of long-term outcomes of interventions primarily identifies the ongoing need for more information that will inform practice. The majority of detailed information reflects clinical trials for pharmacological agents. The large picture remains that receipt of quality interventions confers benefit for many children with ADHD, but that functional impairment continues, albeit to a lesser degree. Psychostimulant medications as a single intervention that is carefully monitored are helpful, primarily for boys ages 7 to 9 at diagnosis of ADHD Combined type (ADHD-C), with or without ODD, who do not have additional comorbid conditions, including learning disorders. This statement leaves out a wide range of other children, teens, and adults with ADHD. Combinations of psychosocial/behavioral interventions with stimulant medications appear to confer benefits for a wider array of children, enhancing acceptance and adherence to treatment, improving parent-child relationships, and potentially decreasing the rate of early adolescent substance use. Some, but not all, studies suggest that following the discontinuation of interventions, a small portion of the children may return to previous levels of functional impairment, eliminating the gains made. Therefore, acknowledging the chronic nature of the condition and the need for ongoing monitoring, resources, and supports of various kinds is important for clinical care.

The broad review of health services information largely reflects information from the United States. The overall picture in the United States is one where diagnoses of ADHD may be offered too frequently, since the rate is higher than the estimates based on epidemiological studies that include both symptoms and impairment. Intertwined with this observation is that ADHD medications are increasingly prescribed, but many individuals discontinue them following a brief trial. Increasing rates of prescription may be due in part to the possibility that children and youth are identified in order to justify a trial of medication, even while there is increasing recognition that populations such as girls, teens and adults not previously identified and treated appears to be an important trend.

It is also important that a better understanding of patients' and families' decisions not to use medication once prescribed be reached. It is possible that other types of interventions should be considered before medication, depending on patient preferences, and pattern of comorbidities. The increasing use of off-label prescriptions for very young children is concerning, especially as PBT is effective for the disruptive behavior which is often the primary impairment when ADHD occurs in preschoolers. However, access to evidence-based PBT programs may be limited in

some regions leading to increased reliance on medications. Certainly, the use of PBT is not identified in the administrative data sources used to examine community care for ADHD.

Over the past two decades, the pharmaceutical industry has responded to the initial evidence that psychostimulants are helpful for children and youth with ADHD and developed improved preparations with sustained effectiveness and improved adverse effect profiles. Many who accept medication have benefited from these agents. However, evidence is slowly accruing that some subgroups require and many patients prefer a range of approaches which are appropriate to the patient's age and level of development, as well as culturally sensitive to the family, including educational and nonpharmacological interventions, often in combination with medications. The evidence for other interventions requires further development before substantive recommendations can be offered.

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Abbreviations

Abbreviation	Definition
%ile	percentile
ADD	Attention Deficit Disorder
ADHD	Attention Deficit Hyperactivity Disorder
ADHD-C	Attention Deficit Hyperactivity Disorder Combined type
ADHD-HI	Attention Deficit Hyperactivity Disorder- Hyperactive Impulsive
ADHD-I	Attention Deficit Hyperactivity Disorder- Inattentive
AE	Adverse Events
AHRQ	Agency for Healthcare Research and Quality
amph	amphetamine
ARCOS	Automation of Reports and Consolidated Orders System
ATX	atomoxetine
B.C.	British Columbia
BELLA	Mental Health Module (German)
BP	Blood Pressure
bpm	Beats per minute
C p/t	Conners parent/teacher
CBCL	Child Behavior Checklist
CBM	Curriculum-based measurement
CC	Community Care
CD	Conduct Disorder
CER	Comparative Effectiveness Review
CGI-IS	Clinical Global Impressions-Impairment scale
CHP-C	Challenging Horizon Program and Consultation
CHQ	child health questionnaire
CI	Confidence interval
cm	centimeter
CP	classroom performance
CT	clinical trial
CVAs	Cerebrovascular Accidents
d/c'd	discontinued
DAWBA	Development and Well-Being Assessment
DBD	Disruptive Behavior Disorder
DEX	dextroamphetamine
diff	difference
DISC-IV	Diagnostic Interview Schedule for Children Version IV
DISC-IV-P	Diagnostic Interview Schedule for Children Version IV – Prevalence
DR	dose related
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders 4th edition
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders 3rd edition - revision
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders 4th edition – text revision
ECBI	Early Child Behavior Inventory
ECG	Electrocardiograph
ED	Emergency Department
EMBASE	Excerpta Medical Database
EPC	Evidence-based Practice Center
ERIC	Education Resources Information Center
f/u	followup
FBB-HKS/ADHS	German ADHD Rating Scale
FDA	Food & Drug Administration
freq	frequency
GP	General Practitioner
GPA	Grade Point Average
GPRD	General Practice Research Database
GRADE	The Grading of Recommendations Assessment, Development and Evaluation

Abbreviation	Definition
GXR	Guanfacine extended release
H.R.	House of Representatives
ICD	International Classification of Diseases
IDAI	Intensive Data-based Academic Intervention
IQ	Intelligence Quotient
IR	immediate release
IYPP	Incredible Years Parenting Program
kg	kilogram
KiGGS	The German Health Interview and Examination Survey for Children and Adolescents
KQ	Key Question
K-SADS-E	Kiddie - Schedule for Affective Disorders and Schizophrenia - Expressive
levo	levoamphetamine
LT	long-term
MAS	Mixed Amphetamine Salts
MAS XR	mixed amphetamine salts extended release
MCI	Multi-component Intervention
MEPS	Medical Expenditure Panel Survey
mg	milligram
mmHg	Millimeters of Mercury
MPH	methylphenidate
MTA	Multimodal Treatment Study of Children with ADHD
NAMCS	National Ambulatory Medical Care Survey
NC	non-compliance
NCHS	National Survey of Child Health
NFPP	New Forest Parenting Program
NHANES	National Health and Nutrition Examination Survey
NHIS	National Health Interview Survey
NIMH	National Institute for Mental Health
NLSCY	National Longitudinal Study of Children and Youth
ODD	Oppositional Defiant Disorder
OLE	Open Label Extension
OROS MPH	Osmotic-controlled Release Oral delivery System methylphenidate
PATS	Preschool ADHD Treatment Study
PCIT	Parent-Child Interaction Therapy
PE	Parent Education
PICOT	population, intervention, comparison, treatment
PSOC	Parent Sense of Competency
PBT	Parent behavior training
Q	Question
QTc	Q T Interval
RCR	retrospective chart review
RCT	Randomized Controlled Trial
RR	Relative Risk
RS IV	Rating Scale version IV
SADS	The Schedule for Affective Disorders and Schizophrenia
SD	Standard Deviations
SDQ	Strengths and Difficulties Questionnaires
SE	Side Effect
SES	Socio-economic status
SET-PC	Supportive Expressive Therapy – Parent Child
SMD	Standardized Mean Difference
SNAP-IV	Swanson, Nolan and Pelham
SRS	Systematic Review Software
stim	stimulant
STP	summer treatment program
t.i.d.	ter in die (three times per day)

