Comparative Effectiveness Review
Number 203

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

AHRQ
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Effective Health Care Program

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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.

This report is based on research conducted by the Duke Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00004-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may periodically be assessed for the currency of conclusions. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program Web site at www.effectivehealthcare.ahrq.gov. Search on the title of the report.

Persons using assistive technology may not be able to fully access information in this report. For assistance contact epc@ahrq.hhs.gov.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

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

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

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

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Key Informants

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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Technical Expert Panel

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

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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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®, Embase®, PsycINFO®, 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.[1] In the United States, there are significant geographical variations in the rate of diagnosis and treatment, and the prevalence has increased over time.[1, 2] The most recent Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[3] 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.[4] 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.[5]

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

Diagnosis

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

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."[8] 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.[8] 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.[9-11] 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.[12]

Adverse Effects of Treatment

Adverse effects associated with pharmacologic treatment can include changes in appetite, growth suppression,[13] 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.[14] 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.[15-17] 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.[4] 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.[4] 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[18] 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.[4,19] 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,[12] 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.

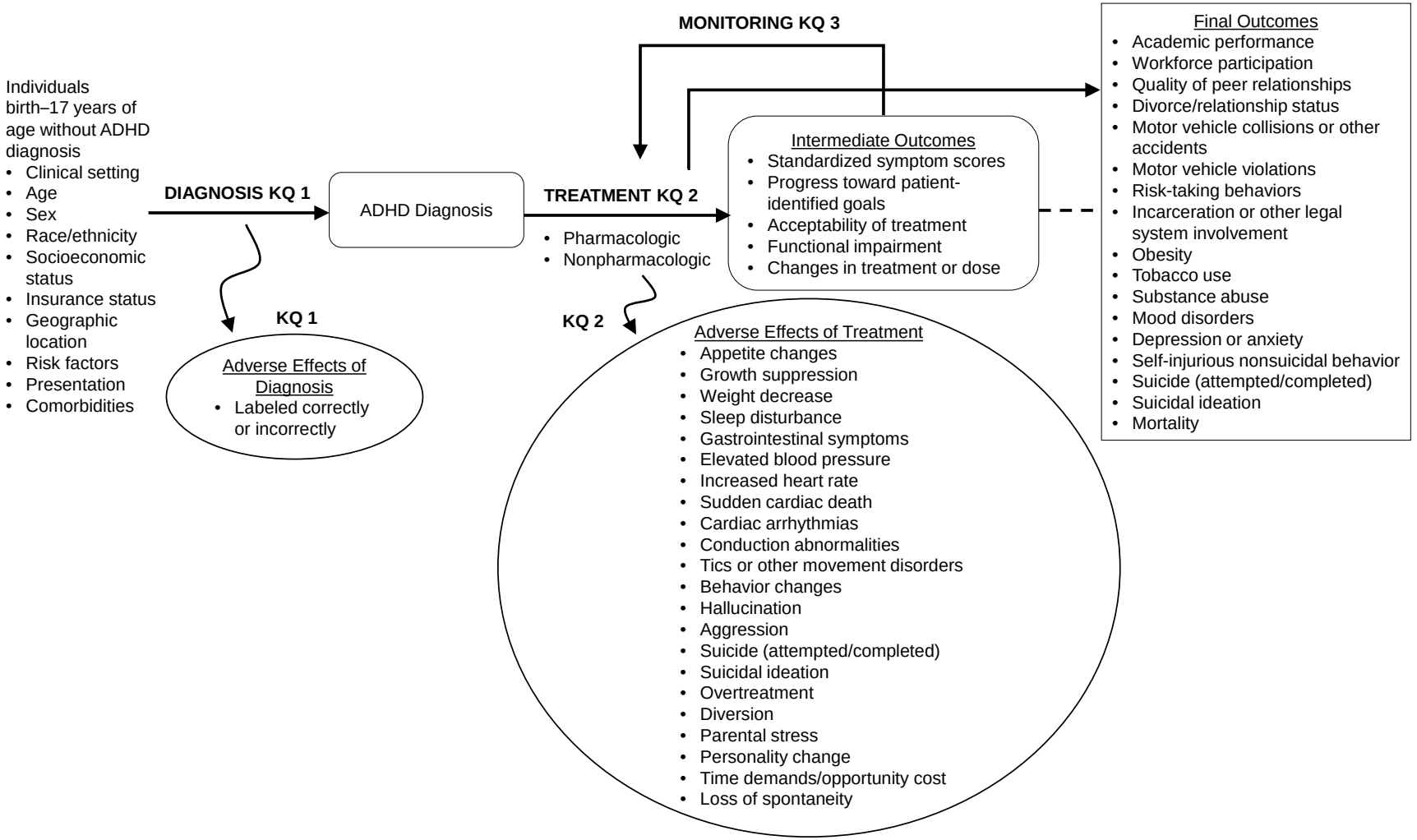
Key Questions

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.[4] 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.[20] 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.[21] 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). The PROSPERO registration is CRD42016029134.

Literature Search Strategy

Search Strategy

To identify relevant published literature, we searched MEDLINE® (via PubMed), Embase®, PsycINFO®, and the Cochrane Database of Systematic Reviews (CDSR), limiting the search to studies conducted in children 17 years of age and younger and published from January 1, 2009, to 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).[4]

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.[22-79] 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).[80] 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	KQ 1: Individuals birth through 17 years of age without the diagnosis of ADHD, divided by subquestion as follows: • KQ 1a considers the initial diagnosis of individuals under 7 years of age. • KQ 1b considers the initial diagnosis of individuals through 17 years of age using EEG, imaging, or executive function approaches. • KQs 1c and 1d considers both populations. KQ 2: Individuals birth through 17 years of age with a diagnosis of ADHD KQ 3: Individuals birth through 17 years of age who have previously begun treatment for ADHD Subgroups of interest for KQs 1-3: • The general population of children and adolescents: ages less than 4, 4–6, 7–12, and 13–17 years • When data are available, findings are separately evaluated by sex or specific risk factors (prenatal tobacco, alcohol, or substance abuse; prematurity or low birth weight; and family history); ADHD presentation; comorbidity; race/ethnicity; socioeconomic status; insurance status; geographic location	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. Administrative claims data used for diagnosis of ADHD

Interventions	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. KQ 2: Any pharmacologic or nonpharmacologic treatment of ADHD, alone or in combination: • Pharmacologic treatments considered are brand name and generic formulations of the following medications[a]: o Psychostimulants ▪ Methylphenidate (MPH) ▪ Dexmethylphenidate (D-TMP) ▪ Dextroamphetamine (DEX) ▪ Lisdexamfetamine (LDX) ▪ Mixed amphetamine salts (MAS) ▪ Amphetamine o Tricyclic antidepressants ▪ *Desipramine ▪ *Nortriptyline o Selective norepinephrine reuptake inhibitors ▪ Atomoxetine (ATX) o Alpha-2 agonists ▪ Clonidine ▪ Guanfacine extended release (GXR) ▪ *Guanfacine immediate release (GIR) o Dopamine reuptake inhibitors ▪ *Modafinil ▪ *Armodafinil o Norepinephrine-dopamine reuptake inhibitors ▪ *Bupropion o Serotonin-norepinephrine reuptake inhibitors ▪ *Duloxetine o Serotonin-norepinephrine-dopamine reuptake inhibitors ▪ *Venlafaxine o Monoamine oxidase type B inhibitors ▪ *Selegiline o N-methyl-D-aspartate receptor antagonists ▪ *Amantadine ▪ *Memantine • Nonpharmacologic therapies considered include psychosocial interventions, behavioral interventions, cognitive behavioral therapy, play therapy, mindfulness-based therapies, school interventions, cognitive training therapies, biofeedback or neurofeedback, parent behavior training, dietary supplements (e.g., omega-3 fatty acids, vitamins, herbal supplements, probiotics), homeopathy, acupuncture, elimination diets, vision training, exercise, and chiropractic treatment. KQ 3: Follow-up visits in primary care with various methods and within times (monthly to annually) for repeat monitoring, independent of treatment.	KQ 1: Validation studies or diagnosis conducted using a nonvalidated instrument 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

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Comparators	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. KQ 2: Specific treatments compared with other treatments as described above or to no treatment. KQ 3: Follow-up compared with differing durations of follow-up or differing settings of follow-up.	KQ 1: Comparison to diagnosis with a nonvalidated instrument

Outcomes	KQ 1: • Accuracy of diagnostic strategy, as measured by: o Diagnostic concordance of primary care provider with specialist o Inter-rater reliability o Internal consistency o Test-retest o Sensitivity o Specificity o Positive predictive value o Negative predictive value o False positives o False negatives o Risk of missed condition that can appear as ADHD (i.e., misdiagnosis) • Labeling is any measure of stigma following diagnosis comparing those with and without ADHD. KQ 2: • Intermediate outcomes: o 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) o Acceptability of treatment o Functional impairment (assessed using the Clinical Global Impressions [CGI] scale or the Impairment Rating Scale [IRS]) • Final outcomes include: o Academic performance ▪ Academic Performance Rating Scale ▪ Academic Competency Evaluation Scale (ACES) ▪ (Actual) School grades ▪ Grade Retention/Not being promoted ▪ Vanderbilt Teacher Form Academic Performance Subscale ▪ Standardized achievement tests (WIAT, WJ, WRAT) o Workforce participation o Quality of peer relationships o Divorce/relationship status o Motor vehicle collisions or other accidents o Motor vehicle violations o Risk-taking behaviors o Incarceration or other interactions with the legal system (juvenile detention, probation, court-mandated interventions, need for residential placement) o Obesity o Tobacco use o Substance abuse o Mood disorders o Depression or anxiety	

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

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Study design	• Original data • Randomized trials, prospective and retrospective observational studies with comparator; for diagnostic accuracy, cross-sectional studies are acceptable if they include patients with diagnostic uncertainty and direct comparison of diagnosis in primary care to diagnosis by a specialist • Randomized controlled trials with sample size: o ≥20 subjects for KQs 1 and 3 o ≥50 subjects for KQ 2 (or 100 subjects for studies comparing two or more pharmacologic treatments approved by the FDA for the treatment of ADHD) • Observational studies with sample size: o ≥20 subjects for KQs 1 and 3 o ≥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)	Editorials, nonsystematic reviews, letters, case series, case reports, abstract-only, pre-post studies 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.
Publications	• English-language publications only • Published on or after January 1, 2009 • Relevant systematic reviews, meta-analyses, or methods articles (used for background only)[b]	Non-English language articles[c]

[a]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.
[b]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.
[c]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=dexmethylphenidate; 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.[81]

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[82] tool for randomized studies and the Newcastle-Ottawa Scale[83] 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.[20] 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
Good (low risk of bias)	These studies had the least bias, and the results were considered valid. These studies adhered to the commonly held concepts of high quality, including the following: a clear description of the population, setting, approaches, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytical methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.
Fair	These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems.
Poor (high risk of bias)	These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

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

Data Synthesis

We began by summarizing key features of the included studies for each KQ. To the degree that data were available, we abstracted information on study design; patient characteristics; clinical settings; interventions; and intermediate, final, and adverse event outcomes. We ordered our findings by treatment or diagnostic comparison and then within these comparisons by outcome with long-term final outcomes emphasized. 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.[20, 84] 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).[84]

Table 3. Required domains: Definitions and scores

Domain	Definition and Elements	Score and Application
Study Limitations	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: • Study design: Whether RCTs or other designs such as nonexperimental or observational studies. • Study conduct. Aggregation of ratings of risk of bias of the individual studies under consideration.	Score as one of three levels, separately by type of study design: • **Low** level of study limitations • **Medium** level of study limitations • **High** level of study limitations
Directness	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. Evidence may be indirect in several situations such as: • 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). • 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. • 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. Indirectness always implies that more than one body of evidence is required to link interventions to the most important health outcome.	Score as one of two levels: • **Direct** • **Indirect** If the domain score is indirect, EPCs should specify what type of indirectness accounts for the rating.
Consistency	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: • 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]) • Magnitude of effect: The range of effect sizes is similar. EPCs may consider the overlap of CIs when making this evaluation. The importance of direction vs. magnitude of effect will depend on the Key Question and EPC judgments.	Score as one of three levels: • **Consistent** • **Inconsistent** • **Unknown** (e.g., single study) Single-study evidence bases (including mega-trials) cannot be judged with respect to consistency. In that instance, use "Consistency unknown (single study)."

Domain	Definition and Elements	Score and Application
Precision	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. • 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. • If EPCs performed a meta-analysis, then EPCs may also consider whether the CI crossed a threshold for an MID. • 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.	Score as one of two levels: • **Precise** • **Imprecise** 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).
Reporting Bias	Reporting bias results from selectively publishing or reporting research findings based on the favorability of direction or magnitude of effect. It includes: • Study publication bias; i.e., nonreporting of the full study. • Selective outcome reporting bias; i.e., nonreporting (or incomplete reporting) of planned outcomes or reporting of unplanned outcomes. • Selective analysis reporting bias, i.e., reporting of one or more favorable analyses for a given outcome while not reporting other, less favorable analyses. 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. Because methods to detect reporting bias in observational studies are less certain, this guidance does not require EPCs to assess it for such studies.	Score as one of two levels: • **Suspected** • **Undetected** Reporting bias is suspected when: • Testing for funnel plot asymmetry demonstrates a substantial likelihood of bias, And/or • A qualitative assessment suggests the likelihood of missing studies, analyses, or outcomes data that may alter the conclusions from the reported evidence. Undetected reporting bias includes all alternative scenarios.

CI=confidence internal; 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

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

Applicability

We assessed applicability across our KQs using the method described in AHRQ's Methods Guide.[20, 85] 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

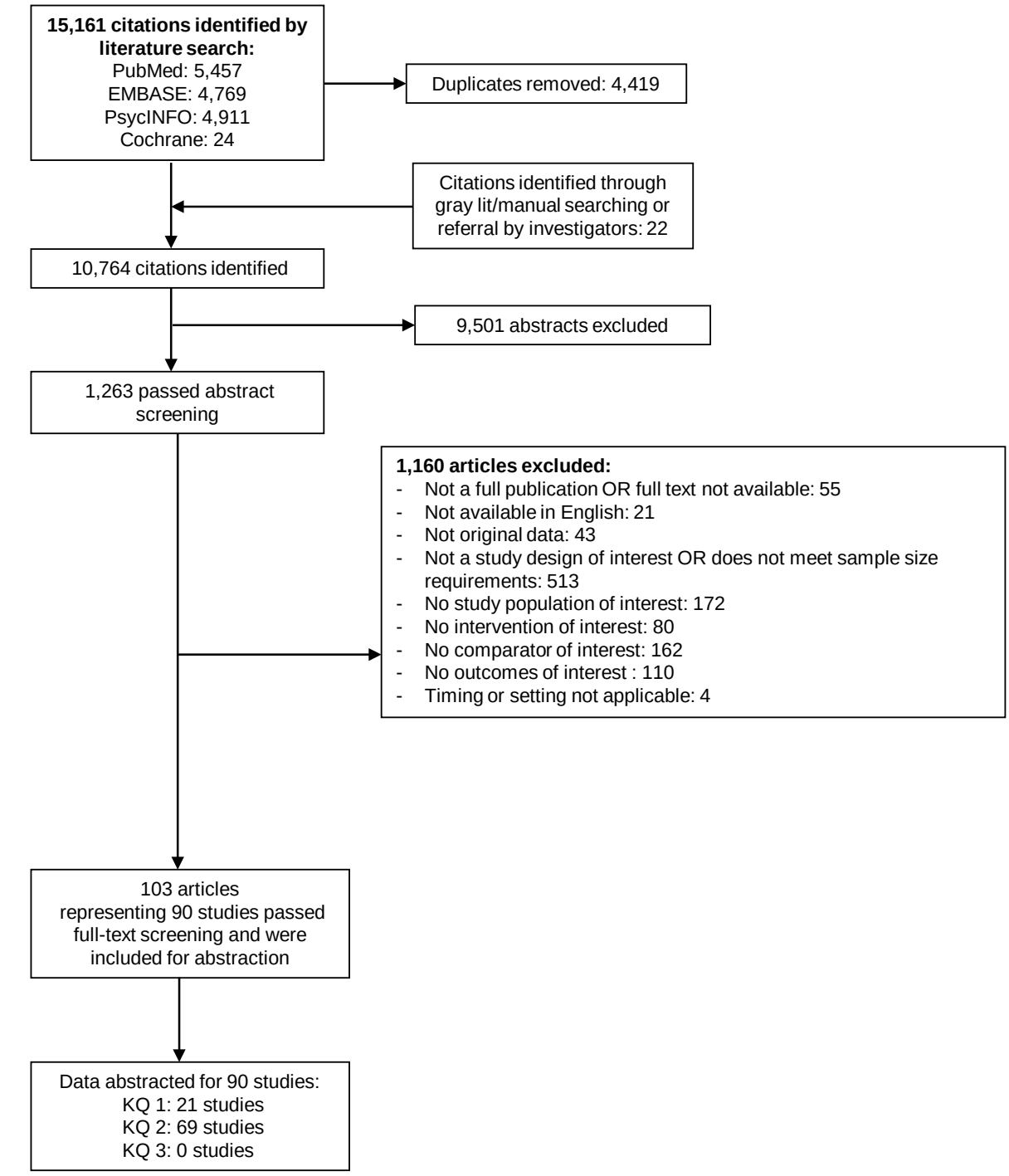
In what follows, we begin by describing the results of our literature searches. We then provide a brief overview description of the included studies. The remainder of the chapter is organized by Key Question (KQ). Under each of the three KQs, we begin by listing the key points of the findings, followed 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®, Embase®, PsycINFO®, 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[86] Thorell, 2010[87]
	Ages 7 through 17	Berger, 2010[88] Bloch, 2012[89] dosReis, 2010[90] Ferrin, 2012[91] Kim, 2015[92] Kim, 2015[93] Klenberg, 2010[94] Liechti, 2013[95] Markovska-Simoska, 2016[96] Martin-Martinez, 2012[97] Ogrim, 2012[98] Ohan, 2011[99] Park, 2016[100] Soliva, 2010[101] Zelnik, 2012[102]
	All ages through 17	Carballo, 2014[103] Castro-Cabrera, 2010[104] Caudal, 2011[105] Gonzalez, 2013[106]
KQ 2	Ages 6 and under	Abikoff, 2015[107]

