

## **Attention Deficit Hyperactivity Disorder: Diagnosis and Treatment in Children and Adolescents**

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## **Key Messages**

### **Purpose of Review**

To update a previous review by comparing strategies to diagnose, treat, and monitor children and adolescents with attention deficit hyperactivity disorder (ADHD).

### **Key Messages**

- Evidence was insufficient on imaging or electroencephalogram to diagnose ADHD in children 7–17 years of age.
- Little evidence adds to the 2011 report that found that methylphenidate is effective for children under age 6 with ADHD and that psychostimulants can be effective for children 6–12 years of age.
- Atomoxetine had slightly higher gastrointestinal effects than methylphenidate.
- Cognitive behavioral therapy may improve ADHD symptoms among children 7–17 years of age.
- Child or parent training improved ADHD symptoms among children 7–17 years of age but did not change academic performance.
- Omega-3/6 supplementation made no difference in ADHD symptoms.
- Future studies are needed to evaluate diagnosis, monitoring, and long-term outcomes for children and adolescents with ADHD managed in usual care settings.





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

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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# Attention Deficit Hyperactivity Disorder: Diagnosis and Treatment in Children and Adolescents

## Structured Abstract

**Objectives.** Attention deficit hyperactivity disorder (ADHD) is a common pediatric neurobehavioral disorder often treated in the primary care setting. This systematic review updates and extends two previous Agency for Healthcare Research and Quality (AHRQ) systematic evidence reviews and focuses on the comparative effectiveness of methods to establish the diagnosis of ADHD, updates the comparative effectiveness of pharmacologic and nonpharmacologic treatments, and evaluates different monitoring strategies in the primary care setting for individuals from birth through 17 years of age.

**Data sources.** We searched PubMed<sup>®</sup>, Embase<sup>®</sup>, PsycINFO<sup>®</sup>, and the Cochrane Database of Systematic Reviews for relevant English-language studies published from January 1, 2011, through November 7, 2016.

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

**Results.** Evidence was contributed from 103 articles describing 90 unique studies. Twenty-one studies related to diagnosis, 69 studies related to treatment, and no studies were identified on monitoring. The Attention and Executive Function Rating Inventory and Childhood Executive Functioning Inventory performed better than the Cambridge Neuropsychological Test Automated Battery for the diagnosis of ADHD for ages 7–17 years (strength of evidence [SOE]=low). Evidence was insufficient on the use of electroencephalography (EEG) or neuroimaging to establish the diagnosis of ADHD for ages 7–17 years. No studies directly assessed the harms to children labeled as having ADHD. Limited additional evidence published since the original 2011 report was available on ADHD medications approved by the Food and Drug Administration (FDA) compared with placebo or compared to different FDA-approved ADHD medications (SOE=insufficient). For atomoxetine and methylphenidate, the most commonly reported adverse events were somnolence and mild gastrointestinal problems. Atomoxetine had slightly higher gastrointestinal effects than methylphenidate (SOE=low). Cognitive behavioral therapy improved ADHD symptoms (SOE=low). Child or parent training improved ADHD symptoms (SOE=moderate) but made no difference in academic performance (SOE=low). Omega-3/6 fatty acid supplementation made no difference in ADHD symptoms (SOE=moderate). Across all treatments, little evidence was reported on the risk of serious adverse events, including cardiovascular risk.

**Conclusions.** The 2011 AHRQ systematic review highlighted the benefit of psychostimulants for children 6–12 years of age with ADHD for up to 24 months and found that adding psychosocial/behavioral interventions to psychostimulants is more effective than psychosocial/behavioral interventions alone for children with ADHD and oppositional defiant disorder. This targeted update found insufficient evidence regarding new approaches to the



diagnosis (e.g., EEGs, neuroimaging). Little is known about the impact of being labeled as having ADHD. Although cognitive behavioral therapy or child or parent training may decrease symptoms of ADHD, more information is needed regarding the relative benefit of these approaches compared to, or combined with, medication treatment. Omega-3/6 supplementation does not appear to improve ADHD outcomes. No information was identified regarding the optimal strategy for monitoring after diagnosis.

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# Introduction

## Background

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

Psychostimulants can be effective in reducing distractibility, improving sustained attention, reducing impulsive behaviors, and improving activity level.<sup>4</sup> Nonpharmacologic therapies (e.g., behavioral therapy, psychotherapy, psychosocial interventions, and complementary and alternative medicine interventions), either alone or in combination with medication management, could potentially address core symptoms of ADHD or the long-term impairments that are associated with the disorder. Understanding the role of nonpharmacologic therapies can be challenging because they encompass a broad range of approaches to care, ranging from highly structured behavioral interventions to complementary medicines.

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

## Population

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

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

## **Diagnosis**

ADHD diagnosis is based on clinician assessment to determine whether the criteria described in the DSM are met. For this review, studies based on the DSM-5 or DSM-IV criteria were included. Rating scales, which can be completed by parents, teachers, and/or patients, are used to evaluate the presence of each of the 18 symptoms as well as the degree of impairment that results from symptoms. Rating scale data are integrated with a clinical interview to determine the onset, course, duration, and impairment associated with symptoms. In addition, screening and clinical evaluation of potential comorbid psychiatric conditions is a key part of the diagnostic process. Important questions remain about the accuracy of this approach in primary care settings. A particular challenge in primary care has been the lack of adequate time and expertise to distinguish ADHD from other conditions that may appear similar (e.g., anxiety, conduct disorders, speech or language delay, other developmental disorders) and to determine whether another condition may better explain ADHD symptoms or is present as a comorbid diagnosis.<sup>7</sup>

Although most previous research has relied on interviews and rating scales for diagnosis, the U.S. Food and Drug Administration (FDA) has recently approved a new device “to aid in the diagnosis of ADHD.”<sup>8</sup> The Neuropsychiatric Electroencephalograph [EEG]-Based Assessment Aid (NEBA; NEBA Health, Augusta, GA) was approved to provide clinical support for an ADHD diagnosis in patients ages 6–17 years but is not intended to replace the clinical evaluation.<sup>8</sup> There is significant interest in the use of tests to either supplement or replace the standard methods of diagnosis used in the primary care setting.

## **Adverse Effects of Diagnosis**

Being diagnosed with ADHD can lead to “labeling harms,” which can lead to stigma, reduced self-esteem, or reduced future educational attainment or career opportunities.<sup>9-11</sup> Misdiagnosis can lead to overdiagnosis or underdiagnosis and can also miss conditions that can be similar in appearance to ADHD (e.g., anxiety, conduct disorders, speech or language delay, other medical disorders/diseases, or other developmental disorders) that may warrant a different course of treatment.

## **Treatment Strategies**

Treatment strategies for ADHD can be divided into pharmacologic and nonpharmacologic therapies. The main categories of pharmacologic therapies include stimulants, selective norepinephrine reuptake inhibitors, alpha-2 agonists, and antidepressants. Nonpharmacologic therapies include psychosocial interventions, behavioral interventions, school interventions, cognitive training therapies, learning training, biofeedback or neurofeedback, parent behavior training (i.e., training parents to reduce unwanted behaviors, foster desired behaviors and interactions, and improve family relationships), dietary supplements (e.g., omega-3 fatty acids, vitamins, herbal supplements, probiotics), elimination diets, vision training, and chiropractic treatment. For the first line of therapy, the American Academy of Pediatrics (AAP) recommends behavior therapy for children 4–5 years of age and preferably both behavior therapy and FDA-approved medications for children 6–18 years of age.<sup>12</sup>

## **Adverse Effects of Treatment**

Adverse effects associated with pharmacologic treatment can include changes in appetite, growth suppression,<sup>13</sup> weight decrease, sleep disturbance, gastrointestinal symptoms, elevated blood pressure, increased heart rate, risk of sudden cardiac death, cardiac arrhythmias, conduction abnormalities, tics or other movement disorders, behavior changes, hallucination, aggression, suicide (attempted or completed), and suicidal ideation. Importantly, suicide and suicidal ideation can be both an adverse effect of treatment and an ADHD-related health outcome. Treatment can also lead to personality changes or loss of spontaneity as perceived by the treated individual, family members, or other close acquaintances.

Individuals who are initially misdiagnosed may be overtreated, and those who have inadequate monitoring may be overtreated or undertreated. Overtreatment leads to risk of treatment with no or little potential benefit. Because many of the pharmacologic treatments are controlled substances, overtreatment could also lead to abuse of a drug to which the treated individual might not otherwise have access.<sup>14</sup> Although reduction of ADHD symptoms can improve family functioning, the need to provide treatments can potentially also lead to parental stress, and depending on the specific treatment, there may be significant time demands, opportunity, or financial costs.

## **Monitoring Strategies With Intermediate Outcomes**

After a child is diagnosed with ADHD and an initial treatment strategy is determined, a monitoring strategy is applied to ensure that outcomes are evaluated over time and modification to treatments are made when needed. Stimulant prescription refills are often required monthly, which can also support the need for frequent re-evaluations. Several instruments are available to monitor treatment response and adverse effects over time, including the Vanderbilt scales, the Conners scales, and the Swanson, Nolan, and Pelham Revision (SNAP-IV) rating scales.<sup>15-17</sup> Monitoring also includes assessment of any adverse effects of treatment. There are variations in the frequency of monitoring, often based on the age of the child, the specific treatment, duration of treatment, previous symptoms and comorbid conditions, and family and health care provider preferences. Rating scale results are intermediate monitoring outcomes associated with the outcomes described below.

## **Long-Term Outcomes**

Outcomes associated with ADHD in childhood are based on measures of performance and/or functional impairment. In childhood and adolescence, individuals with ADHD are at risk for lower academic performance (e.g., grades, scores on standardized tests), lower rates of graduation from high school, higher rates of grade retention, and higher rates of school suspension. In adulthood, outcomes may include limited workforce participation and/or difficulty maintaining a steady job. Throughout the lifespan, social outcomes associated with ADHD may include problematic peer and family relationships. Individuals with ADHD are also at risk for negative outcomes associated with risk-taking behaviors such as motor vehicle collisions or other accidents, substance use (e.g., higher rates of smoking, more difficulty quitting smoking), and unprotected sexual activity. Mental health outcomes that are associated with ADHD include higher rates of mood disorders, depression or anxiety, higher likelihood of having self-injurious nonsuicidal behavior, suicide (attempted or completed), suicidal ideation, and risk of mortality. Because these long-term outcomes can be associated with the known course of illness for

ADHD, with commonly occurring comorbid conditions or in some cases with ADHD treatment, it can be difficult to fully assess and predict long-term outcomes for individuals with ADHD.

## **Key Findings From 2011 Report**

This review updates previous Agency for Healthcare Research and Quality (AHRQ) reports focused on ADHD treatment. This most recent report from 2011 focused on (1) pharmacologic treatments for children under 6 years of age with ADHD and a disruptive behavior disorder; (2) long-term comparative safety and effectiveness of various treatment options for children 6 years of age or older with ADHD; and (3) prevalence of ADHD and rates of diagnosis and treatment for ADHD. The 2011 report concluded that high strength of evidence (SOE) supported parent behavior training and low SOE supported methylphenidate (MPH) for improving the behavior of children aged 6 years or younger. The 2011 report also concluded that there was sparse evidence at the time regarding long-term outcomes following interventions for ADHD, but that treatment for 12 to 24 months with MPH or atomoxetine appeared to be associated with improvements in symptomatic behavior. This current systematic review builds on the 2011 report and also examines evidence on the diagnosis of ADHD. This report was developed to synthesize information for clinicians, scientists, and families with children with ADHD or with children suspected to have ADHD about the accuracy of diagnostic strategies and the harms and benefits of establishing the diagnosis and treating the condition.

Although different in scope, the current report primarily builds on the foundation of the 2011 report.<sup>4</sup> Key findings of that report included:

- Parent behavioral interventions show benefit for ADHD symptoms for children younger than 6 years of age (high SOE).
- MPH is efficacious and generally safe for the treatment of ADHD symptoms for children younger than 6 years (low SOE). However, the studies are of short duration (lasting days to weeks).
- Psychostimulants provide control of ADHD symptoms and are well tolerated in children 6 years and older.
- Combined medication and behavioral treatment are effective in treating ADHD plus oppositional defiant disorder symptoms, primarily in boys 7–9 years of age with primarily combined type of ADHD.
- Sparse evidence at the time regarding long-term outcomes following interventions for ADHD, but treatment for 12 to 24 months with MPH or atomoxetine appeared to be associated with improvements in symptomatic behavior.



# Scope and Key Questions

## Scope of This Review

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

Our review updates a 2011 review that focused on the effectiveness of ADHD treatment in at-risk preschoolers, the long-term effectiveness of ADHD treatment in all ages, and the variability in ADHD prevalence, diagnosis, and treatment.<sup>4</sup> The current review builds on this 2011 report and addresses important gaps in knowledge related to the diagnosis of ADHD, concerns about labeling with ADHD, and conflicting literature about the effectiveness of treatment.

## Rationale and Context

### DSM-5 Criteria for Diagnosis

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

### Patient Preferences

There are differences in patient and family preferences related to both pharmacologic and nonpharmacologic treatment<sup>18</sup> and potential outcomes. These treatment preferences have been shown to be associated with treatment initiation and choice. Findings from this systematic review are intended to help inform patient and family decisions based on the benefits and harms of specific treatments.

### Other Factors

Two previous AHRQ evidence reports have addressed ADHD.<sup>4,19</sup> Because of the number of studies related to ADHD, this report builds on these previous reports with specific attention to issues related to diagnosis, treatment, and management of children and adolescents. In the period since the 2011 publication of the AAP clinical practice guideline,<sup>12</sup> new medication formulations have become available (e.g., MPH transdermal system and suspension, lisdexamfetamine, amphetamine sulfate tablets, and dextroamphetamine sulfate tablets), and the DSM-5 has been released, increasing clinical and decisionmaking uncertainty. A separate report on disruptive behavior disorder is nearly complete and was therefore not targeted in this systematic review. However, we do include disruptive behavior specifically related to ADHD.

### Cost

Cost assessment was not included in this review.

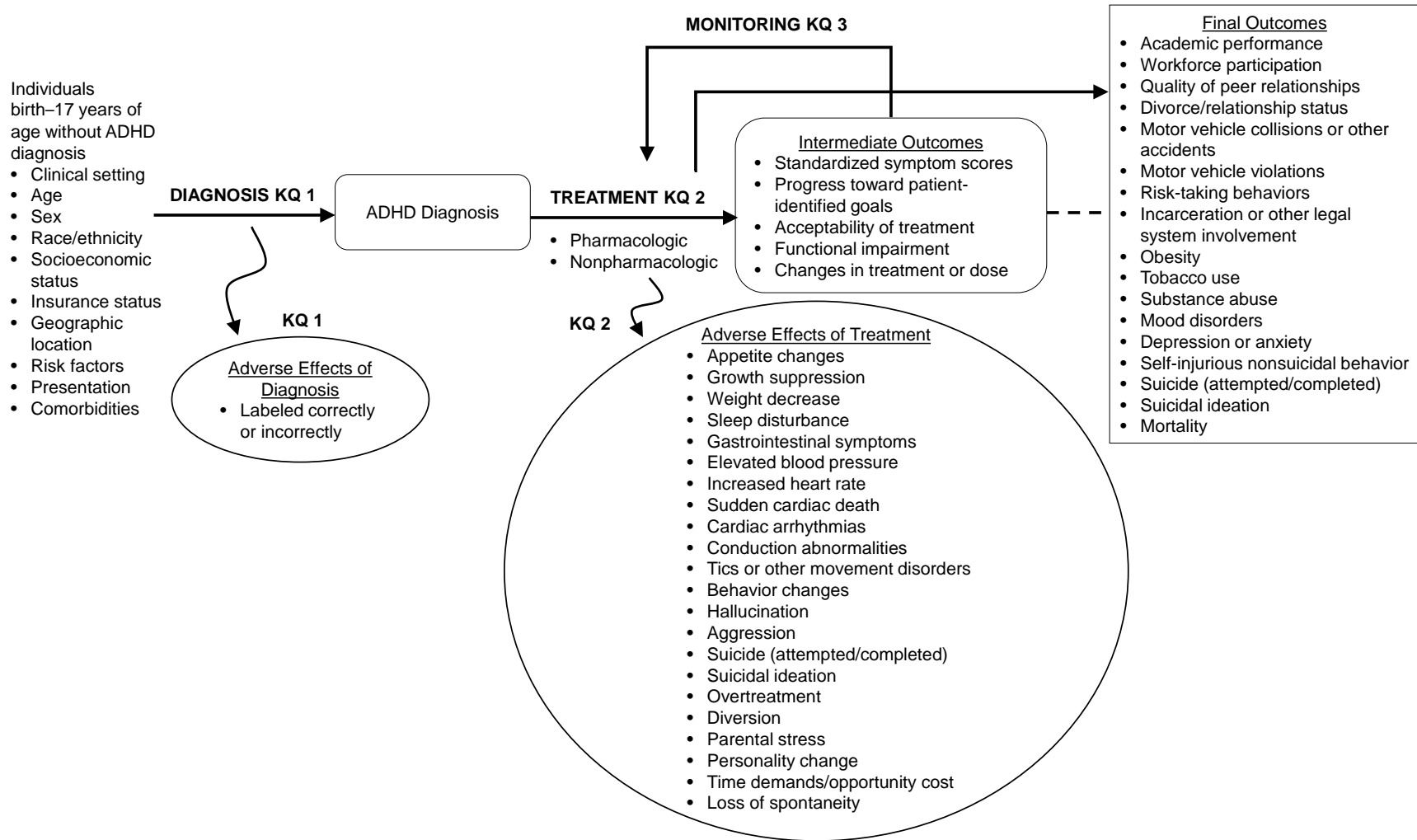
## Key Questions

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

- KQ 1: For the diagnosis of ADHD:
  - a. What is the comparative diagnostic accuracy of approaches that can be used in the primary care practice setting or by specialists to diagnose ADHD among individuals younger than 7 years of age?
  - b. What is the comparative diagnostic accuracy of EEG, imaging, or approaches assessing executive function that can be used in the primary care practice setting or by specialists to diagnose ADHD among individuals aged 7 through 17?
  - c. For both populations, how does the comparative diagnostic accuracy of these approaches vary by clinical setting, including primary care or specialty clinic, or patient subgroup, including age, sex, or other risk factors associated with ADHD?
  - d. What are the adverse effects associated with being labeled correctly or incorrectly as having ADHD?
- KQ 2: What are the comparative safety and effectiveness of pharmacologic and/or nonpharmacologic treatments of ADHD in improving outcomes associated with ADHD? How do these outcomes vary by presentation (inattentive, hyperactive/impulsive, and combined) or other comorbid conditions? What is the risk of diversion of pharmacologic treatment?
- KQ 3: What are the comparative safety and effectiveness of different monitoring strategies to evaluate the effectiveness of treatment or changes in ADHD status (e.g., worsening or resolving symptoms)?

The analytic framework presented in Figure 1 illustrates the population, interventions, outcomes, and adverse effects that guided the literature search and synthesis. This figure shows how individuals through 17 years of age without ADHD may be diagnosed and treated for ADHD, and how treatment is associated with a range of potential adverse effects and outcomes.<sup>4</sup> KQ 1 evaluates the comparative accuracy of approaches used to diagnose ADHD, including how the diagnostic accuracy varies by setting, patient subgroup, or other risk factors. For children younger than 7 years, we included any method available to primary care clinicians (KQ 1a). However, for children 7 through 17 years, we focused on novel approaches only because other reports have assessed the standard screening instruments used for older children. Although the studies were not restricted to primary care settings, the methods have to be ones available directly or easily upon referral to primary care clinicians based on feedback from the Technical Expert Panel and internal clinical experts. KQ 1 also addresses adverse effects of ADHD diagnosis. KQ 2 considers the comparative safety and effectiveness of pharmacologic and nonpharmacologic treatments for ADHD and how the outcomes vary by presentation or other comorbid conditions. KQ 2 also addresses adverse effects of ADHD treatment. KQ 3 considers the comparative safety and effectiveness of different monitoring strategies to evaluate the effectiveness of treatment or changes in ADHD status over time.

**Figure 1. Analytic framework for ADHD**



## Organization of This Report

The remainder of the review first presents our methods followed by an overview of the results of the updated systematic review. Each results section also describes “Findings in Relation to What Is Known” to provide appropriate context for the reader. We then synthesize the literature and provide summary tables and SOE grades for the outcomes. The discussion section offers our conclusions, summarizes our findings, and provides other information relevant to interpreting this work for clinical practice and future research. Within the discussion we also include a summary table of how this updated systematic review compares and contrast to the 2011 AHRQ report in terms of the KQs addressed, populations and outcomes of interest, and the findings of the review.

Appendix A contains the exact search strings for the literature searches. Appendix B presents the data elements abstracted from the included studies. Appendix C lists the included studies. Appendix D lists the excluded studies and the reason for exclusion. Appendix E provides a key to the primary and companion articles. Appendix F presents details on the study characteristics of included studies. Appendix G presents an overview of included studies. Appendix H presents detailed data tables for the different outcomes and comparisons of interest.

A list of acronyms and abbreviations is at the end of this report.

## Methods

For this comparative effectiveness review, we followed the methods from the Agency for Healthcare Research and Quality (AHRQ)'s *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter referred to as the Methods Guide) for the Evidence-based Practice Center (EPC) program.<sup>20</sup> We sought feedback regarding the conduct of the work (such as development of search strategies and identifying outcomes of key importance) from the Task Order Officer and the Technical Expert Panel. Our methods map to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.<sup>21</sup> All methods and analyses were determined *a priori*.

### Topic Refinement and Review Protocol

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

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

### Literature Search Strategy

#### Search Strategy

To identify relevant published literature, we searched MEDLINE<sup>®</sup> (via PubMed), Embase<sup>®</sup>, PsycINFO<sup>®</sup>, and the Cochrane Database of Systematic Reviews (CDSR), limiting the search to studies conducted in children 17 years of age and younger and published from January 1, 2009, to November 7, 2016. These databases were selected based on internal expert opinion that they would identify most of the relevant literature on this topic and following prior related systematic reviews. We believe that the evidence published from 2009 forward both represents the current standard of care for the population of interest in this review and allows this report to build on the previous systematic review published in 2011 (which included literature through May 31, 2010).<sup>4</sup>

We used a combination of medical subject headings and title and abstract keywords, focusing on terms to describe the relevant population and interventions of interest. Exact search strings used for each KQ are in Appendix A. Where possible, we used existing validated search filters. An experienced search librarian guided all searches. We supplemented the electronic searches with a manual search of citations from a set of key primary and review articles.<sup>22-79</sup> The reference list for identified pivotal articles was hand-searched and cross-referenced against our

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

To identify relevant gray literature, the EPC Scientific Resource Center made requests to drug and device manufacturers for scientific information packets solicited through the AHRQ EHC Web site. We also searched study registries for relevant articles from completed studies. Gray literature databases included ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform search portal, and the National Guidelines Clearinghouse.

As an additional step in identifying adverse effects of interest, we reviewed the known adverse effects of attention deficit hyperactivity disorder (ADHD) medications monitored by the Food and Drug Administration (FDA).<sup>80</sup> As a result of that assessment, we added two additional outcomes to consideration for this review: chemical leukoderma and priapism.

## Inclusion and Exclusion Criteria

We specified our inclusion and exclusion criteria based on the PICOTS (Populations, Interventions, Comparators, Outcomes, Timing, Settings) identified in topic refinement. Table 1 specifies inclusion and exclusion criteria.