Abbreviation	Definition
TDAI	Traditional Data-based Academic Intervention
TEP	Technical Expert Panel
TIAs	Transient Ischemic Attacks
TOO	Task Order Officer
Triple P	Positive Parenting of Preschoolers
U.K.	United Kingdom
U.S.A.	United States of American
VADPRS	Vanderbilt ADHD Diagnostic Parent Rating Scale
VARTRS	Vanderbilt ADHD Teacher Rating Scale
vs	versus
WA	Western Australia
yr	year

Appendix A. Search Strategies

ADHD Treatment Search Strategies

OVID-Medline
May 31 2010
1. "attention deficit and Disruptive Behavior Disorders"/ or attention deficit disorder with hyperactivity/ or Conduct Disorder/
2. minimal brain d?sfunction*.tw,sh.
3. (attention deficit* or adhd).ti.
4. addh.tw.
5. or/1-4
6. Hyperkinesis/
7. Impulsive Behavior/
8. Child Behavior Disorders/
9. aggression/ or agonistic behavior/
10. inattent*.tw.
11. Impulse Control Disorders/
12. (disruptive adj4 disorder?).tw.
13. or/6-12
14. limit 13 to ("newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)")
15. exp *Mental Disorders/
16. (attention deficit* or adhd).tw.
17. hyperactiv*.tw.
18. inattent*.tw.
19. Impulsive Behavior/
20. or/16-19
21. 15 and 20
22. 5 or 21
23. limit 22 to yr = "1997 -Current"
24. 14 or 23
25. Drug Therapy/ae, co, ct, mo [Adverse Effects, Complications, Contraindications, Mortality]
26. (side effect? or adverse or harm?).tw.
27. atomoxetine.tw.
28. guanfacine.tw.
29. Lisdexamfetamine.tw.
30. Vyvanse.tw.
31. exp Central Nervous System Stimulants/ae, ct, po, to [Adverse Effects, Contraindications, Poisoning, Toxicity]
32. ritalin.tw.
33. or/25-32
34. (attention deficit* or adhd).tw.
35. 33 and 34
36. 24 or 35
37. (comment or editorial or letter).pt.

38. 36 not 37
39. review.pt,sh.
40. 38 and 39
41. meta-analysis.pt,ti,ab,sh.
42. (meta anal$ or metaanal$).ti,ab,sh.
43. ((methodol$ or systematic$ or quantitativ$) adj3 (review$ or overview$ or survey$)).ti.
44. ((methodol$ or systematic$ or quantitativ$) adj3 (review$ or overview$ or survey$)).ab.
45. ((pool$ or combined or combining) adj (data or trials or studies or results)).ti,ab.
46. (medline or embase or cochrane).ti,ab.
47. or/44-46
48. review.pt,sh.
49. 47 and 48
50. 41 or 49 or 43 or 42
51. 38 and 50
52. 40 not 51
53. 38 not 52
54. limit 53 to humans
55. limit 54 to english language

OVID-Embase
May 31 2010
1. attention deficit disorder/
2. minimal brain d?sfunction*.tw,sh.
3. (attention deficit* or adhd).ti.
4. addh.tw.
5. or/1-4
6. hyperactivity/
7. disruptive behavior/
8. Conduct Disorder/
9. oppositional defiant disorder/
10. hyperkinesia/
11. aggression/ or aggressiveness/ or anger/ or bullying/ or hostility/
12. impulsiveness/
13. inattention.tw.
14. (disruptive adj4 disorder?).tw.
15. or/6-14
16. limit 15 to (infant or child or preschool child <1 to 6 years>)
17. exp *behavior disorder/
18. hyperactiv*.tw.
19. hyperactivity/
20. inattent*.tw.
21. (attention deficit* or adhd).tw.
22. hyperkine*.tw.
23. hyperkinesia/
24. impulsiveness/
25. or/18-24

26. 17 and 25
27. 5 or 26
28. limit 27 to yr = "1997 -Current"
29. 16 or 28
30. limit 29 to human
31. limit 30 to (book or book series or conference paper or editorial or letter or note)
32. 30 not 31
33. review.pt,sh.
34. 32 and 33
35. meta analysis/
36. meta-analysis.ti,ab.
37. (meta anal$ or metaanal$).ti,ab.
38. ((methodol$ or systematic$ or quantitativ$) adj3 (review$ or overview$ or survey$)).ti.
39. ((methodol$ or systematic$ or quantitativ$) adj3 (review$ or overview$ or survey$)).ab.
40. ((pool$ or combined or combining) adj (data or trials or studies or results)).ti,ab.
41. (medline or embase or cochrane).ti,ab.
42. or/39-41
43. review.pt,sh.
44. 42 and 43
45. or/35-38
46. 45 or 44
47. 32 and 46
48. 34 not 47
49. 32 not 48
50. limit 49 to english language

OVID-PsycINFO
May 31 2010
1. attention deficit disorder/ or attention deficit disorder with hyperactivity/
2. minimal brain d?sfunction*.tw,sh.
3. (attention deficit* or adhd).ti.
4. addh.tw.
5. or/1-4
6. Conduct Disorder/
7. aggressive behavior/
8. impulsiveness/
9. exp impulse control disorders/
10. oppositional defiant disorder/
11. distractability/
12. attention span/
13. hyperkinesis/
14. inattent*.tw.
15. (disruptive adj4 disorder?).tw.
16. or/6-15
17. limit 16 to childhood
18. exp *behavior problems/ or *behavior disorders/

19. (attention deficit* or adhd).tw.
20. 18 and 19
21. exp "side effects (treatment)"/
22. (side effect? or adverse or harm?).tw.
23. or/21-22
24. 19 and 23
25. 5 or 20
26. limit 25 to yr = "1997 -Current"
27. 17 or 24 or 26
28. limit 27 to human
29. limit 28 to english language
30. limit 29 to (chapter or "column/opinion" or "comment/reply" or editorial or letter or review-book)
31. 29 not 30

OVID-Cochrane Central
May 31, 2010
1 "attention deficit and Disruptive Behavior Disorders"/ or attention deficit disorder with hyperactivity/ or Conduct Disorder/
2 minimal brain d?sfunction*.tw,sh.
3 (attention deficit* or adhd).ti.
4 addh.tw.
5 or/1-4
6 Hyperkinesis/
7 Impulsive Behavior/
8 Child Behavior Disorders/
9 aggression/ or agonistic behavior/
10 inattent*.tw.
11 Impulse Control Disorders/
12 (disruptive adj4 disorder?).tw.
13 or/6-12
14 limit 13 to ("newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)") [Limit not valid; records were retained]
15 exp *Mental Disorders/
16 (attention deficit* or adhd).tw.
17 hyperactiv*.tw.
18 inattent*.tw.
19 Impulsive Behavior/
20 or/16-19
21 15 and 20
22 5 or 21 (1799)
23 limit 22 to yr = "1997 -Current"
24 14 or 23
25 Drug Therapy/ae, co, ct, mo [Adverse Effects, Complications, Contraindications, Mortality]
26 (side effect? or adverse or harm?).tw.
27 atomoxetine.tw.