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

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

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[176-178]), pharmacologic versus placebo (4 studies[176, 179-181]), and nonpharmacologic versus placebo (1 study[182]). 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

Category	Tool	Domains Assessed	Method	Scoring	Interpretation
Interviews					
	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.
Rating Scales					

Category	Tool	Domains Assessed	Method	Scoring	Interpretation
	NICHQ (National Institute for Children's Health Quality) Vanderbilt Assessment Scale	• ADHD Predominantly Inattentive • ADHD Predominantly Hyperactive/Impulsive • ADHD Combined • Oppositional Defiant Disorder • Conduct Disorder • Anxiety/Depression	• Parent questionnaire • Teacher questionnaire	*Symptom Questions* • Rated based on frequency • 0–3 scale (never, occasionally, often, very often) • Number of symptoms endorsed at a 2 (often) or 3 (very often) is summed for each domain *Performance Questions* • Rated based on problem severity • 0–5 scale (excellent, above average, average, somewhat of a problem, problematic)	• A positive screen indicates the need for further evaluation • The screening measure is positive if both of the following are met for a given domain: - Specific number of Symptom Questions are rated 2 or 3 - At least one Performance Question is rated 4 or 5

Category	Tool	Domains Assessed	Method	Scoring	Interpretation
	Conners Rating Scales • CPRS • CTRS • CRS • Conners 3	Note: Subscale names vary slightly between versions of the Conners Rating Scales, but include: *ADHD-related scales* • Inattention • Hyperactivity/Impulsivity • Learning Problems • Executive Functioning • DSM Symptoms Scales • ADHD Index • Conners Global Index *Behavioral/emotional scales* • Defiance/Aggression • Peer Relations/ Social Problems • Family Relations • Oppositional Defiant Disorder • Conduct Disorder • Cognitive Problems • Anxious-Shy • Perfectionism • Psychosomatic	• Parent questionnaire • Teacher questionnaire • Adolescent questionnaire	• Rated based on how true the question is for the child • 0–3 (not true at all, just a little true, pretty much true, very much true).	• Raw scores for each scale are converted to T scores (mean=50, SD=10) based on a normative sample • Higher scores indicated increased clinical concern • Interpretation guidelines indicate that scores ≥ 60 are above average

Category	Tool	Domains Assessed	Method	Scoring	Interpretation
	SNAP-IV (Swanson, Nolan and Pelham Revision)	• ADHD Predominantly Inattentive • ADHD Predominantly Hyperactive/Impulsive • ADHD Combined	• Parent questionnaire • Teacher questionnaire	• Rated based on frequency • 0–3 scale (not at all, just a little, quite a bit, very much)	• Scores can be interpreted in two different ways: (1) Sum of items for each of the three subscales, with high score indicating more symptoms. (2) 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.
	DBDRS (Disruptive Behavior Disorder Rating Scale)	• ADHD Predominantly Inattentive • ADHD Predominantly Hyperactive/Impulsive • ADHD Combined • Oppositional Defiant Disorder • Conduct Disorder	• Parent questionnaire • Teacher questionnaire	• Rated based on frequency • 4 point scale (not at all, just a little, pretty much, and very much)	• Scales scores are computed by summing the items in each domain. • Scores were considered to be in the clinical range for ADHD if they are between the 95th to 100th percentile.
	ADHD-RS (ADHD Rating Scale)	• ADHD Predominantly Inattentive • ADHD Predominantly Hyperactive/Impulsive • ADHD Combined	• Parent questionnaire • Teacher questionnaire	• Rated based on frequency • 0–3 (does not experience the symptom at all … symptom very often)	• Scores are calculated by summing the items in each domain and the total items.

Category	Tool	Domains Assessed	Method	Scoring	Interpretation
	SDQ (Strengths and Difficulties Questionnaire)	• Emotional symptoms • Conduct problems • Hyperactivity/inattention • Peer relationship problems • Prosocial behavior • Total difficulties	• Parent questionnaire • Teacher questionnaire	• Rated based on how true the question is for the child • 0–2 (not true, somewhat true, certainly true) • Some items are reverse coded.	• Higher scores indicate more concerns in a given area. • Raw scores can be compared to cut-points derived from a typical population.
	BRIEF (Behavior Rating Inventory of Executive Function)	• Behavioral Regulation Index (three scales) • Metacognition Index (five scales) • Global Executive Composite	• Parent questionnaire • Teacher questionnaire	• Rated based on frequency • 3-point scale (never, sometimes often)	• Raw scores are converted to T scores (mean=50; SD=10) and percentiles based on a normative sample. • Higher scores indicate more problems relative age-matched peers.
	CHEXI (Childhood Executive Functioning Inventory)	• Inhibition (inhibition and regulation • Working Memory (working memory and planning)	• Parent questionnaire • Teacher questionnaire	• Rated based on how true the question is for the child • 0-5 point (definitely not true , not true, partially true, true, definitely true)	• Subscale scores are calculated by computing the mean score for items in each scale. • Higher scores are indicative of more severe symptoms.
	ATTEX (Attention and Executive Function Rating Inventory)	• Distractibility • Impulsivity • Motor hyperactivity • Directing attention • Sustaining attention • Shifting attention • Initiative • Planning • Execution of action • Evaluation • Total score	• Teacher questionnaire	• Rated based on severity • 3-point scale (not a problem, sometimes a problem, often a problem)	• Subscale scores are calculated by computing the mean score for items in each scale. • A Total Score is calculated by summing all of the scale scores. • Higher scores indicate greater severity (i.e., the behavior is more often a problems).
Continuous Performance Tests					

Category	Tool	Domains Assessed	Method	Scoring	Interpretation
	Conners CPT (Continuous Performance Test)	• Attention • Impulsivity • Sustained Attention • Vigilance	• Computerized test	• Responses to a target and nontarget	• Raw and standardized scores are calculated using an algorithm for each domain. • T scores and percentiles are provided, with higher scores indicating more problems in a given area.
	IVA CPT (Integrated Visual and Auditory Continuous Performance Test)	• Auditory Response Control • Visual Response Control • Auditory Attention • Visual Attention • Auditory Sustained Attention • Visual sustained Attention	• Computerized test	• Responses to the target (visual or auditory) and to the nontarget (visual or auditory)	• Visual and Auditory domain scores are calculated for a total of 12 quotients. • Omission and commission scores are generated, with more omission errors indicating greater distraction and more commission errors indicating greater impulsivity. • Hyperactivity-impulsiveness and attention deficit scales are calculated from the omission and commission errors, each comprising 3 visual and 3 auditory quotients.
	TOVA (Test of Variables of Attention)	• Attention • Inhibitory control	• Computerized test	• Responses to the target (correct) and responses to the nontarget (incorrect)	• Errors of omission (not responding to the target) yield a measure of inattention. • Errors of commission (responding to a nontarget) yield a measure of impulsivity.

Category	Tool	Domains Assessed	Method	Scoring	Interpretation
	CANTAB (Cambridge Neuro-psychological Test Automated Battery)[a]	• General memory and learning, with subtests including: - Working memory - Executive functioning - Visual memory - Attention - Reaction time - Decision making - Response control	• Computerized test	• Scoring varies by domain and includes scores such as percent correct, number of errors, time to complete, response latency	• Interpretation varies depending on the outcome measures (e.g., higher number of errors indicates more impairment; lower response latency indicates less impairment).

[a] 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[86-106, 183] 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.[92, 93, 96, 98, 106] ERP evaluations yielded consistently higher accuracy scores when conducted independently (91%, the highest imaging accuracy[104]) and in combination with EEG (73%[95]). MRI scans of caudate body volume also had accuracy scores of 84%.[101] 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.[92, 93, 98] Other CPTs, such as the TOVA, demonstrated limitations in their ability to correctly identify non-ADHD patients[88, 89, 102] and subtypes such as inattentive and hyperactive/impulsive.[100] Among the executive function tests, ATTEX[94] and CHEXI[87] performed better with overall accuracy rates of 91 percent to 93 percent, respectively, than the CANTAB,[89] which had low specificity (low SOE). Biometric devices such as EIS and Actigraphy had high sensitivity (80% to 97%) and specificity (84% to 98%).[97, 105] 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.[86, 91, 183]

Few studies examined whether there are differences in accuracy based on age,[91] sex,[94] and ADHD presentation.[86, 94, 100, 103, 183] 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.[90, 99] 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

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

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

Outcome SOE Grade	No. Studies/ Design (N Patients) Age Categories	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Labeling/Stigma Insufficient	2 Obs (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.[90, 99]

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[107-175, 184-195] 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.[110, 115, 120, 121, 123, 127, 135, 151, 166, 173] 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[113, 130, 135, 146, 148, 162, 166, 192] 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,[146] and the other reported blood pressure and heart rate by initial treatment group assignments over 10 years.[192] Three of the six studies were conducted exclusively in the United States,[130, 135, 146] two were conducted in the United States and Europe,[113, 148] one study was conducted in Asia,[166] and one was conducted in Europe, Australia, New Zealand, Israel, and South Africa.[162]

Two studies were rated poor quality[113, 166] 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[135, 166] 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,"[113] one study randomized treatment following an open-label study to either extended release guanfacine or placebo and assessed effects in the "withdrawal period,"[148] and one study (two articles) reported results long after the RCT treatment periods.[146, 192]

Placebo was the comparator in all of the studies except the two observational studies[135, 166] and the MTA study.[146] 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.[130] 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[166] and up to 1.5 mg/kg per day.[135] One study[135] 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[166] 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.[130] Three doses of lisdexamfetamine were compared with placebo. Although no statistical comparisons were made, there was a much smaller proportion of patients receiving placebo when compared with any dose of lisdexamfetamine that had achieved symptomatic remission at 1 month, defined as an ADHD-RS-IV score ≤18 (23.6% placebo, 62.3% lisdexamfetamine 30 mg/day, 67.6% lisdexamfetamine 50 mg/day, and 71.2% lisdexamfetamine 70 mg/day).

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."[148] 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."[148] 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.[135] 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.[162] 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.[113] 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.[113] 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.[146, 192]

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.[146, 192] 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.[162] 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[166] 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,[4] 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),[196] 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.[166] 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

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

Outcome SOE Grade	No. Studies/ Design (N Patients) Age Category	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Motor vehicle collisions Insufficient	1 RCT (436) 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.[146, 192]
Depression or anxiety Insufficient	1 RCT (436) 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.[146, 192]
Changes in appetite Insufficient	1 RCT (394) 7–17	Medium	Direct	NA	Imprecise	None	SOE was insufficient because only one study was included with medium risk of bias and imprecise findings[162]
Elevated blood pressure Insufficient	1 RCT (493) 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.[146, 192]
Gastrointestinal symptoms Insufficient	1 RCT (394) 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.[162]
Growth suppression Insufficient	1 RCT, 1 Obs (569) 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.[162, 166]
Increased heart rate Insufficient	1 RCT (507) 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.[146, 192]

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

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

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

Changes in Standardized Symptom Scores

Two studies reported results of ADHD symptom scores.[118, 156] 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).[118] 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).[156] 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 (± 13.5) for monotherapy and -16.1 (± 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.[120] 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.[110, 121, 123, 151, 156, 157, 173] 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.[173] 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.[110, 121, 123, 151] All of these used data from the Italian National ADHD Registry—three in whole[110, 121, 151] and one from selected sites in a specific region.[123] 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.[110] 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.[121] 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).[151] 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.[156] 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 dexmethylphenidate, or the combination.[157] 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 dexmethylphenidate 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[4] 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;[197] 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.[156] That study is also included in this updated review. Two studies assessed adverse events between ATX and unspecified stimulants,[198] and between MPH and DEX.[199] The remaining four studies compared growth in patients receiving MPH versus MAS,[200] DEX versus MPH,[201] amphetamine versus MPH,[202] and MPH versus DEX.[203]

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

Outcome SOE Grade	No. Studies/ Design (N Patients) Age Category	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Changes in standardized symptom scores Insufficient	1 RCT and 1 Obs (379) 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. [118, 156]
Acceptability of treatment-Discontinuation Rate Insufficient	1 Obs (130) 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.[123]
Behavior changes Insufficient	1 Obs (130) 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.[123]
Cardiac arrhythmias Insufficient	1 Obs (750) 7–17	High	Direct	Consistent	Imprecise	None	SOE was insufficient because of the risk of bias in the one observational study identified.[110]
Changes in appetite Insufficient	3 Obs (1,966) 7–17	Medium	Direct	Inconsistent	Imprecise	None	SOE was insufficient because of the risk of bias and lack of consistency in the observational studies.[121, 123, 151]
Conduction abnormalities Insufficient	1 Obs (1,424) 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.[151]
Elevated blood pressure Insufficient	2 Obs and 1 RCT (2,382) 7–17	High	Direct	Inconsistent	Imprecise	Unclear	SOE was insufficient because of the risk of bias in the 3 studies.[110, 151 157]
Gastrointestinal symptoms Low	3 Obs (1,966) 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.[121, 123, 151]

Outcome SOE Grade	No. Studies/ Design (N Patients) Age Category	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Increased heart rate Insufficient	3 Obs and 1 RCT (1137) 7–17	Low	Direct	Consistent	Imprecise	Unclear	SOE was insufficient because of the risk of bias and lack of consistent outcome assessment.[110, 121, 123, 157]
Sleep disturbance Insufficient	1 Obs (130) 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.[123]
Suicide ideation Insufficient	1 Obs (1424) 1 Obs (NR) 7–17	Medium	Direct	Consistent	Imprecise	None	SOE was insufficient because of study heterogeneity and risk that the outcome measure was not detected.[121, 151]
Tics or other movement disorders Insufficient	2 Obs (1554) 7–17	Medium	Direct	Consistent	Imprecise	None	SOE was insufficient because of study heterogeneity and risk that the outcome measure was not detected.[123, 151]

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 gingko 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[114, 124, 131, 141, 146, 147, 155, 189, 192] 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; gingko 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	
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 gingko biloba,[155] ningdong granule,[141] or omega-3/6 fatty acid.[114] The poor-quality study[114] 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 gingko 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[131, 147] behavioral therapy,[146, 147, 192] and a 3-arm trial combined MPH with neurofeedback.[124, 189] Sample sizes were small in two of the trials (n=57 and 91) and large (n=579) in the 8-year follow-up study.[146, 147, 192] 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.[114, 131, 141, 155] 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.[114, 141, 155] In the fourth study, sleep quality was not affected by any of the received interventions.[131] 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.[204, 205] Previous reviews have not included neurofeedback as an intervention of interest. Our summary findings directly comparing MPH with the supplements of gingko biloba, ningdong granule, or omega-3/6 fatty acids have not been reported in previous reviews. We found insufficient SOE that gingko 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[4] 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.[146, 192] (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[4] 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., gingko 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

Outcome SOE Grade	No. Studies/ Design (N Patients) Age Category	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Changes in standardized symptom scores Insufficient	5 RCTs (356) 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.[114, 124, 141, 147, 155, 189]
Behavior changes Insufficient	3 RCTs (274) 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.[114, 131, 141]
Aggression Insufficient	1 RCT (436) 7–17	Medium	Direct	NA	Imprecise	Unclear	SOE was insufficient because of the risk of bias in the single RCT identified.[146, 192]
Depression or anxiety Insufficient	2 RCTs (486) 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.[146, 155, 192]
Academic performance Insufficient	1 RCT (436) 7–17	Medium	Direct	NA	Imprecise	Unclear	SOE was insufficient because of the risk of bias in the single RCT identified.[146, 192]
Incarceration Insufficient	1 RCT (436) 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.[146, 192]
Motor vehicle collisions Insufficient	1 RCT (436) 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.[146, 192]
Changes in appetite Low	3 RCT (212) 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 ningdong, omega-3/6 or gingko biloba.[114, 141, 155]
Elevated blood pressure Insufficient	1 RCT (493) 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.[146, 192]
Gastrointestinal symptoms Insufficient	2 RCTs (162) 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.[114, 141]

Increased heart rate Insufficient	1 RCT (507) 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.[146, 192]
Sleep disturbance Low	4 RCTs (324) 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, gingko biloba, or neurofeedback.[114, 141, 155] A fourth study found no significant difference in sleep scores between interventions[131]
Weight decrease Insufficient	1 RCT (50) 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.[155]