**Table 1. Inclusion and exclusion criteria**

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

|               |  |  |
|---------------|--|--|
| Interventions | <p>KQ 1: Any standard ADHD diagnostic strategy, including clinician interview or standardized instrument (e.g., Vanderbilt scales, the Conner scales, and the SNAP-IV rating score) for individuals under 7 years of age. The use of EEG-based systems, imaging, or assessment of executive function were evaluated in the diagnosis of ADHD in individuals through 17 years of age.</p> <p>KQ 2: Any pharmacologic or nonpharmacologic treatment of ADHD, alone or in combination:</p> <ul style="list-style-type: none"> <li>• Pharmacologic treatments considered are brand name and generic formulations of the following medications<sup>a</sup>: <ul style="list-style-type: none"> <li>○ Psychostimulants <ul style="list-style-type: none"> <li>▪ Methylphenidate (MPH)</li> <li>▪ Dexmethylphenidate (D-TMP)</li> <li>▪ Dextroamphetamine (DEX)</li> <li>▪ Lisdexamfetamine (LDX)</li> <li>▪ Mixed amphetamine salts (MAS)</li> <li>▪ Amphetamine</li> </ul> </li> <li>○ Tricyclic antidepressants <ul style="list-style-type: none"> <li>▪ *Desipramine</li> <li>▪ *Nortriptyline</li> </ul> </li> <li>○ Selective norepinephrine reuptake inhibitors <ul style="list-style-type: none"> <li>▪ Atomoxetine (ATX)</li> </ul> </li> <li>○ Alpha-2 agonists <ul style="list-style-type: none"> <li>▪ Clonidine</li> <li>▪ Guanfacine extended release (GXR)</li> <li>▪ *Guanfacine immediate release (GIR)</li> </ul> </li> <li>○ Dopamine reuptake inhibitors <ul style="list-style-type: none"> <li>▪ *Modafinil</li> <li>▪ *Armodafinil</li> </ul> </li> <li>○ Norepinephrine-dopamine reuptake inhibitors <ul style="list-style-type: none"> <li>▪ *Bupropion</li> </ul> </li> <li>○ Serotonin-norepinephrine reuptake inhibitors <ul style="list-style-type: none"> <li>▪ *Duloxetine</li> </ul> </li> <li>○ Serotonin-norepinephrine-dopamine reuptake inhibitors <ul style="list-style-type: none"> <li>▪ *Venlafaxine</li> </ul> </li> <li>○ Monoamine oxidase type B inhibitors <ul style="list-style-type: none"> <li>▪ *Selegiline</li> </ul> </li> <li>○ N-methyl-D-aspartate receptor antagonists <ul style="list-style-type: none"> <li>▪ *Amantadine</li> <li>▪ *Memantine</li> </ul> </li> </ul> </li> <li>• Nonpharmacologic therapies considered include psychosocial interventions, behavioral interventions, cognitive behavioral therapy, play therapy, mindfulness-based therapies, school interventions, cognitive training therapies, biofeedback or neurofeedback, parent behavior training, dietary supplements (e.g., omega-3 fatty acids, vitamins, herbal supplements, probiotics), homeopathy, acupuncture, elimination diets, vision training, exercise, and chiropractic treatment.</li> </ul> <p>KQ 3: Follow-up visits in primary care with various methods and within times (monthly to annually) for repeat monitoring, independent of treatment.</p> | <p>KQ 1: Validation studies or diagnosis conducted using a nonvalidated instrument</p> <p>KQ 2: Studies comparing pharmacologic agents approved by the FDA for the treatment of ADHD that have enrollment of fewer than 100 patients with ADHD, or less than 6 months of follow-up</p> |
|---------------|--|--|

| PICOTS Element | Inclusion Criteria  | Exclusion Criteria   |
|----------------|---|--|
| Comparators    | <p>KQ 1: Confirmation of diagnosis by a specialist (gold standard), including psychologist or psychiatrist or other care provider using a well-validated and reliable process of confirming the diagnosis of ADHD according to the DSM-4 or DSM-5.</p> <p>KQ 2: Specific treatments compared with other treatments as described above or to no treatment.</p> <p>KQ 3: Follow-up compared with differing durations of follow-up or differing settings of follow-up.</p> | KQ 1: Comparison to diagnosis with a nonvalidated instrument |



|          |   |  |
|----------|---|--|
| Outcomes | <p>KQ 1:</p> <ul style="list-style-type: none"> <li>• Accuracy of diagnostic strategy, as measured by: <ul style="list-style-type: none"> <li>○ Diagnostic concordance of primary care provider with specialist</li> <li>○ Inter-rater reliability</li> <li>○ Internal consistency</li> <li>○ Test-retest</li> <li>○ Sensitivity</li> <li>○ Specificity</li> <li>○ Positive predictive value</li> <li>○ Negative predictive value</li> <li>○ False positives</li> <li>○ False negatives</li> <li>○ Risk of missed condition that can appear as ADHD (i.e., misdiagnosis)</li> </ul> </li> <li>• Labeling is any measure of stigma following diagnosis comparing those with and without ADHD.</li> </ul> <p>KQ 2:</p> <ul style="list-style-type: none"> <li>• Intermediate outcomes: <ul style="list-style-type: none"> <li>○ Changes on standardized symptom scores or progress toward patient-identified goals. Standardized symptom scores include narrow-band focused instruments (Vanderbilt rating scales, ADHD Rating Scale) and broad-band scales (Child Behavior Checklist and Teacher Report Form, Behavior Assessment System for Children, Conners' Rating Scales-Revised, Conners' 3 Parent, Conners' 3 Teacher)</li> <li>○ Acceptability of treatment</li> <li>○ Functional impairment (assessed using the Clinical Global Impressions [CGI] scale or the Impairment Rating Scale [IRS])</li> </ul> </li> <li>• Final outcomes include: <ul style="list-style-type: none"> <li>○ Academic performance <ul style="list-style-type: none"> <li>▪ Academic Performance Rating Scale</li> <li>▪ Academic Competency Evaluation Scale (ACES)</li> <li>▪ (Actual) School grades</li> <li>▪ Grade Retention/Not being promoted</li> <li>▪ Vanderbilt Teacher Form Academic Performance Subscale</li> <li>▪ Standardized achievement tests (WIAT, WJ, WRAT)</li> </ul> </li> <li>○ Workforce participation</li> <li>○ Quality of peer relationships</li> <li>○ Divorce/relationship status</li> <li>○ Motor vehicle collisions or other accidents</li> <li>○ Motor vehicle violations</li> <li>○ Risk-taking behaviors</li> <li>○ Incarceration or other interactions with the legal system (juvenile detention, probation, court-mandated interventions, need for residential placement)</li> <li>○ Obesity</li> <li>○ Tobacco use</li> <li>○ Substance abuse</li> <li>○ Mood disorders</li> <li>○ Depression or anxiety</li> </ul> </li> </ul> |  |
|----------|---|--|

| PICOTS Element | Inclusion Criteria  | Exclusion Criteria |
|----------------|---|--------------------|
|                | <ul style="list-style-type: none"> <li>○ Self-injurious nonsuicidal behavior</li> <li>○ Suicide (attempted or completed)</li> <li>○ Suicidal ideation</li> <li>○ Mortality</li> <li>● Adverse effects of treatment, including: <ul style="list-style-type: none"> <li>○ Changes in appetite</li> <li>○ Growth suppression</li> <li>○ Weight decrease</li> <li>○ Sleep disturbance</li> <li>○ Gastrointestinal symptoms</li> <li>○ Elevated blood pressure</li> <li>○ Increased heart rate</li> <li>○ Risk of sudden cardiac death</li> <li>○ Cardiac arrhythmias</li> <li>○ Conduction abnormalities</li> <li>○ Tics or other movement disorders</li> <li>○ Behavior changes</li> <li>○ Hallucination</li> <li>○ Aggression</li> <li>○ Suicide (attempted or completed)</li> <li>○ Suicidal ideation</li> <li>○ Overtreatment</li> <li>○ Diversion of pharmacotherapy</li> <li>○ Parental stress</li> <li>○ Personality change</li> <li>○ Time demands/opportunity cost</li> <li>○ Loss of spontaneity</li> <li>○ Chemical leukoderma</li> <li>○ Priapism</li> </ul> </li> </ul> <p>KQ 3:</p> <ul style="list-style-type: none"> <li>● Changes in treatment or dose</li> <li>● Adverse effects of treatment as described under KQ 2</li> <li>● Changes in intermediate outcomes (e.g., standardized symptom scores, progress toward patient-identified goals, functional impairment) as described under KQ 2</li> </ul> |                    |
| Timing         | <p>KQ 1:</p> <ul style="list-style-type: none"> <li>● For assessment of diagnostic accuracy: diagnostic follow-up must be within 4 months of the initial evaluation and must be completed before treatment is initiated</li> <li>● For labeling: any time after the ADHD diagnosis</li> </ul> <p>KQs 2 and 3: Any</p>   |                    |
| Settings       | <p>KQ 1: Primary or specialty care settings</p> <p>KQs 2 and 3: Any</p>   | None               |

| PICOTS Element | Inclusion Criteria   | Exclusion Criteria   |
|----------------|--|--|
| Study design   | <ul style="list-style-type: none"> <li>• Original data</li> <li>• Randomized trials, prospective and retrospective observational studies with comparator; for diagnostic accuracy, cross-sectional studies are acceptable if they include patients with diagnostic uncertainty and direct comparison of diagnosis in primary care to diagnosis by a specialist</li> <li>• Randomized controlled trials with sample size: <ul style="list-style-type: none"> <li>○ ≥20 subjects for KQs 1 and 3</li> <li>○ ≥50 subjects for KQ 2 (or 100 subjects for studies comparing two or more pharmacologic treatments approved by the FDA for the treatment of ADHD)</li> </ul> </li> <li>• Observational studies with sample size: <ul style="list-style-type: none"> <li>○ ≥20 subjects for KQs 1 and 3</li> <li>○ ≥50 subjects for KQ 2 (or 100 subjects for studies comparing two or more pharmacologic treatments approved by the FDA for the treatment of ADHD)</li> </ul> </li> </ul> | <p>Editorials, nonsystematic reviews, letters, case series, case reports, abstract-only, pre-post studies</p> <p>Because studies with fewer than 20 subjects are often pilot studies or studies of lower quality, we excluded them from our review. Given the large evidence base for comparative pharmacologic treatment studies in KQ2 we increased this sample size limit to 50 subjects for KQ2 and to 100 subjects for studies comparing two or more pharmacologic treatments approved by the FDA for the treatment of ADHD. These sample size limits were seen as representing population study sizes that would be needed to substantially impact the assessment of the existing evidence base.</p> |
| Publications   | <ul style="list-style-type: none"> <li>• English-language publications only</li> <li>• Published on or after January 1, 2009</li> <li>• Relevant systematic reviews, meta-analyses, or methods articles (used for background only)<sup>b</sup></li> </ul>  | Non-English language articles <sup>c</sup>   |

<sup>a</sup>Pharmacologic treatments listed are FDA-approved for an indication of ADHD with the exception of those marked with an asterisk, which are available within the United States and are FDA-approved but not specifically approved for ADHD.

<sup>b</sup>Systematic reviews and meta-analyses were excluded from direct abstraction; those representing key sources were hand-searched as potential sources of additional citations to consider in the review.

<sup>c</sup>Non-English language articles were excluded due to: (1) the high volume of literature available in English language publications, (2) the focus of our review on applicability to populations in the United States, and (3) the scope of our KQs. Abbreviations: ADHD=attention deficit hyperactivity disorder; ATX=atomoxetine; DEX=dextroamphetamine; CGI=Clinical Global Impressions scale; DSM=*Diagnostic and Statistical Manual of Mental Disorders*; D-TMP=dexamethylphenidate; EEG=electroencephalograph; GIR=Guanfacine immediate release; GXR=guanfacine extended release; IRS=Impairment Rating Scale; KQ=Key Question; LDX=lisdexamfetamine; MAS=mixed amphetamine salts; MPH=methylphenidate; PICOTS=Populations, Interventions, Comparators, Outcomes, Timing, Settings; RCT=randomized controlled trial; WIAT=Wechsler Individual Achievement Test; WJ=Woodcock-Johnson; WRAT=Wide Range Achievement Test

## Study Selection

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

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

## Data Extraction

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

All data abstraction form templates were pilot-tested with a sample of included articles to ensure that all relevant data elements (Appendix B) were captured and that there was consistency and reproducibility between abstractors. Forms were revised as necessary before full abstraction of all included articles. Final abstracted data will be uploaded to AHRQ's Systematic Review Data Repository.<sup>81</sup>

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

## Quality Assessment of Individual Studies

We assessed the methodological quality, or risk of bias, for each individual study based on the Cochrane Risk of Bias<sup>82</sup> tool for randomized studies and the Newcastle-Ottawa Scale<sup>83</sup> for observational studies. We supplemented these tools with additional assessment questions, such as use of appropriate analysis, based on recommendations in the AHRQ's Methods Guide.<sup>20</sup> We rated each study as being of good, fair, or poor quality based on its adherence to well-accepted standard methodologies. Table 2 defines these quality ratings, which are presented in the results tables in the Results section as well as the strength of evidence (SOE) tables in the Discussion section of the report.

**Table 2. Definition of quality assessment ratings**

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

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

## Data Synthesis

We began by summarizing key features of the included studies for each KQ. To the degree that data were available, we abstracted information on study design; patient characteristics; clinical settings; interventions; and intermediate, final, and adverse event outcomes. We ordered our findings by treatment or diagnostic comparison and then within these comparisons by outcome with long-term final outcomes emphasized. Existing systematic reviews were used to identify potentially eligible studies. Individual studies from previous systematic reviews were not directly synthesized with the included studies if they did not meet our inclusion criteria. We did however compare the findings from our included studies with findings from key systematic reviews.

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

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

## Strength of the Body of Evidence

We assessed the SOE using the approach described in AHRQ’s Methods Guide.<sup>20, 84</sup> We graded the SOE for each outcome assessed; thus, the SOE for two separate outcomes in a given study may be graded differently. These grades are presented in the SOE tables in the Discussion section of the report. The approach requires assessment of five domains: study limitations (previously named risk of bias), consistency, directness, precision, and reporting bias, which includes publication bias, outcome reporting, and analysis reporting bias (Table 3).<sup>84</sup>

**Table 3. Required domains: Definitions and scores**

| Domain            | Definition and Elements   | Score and Application   |
|-------------------|---|---|
| Study Limitations | <p>Study limitations is the degree to which the included studies for a given outcome have a high likelihood of adequate protection against bias (i.e., good internal validity), assessed through two main elements:</p> <ul style="list-style-type: none"> <li>• Study design: Whether RCTs or other designs such as nonexperimental or observational studies.</li> <li>• Study conduct. Aggregation of ratings of risk of bias of the individual studies under consideration.</li> </ul>   | <p>Score as one of three levels, separately by type of study design:</p> <ul style="list-style-type: none"> <li>• <b>Low</b> level of study limitations</li> <li>• <b>Medium</b> level of study limitations</li> <li>• <b>High</b> level of study limitations</li> </ul>  |
| Directness        | <p>Directness relates to (a) whether evidence links interventions directly to a health outcome of specific importance for the review, and (b) for comparative studies, whether the comparisons are based on head-to-head studies. The EPC should specify the comparison and outcome for which the SOE grade applies.</p> <p>Evidence may be indirect in several situations such as:</p> <ul style="list-style-type: none"> <li>• The outcome being graded is considered intermediate (such as laboratory tests) in a review that is focused on clinical health outcomes (such as morbidity, mortality).</li> <li>• Data do not come from head-to-head comparisons but rather from two or more bodies of evidence to compare interventions A and B—e.g., studies of A vs. placebo and B vs. placebo, or studies of A vs. C and B vs. C but not direct comparisons of A vs. B.</li> <li>• Data are available only for proxy respondents (e.g., obtained from family members or nurses) instead of directly from patients for situations in which patients are capable of self-reporting and self-report is more reliable.</li> </ul> <p>Indirectness always implies that more than one body of evidence is required to link interventions to the most important health outcome.</p> | <p>Score as one of two levels:</p> <ul style="list-style-type: none"> <li>• <b>Direct</b></li> <li>• <b>Indirect</b></li> </ul> <p>If the domain score is indirect, EPCs should specify what type of indirectness accounts for the rating.</p>  |
| Consistency       | <p>Consistency is the degree to which included studies find either the same direction or similar magnitude of effect. EPCs can assess this through two main elements:</p> <ul style="list-style-type: none"> <li>• Direction of effect: Effect sizes have the same sign (that is, are on the same side of no effect or a minimally important difference [MID])</li> <li>• Magnitude of effect: The range of effect sizes is similar. EPCs may consider the overlap of CIs when making this evaluation.</li> </ul> <p>The importance of direction vs. magnitude of effect will depend on the Key Question and EPC judgments.</p>   | <p>Score as one of three levels:</p> <ul style="list-style-type: none"> <li>• <b>Consistent</b></li> <li>• <b>Inconsistent</b></li> <li>• <b>Unknown</b> (e.g., single study)</li> </ul> <p>Single-study evidence bases (including mega-trials) cannot be judged with respect to consistency. In that instance, use “Consistency unknown (single study).”</p> |

| Domain         | Definition and Elements   | Score and Application  |
|----------------|---|--|
| Precision      | <p>Precision is the degree of certainty surrounding an effect estimate with respect to a given outcome, based on the sufficiency of sample size and number of events.</p> <ul style="list-style-type: none"> <li>• A body of evidence will generally be imprecise if the optimal information size (OIS) is not met. OIS refers to the minimum number of patients (and events when assessing dichotomous outcomes) needed for an evidence base to be considered adequately powered.</li> <li>• If EPCs performed a meta-analysis, then EPCs may also consider whether the CI crossed a threshold for an MID.</li> <li>• If a meta-analysis is infeasible or inappropriate, EPCs may consider the narrowness of the range of CIs or the significance level of p values in the individual studies in the evidence base.</li> </ul>   | <p>Score as one of two levels:</p> <ul style="list-style-type: none"> <li>• <b>Precise</b></li> <li>• <b>Imprecise</b></li> </ul> <p>A precise estimate is one that would allow users to reach a clinically useful conclusion (e.g., treatment A is more effective than treatment B).</p>  |
| Reporting Bias | <p>Reporting bias results from selectively publishing or reporting research findings based on the favorability of direction or magnitude of effect. It includes:</p> <ul style="list-style-type: none"> <li>• Study publication bias; i.e., nonreporting of the full study.</li> <li>• Selective outcome reporting bias; i.e., nonreporting (or incomplete reporting) of planned outcomes or reporting of unplanned outcomes.</li> <li>• Selective analysis reporting bias, i.e., reporting of one or more favorable analyses for a given outcome while not reporting other, less favorable analyses.</li> </ul> <p>Assessment of reporting bias for individual studies depends on many factors—e.g. availability of study protocols, unpublished study documents, and patient-level data. Detecting such bias is likely with access to all relevant documentation and data pertaining to a journal publication, but such access is rarely available.</p> <p>Because methods to detect reporting bias in observational studies are less certain, this guidance does not require EPCs to assess it for such studies.</p> | <p>Score as one of two levels:</p> <ul style="list-style-type: none"> <li>• <b>Suspected</b></li> <li>• <b>Undetected</b></li> </ul> <p>Reporting bias is suspected when:</p> <ul style="list-style-type: none"> <li>• Testing for funnel plot asymmetry demonstrates a substantial likelihood of bias,</li> </ul> <p>And/or</p> <ul style="list-style-type: none"> <li>• A qualitative assessment suggests the likelihood of missing studies, analyses, or outcomes data that may alter the conclusions from the reported evidence.</li> </ul> <p>Undetected reporting bias includes all alternative scenarios.</p> |

CI=confidence interval; EPC=Evidence-based Practice Center; MID=minimally important difference; OIS=optimal information size; RCT=randomized controlled trial

Additional domains were used when appropriate (most relevant to observational studies) and included coherence, dose-response association, impact of plausible residual confounders, and strength of association (magnitude of effect). These domains were considered qualitatively, and a summary rating of high, moderate, or low SOE was assigned for each outcome after discussion by two reviewers. In some cases, high, moderate, or low ratings were impossible or imprudent to make, for example, when no evidence is available or when evidence on the outcome was too weak, sparse, or inconsistent to permit any conclusion to be drawn. In these situations, a grade of “insufficient” was assigned. Table 4 defines the four-level grading scale.

**Table 4. Definition of strength of evidence grades**

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

## **Applicability**

We assessed applicability across our KQs using the method described in AHRQ’s Methods Guide.<sup>20, 85</sup> In brief, this method uses the PICOTS format as a way to organize information relevant to applicability. The most important issue with respect to applicability is whether the outcomes are different across studies that recruit different populations (e.g., age groups, ADHD presentations, exclusions for comorbidities) or use different methods to implement the interventions of interest; that is, important characteristics are those that affect baseline (control group) rates of events, intervention group rates of events, or both. We used a checklist to guide assessment of the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population in comparison with the target population, characteristics of the intervention used in comparison with care models currently in use, the possibility of diagnostic tool or treatment intervention learning curves, and clinical relevance and timing of the outcome measures (Appendix B). We summarized issues of applicability qualitatively.

## **Peer Review and Public Commentary**

Experts in the fields of pediatrics and child development, child psychiatry and psychology, pharmacology, and public health were invited to provide external peer review of the draft report. AHRQ, an associate editor, and members of the Technical Expert Panel were also given the opportunity to provide comments. In addition, the draft report was posted on the AHRQ EHC Web site for public comment from October 17, 2016, to November 14, 2016. We have addressed all reviewer comments, revising the text as appropriate, and have documented our responses in a disposition of comments report that will be made available 3 months after the Agency posts the final systematic review on the EHC Web site. A list of peer reviewers submitting comments on the draft report is provided in the front matter of this report.



## Results

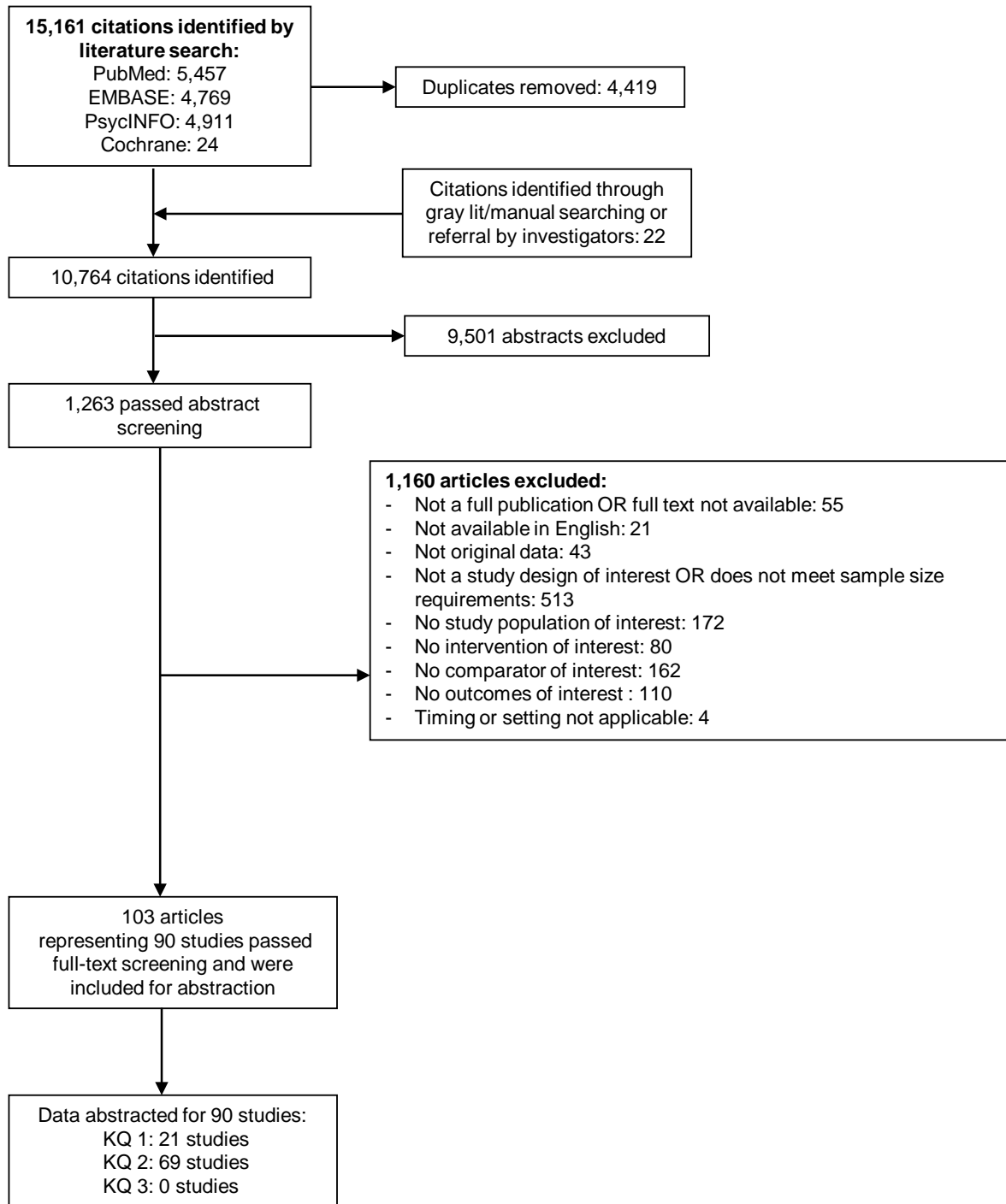
In what follows, we begin by describing the results of our literature searches. We then provide a brief overview description of the included studies. The remainder of the chapter is organized by Key Question (KQ). Under each of the three KQs, we begin by listing the key points of the findings, followed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

### Results of Literature Searches

Figure 2 depicts the flow of articles through the literature search and screening process. Searches of PubMed<sup>®</sup>, Embase<sup>®</sup>, PsycINFO<sup>®</sup>, and the Cochrane Database of Systematic Reviews yielded 10,742 unique citations. Manual searching of gray literature databases and bibliographies of key articles or referral by investigators identified 21 additional citations, for a total of 10,763 citations. After applying inclusion/exclusion criteria at the title-and-abstract level, 1,263 full-text articles were retrieved and screened. Of these, 1,160 were excluded at the full-text screening stage, leaving 103 articles for data abstraction. These 103 articles described 90 unique studies. The relationship of studies to the review questions is as follows: 21 studies relevant to KQ 1, 69 studies relevant to KQ 2, 0 studies relevant to KQ 3.

Appendix C provides a detailed listing of included articles. Appendix D provides a complete list of articles excluded at the full-text screening stage, with reasons for exclusion. Appendix E provides a “study key” table listing the primary and companion publications for the 90 included studies.

**Figure 2. Literature flow diagram**



KQ=Key Question

## Description of Included Studies: Overview

Overall, we included 103 articles representing 90 studies: 21 studies were relevant to KQ 1, 69 studies to KQ 2, and 0 studies to KQ 3. Studies were conducted wholly or partly in continental Europe or the United Kingdom (UK) (35 studies, 38%), the United States or Canada (23 studies, 25%), the Middle East (13 studies, 14%), Asia (12 studies, 13%), Latin America (3 studies, 3%), Australia/New Zealand (NZ) (3 studies, 3%), both in the United States and UK/Europe (2 studies, 2%), both in UK/Europe and Australia/NZ (1 study, 1%), and location not reported (1 study, 1%). Further details on the studies included for each KQ are provided in the relevant results sections below and in Appendixes F and G.

Note that our 90 included studies focused on individuals of varying age. To help the reader, we have categorized the included articles as (1) those that targeted children 6 years of age and under, (2) those that targeted children aged 7 through 17, and (3) those that included children of all ages through 17 years. Table 5 lists all included studies by these categorizations, and then throughout the results tables we indicate which age categories the specific studies addressed.