28 guanfacine.tw.
29 Lisdexamfetamine.tw.
30 Vyvanse.tw.
31 exp Central Nervous System Stimulants/ae, ct, po, to [Adverse Effects, Contraindications, Poisoning, Toxicity]
32 ritalin.tw.
33 or/25-32
34 (attention deficit* or adhd).tw.
35 33 and 34
36 24 or 35

ERIC ADHD Search – May 31, 2009

((**Thesaurus Descriptors**:*"Attention Deficit Disorders"*) or (**Thesaurus Descriptors**:*"Attention Deficit Hyperactivity Disorder"*) or (**Thesaurus Descriptors**:*"Hyperactivity"*) or (**Keywords**:*"attention deficit"*) or (**Keywords**:*ADHD*) or (**Keywords**:*inattention*) and (**Thesaurus Descriptors**:*"Self Control"*)) and (**Publication Type**:"Journal Articles" OR **Publication Type**:"ERIC Publications" OR **Publication Type**:"Information Analyses" OR **Publication Type**:"Numerical Quantitative Data" OR **Publication Type**:"Reference Materials General" OR **Publication Type**:"Reports Evaluative" OR **Publication Type**:"Reports General" OR **Publication Type**:"Reports Research" OR **Publication Type**:"Translations")

ADHD Prevalence Search Strategies

OVID-Medline
March 25 2010
1. ((prescription or administrative or insurance or claims) adj3 (data or database? or claims)).tw.
2. "Databases, Factual"/
3. *Physician's Practice Patterns/
4. Physician's Practice Patterns/sn, td [Statistics & Numerical Data, Trends]
5. insurance claim reporting/ or "insurance claim review"/
6. Epidemiology/
7. Drug Utilization/sn, td [Statistics & Numerical Data, Trends]
8. off-label.tw.
9. "Off-Label Use"/st, sn [Standards, Statistics & Numerical Data]
10. *"Pharmacoepidemiology"/
11. Pharmacoepidemiology/st, sn, td [Standards, Statistics & Numerical Data, Trends]
12. "Drug Utilization Review"/
13. utilization.tw.
14. health surveys/ or population surveillance/ or health care surveys/
15. (trend? or pattern? or rate? or prevalence).ti.
16. ((national or regional or prescribing or prescripton or diagnos*) adj3 (trend? or rate? or pattern? or variation? or prevalence)).tw.
17. Drug Prescriptions/sn, td [Statistics & Numerical Data, Trends]
18. or/1-17
19. *Methylphenidate/tu [Therapeutic Use]
20. exp *Amphetamines/tu [Therapeutic Use]

21. exp *Central Nervous System Stimulants/tu [Therapeutic Use]
22. exp *Psychotropic Drugs/tu [Therapeutic Use]
23. *Attention Deficit Disorder with Hyperactivity/ep [Epidemiology]
24. exp *Antipsychotic Agents/tu [Therapeutic Use]
25. off-label.tw.
26. "Off-Label Use"/
27. *"Pharmacoepidemiology"/
28. Pharmacoepidemiology/st, sn, td [Standards, Statistics & Numerical Data, Trends]
29. *Drug Utilization/sn, td [Statistics & Numerical Data, Trends]
30. "Drug Utilization Review"/
31. or/19-30
32. limit 31 to ("all infant (birth to 23 months)" or "preschool child (2 to 5 years)")
33. "attention deficit and Disruptive Behavior Disorders"/ or attention deficit disorder with hyperactivity/ or Conduct Disorder/
34. minimal brain d?sfunction*.tw,sh.
35. (attention deficit* or adhd).ti.
36. addh.tw.
37. or/33-36
38. Hyperkinesis/
39. Impulsive Behavior/
40. Child Behavior Disorders/
41. aggression/ or agonistic behavior/
42. inattent*.tw.
43. Impulse Control Disorders/
44. (disruptive adj4 disorder?).tw.
45. or/38-44
46. limit 45 to ("newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)")
47. 37 or 46
48. 18 and 47
49. 32 or 48
50. exp *Attention Deficit Disorder with Hyperactivity/di, ep [Diagnosis, Epidemiology]
51. 49 or 50
52. limit 51 to english language
53. limit 52 to yr = "1980 -Current"
54. limit 53 to (comment or congresses or editorial or letter or news)
55. 53 not 54

OVID-Embase
March 25 2010
1. *clinical practice/
2. ((prescription or administrative or insurance or claims) adj3 (data or database? or claims)).tw.
3. factual database/
4. health insurance/
5. pharmacoepidemiology/
6. exp *epidemiology/

7. *"drug use"/ or *drug preference/ or *"off label drug use"/ or *prescription/
8. off-label.tw.
9. health survey/
10. (trend? or pattern? or rate? or prevalence).ti.
11. ((national or regional or prescribing or prescripton or diagnos*) adj3 (trend? or rate? or pattern? or variation? or prevalence)).tw.
12. utilization.tw.
13. "billing and claims"/
14. *geographic distribution/
15. *drug utilization/
16. "utilization review"/
17. trend study/
18. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. *methylphenidate/
20. methylphenidate/dt
21. exp *central nervous system agents/dt [Drug Therapy]
22. *attention deficit disorder/ep [Epidemiology]
23. *"drug use"/ or *drug preference/ or "off label drug use"/ or *prescription/
24. pharmacoepidemiology/
25. "utilization review"/
26. trend study/
27. or/19-26
28. limit 27 to preschool child <1 to 6 years>
29. attention deficit disorder/
30. minimal brain d?sfunction*.tw,sh.
31. (attention deficit* or adhd).ti.
32. addh.tw.
33. or/29-32
34. hyperactivity/
35. disruptive behavior/
36. Conduct Disorder/
37. oppositional defiant disorder/
38. hyperkinesia/
39. aggression/ or aggressiveness/ or anger/ or bullying/ or hostility/
40. impulsiveness/
41. inattention.tw.
42. (disruptive adj4 disorder?).tw.
43. or/34-42
44. limit 43 to (infant or child or preschool child <1 to 6 years>)
45. 33 or 44
46. 18 and 45
47. 28 or 46
48. *attention deficit disorder/ep, pe
49. 47 or 48
50. limit 49 to (human and english language)
51. limit 50 to yr = "1980 -Current"

52. limit 51 to (book or book series or conference paper or editorial or letter or note or proceeding)
53. 51 not 52

OVID-PsycINFO
March 26 2010
1. *clinical practice/
2. ((prescription or administrative or insurance or claims) adj3 (data or database? or claims)).tw.
3. exp databases/
4. exp health insurance/
5. epidemiology/
6. "prescribing (drugs)"/
7. *drug therapy/
8. *drug usage/
9. off-label.tw.
10. exp questionnaires/ or exp surveys/
11. ((national or regional or prescribing or prescripton or diagnos*) adj3 (trend? or rate? or pattern? or variation? or prevalence)).tw.
12. utilization.tw.
13. utilization reviews/
14. *human sex differences/
15. *age differences/
16. *demographic characteristics/
17. (trend? or pattern? or rate? or prevalence).ti.
18. *health care utilization/
19. or/1-18
20. psychotropic.tw.
21. *methylphenidate/
22. exp *cns stimulating drugs/
23. exp *neuroleptic drugs/
24. "prescribing (drugs)"/
25. *drug therapy/
26. *drug usage/
27. off-label.tw.
28. or/20-27
29. limit 28 to (140 infancy or 160 preschool age)
30. attention deficit disorder/ or attention deficit disorder with hyperactivity/
31. minimal brain d?sfunction*.tw,sh.
32. (attention deficit* or adhd).ti.
33. addh.tw.
34. or/30-33
35. Conduct Disorder/
36. aggressive behavior/
37. impulsiveness/
38. exp impulse control disorders/
39. oppositional defiant disorder/