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[204]) 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[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] representing 50 studies that met our inclusion criteria. All but two studies were RCTs.[115, 127] Of the 47 RCTs, 28 were rated as good quality,[107-109, 112, 116, 119, 122, 125, 126, 129, 131-134, 139, 142, 143, 150, 152, 158, 160, 161, 164, 167-169, 172, 174] 19 as fair quality,[111, 117, 128, 137, 138, 140, 144-147, 149, 153, 154, 159, 163, 165, 170, 171, 175] and 1 as poor quality.[136] The two observational studies were was rated as fair quality.[115, 127] 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[116, 131, 132, 160, 186, 193, 194] and 1 fair-quality[147] 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[116] 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.[132, 193, 194] 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.[131]

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.[132, 193, 194] 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.[160, 186] 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.[147] Finally, a fourth study did not find any significant changes between children receiving neurofeedback versus those receiving treatment as usual.[116] 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.[131]

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

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

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

Detailed Synthesis—Cognitive Training

Six good-quality[119, 122, 126, 132, 160, 174, 186, 187] and 2 fair-quality[115, 163] 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. [119] 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.[132, 193, 194]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.[122] 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,[115, 119, 126, 163, 174, 187] three of these studies[119, 126, 174, 187] 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.[115, 163] 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.[115] 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.[163]

Three other studies examined computer-based cognitive training programs.[122, 132, 160, 186, 193, 194] 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.[122] The other two were studies comparing neurofeedback with computer-based cognitive training.[132, 160, 186, 193, 194] There was no difference between cognitive training and control in one,[160, 186] 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.[132, 193, 194]

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

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

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

Detailed Synthesis—Cognitive Behavioral Therapy

One good-quality[164] and 1 fair-quality[117, 185] 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[117, 185] 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[117, 185] 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

Outcome SOE Grade	No. Studies/ Design (N Patients) Age Category	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Changes in standardized symptom scores Low	2 RCTs (278) 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.[117, 164, 185]
Depression or anxiety Insufficient	1 RCT (159) 7–17	Medium	Direct	NA	Imprecise	Suspect (reasons for drop out not adequately described)	SOE was insufficient because only one small trial was identified.[117, 185]

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,[108, 112, 129, 134, 150, 152, 161, 167-169] 2 fair-quality RCTs,[138, 159] and 1 fair-quality observational study[127] 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,[108] one evaluated social skills training,[161] and one evaluated an adolescent-specific, skills-based therapy called Supporting Teens' Autonomy Daily (STAND).[159]

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.[167] 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.[112, 129, 168] 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.[112] 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.[168] 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.[129] 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.[167] 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.[169, 184]

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

A combined behavioral training intervention for parents and teachers found no changes in ADHD scores at 10 weeks as reported by parents or teachers, but at 3 months postintervention did find improvement in parent reported ADHD scale scores, but not on teacher report.[150] Another combined intervention study compared a combination of parent group and child group interventions with parent intervention alone or community care in general.[152] 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.[138] Another study evaluated an adolescent-specific, skills-based therapy called STAND over the course of 6 months.[159] 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.[134]

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.[169, 184] 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.[152] Another good-quality RCT[167] 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.[129] 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[169, 184]

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)[169, 184]

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[4] 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.[206-208] 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

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

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,[109, 133, 139, 142, 143] two fair-quality,[154, 165] and one poor-quality studies[136] 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,[133, 136, 142, 165, 191] omega-6 alone in 1 trial,[154] and a combination of omega-3 and omega-6 in 2 trials.[139, 195] 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[165] 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.[191] The SOE was insufficient given that the imprecision in the findings and the small number of participants who experienced the outcomes of interest.

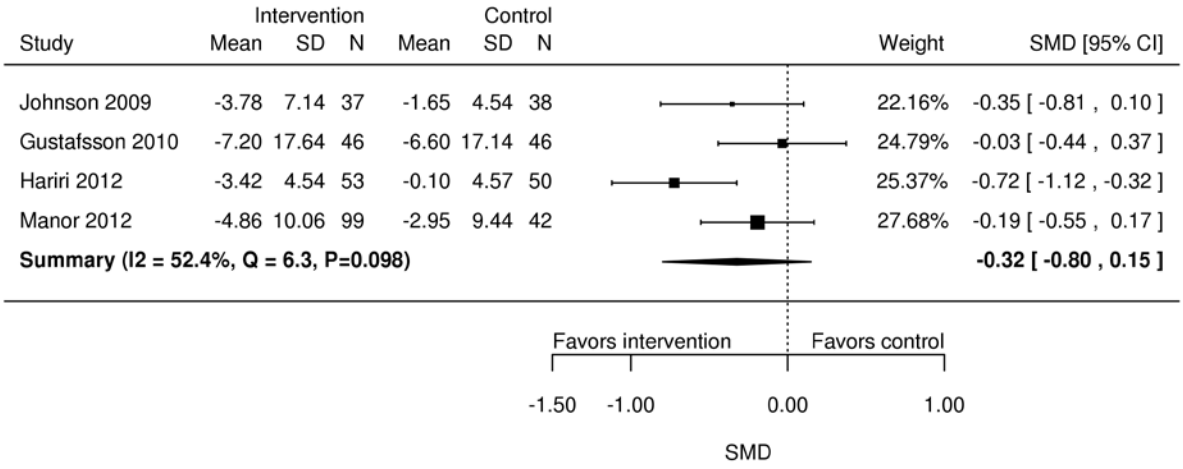
Changes in Standardized Symptom Scores

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.[133, 136, 139, 142, 191, 195] 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 docosahexaenoiac acid for parent ratings of ADHD total symptoms.

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

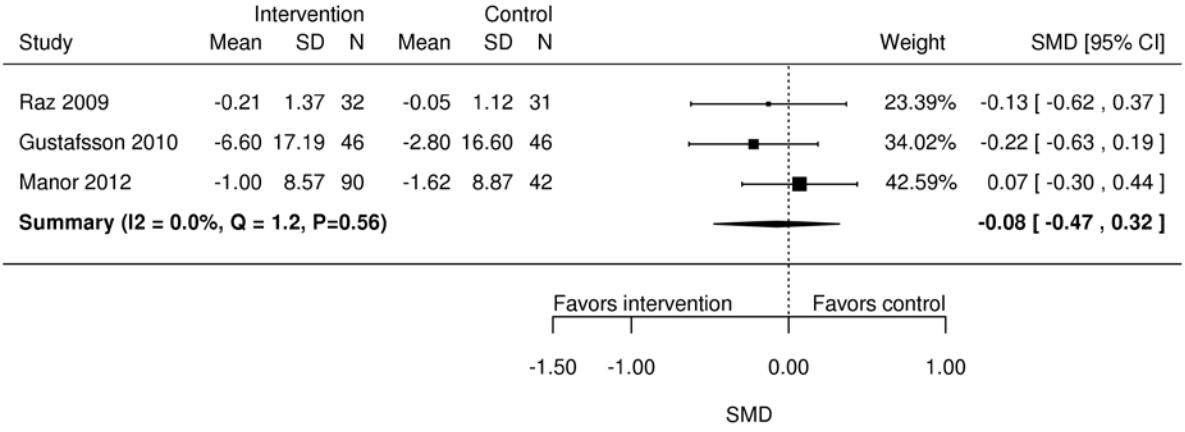


CI=confidence interval; SD=standard deviation; SMD=standardized mean difference

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.[133, 142, 154, 191] Effects were fairly consistent and studies were homogeneous; however, we found no statistical evidence that omega-3/6 was superior to placebo with the outcome of teacher rated total ADHD symptoms (n=287, SMD -0.08, 95% CI -0.47 to 0.32, I^2=0.0%; Q=1.2, p=0.56) (Figure 4). The two RCTs excluded in this meta-analysis[109, 165] 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.[139, 195] 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.[142, 191] 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.[4] However, a systematic review and meta-analysis comparing omega-3 fatty acid supplementation with placebo was conducted in 2011 by Bloch and Qawasmi.[204] 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.[209] 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.[210] 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

Outcome SOE Grade	No. Studies/ Design (N Patients) Age Category	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Behavior changes Insufficient	1 RCTs (200) 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.[142, 191]
Changes in standardized symptom scores Moderate	7 RCTs (795) 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^2=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^2=0.0%; Q=1.2, p=0.56).[133, 136, 139, 142, 143, 154, 190, 191, 195]
Functional impairment Insufficient	1 RCT (75) 7–17	Low	Direct	NA	Imprecise	None	SOE was insufficient because only one small trial was identified.[139, 195]
Chemical Leukoderma Insufficient	1 RCT (200) 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.[142, 191]
Elevated blood pressure Insufficient	1 RCT (200) 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.[142, 191]
Sleep disturbance Insufficient	1 RCT (200) 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.[142, 191]
Tics or other movement disorders Insufficient	1 RCT (200) 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.[142, 191]

Outcome SOE Grade	No. Studies/ Design (N Patients) Age Category	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Gastrointestinal symptoms Insufficient	1 RCT (200) 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.[142, 191]
Growth suppression Insufficient	1 RCT (200) 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.[142, 191]
Increased heart rate Insufficient	1 RCT (200) 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.[142, 191]
Personality change Insufficient	1 RCT (200) 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.[142, 191]
Weight decrease Insufficient	1 RCT (200) 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.[142, 191]

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

Detailed Synthesis—Herbal Interventions or Dietary Approaches

Three good-quality[125, 158, 172] and 3 fair-quality[111, 140, 144] 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, gingko 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 gingko biloba was associated with improved parent and teacher ADHD-RS-Inattention scores but not ADHD-RS-Hyperactivity scores relative to placebo.[158] 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.[144] A third RCT (fair-quality) did not find statistically significant differences between patients on placebo and those taking zinc supplementation.[111] 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,[111] or an herbal preparation compared with placebo.[140] 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.[172] The other three RCTs found that neither Memomet syrup nor zinc supplementation nor vitamin D improved ADHD symptoms compared with placebo (low SOE).[111, 125, 144]

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[111] or herbal preparation[140] 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[111] 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.[140] 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

Outcome SOE Grade	No. Studies/ Design (N Patients) Age Category	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Behavior changes Insufficient	3 RCTs (172) 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.[158 111, 144]
Changes in appetite Insufficient	2 RCTs (172) 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..[111, 140]
Changes in standardized symptom scores Low	4 RCTs (292) 7–17, all through 17	Low	Direct	Inconsistent	Imprecise	None	An elimination diet improved ADHD-RS scores relative to a non-restricted diet,[172] but did not find a reduction in ADHD symptoms relative to placebo for either Memomet syrup or zinc supplementation.[111, 125, 144]
Gastrointestinal symptoms Insufficient	2 RCTs (172) 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[111, 140]
Mood disorders Insufficient	1 RCT (120) 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..[140]
Motor vehicle collisions Insufficient	1 RCT (120) 7–17	Medium	Direct	NA	Imprecise	None	The SOE was considered insufficient because only one small study was identified.[140]
Sleep disturbance Insufficient	2 RCTs (172) 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[111, 140]}
Suicide ideation Insufficient	1 RCT (52) 7–17	Medium	Direct	NA	Imprecise	None	The SOE was considered insufficient because only one small study was identified.[111]
Tics or other movement disorders Insufficient	1 RCT (52) 7–17	Medium	Direct	NA	Imprecise	None	The SOE was considered insufficient because only one small study was identified.[111]

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

Detailed Synthesis—Other Approaches

One good-quality[107] and 8 fair-quality studies[128, 137, 145, 149, 153, 170, 171, 175] 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,[128] multisystemic intervention at school and with parents,[153, 170] in-home family training intervention,[107] a general parenting program,[175] 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,[107, 128, 153, 170, 175] 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[4] 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.[211-215] 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.[153, 170] 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

Outcome SOE Grade	No. Studies/ Design (N Patients) Age Category	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Findings
Academic performance Low	3 RCTs (586) 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.[128, 153, 170]
Behavior changes Insufficient	4 RCTs (508) 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. [107, 145, 149, 171 188]
Changes in appetite Insufficient	1 RCT (60) 7–17	Medium	Direct	NA	Imprecise	None	The SOE was considered insufficient because only one small study was identified.[145, 188]
Changes in standardized symptom scores Insufficient	3 RCTs (252) 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.[137, 145, 175, 188]
Functional impairment Insufficient	1 RCT (326) 7–17	Medium	Direct	NA	Imprecise	None	The SOE was considered insufficient because only one small study was identified.[128]
Gastrointestinal symptoms Insufficient	1 RCT (60) 7–17	Medium	Direct	NA	Imprecise	None	The SOE was considered insufficient because only one small study was identified.[145, 188]
Sleep disturbance Insufficient	1 RCTs (60) 7–17	Medium	Direct	NA	Imprecise	None	The SOE was considered insufficient because only one small study was identified.[145, 188]
Tics or other movement disorders Insufficient	1 RCT (60) 7–17	Medium	Direct	NA	Imprecise	None	The SOE was considered insufficient because only one small study was identified.[145, 188]
Weight decrease Insufficient	1 RCT (60) 7–17	Medium	Direct	NA	Imprecise	None	The SOE was considered insufficient because only one small study was identified.[145, 188]

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

Outcome	No. Studies/ Design (N Patients) Age Category	Findings	SOE Grade
Pharmacologic vs. Placebo Treatments: NA			
Pharmacologic vs. Pharmacologic Treatments			
Gastrointestinal symptoms	3 Obs (1,966) 7–17	Atomoxetine has slightly higher GI effects or disease than MPH.[121, 123, 151]	Low
Pharmacologic vs. Nonpharmacologic Treatments			
Changes in appetite	3 RCTs (212) 7–17	MPH decreased appetite compared to ningdong, omega-3/6 or gingko biloba.[114, 141, 155]	Low
Sleep disturbance	4 RCTs (324) 7–17	MPH resulted in increased sleep disturbances compared to ningdong, gingko biloba, omega-3/6, or neurofeedback.[114, 141, 155]	Low
Nonpharmacologic vs. Nonpharmacologic or Other Treatments			
Neurofeedback: NA			
Cognitive Training			
Changes in standardized symptom scores	9 RCTs (768) 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.[115, 119, 122, 126, 132, 160, 163, 174]	Low
Cognitive Behavioral Therapy			
Changes in standardized symptoms scores	2 RCTs (278) 7–17	CBT improved ADHD symptoms relative to usual care or a limited CBT intervention.[117, 164]	Low
Child or Parent Training or Behavioral			
Changes in standardized symptom scores	8 RCTs, 1 Obs (966) 7–17	ADHD symptoms were significantly improved with child or parent training, sleep hygiene, or behavioral interventions.[112, 127, 129, 138, 150, 152, 167-169, 184]	Moderate
Academic performance	2 RCTs (356) 7–17	There were no differences in academic performance associated with organizational skills or social skills training relative to no intervention.[108, 161]	Low

Outcome	No. Studies/ Design (N Patients) Age Category	Findings	SOE Grade
Omega-3 Supplementation			
Changes in standardized symptom scores	7 RCTs (795) 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).[133, 136, 139, 142, 143, 154, 190, 191, 195]	Moderate
Herbal Interventions or Dietary Approaches			
Changes in standardized symptom scores	3 RCTs (238) 7–17, all through 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.[111, 125, 172]	Low
Other Approaches			
Academic performance	3 RCTs (586) 7–17, all through 17	Neither the Challenging Horizons Program-After School version nor the Family School Success-Early Elementary interventions improved academic performance.[128, 153, 170]	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,[4] along with our main findings.

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

	2011 Report	Current Report
Key Questions (KQs)	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. Specifically, the KQs included: 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? 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? 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?	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. Specifically, the KQs include: 1. For the diagnosis of ADHD: a. What is the comparative diagnostic accuracy of approaches that can be used in the primary care practice setting or by specialists to diagnose ADHD among individuals younger than 7 years of age? b. What is the comparative diagnostic accuracy of EEG, imaging, or executive function approaches that can be used in the primary care practice setting or by specialists to diagnose ADHD among individuals aged 7 through 17? c. For both populations, how does the comparative diagnostic accuracy of these approaches vary by clinical setting, including primary care or specialty clinic, or patient subgroup, including age, sex, or other risk factors associated with ADHD? d. What are the adverse effects associated with being labeled correctly or incorrectly as having ADHD? 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?

	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)?
Publication dates for included studies	By KQ: 1. Inception to 2010 2. 1997-2010 3. 1980-2010	2009-2016
ADHD diagnosis	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
Treatment of preschoolers with disruptive behavior disorders, including those at risk of ADHD	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
Long-term effectiveness and safety of treatment in people aged 6 and older	• MPH is effective for ADHD treatment for 14 months and atomoxetine (ATX) for over 12 months. SOE was low. • 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.	• 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). • Gastrointestinal side effects are slightly higher for ATX compared with MPH; however, the SOE was low. • 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.