**Table 5. Ages of individuals represented in included ADHD studies**

| KQ   | Age Category of Included Participants | Studies   |
|------|---------------------------------------|---|
| KQ 1 | Ages 6 and under                      | Bunte, 2013 <sup>86</sup><br>Thorell, 2010 <sup>87</sup>  |
|      | Ages 7 through 17                     | Berger, 2010 <sup>88</sup><br>Bloch, 2012 <sup>89</sup><br>dosReis, 2010 <sup>90</sup><br>Ferrin, 2012 <sup>91</sup><br>Kim, 2015 <sup>92</sup><br>Kim, 2015 <sup>93</sup><br>Klenberg, 2010 <sup>94</sup><br>Liechti, 2013 <sup>95</sup><br>Markovska-Simoska, 2016 <sup>96</sup><br>Martin-Martinez, 2012 <sup>97</sup><br>Ogrim, 2012 <sup>98</sup><br>Ohan, 2011 <sup>99</sup><br>Park, 2016 <sup>100</sup><br>Soliva, 2010 <sup>101</sup><br>Zelnik, 2012 <sup>102</sup> |
|      | All ages through 17                   | Carballo, 2014 <sup>103</sup><br>Castro-Cabrera, 2010 <sup>104</sup><br>Caudal, 2011 <sup>105</sup><br>Gonzalez, 2013 <sup>106</sup>  |
| KQ 2 | Ages 6 and under                      | Abikoff, 2015 <sup>107</sup>  |

| KQ | Age Category of Included Participants | Studies  |
|----|---------------------------------------|--|
|    | Ages 7 through 17                     | Abikoff, 2013 <sup>108</sup><br>Anand, 2016 <sup>109</sup><br>Arcieri, 2012 <sup>110</sup><br>Arnold, 2011 <sup>111</sup><br>Bai, 2015 <sup>112</sup><br>Banaschewski, 2014 <sup>113</sup><br>Barragan, 2014 <sup>114</sup><br>Beck, 2010 <sup>115</sup><br>Bink, 2015 <sup>116</sup><br>Boyer, 2015 <sup>117</sup><br>Cetin, 2015 <sup>118</sup><br>Chacko, 2014 <sup>119</sup><br>Clemow, 2015 <sup>120</sup><br>Cortese, 2015 <sup>121</sup><br>DAVIS, 2015 <sup>122</sup><br>Didoni, 2011 <sup>123</sup><br>Duric, 2012 <sup>124</sup><br>Dutta, 2012 <sup>125</sup><br>Egeland, 2013 <sup>126</sup><br>Ercan, 2014 <sup>127</sup><br>Evans, 2016 <sup>128</sup><br>Ferrin, 2016 <sup>129</sup><br>Findling, 2010 <sup>130</sup><br>Gelade, 2016 <sup>131</sup><br>Gevensleben, 2009 <sup>132</sup><br>Gustafsson, 2010 <sup>133</sup><br>Hahn-Markowitz, 2016 <sup>134</sup><br>Hammerness, 2012 <sup>135</sup><br>Hariri, 2012 <sup>136</sup><br>Hong, 2015 <sup>137</sup><br>Huang, 2015 <sup>138</sup><br>Johnson, 2009 <sup>139</sup><br>Katz, 2010 <sup>140</sup><br>Li, 2011 <sup>141</sup><br>Manor, 2012 <sup>142</sup><br>Milte, 2012 <sup>143</sup><br>Mohammadpour, 2016 <sup>144</sup><br>Mohammadi, 2012 <sup>145</sup><br>Molina, 2009 <sup>146</sup><br>Moreno-Garcia, 2015 <sup>147</sup><br>Newcorn, 2016 <sup>148</sup><br>Oberai, 2013 <sup>149</sup><br>Ostberg, 2012 <sup>150</sup><br>Panei, 2010 <sup>151</sup><br>Pfiffner, 2014 <sup>152</sup><br>Power, 2012 <sup>153</sup><br>Raz, 2009 <sup>154</sup><br>Salehi, 2010 <sup>155</sup><br>Sallee, 2009 <sup>156</sup><br>Sayer, 2016 <sup>157</sup><br>Shakibaei, 2015 <sup>158</sup><br>Sibley, 2016 <sup>159</sup><br>Steiner, 2014 <sup>160</sup><br>Storebo, 2012 <sup>161</sup><br>Trzepacz, 2011 <sup>162</sup><br>van der Donk, 2015 <sup>163</sup><br>Vidal, 2015 <sup>164</sup><br>Widenhorn-Muller, 2014 <sup>165</sup><br>Zhang, 2010 <sup>166</sup> |

| KQ | Age Category of Included Participants | Studies  |
|----|---------------------------------------|--|
|    | All ages through 17                   | Chacko, 2009 <sup>167</sup><br>Ferrin, 2014 <sup>168</sup><br>Hiscock, 2015 <sup>169</sup><br>Mautone, 2012 <sup>170</sup><br>Myers, 2015 <sup>171</sup><br>Pelsser, 2011 <sup>172</sup><br>Tobaiqy, 2011 <sup>173</sup><br>van Dongen-Boomsma, 2014 <sup>174</sup><br>Webster-Stratton, 2011 <sup>175</sup> |

ADHD=attention deficit hyperactivity disorder; KQ=Key Question

We searched the ClinicalTrials.gov study registry as a mechanism for ascertaining publication bias by identifying studies that have been completed but are as yet unpublished. We acknowledge that this is not an exhaustive strategy, as several other registries also exist with differing geographical focus and varying degrees of overlap in their trial listings; however, in the opinion of the investigators, the widely used, U.S.-based ClinicalTrials.gov registry provided the most relevant information to the populations and interventions of interest in this review. Our search yielded 348 records of completed trials in the ClinicalTrials.gov registry. Manual review identified 51 of the records from ClinicalTrials.gov as potentially relevant to this review. Of those 51 records, we were not able to identify publications for 7 studies that had expected completion dates 3 years or more prior to our search. Of the 43 studies for which we could identify publications, all were considered potentially relevant to KQ 2. However, all publications had been previously identified in our PubMed, Embase, PsycINFO, and the Cochrane Database of Systematic Reviews searches. No novel publications were identified from our clinical trial registry searches.

Comparisons assessed in the 7 studies that did not have publications were pharmacologic versus pharmacologic (3 studies<sup>176-178</sup>), pharmacologic versus placebo (4 studies<sup>176, 179-181</sup>), and nonpharmacologic versus placebo (1 study<sup>182</sup>). One study contained three different arms evaluating both pharmacologic versus pharmacologic and pharmacologic versus placebo comparisons. We did identify trial results posted online for one study comparing lisdexamfetamine dimesylate versus methylphenidate hydrochloride versus placebo, and we also identified a press release for another study comparing a d-amphetamine transdermal system versus a placebo patch, but no corresponding peer-reviewed articles were found. These 7 studies if completed would add 1,357 patients to our analysis. The included studies in KQ 2 represent evidence from 14,737 patients and so although this is a substantial evidence base the inclusion of an additional 1,357 patients would increase by approximately 9 percent. Given the range of interventions studied and that 4 of them included placebo as a comparator of interest, we do not believe that the 7 “missing” trials are likely to have had a meaningful impact on our review’s results. Because of the relatively low proportion of unpublished studies identified through our ClinicalTrials.gov registry analysis, we do not believe these findings indicate significant publication bias in the evidence base that would impact our overall conclusions.

## **Key Question 1: ADHD Diagnosis**

KQ 1 examined the comparative diagnostic accuracy of approaches that can be used in the primary care practice setting or specialty clinic to initially diagnose attention deficit hyperactivity disorder (ADHD). KQ 1a focuses on the comparative diagnostic accuracy of approaches for diagnosing ADHD among individuals younger than 7 years of age. KQ 1b examines the comparative diagnostic accuracy of electroencephalography (EEG), imaging, or assessment of executive function that can be used to diagnose ADHD among individuals aged 7 through 17. KQ 1c focuses on how the comparative diagnostic accuracy of these approaches varies by clinical setting or patient subgroup including age, sex, or other risk factors associated with ADHD. KQ 1d examines the adverse effects associated with being labeled correctly or incorrectly as having ADHD. This KQ was not addressed in the prior reports.

To help the reader, Table 6 summarizes the available tools for individuals across the age spectrum and provides details on the domains assessed, the methods used for assessment, scoring methods, and interpretation. Tools are listed within categories of interviews, rating scales, and continuous performance tests.

**Table 6. Description of available tools for ADHD assessment**

| <b>Category</b>      | <b>Tool</b>   | <b>Domains Assessed</b>                              | <b>Method</b>  | <b>Scoring</b>   | <b>Interpretation</b>  |
|----------------------|---|--|--|--|--|
| <b>Interviews</b>    |   |  |  |  |  |
|                      | Standard clinical interview                               | ADHD diagnosis according to DSM-IV or DSM-5 criteria | Parent and/or child interview                              | NA   | Diagnostic interview that determines whether an individual has ADHD.   |
|                      | K-SADS (Kiddie SADS)                                      | ADHD diagnosis according to DSM-IV or DSM-5 criteria | Semi-structured diagnostic interview with parent and child | Items rated on a 3-point scale for severity (not present, subthreshold, and threshold—which combines both moderate and severe presentations). Parent, child, and summary ratings are made. | A diagnostic algorithm that includes all DSM criteria for ADHD. Results of the semi-structured interview indicate whether the individual has ADHD. |
|                      | DISC/DISC IV (Diagnostic Interview Schedule for Children) | ADHD diagnosis according to DSM-IV criteria          | Structured diagnostic interview with parent and/or child   | Items rated as yes, no, somewhat or sometimes  | A diagnostic algorithm that includes the DSM criteria for ADHD. Results of the diagnostic interview indicate whether the individual has ADHD.      |
| <b>Rating Scales</b> |   |  |  |  |  |

| Category | Tool   | Domains Assessed   | Method  | Scoring   | Interpretation  |
|----------|--|--|---|---|---|
|          | NICHQ (National Institute for Children's Health Quality) Vanderbilt Assessment Scale | <ul style="list-style-type: none"> <li>• ADHD Predominantly Inattentive</li> <li>• ADHD Predominantly Hyperactive/Impulsive</li> <li>• ADHD Combined</li> <li>• Oppositional Defiant Disorder</li> <li>• Conduct Disorder</li> <li>• Anxiety/Depression</li> </ul> | <ul style="list-style-type: none"> <li>• Parent questionnaire</li> <li>• Teacher questionnaire</li> </ul> | <p><i>Symptom Questions</i></p> <ul style="list-style-type: none"> <li>• Rated based on frequency</li> <li>• 0–3 scale (never, occasionally, often, very often)</li> <li>• Number of symptoms endorsed at a 2 (often) or 3 (very often) is summed for each domain</li> </ul> <p><i>Performance Questions</i></p> <ul style="list-style-type: none"> <li>• Rated based on problem severity</li> <li>• 0–5 scale (excellent, above average, average, somewhat of a problem, problematic)</li> </ul> | <ul style="list-style-type: none"> <li>• A positive screen indicates the need for further evaluation</li> <li>• The screening measure is positive if both of the following are met for a given domain:               <ul style="list-style-type: none"> <li>- Specific number of Symptom Questions are rated 2 or 3</li> <li>- At least one Performance Question is rated 4 or 5</li> </ul> </li> </ul> |



| Category | Tool   | Domains Assessed   | Method  | Scoring   | Interpretation  |
|----------|--|--|---|---|---|
|          | Conners Rating Scales <ul style="list-style-type: none"> <li>• CPRS</li> <li>• CTRS</li> <li>• CRS</li> <li>• Conners 3</li> </ul> | Note: Subscale names vary slightly between versions of the Conners Rating Scales, but include:<br><br><i>ADHD-related scales</i> <ul style="list-style-type: none"> <li>• Inattention</li> <li>• Hyperactivity/Impulsivity</li> <li>• Learning Problems</li> <li>• Executive Functioning</li> <li>• DSM Symptoms Scales</li> <li>• ADHD Index</li> <li>• Conners Global Index</li> </ul><br><i>Behavioral/emotional scales</i> <ul style="list-style-type: none"> <li>• Defiance/Aggression</li> <li>• Peer Relations/Social Problems</li> <li>• Family Relations</li> <li>• Oppositional Defiant Disorder</li> <li>• Conduct Disorder</li> <li>• Cognitive Problems</li> <li>• Anxious-Shy</li> <li>• Perfectionism</li> <li>• Psychosomatic</li> </ul> | <ul style="list-style-type: none"> <li>• Parent questionnaire</li> <li>• Teacher questionnaire</li> <li>• Adolescent questionnaire</li> </ul> | <ul style="list-style-type: none"> <li>• Rated based on how true the question is for the child</li> <li>• 0–3 (not true at all, just a little true, pretty much true, very much true).</li> </ul> | <ul style="list-style-type: none"> <li>• Raw scores for each scale are converted to T scores (mean=50, SD=10) based on a normative sample</li> <li>• Higher scores indicated increased clinical concern</li> <li>• Interpretation guidelines indicate that scores <math>\geq 60</math> are above average</li> </ul> |

| Category | Tool   | Domains Assessed   | Method  | Scoring   | Interpretation   |
|----------|--|--|---|---|--|
|          | SNAP-IV (Swanson, Nolan and Pelham Revision)       | <ul style="list-style-type: none"> <li>ADHD Predominantly Inattentive</li> <li>ADHD Predominantly Hyperactive/Impulsive</li> <li>ADHD Combined</li> </ul>  | <ul style="list-style-type: none"> <li>Parent questionnaire</li> <li>Teacher questionnaire</li> </ul> | <ul style="list-style-type: none"> <li>Rated based on frequency</li> <li>0–3 scale (not at all, just a little, quite a bit, very much)</li> </ul>         | <ul style="list-style-type: none"> <li>Scores can be interpreted in two different ways:               <ol style="list-style-type: none"> <li>Sum of items for each of the three subscales, with high score indicating more symptoms.</li> <li>Average rating per item for each of the three subscales. This rating is compared to the parent/teacher 5% cut off and a higher score indicates more symptoms.</li> </ol> </li> </ul> |
|          | DBDRS (Disruptive Behavior Disorder Rating Scale ) | <ul style="list-style-type: none"> <li>ADHD Predominantly Inattentive</li> <li>ADHD Predominantly Hyperactive/Impulsive</li> <li>ADHD Combined</li> <li>Oppositional Defiant Disorder</li> <li>Conduct Disorder</li> </ul> | <ul style="list-style-type: none"> <li>Parent questionnaire</li> <li>Teacher questionnaire</li> </ul> | <ul style="list-style-type: none"> <li>Rated based on frequency</li> <li>4 point scale (not at all, just a little, pretty much, and very much)</li> </ul> | <ul style="list-style-type: none"> <li>Scales scores are computed by summing the items in each domain.</li> <li>Scores were considered to be in the clinical range for ADHD if they are between the 95th to 100th percentile.</li> </ul>   |
|          | ADHD-RS (ADHD Rating Scale)                        | <ul style="list-style-type: none"> <li>ADHD Predominantly Inattentive</li> <li>ADHD Predominantly Hyperactive/Impulsive</li> <li>ADHD Combined</li> </ul>  | <ul style="list-style-type: none"> <li>Parent questionnaire</li> <li>Teacher questionnaire</li> </ul> | <ul style="list-style-type: none"> <li>Rated based on frequency</li> <li>0–3 (does not experience the symptom at all ... symptom very often)</li> </ul>   | <ul style="list-style-type: none"> <li>Scores are calculated by summing the items in each domain and the total items.</li> </ul>   |

| Category                            | Tool  | Domains Assessed   | Method  | Scoring   | Interpretation  |
|-------------------------------------|---|--|---|---|---|
|                                     | SDQ (Strengths and Difficulties Questionnaire)            | <ul style="list-style-type: none"> <li>Emotional symptoms</li> <li>Conduct problems</li> <li>Hyperactivity/inattention</li> <li>Peer relationship problems</li> <li>Prosocial behavior</li> <li>Total difficulties</li> </ul>  | <ul style="list-style-type: none"> <li>Parent questionnaire</li> <li>Teacher questionnaire</li> </ul> | <ul style="list-style-type: none"> <li>Rated based on how true the question is for the child</li> <li>0–2 (not true, somewhat true, certainly true)</li> <li>Some items are reverse coded.</li> </ul> | <ul style="list-style-type: none"> <li>Higher scores indicate more concerns in a given area.</li> <li>Raw scores can be compared to cut-points derived from a typical population.</li> </ul>  |
|                                     | BRIEF (Behavior Rating Inventory of Executive Function)   | <ul style="list-style-type: none"> <li>Behavioral Regulation Index (three scales)</li> <li>Metacognition Index (five scales)</li> <li>Global Executive Composite</li> </ul>  | <ul style="list-style-type: none"> <li>Parent questionnaire</li> <li>Teacher questionnaire</li> </ul> | <ul style="list-style-type: none"> <li>Rated based on frequency</li> <li>3-point scale (never, sometimes often)</li> </ul>  | <ul style="list-style-type: none"> <li>Raw scores are converted to T scores (mean=50; SD=10) and percentiles based on a normative sample.</li> <li>Higher scores indicate more problems relative age-matched peers.</li> </ul>  |
|                                     | CHEXI (Childhood Executive Functioning Inventory)         | <ul style="list-style-type: none"> <li>Inhibition (inhibition and regulation)</li> <li>Working Memory (working memory and planning)</li> </ul>   | <ul style="list-style-type: none"> <li>Parent questionnaire</li> <li>Teacher questionnaire</li> </ul> | <ul style="list-style-type: none"> <li>Rated based on how true the question is for the child</li> <li>0-5 point (definitely not true, not true, partially true, true, definitely true)</li> </ul>     | <ul style="list-style-type: none"> <li>Subscale scores are calculated by computing the mean score for items in each scale.</li> <li>Higher scores are indicative of more severe symptoms.</li> </ul>  |
|                                     | ATTEX (Attention and Executive Function Rating Inventory) | <ul style="list-style-type: none"> <li>Distractibility</li> <li>Impulsivity</li> <li>Motor hyperactivity</li> <li>Directing attention</li> <li>Sustaining attention</li> <li>Shifting attention</li> <li>Initiative</li> <li>Planning</li> <li>Execution of action</li> <li>Evaluation</li> <li>Total score</li> </ul> | <ul style="list-style-type: none"> <li>Teacher questionnaire</li> </ul>                               | <ul style="list-style-type: none"> <li>Rated based on severity</li> <li>3-point scale (not a problem, sometimes a problem, often a problem)</li> </ul>  | <ul style="list-style-type: none"> <li>Subscale scores are calculated by computing the mean score for items in each scale.</li> <li>A Total Score is calculated by summing all of the scale scores.</li> <li>Higher scores indicate greater severity (i.e., the behavior is more often a problem).</li> </ul> |
| <b>Continuous Performance Tests</b> |   |  |   |   |   |

| Category | Tool   | Domains Assessed   | Method  | Scoring  | Interpretation  |
|----------|--|--|---|--|---|
|          | Conners CPT (Continuous Performance Test)                            | <ul style="list-style-type: none"> <li>• Attention</li> <li>• Impulsivity</li> <li>• Sustained Attention</li> <li>• Vigilance</li> </ul>   | <ul style="list-style-type: none"> <li>• Computerized test</li> </ul> | <ul style="list-style-type: none"> <li>• Responses to a target and nontarget</li> </ul>  | <ul style="list-style-type: none"> <li>• Raw and standardized scores are calculated using an algorithm for each domain.</li> <li>• T scores and percentiles are provided, with higher scores indicating more problems in a given area.</li> </ul>   |
|          | IVA CPT (Integrated Visual and Auditory Continuous Performance Test) | <ul style="list-style-type: none"> <li>• Auditory Response Control</li> <li>• Visual Response Control</li> <li>• Auditory Attention</li> <li>• Visual Attention</li> <li>• Auditory Sustained Attention</li> <li>• Visual sustained Attention</li> </ul> | <ul style="list-style-type: none"> <li>• Computerized test</li> </ul> | <ul style="list-style-type: none"> <li>• Responses to the target (visual or auditory) and to the nontarget (visual or auditory)</li> </ul> | <ul style="list-style-type: none"> <li>• Visual and Auditory domain scores are calculated for a total of 12 quotients.</li> <li>• Omission and commission scores are generated, with more omission errors indicating greater distraction and more commission errors indicating greater impulsivity.</li> <li>• Hyperactivity-impulsiveness and attention deficit scales are calculated from the omission and commission errors, each comprising 3 visual and 3 auditory quotients.</li> </ul> |
|          | TOVA (Test of Variables of Attention)                                | <ul style="list-style-type: none"> <li>• Attention</li> <li>• Inhibitory control</li> </ul>  | <ul style="list-style-type: none"> <li>• Computerized test</li> </ul> | <ul style="list-style-type: none"> <li>• Responses to the target (correct) and responses to the nontarget (incorrect)</li> </ul>           | <ul style="list-style-type: none"> <li>• Errors of omission (not responding to the target) yield a measure of inattention.</li> <li>• Errors of commission (responding to a nontarget) yield a measure of impulsivity.</li> </ul>   |

| Category | Tool   | Domains Assessed   | Method  | Scoring  | Interpretation   |
|----------|--|--|---|--|--|
|          | CANTAB (Cambridge Neuro-psychological Test Automated Battery) <sup>a</sup> | <ul style="list-style-type: none"> <li>• General memory and learning, with subtests including:               <ul style="list-style-type: none"> <li>- Working memory</li> <li>- Executive functioning</li> <li>- Visual memory</li> <li>- Attention</li> <li>- Reaction time</li> <li>- Decision making</li> <li>- Response control</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>• Computerized test</li> </ul> | <ul style="list-style-type: none"> <li>• Scoring varies by domain and includes scores such as percent correct, number of errors, time to complete, response latency</li> </ul> | <ul style="list-style-type: none"> <li>• Interpretation varies depending on the outcome measures (e.g., higher number of errors indicates more impairment; lower response latency indicates less impairment).</li> </ul> |

<sup>a</sup> CANTAB description from personal communication with Cambridge Cognition Ltd. (January 2017).

Abbreviations: ADHD=attention deficit hyperactivity disorder; CPRS=Conners Parent Rating Scale; CTRS=Conners Teacher Rating Scale; DSM=Diagnostic and Statistical Manual of Mental Disorders

## Description of Included Studies

For KQ 1, we identified 22 articles<sup>86-106, 183</sup> representing 21 studies, 19 of which examined the comparative diagnostic accuracy of approaches used to diagnose ADHD, and 2 of which evaluated adverse effects of being labeled with ADHD. One study was described in more than one publication; Appendix E provides a key to primary and companion articles. Primary and companion papers are cited together in the text and tables that follow.

All 19 studies examining diagnostic accuracy were observational in design and represented a total of 4,339 enrolled patients. The 2 studies examining the adverse effects of ADHD labeling were observational in design and represented a total of 104 enrolled patients. Details of the study characteristics of the included studies are in Appendix F. Appendix G provides an overview of the included studies.

## Key Points

- Among executive function tests, Attention and Executive Function Rating Inventory (ATTEX) and Childhood Executive Function Inventory (CHEXI) performed better than Cambridge Neuropsychological Testing Automated Battery (CANTAB) for individuals aged 7–17 (strength of evidence [SOE]=low).
- This systematic evidence review identified limited studies with variable and inconsistent findings for diagnostic accuracy for all other diagnostics tools evaluated, including imagining and EEG-based tests (SOE=insufficient).
- Insufficient evidence was found regarding labeling or stigma of children with ADHD.

## Detailed Synthesis—Diagnosis

### Diagnostic Comparative Studies

Across the 19 diagnostic comparative studies, 14 different assessment tools were evaluated, including electroencephalography (EEG), integrated visual and auditory computerized performance test (IVA-CPT), continuous performance function tests (CPFT), event-related potentials (ERP), magnetic resonance imaging (MRI) of caudate body volume, Test of Variables of Attention (TOVA), CANTAB, ATTEX, CHEXI, electro interstitial scans (EIS), Disruptive Behavior-Diagnostic Observation Schedule (DB-DOS), neurological subtle signs (NSS), Kiddie-Disruptive Behavior Disorder Schedule (K-DBDS), and Strengths and Difficulties Questionnaire (SDQ). The diagnostic accuracy of the tools was measured primarily by receiver operator characteristics (ROC) for overall accuracy and area under the curve (AUC), from which sensitivity, specificity, false positives, and false negatives could be derived as shown in Table H-1, which summarizes findings from studies with subjects aged 6 years and younger, and Table H-2, which summarizes findings from studies with older children and adolescents, in Appendix H. The heterogeneity in methods and outcomes of these studies prevented quantitative meta-analysis.

Among the imaging studies, EEG was variable in its accuracy, ranging from 46 percent to 87 percent in five studies.<sup>92, 93, 96, 98, 106</sup> ERP evaluations yielded consistently higher accuracy scores when conducted independently (91%, the highest imaging accuracy<sup>104</sup>) and in combination with EEG (73%<sup>95</sup>). MRI scans of caudate body volume also had accuracy scores of 84%.<sup>101</sup> IVA-CPT had 75 percent to 82 percent based on outcomes assessed with omission errors and 68 percent to

85 percent based on outcomes assessed with omission errors.<sup>92, 93, 98</sup> Other CPTs, such as the TOVA, demonstrated limitations in their ability to correctly identify non-ADHD patients<sup>88, 89, 102</sup> and subtypes such as inattentive and hyperactive/impulsive.<sup>100</sup> Among the executive function tests, ATTEX<sup>94</sup> and CHEXI<sup>87</sup> performed better with overall accuracy rates of 91 percent to 93 percent, respectively, than the CANTAB,<sup>89</sup> which had low specificity (low SOE). Biometric devices such as EIS and Actigraphy had high sensitivity (80% to 97%) and specificity (84% to 98%).<sup>97, 105</sup> Additional approaches to diagnosing ADHD with promising clinical utility included neurological examinations for subtle signs of abnormal functioning (overall accuracy 84%), observational assessments of disruptive behaviors (92% AUC, 87% sensitivity, 79% specificity), and interviews using the K-DBDS (98% AUC, 77% sensitivity, 98% specificity).<sup>86, 91, 183</sup>

Few studies examined whether there are differences in accuracy based on age,<sup>91</sup> sex,<sup>94</sup> and ADHD presentation.<sup>86, 94, 100, 103, 183</sup> Also, there were no studies that compared how approaches to diagnosing ADHD differed by clinical settings. Collectively, a variety of approaches were tested in primary care and specialty clinics. Approaches in primary care clinics (five studies) included imaging, computerized function tests, executive function tests, and standardized questionnaires. Similarly, studies conducted in specialty clinics (13 studies) investigated these same approaches as well as biometric tools and observational assessments.

### **ADHD Labeling/Stigma Studies**

Only two studies evaluated the adverse effects associated with being labeled correctly or incorrectly as having ADHD.<sup>90, 99</sup> These good-quality studies did not address the negative experiences or outcomes of the children with ADHD but rather teachers' reactions and parents' concerns regarding ADHD labels for affected youth. Insufficient evidence was found regarding labeling or stigma. This KQ was not addressed with the 2011 review.

### **Strength of Evidence—Diagnosis**

Tables 7 and 8 summarize the SOE for the KQ 1 findings based on this report's included studies. The studies evaluated diverse tools and the heterogeneity in their findings and precision led to insufficient SOE for most tools.

**Table 7. Strength of evidence for major outcomes—diagnosis**

| <b>Diagnostic Tool</b>        | <b>No. Studies/<br/>Design<br/>(N Patients)</b> | <b>Study<br/>Limitations</b> | <b>Directness</b> | <b>Consistency</b> | <b>Precision</b> | <b>Reporting<br/>Bias</b> | <b>Findings</b>   |
|-------------------------------|---|------------------------------|-------------------|--------------------|------------------|---------------------------|---|
| EEG and Imaging               | 5 Obs<br>(259)                                  | Medium                       | Direct            | Inconsistent       | Imprecise        | None                      | EEG demonstrated variability in five studies. <sup>95, 101, 104, 106 96</sup>                               |
| Insufficient                  | 7–17, all<br>through 17                         |                              |                   |                    |                  |                           |   |
| EEG, Imaging,<br>and CPT      | 3 Obs<br>(355)                                  | Medium                       | Direct            | Inconsistent       | Imprecise        | None                      | EEG demonstrated variability in four studies.. <sup>92, 93, 98</sup>  |
| Insufficient                  | 7–17  |                              |                   |                    |                  |                           |   |
| CPT                           | 3 Obs<br>(402)                                  | Medium                       | Direct            | Inconsistent       | Imprecise        | None                      | CPT demonstrated variability in 3 observational studies. <sup>88, 100, 102</sup>                            |
| Insufficient                  | 7–17  |                              |                   |                    |                  |                           |   |
| CPT and<br>executive function | 1 Obs<br>(34)                                   | Medium                       | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient because of the sample size of the single observational study available. <sup>89</sup>  |
| Insufficient                  | 7–17  |                              |                   |                    |                  |                           |   |
| Executive<br>function         | 2 Obs<br>(961)                                  | Medium                       | Direct            | Consistent         | Precise          | None                      | Among executive function tests, ATTEX and CHEXI performed better than the CANTAB. <sup>87, 94</sup>         |
| Low                           | 6 and under,<br>7–17                            |                              |                   |                    |                  |                           |   |
| Biometric Devices             | 2 Obs<br>(175)                                  | Medium                       | Direct            | Inconsistent       | Imprecise        | None                      | Biometric devices for EIS and actigraphy demonstrated variability in the 2 studies. <sup>97, 105</sup>      |
| Insufficient                  | 7–17, all<br>through 17                         |                              |                   |                    |                  |                           |   |
| Observational<br>assessment   | 2 Obs<br>(1,436)                                | Medium                       | Direct            | Inconsistent       | Imprecise        | None                      | SOE was insufficient because of variations across the 2 available observational studies. <sup>91, 183</sup> |
| Insufficient                  | 6 and under,<br>7–17                            |                              |                   |                    |                  |                           |   |
| Standardized<br>questionnaire | 2 Obs<br>(774)                                  | Medium                       | Direct            | Inconsistent       | Imprecise        | None                      | SOE was insufficient because of variations across the 2 available observational studies. <sup>86, 103</sup> |
| Insufficient                  | 6 and under,<br>all through 17                  |                              |                   |                    |                  |                           |   |

Abbreviations: ATTEX=Attention and Executive Function Rating Inventory; CANTAB=Cambridge Neuropsychological Testing Automated Battery; CHEXI=Childhood Executive Function Inventory; CPT=continuous performance test; EEG=electroencephalography; NA=not applicable; Obs=observational; SOE=strength of evidence



**Table 8. Strength of evidence for major outcomes—labeling/stigma**

| <b>Outcome</b>  | <b>No. Studies/<br/>Design<br/>(N Patients)</b> | <b>Study<br/>Age<br/>Categories</b> | <b>Study<br/>Limitations</b> | <b>Directness</b> | <b>Consistency</b> | <b>Precision</b> | <b>Reporting<br/>Bias</b> | <b>Findings</b>  |
|-----------------|---|-------------------------------------|------------------------------|-------------------|--------------------|------------------|---------------------------|--|
| Labeling/Stigma | 2 Obs<br>(104)                                  | 7–17                                | Low                          | Indirect          | Consistent         | Imprecise        | None                      | SOE was insufficient because the studies did not address the negative experiences or outcomes of the children with ADHD but rather teachers' reactions and parents' concerns regarding ADHD labels for affected youth. <sup>90, 99</sup> |

Abbreviations: ADHD=attention deficit hyperactivity disorder; Obs=Observational; SOE=strength of evidence

## Key Question 2: ADHD Treatment

KQ 2 examined the comparative safety and effectiveness of pharmacologic and nonpharmacologic treatments for improving outcomes associated with ADHD. KQ 2 also evaluates how these outcomes vary by presentation (inattentive, hyperactive/impulsive, and combined) or other comorbid conditions, and assesses the risk of diversion of pharmacologic treatment. For the purposes of this review, supplements were classified as nonpharmacologic treatments because they are not regulated by the FDA.