40. distractability/
41. attention span/
42. hyperkinesis/
43. inattent*.tw.
44. (disruptive adj4 disorder?).tw.
45. or/35-44
46. limit 45 to (140 infancy or 160 preschool age)
47. 34 or 46
48. 19 and 47
49. 29 or 48
50. limit 49 to english language
51. limit 50 to human
52. limit 51 to yr = "1980 -Current"
53. limit 52 to ("0200 book" or "0240 authored book" or "0280 edited book" or "0300 encyclopedia" or "0400 dissertation abstract" or (chapter or "column/opinion" or "comment/reply" or dissertation or editorial or encyclopedia entry or letter or obituary or review-book or review-software & other))
54. 52 not 53

Appendix B. Forms

Level 1 Title and Abstract Screening Form

1. Should this report be excluded for any of the following reasons?

□ Not English
□ Not a full report of a study (meeting abstract, review, opinion, or guideline, etc.)
□ Published before 1997
□ None of the above

2. Does this report describe outcomes (positive or negative) for any <u>treatment</u> for ADHD, Disruptive Behavior Disorder (DBD), or Oppositional Defiant Disorder (ODD), Conduct Disorder (CD), or for those at risk for ADHD?

□ Yes
□ Cannot tell
□ No

3. Does this report present results for children <6 years of age, <u>OR</u> for those of any age when the combination of treatment and followup is at least 12 months?

□ Yes
□ Cannot tell
□ No

ADHD Level 1 Screening Guide

Question 1.
This question is to remove papers for reasons of the publication characteristics rather than the study characteristics. Only one choice is possible, so please go in order of the answers.

Not English: If the abstract is not English, or if there is another language listed at the end of the title in square brackets, check not English. If the journal name seems to be a foreign language, do not check Not English, because some of those are published in English.

Not a full report: If this is a letter to the editor, a proceeding from a meeting, or if in some other way, you know that it is not a full report of a study, check Not a full report.

Published before 1997: Check the year in the Citation line at the top of the page. If there is no year given (or it is really strange, such as pre 1960), do not check this line.

Question 2.
This question is to remove citations that are examining only a population that is not included in our review. We initially were looking for just those with ADHD, but have expanded that to include those who have symptoms of ADHD or who were treated for ADHD. Please be inclusive here by answering Cannot tell if you are unsure.

The report must describe outcomes for the treatment. This means that changes due to the treatment should be measured in some way, or differences between one treatment and another should have the results presented.

Question 3.
We are not studying all ADHD populations, only those less than 6 years of age and those of any age if they were treated and followed for a year or more. This will be difficult to tell from the abstract, but if enough information is there, answer Yes or No. If there is no mention of age, or length of followup, answer Cannot tell. If it is a paper that examines the adult outcomes of childhood treatment, answer Yes.

Level 2 Title and Abstract Screening Form

1. What is the study design described in this report?

□ RCT or CCT
□ Case-control
□ Cohort/longitude
□ Cross-sectional
□ Before-after [[STOP NOW]]
□ Review/meta-analysis [[STOP NOW]]
□ Case report [[STOP NOW]]
□ Other [[STOP NOW]]
□ Cannot tell

2. What is the diagnosis of the treatment population?
□ ADHD or ADD
□ Disruptive Behavior Disorder (including Oppositional Defiant Disorder – ODD, and Conduct Disorder- CD)
□ Aggressiveness, hyperactivity, inattentiveness, impulsivity
□ At risk for ADHD
□ Cannot tell
□ Other related
□ None of the above [[STOP NOW]]

3. What comparisons between included populations have outcomes reported in this study? Included populations are: Attention Deficit Hyperactivity Disorder (ADHD), Attention Deficit Disorder (ADD), Disruptive Behavior Disorder (DBD), Oppositional Defiant Disorder (ODD), Conduct Disorder (CD), at risk for ADHD (aggressive, hyperactive, inattentive, impulsive).

□ Two or more different treatments or two or more different timing or dose of same treatment
□ One part treated and one part given placebo
□ On part treated and one part no treatment
□ Other for included population
□ None of the above included population
□ Cannot tell

Level 3 Full Text Screening Form

1. What is the population for which treatment outcomes are reported?
□ ADHD by DSM or ICD diagnoses
□ Disruptive Behavior Syndrome (included ODD and CD)
□ At risk for ADHD- aggressive, inattentive, hyperactive, temper tantrums, etc
□ Two or more of the above conditions
□ Cannot tell
□ None of the above

2. What treatment or intervention is applied to population described in Question 1?
□ Drug/pharmacological
□ Psychosocial or Behavioral
□ Parent behavior training
□ School or group based intervention
□ Combination or two or more of above treatments
□ Unsure
□ None of the Above

3. Were outcomes reported for two or more treatment groups (any treatment, placebo, control, waitlist, etc.) of the included population?
"Treatment" can be drug, psychosocial, behavioral, or a combination.
"Outcomes" can be for a treatment compared to:
i) another dose or different timing or the same treatment?
ii) another treatment?
iii) another type of treatment?
iv) placebo treatment?
v) no treatment?
vi) wait list?

□ Yes
□ No
□ Unsure

4. Are Treatment results reported for:
□ Children less than 6 years of age, separately from any subjects greater than or equal to 12 months
□ A population of any age where the diagnosis of ADHD was by ICD or DSM criteria, AND the combination of treatment and followup was greater than or equal to 12 months?
□ Both of above
□ None of the above

Full Text Sorting Level

1. New exclusion status of paper.
□ Include
□ Include, but not useful
□ Exclude for population, >5y without ADHD dx or <6y without included behavior disorder dx
□ Exclude for intervention, no treatment or no comparison of treatments on at least two included population groups
□ Exclude for outcomes, age is >5y and treatment + followup is less than 12 months
□ Exclude other –specify _____

2. Does this paper compare outcomes for children <6 years with an included diagnosis, treated at least two different ways?
□ Yes
□ No

3. Does this paper compare outcomes for subjects >5 years, diagnosed with ADHD, or <6 years with an included diagnosis treated at least two different ways with treatment + followup of 12 months or longer?
□ Yes
□ No

Quality Assessment Tool for Quantitative Studies

COMPONENT RATINGS

A) SELECTION BIAS

(Q1) Are the individuals selected to participate in the study likely to be representative of the target population?

1 Very likely
2 Somewhat likely
3 Not likely
4 Can't tell

(Q2) What percentage of selected individuals agreed to participate?