	2011 Report	Current Report
		• Compared with placebo, omega-3 fatty acid supplementation had no difference on ADHD symptoms. SOE was moderate. • Cognitive behavioral therapy improved ADHD symptom scores. SOE was low
Prevalence and variations in diagnosis and treatment	There is significant variation in diagnosis and treatment, with an overall increase in the use of pharmacotherapy.	Not addressed
Monitoring strategies	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.[77] 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.[70] That review only included studies of subjects 12–18 years of age published from 1999 through January 2016. As with the Cochrane review,[77] 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.[216] 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.[217] 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
Population (P)	
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
Intervention (I)	
Diagnostic tools used differently than as recommended or commonly used in practice	0
Dosing not reflective of current practice	0
Co-interventions that are likely to modify the effectiveness of therapy	0
Highly selected intervention team or level of training/proficiency not widely available	1
Follow-up not reflective of current practice	0
Co-intervention that are likely to modify monitoring strategies	0
Comparator (C)	
Diagnostic tools used differently than as recommended or commonly used in practice	0
Comparator unclear	0
Inadequate comparison therapy or use of a substandard alternative therapy	0
Outcomes (O)	
Composite outcomes that mix outcomes of different significance	0
Short-term follow-up	0
Surrogate outcomes	0
Setting (S)	
Level of care different from that in the community	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 N=9	Pharm vs. Nonpharm N=7	Pharm vs. Placebo N=7	Nonpharm vs. Nonpharm N=15	Nonpharm vs. Placebo N=37
Population (P)					
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
Intervention (I)					
Diagnostic tools used differently than as recommended or commonly used in practice	0	0	0	0	0
Dosing not reflective of current practice	0	0	0	0	0
Co-interventions that are likely to modify the effectiveness of therapy	1	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
Comparator (C)					
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
Outcomes (O)					
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
Setting (S)					
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.[4, 19] 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

Acronym/Abbreviation	Definition
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 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

Acronym/Abbreviation	Definition
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	Docosahexaenoiacid
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, 5th Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th 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

Acronym/Abbreviation	Definition
ICD-10	10th 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

Acronym/Abbreviation	Definition
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

Appendix A. Exact Search Strings

PubMed® Search Strategy (November 4, 2016)

Key Question 1

Set #	Terms
#1	"Attention Deficit Disorder with Hyperactivity"[Mesh] OR "attention deficit hyperactivity disorder"[tiab] OR "ADHD"[tiab] OR "attention deficit disorder"[tiab]
#2	"Pediatrics"[Mesh] OR "Adolescent"[Mesh] OR "Infant"[Mesh] OR "Child"[Mesh] OR child[tiab] OR children[tiab] OR infant[tiab] OR infants[tiab] OR preschool[tiab] OR preschooler[tiab] OR pediatric[tiab] OR teenager[tiab] OR teenagers[tiab] OR teenaged[tiab] OR teen[tiab] OR teens[tiab] OR adolescent[tiab] OR adolescents[tiab] OR adolescence[tiab] OR youth[tiab]
#3	"Attention Deficit and Disruptive Behavior Disorders/diagnosis"[Majr] OR mass screening[mesh] OR questionnaires[mesh] OR Interviews as Topic[Mesh] OR Psychometrics[Mesh] OR Psychiatric Status Rating Scales[Mesh] OR diagnosis[mesh:noexp] OR "Diagnostic Techniques and Procedures"[Mesh] OR "Diagnostic and Statistical Manual of Mental Disorders"[Mesh] OR "Referral and Consultation"[Mesh] OR questionnaire[tiab] OR questionnaires[tiab] OR screening[tiab] OR screen[tiab] OR scale[tiab] OR instrument[tiab] OR instruments[tiab] OR interview[tiab] OR interviews[tiab] OR DSM*[tiab] OR diagnosis[tiab] OR diagnostic[tiab] OR diagnosed[tiab] OR (Vanderbilt[tiab] AND scale[tiab]) OR conners[tiab] OR cprs[tiab] OR ctrs[tiab] OR cprs[tiab] OR crs[tiab] OR "snap-IV"[tiab] OR "snap-4"[tiab] OR "basc-2"[tiab] OR "behavioral assessment system for children"[tiab] OR dbdrs[tiab] OR "disruptive behavior disorder rating scale"[tiab] OR adhd-rs[tiab] OR "adhd rating scale"[tiab] OR ksads[tiab] OR k-sads[tiab] OR kiddie-sads[tiab] OR DISC[tiab] OR "dominance inducement submission and compliance"[tiab] OR "diagnostic interview schedule for children"[tiab] OR "diagnostic inventory for screening children"[tiab] OR "mini-kid"[tiab] OR "Mini Interational Neuropsychiatric interview"[tiab] OR "iva-2"[tiab] OR "iva-qs"[tiab] OR "iva-ae2"[tiab] OR tova[tiab] OR "test of variables of attention"[tiab] OR "neuropsychiatric eeg-based assessment aid"[tiab] OR neba[tiab]
#4	"Sensitivity and Specificity"[Mesh] OR "Diagnostic Errors"[Mesh] OR sensitivity[tiab] OR specificity[tiab] OR accuracy[tiab] OR accurate[tiab] OR accurately[tiab] OR misdiagnos*[tiab] OR (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR “clinical trial”[tiab] OR “clinical trials”[tiab] OR "evaluation studies"[pt] OR "evaluation studies as topic"[MeSH] OR "evaluation study"[tiab] OR evaluation studies[tiab] OR "intervention studies"[MeSH] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "case-control studies"[MeSH] OR "case-control"[tiab] OR "cohort studies"[MeSH] OR cohort[tiab] OR "longitudinal studies"[MeSH] OR "longitudinal"[tiab] OR longitudinally[tiab] OR "prospective"[tiab] OR prospectively[tiab] OR "retrospective studies"[MeSH] OR "retrospective"[tiab] OR "Cross-Sectional Studies"[Mesh] OR cross-sectional[tiab] OR "comparative study"[pt] OR "comparative study"[tiab] OR systematic[sb] OR "meta-analysis"[pt] OR "meta-analysis as topic"[MeSH] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab]) NOT (Editorial[ptyp] OR Letter[pt] OR Case Reports[pt] OR Comment[pt]) NOT (animals[mh] NOT humans[mh]) AND English[la]
#5	#1 AND #2 AND #3 AND #4
	Publication date from 2009/01/01

Key Question 2

Set #	Terms
#1	"Attention Deficit Disorder with Hyperactivity"[Mesh] OR "attention deficit hyperactivity disorder"[tiab] OR "ADHD"[tiab] OR "attention deficit disorder"[tiab]
#2	"Pediatrics"[Mesh] OR "Adolescent"[Mesh] OR "Infant"[Mesh] OR "Child"[Mesh] OR child[tiab] OR children[tiab] OR infant[tiab] OR infants[tiab] OR preschool[tiab] OR preschooler[tiab] OR pediatric[tiab] OR teenager[tiab] OR teenagers[tiab] OR teenaged[tiab] OR teen[tiab] OR teens[tiab] OR adolescent[tiab] OR adolescents[tiab] OR adolescence[tiab] OR youth[tiab]
#3	#1 AND #2
#4	"Attention Deficit Disorder with Hyperactivity/drug therapy"[Majr] OR "Central Nervous System Stimulants"[MeSH] OR "Methylphenidate"[MeSH] OR "Dexmethylphenidate"[MeSH] OR "Dextroamphetamine"[MeSH] OR "Adderall"[Supplementary Concept] OR "lisdexamfetamine dimesylate"[Supplementary Concept] OR "Amphetamine"[MeSH] OR "Guanfacine"[MeSH] OR "Sympatholytics"[MeSH] OR "Clonidine"[MeSH] OR “Adrenergic Uptake Inhibitors"[MeSH] OR "Adrenergic Uptake Inhibitors"[Pharmacological Action] OR "Receptors, Adrenergic, alpha-2"[MeSH] OR "Adrenergic alpha-Agonists"[Mesh] OR "Adrenergic alpha-2 Receptor Agonists"[Mesh] OR "atomoxetine"[Supplementary Concept] OR "Antidepressive Agents, Tricyclic"[MeSH] OR "Desipramine"[MeSH] OR "Dopamine Uptake Inhibitors"[MeSH] OR "Sympathomimetics"[MeSH] OR "modafinil"[Supplementary Concept] OR "Serotonin Uptake Inhibitors"[MeSH] OR "Serotonin Uptake Inhibitors"[Pharmacological Action] OR "duloxetine" [Supplementary Concept] OR "Monoamine Oxidase Inhibitors"[MeSH] OR "Monoamine Oxidase"[MeSH] OR "Selegiline"[MeSH] OR "Bupropion"[MeSH] OR "armodafinil" [Supplementary Concept] OR "venlafaxine"[Supplementary Concept] OR "Receptors, N-Methyl-D-Aspartate"[MeSH] OR "Memantine"[MeSH] OR "Amantadine"[MeSH] OR "duloxetine"[Supplementary Concept] OR "Central Nervous System Stimulants" [Pharmacological Action] OR "Adrenergic alpha-2 Receptor Agonists" [Pharmacological Action] OR "Antidepressive Agents, Tricyclic" [Pharmacological Action] OR "Dopamine Uptake Inhibitors" [Pharmacological Action] OR "Monoamine Oxidase Inhibitors" [Pharmacological Action] OR "Central Nervous System Stimulants"[tiab] OR “psychostimulant”[tiab] OR “Methylphenidate”[tiab] OR "Methylphenidate Hydrochloride"[tiab] OR “Aptensio”[tiab] OR “Concerta”[tiab] OR “Ritalin”[tiab] OR “Ritalin LA”[tiab] OR “Medikinet”[tiab] OR “Equasym”[tiab] OR “Quillivant”[tiab] OR “Metadate”[tiab] OR “Daytrana”[tiab] OR "Dexmethylphenidate"[tiab] OR “Dexmethylphenidate Hydrochloride”[tiab] OR “Focalin”[tiab] OR “Dextroamphetamine”[tiab] OR “Dexedrine”[tiab] OR “Dextrostat”[tiab] OR “ProCentra”[tiab] OR “Zenzedi”[tiab] OR “mixed amphetamine salts”[tiab] OR "Adderall" [tiab] OR “lisdexamfetamine”[tiab] OR “lisdexamfetamine dimesylate”[tiab] OR “Vyvanse”[tiab] OR "Venvanse"[tiab] OR "Elvanse"[tiab] OR "Tyvense"[tiab] OR "Dyanavel"[tiab] OR “Evekeo”[tiab] OR "Guanfacine"[tiab] OR "Sympatholytics"[tiab] OR “Central alpha-2 Adrenergic Agonist”[tiab] OR “Clonidine”[tiab] OR "Intuniv"[tiab] OR "Estulic"[tiab] OR “Tenex”[tiab] OR “Catapres”[tiab] OR “Clophelin”[tiab] OR "Kapvay"[tiab] OR “Nexiclon”[tiab] OR "Duraclon"[tiab] OR “Norepinephrine Reuptake Inhibitors”[tiab] OR “Selective Norepinephrine Reuptake Inhibitors”[tiab] OR “Adrenergic Uptake Inhibitors"[tiab] OR "atomoxetine"[tiab] OR "Strattera"[tiab] OR "Tricyclic antidepressants"[tiab] OR "Desipramine"[tiab] OR "Norpramin"[tiab] OR "Nortriptyline"[tiab] OR "Pamelor"[tiab] OR “Dopamine Reuptake Inhibitors”[tiab] OR "modafinil"[tiab] OR “Provigil”[tiab] OR “Armodafinil”[tiab] OR “Norepinephrine-dopamine Reuptake Inhibitors"[tiab] OR "Bupropion"[tiab] OR “Wellbutrin”[tiab] OR “Forfivo”[tiab] OR “Cymbalta”[tiab] OR "venlafaxine"[tiab] OR “reboxetine”[tiab] OR “Monoamine Oxidase Type B inhibitors”[tiab] OR "Selegiline"[tiab] OR “Eldepryl”[tiab] OR “Zelapar”[tiab] OR “NMDA receptors”[tiab] OR “N-Methyl-D-aspartate receptor Antagonists”[tiab] OR "Amantadine"[tiab] OR "Memantine"[tiab] OR “Pertofrane”[tiab] OR “Nuvigil”[tiab] OR “Cymbalta”[tiab] OR "duloxetine"[tiab] OR "Effexor"[tiab] OR "Eldepryl"[tiab] OR "Emsam"[tiab] OR "Trevilor"[tiab] OR "Symmetrel"[tiab] OR "Namenda"[tiab] OR "Zelapar"[tiab]

Set #	Terms
#5	"Attention Deficit Disorder with Hyperactivity/diet therapy"[Majr] OR "Attention Deficit Disorder with Hyperactivity/rehabilitation"[Majr] OR "Psychotherapy"[MeSH] OR "Behavior Therapy"[MeSH] OR "Parent-Child Relations"[MeSH] OR "Play Therapy"[MeSH] OR "Cognitive Therapy"[MeSH] OR "Time Management"[MeSH] OR "Computer-Assisted Instruction"[MeSH] OR "Diet Therapy"[MeSH] OR "Fatty Acids, Omega-3/therapeutic use"[MeSH] OR "Vitamins/administration and dosage"[Mesh] OR "Vitamins/therapeutic use"[MeSH] OR "Food Additives/adverse effects"[MeSH] OR "Probiotics/therapeutic use"[MeSH] OR "Acupuncture Therapy"[MeSH] OR "Remedial Teaching"[MeSH] OR "Early Intervention (Education)"[MeSH] OR "Complementary Therapies"[MeSH] OR "Combined Modality Therapy"[MeSH] OR "psychosocial therapy"[tiab] OR "psychosocial intervention"[tiab] OR "psychosocial interventions"[tiab] OR "psychosocial approach"[tiab] OR "psychosocial approaches"[tiab] OR "psychosocial treatment"[tiab] OR "psychosocial support"[tiab] OR "psychoeducation"[tiab] OR "nonpharmacologic therapy"[tiab] OR "nondrug therapy"[tiab] OR "non-drug therapy"[tiab] OR "Play Therapy"[tiab] OR "cognitive behavioral therapy"[tiab] OR "cognitive behavior therapy"[tiab] OR "cognitive behavioural therapy"[tiab] OR "cognitive behaviour therapy"[tiab] OR Mindfulness[tiab] OR complementary[tiab] OR "alternative medicine"[tiab] OR "alternative therapy"[tiab] OR "alternative therapies"[tiab] OR "Interpersonal skills training"[tiab] OR "Parent-Child Interaction Therapy"[tiab] OR "parent training"[tiab] OR "parent engagement"[tiab] OR "parent management"[tiab] OR "parenting skills"[tiab] OR "parenting intervention"[tiab] OR "parenting interventions"[tiab] OR "Barkley's defiant child"[tiab] OR "Teacher-Child Interaction Training"[tiab] OR "Incredible Years"[tiab] OR "New Forest Parenting"[tiab] OR "Triple P"[tiab] OR "Helping the Noncompliant Child"[tiab] OR "child life and attention skills"[tiab] OR "clas"[tiab] OR PCIT[tiab] OR "parent child interaction therapy"[tiab] OR "Summer Treatment Program"[tiab] OR "Daily Report Card"[tiab] OR "organization skills"[tiab] OR "organizational skills"[tiab] OR "time management"[tiab] OR "homework intervention"[tiab] OR braintrain[tiab] OR "memory training"[tiab] OR "Captain's log mindpower builder"[tiab] OR "memory gyms"[tiab] OR "attention gym"[tiab] OR "smartdriver plus"[tiab] OR "smartmind pro"[tiab] OR "RoboMemo"[tiab] OR "play attention"[tiab] OR metronome[tiab] OR brainmaster[tiab] OR mindmed[tiab] OR "attention lab"[tiab] OR (activate[tiab] AND c8[tiab]) OR "attention training"[tiab] OR "CogniPlus"[tiab] OR cogmed[tiab] OR "working memory training"[tiab] OR biofeedback[tiab] OR neurofeedback[tiab] OR neuroagility[tiab] OR neuroptimal[tiab] OR acupuncture[tiab] OR "vision training"[tiab] OR "visual training"[tiab] OR "vision therapy"[tiab] OR "education intervention"[tiab] OR "cognitive remediation"[tiab] OR neurotherapy[tiab] OR "elimination diet"[tiab] OR "diet therapy"[tiab] OR (("low carb" OR "low carbohydrate" OR "low carbohydrates"[tiab] OR "gluten free") AND diet[tiab]) OR "feingold diet"[tiab] OR "red dye"[tiab] OR ((vitamin[tiab] OR vitamins[tiab]) AND (supplement[tiab] OR supplements[tiab])) OR "herbal supplement"[tiab] OR "herbal supplements"[tiab] OR probiotics[tiab] OR "omega 3"[tiab] OR "slow cortical potentials"[tiab] OR "few foods diet"[tiab] OR "oligoantigenic diet"[tiab] OR "restriction diet"[tiab] OR "food intolerance"[tiab] OR "food allergy"[tiab] OR "food allergies"[tiab] OR "food sensitivity"[tiab] OR "food sensitivities"[tiab] OR "multimodal treatment"[tiab] OR homeopathy[tiab] OR homeopathic[tiab] OR chiropractic[tiab] OR chiropractor[tiab]
#6	#4 OR #5
#7	#3 AND #6
#8	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tiab] OR "clinical trials"[tiab] OR "evaluation studies"[pt] OR "evaluation studies as topic"[MeSH] OR "evaluation study"[tiab] OR "evaluation studies"[tiab] OR "intervention studies"[MeSH] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "case-control studies"[MeSH] OR "case-control"[tiab] OR "cohort studies"[MeSH] OR cohort[tiab] OR "longitudinal"[tiab] OR longitudinally[tiab] OR "prospective"[tiab] OR prospectively[tiab] OR "retrospective"[tiab] OR "comparative study"[pt] OR "comparative study"[tiab] OR systematic[sb] OR "meta-analysis"[pt] OR "meta-analysis as topic"[MeSH] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab]) NOT (Editorial[ptyp] OR Letter[pt] OR Case Reports[pt] OR Comment[pt]) NOT (animals[mh] NOT humans[mh]) AND English[la]
#9	#7 AND #8
	Publication date from 2009/01/01