### Description of Included Studies

For KQ 2, we identified 81 articles<sup>107-175, 184-195</sup> representing 69 studies that examined the comparative safety and effectiveness of pharmacologic and nonpharmacologic treatments for the treatment of ADHD. Eleven studies were described in more than one publication; Appendix E provides a key to primary and companion articles. Primary and companion papers are cited together in the text and tables that follow.

Of the 69 included studies, 10 were observational, representing a total of 6,523 enrolled patients.<sup>110, 115, 120, 121, 123, 127, 135, 151, 166, 173</sup> The 59 remaining studies were randomized controlled trials (RCTs), representing a total of 8,346 enrolled patients. Details of the study characteristics of the included studies are in Appendix F. Appendix G provides an overview of the included studies.

The next sections are organized by treatment comparisons as follows:

1. Pharmacologic versus placebo/usual care
2. Pharmacologic versus pharmacologic
3. Pharmacologic versus nonpharmacologic
4. Nonpharmacologic versus nonpharmacologic/placebo

### Key Point for Pharmacologic Versus Placebo/Usual Care

- There was limited additional evidence concerning FDA-approved ADHD medications compared with placebo or usual care across all outcomes in this updated systematic evidence review (SOE=insufficient).

### Detailed Synthesis—Pharmacologic Versus Placebo/Usual Care

For this comparison, we identified eight articles<sup>113, 130, 135, 146, 148, 162, 166, 192</sup> representing seven studies that compared an FDA-approved medication for ADHD with placebo or usual care. The study with two publications was the National Institute of Mental Health (NIMH) Collaborative Multisite Multimodal Treatment Study of Children with ADHD (MTA) in which one publication reported academic performance, psychiatric outcomes, and antisocial behavior between treatment arms at 8 years following the 14 months of active treatment,<sup>146</sup> and the other reported blood pressure and heart rate by initial treatment group assignments over 10 years.<sup>192</sup> Three of the six studies were conducted exclusively in the United States,<sup>130, 135, 146</sup> two were conducted in the United States and Europe,<sup>113, 148</sup> one study was conducted in Asia,<sup>166</sup> and one was conducted in Europe, Australia, New Zealand, Israel, and South Africa.<sup>162</sup>

Two studies were rated poor quality<sup>113, 166</sup> and the remaining rated fair quality. Both studies rated as poor quality had incomplete reporting of methods and results along with a high dropout rate. All but two<sup>135, 166</sup> were multicenter studies, and all of the multicenter studies were classified

as RCTs; however, one study randomized subjects to treatment following an initial RCT (withdrawal) to either continue lisdexamfetamine or placebo and assessed effects in the “withdrawal period,”<sup>113</sup> one study randomized treatment following an open-label study to either extended release guanfacine or placebo and assessed effects in the “withdrawal period,”<sup>148</sup> and one study (two articles) reported results long after the RCT treatment periods.<sup>146, 192</sup>

Placebo was the comparator in all of the studies except the two observational studies<sup>135, 166</sup> and the MTA study.<sup>146</sup> For the findings from the MTA study discussed in this section, only the comparison between the medication arm and community care arm are reported. There were only two treatment arms in all of the RCTs with placebo comparators except for one study in which there were three doses of lisdexamfetamine compared with placebo.<sup>130</sup> In the MTA study, there were also 4 treatment arms—medication management, behavioral management, combination of medications and behavior management, and community care (usual care). Medication management in MTA included 1-month double-blind titration with methylphenidate for best dose, progressing to an open titration with other drugs, such as d-amphetamine, pemoline, or imipramine if methylphenidate was unsatisfactory.

The two observational studies evaluated longer term outcomes. Methylphenidate (MPH) was the pharmaceutical in both studies, with doses of 0.3 to 0.6 mg/kg per day<sup>166</sup> and up to 1.5 mg/kg per day.<sup>135</sup> One study<sup>135</sup> compared study participants in the treatment group with a naturalistic sample as a control. The goal of that study was to determine if the 24-month use of MPH affected the risk of alcohol and illicit drug outcomes. The other study<sup>166</sup> also examined long-term (2–4 years) use of MPH and the risk of height and weight gaps or growth deficits.

## Changes in Standardized Symptom Scores

One fair-quality study presented results of ADHD symptom scores in children with active pharmacologic treatment versus placebo.<sup>130</sup> Three doses of lisdexamfetamine were compared with placebo. Although no statistical comparisons were made, there was a much smaller proportion of patients receiving placebo when compared with any dose of lisdexamfetamine that had achieved symptomatic remission at 1 month, defined as an ADHD-RS-IV score  $\leq 18$  (23.6% placebo, 62.3% lisdexamfetamine 30 mg/day, 67.6% lisdexamfetamine 50 mg/day, and 71.2% lisdexamfetamine 70 mg/day).

A second fair-quality study presented results of ADHD symptom scores in children initially stabilized on extended release guanfacine and then randomized to either continuation of the extended release guanfacine or placebo during a 26-week “withdrawal period.”<sup>148</sup> The difference in the LS mean of the ADHD-RS-IV total score at the end of the “withdrawal period” for those continuing extended release guanfacine was statistically significantly lower than those who received placebo indicating that the effect of the treatment was better maintained with continuation of extended release guanfacine as compared to placebo (-6.24; 95% confidence interval [CI] -9.01 to -3.48; ES=0.51,  $p < 0.001$ ). These inconsistent and imprecise findings resulted in insufficient SOE.

## Functional Impairment

One fair-quality study presented results of the Clinical Global Impression-Severity scores in children initially stabilized on extended release guanfacine and then randomized to either continuation of the extended release guanfacine or placebo during a 26 week “withdrawal period.”<sup>148</sup> The proportion of children with low severity score (score 1 or 2) at the end of the “withdrawal period” was statistically significantly lower in those who continued extended

release guanfacine versus placebo in the “withdrawal period” (50% vs. 32.5%,  $p = 0.001$ ). The SOE was insufficient given findings from this one study with imprecise findings and medium risk of bias.

## **Alcohol Use**

One fair-quality study focused on assessing youth self-reported alcohol use using the Drug Use Screen Inventory in children aged 12 to 17 who were mostly male.<sup>135</sup> The study groups for this observational study conducted in the United States were clinical trial participants receiving open label MPH, nonclinical trial youth receiving MPH or amphetamine per their primary care provider, nonclinical trial youth not receiving any ADHD medications, and youth without ADHD. A lower proportion of clinical trial participants reported alcohol use in the preceding year (10%) than nonclinical trial youth receiving MPH or amphetamine (33%,  $p = 0.008$  compared with clinical trial participants) or nonclinical trial youth not receiving any ADHD medications (35%,  $p = 0.002$  compared with clinical trial participants). However, it is not clear whether the clinical trial participation or the more rigorous screening for the clinical trial created a selection bias (insufficient SOE).

## **Sexual Development**

One fair-quality study focused on sexual development in children initially aged 6 to 15 years who were randomized to atomoxetine versus placebo.<sup>162</sup> Among 394 patients who were mostly male, no statistically significant differences were seen in median age of puberty (12.6 in atomoxetine [ATX] group and 12.3 in placebo group,  $p = 0.88$ ) or frequency of onset of puberty (26% in ATX group and 26.9% in placebo group  $p = 0.88$ ). However, the mean height change was higher in the placebo group (3.2 inches in ATX group and 4.22 in placebo group,  $p = 0.01$ ). The SOE was insufficient given imprecise evidence from this one study.

## **Peer Relationships**

One poor-quality study reported results of the quality of peer relationships on the CHIP-CE PRF subdomain for peer relationships at the end of a 6-week period in which one group had their lisdexamfetamine continued and the other group was switched to placebo.<sup>113</sup> The effect size was 0.434 ( $p < 0.001$ ) for the lisdexamfetamine group versus placebo, indicating better peer relationships in the lisdexamfetamine group than placebo. The SOE was insufficient given evidence from this one study with incomplete reporting of both methods and outcomes, along with high dropout rates.

## **Risk Avoidance**

One poor-quality study reported results of risk avoidance on the Child and Health Illness Profile Child Edition, Parent Report Form (CHIP-CE PRF) subdomain risk avoidance at the end of a 6-week period in which one group had their lisdexamfetamine continued and the other group was switched to placebo.<sup>113</sup> The effect size was 0.613 ( $p < 0.01$ ) for the lisdexamfetamine group versus placebo, indicating greater risk avoidance in the lisdexamfetamine group than placebo. Again limitations of the study, combined with imprecise findings led to an insufficient SOE.

## **Academic Performance**

The four-arm MTA study reported results of academic performance at 8 years, finding no statistically significant treatment effects identified for reading, math, or GPA at 8 years.<sup>146, 192</sup>

Insufficient evidence is available to know whether this is due to a lack of long-term treatment benefit or reflects the need for more intensive care for the subjects after completion of the MTA study.

## **Antisocial Behavior, Accidents, and Psychiatric Illness**

The four-arm MTA study found no statistically significant treatment effects on incarceration, aggression, or motor vehicle accidents at 8 years.<sup>146, 192</sup> There was a statistically significant treatment effect with anxiety at 8 years (14.9% medication management, 16.7% behavioral management, 18.3% combination, and 19.7% placebo; p value for treatment effect=0.0217). The SOE was insufficient as these findings were based on a stepped approach and it was unclear which specific medications subjects received.

## **Adverse Effects**

In one study, selected adverse effects of ATX versus placebo were reported.<sup>162</sup> There was a higher rate of increased appetite (7.1% vs 1.4%, p=0.006) and gastrointestinal symptoms (8.2% vs. 2.7%, p=0.046) in patients receiving ATX versus placebo (insufficient SOE for both others). Findings from this same study and the one poor-quality observational study<sup>166</sup> indicate small significant reductions in height and weight among the MPH groups and higher rates of alcohol or drug use during the past year. Both studies compared ADHD participants with non-ADHD participants. The SOE was insufficient given the findings were the large loss to followup and potential risk of bias.

## **Findings in Relation to What Is Already Known—Pharmacologic Versus Placebo/Usual Care**

In the 2011 report,<sup>4</sup> 13 short-term studies compared MPH with placebo (one also compared mixed amphetamine salts [MAS] with placebo) in children under 6 years of age; 9 longer term studies compared pharmacologic agents (4 MPH, 2 ATX, 1 amphetamine or MAS, and 2 any stimulant) with placebo. The studies in children under 6 years of age were relatively small and thus most of the conclusions are based on a single larger RCT of good quality, the Preschool ADHD Treatment Study (PATS),<sup>196</sup> indicating that for children without comorbidities, MPH was very effective (SOE=low).

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

Our update evaluates one additional poor-quality study, observational in design, by Zhang et al.<sup>166</sup> that specifically looked at the long-term outcomes of height and weight from MPH use. Findings from that study indicate small but significant reductions in height and weight among the MPH groups compared with non-ADHD participants. Given the large rate of loss to follow up within this study and inadequate reporting of methods and results the SOE was insufficient.

This updated systematic review—although focused on assessing the comparative efficacy and safety of FDA approved ADHD medications versus placebo—was likewise unable to make definitive conclusions given the small number of studies during the current time period and the limited quality of those studies. There is insufficient overlap in study design and outcomes between the findings in this updated systematic review and the 2011 report to qualitatively improve the certainty regarding the benefits and harms of treatment beyond the individual reviews' findings.

## **Strength of Evidence—Pharmacologic Versus Placebo/Usual Care**

Table 9 summarizes the SOE for comparisons between pharmacologic and placebo/usual care treatments based on this report's included studies. For most outcomes there was only one either low- or fair-quality study exploring the outcome of interest with imprecise findings and so the evidence was given an insufficient SOE grade.

**Table 9. Strength of evidence for major outcomes—comparisons between pharmacologic and placebo/usual care treatments**

| <b>Outcome</b>                         | <b>No. Studies/<br/>Design<br/>(N Patients)</b> | <b>Study<br/>Limitations</b> | <b>Directness</b> | <b>Consistency</b> | <b>Precision</b> | <b>Reporting<br/>Bias</b> | <b>Findings</b>   |
|--|---|------------------------------|-------------------|--------------------|------------------|---------------------------|---|
| <b>SOE Grade</b>                       | <b>Age Category</b>                             |                              |                   |                    |                  |                           |   |
| <b>Major outcomes</b>                  |   |                              |                   |                    |                  |                           |   |
| Changes in standardized symptom scores | 2 RCTs (359)<br>7–17                            | Medium                       | Direct            | Inconsistent       | Imprecise        | Unclear                   | SOE was insufficient because of inconsistent and imprecise findings within 2 studies with medium risk of bias. <sup>130, 148</sup>                                      |
| Insufficient                           |   |                              |                   |                    |                  |                           |   |
| Functional Impairment                  | 1 RCT (219)<br>7–17                             | Medium                       | Direct            | NA                 | Imprecise        | Unclear                   | SOE was insufficient because of only one study was included with medium risk of bias and imprecise findings. <sup>148</sup>   |
| Insufficient                           |   |                              |                   |                    |                  |                           |   |
| Substance abuse                        | 1 Obs (211)<br>7–17                             | Medium                       | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient given medium risk of bias within one observational study. <sup>135</sup>   |
| Insufficient                           |   |                              |                   |                    |                  |                           |   |
| Sexual Development                     | 1 RCT (394)<br>7–17                             | Medium                       | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient because only one study was included with medium risk of bias and imprecise findings. <sup>162</sup>  |
| Insufficient                           |   |                              |                   |                    |                  |                           |   |
| Quality of peer relationships          | 1 RCT (Unclear)<br>7–17                         | High                         | Direct            | NA                 | Imprecise        | Unclear                   | SOE was insufficient given evidence from one low-quality study with imprecise findings. <sup>113</sup>  |
| Insufficient                           |   |                              |                   |                    |                  |                           |   |
| Risk-taking behaviors                  | 1 RCT (Unclear)<br>7–17                         | High                         | Direct            | NA                 | Imprecise        | Unclear                   | SOE was insufficient given evidence from one low-quality study with imprecise findings. <sup>113</sup>  |
| Insufficient                           |   |                              |                   |                    |                  |                           |   |
| Academic performance                   | 1 RCT (436)<br>7–17                             | Medium                       | Direct            | NA                 | Imprecise        | Unclear                   | SOE was insufficient because medication management was based on a stepped approach and it was unclear which specific medications subjects received. <sup>146, 192</sup> |
| Insufficient                           |   |                              |                   |                    |                  |                           |   |
| Aggression                             | 1 RCT (436)<br>7–17                             | Medium                       | Direct            | NA                 | Imprecise        | Unclear                   | SOE was insufficient because medication management was based on a stepped approach and it was unclear which specific medications subjects received. <sup>146, 192</sup> |
| Insufficient                           |   |                              |                   |                    |                  |                           |   |
| Incarceration                          | 1 RCT (436)<br>7–17                             | Medium                       | Direct            | NA                 | Imprecise        | Unclear                   | SOE was insufficient because medication management was based on a stepped approach and it was unclear which specific medications subjects received. <sup>146, 192</sup> |
| Insufficient                           |   |                              |                   |                    |                  |                           |   |

| <b>Outcome</b>            | <b>No. Studies/<br/>Design<br/>(N Patients)</b> | <b>Study<br/>Limitations</b> | <b>Directness</b> | <b>Consistency</b> | <b>Precision</b> | <b>Reporting<br/>Bias</b> | <b>Findings</b>   |
|---------------------------|---|------------------------------|-------------------|--------------------|------------------|---------------------------|---|
| Motor vehicle collisions  | 1 RCT (436)<br>7–17                             | Medium                       | Direct            | NA                 | Imprecise        | Unclear                   | SOE was insufficient because medication management was based on a stepped approach and it was unclear which specific medications subjects received. <sup>146, 192</sup> |
| Insufficient              |   |                              |                   |                    |                  |                           |   |
| Depression or anxiety     | 1 RCT (436)<br>7–17                             | Medium                       | Direct            | NA                 | Imprecise        | Unclear                   | SOE was insufficient because medication management was based on a stepped approach and it was unclear which specific medications subjects received. <sup>146, 192</sup> |
| Insufficient              |   |                              |                   |                    |                  |                           |   |
| Changes in appetite       | 1 RCT (394)<br>7–17                             | Medium                       | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient because only one study was included with medium risk of bias and imprecise findings. <sup>162</sup>  |
| Insufficient              |   |                              |                   |                    |                  |                           |   |
| Elevated blood pressure   | 1 RCT (493)<br>7–17                             | Medium                       | Direct            | NA                 | Imprecise        | Unclear                   | SOE was insufficient because medication management was based on a stepped approach and it was unclear which specific medications subjects received. <sup>146, 192</sup> |
| Insufficient              |   |                              |                   |                    |                  |                           |   |
| Gastrointestinal symptoms | 1 RCT (394)<br>7–17                             | Medium                       | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient because of only one study was included with medium risk of bias and imprecise findings. <sup>162</sup>   |
| Insufficient              |   |                              |                   |                    |                  |                           |   |
| Growth suppression        | 1 RCT, 1 Obs<br>(569)<br>7–17                   | High                         | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient because of high risk of bias given high loss to follow up combined with imprecise findings. <sup>162, 166</sup>                                    |
| Insufficient              |   |                              |                   |                    |                  |                           |   |
| Increased heart rate      | 1 RCT (507)<br>7–17                             | Medium                       | Direct            | NA                 | Imprecise        | Unclear                   | SOE was insufficient because medication management was based on a stepped approach and it was unclear which specific medications subjects received. <sup>146, 192</sup> |
| Insufficient              |   |                              |                   |                    |                  |                           |   |

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



## Key Points for Pharmacologic Versus Pharmacologic

- Based on evidence from 3 observational studies identified in this systematic evidence review, the proportion of patients reporting gastrointestinal (GI) effects was slightly higher for ATX than MPH (SOE=low).
- Since the 2011 report which described the benefit of psychostimulant therapy for up to 24 months, little additional evidence has been generated for comparing safety and efficacy of select FDA-approved medications for treatment of ADHD and SOE was insufficient for all other outcomes.

## Detailed Synthesis—Pharmacologic Versus Pharmacologic

For this comparison, we identified nine studies.<sup>110, 118, 120, 121, 123, 151, 156, 157, 173</sup> Of these, seven were multisite studies,<sup>110, 120, 121, 123, 151, 156, 173</sup> and two were a single site.<sup>118, 157</sup> Two studies were RCTs.<sup>118, 157</sup> Among the seven observational studies, four analyzed data from the Italian National ADHD Registry—three from a whole region<sup>110, 121, 151</sup> and one from selected sites in a specific region.<sup>123</sup> Government funding was reported for five studies,<sup>110, 123, 151, 157, 173</sup> industry funding for two studies,<sup>120, 156</sup> and unknown funding for two studies.<sup>118, 121</sup>

Treatments compared in five of the studies were ATX versus MPH.<sup>110, 118, 121, 123, 151</sup> One study compared extended-release guanfacine monotherapy with extended release guanfacine plus either amphetamine or MPH,<sup>156</sup> one assessed ATX monotherapy compared with ATX combined with any other ADHD medication,<sup>120</sup> one was a survey collecting patient-reported adverse events from any ADHD medication,<sup>173</sup> and one study compared cardiovascular effects of immediate release guanfacine, extended release dexamethylphenidate, or their combination.<sup>157</sup>

Of the nine studies, two reported results using one of the selected ADHD symptom scores, the Conner Rating Scale-Parent<sup>118</sup> and the ADHD Rating Scale.<sup>156</sup> One study reported results from one of the selected functional impairment tests, the Clinical Global Impression.<sup>120</sup> Of the nine studies, seven only reported adverse events of interest for this systematic review.<sup>110, 121, 123, 151, 156, 157, 173</sup>

## Changes in Standardized Symptom Scores

Two studies reported results of ADHD symptom scores.<sup>118, 156</sup> One study was an RCT conducted in a single site in Turkey in which children between the ages of 7 and 16 were randomly assigned to receive ATX (59 evaluable) or osmotic release oral system MPH (OROS-MPH) (61 evaluable).<sup>118</sup> The Conners Comprehensive Behavior Rating Scale-Teacher was used to assess and compare changes on the hyperactive, inattentive, and behavior subscales from baseline to 6 months and to compare the proportion of children achieving at least a 40-percent reduction in the hyperactive, inattentive, and behavior subscales at 6 months. There were no statistically significant differences between the children taking ATX and those taking OROS-MPH in any of these measures. This study was rated as fair quality.

The second study was an observational study enrolling children from two prior RCTs conducted in the United States evaluating extended-release guanfacine (one of which permitted use of amphetamine or MPH with the extended-release guanfacine).<sup>156</sup> In this observational extension study, children aged 6 to 17 at initiation received one of four doses of extended-release guanfacine monotherapy (n=206) or any dose of extended-release guanfacine in combination with amphetamine or MPH as the combination group (n=53). The ADHD Rating Scale was used

to assess ADHD symptoms at various time points. The change in score within each treatment arm (monotherapy or combination therapy) from baseline to last assessment (time varied up to 24 months) was determined, but treatment arms were not compared. There was a statistically significant decrease in mean score in each arm; -20.1 ( $\pm$  13.5) for monotherapy and -16.1 ( $\pm$  11) for combination therapy (both  $p < 0.001$ ). This study was rated as poor quality given several potential risks of bias including lack of allocation concealment and blinding. In addition participants were subjects from prior studies who were titrated to tolerated dose of guanfacine then assessed for changes in ADHD symptoms increasing potential bias.

The SOE was insufficient given the heterogeneity between the symptom scores, inconsistency in findings, and the potential high risk of bias.

## Functional Impairment Scores

Only one study presented results using a selected functional impairment tool.<sup>120</sup> This study was an industry-funded, observational study conducted in two U.S. sites. Chart-abstracted data were used to compare least-square means of the Clinical Global Impression scale assessed at least 50 days after the start of pharmacologic therapy in children aged 6 to 17 receiving ATX monotherapy ( $n=37$ ) compared with children receiving ATX combination therapy (combined with any other ADHD medication) ( $n=34$ ). The statistical model was adjusted using propensity scores. No statistically significant difference in least-square mean Clinical Global Impressions Score was found between the treatment groups ( $p=0.4072$ ). This study was rated as poor quality given its retrospective nature, lack of power, and issues with reporting of its methods and outcomes (SOE=insufficient).

## Adverse Events

Seven studies presented adverse events from ADHD pharmacologic therapies.<sup>110, 121, 123, 151, 156, 157, 173</sup> One fair-quality study presented results from a single survey of the parents of 578 children aged 3 to 16 conducted in the UK to ascertain recalled adverse drug reactions to any ADHD medication.<sup>173</sup> Among 200 completed surveys, 80 percent were from children taking MPH alone or in combination. Because the number of patients exposed to each drug or drug combination was not reported, it is difficult to draw any conclusions from these results.

Four studies reporting adverse effects were observational studies comparing ATX with MPH.<sup>110, 121, 123, 151</sup> All of these used data from the Italian National ADHD Registry—three in whole<sup>110, 121, 151</sup> and one from selected sites in a specific region.<sup>123</sup> Thus, it is not possible to determine the total number of unique patients, as patients may have been included in more than one study. Of these four studies, one poor-quality study focused on electrocardiogram (ECG), blood pressure, and heart rate changes only.<sup>110</sup> In this study, there was a higher risk of having at least one altered ECG (right bundle branch block [RBBB], sinus bradycardia, sinus tachycardia, increased QTc, and/or atrioventricular [AV] block) at 6 months (relative risk [RR] 1.29; 95% CI 0.52 to 3.21) and 12 months (RR 2.41; 95% CI 1.04 to 5.60) in patients receiving MPH versus ATX, although the increased risk at 6 months was not statistically significant. Systolic blood pressure, diastolic blood pressure, and heart rate were not compared by treatment arms but rather by changes at 6, 12, and 24 months. The only statistically significant change in patients taking MPH was an increase in heart rate at 6 months. The only statistically significant changes in patients taking ATX were an increase in heart rate as measured at 6 and 12 months and an increase in diastolic blood pressure as measured at 6 months. Given the short time frame for this

study and therefore lack of patients with events, there is concern that this study was not representative.

The other three studies using the Italian National ADHD Registry and comparing ATX with MPH reported on numerous adverse events (Table H-3 in Appendix H). Overall, gastrointestinal side effects or decreased appetite were the most commonly reported problems. In one of these studies after controlling for presence of comorbid psychiatric conditions, there was a statistically higher incidence rate ratio for gastrointestinal side effects (4.56; 95% CI 2 to 10.43), cardiovascular side effects (3.43; 95% CI 1.21 to 9.76), and neuropsychiatric side effects (2.54; 95% CI 1.34 to 4.74) for ATX versus MPH.<sup>121</sup> In another, there was a statistically significant greater risk of adverse reactions to ATX versus MPH (RR 3.57; 95% CI 1.92 to 6.64).<sup>151</sup> These studies were rated as fair to good quality.

A sixth study reporting adverse effects was a poor-quality RCT comparing extended-release guanfacine monotherapy versus combination therapy with amphetamine or MPH.<sup>156</sup> The rates of selected adverse events are presented in Table H-4 in Appendix H. Among the adverse events listed, somnolence and headache were the most common but were similar between the different groups.