1 80 - 100% agreement
2 60 – 79% agreement
3 less than 60% agreement
4 Not applicable
5 Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

B) STUDY DESIGN

Indicate the study design

1 Randomized controlled trial
2 Controlled clinical trial
3 Cohort analytic (two groups pre + post (before and after))
4 Case-control
5 Cohort (one group pre + post (before and after))
6 Interrupted time series
7 Other specify _____
8 Can't tell

Was the study described as randomized? If NO, go to Component C.
No Yes

If Yes, was the method of randomization described? (See dictionary)
No Yes

If Yes, was the method appropriate? (See dictionary)
No Yes

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

C) CONFOUNDERS
(Q1) Were there important differences between groups prior to the intervention?

1 Yes
2 No
3 Can't tell

The following are examples of confounders:
1 Race
2 Sex
3 Marital status/family
4 Age
5 SES (income or class)
6 Education
7 Health status
8 Pre-intervention score on outcome measure

(Q2) If yes, indicate the percentage of relevant confounders that were controlled (either in the design (e.g., stratification, matching) or analysis)?

1 80 – 100% (most)
2 60 – 79% (some)
3 Less than 60% (few or none)
4 Can't Tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

D) BLINDING
(Q1) Was (were) the outcome assessor(s) aware of the intervention or exposure status of participants?

1 Yes
2 No
3 Can't tell

(Q2) Were the study participants aware of the research question?

1 Yes
2 No
3 Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

E) DATA COLLECTION METHODS
(Q1) Were data collection tools shown to be valid?

1 Yes
2 No
3 Can't tell

(Q2) Were data collection tools shown to be reliable?

1 Yes
2 No
3 Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

F) WITHDRAWALS AND DROP-OUTS
(Q1) Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group?

1 Yes
2 No
3 Can't tell
4 Not Applicable (i.e., one-time surveys or interviews)

(Q2) Indicate the percentage of participants completing the study. (If the percentage differs by groups, record the lowest).

1 80 -100%
2 60 - 79%
3 Less than 60%
4 Can't tell
5 Not Applicable (i.e., Retrospective case-control)

RATE THIS SECTION	STRONG	MODERATE	WEAK	
See dictionary	1	2	3	Not Applicable

G) INTERVENTION INTEGRITY

(Q1) What percentage of participants received the allocated intervention or exposure of interest?

1 80 -100%
2 60 - 79%
3 Less than 60%
4 Can't tell

(Q2) Was the consistency of the intervention measured?

1 Yes
2 No
3 Can't tell

(Q3) Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?

4 Yes
5 No
6 Can't tell

H) ANALYSES

(Q1) Indicate the unit of allocation (circle one)
community organization/institution practice/office individual
(Q2) Indicate the unit of analysis (circle one)
community organization/institution practice/office individual
(Q3) Are the statistical methods appropriate for the study design?

1 Yes
2 No
3 Can't tell

(Q4) Is the analysis performed by intervention allocation status (i.e., intention to treat) rather than the actual intervention received?

1 Yes
2 No
3 Can't tell

GLOBAL RATING

COMPONENT RATINGS

Please transcribe the information from the gray boxes on pages 1-4 onto this page. See dictionary on how to rate this section.

A	**SELECTION BIAS**	**STRONG**	**MODERATE**	**WEAK**
		1	2	3
B	**STUDY DESIGN**	**STRONG**	**MODERATE**	**WEAK**
		1	2	3
C	**CONFOUNDERS**	**STRONG**	**MODERATE**	**WEAK**
		1	2	3
D	**BLINDING**	**STRONG**	**MODERATE**	**WEAK**
		1	2	3
E	**DATA COLLECTION METHOD**	**STRONG**	**MODERATE**	**WEAK**
		1	2	3
F	**WITHDRAWALS AND DROPOUTS**	**STRONG**	**MODERATE**	**WEAK**
		1	2	3

Quality Assessment Tool for Quantitative Studies Dictionary

The purpose of this dictionary is to describe items in the tool thereby assisting raters to score study quality. Due to under-reporting or lack of clarity in the primary study, raters will need to make judgments about the extent that bias may be present. When making judgments about each component, raters should form their opinion based upon information contained in the study rather than making inferences about what the authors intended. Mixed methods studies can be quality assessed using this tool with the quantitative component of the study.

A) Selection Bias

(Q1) Participants are more likely to be representative of the target population if they are randomly selected from a comprehensive list of individuals in the target population (score very likely). They may not be representative if they are referred from a source (e.g., clinic) in a systematic manner (score somewhat likely) or self-referred (score not likely).
(Q2) Refers to the % of subjects in the control and intervention groups that agreed to participate in the study before they were assigned to intervention or control groups.

B) Study Design

In this section, raters assess the likelihood of bias due to the allocation process in an experimental study. For observational studies, raters assess the extent that assessments of exposure and outcome are likely to be independent. Generally, the type of design is a good indicator of the extent of bias. In stronger designs, an equivalent control group is present and the allocation process is such that the investigators are unable to predict the sequence.

Randomized Controlled Trial (RCT)
An experimental design where investigators randomly allocate eligible people to an intervention or control group. A rater should describe a study as an RCT if the randomization sequence allows each study participant to have the same chance of receiving each intervention and the investigators could not predict which intervention was next. If the investigators do not describe the allocation process and only use the words ‘random’ or ‘randomly,’ the study is described as a controlled clinical trial.
See below for more details.

Was the study described as randomized?
Score **YES**, if the authors used words such as random allocation, randomly assigned, and random assignment.
Score **NO**, if no mention of randomization is made.

Was the method of randomization described?
Score **YES**, if the authors describe any method used to generate a random allocation sequence.

Score **NO**, if the authors do not describe the allocation method or describe methods of allocation such as alternation, case record numbers, dates of birth, day of the week, and any allocation procedure that is entirely transparent before assignment, such as an open list of random numbers of assignments.
If **NO** is scored, then the study is a controlled clinical trial.

Was the method appropriate?
Score **YES**, if the randomization sequence allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which intervention was next. Examples of appropriate approaches include assignment of subjects by a central office unaware of subject characteristics, or sequentially numbered, sealed, opaque envelopes.
Score **NO**, if the randomization sequence is open to the individuals responsible for recruiting and allocating participants or providing the intervention, since those individuals can influence the allocation process, either knowingly or unknowingly.
If **NO** is scored, then the study is a controlled clinical trial.

Controlled Clinical Trial (CCT)
An experimental study design where the method of allocating study subjects to intervention or control groups is open to individuals responsible for recruiting subjects or providing the intervention. The method of allocation is transparent before assignment, e.g., an open list of random numbers or allocation by date of birth, etc.).

Cohort analytic (two groups pre and post (before and after))
An observational study design where groups are assembled according to whether or not exposure to the intervention has occurred. Exposure to the intervention is not under the control of the investigators. Study groups might be nonequivalent or not comparable on some feature that affects outcome.

Case control study
A retrospective study design where the investigators gather ‘cases’ of people who already have the outcome of interest and ‘controls’ who do not. Both groups are then questioned or their records examined about whether they received the intervention exposure of interest.

Cohort (one group pre and post (before and after))
The same group is pretested, given an intervention, and tested immediately after the intervention. The intervention group, by means of the pretest, acts as its own control group.