Key Question 3

Set #	Terms
#1	"Attention Deficit Disorder with Hyperactivity"[Mesh] OR "attention deficit hyperactivity disorder"[tiab] OR "ADHD"[tiab] OR "attention deficit disorder"[tiab]
#2	"Pediatrics"[Mesh] OR "Adolescent"[Mesh] OR "Infant"[Mesh] OR "Child"[Mesh] OR child[tiab] OR children[tiab] OR infant[tiab] OR infants[tiab] OR preschool[tiab] OR preschooler[tiab] OR pediatric[tiab] OR teenager[tiab] OR teenagers[tiab] OR teenaged[tiab] OR teen[tiab] OR teens[tiab] OR adolescent[tiab] OR adolescents[tiab] OR adolescence[tiab] OR youth[tiab]
#3	"Secondary Care"[Mesh] OR "Comprehensive Health Care"[Mesh] OR "primary care"[tiab] OR monitor[tiab] OR monitored[tiab] OR monitoring[tiab] OR "follow up"[tiab] OR "followed up"[tiab] OR visit[tiab] OR visits[tiab] OR session[tiab] OR sessions[tiab] OR appointment[tiab] OR appointments[tiab]
#4	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR “clinical trial”[tiab] OR “clinical trials”[tiab] OR "evaluation studies"[pt] OR "evaluation studies as topic"[MeSH] OR "evaluation study"[tiab] OR "evaluation studies"[tiab] OR "intervention studies"[MeSH] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "case-control studies"[MeSH] OR "case-control"[tiab] OR "cohort studies"[MeSH] OR cohort[tiab] OR "longitudinal"[tiab] OR longitudinally[tiab] OR "prospective"[tiab] OR prospectively[tiab] OR "retrospective"[tiab] OR "comparative study"[pt] OR "comparative study"[tiab] OR systematic[sb] OR "meta-analysis"[pt] OR "meta-analysis as topic"[MeSH] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab]) NOT (Editorial[ptyp] OR Letter[pt] OR Case Reports[pt] OR Comment[pt]) NOT (animals[mh] NOT humans[mh]) AND English[la]
#5	#1 AND #2 AND #3 AND #4
	Publication date from 2009/01/01

Embase® Search Strategy (November 7, 2016)

Platform: Embase.com

Key Question 1

Set #	Terms
#1	'attention deficit disorder'/exp OR "attention deficit hyperactivity disorder":ab,ti OR "ADHD":ab,ti OR "attention deficit disorder":ab,ti
#2	'pediatrics'/exp OR 'adolescent'/exp OR 'infant'/exp OR 'child'/exp OR child:ab,ti OR children:ab,ti OR infant:ab,ti OR infants:ab,ti OR preschool:ab,ti OR preschooler:ab,ti OR pediatric:ab,ti OR teenager:ab,ti OR teenagers:ab,ti OR teenaged:ab,ti OR teen:ab,ti OR teens:ab,ti OR adolescent:ab,ti OR adolescents:ab,ti OR adolescence:ab,ti OR youth:ab,ti
#3	'attention deficit disorder'/exp/mj/dm_di OR 'screening'/exp OR 'questionnaire'/exp OR 'interview'/exp OR 'psychometry'/exp OR 'psychological rating scale'/exp OR 'diagnosis'/exp OR 'assessment of humans'/exp OR 'checklist'/exp OR 'clinical assessment tool'/exp OR 'clinical observation'/exp OR 'Diagnostic and Statistical Manual of Mental Disorders'/exp OR 'patient referral'/exp OR questionnaire:ab,ti OR questionnaires:ab,ti OR screening:ab,ti OR screen:ab,ti OR scale:ab,ti OR instrument:ab,ti OR instruments:ab,ti OR interview:ab,ti OR interviews:ab,ti OR DSM*:ab,ti OR diagnosis:ab,ti OR diagnostic:ab,ti OR diagnosed:ab,ti OR (Vanderbilt:ab,ti AND scale:ab,ti) OR conners:ab,ti OR cprs:ab,ti OR ctrs:ab,ti OR cprs:ab,ti OR crs:ab,ti OR "snap-IV":ab,ti OR "snap-4":ab,ti OR "basc-2":ab,ti OR "behavioral assessment system for children":ab,ti OR dbdrs:ab,ti OR "disruptive behavior disorder rating scale":ab,ti OR adhd-rs:ab,ti OR "adhd rating scale":ab,ti OR ksads:ab,ti OR k-sads:ab,ti OR kiddie-sads:ab,ti OR DISC:ab,ti OR "dominance inducement submission and compliance":ab,ti OR "diagnostic interview schedule for children":ab,ti OR "diagnostic inventory for screening children":ab,ti OR "mini-kid":ab,ti OR "Mini Interational Neuropsychiatric interview":ab,ti OR "iva-2":ab,ti OR "iva-qs":ab,ti OR "iva-ae2":ab,ti OR tova:ab,ti OR "test of variables of attention":ab,ti OR "neuropsychiatric eeg-based assessment aid":ab,ti OR neba:ab,ti
#4	('sensitivity and specificity'/exp OR 'predictive value'/exp OR 'diagnostic error'/exp OR sensitivity:ab,ti OR specificity:ab,ti OR accuracy:ab,ti OR accurate:ab,ti OR accurately:ab,ti OR misdiagnos*:ab,ti OR 'randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR (cross NEAR/1 over*):ab,ti OR placebo*:ab,ti OR (doubl* NEAR/1 blind*):ab,ti OR (singl* NEAR/1 blind*):ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR 'clinical study'/exp OR ‘clinical trial’:ti,ab OR ‘clinical trials’:ti,ab OR 'controlled study'/exp OR 'evaluation'/exp OR ‘evaluation study’:ab,ti OR ‘evaluation studies’:ab,ti OR ‘intervention study’:ab,ti OR ‘intervention studies’:ab,ti OR ‘case control’:ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR prospectively:ab,ti OR retrospective:ab,ti OR 'follow up'/exp OR ‘follow up’:ab,ti OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR ‘comparative study’:ab,ti OR ‘comparative studies’:ab,ti OR 'evidence based medicine'/exp OR ‘systematic review’:ab,ti OR ‘meta-analysis’:ab,ti OR ‘meta-analyses’:ab,ti) NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp)
#5	#1 AND #2 AND #3 AND #4
#6	#5 AND [embase]/lim NOT [medline]/lim
#7	#6 AND [humans]/lim AND [2009-2015]/py

Key Question 2

Set #	Terms
#1	'attention deficit disorder'/exp OR "attention deficit hyperactivity disorder":ab,ti OR "ADHD":ab,ti OR "attention deficit disorder":ab,ti
#2	'pediatrics'/exp OR 'adolescent'/exp OR 'infant'/exp OR 'child'/exp OR child:ab,ti OR children:ab,ti OR infant:ab,ti OR infants:ab,ti OR preschool:ab,ti OR preschooler:ab,ti OR pediatric:ab,ti OR teenager:ab,ti OR teenagers:ab,ti OR teenaged:ab,ti OR teen:ab,ti OR teens:ab,ti OR adolescent:ab,ti OR adolescents:ab,ti OR adolescence:ab,ti OR youth:ab,ti
#3	#1 AND #2
#4	'attention deficit disorder'/exp/mj/dm_dt OR 'central stimulant agent'/exp OR 'psychostimulant agent'/exp OR 'guanfacine'/exp OR 'adrenergic receptor affecting agent'/exp OR 'atomoxetine'/exp OR 'antidepressant agent'/exp OR 'dopamine uptake inhibitor'/exp OR 'n methyl dextro aspartic acid receptor'/exp OR 'memantine'/exp OR 'amantadine'/exp OR 'dopamine uptake inhibitor'/exp OR 'Central Nervous System Stimulants':ab,ti OR 'psychostimulant':ab,ti OR 'Methylphenidate':ab,ti OR 'Methylphenidate Hydrochloride':ab,ti OR 'Aptensio':ab,ti OR 'Concerta':ab,ti OR 'Ritalin':ab,ti OR 'Ritalin LA':ab,ti OR 'Medikinet':ab,ti OR 'Equasym':ab,ti OR 'Quillivant':ab,ti OR 'Metadate':ab,ti OR 'Daytrana':ab,ti OR 'Dexmethylphenidate':ab,ti OR 'Dexmethylphenidate Hydrochloride':ab,ti OR 'Focalin':ab,ti OR 'Dextroamphetamine':ab,ti OR 'Dexedrine':ab,ti OR 'Dextrostat':ab,ti OR 'ProCentra':ab,ti OR 'Zenzedi':ab,ti OR 'mixed amphetamine salts':ab,ti OR 'Adderall':ab,ti OR 'lisdexamfetamine':ab,ti OR 'lisdexamfetamine dimesylate':ab,ti OR 'Vyvanse':ab,ti OR 'Venvanse':ab,ti OR 'Elvanse':ab,ti OR 'Tyvense':ab,ti OR 'Dyanavel':ab,ti OR 'Evekeo':ab,ti OR 'Guanfacine':ab,ti OR 'Sympatholytics':ab,ti OR 'Central alpha-2 Adrenergic Agonist':ab,ti OR 'Clonidine':ab,ti OR 'Intuniv':ab,ti OR 'Estulic':ab,ti OR 'Tenex':ab,ti OR 'Catapres':ab,ti OR 'Clophelin':ab,ti OR 'Kapvay':ab,ti OR 'Nexiclon':ab,ti OR 'Duraclon':ab,ti OR 'Norepinephrine Reuptake Inhibitors':ab,ti OR 'Selective Norepinephrine Reuptake Inhibitors':ab,ti OR 'Adrenergic Uptake Inhibitors':ab,ti OR 'atomoxetine':ab,ti OR 'Strattera':ab,ti OR 'Tricyclic antidepressants':ab,ti OR 'Desipramine':ab,ti OR 'Norpramin':ab,ti OR 'Nortriptyline':ab,ti OR 'Pamelor':ab,ti OR 'Dopamine Reuptake Inhibitors':ab,ti OR 'modafinil':ab,ti OR 'Provigil':ab,ti OR 'Armodafinil':ab,ti OR 'Norepinephrine-dopamine Reuptake Inhibitors':ab,ti OR 'Bupropion':ab,ti OR 'Wellbutrin':ab,ti OR 'Forfivo':ab,ti OR 'Cymbalta':ab,ti OR 'venlafaxine':ab,ti OR 'reboxetine':ab,ti OR 'Monoamine Oxidase Type B inhibitors':ab,ti OR 'Selegiline':ab,ti OR 'Eldepryl':ab,ti OR 'Zelapar':ab,ti OR 'NMDA receptors':ab,ti OR 'N-Methyl-D-aspartate receptor Antagonists':ab,ti OR 'Amantadine':ab,ti OR 'Memantine':ab,ti OR 'Pertofrane':ab,ti OR 'Nuvigil':ab,ti OR 'Cymbalta':ab,ti OR 'duloxetine':ab,ti OR 'Effexor':ab,ti OR 'Eldepryl':ab,ti OR 'Emsam':ab,ti OR 'Trevilor':ab,ti OR 'Symmetrel':ab,ti OR 'Namenda':ab,ti OR 'Zelapar':ab,ti

Set #	Terms
#5	'attention deficit disorder'/exp/mj/dm_rh,dm_dm OR 'psychotherapy'/exp OR 'child psychiatry'/exp OR 'child parent relation'/exp OR 'time management'/exp OR 'feedback system'/exp OR 'teaching'/exp OR 'adaptive behavior'/exp OR 'diet therapy'/exp OR 'omega 3 fatty acid'/exp OR 'vitamin'/exp/dd_do,dd_dt,dd_ad OR 'food additive'/exp/dd_ae OR 'probiotic agent'/exp OR 'acupuncture'/exp OR 'early childhood intervention'/exp OR 'alternative medicine'/exp OR 'psychosocial therapy':ab,ti OR 'psychosocial intervention':ab,ti OR 'psychosocial interventions':ab,ti OR 'psychosocial approach':ab,ti OR 'psychosocial approaches':ab,ti OR 'psychosocial treatment':ab,ti OR 'psychosocial support':ab,ti OR 'psychoeducation':ab,ti OR 'nonpharmacologic therapy':ab,ti OR 'nondrug therapy':ab,ti OR 'non-drug therapy':ab,ti OR 'Play Therapy':ab,ti OR 'cognitive behavioral therapy':ab,ti OR 'cognitive behavior therapy':ab,ti OR 'cognitive behavioural therapy':ab,ti OR 'cognitive behaviour therapy':ab,ti OR Mindfulness:ab,ti OR complementary:ab,ti OR 'alternative medicine':ab,ti OR 'alternative therapy':ab,ti OR 'alternative therapies':ab,ti OR 'Interpersonal skills training':ab,ti OR 'Parent-Child Interaction Therapy':ab,ti OR 'parent training':ab,ti OR 'parent engagement':ab,ti OR 'parent management':ab,ti OR 'parenting skills':ab,ti OR 'parenting intervention':ab,ti OR 'parenting interventions':ab,ti OR 'Barkleys defiant child':ab,ti OR 'Teacher-Child Interaction Training':ab,ti OR 'Incredible Years':ab,ti OR 'New Forest Parenting':ab,ti OR 'Triple P':ab,ti OR 'Helping the Noncompliant Child':ab,ti OR 'child life and attention skills':ab,ti OR 'clas':ab,ti OR PCIT:ab,ti OR 'parent child interaction therapy':ab,ti OR 'Summer Treatment Program':ab,ti OR 'Daily Report Card':ab,ti OR 'organization skills':ab,ti OR 'organizational skills':ab,ti OR 'time management':ab,ti OR 'homework intervention':ab,ti OR braintrain:ab,ti OR 'memory training':ab,ti OR 'Captains log mindpower builder':ab,ti OR 'memory gyms':ab,ti OR 'attention gym':ab,ti OR 'smartdriver plus':ab,ti OR 'smartmind pro':ab,ti OR 'RoboMemo':ab,ti OR 'play attention':ab,ti OR metronome:ab,ti OR brainmaster:ab,ti OR mindmed:ab,ti OR 'attention lab':ab,ti OR (activate:ab,ti AND c8:ab,ti) OR 'attention training':ab,ti OR 'CogniPlus':ab,ti OR cogmed:ab,ti OR 'working memory training':ab,ti OR biofeedback:ab,ti OR neurofeedback:ab,ti OR neuroagility:ab,ti OR neuroptimal:ab,ti OR acupuncture:ab,ti OR 'vision training':ab,ti OR 'visual training':ab,ti OR 'vision therapy':ab,ti OR 'education intervention':ab,ti OR 'cognitive remediation':ab,ti OR neurotherapy:ab,ti OR 'elimination diet':ab,ti OR 'diet therapy':ab,ti OR (('low carb' OR 'low carbohydrate' OR 'low carbohydrates':ab,ti OR 'gluten free') AND diet:ab,ti) OR 'feingold diet':ab,ti OR 'red dye':ab,ti OR ((vitamin:ab,ti OR vitamins:ab,ti) AND (supplement:ab,ti OR supplements:ab,ti)) OR 'herbal supplement':ab,ti OR 'herbal supplements':ab,ti OR probiotics:ab,ti OR 'omega 3':ab,ti OR 'slow cortical potentials':ab,ti OR 'few foods diet':ab,ti OR 'oligoantigenic diet':ab,ti OR 'restriction diet':ab,ti OR 'food intolerance':ab,ti OR 'food allergy':ab,ti OR 'food allergies':ab,ti OR 'food sensitivity':ab,ti OR 'food sensitivities':ab,ti OR 'multimodal treatment':ab,ti OR homeopathy:ab,ti OR homeopathic:ab,ti OR chiropractic:ab,ti OR chiropractor:ab,ti
#6	#4 OR #5
#7	#3 AND #6
#8	('randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR (cross NEAR/1 over*):ab,ti OR placebo*:ab,ti OR (doubl* NEAR/1 blind*):ab,ti OR (singl* NEAR/1 blind*):ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR 'clinical study'/exp OR ‘clinical trial’:ti,ab OR ‘clinical trials’:ti,ab OR 'controlled study'/exp OR 'evaluation'/exp OR ‘evaluation study’:ab,ti OR ‘evaluation studies’:ab,ti OR ‘intervention study’:ab,ti OR ‘intervention studies’:ab,ti OR ‘case control’:ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR prospectively:ab,ti OR retrospective:ab,ti OR 'follow up'/exp OR ‘follow up’:ab,ti OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR ‘comparative study’:ab,ti OR ‘comparative studies’:ab,ti OR 'evidence based medicine'/exp OR ‘systematic review’:ab,ti OR ‘meta-analysis’:ab,ti OR ‘meta-analyses’:ab,ti) NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp)
#9	#7 AND #8
#10	#9 AND [embase]/lim NOT [medline]/lim
#11	#10 AND [humans]/lim AND [2009-2015]/py