The last study reporting only side effects of interest was a single-center RCT of good quality in which heart rate, systolic blood pressure, and diastolic blood pressure were reported over a 12 month open label follow-up period to a three armed RCT of immediate release guanfacine, extended release dexamethylphenidate, or the combination.<sup>157</sup> The number of patients who continued in the follow-up period was not reported. There was no statistically significant difference in heart rate over the 12 months between groups ( $p=0.09$ ), but there were statistically significant differences between groups in systolic and diastolic blood pressure ( $p=0.0005$  and  $p=0.01$ , respectively) with both systolic and diastolic blood pressure being higher for those who received extended release dexamethylphenidate as compared to the other two treatment arms.

The SOE for a slight increase in gastrointestinal symptoms for patients on ATX compared with MPH was low. For all other adverse effects the SOE was insufficient.

## **Findings in Relation to What Is Already Known—Pharmacologic Versus Pharmacologic**

The 2011 report<sup>4</sup> included comparisons of pharmacologic agents (MPH, DEX, MAS, ATX, and extended release guanfacine) in children under 6 years of age with ADHD or disruptive behavior disorder as part of KQ 1 and in people 6 years of age and older (including adults) with ADHD in KQ 2. In that systematic review, there were relatively few studies that directly compared pharmacologic agents relative to the number of studies that compared medications to placebo, nonpharmacologic assessment, and noncomparative studies. In children under 6 years of age, no studies directly compared pharmacologic agents. Our review did not specifically focus on this population of patients; however, children as young as 3 years of age were included in studies reported on adverse events associated with pharmacologic agents in comparative assessments.

In people aged 6 years and older, there were nine comparative studies of pharmacologic agents in the 2011 report; however, that report was focused on ascertaining only longer-term efficacy and safety. Because of the small number of comparative studies of pharmacologic agents, no specific conclusions were made regarding the comparative efficacy or safety of the included pharmacologic agents. The included studies spanned the following comparisons: one study compared efficacy in people receiving MPH compared with pemoline,<sup>197</sup> but pemoline is

not a pharmacologic agent of interest in this updated review as it has been removed from the US market. One other study compared extended-release guanfacine monotherapy with extended release guanfacine plus either amphetamine or MPH.<sup>156</sup> That study is also included in this updated review. Two studies assessed adverse events between ATX and unspecified stimulants,<sup>198</sup> and between MPH and DEX.<sup>199</sup> The remaining four studies compared growth in patients receiving MPH versus MAS,<sup>200</sup> DEX versus MPH,<sup>201</sup> amphetamine versus MPH,<sup>202</sup> and MPH versus DEX.<sup>203</sup>

This updated systematic review provides results from a larger number of studies comparing FDA-approved pharmacologic agents, especially comparisons of ATX and MPH; however, the SOE for efficacy or safety remains insufficient for most outcomes. There were no new conclusions regarding the effectiveness of pharmacologic treatments as compared to one another other than slightly higher gastrointestinal side effects for patients taking ATX as compared to MPH (SOE low).

### **Strength of Evidence—Pharmacologic Versus Pharmacologic**

Table 10 summarizes the SOE for comparisons of pharmacologic therapies based on this report's included studies. Small numbers of studies with variable quality demonstrating inconsistent and imprecise findings caused insufficient SOE grades for all outcomes other than GI symptoms.

**Table 10. Strength of evidence for major outcomes—comparisons of pharmacologic treatments**

| <b>Outcome</b>                                  | <b>No. Studies/<br/>Design<br/>(N Patients)</b> | <b>Study<br/>Limitations</b> | <b>Directness</b> | <b>Consistency</b> | <b>Precision</b> | <b>Reporting<br/>Bias</b> | <b>Findings</b>  |
|---|---|------------------------------|-------------------|--------------------|------------------|---------------------------|--|
| Changes in standardized symptom scores          | 1 RCT and 1 Obs (379)<br>7–17                   | High                         | Direct            | Inconsistent       | Imprecise        | Unclear                   | SOE was insufficient across these 2 studies because of heterogeneity in outcome measures, inconsistency in findings, and high risk of bias. <sup>118, 156</sup>    |
| Insufficient                                    |   |                              |                   |                    |                  |                           |  |
| Acceptability of treatment-Discontinuation Rate | 1 Obs (130)<br>7–17                             | Medium                       | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient because of the sample size and risk of bias related to the assessment of adherence. <sup>123</sup>  |
| Insufficient                                    |   |                              |                   |                    |                  |                           |  |
| Behavior changes                                | 1 Obs (130)<br>7–17                             | Medium                       | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient because of the study design and limitations in the pre-post assessment of behavior changes. <sup>123</sup>                                    |
| Insufficient                                    |   |                              |                   |                    |                  |                           |  |
| Cardiac arrhythmias                             | 1 Obs (750)<br>7–17                             | High                         | Direct            | Consistent         | Imprecise        | None                      | SOE was insufficient because of the risk of bias in the one observational study identified. <sup>110</sup>   |
| Insufficient                                    |   |                              |                   |                    |                  |                           |  |
| Changes in appetite                             | 3 Obs (1,966)<br>7–17                           | Medium                       | Direct            | Inconsistent       | Imprecise        | None                      | SOE was insufficient because of the risk of bias and lack of consistency in the observational studies. <sup>121, 123, 151</sup>                                    |
| Insufficient                                    |   |                              |                   |                    |                  |                           |  |
| Conduction abnormalities                        | 1 Obs (1,424)<br>7–17                           | Medium                       | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient because only one observational study was available and there was a risk that the outcome would not be identified. <sup>151</sup>              |
| Insufficient                                    |   |                              |                   |                    |                  |                           |  |
| Elevated blood pressure                         | 2 Obs and 1 RCT (2,382)<br>7–17                 | High                         | Direct            | Inconsistent       | Imprecise        | Unclear                   | SOE was insufficient because of the risk of bias in the 3 studies. <sup>110, 151 157</sup>   |
| Insufficient                                    |   |                              |                   |                    |                  |                           |  |
| Gastrointestinal symptoms                       | 3 Obs (1,966)<br>7–17                           | Medium                       | Direct            | Consistent         | Imprecise        | None                      | The proportion of patients reporting gastrointestinal effects or disease was small in all 3 studies and slightly higher for ATX than MPH. <sup>121, 123, 151</sup> |
| Low   |   |                              |                   |                    |                  |                           |  |

| <b>Outcome</b>                   | <b>No. Studies/<br/>Design<br/>(N Patients)</b> | <b>Study<br/>Limitations</b> | <b>Directness</b> | <b>Consistency</b> | <b>Precision</b> | <b>Reporting<br/>Bias</b> | <b>Findings</b>  |
|----------------------------------|---|------------------------------|-------------------|--------------------|------------------|---------------------------|--|
| Increased heart rate             | 3 Obs and 1 RCT (1137)<br>7-17                  | Low                          | Direct            | Consistent         | Imprecise        | Unclear                   | SOE was insufficient because of the risk of bias and lack of consistent outcome assessment. <sup>110, 121, 123, 157</sup>  |
| Insufficient                     |   |                              |                   |                    |                  |                           |  |
| Sleep disturbance                | 1 Obs (130)<br>7-17                             | Medium                       | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient because only one small observational study was identified, and because of the risk of bias in the assessment of the outcome measure. <sup>123</sup> |
| Insufficient                     |   |                              |                   |                    |                  |                           |  |
| Suicide ideation                 | 1 Obs (1424)<br>1 Obs (NR)<br>7-17              | Medium                       | Direct            | Consistent         | Imprecise        | None                      | SOE was insufficient because of study heterogeneity and risk that the outcome measure was not detected. <sup>121, 151</sup>  |
| Insufficient                     |   |                              |                   |                    |                  |                           |  |
| Tics or other movement disorders | 2 Obs (1554)<br>7-17                            | Medium                       | Direct            | Consistent         | Imprecise        | None                      | SOE was insufficient because of study heterogeneity and risk that the outcome measure was not detected. <sup>123, 151</sup>  |
| Insufficient                     |   |                              |                   |                    |                  |                           |  |

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

## Key Points for Pharmacologic Versus Nonpharmacologic

- MPH decreases appetite and causes more sleep disturbance than supplements including ginkgo biloba, ningdong granule, or omega-3/6 fatty acids (SOE=low).
- Evidence identified in this systematic review was insufficient for all other outcomes.

## Detailed Synthesis—Pharmacologic Versus Nonpharmacologic

For this KQ 2 comparison, we identified nine articles<sup>114, 124, 131, 141, 146, 147, 155, 189, 192</sup> representing seven RCT studies published between 2009 and 2016 that met our inclusion criteria. There was a total of 1,072 participants with a mean age ranging from 8.11 to 16.8, and the majority were male (65% to 85.3%). Country sites varied, with the majority conducted in the UK or Europe (n=3). More than half the studies (n=5) were government-sponsored research, most were single site (n=5), and the majority of studies recruited participants from specialty clinics (n=5). Study characteristics are in Table 11.

Of the 7 RCTs, MPH was the primary pharmaceutical intervention. Four trials were 3-arm studies comparing MPH alone or in combination with a nonpharmacologic intervention. The dosage of MPH was clinically adjusted according to tolerability and efficacy, ranging from 0.3 mg/kg per day to 1.5 mg/kg per day. Comparators in the trials included supplements (n=3; ginkgo biloba, omega-3/6, and ningdong), neurofeedback (n=3), behavioral therapy (n=1), or a combination of behavioral therapy, education, and physical activity (n=2). The duration of studies ranged from 6 weeks to 8 years.

## Outcome Measures

The selected outcome measures varied considerably across the 7 included studies (Table 11). Change in the ADHD rating scale for parent (n=3) and teacher (n=2) was the most commonly used outcome measure. Behavioral changes and academic performance were also commonly measured outcomes.

**Table 11. Characteristics of included studies**

| Characteristic                                | Value                 |
|---|-----------------------|
| Study design, number of studies<br>RCTs       | 7                     |
| Combined number of patients; range of % males | 1,072; 65.0% to 85.3% |
| Range of mean ages, years                     | 8.11 to 16.8          |
| Study years                                   | 2009-2016             |
| Length of intervention / follow-up period     | 6 weeks to 8 years    |
| Countries, number of studies                  |                       |
| Asia  | 1                     |
| UK or Europe                                  | 3                     |
| Middle East                                   | 1                     |
| South America                                 | 1                     |
| USA   | 1                     |
| Funding source, number of studies             |                       |
| Government                                    | 5                     |
| Industry                                      | 1                     |
| Nongovernment, nonindustry                    | 1                     |
| Study Sites, number of studies                |                       |
| Single site                                   | 5                     |
| Multisite                                     | 2                     |

| Characteristic  | Value |
|---|-------|
| Setting, number of studies  |       |
| Specialty clinic  | 5     |
| Primary clinic  | 1     |
| Academic setting  | 1     |
| Interventions, number of studies  |       |
| Supplements   | 3     |
| Neurofeedback   | 3     |
| Behavioral therapy  | 1     |
| Physical exercise, education, behavioral modification                     | 2     |
| Pharmaceutical intervention and dosage, number of studies                 |       |
| Methylphenidate   | 7     |
| 0.3-1 mg/kg/day   | 6     |
| 1.5 mg/kg/day   | 1     |
| Timing of last outcome assessment, number of studies                      |       |
| Short-term: ≤3 months   | 5     |
| Long-term: 6+ months  | 2     |
| Change in standardized scale outcomes, number of studies                  |       |
| ADHD Rating Scale–Parent  | 3     |
| ADHD Rating Scale–Teacher   | 2     |
| Barkley Rating Scale  | 1     |
| Clinician Global Impression–Clinician                                     | 1     |
| Clinician Global Impression–Parent  | 1     |
| Visual and Auditory Continuous Performance                                | 1     |
| Other outcomes, number of studies   |       |
| Behavior changes (sadness, aggression, irritability, anxiety, depression) | 7     |
| Academic performance  | 3     |
| Incarceration   | 2     |
| Motor vehicle collision   | 1     |
| Sleep   | 1     |
| Adverse effects of treatment, number of studies                           |       |
| Height and weight change  | 1     |
| Gastrointestinal symptoms (nausea, dyspepsia, stomach pain)               | 2     |
| Sleep disturbances (insomnia, hypersomnia, trouble falling asleep)        | 4     |
| Changes in appetite (suppression, decreased, increased)                   | 3     |

Abbreviations: ADHD=attention deficit hyperactivity disorder; RCT=randomized controlled trial

We identified three RCTs (2 good quality, 1 poor quality) comparing MPH with a supplement of ginkgo biloba,<sup>155</sup> ningdong granule,<sup>141</sup> or omega-3/6 fatty acid.<sup>114</sup> The poor-quality study<sup>114</sup> was unblinded and had high withdrawals (which differed between arms). Sample sizes were small, consisting of 50 to 90 participants, with one 3-arm trial comparing the combination of MPH plus omega-3/6. Changes in the ADHD Rating Scale were the primary outcome for all three trials. Individual study findings suggest that ginkgo biloba was less effective while ningdong granule and omega-3/6 had effects similar to MPH although the SOE was insufficient given the small overall sample size, short-term outcomes (6-8 weeks for the two good-quality RCTs), and lack of consistency and precision in the outcome measure.

Four RCTs (1 good quality, 2 fair quality, 1 poor quality) compared MPH with neurofeedback or<sup>131, 147</sup> behavioral therapy,<sup>146, 147, 192</sup> and a 3-arm trial combined MPH with neurofeedback.<sup>124, 189</sup> Sample sizes were small in two of the trials (n=57 and 91) and large (n=579) in the 8-year follow-up study.<sup>146, 147, 192</sup> The primary outcome measures varied among the trials. Study quality was reduced because of lack of blinding and variation in outcome measurement.

Table H-5 in Appendix H summarizes these findings across the 7 studies.



## **Adverse Effects of Supplementation**

Adverse effects were identified in four of the included studies.<sup>114, 131, 141, 155</sup> Changes in gastrointestinal symptoms (nausea, dyspepsia, stomach pain), sleep disturbances (insomnia, hypersomnia, trouble falling asleep), and changes in appetite (suppression, decreased, increased) were measured. A higher proportion of participants experienced adverse effects on sleep (low SOE) or appetite (low SOE) when assigned to the MPH or combined group with MPH as compared to the nonpharmacologic interventions in three studies.<sup>114, 141, 155</sup> In the fourth study, sleep quality was not affected by any of the received interventions.<sup>131</sup> Table H-6 in Appendix H summarizes the proportion of participants with adverse effects.

## **Findings in Relation to What Is Already Known—Pharmacologic Versus Nonpharmacologic**

Previous reviews have examined the relationship between pharmacologic and nonpharmacologic treatments comparing omega-3/6 with placebo.<sup>204, 205</sup> Previous reviews have not included neurofeedback as an intervention of interest. Our summary findings directly comparing MPH with the supplements of ginkgo biloba, ningdong granule, or omega-3/6 fatty acids have not been reported in previous reviews. We found insufficient SOE that ginkgo biloba, ningdong granule, or omega-3/6 supplements produced greater improvements in changes in standardized symptom scores (ADHD Rating Scale) compared to MPH. Several limitations existed among this literature including small sample sizes, and measuring only short-term outcomes in the good-quality studies.

The 2011 report<sup>4</sup> found that the evidence on long-term outcomes of MPH treatment was sparse and inconclusive. One exception to this was the study by Molina et al.<sup>146, 192</sup> (also included in this updated review) that showed reduced ADHD symptoms in a mostly male sample with ADHD combined type following 14 to 24 months of MPH treatment.

The 2011 report<sup>4</sup> also reported on adverse effects of pharmacologic interventions. The findings from that report were determined to be inconclusive due to information from observational studies and uncontrolled extensions to clinical trials. However, that review did not examine adverse effects of pharmacologic treatments when compared with supplements (i.e., ginkgo biloba, ningdong granule, and omega-3/6). Generally, a higher proportion of adverse effects was reported with MPH or combination of supplements and MPH compared with supplement (low SOE for both sleep disturbances and decreased appetite). Our SOE comparing MPH with these supplements are limited due to small sample sizes, overall quality of the studies, and assessment of short-term outcomes.

## **Strength of Evidence—Pharmacologic Versus Nonpharmacologic**

Table 12 summarizes the SOE for pharmacologic versus nonpharmacologic treatments based on this report's included studies. Small numbers of studies with potential limitations and inconsistent and imprecise findings caused insufficient SOE grades for all outcomes other than sleep disturbance and changes in appetite.

**Table 12. Strength of evidence for major outcomes—comparisons between pharmacologic and nonpharmacologic treatments**

| <b>Outcome</b>                         | <b>No. Studies/<br/>Design<br/>(N Patients)</b> | <b>Study<br/>Limitations</b> | <b>Directness</b> | <b>Consistency</b> | <b>Precision</b> | <b>Reporting<br/>Bias</b> | <b>Findings</b>  |
|--|---|------------------------------|-------------------|--------------------|------------------|---------------------------|--|
| Changes in standardized symptom scores | 5 RCTs (356)<br>7–17                            | Medium                       | Direct            | Inconsistent       | Imprecise        | Unclear                   | SOE was insufficient because of the small overall sample size and lack of consistency and precision in the outcome measure. <sup>114, 124, 141, 147, 155, 189</sup>  |
| Insufficient                           |   |                              |                   |                    |                  |                           |  |
| Behavior changes                       | 3 RCTs (274)<br>7–17                            | Medium                       | Direct            | Inconsistent       | Imprecise        | None                      | SOE was insufficient because of the small overall sample size and lack of consistency and precision in the outcome measure. <sup>114, 131, 141</sup>   |
| Insufficient                           |   |                              |                   |                    |                  |                           |  |
| Aggression                             | 1 RCT (436)<br>7–17                             | Medium                       | Direct            | NA                 | Imprecise        | Unclear                   | SOE was insufficient because of the risk of bias in the single RCT identified. <sup>146, 192</sup>   |
| Insufficient                           |   |                              |                   |                    |                  |                           |  |
| Depression or anxiety                  | 2 RCTs (486)<br>7–17                            | Medium                       | Direct            | Consistent         | Imprecise        | Unclear                   | SOE was insufficient because of the small overall sample size and lack of consistency and precision in the outcome measure. <sup>146, 155, 192</sup>   |
| Insufficient                           |   |                              |                   |                    |                  |                           |  |
| Academic performance                   | 1 RCT (436)<br>7–17                             | Medium                       | Direct            | NA                 | Imprecise        | Unclear                   | SOE was insufficient because of the risk of bias in the single RCT identified. <sup>146, 192</sup>   |
| Insufficient                           |   |                              |                   |                    |                  |                           |  |
| Incarceration                          | 1 RCT (436)<br>7–17                             | Medium                       | Direct            | NA                 | Imprecise        | Unclear                   | SOE was insufficient because of the small overall sample size and lack of consistency and precision in the outcome measure. <sup>146, 192</sup>  |
| Insufficient                           |   |                              |                   |                    |                  |                           |  |
| Motor vehicle collisions               | 1 RCT (436)<br>7–17                             | Medium                       | Direct            | NA                 | Imprecise        | Unclear                   | SOE was rated insufficient because of the small overall sample size and lack of consistency and precision in the outcome measure. <sup>146, 192</sup>  |
| Insufficient                           |   |                              |                   |                    |                  |                           |  |
| Changes in appetite                    | 3 RCT (212)<br>7–17                             | Medium                       | Direct            | Consistent         | Imprecise        | None                      | All three studies found the MPH medication group to have a significantly greater number of participants with decreased appetite when compared to supplementation by ningsong, omega-3/6 or ginkgo biloba. <sup>114, 141, 155</sup> |
| Low                                    |   |                              |                   |                    |                  |                           |  |
| Elevated blood pressure                | 1 RCT (493)<br>7–17                             | Medium                       | Direct            | NA                 | Imprecise        | Unclear                   | SOE was insufficient because of the small overall sample size and lack of consistency and precision in the outcome measure. <sup>146, 192</sup>  |
| Insufficient                           |   |                              |                   |                    |                  |                           |  |
| Gastrointestinal symptoms              | 2 RCTs (162)<br>7–17                            | Medium                       | Direct            | Inconsistent       | Imprecise        | None                      | SOE was insufficient because of the small overall sample size and lack of consistency and precision in the outcome measure. <sup>114, 141</sup>  |
| Insufficient                           |   |                              |                   |                    |                  |                           |  |

|  |                      |        |        |              |           |         |   |
|--|----------------------|--------|--------|--------------|-----------|---------|---|
| Increased heart rate   | 1 RCT (507)<br>7-17  | Medium | Direct | NA           | Imprecise | Unclear | SOE was rated insufficient because of the small overall sample size and lack of consistency and precision in the outcome measure. <sup>146, 192</sup>   |
| Insufficient   |                      |        |        |              |           |         |   |
| Sleep disturbance  | 4 RCTs (324)<br>7-17 | Medium | Direct | Inconsistent | Imprecise | None    | There was a greater proportion of sleep disturbance outcomes in the MPH medication group compared to supplementation by ningdong granule, ginkgo biloba, or neurofeedback. <sup>114, 141, 155</sup> A fourth study found no significant difference in sleep scores between interventions <sup>131</sup> |
| Low  |                      |        |        |              |           |         |   |
| Weight decrease  | 1 RCT (50)<br>7-17   | Medium | Direct | NA           | Imprecise | None    | SOE was insufficient because of the sample size in the single study and risk of bias measuring the outcome. <sup>155</sup>  |
| Insufficient   |                      |        |        |              |           |         |   |
| Abbreviations: MPH=methylphenidate NA=not applicable; Obs=observational; RCT=randomized controlled trial; SOE=strength of evidence |                      |        |        |              |           |         |   |

## Key Points for Nonpharmacologic Versus Nonpharmacologic/Placebo

- There is insufficient evidence based on the studies identified in this systematic evidence review to evaluate the effectiveness of neurofeedback in reducing ADHD symptoms.
- There is some evidence that cognitive training strategies such as the computer-based Cogmed cognitive training program may reduce ADHD symptoms in the short term but not the long term (SOE=low).
- Cognitive behavioral therapy resulted in improvement in ADHD symptoms (SOE=low).
- Child or parent training did not demonstrate differences in academic performance (SOE=low).
- Child or parent training improves ADHD symptoms (SOE=moderate).
- Omega-3 fatty acid supplementation was no different than placebo on ADHD symptoms (SOE=moderate).

## Categories of Interventions for This Comparison

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

1. Neurofeedback
2. Cognitive training
3. Cognitive behavioral therapy (CBT), focusing on the development of specific skills for patients to be aware of their symptoms of ADHD and developing strategies to minimize the effects of these symptoms
4. Child or parent training or behavioral intervention
5. Dietary supplementation with omega-3/6 fatty acids
6. Herbal or dietary approaches
7. Other approaches

Other approaches included community programs and programs that addressed mentoring and parent support, multisystemic intervention at school and with parents, in-home family training intervention, a general parenting program, using melatonin as an adjunct treatment, acupuncture, and a homeopathic intervention). Studies were included in these comparisons that had subjects in all study arms that received other ADHD treatment, including psychostimulants.

As previously described, there is insufficient evidence to directly compare omega-3/6 fatty acid supplementation to MPH or other psychostimulants. The effectiveness of omega-3/6 for the treatment of ADHD symptoms was not included in the 2011 report. This current review identified a single previous systematic review and meta-analysis (Bloch and Qawasmi<sup>204</sup>) comparing omega-3 fatty acid supplementation with placebo and found a small but statistically significant benefit on ADHD symptoms. The Bloch and Qawasmi systematic review included ten trials of 699 children. Only two trials found a benefit and the overall effect size from the meta-analysis was small (0.31). The meta-analysis conducted within this report found no benefit for omega-3 fatty acid supplementation. In summary, omega-3/6 supplementation is unlikely to have benefit.

Of the 7 intervention categories, only 2 had data from the previous systematic review thereby allowing us to discuss our new findings in relation to what is already known: (1) child or parent

training or behavioral interventions and (2) other approaches. These findings are described in their corresponding sections below.

## Detailed Synthesis—Overview

For this KQ 2 comparison, we identified 61 articles<sup>107-109, 111, 112, 115-117, 119, 122, 125-129, 131-134, 136-140, 142-147, 149, 150, 152-154, 158-161, 163-165, 167-172, 174, 175, 184-188, 190-195</sup> representing 50 studies that met our inclusion criteria. All but two studies were RCTs.<sup>115, 127</sup> Of the 47 RCTs, 28 were rated as good quality,<sup>107-109, 112, 116, 119, 122, 125, 126, 129, 131-134, 139, 142, 143, 150, 152, 158, 160, 161, 164, 167-169, 172, 174</sup> 19 as fair quality,<sup>111, 117, 128, 137, 138, 140, 144-147, 149, 153, 154, 159, 163, 165, 170, 171, 175</sup> and 1 as poor quality.<sup>136</sup> The two observational studies were was rated as fair quality.<sup>115, 127</sup> Of these, 20 were multisite studies, 29 were single-site studies, and one did not report the number of sites. Fifteen studies included patients in the United States, 19 were conducted in Europe, and 16 included patients from the Middle East, Asia, Australia, or New Zealand. Government funding supported 26 studies, industry supported 3 studies, nongovernment and nonindustry funding supported 11 studies. External funding was either not provided or not reported for 15 studies.

The 50 studies reported 54 comparisons of a nonpharmacologic therapy with either another nonpharmacologic therapy or no therapy (e.g., a placebo intervention, usual care, or a waitlist control). Of the 7 intervention categories, 5 evaluated neurofeedback; 10, cognitive training; 2, CBT; 13, child or parent training or behavioral intervention; 8, dietary supplementation with omega-3/6 fatty acids; 6, herbal or dietary approaches; and 9, other approaches. Details of these comparisons are reported below, organized by intervention category.

## Detailed Synthesis—Neurofeedback

Neurofeedback is a computer-aided type of nonpharmacologic treatment for ADHD that is based on biofeedback principles. Treatment typically involves patients using a computer monitor that shows brainwave activity through EEG. In the neurofeedback process, patients are trained to adjust their attention and thereby their brainwave activity. Four good-quality<sup>116, 131, 132, 160, 186, 193, 194</sup> and 1 fair-quality<sup>147</sup> studies representing 353 patients evaluated neurofeedback. Findings are summarized by outcome and described in Table H-7 in Appendix H. These studies had short periods of intervention, with only one study<sup>116</sup> describing findings to 6 months. Therefore, the overall SOE was insufficient.

## Acceptability of Treatment

Only one study examined parent-rated motivation of children to participate in treatment and the effectiveness of treatment, finding no difference between neurofeedback and the attention skills control condition.<sup>132, 193, 194</sup> The SOE was insufficient given that the evidence was from only one study which might have been underpowered.