Interrupted time series
A time series consists of multiple observations over time. Observations can be on the same units (e.g., individuals over time) or on different but similar units (e.g., student achievement scores for particular grade and school). Interrupted time series analysis requires knowing the specific point in the series when an intervention occurred.

Other
One time surveys or interviews

C) CONFOUNDERS

By definition, a confounder is a variable that is associated with the intervention or exposure and causally related to the outcome of interest. Even in a robust study design, groups may not be balanced with respect to important variables prior to the intervention. The authors should indicate if confounders were controlled in the design (by stratification or matching) or in the analysis. If the allocation to intervention and control groups is randomized, the authors must report that the groups were balanced at baseline with respect to confounders (either in the text or a table).

D) BLINDING

(Q1) Assessors should be described as blinded to which participants were in the control and intervention groups. The purpose of blinding the outcome assessors (who might also be the care providers) is to protect against detection bias.

(Q2) Study participants should not be aware of (i.e., blinded to) the research question. The purpose of blinding the participants is to protect against reporting bias.

E) DATA COLLECTION METHODS

Tools for primary outcome measures must be described as reliable and valid. If 'face' validity or 'content' validity has been demonstrated, this is acceptable. Some sources from which data may be collected are described below:

Self reported data includes data that is collected from participants in the study (e.g., completing a questionnaire, survey, answering questions during an interview, etc.).

Assessment/Screening includes objective data that is retrieved by the researchers. (e.g., observations by investigators).

Medical Records/Vital Statistics refers to the types of formal records used for the extraction of the data.

Reliability and validity can be reported in the study or in a separate study. For example, some standard assessment tools have known reliability and validity.

F) WITHDRAWALS AND DROP-OUTS

Score **YES** if the authors describe BOTH the numbers and reasons for withdrawals and drop-outs.

Score **NO** if either the numbers or reasons for withdrawals and drop-outs are not reported.

Score **NOT APPLICABLE** if the study was a one-time interview or survey where there was not followup data reported.

The percentage of participants completing the study refers to the % of subjects remaining in the study at the final data collection period in all groups (i.e., control and intervention groups).

G) INTERVENTION INTEGRITY

The number of participants receiving the intended intervention should be noted (consider both frequency and intensity). For example, the authors may have reported that at least 80 percent of the participants received the complete intervention. The authors should describe a method of measuring if the intervention was provided to all participants the same way. As well, the authors should indicate if subjects received an unintended intervention that may have influenced the outcomes. For example, co-intervention occurs when the study group receives an additional intervention (other than that intended). In this case, it is possible that the effect of the intervention may be over-estimated. Contamination refers to situations where the control group accidentally receives the study intervention. This could result in an underestimation of the impact of the intervention.

H) ANALYSIS APPROPRIATE TO QUESTION

Was the quantitative analysis appropriate to the research question being asked?

An intention-to-treat analysis is one in which all the participants in a trial are analyzed according to the intervention to which they were allocated, whether they received it or not. Intention-to-treat analyses are favored in assessments of effectiveness, as they mirror the noncompliance and treatment changes that are likely to occur when the intervention is used in practice, and because of the risk of attrition bias when participants are excluded from the analysis.

Component Ratings of Study:

For each of the six components A – F, use the following descriptions as a roadmap.

A) SELECTION BIAS

Strong: The selected individuals are very likely to be representative of the target population (Q1 is 1); **and** there is greater than 80% participation (Q2 is 1).

Moderate: The selected individuals are at least somewhat likely to be representative of the target population (Q1 is 1 or 2); **and** there is 60 - 79% participation (Q2 is 2). 'Moderate' may also be assigned if Q1 is 1 or 2 and Q2 is 5 (can't tell).

Weak: The selected individuals are not likely to be representative of the target population (Q1 is 3); **or** there is less than 60% participation (Q2 is 3); **or** selection is not described (Q1 is 4); **and** the level of participation is not described (Q2 is 5).

B) DESIGN

Strong: will be assigned to those articles that described RCTs and CCTs.

Moderate: will be assigned to those that described a cohort analytic study, a case control study, a cohort design, or an interrupted time series.

Weak: will be assigned to those that used any other method or did not state the method used.

C) CONFOUNDERS

Strong: will be assigned to those articles that controlled for at least 80% of relevant confounders (Q1 is 2); **or** (Q2 is 1).

Moderate: will be given to those studies that controlled for 60 – 79% of relevant confounders (Q1 is 1); **and** (Q2 is 2).

Weak: will be assigned when less than 60% of relevant confounders were controlled (Q1 is 1); **and** (Q2 is 3); **or** control of confounders was not described (Q1 is 3); **and** (Q2 is 4).

D) BLINDING

Strong: The outcome assessor is not aware of the intervention status of participants (Q1 is 2); **and** the study participants are not aware of the research question (Q2 is 2).

Moderate: The outcome assessor is not aware of the intervention status of participants (Q1 is 2); **or** the study participants are not aware of the research question (Q2 is 2).

Weak: The outcome assessor is aware of the intervention status of participants (Q1 is 1); **and** the study participants are aware of the research question (Q2 is 1); **or** blinding is not described (Q1 is 3 and Q2 is 3).

E) DATA COLLECTION METHODS

Strong: The data collection tools have been shown to be valid (Q1 is 1); **and** the data collection tools have been shown to be reliable (Q2 is 1).

Moderate: The data collection tools have been shown to be valid (Q1 is 1); **and** the data collection tools have not been shown to be reliable (Q2 is 2); **or** reliability is not described (Q2 is 3).

Weak: The data collection tools have not been shown to be valid (Q1 is 2); **or** both reliability and validity are not described (Q1 is 3 and Q2 is 3).

F) WITHDRAWALS AND DROP-OUTS

Strong: will be assigned when the followup rate is 80% or greater (Q1 is 1 and Q2 is 1).

Moderate: will be assigned when the followup rate is 60 – 79% (Q2 is 2); **or** Q1 is 4 or Q2 is 5.

Weak: will be assigned when a followup rate is less than 60% (Q2 is 3); **or** if the withdrawals and drop-outs were not described (Q1 is No or Q2 is 4).

Not Applicable: if Q1 is 4 or Q2 is 5.

KQ3. ADHD Prevalence. Level 1 Title and Abstract Screening Form

1. Mark if any of the reasons below should exclude this report.

Not English
Not a review or full report of a study (it is a meeting abstract or opinion or guideline etc)
Published before 1985
None of the above

2. Does this report describe and compare the prevalence of the diagnosis or treatment of signs of ADHD, or Disruptive Behavior Disorder, Oppositional Defiant Disorder (ODD), Conduct Disorder (CD), or for those at risk for ADHD across any factor (e.g., socioeconomic status, gender, age)?

Yes
Maybe/Cannot tell/Unsure
No
No, but mark for other reason.

KQ3. ADHD Prevalence. Level 2 Diagnostic or Treatment Prevalence?