Key Question 3

Set #	Terms
#1	'attention deficit disorder'/exp OR "attention deficit hyperactivity disorder":ab,ti OR "ADHD":ab,ti OR "attention deficit disorder":ab,ti
#2	'pediatrics'/exp OR 'adolescent'/exp OR 'infant'/exp OR 'child'/exp OR child:ab,ti OR children:ab,ti OR infant:ab,ti OR infants:ab,ti OR preschool:ab,ti OR preschooler:ab,ti OR pediatric:ab,ti OR teenager:ab,ti OR teenagers:ab,ti OR teenaged:ab,ti OR teen:ab,ti OR teens:ab,ti OR adolescent:ab,ti OR adolescents:ab,ti OR adolescence:ab,ti OR youth:ab,ti
#3	'evaluation and follow up'/exp OR 'primary health care'/exp OR 'secondary health care'/exp OR 'clinical handover'/exp OR 'patient monitoring'/exp OR monitor:ab,ti OR monitored:ab,ti OR monitoring:ab,ti OR "follow up":ab,ti OR "followed up":ab,ti OR visit:ab,ti OR visits:ab,ti OR session:ab,ti OR sessions:ab,ti OR appointment:ab,ti OR appointments:ab,ti
#4	('randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR (cross NEAR/1 over*):ab,ti OR placebo*:ab,ti OR (doubl* NEAR/1 blind*):ab,ti OR (singl* NEAR/1 blind*):ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti OR 'clinical study'/exp OR ‘clinical trial’:ti,ab OR ‘clinical trials’:ti,ab OR 'controlled study'/exp OR 'evaluation'/exp OR ‘evaluation study’:ab,ti OR ‘evaluation studies’:ab,ti OR ‘intervention study’:ab,ti OR ‘intervention studies’:ab,ti OR ‘case control’:ab,ti OR 'cohort analysis'/exp OR cohort:ab,ti OR longitudinal*:ab,ti OR prospective:ab,ti OR prospectively:ab,ti OR retrospective:ab,ti OR 'follow up'/exp OR ‘follow up’:ab,ti OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR ‘comparative study’:ab,ti OR ‘comparative studies’:ab,ti OR 'evidence based medicine'/exp OR ‘systematic review’:ab,ti OR ‘meta-analysis’:ab,ti OR ‘meta-analyses’:ab,ti) NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp)
#5	#1 AND #2 AND #3 AND #4
#6	#5 AND [humans]/lim AND [2009-2015]/py
#7	#6 AND [embase]/lim NOT [medline]/lim

PsycInfo Search Strategy (November 7, 2016)

Key Question 1

Set #	Terms
#1	DE "Attention Deficit Disorder with Hyperactivity" OR TI ("attention deficit hyperactivity disorder" OR ADHD OR "attention deficit disorder") OR AB ("attention deficit hyperactivity disorder" OR ADHD OR "attention deficit disorder"
#2	AG (childhood OR adolescence) OR DE "Pediatrics" OR TI (child OR children OR infant OR infants OR preschool OR preschooler OR pediatric OR teenager OR teenagers OR teenaged OR teen OR teens OR adolescent OR adolescents OR adolescence OR youth) OR AB (child OR children OR infant OR infants OR preschool OR preschooler OR pediatric OR teenager OR teenagers OR teenaged OR teen OR teens OR adolescent OR adolescents OR adolescence OR youth)
#3	DE "Screening" OR DE "Health Screening" OR DE "Questionnaires" OR DE "Screening Tests" OR DE "Psychological Screening Inventory" OR DE "Psychiatric Evaluation" OR DE "Psychodiagnosis" OR DE "Psychodiagnostic Interview" OR DE "Psychometrics" OR DE "Rating Scales" OR DE "Diagnosis" OR DE "Diagnostic and Statistical Manual" OR DE "Professional Referral" OR DE "Diagnostic Interview Schedule" OR DE "Behavioral Assessment" OR TI (questionnaire OR questionnaires OR screening OR screen OR scale OR instrument OR instruments OR interview OR interviews OR DSM* OR diagnosis OR diagnostic OR diagnosed OR (Vanderbilt AND scale) OR conners OR cprs OR ctrs OR cprs OR crs OR "snap-IV" OR "snap-4" OR "basc-2" OR "behavioral assessment system for children" OR dbdrs OR "disruptive behavior disorder rating scale" OR adhd-rs OR "adhd rating scale" OR ksads OR k-sads OR kiddie-sads OR DISC OR "dominance inducement submission and compliance" OR "diagnostic interview schedule for children" OR "diagnostic inventory for screening children" OR "mini-kid" OR "Mini Interational Neuropsychiatric interview" OR "iva-2" OR "iva-qs" OR "iva-ae2" OR tova OR "test of variables of attention" OR "neuropsychiatric eeg-based assessment aid" OR neba) OR AB (questionnaire OR questionnaires OR screening OR screen OR scale OR instrument OR instruments OR interview OR interviews OR DSM* OR diagnosis OR diagnostic OR diagnosed OR (Vanderbilt AND scale) OR conners OR cprs OR ctrs OR cprs OR crs OR "snap-IV" OR "snap-4" OR "basc-2" OR "behavioral assessment system for children" OR dbdrs OR "disruptive behavior disorder rating scale" OR adhd-rs OR "adhd rating scale" OR ksads OR k-sads OR kiddie-sads OR DISC OR "dominance inducement submission and compliance" OR "diagnostic interview schedule for children" OR "diagnostic inventory for screening children" OR "mini-kid" OR "Mini Interational Neuropsychiatric interview" OR "iva-2" OR "iva-qs" OR "iva-ae2" OR tova OR "test of variables of attention" OR "neuropsychiatric eeg-based assessment aid" OR neba)
#4	(DE "Misdiagnosis" OR ZC "longitudinal study" OR ZC "empirical study" OR ZC "followup study" OR ZC "longitudinal study" OR ZC "meta analysis" OR ZC "prospective study" OR ZC "retrospective study" OR ZC "systematic review" OR ZC "treatment outcome/clinical trial"OR DE "Clinical Trials" OR DE "Cohort Analysis" OR DE "Followup Studies" OR DE "Longitudinal Studies" OR DE "Prospective Studies" OR DE "Meta Analysis" OR TI (sensitivity OR specificity OR accuracy OR accurate OR accurately OR misdiagnos* OR randomized OR randomised OR randomization OR randomisation OR randomly OR trial OR groups OR trials OR "evaluation study" OR evaluation studies OR "intervention study" OR "intervention studies" OR "case-control" OR cohort OR "cross-sectional" OR longitudinal OR longitudinally OR prospective OR prospectively OR retrospective OR "comparative study" OR "meta-analysis" OR "meta-analyses") OR AB (sensitivity OR specificity OR accuracy OR accurate OR accurately OR misdiagnos* OR randomized OR randomised OR randomization OR randomisation OR randomly OR trial OR groups OR trials OR "evaluation study" OR evaluation studies OR "intervention study" OR "intervention studies" OR "case-control" OR cohort OR "cross-sectional" OR longitudinal OR longitudinally OR prospective OR prospectively OR retrospective OR "comparative study" OR "meta-analysis" OR "meta-analyses")) AND (ZZ "journal article")
#5	#1 AND #2 AND #3 AND #4
#6	#5, since 2009, English

Key Question 2

Set #	Terms
#1	DE "Attention Deficit Disorder with Hyperactivity" OR TI ("attention deficit hyperactivity disorder" OR ADHD OR "attention deficit disorder") OR AB ("attention deficit hyperactivity disorder" OR ADHD OR "attention deficit disorder"
#2	AG (childhood OR adolescence) OR DE "Pediatrics" OR TI (child OR children OR infant OR infants OR preschool OR preschooler OR pediatric OR teenager OR teenagers OR teenaged OR teen OR teens OR adolescent OR adolescents OR adolescence OR youth) OR AB (child OR children OR infant OR infants OR preschool OR preschooler OR pediatric OR teenager OR teenagers OR teenaged OR teen OR teens OR adolescent OR adolescents OR adolescence OR youth)
#3	#1 AND #2
#4	DE "CNS Stimulating Drugs" OR DE "Methylphenidate" OR DE "Dextroamphetamine" OR DE "Amphetamine" OR DE "Clonidine" OR DE "Serotonin Norepinephrine Reuptake Inhibitors" OR DE "Atomoxetine" OR DE "Tricyclic Antidepressant Drugs" OR DE "Desipramine" OR DE "Nortriptyline" OR DE "Bupropion" OR DE "Serotonin Norepinephrine Reuptake Inhibitors" OR DE "Venlafaxine" OR DE "Monoamine Oxidase Inhibitors" OR DE "Amantadine" OR TI (psychostimulants OR "CNS stimulating" OR "Central Nervous System stimulants" OR methylphenidate OR Dexmethylphenidate OR Dextroamphetamine OR lisdexamfetamine OR Amphetamine OR aptensio OR concerta OR Ritalin OR methylin OR medikinet OR equasym OR quillivant OR metadate OR daytrana OR focalin OR Dexedrine OR dextrostat OR procentra OR zenzedi OR Adderall OR vyvanse OR elvanse OR tyvense OR dyanavel OR evekeo OR "alpha-2 agonists" OR guanfacine OR intuniv OR tenex OR estulic OR afken OR clonidine OR catapres OR clophelin OR kapvay OR nexiclon OR duraclon OR "Serotonin Norepinephrine Reuptake Inhibitors" OR Strattera OR atomoxetine OR "Tricyclic Antidepressants " OR "Desipramine" OR "Nortriptyline" OR norpramin OR pertofrane OR pamelor OR "dopamine reuptake inhibitors" OR modanifil OR Provigil OR alertec OR modavigil OR modiodal OR modalert OR armodafinil OR nuvigil OR "norepinephrine-dopamine reuptake inhibitors" OR bupropion OR Wellbutrin OR zyban OR forfivo OR "Serotonin Norepinephrine Reuptake Inhibitors" OR duloxetine OR Cymbalta OR "serotonin norepinephrine dopamine reuptake inhibitors" OR "Venlafaxine" OR Effexor OR trevilor OR (Monoamine Oxidase AND Inhibitors) OR selegiline OR eldepryl OR emsam OR selgene OR zelapar OR "n methyl d aspartate receptor agonists" OR "Amantadine" OR symmetrel OR memantine OR Namenda)) OR AB (psychostimulants OR "CNS stimulating" OR "Central Nervous System stimulants" OR methylphenidate OR Dexmethylphenidate OR Dextroamphetamine OR lisdexamfetamine OR Amphetamine OR aptensio OR concerta OR Ritalin OR methylin OR medikinet OR equasym OR quillivant OR metadate OR daytrana OR focalin OR Dexedrine OR dextrostat OR procentra OR zenzedi OR Adderall OR vyvanse OR elvanse OR tyvense OR dyanavel OR evekeo OR "alpha-2 agonists" OR guanfacine OR intuniv OR tenex OR estulic OR afken OR clonidine OR catapres OR clophelin OR kapvay OR nexiclon OR duraclon OR "Serotonin Norepinephrine Reuptake Inhibitors" OR Strattera OR atomoxetine OR "Tricyclic Antidepressants " OR "Desipramine" OR "Nortriptyline" OR norpramin OR pertofrane OR pamelor OR "dopamine reuptake inhibitors" OR modanifil OR Provigil OR alertec OR modavigil OR modiodal OR modalert OR armodafinil OR nuvigil OR "norepinephrine-dopamine reuptake inhibitors" OR bupropion OR Wellbutrin OR zyban OR forfivo OR "Serotonin Norepinephrine Reuptake Inhibitors" OR duloxetine OR Cymbalta OR "serotonin norepinephrine dopamine reuptake inhibitors" OR "Venlafaxine" OR Effexor OR trevilor OR (Monoamine Oxidase AND Inhibitors) OR selegiline OR eldepryl OR emsam OR selgene OR zelapar OR "n methyl d aspartate receptor agonists" OR "Amantadine" OR symmetrel OR memantine OR Namenda))

Set #	Terms
#5	DE "Psychotherapy" OR DE "Adolescent Psychotherapy" OR DE "Multisystemic Therapy" OR DE "Behavior Therapy" OR DE "Dialectical Behavior Therapy" OR DE "Brief Psychotherapy" OR DE "Child Psychotherapy" OR DE "Play Therapy" OR DE "Client Centered Therapy" OR DE "Cognitive Behavior Therapy" OR DE "Group Psychotherapy" OR DE "Therapeutic Community" OR DE "Integrative Psychotherapy" OR DE "Psychotherapeutic Counseling" OR DE "Family Therapy" OR DE "Supportive Psychotherapy" OR DE "Cognitive Therapy" OR DE "Parent Training" OR DE "Parent Child Relations" OR DE "Time Management" OR DE "Mindfulness" OR DE "School Based Intervention" OR DE "Memory Training" OR DE "Biofeedback Training" OR DE "Biofeedback" OR DE "Computer Assisted Instruction" OR DE "Intelligent Tutoring Systems" OR DE "Diets" OR DE "Dietary Supplements" OR DE "Food Additives" OR DE "Fatty Acids" OR DE "Acupuncture" OR DE "Remedial Education" OR DE "Early Intervention" OR DE "Alternative Medicine" OR TI ("psychosocial therapy" OR "psychosocial intervention" OR "psychosocial interventions" OR "psychosocial approach" OR "psychosocial approaches" OR "psychosocial treatment" OR "psychosocial support" OR "psychoeducation" OR "nonpharmacologic therapy" OR "nondrug therapy" OR "non-drug therapy" OR "Play Therapy" OR "cognitive behavioral therapy" OR "cognitive behavior therapy" OR "cognitive behavioural therapy" OR "cognitive behaviour therapy" OR Mindfulness OR complementary OR "alternative medicine" OR "alternative therapy" OR "alternative therapies" OR "Interpersonal skills training" OR "Parent-Child Interaction Therapy" OR "parent training" OR "parent engagement" OR "parent management" OR "parenting skills" OR "parenting intervention" OR "parenting interventions" OR "Barkley's defiant child" OR "Teacher-Child Interaction Training" OR "Incredible Years" OR "New Forest Parenting" OR "Triple P" OR "Helping the Noncompliant Child" OR "child life and attention skills" OR "clas" OR PCIT OR "parent child interaction therapy" OR "Summer Treatment Program" OR "Daily Report Card" OR "organization skills" OR "organizational skills" OR "time management" OR "homework intervention" OR braintrain OR "memory training" OR "Captain's log mindpower builder" OR "memory gyms" OR "attention gym" OR "smartdriver plus" OR "smartmind pro" OR “RoboMemo” OR "play attention" OR metronome OR brainmaster OR mindmed OR "attention lab" OR (activate AND c8) OR "attention training" OR “CogniPlus” OR cogmed OR "working memory training" OR biofeedback OR neurofeedback OR neuroagility OR neuroptimal OR acupuncture OR "vision training" OR "visual training" OR "vision therapy" OR "education intervention" OR "cognitive remediation" OR neurotherapy OR "elimination diet" OR "diet therapy" OR (("low carb" OR "low carbohydrate" OR "low carbohydrates" OR "gluten free") AND diet) OR "feingold diet" OR "red dye" OR ((vitamin OR vitamins) AND (supplement OR supplements)) OR "herbal supplement" OR "herbal supplements" OR probiotics OR "omega 3" OR "slow cortical potentials" OR "few foods diet" OR "oligoantigenic diet" OR "restriction diet" OR "food intolerance" OR "food allergy" OR "food allergies" OR "food sensitivity" OR "food sensitivities" OR “multimodal treatment” OR homeopathy OR homeopathic OR chiropractic OR chiropractor) OR AB ("psychosocial therapy" OR "psychosocial intervention" OR "psychosocial interventions" OR "psychosocial approach" OR "psychosocial approaches" OR "psychosocial treatment" OR "psychosocial support" OR "psychoeducation" OR "nonpharmacologic therapy" OR "nondrug therapy" OR "non-drug therapy" OR "Play Therapy" OR "cognitive behavioral therapy" OR "cognitive behavior therapy" OR "cognitive behavioural therapy" OR "cognitive behaviour therapy" OR Mindfulness OR complementary OR "alternative medicine" OR "alternative therapy" OR "alternative therapies" OR "Interpersonal skills training" OR "Parent-Child Interaction Therapy" OR "parent training" OR "parent engagement" OR "parent management" OR "parenting skills" OR "parenting intervention" OR "parenting interventions" OR "Barkley's defiant child" OR "Teacher-Child Interaction Training" OR "Incredible Years" OR "New Forest Parenting" OR "Triple P" OR "Helping the Noncompliant Child" OR "child life and attention skills" OR "clas" OR PCIT OR "parent child interaction therapy" OR "Summer Treatment Program" OR "Daily Report Card" OR "organization skills" OR "organizational skills" OR "time management" OR "homework intervention" OR braintrain OR "memory training" OR "Captain's log mindpower builder" OR "memory gyms" OR "attention gym" OR "smartdriver plus" OR "smartmind pro" OR “RoboMemo” OR "play attention" OR metronome OR brainmaster OR mindmed OR "attention lab" OR (activate AND c8) OR "attention training" OR “CogniPlus” OR cogmed OR "working memory training" OR biofeedback OR neurofeedback OR neuroagility OR neuroptimal OR acupuncture OR "vision training" OR "visual training" OR "vision therapy" OR "education intervention" OR "cognitive remediation" OR neurotherapy OR "elimination diet" OR "diet therapy" OR (("low carb" OR "low carbohydrate" OR "low carbohydrates" OR "gluten free") AND diet) OR "feingold diet" OR "red dye" OR ((vitamin OR vitamins) AND (supplement OR supplements)) OR "herbal supplement" OR "herbal supplements" OR probiotics OR "omega 3" OR "slow cortical potentials" OR "few foods diet" OR "oligoantigenic diet" OR "restriction diet" OR "food intolerance" OR "food allergy" OR "food allergies" OR "food sensitivity" OR "food sensitivities" OR “multimodal treatment” OR homeopathy OR homeopathic OR chiropractic OR chiropractor)
6	#4 OR #5