## Behavior Changes

Only one small but good-quality study assessed behavior changes associated with a 12-week course of neurofeedback sessions. This study found no statistically significant differences in postintervention mean scores for the Inattention and Hyperactivity/Impulsiveness subscales of the Strengths and Weaknesses of ADHD and Normal Behavior (SWAN) questionnaire. The single small study resulted in an insufficient SOE.<sup>131</sup>

## **Changes in Standardized Symptom Scores**

One study found a statistically significant decrease in ADHD symptoms using a standard scale comparing neurofeedback with an attention skills control condition.<sup>132, 193, 194</sup> A second study found no difference between neurofeedback and cognitive training, but did find significant improvements in ADHD symptoms according to parent and teacher reporting for neurofeedback compared with control.<sup>160, 186</sup> A third study compared neurofeedback with standard pharmacologic treatment and a behavioral treatment and found that the group treated with neurofeedback showed greater improvement in a continuous performance test score when compared with each of the other groups.<sup>147</sup> Finally, a fourth study did not find any significant changes between children receiving neurofeedback versus those receiving treatment as usual.<sup>116</sup> The SOE was insufficient given the small sample sizes of all studies and the variation in outcomes reported.

## **Sleep Disturbance**

Only one study assessed sleep disturbance associated with a 12-week course of neurofeedback sessions. This study found no significant difference in postintervention mean scores in the Sleep Disturbance Scale for Children (SDSC) between neurofeedback and physical activity. The single small study resulted in an insufficient SOE.<sup>131</sup>

## **Adverse Effects of Neurofeedback**

No adverse effects from neurofeedback were reported.

## **Strength of Evidence—Neurofeedback**

Table 13 summarizes the SOE for neurofeedback based on this report's included studies. Inconsistent findings and heterogeneous interventions caused the insufficient SOE grades.

**Table 13. Strength of evidence for major outcomes—neurofeedback**

| <b>Outcome</b>                         | <b>No. Studies/<br/>Design<br/>(N Patients)</b> | <b>Study<br/>Limitations</b> | <b>Directness</b> | <b>Consistency</b> | <b>Precision</b> | <b>Reporting<br/>Bias</b> | <b>Findings</b>  |
|--|---|------------------------------|-------------------|--------------------|------------------|---------------------------|--|
| <b>SOE Grade</b>                       | <b>Age Category</b>                             |                              |                   |                    |                  |                           |  |
| Acceptability of treatment             | 1 RCT (102)<br>7–17                             | Low                          | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient because only one trial that might have been underpowered was identified. <sup>132, 193, 194</sup>                           |
| Insufficient                           |   |                              |                   |                    |                  |                           |  |
| Behavior change                        | 1 RCT (103)<br>7–17                             | Low                          | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient given findings from only one small study. <sup>131</sup>  |
| Insufficient                           |   |                              |                   |                    |                  |                           |  |
| Changes in standardized symptom scores | 4 RCTs (353)<br>7–17                            | Low                          | Direct            | Inconsistent       | Imprecise        | Unclear                   | SOE was insufficient because of the small sample size in the 4 trials and the variation in outcomes reported. <sup>116, 132, 147, 160, 186</sup> |
| Insufficient                           |   |                              |                   |                    |                  |                           |  |
| Sleep disturbance                      | 1 RCT (103)<br>7–17                             | Low                          | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient given findings from only one small study. <sup>131</sup>  |
| Insufficient                           |   |                              |                   |                    |                  |                           |  |

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

## Detailed Synthesis—Cognitive Training

Six good-quality<sup>119, 122, 126, 132, 160, 174, 186, 187</sup> and 2 fair-quality<sup>115, 163</sup> studies representing 768 patients evaluated cognitive training interventions. All but one study involved computer-based cognitive training programs, and of those five used a specific brand of intervention (Cogmed). Findings are summarized by outcome and described in Table H-8 in Appendix H. Meta-analysis was not possible given heterogeneity in outcomes and time frame. The specific findings detailed in the table are described below.

### Academic Performance

A single, good-quality RCT found no significant treatment effects in improvement in Wide Range Achievement Test 4 Progress Monitoring Version (WRAT) scores compared with a low-level (placebo) working memory training program that was identical to active intervention with respect to the types of training games utilized and the number of training trials per session, but for which difficulty level was not adjusted according to each user's performance parameters.<sup>119</sup> The SOE was insufficient given the small size of the single included study.

### Acceptability of Treatment

A single study examined parent-rated motivation of children to participate in treatment and the effectiveness of treatment, finding no difference between cognitive training and neurofeedback.<sup>132, 193, 194</sup> The SOE was insufficient given the small size of the single included study.

### Behavior Changes

A good-quality RCT found no significant between-group differences in scores on the Disruptive Behavior Disorder Rating Scale (DBDRS) compared with a partially-active-condition where inhibition and cognitive-flexibility were trained and the working memory-training task was presented in placebo-mode, or to a full placebo-condition.<sup>122</sup> The SOE was insufficient given the small size of the single included study.

### Changes in Standardized Symptom Scores

Of studies examining the Cogmed cognitive training programs,<sup>115, 119, 126, 163, 174, 187</sup> three of these studies<sup>119, 126, 174, 187</sup> found no significant changes on standard ADHD scales compared with low-level working memory games or a waitlist control. Two studies found a significant improvement on standardized scales.<sup>115, 163</sup> Of those, one compared the Cogmed intervention with a waitlist control, and at 4 months the treatment group had significantly better scores on parent report on the ADHD Index, Conners Cognitive Problems/Inattention, Conners Hyperactivity Parent, and BRIEF Metacognition Index.<sup>115</sup> No teacher measures showed any significant changes. In the other study, there was improvement at 2 and 6 months on the parent rated BRIEF Metacognition Index, and at 2 months (but not 6 months) on the BRIEF parent-rated behavioral index.<sup>163</sup>

Three other studies examined computer-based cognitive training programs.<sup>122, 132, 160, 186, 193, 194</sup> One compared the Braingame program to a computer game that did not have any cognitive training characteristics, finding no significant effect of this type of training.<sup>122</sup> The other two were studies comparing neurofeedback with computer-based cognitive training.<sup>132, 160, 186, 193, 194</sup> There was no difference between cognitive training and control in one,<sup>160, 186</sup> but neurofeedback



was found to be superior to both. The other directly compared the two interventions and found neurofeedback superior to cognitive attention skills training on a standardized ADHD scale.<sup>132, 193, 194</sup>

Overall the evidence from these studies provided low SOE that cognitive training improved standardized symptoms scores.

### **Adverse Effects of Cognitive Training**

No adverse effects from cognitive training were reported in any of the included studies.

### **Findings in Relation to What Is Already Known—Cognitive Training**

The 2011 review did not evaluate cognitive training. Our current systematic review demonstrates that cognitive training may improve symptoms scores (SOE=low).

### **Strength of Evidence—Cognitive Training**

Table 14 summarizes the SOE for cognitive training based on this report's included studies. Small numbers of studies with imprecise findings caused insufficient SOE grades for all outcomes other than changes in standardized symptom scores which had low SOE for a benefit with cognitive training.

**Table 14. Strength of evidence for major outcomes—cognitive training**

| <b>Outcome</b>                           | <b>No. Studies/<br/>Design<br/>(N Patients)</b> | <b>Study<br/>Limitations</b> | <b>Directness</b> | <b>Consistency</b> | <b>Precision</b> | <b>Reporting<br/>Bias</b> | <b>Findings</b>  |
|--|---|------------------------------|-------------------|--------------------|------------------|---------------------------|--|
| <b>SOE Grade</b><br>Academic performance | 1 RCT (85)<br>7–17                              | Low                          | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient because only one small trial was identified. <sup>119</sup>                                     |
| Insufficient                             |   |                              |                   |                    |                  |                           |  |
| Acceptability of treatment               | 1 RCT (102)<br>7–17                             | Low                          | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient because only one small trial was identified. <sup>132, 193, 194</sup>                           |
| Insufficient                             |   |                              |                   |                    |                  |                           |  |
| Behavior changes                         | 1 RCT (89)<br>7–17                              | Low                          | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient because only one small trial was identified. <sup>122</sup>                                     |
| Insufficient                             |   |                              |                   |                    |                  |                           |  |
| Changes in standardized symptom scores   | 9 RCTs (768)<br>7–17, all through 17            | Medium                       | Direct            | Inconsistent       | Imprecise        | None                      | Cognitive training may improve symptom scores. <sup>115, 119, 122, 126, 132, 160, 163, 174, 186, 187, 193, 194</sup> |
| Low                                      |   |                              |                   |                    |                  |                           |  |

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

## **Detailed Synthesis—Cognitive Behavioral Therapy**

One good-quality<sup>164</sup> and 1 fair-quality<sup>117, 185</sup> study representing 278 patients evaluated CBT. Findings are summarized by outcome and described below and in Table H-9 in Appendix H.

### **Changes in Standardized Symptom Scores**

Both studies found a statistically significant improvement in ADHD symptom scores for the CBT program as opposed to the control condition after the initial treatment (low SOE). One fair-quality study<sup>117, 185</sup> followed patients through 12 months and found the CBT condition maintained superiority in terms of ADHD scale scores. In addition, this study found that there was a greater improvement in the CBCL conduct disorder/oppositional defiant disorder subscale both immediately after treatment and at 12 months.

### **Depression or Anxiety**

The fair-quality study<sup>117, 185</sup> examined changes in the depression anxiety scale scores and found that the CBT group had greater improvement in depression and anxiety scores as opposed to the control group at 3 months and that the depression score improvements were maintained at 12 months. The SOE was insufficient given the evidence coming from only a single included study with medium risk of bias.

### **Adverse Effects of CBT**

No adverse effects from CBT were reported.

## **Strength of Evidence—Cognitive Behavioral Therapy**

Table 15 summarizes the SOE for CBT based on this report's included studies. Small numbers of studies with imprecise findings caused insufficient SOE grades for all outcomes other than changes in standardized symptom scores which had low SOE for a benefit from cognitive behavioral therapy.

**Table 15. Strength of evidence for major outcomes—cognitive behavioral therapy**

| <b>Outcome</b>                         | <b>No. Studies/<br/>Design<br/>(N Patients)</b> | <b>Study<br/>Limitations</b> | <b>Directness</b> | <b>Consistency</b> | <b>Precision</b> | <b>Reporting<br/>Bias</b>                               | <b>Findings</b>   |
|--|---|------------------------------|-------------------|--------------------|------------------|---|---|
| Changes in standardized symptom scores | 2 RCTs (278)<br>7–17                            | Low                          | Direct            | Consistent         | Imprecise        | Suspect (reasons for drop out not adequately described) | There was statistically significant improvement in ADHD symptoms associated with CBT relative to usual care or a limited CBT intervention. <sup>117, 164, 185</sup> |
| Low                                    |   |                              |                   |                    |                  |   |   |
| Depression or anxiety                  | 1 RCT (159)<br>7–17                             | Medium                       | Direct            | NA                 | Imprecise        | Suspect (reasons for drop out not adequately described) | SOE was insufficient because only one small trial was identified. <sup>117, 185</sup>   |
| Insufficient                           |   |                              |                   |                    |                  |   |   |

Abbreviations: ADHD=attention deficit hyperactivity disorder; CBT=cognitive behavioral therapy; NA=not applicable; RCT=randomized controlled trial; SOE=strength of evidence

## **Detailed Synthesis—Child or Parent Training or Behavioral Interventions**

Ten good-quality RCTs,<sup>108, 112, 129, 134, 150, 152, 161, 167-169</sup> 2 fair-quality RCTs,<sup>138, 159</sup> and 1 fair-quality observational study<sup>127</sup> representing 1,583 patients evaluated child or parent training or behavioral interventions. These included a range of different types of non-CBT behavioral interventions including organizational skills, social skills, attention skills, positive parenting, psychoeducational, sleep hygiene/behavioral, or parent or teacher behavioral training interventions. Findings are summarized by outcome and described below and in Table H-10 in Appendix H. Note that the interventions were mixed in terms of their strategies: some were interventions which helped parents learn how to cope with their own emotions, most strategies focused on how parents could manage specific behaviors from their children with ADHD.

### **Academic Performance**

Three RCTs of child-focused interventions evaluated academic performance outcomes. These trials found no change compared with the control condition (low SOE). One of these trials evaluated organizational skills training,<sup>108</sup> one evaluated social skills training,<sup>161</sup> and one evaluated an adolescent-specific, skills-based therapy called Supporting Teens' Autonomy Daily (STAND).<sup>159</sup>

### **Acceptability of Treatment**

The single RCT that assessed the outcome of acceptability of treatment found that parent satisfaction with process was superior with the behavioral intervention compared to the control group.<sup>167</sup> The SOE was insufficient given the small size of the single included study.

### **Changes in Standardized Symptom Scores**

Three RCTs examined psychoeducational programs for parents or families of children with ADHD.<sup>112, 129, 168</sup> All three found significant improvement on some standard measures of ADHD symptoms with child or parent training (moderate SOE). One study that examined children 6 to 16 years of age compared psychoeducation with a general counseling control and found significant improvement in overall ADHD scores for the intervention group compared with control.<sup>112</sup> Another study comparing psychoeducation with a control in children 5–18 years of age found significantly better ADHD scores on a standard scale at 12 weeks for overall symptoms and attention, and at 12 months there was significant difference only on inattention/cognition standard scores.<sup>168</sup> Another study compared a structured psychoeducation program for family members of children with ADHD to usual care, with outcomes assessed at 6 weeks and 6 months.<sup>129</sup> This study demonstrated significant improvements over time associated with psychoeducation in the CPRS index, CPRS inattention and cognition, and CPRS hyperactivity and impulsivity.

Other parenting interventions included a positive parenting program that did not find a strong effect on ADHD symptoms, but did find a significant effect on overall impairment rating compared to a behavioral parenting program and an even greater effect compared to a waitlist control.<sup>167</sup> There was a significant improvement in ADHD symptoms when comparing the positive parenting program to the waitlist control. Another parenting intervention that evaluated sleep hygiene and behavioral training for parents found improvements at 6 months in all parent-reported ADHD scores, but no difference between controls on teacher reported scores.<sup>169, 184</sup>

Another parent study compared children on MPH who received MPH alone or medication plus parent training; this study found no significant difference between groups.<sup>127</sup>

A combined behavioral training intervention for parents and teachers found no changes in ADHD scores at 10 weeks as reported by parents or teachers, but at 3 months postintervention did find improvement in parent reported ADHD scale scores, but not on teacher report.<sup>150</sup>

Another combined intervention study compared a combination of parent group and child group interventions with parent intervention alone or community care in general.<sup>152</sup> This study found improvement on symptoms of the combined groups, compared to both comparison conditions at 3 months. At approximately 6 months the improvements in parent reported ADHD symptoms were maintained. In terms of functional impairment there was no difference at 3 months between groups, while at 6 months the parent-reported, but not teacher-rated, functional impairment was improved in the intervention as compared to the parent group alone or the community control. One study examined social skills for children with a parallel parent group and found significant changes on the CBCL attention problem subscale as compared to a control condition including treatment as usual.<sup>138</sup> Another study evaluated an adolescent-specific, skills-based therapy called STAND over the course of 6 months.<sup>159</sup> This study found that the STAND intervention was associated with statistically significant improvements in standardized scores that assessed the severity of ADHD symptoms. Another study that evaluated the impact of 10 parent-child weekly cognitive-functional (Cog-Fun) intervention sessions found that the Cog-Fun intervention was associated with significant improvements in the CPRS-R global index total score when rated by parents but not when rated by teachers.<sup>134</sup>

In summary, of the 11 studies that included a parent intervention component, 9 showed improvement in some standard measure of ADHD symptoms, often on parent report (Moderate SOE). One of the two studies that did not show improvement on ADHD symptoms did show improvement on functional impairment.

## **Depression or Anxiety**

No differences in depression and anxiety were found in an RCT that evaluated sleep hygiene counseling for parents combined with behavior therapy.<sup>169, 184</sup> The SOE was insufficient given the evidence of a single included study.

## **Functional Impairment**

A good-quality RCT found that Child Life and Attention Skills Treatment was associated with improved parent and teacher CGI scores relative to parent training alone or no intervention.<sup>152</sup> Another good-quality RCT<sup>167</sup> found that the Strategies to Enhance Positive Parenting (STEPP) program was more effective at reducing functional impairment than a waitlist control, but not more effective than traditional behavioral parent training. Another study compared a structured psychoeducation program for family members of children with ADHD to usual care, with outcomes assessed at 6 weeks and 6 months.<sup>129</sup> This study demonstrated significant improvements over time associated with CGI global improvement, but not in the CTRS index of CGI severity of illness. The SOE was insufficient given the evidence of a single included study.

## **Sleep Disturbance**

Sleep habits at 6 months were improved in a good-quality study which randomized patients to an intervention that combined sleep hygiene counseling for parents and behavior therapy. SOE was insufficient given imprecision of the findings and that there was only one study<sup>169, 184</sup>

## **Workforce Participation**

A single RCT found that an intervention that combined sleep hygiene counseling for parents and behavior therapy found that the intervention was associated with fewer days late for work and fewer missed days of work for the parents (insufficient SOE)<sup>169, 184</sup>

## **Adverse Effects of Child or Parent Training or Behavioral Interventions**

No adverse effects of these behavioral treatments were examined.

## **Findings in Relation to What Is Already Known—Child or Parent Training or Behavioral Interventions**

The 2011 report<sup>4</sup> identified 31 studies that evaluated parent behavior training for preschoolers with disruptive behavior disorders. Of these, three RCTs included only preschoolers who exhibited ADHD symptoms but who were not necessarily formally diagnosed with ADHD.<sup>206-208</sup> All three RCTs demonstrated significant improvement in the preschoolers' behavior or symptoms relative to usual care only. In contrast, this updated review provides results from 12 RCTs and 1 observational study that evaluated the effectiveness of either parent or child behavior training on outcomes among children with a wider age range who had been formally diagnosed with ADHD. Behavioral therapy appears effective for certain children with ADHD, however there are still questions related to the comparative effectiveness with pharmacotherapy alone or in combination with behavioral therapy. This reflects the complex nature of ADHD and the specific factors related to the child including age.

## **Strength of Evidence—Child or Parent Training or Behavioral Interventions**

Table 16 summarizes the SOE for child or parent training or behavioral interventions based on this report's included studies. Small numbers of studies with imprecise findings caused insufficient SOE grades for all outcomes other than academic performance (SOE=low) and changes in standardized symptom scores (SOE=moderate) which did not demonstrate an effect of child or parent training/behavioral interventions.

**Table 16. Strength of evidence for major outcomes—child or parent training or behavioral interventions**

| <b>Outcome</b>                         | <b>No. Studies/<br/>Design<br/>(N Patients)</b>   | <b>Study<br/>Limitations</b> | <b>Directness</b> | <b>Consistency</b> | <b>Precision</b> | <b>Reporting<br/>Bias</b> | <b>Findings</b>   |
|--|---|------------------------------|-------------------|--------------------|------------------|---------------------------|---|
| Academic performance                   | 2 RCTs (356)<br>6 and under,<br>7–17              | Low                          | Direct            | Consistent         | Imprecise        | None                      | There were no differences in academic performance associated with organizational skills or social skills training relative to no intervention. <sup>108, 161</sup>    |
| Low                                    |   |                              |                   |                    |                  |                           |   |
| Acceptability of treatment             | 1 RCT (120)<br>All through 17                     | Low                          | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient because only one small trial was identified. <sup>167</sup>  |
| Insufficient                           |   |                              |                   |                    |                  |                           |   |
| Changes in standardized symptom scores | 8 RCTs, 1<br>Obs (966)<br>7–17, all<br>through 17 | Low                          | Direct            | Consistent         | Imprecise        | None                      | There was a significant improvement in ADHD symptoms associated with child or parent training or sleep hygiene. <sup>112, 127, 129, 138, 150, 152, 167-169, 184</sup> |
| Moderate                               |   |                              |                   |                    |                  |                           |   |
| Depression or anxiety                  | 1 RCT (244)<br>All through 17                     | Low                          | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient because only one small trial was identified. <sup>169, 184</sup>   |
| Insufficient                           |   |                              |                   |                    |                  |                           |   |
| Functional impairment                  | 1.RCT (199)<br>7–17                               | Low                          | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient because only one small trial was identified. <sup>152</sup>  |
| Insufficient                           |   |                              |                   |                    |                  |                           |   |
| Sleep disturbance                      | 1 RCT (244)<br>All through 17                     | Low                          | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient because of findings from only one study which was imprecise <sup>169, 184</sup>  |
| Insufficient                           |   |                              |                   |                    |                  |                           |   |
| Workforce participation                | 1 RCT (244)<br>All through 17                     | Low                          | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient because of findings from only one study which was imprecise. <sup>169, 184</sup>   |
| Insufficient                           |   |                              |                   |                    |                  |                           |   |

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



## Detailed Synthesis—Omega-3/6 Fatty Acid Supplementation

We identified five good-quality,<sup>109, 133, 139, 142, 143</sup> two fair-quality,<sup>154, 165</sup> and one poor-quality studies<sup>136</sup> representing 1,130 patients evaluated essential fatty acid supplementation. Seven of these trials compared essential fatty acid supplementation with placebo. Of these, the active intervention was omega-3 alone in four trials,<sup>133, 136, 142, 165, 191</sup> omega-6 alone in 1 trial,<sup>154</sup> and a combination of omega-3 and omega-6 in 2 trials.<sup>139, 195</sup> Treatment duration ranged between 7-weeks and 6-months. The enrolled children ranged 6–18 years of age and the range of included male children was 59.4 percent to 77.3 percent across the trials. Inclusion of ADHD subtypes varied with a mixed grouping of ADHD subtypes included in 3 of the trials, a specific oppositional sub-type in one trial and three trials did not specify an ADHD sub-type of included children. One of the 8 trials<sup>165</sup> measured outcomes of ADHD symptoms with scales that were not part of our inclusion criteria and were excluded from the meta-analysis. The remaining 7 trials measured ADHD symptoms with the Conners Scale (full or abbreviated version) or the ADHD Rating Scale. Findings are summarized below by outcome below and described in Table H-11 in Appendix H. Overall, supplementation was not observed to be effective.

### Behavior Changes

A good-quality RCT did not find a difference in the proportion of patients who were prone to crying or who talked less after supplementation with omega-3 fatty acids, relative to placebo.<sup>191</sup> The SOE was insufficient given that the imprecision in the findings and the small number of participants who experienced the outcomes of interest.

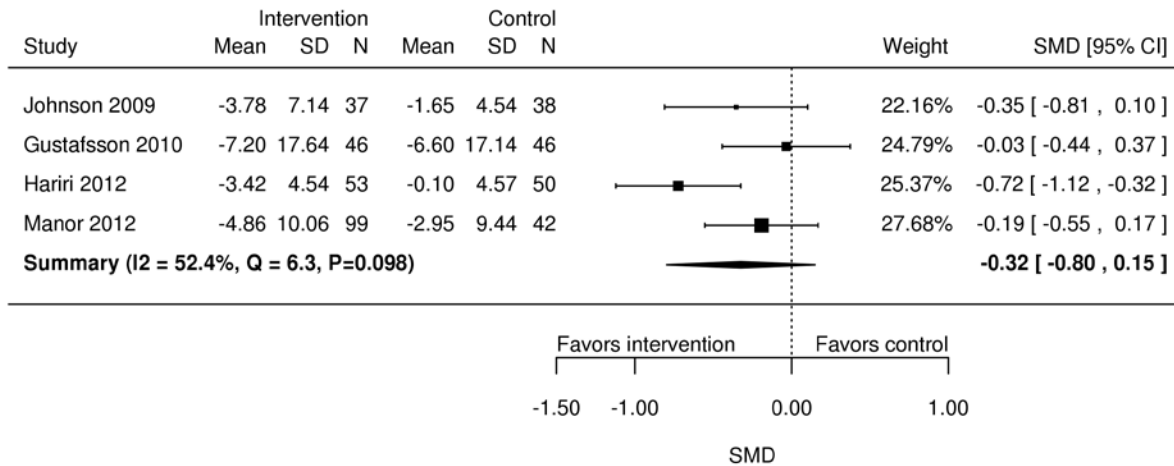
### Changes in Standardized Symptom Scores

We conducted meta-analyses of 4 eligible RCTs that reported parent ratings of ADHD total symptoms and 3 eligible RCTs that reported teacher ratings of ADHD total symptoms. These analyses demonstrated no significant differences between omega 3/6 and placebo for either parent or teacher ratings (moderate SOE).

### Parent Ratings of ADHD Total Symptoms

We summarized four RCTs, with random-effects meta-analysis, examining omega-3/6 supplementation versus placebo only with the outcome of parent-rated total ADHD symptoms.<sup>133, 136, 139, 142, 191, 195</sup> Effects were consistent and studies demonstrated moderate heterogeneity; however, no statistical evidence was found that omega-3/6 was superior to placebo with the outcome of parent rating of ADHD total symptoms (n=411, SMD -0.32, 95% CI -0.80 to 0.15,  $I^2=52.4\%$ ,  $Q=6.3$ ,  $p=0.098$ ) (Figure 3). The three trials that we excluded from the meta-analysis found no significant differences between omega-3/6 versus placebo, versus usual care, or between eicosapentaenoic acid and versus docosahexaenoic acid for parent ratings of ADHD total symptoms.

**Figure 3. Meta-analysis for effects of omega-3/6 supplementation compared with placebo—parent ratings**

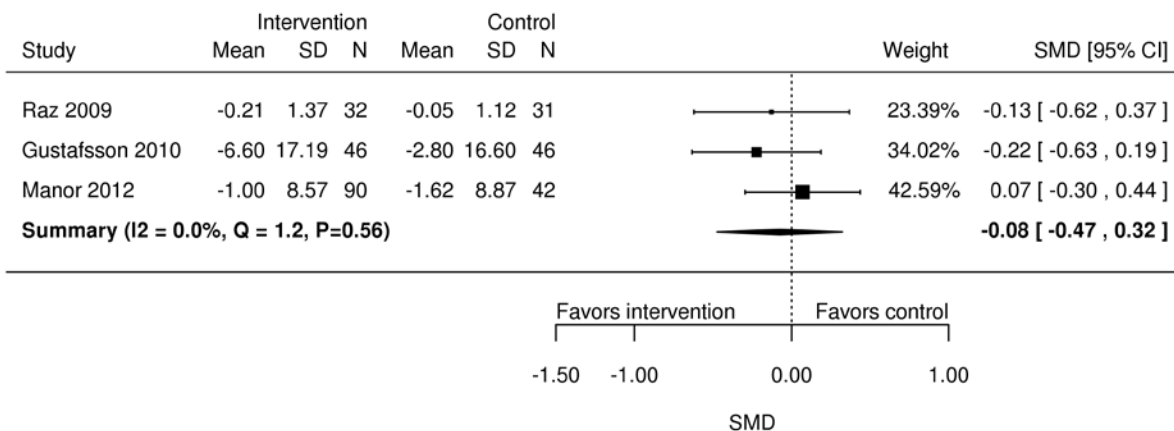


CI=confidence interval; SD=standard deviation; SMD=standardized mean difference

### Teacher Ratings of ADHD Total Symptoms

We summarized three RCTs, with random effects meta-analysis, examining omega-3/6 versus placebo with the outcome of teacher rated total ADHD symptoms.<sup>133, 142, 154, 191</sup> Effects were fairly consistent and studies were homogeneous; however, we found no statistical evidence that omega-3/6 was superior to placebo with the outcome of teacher rated total ADHD symptoms (n=287, SMD -0.08, 95% CI -0.47 to 0.32, I<sup>2</sup>=0.0%; Q=1.2, p=0.56) (Figure 4). The two RCTs excluded in this meta-analysis<sup>109, 165</sup> also found no significant difference between omega-3 and placebo or usual care for teacher ratings of ADHD total symptoms.