1. Prevalence presented in report:

ADHD diagnosis made
ADHD treatment given
Neither of the above

2. Possible comparison analyzed:

Age
Sex
Geography
Provider type
Socioeconomic
Family status
Medicare beneficiary/health insurance status
Race
Other
None

KQ3. ADHD Prevalence. Level 3 Full Text

1. Prevalence presented in report:
(Paper must report the number/percentage/statistic for one group diagnosed or treated vs another group diagnosed or treated. We are not looking for treatment effectiveness)

ADHD diagnosis made
ADHD treatment given
Neither of the above

2. Comparison analyzed:

(Treatment comparison can be derived from a large database such as the Medicare database in the United States)

Age
Sex
Geography
Provider type
Socioeconomic
Family status
Medicare beneficiary/health insurance status

Race
Other
None

KQ3. ADHD Prevalence. Level 4 Citations Used in Report

1. Is this paper cited in the ADHD report?

YES
NO

2. This paper refers to data primarily from:

United States (incl Hawaii and Alaska)
Canada
Mexico and Central America
South America
U.K.
Western Europe
Eastern Europe (Russia, Byeloruss, etc)
Middle East
Africa
South Asia (India, Pakistan, etc.)
Asia (China, Japan, Thailand, etc.)
Australia/New Zealand
INTERNATIONAL SURVEYS (WHO, UN, etc)
other supporting papers (RefID recorded here, cited in KQ3 but not derived through systematic review methodology)

Template Used To Determine Strength of Evidence

Number of Studies (Subjects)	Domains Pertaining to Strength of Evidence				Magnitude of Effect and Strength of Evidence (SOE)	
	Risk of Bias; Design/Quality	Consistency	Directness	Precision	Absolute Risk Difference per 100 Patients	Harms

Appendix C. Excluded Studies

Evaluation of the first 3 years of the Fast Track prevention trial with children at high risk for adolescent conduct problems. J Abnorm Child Psychol 2002;30(1):19-35. PMID:11930969
Exclude: No included comparisons of outcomes, OVID-Medline.

Alternative treatments for attention deficit hyperactivity disorder. Paediatr Child Health 2003;(4):243-6. PMID:2003242414
Exclude: Not an included population, OVID-EMBASE.

The effects of the Fast Track Program on serious problem outcomes at the end of elementary school. J Clin Child Adolesc Psychol 2004;33(4):650-61.
Exclude: Not an included population, OVID-PsycINFO.

Aarskog D, Fevang FO, Klove H, et al. The effect of the stimulant drugs, dextroamphetamine and methylphenidate, on secretion of growth hormone in hyperactive children. J Pediatr 1977;90(1):136-9.
Exclude: No included comparisons of outcomes,

Abikoff H, Gittelman R. Does behavior therapy normalize the classroom behavior of hyperactive children? Arch Gen Psychiatry 1984;(5):449-54. PMID:1984116616
Exclude: No included comparisons of outcomes, OVID-EMBASE.

Abikoff H, Gittelman R. The normalizing effects of methylphenidate on the classroom behavior of ADDH children. J Abnorm Child Psychol 1985;(1):33-44. PMID:1985072736
Exclude: No included comparisons of outcomes, OVID-EMBASE.

Abramson PR, Abramson SD. A fractorial study of a multidimensional approach to aggressive behavior in black preschool age children. J Genet Psychol 1974;125(1st Half):31-6. PMID:4457611
Exclude: Not an included population, OVID-Medline.

Ackerman PT, Dykman RA, Holcomb PJ, et al. Methylphenidate effects on cognitive style and reaction time in four groups of children. Psychiatry Res 1982;7(2):199-213.
Exclude: No included comparisons of outcomes,

Ackerman PT, Dykman RA, Holcomb PJ, et al. Effects of high and low dosages of methylphenidate in children with strong and sensitive nervous systems. Pavlovian J Biol Sci 1983;(1):36-48. PMID:1983145425
Exclude: No included comparisons of outcomes, OVID-EMBASE.

Ackerman PT, Holcomb PJ, Dykman RA. Effects of reward and methylphenidate on heart rate response morphology of augmenting and reducing children. Int J Psychophysiol 1984;1(4):301-16.
Exclude: No included comparisons of outcomes,

Ad-Dab'bagh Y, Greenfield B, Milne-Smith J, et al. Inpatient treatment of severe disruptive behavior disorders with risperidone and milieu therapy. Can J Psychiatr 2000;45(4):376-82. PMID:10813072
Exclude: No included comparisons of outcomes, OVID-Medline.

Adams D, Allen D. Assessing the need for reactive behavior management strategies in children with intellectual disability and severe challenging behavior. J Intell Disabil Res 2001;(4):335-43. PMID:2001282054
Exclude: No included intervention compared, OVID-EMBASE.

Adler L, Dietrich A, Reimherr FW, et al. Safety and tolerability of once versus twice daily atomoxetine in adults with ADHD. Ann Clin Psychiatry 2006;18(2):107-13. PMID:16754416
Exclude: No included comparisons of outcomes, OVID-Medline.

Adler L, Wilens T, Zhang S, et al. Retrospective safety analysis of atomoxetine in adult ADHD patients with or without comorbid alcohol abuse and dependence. Am J Addict 2009;18(5):393-401. PMID:19874159
Exclude: No included comparisons of outcomes, OVID-Medline.

Agarwala S. Behavior modification in nursery school children. Dayalbagh Educ Inst Res J Educ 1985;3(1):30-3.
Exclude: Not able to retrieve full report, OVID-PsycINFO.

Ahmann PA, Waltonen SJ, Olson KA, et al. Placebo-controlled evaluation of Ritalin side effects. Pediatrics 1993;91(6):1101-6. PMID:8502509
Exclude: No included comparisons of outcomes, OVID-Medline.

Ahmann PA, Theye FW, Berg R, et al. Placebo-controlled evaluation of amphetamine mixture-dextroamphetamine salts and amphetamine salts (Adderall): efficacy rate and side effects. Pediatrics 2001;107(1):E10 PMID:11134474
Exclude: No included comparisons of outcomes, OVID-Medline.

Aird RB, Yamamoto T. Behavior disorders of childhood. Electroencephalogr Clin Neurophysiol 1966;21(2):148-56. PMID:4162007
Exclude: Not an included population, OVID-Medline.

Akhondzadeh S, Tavakolian R, Davari-Ashtiani R, et al. Selegiline in the treatment of attention deficit hyperactivity disorder in children: a double blind and randomized trial. Prog Neuropsychopharmacol Biol Psychiatr 2003;27(5):841-5. PMID:12921918
Exclude: No included comparisons of outcomes, OVID-Medline.

Akhondzadeh S, Mohammadi MR, Khademi M. Zinc sulfate as an adjunct to methylphenidate for the treatment of attention deficit hyperactivity disorder in children: a double blind and randomized trial. BMC Psychiatr 2004;4:9 PMID:15070418
Exclude: No included comparisons of outcomes, OVID-Medline.

Alderton HR, Hoddinott BA. A controlled study of the use of thioridazine in the treatment of hyperactive and aggressive children in a children's psychiatric hospital. Can Psychiatr Assoc J 1964;9(3):239-47.
Exclude: No included comparisons of outcomes,

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Exclude: No included comparisons of outcomes,

Alger I. Attention-deficit hyperactivity disorder; AIDS in children and adolescents. Hosp Community Psychiatr 1989;(12):1222-3. PMID:1990046179
Exclude: Not an included population, OVID-EMBASE.