Set #	Terms
7	#3 AND #6
8	ZC "longitudinal study" OR ZC "empirical study" OR ZC "followup study" OR ZC "longitudinal study" OR ZC "meta analysis" OR ZC "prospective study" OR ZC "retrospective study" OR ZC "systematic review" OR ZC "treatment outcome/clinical trial"OR DE "Clinical Trials" OR DE "Cohort Analysis" OR DE "Followup Studies" OR DE "Longitudinal Studies" OR DE "Prospective Studies" OR DE "Meta Analysis" OR TI (randomized OR randomised OR randomization OR randomisation OR randomly OR trial OR groups OR trials OR "evaluation study" OR evaluation studies OR "intervention study" OR "intervention studies" OR "case-control" OR cohort OR longitudinal OR longitudinally OR prospective OR prospectively OR retrospective OR "comparative study" OR "meta-analysis" OR "meta-analyses") OR AB (randomized OR randomised OR randomization OR randomisation OR randomly OR trial OR groups OR trials OR "evaluation study" OR evaluation studies OR "intervention study" OR "intervention studies" OR "case-control" OR cohort OR longitudinal OR longitudinally OR prospective OR prospectively OR retrospective OR "comparative study" OR "meta-analysis" OR "meta-analyses") AND (ZZ "journal article")
9	#7 AND #8
10	#9, since 2009

Key Question 3

Set #	Terms
#1	DE "Attention Deficit Disorder with Hyperactivity" OR TI ("attention deficit hyperactivity disorder" OR ADHD OR "attention deficit disorder") OR AB ("attention deficit hyperactivity disorder" OR ADHD OR "attention deficit disorder"
#2	AG (childhood OR adolescence) OR DE "Pediatrics" OR TI (child OR children OR infant OR infants OR preschool OR preschooler OR pediatric OR teenager OR teenagers OR teenaged OR teen OR teens OR adolescent OR adolescents OR adolescence OR youth) OR AB (child OR children OR infant OR infants OR preschool OR preschooler OR pediatric OR teenager OR teenagers OR teenaged OR teen OR teens OR adolescent OR adolescents OR adolescence OR youth)
#3	(((((DE "Continuum of Care") OR (DE "Outpatient Treatment")) OR (DE "Primary Health Care")) OR (DE "Monitoring")) OR (DE "Community Psychiatry")) OR TI ("primary care" OR monitor OR monitored OR monitoring OR "follow up" OR "followed up" OR visit OR visits OR session OR sessions OR appointment OR appointments) OR AB ("primary care" OR monitor OR monitored OR monitoring OR "follow up" OR "followed up" OR visit OR visits OR session OR sessions OR appointment OR appointments)
#4	ZC "longitudinal study" OR ZC "empirical study" OR ZC "followup study" OR ZC "longitudinal study" OR ZC "meta analysis" OR ZC "prospective study" OR ZC "retrospective study" OR ZC "systematic review" OR ZC "treatment outcome/clinical trial"OR DE "Clinical Trials" OR DE "Cohort Analysis" OR DE "Followup Studies" OR DE "Longitudinal Studies" OR DE "Prospective Studies" OR DE "Meta Analysis" OR TI (randomized OR randomised OR randomization OR randomisation OR randomly OR trial OR groups OR trials OR "evaluation study" OR evaluation studies OR "intervention study" OR "intervention studies" OR "case-control" OR cohort OR longitudinal OR longitudinally OR prospective OR prospectively OR retrospective OR "comparative study" OR "meta-analysis" OR "meta-analyses") OR AB (randomized OR randomised OR randomization OR randomisation OR randomly OR trial OR groups OR trials OR "evaluation study" OR evaluation studies OR "intervention study" OR "intervention studies" OR "case-control" OR cohort OR longitudinal OR longitudinally OR prospective OR prospectively OR retrospective OR "comparative study" OR "meta-analysis" OR "meta-analyses") AND (ZZ "journal article")
#5	#1 AND #2 AND #3 AND #4
#6	#5, since 2009 and English

Cochrane Search Strategy (November 7, 2016)

Platform: Wiley
Database searched: Cochrane Database of Systematic Reviews

Key Question 1

Set #	Terms
#1	[mh "Attention Deficit Disorder with Hyperactivity"]
#2	"attention deficit hyperactivity disorder":ab,ti OR "ADHD":ab,ti OR "attention deficit disorder":ab,ti
#3	#1 OR #2
#4	[mh Pediatrics] OR [mh Adolescent] OR [mh Infant] OR [mh Child]
#5	child:ab,ti OR children:ab,ti OR infant:ab,ti OR infants:ab,ti OR preschool:ab,ti OR preschooler:ab,ti OR pediatric:ab,ti OR teenager:ab,ti OR teenagers:ab,ti OR teenaged:ab,ti OR teen:ab,ti OR teens:ab,ti OR adolescent:ab,ti OR adolescents:ab,ti OR adolescence:ab,ti OR youth:ab,ti
#6	#4 OR #5
#7	[mh "Attention Deficit Disorder with Hyperactivity"/DI] OR [mh "mass screening"] OR [mh questionnaires] OR [mh "Interviews as Topic"] OR [mh Psychometrics] OR [mh "Psychiatric Status Rating Scales"] OR [mh ^diagnosis] OR [mh "Diagnostic Techniques and Procedures"] OR [mh "Diagnostic and Statistical Manual of Mental Disorders"] OR [mh "Referral and Consultation"]
#8	questionnaire:ab,ti OR questionnaires:ab,ti OR screening:ab,ti OR screen:ab,ti OR scale:ab,ti OR instrument:ab,ti OR instruments:ab,ti OR interview:ab,ti OR interviews:ab,ti OR DSM*:ab,ti OR diagnosis:ab,ti OR diagnostic:ab,ti OR diagnosed:ab,ti OR (Vanderbilt:ab,ti AND scale:ab,ti) OR conners:ab,ti OR cprs:ab,ti OR ctrs:ab,ti OR cprs:ab,ti OR crs:ab,ti OR "snap-IV":ab,ti OR "snap-4":ab,ti OR "basc-2":ab,ti OR "behavioral assessment system for children":ab,ti OR dbdrs:ab,ti OR "disruptive behavior disorder rating scale":ab,ti OR adhd-rs:ab,ti OR "adhd rating scale":ab,ti OR ksads:ab,ti OR k-sads:ab,ti OR kiddie-sads:ab,ti OR DISC:ab,ti OR "dominance inducement submission and compliance":ab,ti OR "diagnostic interview schedule for children":ab,ti OR "diagnostic inventory for screening children":ab,ti OR "mini-kid":ab,ti OR "Mini Interational Neuropsychiatric interview":ab,ti OR "iva-2":ab,ti OR "iva-qs":ab,ti OR "iva-ae2":ab,ti OR tova:ab,ti OR "test of variables of attention":ab,ti OR "neuropsychiatric eeg-based assessment aid":ab,ti OR neba:ab,ti
#9	#7 OR #8
#10	#3 AND #6 AND #9
#11	#10, since 2009, in CDSR only

Key Question 2

Set #	Terms
#1	[mh "Attention Deficit Disorder with Hyperactivity"]
#2	"attention deficit hyperactivity disorder":ab,ti OR "ADHD":ab,ti OR "attention deficit disorder":ab,ti
#3	#1 OR #2
#4	[mh Pediatrics] OR [mh Adolescent] OR [mh Infant] OR [mh Child]
#5	child:ab,ti OR children:ab,ti OR infant:ab,ti OR infants:ab,ti OR preschool:ab,ti OR preschooler:ab,ti OR pediatric:ab,ti OR teenager:ab,ti OR teenagers:ab,ti OR teenaged:ab,ti OR teen:ab,ti OR teens:ab,ti OR adolescent:ab,ti OR adolescents:ab,ti OR adolescence:ab,ti OR youth:ab,ti
#6	#4 OR #5
#7	[mh "Attention Deficit Disorder with Hyperactivity"/DT] OR [mh "Central Nervous System Stimulants"] OR [mh Methylphenidate] OR [mh Dexmethylphenidate] OR [mh Dextroamphetamine] OR [mh Amphetamine] OR [mh Guanfacine] OR [mh Sympatholytics] OR [mh Clonidine] OR [mh "Adrenergic Uptake Inhibitors"] OR [mh "alpha-2 Adrenergic Receptors"] OR [mh "Adrenergic alpha-Agonists"] OR [mh "Adrenergic alpha-2 Receptor Agonists"] OR [mh "Tricyclic Antidepressive Agents"] OR [mh Desipramine] OR [mh "Dopamine Uptake Inhibitors"] OR [mh Sympathomimetics] OR [mh "Serotonin Uptake Inhibitors"] OR [mh "Monoamine Oxidase Inhibitors"] OR [mh "Monoamine Oxidase"] OR [mh Selegiline] OR [mh Bupropion] OR [mh "N-Methyl-D-Aspartate Receptors"] OR [mh Memantine] OR [mh Amantadine]
#8	"Central Nervous System Stimulants":ab,ti OR "psychostimulant":ab,ti OR "Methylphenidate":ab,ti OR "Methylphenidate Hydrochloride":ab,ti OR "Aptensio":ab,ti OR "Concerta":ab,ti OR "Ritalin":ab,ti OR "Ritalin LA":ab,ti OR "Medikinet":ab,ti OR "Equasym":ab,ti OR "Quillivant":ab,ti OR "Metadate":ab,ti OR "Daytrana":ab,ti OR "Dexmethylphenidate":ab,ti OR "Dexmethylphenidate Hydrochloride":ab,ti OR "Focalin":ab,ti OR "Dextroamphetamine":ab,ti OR "Dexedrine":ab,ti OR "Dextrostat":ab,ti OR "ProCentra":ab,ti OR "Zenzedi":ab,ti OR "mixed amphetamine salts":ab,ti OR "Adderall" :ab,ti OR "lisdexamfetamine":ab,ti OR "lisdexamfetamine dimesylate":ab,ti OR "Vyvanse":ab,ti OR "Venvanse":ab,ti OR "Elvanse":ab,ti OR "Tyvense":ab,ti OR "Dyanavel":ab,ti OR "Evekeo":ab,ti OR "Guanfacine":ab,ti OR "Sympatholytics":ab,ti OR "Central alpha-2 Adrenergic Agonist":ab,ti OR "Clonidine":ab,ti OR "Intuniv":ab,ti OR "Estulic":ab,ti OR "Tenex":ab,ti OR "Catapres":ab,ti OR "Clophelin":ab,ti OR "Kapvay":ab,ti OR "Nexiclon":ab,ti OR "Duraclon":ab,ti OR "Norepinephrine Reuptake Inhibitors":ab,ti OR "Selective Norepinephrine Reuptake Inhibitors":ab,ti OR "Adrenergic Uptake Inhibitors":ab,ti OR "atomoxetine":ab,ti OR "Strattera":ab,ti OR "Tricyclic antidepressants":ab,ti OR "Desipramine":ab,ti OR "Norpramin":ab,ti OR "Nortriptyline":ab,ti OR "Pamelor":ab,ti OR "Dopamine Reuptake Inhibitors":ab,ti OR "modafinil":ab,ti OR "Provigil":ab,ti OR "Armodafinil":ab,ti OR "Norepinephrine-dopamine Reuptake Inhibitors":ab,ti OR "Bupropion":ab,ti OR "Wellbutrin":ab,ti OR "Forfivo":ab,ti OR "Cymbalta":ab,ti OR "venlafaxine":ab,ti OR "reboxetine":ab,ti OR "Monoamine Oxidase Type B inhibitors":ab,ti OR "Selegiline":ab,ti OR "Eldepryl":ab,ti OR "Zelapar":ab,ti OR "NMDA receptors":ab,ti OR "N-Methyl-D-aspartate receptor Antagonists":ab,ti OR "Amantadine":ab,ti OR "Memantine":ab,ti OR "Pertofrane":ab,ti OR "Nuvigil":ab,ti OR "Cymbalta":ab,ti OR "duloxetine":ab,ti OR "Effexor":ab,ti OR "Eldepryl":ab,ti OR "Emsam":ab,ti OR "Trevilor":ab,ti OR "Symmetrel":ab,ti OR "Namenda":ab,ti OR "Zelapar":ab,ti
#9	#7 OR #8
#10	[mh "Attention Deficit Disorder with Hyperactivity"/DH] OR [mh "Attention Deficit Disorder with Hyperactivity"/RH] OR [mh Psychotherapy] OR [mh "Behavior Therapy"] OR [mh "Parent-Child Relations"] OR [mh "Play Therapy"] OR [mh "Cognitive Therapy"] OR [mh "Time Management"] OR [mh "Computer-Assisted Instruction"] OR [mh "Diet Therapy"] OR [mh "Omega-3 Fatty Acids"/TU] OR [mh Vitamins/AD] OR [mh Vitamins/TU] OR [mh "Food Additives"/AE] OR [mh Probiotics/TU] OR [mh "Acupuncture Therapy"] OR [mh "Remedial Teaching"] OR [mh "Early Intervention (Education)"] OR [mh "Complementary Therapies"] OR [mh "Combined Modality Therapy"]

Set #	Terms
#11	"psychosocial therapy":ab,ti OR "psychosocial intervention":ab,ti OR "psychosocial interventions":ab,ti OR "psychosocial approach":ab,ti OR "psychosocial approaches":ab,ti OR "psychosocial treatment":ab,ti OR "psychosocial support":ab,ti OR "psychoeducation":ab,ti OR "nonpharmacologic therapy":ab,ti OR "nondrug therapy":ab,ti OR "non-drug therapy":ab,ti OR "Play Therapy":ab,ti OR "cognitive behavioral therapy":ab,ti OR "cognitive behavior therapy":ab,ti OR "cognitive behavioural therapy":ab,ti OR "cognitive behaviour therapy":ab,ti OR Mindfulness:ab,ti OR complementary:ab,ti OR "alternative medicine":ab,ti OR "alternative therapy":ab,ti OR "alternative therapies":ab,ti OR "Interpersonal skills training":ab,ti OR "Parent-Child Interaction Therapy":ab,ti OR "parent training":ab,ti OR "parent engagement":ab,ti OR "parent management":ab,ti OR "parenting skills":ab,ti OR "parenting intervention":ab,ti OR "parenting interventions":ab,ti OR "Barkley's defiant child":ab,ti OR "Teacher-Child Interaction Training":ab,ti OR "Incredible Years":ab,ti OR "New Forest Parenting":ab,ti OR "Triple P":ab,ti OR "Helping the Noncompliant Child":ab,ti OR "child life and attention skills":ab,ti OR "clas":ab,ti OR PCIT:ab,ti OR "parent child interaction therapy":ab,ti OR "Summer Treatment Program":ab,ti OR "Daily Report Card":ab,ti OR "organization skills":ab,ti OR "organizational skills":ab,ti OR "time management":ab,ti OR "homework intervention":ab,ti OR braintrain:ab,ti OR "memory training":ab,ti OR "Captain's log mindpower builder":ab,ti OR "memory gyms":ab,ti OR "attention gym":ab,ti OR "smartdriver plus":ab,ti OR "smartmind pro":ab,ti OR “RoboMemo”:ab,ti OR "play attention":ab,ti OR metronome:ab,ti OR brainmaster:ab,ti OR mindmed:ab,ti OR "attention lab":ab,ti OR (activate:ab,ti AND c8:ab,ti) OR "attention training":ab,ti OR “CogniPlus”:ab,ti OR cogmed:ab,ti OR "working memory training":ab,ti OR biofeedback:ab,ti OR neurofeedback:ab,ti OR neuroagility:ab,ti OR neuroptimal:ab,ti OR acupuncture:ab,ti OR "vision training":ab,ti OR "visual training":ab,ti OR "vision therapy":ab,ti OR "education intervention":ab,ti OR "cognitive remediation":ab,ti OR neurotherapy:ab,ti OR "elimination diet":ab,ti OR "diet therapy":ab,ti OR (("low carb" OR "low carbohydrate" OR "low carbohydrates":ab,ti OR "gluten free") AND diet:ab,ti) OR "feingold diet":ab,ti OR "red dye":ab,ti OR ((vitamin:ab,ti OR vitamins:ab,ti) AND (supplement:ab,ti OR supplements:ab,ti)) OR "herbal supplement":ab,ti OR "herbal supplements":ab,ti OR probiotics:ab,ti OR "omega 3":ab,ti OR "slow cortical potentials":ab,ti OR "few foods diet":ab,ti OR "oligoantigenic diet":ab,ti OR "restriction diet":ab,ti OR "food intolerance":ab,ti OR "food allergy":ab,ti OR "food allergies":ab,ti OR "food sensitivity":ab,ti OR "food sensitivities":ab,ti OR “multimodal treatment”:ab,ti OR homeopathy:ab,ti OR homeopathic:ab,ti OR chiropractic:ab,ti OR chiropractor:ab,ti
#12	#10 OR #11
#13	#12 OR #9
#14	#3 AND #6 AND #13
#15	#14, since 2009, limited to CDSR

Key Question 3

Set #	Terms
#1	[mh "Attention Deficit Disorder with Hyperactivity"]
#2	"attention deficit hyperactivity disorder":ab,ti OR "ADHD":ab,ti OR "attention deficit disorder":ab,ti
#3	#1 OR #2
#4	[mh Pediatrics] OR [mh Adolescent] OR [mh Infant] OR [mh Child]
#5	child:ab,ti OR children:ab,ti OR infant:ab,ti OR infants:ab,ti OR preschool:ab,ti OR preschooler:ab,ti OR pediatric:ab,ti OR teenager:ab,ti OR teenagers:ab,ti OR teenaged:ab,ti OR teen:ab,ti OR teens:ab,ti OR adolescent:ab,ti OR adolescents:ab,ti OR adolescence:ab,ti OR youth:ab,ti
#6	#4 OR #5
#7	[mh "Secondary Care"] OR [mh "Comprehensive Health Care"]
#8	"primary care":ab,ti OR monitor:ab,ti OR monitored:ab,ti OR monitoring:ab,ti OR "follow up":ab,ti OR "followed up":ab,ti OR visit:ab,ti OR visits:ab,ti OR session:ab,ti OR sessions:ab,ti OR appointment:ab,ti OR appointments:ab,ti
#9	#7 OR #8
#10	#3 AND #6 AND #9
#11	#10, since 2009, limit to CDSR

Gray Literature Searches

ClinicalTrials.gov (November 28, 2016)

Category	Description
Conditions	ADHD OR attention deficit
Recruitment	Completed studies
Study Results	All studies
Study type	Interventional studies
Age group	Child
Phase	Phase 2, Phase 3, Phase 4

Total number of results for screening: 377

WHO: International Clinical Trials Registry Platform Search Portal (November 28, 2016)

Category	Description
Conditions	ADHD OR attention deficit
Recruiting status	All

Total number of results exported: 945 records/828 trials

Results were imported into an excel file and refined as follows:

1. Removed records with a registration date of December 31, 2004 or earlier; records with an enrollment start date of December 31, 2004 or earlier; records of recruiting studies; records with a population age above 17 years; studies that were explicitly designated as Phase 0 or 1—497 records.
2. Removal of records originating from ClinicalTrials.gov (the ClinicalTrials.gov database was searched separately)—302 records removed, 195 remaining.