**Figure 4. Meta-analysis for effects of omega-3/6 supplementation compared with placebo—teacher ratings**



CI=confidence interval; SD=standard deviation; SMD=standardized mean difference

### Functional Impairment

A good-quality RCT found no difference in Clinical Global Impression scores associated with omega-3 fatty acid supplementation compared with placebo.<sup>139, 195</sup> The SOE was insufficient given evidence from one small included study.

## **Adverse Effects of Omega-3 Fatty Acid Supplementation**

A single good-quality RCT reported the incidence of adverse effects associated with omega-3 fatty acid supplementation compared with placebo.<sup>142, 191</sup> This trial did not report statistically significant between-group differences for any of the following adverse effects: chemical leukoderma; elevated blood pressure; sleep disturbance; tics or other movement disorders; gastrointestinal symptoms; growth suppression; increased heart rate; personality change; or weight decrease. The SOE was insufficient however given the small number of patients in either arm that experienced any of the outcomes of interest and the inconsistency between positive, negative, and no effects that were observed for individual outcomes at varying time points.

## **Findings in Relation to What Is Already Known—Omega-3 Fatty Acid Supplementation**

The effectiveness of omega-3/6 for the treatment of ADHD symptoms was not included in the 2011 report.<sup>4</sup> However, a systematic review and meta-analysis comparing omega-3 fatty acid supplementation with placebo was conducted in 2011 by Bloch and Qawasmi.<sup>204</sup> Using only PubMed, they searched from database inception to December 2010. Their findings, using fixed-effects meta-analysis, indicated a small significant effect (SMD 0.31, 95% CI 0.16 to 0.47) on ADHD symptoms with omega-3 use associated with improved symptoms. Due to an overlap in search dates, our review includes 3 of the 10 studies that were also included in the Bloch and Qawasmi review. Our inclusion and exclusion criteria differed from that review as we excluded studies where the sample size was less than 50 participants.<sup>209</sup> Given the differences in measurement and perspective, our review also conducted a separate meta-analysis for teacher- and parent-reported ADHD symptoms whereas the Bloch and Qawasmi review included only the parent- or teacher-reported ADHD symptoms depending on the number of completed ADHD subscales. Our meta-analysis (Figure 3) used random-effects models and corrected the standard errors for a small sample meta-analysis using the Knapp-Hartung method, both techniques that create a more conservative confidence interval.<sup>210</sup> As such, due to differences in search dates, inclusion/exclusion criteria and analytical approaches, differences in pooled estimates between the two reviews would be expected. Note that given the wider confidence interval within our analysis compared to the Bloch and Qawasmi meta-analysis, we did not find evidence of a benefit.

## **Strength of Evidence—Omega-3 Supplementation**

Table 17 summarizes the SOE for omega-3 supplementation based on this report's included studies. Small numbers of studies with imprecise findings caused insufficient SOE for all outcomes other than changes in standardized symptom scores, for which we found moderate SOE for no difference.

**Table 17. Strength of evidence for major outcomes—omega-3 fatty acid supplementation**

| <b>Outcome</b>                         | <b>No. Studies/<br/>Design<br/>(N Patients)</b> | <b>Study<br/>Limitations</b> | <b>Directness</b> | <b>Consistency</b> | <b>Precision</b> | <b>Reporting<br/>Bias</b> | <b>Findings</b>  |
|--|---|------------------------------|-------------------|--------------------|------------------|---------------------------|--|
| Behavior changes                       | 1 RCTs (200)<br>7–17                            | Low                          | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient because only one trial was identified with imprecise findings and a small number of events of the outcomes of interest. <sup>142, 191</sup>   |
| Insufficient                           |   |                              |                   |                    |                  |                           |  |
| Changes in standardized symptom scores | 7 RCTs (795)<br>7–17                            | Low                          | Direct            | Consistent         | Precise          | None                      | Two meta-analyses of 4 and 3 good-quality studies respectively found no significant differences between Omega-3/6 and placebo for parent ratings (n=411, SMD -0.32, 95% CI -0.80 to 0.15, I <sup>2</sup> =52.4%, Q=6.3, p=0.098) or teacher ratings of total ADHD symptoms (n=287, SMD -0.08, 95% CI -0.47 to 0.32, I <sup>2</sup> =0.0%; Q=1.2, p=0.56). <sup>133, 136, 139, 142, 143, 154, 190, 191, 195</sup> |
| Moderate                               |   |                              |                   |                    |                  |                           |  |
| Functional impairment                  | 1 RCT (75)<br>7–17                              | Low                          | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient because only one small trial was identified. <sup>139, 195</sup>  |
| Insufficient                           |   |                              |                   |                    |                  |                           |  |
| Chemical Leukoderma                    | 1 RCT (200)<br>7–17                             | Low                          | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient given the small number of patients in either arm that experienced any of the outcomes of interest and the inconsistency between positive, negative, and no effects that were observed for individual adverse effects at varying timepoints. <sup>142, 191</sup>   |
| Insufficient                           |   |                              |                   |                    |                  |                           |  |
| Elevated blood pressure                | 1 RCT (200)<br>7–17                             | Low                          | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient given the small number of patients in either arm that experienced any of the outcomes of interest and the inconsistency between positive, negative, and no effects that were observed for individual adverse effects at varying timepoints. <sup>142, 191</sup>   |
| Insufficient                           |   |                              |                   |                    |                  |                           |  |
| Sleep disturbance                      | 1 RCT (200)<br>7–17                             | Low                          | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient given the small number of patients in either arm that experienced any of the outcomes of interest and the inconsistency between positive, negative, and no effects that were observed for individual adverse effects at varying timepoints. <sup>142, 191</sup>   |
| Insufficient                           |   |                              |                   |                    |                  |                           |  |
| Tics or other movement disorders       | 1 RCT (200)<br>7–17                             | Low                          | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient given the small number of patients in either arm that experienced any of the outcomes of interest and the inconsistency between positive, negative, and no effects that were observed for individual adverse effects at varying timepoints. <sup>142, 191</sup>   |
| Insufficient                           |   |                              |                   |                    |                  |                           |  |

| <b>Outcome</b>            | <b>No. Studies/<br/>Design<br/>(N Patients)</b> | <b>Study<br/>Limitations</b> | <b>Directness</b> | <b>Consistency</b> | <b>Precision</b> | <b>Reporting<br/>Bias</b> | <b>Findings</b>  |
|---------------------------|---|------------------------------|-------------------|--------------------|------------------|---------------------------|--|
| Gastrointestinal symptoms | 1 RCT (200)<br>7–17                             | Low                          | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient given the small number of patients in either arm that experienced any of the outcomes of interest and the inconsistency between positive, negative, and no effects that were observed for individual adverse effects at varying timepoints. <sup>142, 191</sup> |
| Insufficient              |   |                              |                   |                    |                  |                           |  |
| Growth suppression        | 1 RCT (200)<br>7–17                             | Low                          | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient given the small number of patients in either arm that experienced any of the outcomes of interest and the inconsistency between positive, negative, and no effects that were observed for individual adverse effects at varying timepoints. <sup>142, 191</sup> |
| Insufficient              |   |                              |                   |                    |                  |                           |  |
| Increased heart rate      | 1 RCT (200)<br>7–17                             | Low                          | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient given the small number of patients in either arm that experienced any of the outcomes of interest and the inconsistency between positive, negative, and no effects that were observed for individual adverse effects at varying timepoints. <sup>142, 191</sup> |
| Insufficient              |   |                              |                   |                    |                  |                           |  |
| Personality change        | 1 RCT (200)<br>7–17                             | Low                          | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient given the small number of patients in either arm that experienced any of the outcomes of interest and the inconsistency between positive, negative, and no effects that were observed for individual adverse effects at varying timepoints. <sup>142, 191</sup> |
| Insufficient              |   |                              |                   |                    |                  |                           |  |
| Weight decrease           | 1 RCT (200)<br>7–17                             | Low                          | Direct            | NA                 | Imprecise        | None                      | SOE was insufficient given the small number of patients in either arm that experienced any of the outcomes of interest and the inconsistency between positive, negative, and no effects that were observed for individual adverse effects at varying timepoints. <sup>142, 191</sup> |
| Insufficient              |   |                              |                   |                    |                  |                           |  |

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

## **Detailed Synthesis—Herbal Interventions or Dietary Approaches**

Three good-quality<sup>125, 158, 172</sup> and 3 fair-quality<sup>111, 140, 144</sup> studies representing 486 patients evaluated herbal interventions or dietary approaches. Findings are summarized by outcome and described in Table H-12 in Appendix H. A wide range of interventions were evaluated in these studies, including an elimination diet, ginkgo biloba, Memomet syrup, zinc, and other patented herbal preparations. Although some interventions appeared effective, findings are difficult to interpret in studies that also allowed use of pharmacotherapy.

### **Behavior Changes**

One good-quality RCT found that ginkgo biloba was associated with improved parent and teacher ADHD-RS-Inattention scores but not ADHD-RS-Hyperactivity scores relative to placebo.<sup>158</sup> One fair-quality RCT found that an 8-week course of vitamin D supplementation given with MPH was associated with improvement in Weekly Parent Ratings of Evening and Morning Behavior (WPREMB) evening symptom scores and total score, but not WPREMB morning scores compared to MPH and placebo.<sup>144</sup> A third RCT (fair-quality) did not find statistically significant differences between patients on placebo and those taking zinc supplementation.<sup>111</sup> The variability in interventions, outcomes assessed and the inconsistency in the findings resulted in an insufficient SOE.

### **Changes in Appetite**

Two fair-quality RCTs did not report statistical significance of the proportion of patients in each study arm who reported changes in appetite associated with two doses of zinc supplementation compared with placebo,<sup>111</sup> or an herbal preparation compared with placebo.<sup>140</sup> Given the variability in interventions, the small number of patients in each study experiencing the outcome, and differential loss to followup resulted in insufficient SOE.

### **Changes in Standardized Symptom Scores**

Four RCTs reported changes in symptom scores. One demonstrated improvement in ADHD-RS scores associated with an elimination diet relative to a nonrestricted diet.<sup>172</sup> The other three RCTs found that neither Memomet syrup nor zinc supplementation nor vitamin D improved ADHD symptoms compared with placebo (low SOE).<sup>111, 125, 144</sup>

### **Gastrointestinal Symptoms**

Two RCTs did not report statistical significance of the proportion of patients in each study arm who reported stomach aches or other gastrointestinal symptoms associated with two doses of zinc supplementation<sup>111</sup> or herbal preparation<sup>140</sup> compared with placebo. The variability in interventions, outcomes assessed and the loss to followup resulted in insufficient SOE.

### **Adverse Effects of Herbal Interventions or Dietary Approaches**

An RCT that evaluated two doses of zinc supplementation compared with placebo<sup>111</sup> did not report statistical significance in the difference in proportion of patients in each study arm who reported changes in appetite, stomach aches or other gastrointestinal symptoms, sleep disturbance, harm to self or others, or stereotypical behaviors. Another RCT found no between-group differences between an herbal preparation and placebo in gastrointestinal symptoms, emotional lability, accidental injury, or sleep disturbance.<sup>140</sup> The SOE was considered

insufficient because identified studies varied in the interventions and outcomes assessed and had differential loss to follow up.

### **Strength of Evidence—Herbal Interventions or Dietary Approaches**

Table 18 summarizes the SOE for herbal interventions or dietary approaches based on this report's included studies. Small numbers of studies with imprecise findings caused insufficient SOe grades for all outcomes other than changes in standardized symptom scores.

**Table 18. Strength of evidence for major outcomes—herbal interventions or dietary approaches**

| <b>Outcome</b>                         | <b>No. Studies/<br/>Design<br/>(N Patients)</b> | <b>Study<br/>Limitations</b> | <b>Directness</b> | <b>Consistency</b> | <b>Precision</b> | <b>Reporting<br/>Bias</b> | <b>Findings</b>  |
|--|---|------------------------------|-------------------|--------------------|------------------|---------------------------|--|
| <b>SOE Grade</b>                       | <b>Age Category</b>                             |                              |                   |                    |                  |                           |  |
| Behavior changes                       | 3 RCTs (172)<br>All through 17                  | Low                          | Direct            | Inconsistent       | Imprecise        | None                      | The SOE was considered insufficient because identified studies varied in intervention and outcomes assessed and then demonstrated inconsistent findings. <sup>158 111, 144</sup>   |
| Insufficient                           |   |                              |                   |                    |                  |                           |  |
| Changes in appetite                    | 2 RCTs (172)<br>7–17                            | Medium                       | Direct            | Consistent         | Imprecise        | None                      | The SOE was considered insufficient given the variability in interventions, the small number of patients in each study experiencing the outcome, and differential loss to followup. <sup>111, 140</sup>                                    |
| Insufficient                           |   |                              |                   |                    |                  |                           |  |
| Changes in standardized symptom scores | 4 RCTs (292)<br>7–17, all through 17            | Low                          | Direct            | Inconsistent       | Imprecise        | None                      | An elimination diet improved ADHD-RS scores relative to a non-restricted diet, <sup>172</sup> but did not find a reduction in ADHD symptoms relative to placebo for either Memomet syrup or zinc supplementation. <sup>111, 125, 144</sup> |
| Low                                    |   |                              |                   |                    |                  |                           |  |
| Gastrointestinal symptoms              | 2 RCTs (172)<br>7–17                            | Medium                       | Direct            | Inconsistent       | Imprecise        | None                      | The SOE was considered insufficient because identified studies varied in the interventions and outcomes assessed and had differential loss to follow up <sup>111, 140</sup>  |
| Insufficient                           |   |                              |                   |                    |                  |                           |  |
| Mood disorders                         | 1 RCT (120)<br>7–17                             | Medium                       | Direct            | NA                 | Imprecise        | None                      | The SOE was considered insufficient because only one study was identified which had imprecise findings and differential loss to follow up. <sup>140</sup>  |
| Insufficient                           |   |                              |                   |                    |                  |                           |  |
| Motor vehicle collisions               | 1 RCT (120)<br>7–17                             | Medium                       | Direct            | NA                 | Imprecise        | None                      | The SOE was considered insufficient because only one small study was identified. <sup>140</sup>  |
| Insufficient                           |   |                              |                   |                    |                  |                           |  |
| Sleep disturbance                      | 2 RCTs (172)<br>7–17                            | Medium                       | Direct            | Consistent         | Imprecise        | None                      | The SOE was considered insufficient because identified studies varied in the interventions and outcomes assessed and had differential loss to follow up <sup>111, 140</sup>  |
| Insufficient                           |   |                              |                   |                    |                  |                           |  |
| Suicide ideation                       | 1 RCT (52)<br>7–17                              | Medium                       | Direct            | NA                 | Imprecise        | None                      | The SOE was considered insufficient because only one small study was identified. <sup>111</sup>  |
| Insufficient                           |   |                              |                   |                    |                  |                           |  |
| Tics or other movement disorders       | 1 RCT (52)<br>7–17                              | Medium                       | Direct            | NA                 | Imprecise        | None                      | The SOE was considered insufficient because only one small study was identified. <sup>111</sup>  |
| Insufficient                           |   |                              |                   |                    |                  |                           |  |

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



## **Detailed Synthesis—Other Approaches**

One good-quality<sup>107</sup> and 8 fair-quality studies<sup>128, 137, 145, 149, 153, 170, 171, 175</sup> representing 1,286 enrolled patients evaluated other approaches. These studies looked at a range of programs including community programs and programs that addressed mentoring and parent support,<sup>128</sup> multisystemic intervention at school and with parents,<sup>153, 170</sup> in-home family training intervention,<sup>107</sup> a general parenting program,<sup>175</sup> using melatonin as an adjunct treatment, acupuncture, and a homeopathic intervention. This diverse range of interventions share some features with other interventions with several having parent components,<sup>107, 128, 153, 170, 175</sup> but each were different from typical parent focused interventions in that there were other major components or they were generic parenting programs. Findings are summarized by outcome and described in Table H-13 in Appendix H. Neither the Challenging Horizons Program – after school version nor the Family School Success – Early Elementary Program improved academic performance (SOE=low). The SOE was insufficient for all other outcomes for each of the interventions considered.

## **Findings in Relation to What Is Already Known—Other Approaches**

The 2011 report<sup>4</sup> identified 7 studies that examined multiple component psychosocial and/or behavioral interventions for preschool children with disruptive behavior disorder. Of these, five RCTs included only preschoolers who exhibited ADHD symptoms but who were not necessarily formally diagnosed with ADHD.<sup>211-215</sup> All five of these RCTs demonstrated significant improvement in the preschoolers' behavior or symptoms relative to their comparison groups, most of which were usual care only. In contrast, this updated review provides results from two RCTs that examined a multiple component intervention for children specifically diagnosed with ADHD that included both school and parent components.<sup>153, 170</sup> Findings of these two studies are summarized by outcome and described in Table H-13 in Appendix H. Despite the support for behavioral interventions from the 2011 report, this report found insufficient SOE to evaluate the impact of these interventions on ADHD symptoms. In part, this is because we only included studies where children received formal diagnosis of ADHD.

## **Strength of Evidence—Other Approaches**

Table 19 summarizes the SOE for other approaches based on this report's included studies. Small numbers of studies with imprecise findings caused insufficient SOE grades for all outcomes other than academic performance.

**Table 19. Strength of evidence for major outcomes—other approaches**

| <b>Outcome</b>                           | <b>No. Studies/<br/>Design<br/>(N Patients)</b>   | <b>Study<br/>Limitations</b> | <b>Directness</b> | <b>Consistency</b> | <b>Precision</b> | <b>Reporting<br/>Bias</b>   | <b>Findings</b>  |
|--|---|------------------------------|-------------------|--------------------|------------------|---|--|
| <b>SOE Grade</b><br>Academic performance | 3 RCTs (586)<br>7–17, all through 17              | Medium                       | Direct            | Consistent         | Imprecise        | None  | Neither the Challenging Horizons Program (After School version) nor the Family School Success (Early Elementary) interventions were found to improve academic performance in 3 fair-quality RCTs. <sup>128, 153, 170</sup> |
| Low                                      |   |                              |                   |                    |                  |   |  |
| Behavior changes                         | 4 RCTs (508)<br>6 and under, 7–17, all through 17 | Medium                       | Direct            | Consistent         | Imprecise        | Suspect (given dropout and lack of clarity in reporting findings) | The SOE was considered insufficient because of concerns about risk of reporting bias and lack of precision in study results. <sup>107, 145, 149, 171, 188</sup>  |
| Insufficient                             |   |                              |                   |                    |                  |   |  |
| Changes in appetite                      | 1 RCT (60)<br>7–17                                | Medium                       | Direct            | NA                 | Imprecise        | None  | The SOE was considered insufficient because only one small study was identified. <sup>145, 188</sup>   |
| Insufficient                             |   |                              |                   |                    |                  |   |  |
| Changes in standardized symptom scores   | 3 RCTs (252)<br>7–17, all through 17              | Medium                       | Direct            | Consistent         | Imprecise        | None  | The SOE was considered insufficient because of lack of precision across the 3 fair-quality studies with varying mean changes between different standardized scores. <sup>137, 145, 175, 188</sup>                          |
| Insufficient                             |   |                              |                   |                    |                  |   |  |
| Functional impairment                    | 1 RCT (326)<br>7–17                               | Medium                       | Direct            | NA                 | Imprecise        | None  | The SOE was considered insufficient because only one small study was identified. <sup>128</sup>  |
| Insufficient                             |   |                              |                   |                    |                  |   |  |
| Gastrointestinal symptoms                | 1 RCT (60)<br>7–17                                | Medium                       | Direct            | NA                 | Imprecise        | None  | The SOE was considered insufficient because only one small study was identified. <sup>145, 188</sup>   |
| Insufficient                             |   |                              |                   |                    |                  |   |  |
| Sleep disturbance                        | 1 RCTs (60)<br>7–17                               | Medium                       | Direct            | NA                 | Imprecise        | None  | The SOE was considered insufficient because only one small study was identified. <sup>145, 188</sup>   |
| Insufficient                             |   |                              |                   |                    |                  |   |  |
| Tics or other movement disorders         | 1 RCT (60)<br>7–17                                | Medium                       | Direct            | NA                 | Imprecise        | None  | The SOE was considered insufficient because only one small study was identified. <sup>145, 188</sup>   |
| Insufficient                             |   |                              |                   |                    |                  |   |  |
| Weight decrease                          | 1 RCT (60)<br>7–17                                | Medium                       | Direct            | NA                 | Imprecise        | None  | The SOE was considered insufficient because only one small study was identified. <sup>145, 188</sup>   |
| Insufficient                             |   |                              |                   |                    |                  |   |  |

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

### **Key Question 3: ADHD Monitoring**

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

# Discussion

## Key Findings and Strength of Evidence

In this Comparative Effectiveness Review (CER), we reviewed 21 studies involving 4,346 patients that evaluated attentional deficit hyperactivity disorder (ADHD) diagnostic strategies for children and adolescents that could be used in the primary care setting and evaluated the impact of being labeled as having ADHD (Key Question [KQ] 1) and 69 studies involving 14,737 patients to evaluate the comparative effectiveness of different pharmacologic and nonpharmacologic therapies for ADHD (KQ 2). Because of variations in “usual care” often used as the comparator, detailed descriptions of the comparator were made and considered in the evaluation of the available evidence. We hoped to evaluate the comparative effectiveness of different follow-up strategies for children and adolescents with ADHD (KQ 3). However, no study was identified that met the criteria for inclusion.

### KQ 1: ADHD Diagnosis

This review focused on evidence evaluating diagnosis in children under 7 years of age or for older children (up to 17 years of age) using novel diagnostic techniques including imaging, electroencephalography (EEG), or assessment of executive function. The strength of evidence (SOE) was insufficient to evaluate the validity of diagnostic approaches for children under 7 years. The Attention and Executive Function Rating Inventory and Childhood Executive Functioning Inventory performed better than the Cambridge Neuropsychological Test Automated Battery for the diagnosis of ADHD in children and adolescents 7 through 17 years of age (strength of evidence [SOE]=low).

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

### KQ 2: ADHD Treatment

ADHD treatment options include pharmacologic and nonpharmacologic therapies. The 2011 AHRQ report highlighted the benefit of psychostimulants for children 6 through 12 years of age and the potential benefit of additional behavior therapy, especially for those with oppositional defiant disorder. For younger children, the 2011 AHRQ report found parent behavioral interventions to be effective

Atomoxetine and MPH were the most common drugs evaluated in the studies included in this review (evaluated in 8 studies). The SOE was insufficient to determine which drug is more effective or whether the side-effect profiles are different. There was also little evidence regarding serious cardiovascular risk with use of these medications.

Of the nonpharmacologic therapies, the SOE since the last review was insufficient to evaluate neurofeedback. Studies since the last review found that child or parent training appear to improve standardized ADHD symptom scores (SOE=moderate) but had no difference in academic performance (SOE=low). Cognitive training and cognitive behavioral therapy was associated with improved standardized symptoms scores (SOE=low each).

The most well-studied nutritional therapy is dietary supplementation with omega-3/6 fatty acids. However, based on our meta-analysis, there was no impact of omega-3/6 supplements on parent or teacher rating scales of ADHD symptoms.

Table 20 summarizes the SOE findings for KQ 2 that were graded as low, moderate, or high.

**Table 20. Summary strength of evidence for major outcomes for KQ 2**

| <b>Outcome</b>   | <b>No. Studies/<br/>Design<br/>(N Patients)<br/>Age Category</b> | <b>Findings</b>  | <b>SOE Grade</b> |
|--|--|--|------------------|
| <b>Pharmacologic vs. Placebo Treatments: NA</b>                  |  |  |                  |
| <b>Pharmacologic vs. Pharmacologic Treatments</b>                |  |  |                  |
| Gastrointestinal symptoms  | 3 Obs (1,966)<br>7–17  | Atomoxetine has slightly higher GI effects or disease than MPH. <sup>121, 123, 151</sup>   | Low              |
| <b>Pharmacologic vs. Nonpharmacologic Treatments</b>             |  |  |                  |
| Changes in appetite  | 3 RCTs (212)<br>7–17   | MPH decreased appetite compared to ningdong, omega-3/6 or ginkgo biloba. <sup>114, 141, 155</sup>  | Low              |
| Sleep disturbance  | 4 RCTs (324)<br>7–17   | MPH resulted in increased sleep disturbances compared to ningdong, ginkgo biloba, omega-3/6, or neurofeedback. <sup>114, 141, 155</sup>  | Low              |
| <b>Nonpharmacologic vs. Nonpharmacologic or Other Treatments</b> |  |  |                  |
| <b>Neurofeedback: NA</b>   |  |  |                  |
| <b>Cognitive Training</b>  |  |  |                  |
| Changes in standardized symptom scores                           | 9 RCTs (768)<br>7–17, all through 17                             | There is some evidence that cognitive training strategies such as the computer-based Cogmed cognitive training program may reduce ADHD symptoms in the short term but not the long term. <sup>115, 119, 122, 126, 132, 160, 163, 174</sup> | Low              |
| <b>Cognitive Behavioral Therapy</b>                              |  |  |                  |
| Changes in standardized symptoms scores                          | 2 RCTs (278)<br>7–17   | CBT improved ADHD symptoms relative to usual care or a limited CBT intervention. <sup>117, 164</sup>   | Low              |
| <b>Child or Parent Training or Behavioral</b>                    |  |  |                  |
| Changes in standardized symptom scores                           | 8 RCTs, 1 Obs (966)<br>7–17                                      | ADHD symptoms were significantly improved with child or parent training, sleep hygiene, or behavioral interventions. <sup>112, 127, 129, 138, 150, 152, 167-169, 184</sup>   | Moderate         |
| Academic performance   | 2 RCTs (356)<br>7–17   | There were no differences in academic performance associated with organizational skills or social skills training relative to no intervention. <sup>108, 161</sup>   | Low              |

| <b>Outcome</b>                                    | <b>No. Studies/<br/>Design<br/>(N Patients)<br/>Age Category</b> | <b>Findings</b>   | <b>SOE Grade</b> |
|---|--|---|------------------|
| <b>Omega-3 Supplementation</b>                    |  |   |                  |
| Changes in standardized symptom scores            | 7 RCTs (795)<br>7–17   | Omega-3/6 did not improve parent ratings compared to placebo (SMD -0.32, 95% CI -0.80 to 0.15) or teacher ] (SMD -0.08, 95% CI -0.47 to 0.32). <sup>133, 136, 139, 142, 143, 154, 190, 191, 195</sup>                   | Moderate         |
| <b>Herbal Interventions or Dietary Approaches</b> |  |   |                  |
| Changes in standardized symptom scores            | 3 RCTs (238)<br>7–17, all through<br>17                          | ADHD-RS scores improved with an elimination diet relative to a nonrestricted diet, while ADHD symptoms were not reduced with either Memomet syrup or zinc supplementation relative to placebo. <sup>111, 125, 172</sup> | Low              |
| <b>Other Approaches</b>                           |  |   |                  |
| Academic performance                              | 3 RCTs (586)<br>7–17, all through<br>17                          | Neither the Challenging Horizons Program-After School version nor the Family School Success- Early Elementary interventions improved academic performance. <sup>128, 153, 170</sup>                                     | Low              |

Abbreviations: ADHD=attention deficit hyperactivity disorder; CBT=cognitive behavioral therapy; GI=gastrointestinal; Obs=observational; RCT=randomized controlled trial; RS=rating scale; SMD=standardized mean difference; SOE=strength of evidence

## **Findings in Relation to What Is Already Known**

Table 21 summarizes the differences and similarities in scope across this current systematic review compared with the 2011 review,<sup>4</sup> along with our main findings.