Alhambra MA, Fowler TP, Alhambra AA. EEG biofeedback: A new treatment option for ADD/ADHD. J Neurother 1995;1(2):39-43.
Exclude: No included comparisons of outcomes, OVID-PsycINFO.

Allakhverdiev AR, Horunzheva Y, Kadyrova KG. Influence of functional biocontrol on brain non-specific systems in children with neurotic hyperkinesis. Hum Physiol 1995;21(4):341-3.
Exclude: Not an included population, OVID-PsycINFO.

Allen KE, Henke LB, Harris FR, et al. Control of hyperactivity by social reinforcement of attending behavior. J Educ Psychol 1967;58(4):231-7. PMID:6062455
Exclude: Not an included population, OVID-Medline.

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Exclude: No included comparisons of outcomes, OVID-Medline.

Aman MG, Werry JS. Methylphenidate in children: Effects upon cardiorespiratory function on exertion. Int J Ment Health 1975;4(1-2):119-31.
Exclude: No included comparisons of outcomes, OVID-PsycINFO.

Aman MG, Mitchell EA, Turbott SH. The effects of essential fatty acid supplementation by Efamol in hyperactive children. J Abnorm Child Psychol 1987;(1):75-90. PMID:1987106938
Exclude: No included comparisons of outcomes, OVID-EMBASE.

Aman MG, Marks RE, Turbott SH, et al. Clinical effects of methylphenidate and thioridazine in intellectually subaverage children. J Am Acad Child Adolesc Psychiatry 1991;30(2):246-56. PMID:2016229
Exclude: No included comparisons of outcomes, OVID-Medline.

Aman MG, Kern RA, McGhee DE, et al. Fenfluramine and methylphenidate in children with mental retardation and attention deficit hyperactivity disorder: laboratory effects. J Autism Dev Disord 1993;23(3):491-506.
Exclude: No included comparisons of outcomes,

Aman MG, Kern RA, McGhee DE, et al. Fenfluramine and methylphenidate in children with mental retardation and ADHD: clinical and side effects. J Am Acad Child Adolesc Psychiatry 1993;32(4):851-9. PMID:8340309
Exclude: No included comparisons of outcomes, OVID-Medline.

Aman MG, Armstrong S, Buican B, et al. Four-year follow-up of children with low intelligence and ADHD: a replication. Res Dev Disabil 2002;23(2):119-34. PMID:12061750
Exclude: No included intervention compared, OVID-Medline.

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Exclude: No included comparisons of outcomes, OVID-Medline.

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Arnold LE, Wender PH, McCloskey K, et al. Levoamphetamine and dextroamphetamine: comparative efficacy in the hyperkinetic syndrome. Assessment by target symptoms. Arch Gen Psychiatry 1972;27(6):816-22.
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Arnold LE, Abikoff HB, Cantwell DP, et al. National Institute of Mental Health collaborative multimodal treatment study of children with ADHD (the MTA). Design challenges and choices. Arch Gen Psychiatry 1997;54(9):865-70. PMID:9294378
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Arnold LE, Pinkham SM, Votolato N. Does zinc moderate essential fatty acid and amphetamine treatment of attention-deficit/hyperactivity disorder? J Child Adolesc Psychopharmacol 2000;10(2):111-7. PMID:10933121
Exclude: Not an included population, OVID-Medline.

Arnold LE, Lindsay RL, Conners CK, et al. A double-blind, placebo-controlled withdrawal trial of dexmethylphenidate hydrochloride in children with attention deficit hyperactivity disorder. J Child Adolesc Psychopharmacol 2004;14(4):542-54. PMID:15662146
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August GJ, Hektner JM, Egan EA, et al. The early risers longitudinal prevention trial: examination of 3-year outcomes in aggressive children with intent-to-treat and as-intended analyses. Psychol Addict Behav 2002;16(4 Suppl):S27-39. PMID:12502275
Exclude: No included comparisons of outcomes, OVID-Medline.

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Appendix D. Strength of Evidence/Grading Tables

Table SOE1. Strength of evidence: ADHD interventions for children younger than 6 years of age: behavioral change after intervention

Number of Studies (Subjects)	Domains Pertaining to Strength of Evidence				Strength of Evidence (SOE)	
	Risk of Bias; Design/Quality	Consistency	Directness	Precision		Harms
Parent behavior training – immediately post-intervention – data from strongest studies only					**Strong SOE**	
8(421)	RCT/Low risk	Consistent	Direct	Precise	SMD = -0.86 [-1.07, -0.65]	Not reported
Bagner 2007; Bor 2002; Hutchings 2007; Markie-Dadds 2006; Nixon 2001; Pisterman 1992, Sonuga-Barke 2001; Thompson 2008						
Parent behavior training - extension					**Insufficient SOE**	
Insufficient data						
Pharmacological					**Low SOE**	
1 (114)	RCT/Low risk	Consistent	Direct	Precise	SMD = -0.83 [-1.21, -0.44]	Reviewed separately
PATS 2007						
Multi-component – non-pharmacological					**Insufficient SOE**	
Insufficient data						
Multi-component including pharmacological					**Insufficient SOE**	
Insufficient data						
Pharmacological ADVERSE EVENTS – Growth, G/I, Behavioral					**Insufficient SOE**	
Insufficient data						

Table SOE2. Strength of evidence: Long-term ADHD interventions for people 6 years of age or older

Number of Studies (Subjects)	Domains Pertaining to Strength of Evidence				Strength of Evidence (SOE)
	Risk of Bias; Design/Quality	Consistency	Directness	Precision	
Parent behavior training					**Insufficient SOE**
Insufficient data					
Behavioral/Psychosocial					**Insufficient SOE**
Insufficient data					
Academic Interventions (non-Pharmacological)					**Insufficient SOE**
Combined					**Low SOE**
1(263)	RCT/Low risk	Consistent	Direct	Precise	SMD = -.070 [-0.95, -0.46]
MTA 1999					
Pharmacological - Effectiveness					**Low SOE**
1(251)	RCT/Low risk	Consistent	Direct	Precise	MPH: SMD = -0.54 [-0.79, -0.29] ATX: SMD = -0.40 [-0.61, -0.18]
MTA 1999					
Pharmacological extension studies. Risk of withdrawing before end of study period (1.5 to 3 yrs)					**Insufficient SOE**
Insufficient data					
Long Term Use of Psychostimulants – Adverse Events - Specific					
Growth					**Insufficient SOE**
Insufficient data					
Cardiac					**Insufficient SOE**
Insufficient data					
Cerebrovascular					**Insufficient SOE**
Insufficient data					
Tic					**Insufficient SOE**
Insufficient data					
Long Term Use of Psychostimulants – Potential benefits					
Academic					**Insufficient SOE**
Insufficient data					
Smoking					**Insufficient SOE**
Insufficient data					
Substance Use Disorder					**Insufficient SOE**
Insufficient data					
Criminality					**Insufficient SOE**
Insufficient data					
Psychiatric					**Insufficient SOE**
Insufficient data					
Emergency Room Usage					**Insufficient SOE**
Insufficient data					