**Table 21. Differences in scope between the 2011 and current evidence reports**

|                            | <b>2011 Report</b>   | <b>Current Report</b>  |
|----------------------------|--|--|
| <b>Key Questions (KQs)</b> | <p>This systematic review compared effectiveness and adverse events of interventions for preschoolers at high risk for ADHD; compared long-term effectiveness and adverse events of interventions for ADHD among persons of all ages; and described how identification and treatment for ADHD varied.</p> <p>Specifically, the KQs included:</p> <ol style="list-style-type: none"> <li>1. Among children younger than 6 years of age with ADHD or disruptive behavior disorders, what are the effectiveness and adverse event outcomes following treatment?</li> <li>2. 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?</li> <li>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?</li> </ol> | <p>This systematic review updates and extends two previous systematic evidence reviews and focuses on the comparative effectiveness of methods to establish the diagnosis of ADHD, updates the comparative effectiveness of pharmacologic and nonpharmacologic treatments, and evaluates different monitoring strategies in the primary care setting for individuals from birth through 17 years of age.</p> <p>Specifically, the KQs include:</p> <ol style="list-style-type: none"> <li>1. For the diagnosis of ADHD: <ol style="list-style-type: none"> <li>a. What is the comparative diagnostic accuracy of approaches that can be used in the primary care practice setting or by specialists to diagnose ADHD among individuals younger than 7 years of age?</li> <li>b. What is the comparative diagnostic accuracy of EEG, imaging, or executive function approaches that can be used in the primary care practice setting or by specialists to diagnose ADHD among individuals aged 7 through 17?</li> <li>c. For both populations, how does the comparative diagnostic accuracy of these approaches vary by clinical setting, including primary care or specialty clinic, or patient subgroup, including age, sex, or other risk factors associated with ADHD?</li> <li>d. What are the adverse effects associated with being labeled correctly or incorrectly as having ADHD?</li> </ol> </li> <li>2. What are the comparative safety and effectiveness of pharmacologic and/or nonpharmacologic treatments of ADHD in improving outcomes associated with ADHD? How do these outcomes vary by presentation (inattentive, hyperactive/impulsive, and combined) or other comorbid conditions? What is the risk of diversion of pharmacologic treatment?</li> </ol> |

|  | 2011 Report   | Current Report   |
|--|---|--|
|  |   | 3. What are the comparative safety and effectiveness of different monitoring strategies to evaluate the effectiveness of treatment or changes in ADHD status (e.g., worsening or resolving symptoms)?  |
| <b>Publication dates for included studies</b>  | By KQ:<br>1. Inception to 2010<br>2. 1997-2010<br>3. 1980-2010  | 2009-2016  |
| <b>ADHD diagnosis</b>  | Not addressed   | The Attention and Executive Function Rating Inventory and Childhood Executive Functioning Inventory performed better than the Cambridge Neuropsychological Test Automated Battery for the diagnosis of ADHD between 7 and 17 years of age (SOE=low). This systematic evidence review identified limited studies with variable and inconsistent findings for diagnostic accuracy for all other diagnostics tools evaluated, including imagining and EEG-based tests   |
| <b>Treatment of preschoolers with disruptive behavior disorders, including those at risk of ADHD</b> | Evidence favored treatment with parent behavior training. Only one good-quality study of the effectiveness of methylphenidate (MPH) was identified, which found therapy to be effective.  | Not addressed  |
| <b>Long-term effectiveness and safety of treatment in people aged 6 and older</b>                    | <ul style="list-style-type: none"> <li>• MPH is effective for ADHD treatment for 14 months and atomoxetine (ATX) for over 12 months. SOE was low.</li> <li>• Combining medication and behavioral treatment can improve outcome compared to medication alone for some outcomes for those with ADHD combined type. SOE was low and the population were not necessarily formally diagnosed with ADHD.</li> </ul> | <ul style="list-style-type: none"> <li>• There are no new conclusions regarding the effectiveness of pharmacotherapy vs. placebo, of comparing different pharmacologic treatments, or of comparing combined therapeutic approaches (i.e., pharmacotherapy and nonpharmacotherapy).</li> <li>• Gastrointestinal side effects are slightly higher for ATX compared with MPH; however, the SOE was low.</li> <li>• Compared with placebo, child or parent training can improve ADHD symptoms. SOE was moderate. It did not however improve academic performance (SOE low) There are still questions related to the comparative effectiveness with pharmacotherapy alone or in combination with behavioral therapy.</li> </ul> |

|   | 2011 Report  | Current Report  |
|---|--|---|
|   |  | <ul style="list-style-type: none"> <li>• Compared with placebo, omega-3 fatty acid supplementation had no difference on ADHD symptoms. SOE was moderate.</li> <li>• Cognitive behavioral therapy improved ADHD symptom scores. SOE was low</li> </ul> |
| <b>Prevalence and variations in diagnosis and treatment</b> | There is significant variation in diagnosis and treatment, with an overall increase in the use of pharmacotherapy. | Not addressed   |
| <b>Monitoring strategies</b>                                | Not addressed  | There were no studies found that compared monitoring strategies after the diagnosis of ADHD.  |

Abbreviations: ADHD=attention deficit hyperactivity disorder; ATX=atomoxetine; EEG=electroencephalography; KQ=Key Question; MPH=methylphenidate; SOE=strength of evidence

Since publication of the American Academy of Pediatrics (AAP) clinical practice guideline, there has been significant interest in the use of objective tests that could overcome the inherent limitations in the use of behavioral rating scales. Our systematic review could not find sufficient evidence to recommend that such tests now be incorporated into care, although the review was limited to studies published in 2009 and later. The AAP guideline also recognized the potential harm of labeling an individual with ADHD, but our review did not identify studies that would allow an estimate of this potential harm.

The AAP clinical practice guideline, based on the 2011 review, recommends behavioral therapy for children 4 through 5 years of age as the first line of therapy, with consideration of methylphenidate (MPH) if such interventions fail. In contrast, the AAP preferably recommends Food and Drug Administration (FDA)-approved medications and behavioral interventions for older children and adolescents. A recent Cochrane review of randomized controlled trials for the treatment of ADHD found that although MPH might improve ADHD symptoms, the level of certainty was low because most trials were underpowered, of low quality, and had short duration of follow-up.<sup>77</sup> That review included studies of children and adolescents 18 years and younger with ADHD according to DSM 3, 4, or 5 published by March 2015. Another systematic review supported the use of MPH, atomoxetine, and extended-release guanfacine to improve ADHD symptoms in adolescents.<sup>70</sup> That review only included studies of subjects 12–18 years of age published from 1999 through January 2016. As with the Cochrane review,<sup>77</sup> limitations in study quality were identified.

Our systematic review was not able to provide further evidence regarding the comparative effectiveness of FDA-approved medications. Other than omega-3 supplements which had moderate SOE for no difference in ADHD symptom scores, none of the other dietary supplements for ADHD therapy has sufficient SOE. However, the behavioral interventions were of did demonstrate effectiveness based on the studies included in this update. We found low SOE for cognitive behavioral therapy and moderate SOE for child or parent training but no difference in academic performance (SOE=low). Insufficient data were available to determine whether there is a subgroup of children and adolescents with ADHD (e.g., based on age or other characteristics) for whom these therapies might be more effective.

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

Prior to the publication of the AAP clinical practice guideline, the American Academy of Child and Adolescent Psychiatry released recommendations for establishing the diagnosis of ADHD and treating the condition.<sup>216</sup> These recommendations were consistent with the AAP clinical practice guideline, including the need for a comprehensive evaluation to establish the diagnosis and the need to personalize therapy, using behavioral interventions and/or stimulant therapy. Since the publication of the AAP clinical practice guideline, the American Academy of Neurology has released a guideline recommending against the use of EEG to confirm ADHD or to support further testing within the context of usual clinical care.<sup>217</sup> The 2011 review did not address approaches to diagnosis. The current review did not find sufficient evidence to recommend for or against the use of EEGs to confirm ADHD.

## Applicability

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

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

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

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

Table 22 shows potential issues with applicability for studies included for KQ 1. Table 23 shows similar information for studies included in KQ 2 and is broken down by type of intervention.

**Table 22. Potential issues with applicability of included studies for Key Question 1**

| Issue   | N=21 Studies |
|---|--------------|
| <b>Population (P)</b>   |              |
| Narrow eligibility criteria and exclusion of those with comorbidities                   | 2            |
| More complex patients than typical of the community                                     | 2            |
| Run-in period with high exclusion rate for non-adherence or side effects                | 0            |
| DSM-4/5 diagnosis unclear   | 0            |
| <b>Intervention (I)</b>   |              |
| Diagnostic tools used differently than as recommended or commonly used in practice      | 0            |
| Dosing not reflective of current practice   | 0            |
| Co-interventions that are likely to modify the effectiveness of therapy                 | 0            |
| Highly selected intervention team or level of training/proficiency not widely available | 1            |
| Follow-up not reflective of current practice  | 0            |
| Co-intervention that are likely to modify monitoring strategies                         | 0            |
| <b>Comparator (C)</b>   |              |
| Diagnostic tools used differently than as recommended or commonly used in practice      | 0            |
| Comparator unclear  | 0            |
| Inadequate comparison therapy or use of a substandard alternative therapy               | 0            |
| <b>Outcomes (O)</b>   |              |
| Composite outcomes that mix outcomes of different significance                          | 0            |
| Short-term follow-up  | 0            |
| Surrogate outcomes  | 0            |
| <b>Setting (S)</b>  |              |
| Level of care different from that in the community                                      | 9            |

DSM=Diagnostic and Statistical Manual of Mental Disorders

**Table 23. Potential issues with applicability of included studies for Key Question 2**

| Issue   | N=69 Studies           |                           |                          |                               |                              |
|---|------------------------|---------------------------|--------------------------|-------------------------------|------------------------------|
|   | Pharm vs. Pharm<br>N=9 | Pharm vs. Nonpharm<br>N=7 | Pharm vs. Placebo<br>N=7 | Nonpharm vs. Nonpharm<br>N=15 | Nonpharm vs. Placebo<br>N=37 |
| <b>Population (P)</b>   |                        |                           |                          |                               |                              |
| Narrow eligibility criteria and exclusion of those with comorbidities                   | 0                      | 0                         | 1                        | 2                             | 1                            |
| More complex patients than typical of the community                                     | 0                      | 0                         | 0                        | 0                             | 0                            |
| Run-in period with high exclusion rate for non-adherence or side effects                | 0                      | 0                         | 0                        | 0                             | 0                            |
| DSM-4/5 diagnosis unclear   | 0                      | 0                         | 0                        | 0                             | 1                            |
| <b>Intervention (I)</b>   |                        |                           |                          |                               |                              |
| Diagnostic tools used differently than as recommended or commonly used in practice      | 0                      | 0                         | 0                        | 0                             | 0                            |
| Dosing not reflective of current practice   | 0                      | 0                         | 0                        | 0                             | 0                            |
| Co-interventions that are likely to modify the effectiveness of therapy                 | 1                      | 1                         | 2                        | 0                             | 4                            |
| Highly selected intervention team or level of training/proficiency not widely available | 0                      | 1                         | 1                        | 1                             | 4                            |
| Follow-up not reflective of current practice  | 0                      | 0                         | 1                        | 0                             | 1                            |
| Co-intervention that are likely to modify monitoring strategies                         | 0                      | 0                         | 0                        | 0                             | 0                            |
| <b>Comparator (C)</b>   |                        |                           |                          |                               |                              |
| Diagnostic tools used differently than as recommended or commonly used in practice      | 0                      | 0                         | 0                        | 0                             | 0                            |
| Comparator unclear  | 1                      | 0                         | 1                        | 0                             | 0                            |
| Inadequate comparison therapy or use of a substandard alternative therapy               | 1                      | 0                         | 0                        | 1                             | 3                            |
| <b>Outcomes (O)</b>   |                        |                           |                          |                               |                              |
| Composite outcomes that mix outcomes of different significance                          | 0                      | 0                         | 0                        | 0                             | 0                            |
| Short-term follow-up  | 0                      | 2                         | 1                        | 4                             | 10                           |
| Surrogate outcomes  | 0                      | 0                         | 0                        | 0                             | 0                            |
| <b>Setting (S)</b>  |                        |                           |                          |                               |                              |
| Level of care different from that in the community                                      | 0                      | 1                         | 2                        | 2                             | 4                            |

Abbreviations: DSM=Diagnostic and Statistical Manual of Mental Disorders; Pharm=pharmacologic; Nonpharm=nonpharmacologic

## Implications for Clinical and Policy Decisionmaking

The lack of strong evidence for objective tests for the diagnosis of ADHD suggests that behavior rating scales should continue to be used as the primary strategy for diagnosing the condition. Overall, pharmacotherapy has been more studied than other treatment approaches and is generally considered the first approach to treatment for children and adolescents over 7 years of age. Insufficient data were available to determine whether they should be the first line of therapy for children under 7 years of age. Cognitive behavioral therapy (low SOE) or child or

parent training (moderate SOE) may reduce symptoms of ADHD but had no difference in academic performance (low SOE). Insufficient data were available to evaluate the effect of combining medication therapy with these approaches to care. There is a lack of supportive data for other complementary therapies. Although regular follow-up is recommended for children and adolescents with ADHD, no evidence was found about the comparative benefits and harms of different approaches.

## **Limitations of the Systematic Review Process**

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

Our review methods also have limitations. This review was designed to extend two previous systematic reviews.<sup>4, 19</sup> However, these two previous reviews did not have the same focus on issues related to the diagnosis and management of ADHD as this review. The time period of this systematic review led to the exclusion of earlier larger studies. In addition, some of the earlier reports regarding studies (e.g., the Multisite Multimodal Treatment Study of Children with ADHD [MTA]) included in this review might have been excluded. Our study was limited to English-language publications. Note that during the protocol development phase of our review we made two scoping revisions in consultation with our Technical Expert Panel (TEP). Specifically the review focused on:

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

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

Another limitation of this review is that medication doses were not abstracted. Abstracting specific doses is challenging because many of the studies are based on dose escalation and there is often insufficient information to be able to determine the dose per subject body weight.

## **Research Recommendations**

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

## **KQ 1: ADHD Diagnosis Research Gaps**

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

- Validity and reliability of behavior scales in direct comparison to new strategies for diagnosis:
  - Studies should include a typical population of children and adolescents in primary care seeking initial diagnosis.
  - The tools should be performed in the primary care setting.
  - Confirmation should be based on DSM-5 criteria by an expert within a short period of time to evaluate in the primary care setting. The expert should be blinded to the results in primary care.
  - Receiver operator characteristic (ROC) curves should be generated to evaluate the validity of diagnosis using different cut-offs for the behavior scales and consider the impact of combining behavior scales with other diagnostic strategies.
  - Results should be stratified by age group and ADHD subtype.
  - Reliability (test-retest reliability, inter-observer reliability, and intra-observer reliability) should be evaluated.
- Harms of labeling: These can be assessed in a longitudinal cohort of patients diagnosed with ADHD as part of an overall study to evaluate the effectiveness of interventions (see KQ 2).

## **KQ 2: ADHD Treatment Research Gaps**

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

- Effectiveness of treatment:
  - Secondary data analysis of electronic record data could be used to assess outcomes from large cohorts of patients, but would be limited to the available data and lack of randomization.
  - Typical care would be better informed by a pragmatic randomized trial that includes the typical spectrum of patients seen in primary care. Pragmatic trials can be embedded with electronic medical records, making prospective studies more feasible.
  - Three-arm studies, using pharmacologic, nonpharmacologic treatments (e.g., behavioral interventions), and a combination of approaches are needed. In a pragmatic trial, therapy could be escalated or combined, based on the responsiveness to treatment.
  - Although behavioral interventions are recommended, more research is needed about the comparative effectiveness of different approaches and how behavioral interventions can be personalized within the context of care in which most children and adolescents are treated.
  - Studies should include a wide range of outcomes, including behavior rating scales, school functioning, risk-taking behaviors, growth and development, comorbid psychiatric disorders, and the typical adverse events monitored in drug trials.
  - Studies should have a meaningful duration. Ideally, those enrolled in a pragmatic trial would be followed for multiple years.



- Studies should include the full spectrum of children and adolescents seeking care in the primary care setting.
- Follow-up monitoring should be evaluated, as described for KQ 3.

### **KQ 3: ADHD Monitoring Research Gaps**

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

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

### **Conclusions**

Additional benefit of new strategies for diagnosing ADHD (e.g., imaging, EEG) is unclear. Little is known about the harm of labeling. For ADHD treatment, the 2011 report found benefits for psychostimulant therapy and behavioral therapy. This report using more stringent criteria for inclusion (e.g., diagnostic confirmation of ADHD) found evidence for behavioral therapy improving ADHD symptoms but no difference in academic performance and insufficient evidence for other outcomes. In addition, we found that omega-3/6 fatty acid supplementation does not appear to be effective in reducing ADHD symptoms. Overall, this review highlights the need for more research regarding behavioral therapies. There are insufficient data available to determine whether variations exist in effectiveness by age, sex, or presenting ADHD symptoms. No data were identified to determine the optimal strategy for monitoring children and adolescents with ADHD.

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## Acronyms and Abbreviations

| <b>Acronym/Abbreviation</b> | <b>Definition</b>  |
|-----------------------------|--|
| AAP                         | American Academy of Pediatrics   |
| AACAP                       | American Academy of Child and Adolescent Psychiatry  |
| ACES                        | Adverse Childhood Experiences Study  |
| ADHD                        | Attention deficit hyperactivity disorder   |
| ADHD-C                      | Attention deficit hyperactivity disorder-combined type   |
| ADHD-HI                     | Attention deficit hyperactivity disorder-hyperactive/impulsive type                                  |
| ADHD-I                      | Attention deficit hyperactivity disorder-inattentive type  |
| ADHD-RS                     | Attention Deficit Hyperactivity Disorder Rating Scale  |
| ADHD RS-IV                  | Attention Deficit Hyperactivity Disorder Rating Scale 4  |
| AHRQ                        | Agency for Healthcare Research and Quality   |
| ATTEX                       | Attention and Executive Function Rating Inventory  |
| ATX                         | Atomoxetine  |
| AUC                         | Area under the curve   |
| AV                          | Atrioventricular   |
| BASC-2                      | Behavior Assessment System for Children, Second Edition  |
| BASC-2 BESS                 | Behavior Assessment System for Children, Second Edition<br>Behavioral and Emotional Screening System |
| BPT                         | Behavioral parent training   |
| BRIEF                       | Behavior Rating Inventory of Executive Function  |
| CANTAB                      | Cambridge Neuropsychological Test Automated Battery  |
| CARE                        | Coping With ADHD Through Relationships and Education   |
| CBCL                        | Child Behavior Checklist   |
| CBRS                        | Comprehensive Behavior Rating Scale  |
| CBT                         | Cognitive behavioral therapy   |
| CBV                         | Caudate body volume  |
| CD                          | Conduct disorder   |
| CDI                         | Children's Depression Inventory  |
| CDSR                        | Cochrane Database of Systematic Reviews  |
| CER                         | Comparative effectiveness review   |
| CGI                         | Conners' Global Index; Clinical Global Impression  |
| CGI-S                       | Clinical Global Impression Severity  |
| CGI-SS                      | Clinical Global Impression of Severity of Suicidality  |
| CHEXI                       | Childhood Executive Functioning Inventory  |
| CHIP-CE-PRF                 | Child and Health Illness Profile Child Edition, Parent Report Form                                   |
| CHP-AS                      | Challenging Horizons Program After School  |
| CHP-M                       | Challenging Horizons Program Mentoring   |
| CI                          | Confidence interval  |
| CDI                         | Children's Depression Inventory  |
| CLAS                        | Child Life and Attention Skills  |

| <b>Acronym/Abbreviation</b> | <b>Definition</b>   |
|-----------------------------|---|
| Cog-Fun                     | Cognitive Functional intervention   |
| Cogmed                      | Computerized memory training program  |
| Conners 3                   | Conners 3rd Edition   |
| Conners CPT                 | Conners Continuous Performance Test   |
| CPFT                        | Continuous Performance Function Test  |
| CPRS                        | Conners Parent Rating Scale   |
| CPT                         | Continuous Performance Test   |
| CRS                         | Conners Rating Scale  |
| CRS-P                       | Conners Rating Scale Parent   |
| CRS-T                       | Conners Rating Scale Teacher  |
| CTRS                        | Conners Teacher Rating Scale  |
| DASS                        | Depression Anxiety Stress Scale   |
| DB-DOS                      | Disruptive Behavior Diagnostic Observation Schedule   |
| DBDRS                       | Disruptive Behavior Disorder Rating Scale   |
| DBRS                        | Disruptive Behavior Rating Scale  |
| DBP                         | Diastolic blood pressure  |
| DEX                         | Dextroamphetamine   |
| DHA                         | Docosahexaenoic acid  |
| DICA-IV                     | Diagnostic Interview for Children and Adolescents 4   |
| DISC-IV                     | Diagnostic Interview Schedule for Children Version IV   |
| DSM-5                       | Diagnostic and Statistical Manual of Mental Disorders, 5 <sup>th</sup> Edition                |
| DSM-IV-TR                   | Diagnostic and Statistical Manual of Mental Disorders, 4 <sup>th</sup> Edition, Text Revision |
| D-TMP                       | Dexmethylphenidate  |
| ECG                         | Electrocardiograph  |
| ED                          | Emergency department  |
| EEG                         | Electroencephalograph, electroencephalogram, electroencephalography                           |
| EHC                         | Effective Health Care   |
| EIS                         | Electro-interstitial scan   |
| EMBASE                      | Excerpta Medica Database  |
| EPA                         | Eicosapentaenoic acid   |
| EPC                         | Evidence-based Practice Center  |
| ERP                         | Event-related potentials  |
| ES                          | Effect size   |
| FDA                         | Food and Drug Administration  |
| FSSEE                       | Family-School Success–Early Elementary  |
| GIR                         | Guanfacine immediate release  |
| GPA                         | Grade point average   |
| GXR                         | Guanfacine extended release   |
| HR                          | Hazard ratio  |

| <b>Acronym/Abbreviation</b>               | <b>Definition</b>   |
|---|---|
| ICD-10                                    | 10 <sup>th</sup> revision of the International Statistical Classification of Diseases and Related Health Problems |
| ICTRP                                     | International Clinical Trials Registry Platform   |
| IRS                                       | Impairment Rating Scale   |
| IVA-2 (BrainTrain, Inc)                   | Integrated Visual and Auditory 2  |
| IVA-AE2 (BrainTrain, Inc)                 | Integrated Visual and Auditory Advanced Edition 2   |
| IVA-CPT                                   | Integrated Visual and Auditory Continuous Performance Test  |
| IVA-QS (BrainTrain, Inc)                  | Integrated Visual and Auditory Quick Screening  |
| K-DBDS                                    | Kiddie Disruptive Behavior Disorder Schedule  |
| K-DISC-IV                                 | Kiddie Computerized Diagnostic Interview Schedule for Children  |
| KQ  | Key Question  |
| K-SADS-PL                                 | Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version                            |
| LA  | Linoleic acid   |
| LDX                                       | Lisdexamfetamine  |
| MAS                                       | Mixed amphetamine salts   |
| MASC                                      | Multidimensional Anxiety Scale for Children   |
| MATH-CPT                                  | Mathematics Continuous Performance Test   |
| MEDLINE                                   | National Library of Medicine bibliographic database   |
| Mini KID                                  | Mini International Neuropsychiatric Interview for Children and Adolescents  |
| MPH                                       | Methylphenidate   |
| MRI                                       | Magnetic resonance imaging  |
| MTA                                       | Multisite Multimodal Treatment Study of Children with ADHD  |
| NA  | Not applicable  |
| NDG                                       | Ningdong granule  |
| NEBA                                      | Neuropsychiatric EEG-Based Assessment AID   |
| NICHQ Vanderbilt Assessment Scale–PARENT  | National Institute for Children’s Health Quality Vanderbilt Assessment Scale Parent                               |
| NICHQ Vanderbilt Assessment Scale–TEACHER | National Institute for Children’s Health Quality Vanderbilt Assessment Scale Teacher                              |
| NIMH                                      | National Institute of Mental Health   |
| NS  | Not significant   |
| NSS                                       | Neurological subtle signs   |
| ODD/CD                                    | Oppositional defiant disorder/Conduct disorder  |
| OROS-MPH                                  | Osmotic release oral system methylphenidate   |
| PACS                                      | Parental account of children’s symptoms   |
| PATS                                      | Preschool ADHD Treatment Study  |
| P-DBDRS                                   | Parent Disruptive Behavior Disorder Rating Scale  |

| <b>Acronym/Abbreviation</b> | <b>Definition</b>   |
|-----------------------------|---|
| PICOTS                      | Populations, Interventions, Comparators, Outcomes, Timing, Settings |
| PRISMA                      | Preferred Reporting Items for Systematic Reviews and Meta-Analyses  |
| PROSPERO                    | Prospective Register of Systematic Reviews                          |
| PS                          | Phosphatidylserine  |
| RBBB                        | Right bundle branch block   |
| RR                          | Relative risk   |
| RCT                         | Randomized controlled trial   |
| ROC                         | Receiver operator characteristic                                    |
| SBP                         | Systolic blood pressure   |
| SD                          | Standard deviation  |
| SDQ                         | Strengths and Difficulties Questionnaire                            |
| SDSC                        | Sleep Disturbance Scale for Children                                |
| SE                          | Standard error  |
| SMD                         | Standardized mean difference  |
| SNAP-IV                     | Swanson, Nolan and Pelham Revision                                  |
| SOE                         | Strength of evidence  |
| STAND                       | Supporting Teens' Autonomy Daily                                    |
| STEPP                       | Strategies to Enhance Positive Parenting                            |
| SWAN                        | Strengths and Weaknesses of ADHD and Normal Behavior                |
| TBR                         | Theta/beta ratio  |
| TEP                         | Technical expert panel  |
| TOVA                        | Test of Variables of Attention                                      |
| WHO                         | World Health Organization   |
| WIAT                        | Wechsler Individual Achievement Test                                |
| WJ                          | Woodcock-Johnson test of achievement                                |
| WRAT                        | Wide Range Achievement Test   |
| WPREMB                      | Weekly Parent Ratings of Evening and Morning Behavior               |
| XR                          | Extended release  |