Total number of results for screening: 195

National Guidelines Clearinghouse (November 28, 2016)

Platform: www.guideline.gov

Category	Description
Keywords	ADHD OR "attention deficit disorder" OR "attention deficit hyperactivity disorder"
Age of Target Population	Adolescent (13 to 18 years), Child (2 to 12 years), Infant (1 to 23 months), Infant, Newborn (to 1 month)
Publication Year	2009, 2010, 2011, 2012, 2013, 2014, 2015

Total number of results: 37

Appendix B. Data Abstraction Elements

Study Characteristics

- Study Identifiers
    - Study Name or Acronym
    - NCT number or other trial registry identifier
    - Last name of first author
- Additional Articles Used in This Abstraction
- Study Sites
    - Single center, Multicenter, Unclear/Not reported
    - Number of sites
- Geographic Location (Select all that apply)
    - US, Canada, UK/Europe, Latin America, Middle East (including Israel), Asia, Africa, Australia/NZ, Unclear/Not reported
- Study Design
    - RCT
    - Observational
- Funding Source (Select all that apply)
    - Government, Industry, Non-government/non-industry, Unclear/Not reported
- Setting (Select all that apply)
    - Primary Care; Specialty Care; Community Resource; School; Other; Unclear/Not reported
- Study Enrollment/Study Completion
    - N enrolled/included
    - N completed
- Key Question Applicability (Select all that apply)
    - KQ1, KQ2, KQ3
- Comments

Baseline Characteristics – Record the following elements for Total Population, Total ADHD Population, Arm 1, Arm 2, Arm 3, and Arm 4 (as applicable)

- Number of Patients (N and %)
- Gender (N and %)
    - Male
    - Female
- Age in years
    - Mean
    - Median
    - Standard Deviation
    - Min. age
    - Max. age
    - 25% IQR
    - 75% IQR
    - Categorical
    - Other, specify

    - Race/Ethnicity (N and %)
        - Hispanic or Latino
        - Black/African American
        - American Indian or Alaska Native
        - Asian
        - Native Hawaiian or Pacific Islander
        - White
        - Multiracial
        - Other (specify)
    - ADHD Subtype (N and %)
        - Inattentive
        - Hyperactive
        - Combined
- Were there significant differences noted between groups in any baseline characteristic? (Yes/No)
    - If yes, please explain the differences
- Comments

Intervention Characteristics

- What intervention comparison is being tested in this study? Mark all that apply.
    - Pharmacological vs. pharmacological,
    - Pharmacological vs. non-pharmacological
    - Pharmacological vs. placebo/usual care
        - Placebo, Pharmacological Usual Care, Non-pharmacological Usual Care
    - Non-pharmacological vs. non-pharmacological
    - Non-pharmacological vs. placebo/usual care
        - Placebo, Pharmacological Usual Care, Non-pharmacological Usual Care
- Intervention Descriptors
    - Describe the intervention received by each patient group (For each Arm).
- Indicate components of the intervention (For each Arm)
    - Pharmacological
    - Nonpharmacological
    - Placebo or usual/standard care
- Indicate all intervention characteristics that are varied in this study
    - Pharmacological Details
        - Psychostimulants
            - Methylphenidate, Dexmethylphenidate, Dextroamphetamine, Lisdexamphetamine, Mixed amphetamine salts, Amphetamine
        - Tricyclic antidepressants
            - Desipramine, Nortriptyline
        - Selective norepinephrine reuptake inhibitors
            - Atomoxetine
        - Alpha-2 agonists
            - Clonidine, Guanfacine extended release
        - Dopamine reuptake inhibitors
            - Modafinil

        - Armodafinil
    - Norepinephrine-dopamine reuptake inhibitors
        - Bupropion
    - Serotonin-norepinephrine reuptake inhibitors
        - Duloxetine
    - Serotonin-norepinephrine-dopamine reuptake inhibitors
        - Venlafaxine
    - Monoamine oxidase type B inhibitors
        - Selegiline
    - N-methyl-D-aspartate receptor antagonists
        - Amantadine, Memantine
- Nonpharmacological Details
    - 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
    - Homeopathy
    - Acupuncture
    - Elimination diets
    - Vision training
    - Exercise
    - Chiropractic treatment
- Placebo/Control details
    - Placebo
    - Usual care control/optimal medical therapy
    - Other (specify)
- Indicate the intervention target
    - ADHD patients
    - Parents
    - Teachers
    - Other (Specify)
- Indicate the Intervention Setting
    - Primary Care
    - Specialty Care
    - Home
    - School
    - Other (specify)

- Duration of Follow-up reported for Total overall study f/u, Arm 1 f/u, Arm 2 f/u, Arm 3 f/u, Arm 4 f/u (Reported or Not reported)
    - Mean follow-up in months or years (include units)

        - Mean Variability
            - SD, SE, IQR, NR
        - Median Follow-up in months or years (include units)
        - Median variability
            - SD, SE, IQR, NR
- Comments

KQ 1 Diagnostic Tools

- Gold Standard
    - Is confirmation of diagnosis by a specialist 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-IV or DSM-V the gold standard?
        - Yes (Describe the gold standard)
        - No (Article may be eligible for exclusion. Please check with the team)
    - Who performed the diagnosis?
        - Specialist, other care, provider, researcher, unclear/NR, other (specify)
- Select the outcome(s) reported on this form:
    - Diagnostic Accuracy, Misdiagnosis/risk of missed condition, labeling/stigma
- Select the Age Group
    - Under 7 with any diagnostic tool, 7-17 with a novel diagnostic tool, labeling/stigma
- Subgroup Analyses
    - Is this outcome form for a subgroup of interest? (Y or N)
        - If Y, indicate the factor being considered
            - Age
            - Sex
            - ADHD presentation
            - Comorbidity (e.g. anxiety, depression)
            - Risk factors
            - Race/ethnicity
            - Socioeconomic status
            - Insurance status
            - Geographic location
            - Clinical setting
            - Any additional description/clarification of subgroup reported on this form
- Diagnostic Accuracy
    - Timing of the outcome data
    - Test results reported for Instrument 1, Instrument 2, Instrument 3 (Select instrument used)
        - True positive (# patients)
        - True negative (# patients)
        - False positive (# patients)
        - False negative (# patients)
        - Sensitivity

            - %, Std dev, Upper confidence interval bound, lower confidence interval bound
        - Specificity
            - %, Std dev, Upper confidence interval bound, lower confidence interval bound
        - Positive predictive value
            - %, Std dev, Upper confidence interval bound, lower confidence interval bound
        - Negative predictive value
            - %, Std dev, Upper confidence interval bound, lower confidence interval bound
        - Positive likelihood ratio
        - Negative likelihood ratio
    - Reliability
        - Test-retest
        - Kappa statistics
        - Inter-rater
        - Intra-rater
        - Intraclass correlation
        - Diagnostic concordance of primary care provider with specialist
        - Internal consistency
- Misdiagnosis/Risk of Missed Condition Measure
    - Timing of the outcome reported
    - Describe outcome
- Labeling/Stigma
    - Timing of the outcome data reported
    - Describe outcome
- Comments

KQ 2 Outcomes

- Specific RefID
- Where was this data in the article found? (pg #, table #, etc)
- Select the outcome reported on this form:
    - Academic performance
    - Acceptability of treatment
    - Aggression
    - Behavior changes
    - Cardiac arrhythmias
    - Changes in appetite
    - Changes in standardized symptom scores or progress toward patient-identified goals
    - Chemical leukoderma
    - Conduction abnormalities
    - Depression or anxiety
    - Diversion of pharmacotherapy
    - Divorce/relationship status

    - Elevated blood pressure
    - Functional impairment
    - Gastrointestinal symptoms
    - Growth suppression
    - Hallucination
    - Incarceration or other interactions with the legal system
    - Increased heart rate
    - Loss of spontaneity
    - Mood disorders
    - Mortality
    - Motor vehicle collisions or other accidents
    - Motor vehicle violations
    - Obesity
    - Overtreatment
    - Parental stress
    - Personality change
    - Priapism
    - Quality of peer relationships
    - Risk of sudden cardiac death
    - Risk-taking behaviors
    - Self-injurious non-suicidal behavior
    - Sleep disturbance
    - Substance abuse
    - Suicide (attempted or completed)
    - Suicide ideation
    - Tics or other movement disorders
    - Time demands/opportunity cost
    - Tobacco use
    - Weight decrease
    - Workforce participation
- Any additional description / clarification of the outcome reported on this form
- Is this outcome form for a subgroup of interest? (Yes/No)
    - What subpopulation is this outcome reported for on this form?
        - Age
        - Sex
        - ADHD presentation
        - Comorbidity
        - Risk factors
        - Race/ethnicity
        - Socioeconomic status
        - Insurance status
        - Geographic location
        - Clinical setting
    - Any additional description / clarification of subgroup reported on this form
- Total N Analyzed for this outcome
- Timepoint reported on this form

    - Short-term
    - Long-term
- Specify actual timing of the outcome (in months)
- For each arm:
    - N Analyzed (enter UNK if unknown)
    - Unadjusted Result
        - Number of patients with outcome
        - % of patients with outcome
        - Events/denominator
        - Odds ratio
        - Hazard ratio
        - Relative risk
        - Mean
        - Median
        - Mean within group change
        - Mean between group change
        - Other (specify)
    - Unadjusted Result Variability
        - 95% CI
        - IQR
        - Standard Error (SE)
        - Standard Deviation (SD)
        - Other % CI (specify)
        - Other (specify)
    - Unadjusted Result, p-value between groups
    - Unadjusted Result, indicate reference group (for comparison between groups)
    - Adjusted Result
        - Number of patients with outcome
        - % of patients with outcome
        - Events/denominator
        - Odds ratio
        - Hazard ratio
        - Relative risk
        - Mean
        - Median
        - Mean within group change
        - Mean between group change
        - Other (specify)
    - Adjusted Result Variability
        - 95% CI
        - IQR
        - Standard Error (SE)
        - Standard Deviation (SD)
        - Other % CI (specify)
        - Other (specify)
    - Adjusted Result, p-value between groups

- Adjusted Result, indicate reference group (for comparison between groups)
- If adjusted data is recorded, indicate the adjustments applied

- Comments

Quality

- Study Type (select one): RCT, Observational
- If RCT, select Yes/No/Unclear for each of the following questions:
  - Sequence Generation
    - Was the allocation sequence generated adequately (e.g., random number table, computer-generated randomization)?
  - Allocation concealment
    - Was the allocation of treatment adequately concealed (e.g., pharmacy-controlled randomization or use of sequentially numbered sealed envelopes)?
  - Blinding of participants, personnel and outcome assessors
    - Was knowledge of the allocated intervention adequately prevented during the study?
  - Incomplete outcome data
    - Were incomplete outcome data adequately addressed?
  - Selective outcome reporting
    - Are reports of the study free of suggestion of selective outcome reporting?
  - Other sources of bias
    - Was the study apparently free of other problems that could put it at a high risk of bias?
  - Comments
- If Observational, Study design (select one)
    - Case-control, Cohort
- If Case-Control:
  - Selection
    - Is the case definition adequate?
      - Yes, with independent validation
      - Yes, eg record linkage or based on self reports?
      - No description
      - comments
    - Representativeness of the cases
      - Consecutive or obviously representative series of cases
      - Potential for selection biases or not stated
      - comments
    - Selection of controls
      - Community controls
      - Hospital controls
      - No description
      - Comments
    - Definition of controls
      - No history of disease (endpoint)

            - No description of source
            - Comments
    - Comparability
        - Comparability of cases and controls on the basis of the design or analysis
            - Study controls for severity of ADHD
            - Study controls for any additional factor
            - Comments
    - Exposure
        - Ascertainment of exposure
            - Secure record
            - Structured interview where blind to case/control status
            - Interview not blinded to case/control status
            - Written self report or medical record only
            - No description
            - comments
        - Same method of ascertainment for cases and controls (Y, N, comments)
        - Non-response rate
            - Same rate for both groups
            - Non respondent described
            - Rate different and no designation
            - Comments
- If Cohort:
    - Selection
        - Representativeness of the exposed cohort Yes, with independent validation
            - Truly representative of the average ADHD patient in the community
            - Somewhat representative of the average ADHD patient in the community
            - Selected group of users (eg nurses, volunteers)
            - No description of the derivation of the cohort
            - Comments
        - Selection of the non-exposed cohort
            - Drawn from the same community as the exposed cohort
            - Drawn from a different source
            - No description of the derivation of the non-exposed cohort
            - Comments
        - Ascertainment of exposure
            - Secure record (e.g., surgical records)
            - Structured interview
            - Written self-report
            - No description
            - Comments
        - Demonstration that outcome of interest was not present at start of study (Y, N, Comments)

    - Comparability
        - Comparability of cohorts on the basis of the design or analysis
            - Study controls for severity of ADHD
            - Study controls for any additional factor
            - Comments
    - Outcome
        - Assessment of Outcome
            - Independent blind assortment
            - Record linkage
            - Self report
            - No description
            - comments
        - Was follow-up long enough for outcome to occur (Y, N, comments)
        - Adequacy of follow up of cohorts
            - Complete follow up - all subjects accounted for
            - Subjects lost to follow up unlikely to introduce bias - small number lost - >80% follow up, or description provided of those lost
            - Follow up rate
            - No statement
            - Comments
- Overall Study Rating (Good/Fair/Poor)
    - **Good** (low risk of bias). These studies have the least bias, and the results are considered valid. These studies adhere to the commonly held concepts of high quality, including the following: a clear description of the population, setting, approaches, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytical methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.
    - **Fair**. These studies are susceptible to some bias, but not enough to invalidate the results. They do not meet all the criteria required for a rating of good quality because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
    - **Poor** (high risk of bias). These studies have significant flaws that may have invalidated the results. They have serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.
    - If the study is rated as “Fair” or “Poor,” provide rationale.
- Outcome-specific quality rating
    - Do you think that any of the outcomes abstracted for this study should be assigned a quality rating DIFFERENT from the overall study rating? (No/Yes)
        - If you think any of the abstracted outcomes should have a quality rating different from the overall study, please provide the outcome(s), rating(s) and rationale(s).

Applicability – Use the PICOS format to identify specific issues, if any, that may limit the applicability of the study.

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

Appendix C. List of Included Studies

Abikoff H, Gallagher R, Wells KC, et al. Remediating organizational functioning in children with ADHD: immediate and long-term effects from a randomized controlled trial. J Consult Clin Psychol 2013;81(1):113-28. PMID: 22889336.

Abikoff HB, Thompson M, Laver-Bradbury C, et al. Parent training for preschool ADHD: a randomized controlled trial of specialized and generic programs. J Child Psychol Psychiatry 2015;56(6):618-31. PMID: 25318650.

Anand P and Sachdeva A. Effect of Poly Unsaturated Fatty Acids Administration on Children with Attention Deficit Hyperactivity Disorder: A Randomized Controlled Trial. J Clin Diagn Res 2016;10(9):Oc01-oc05. PMID: 27790483.

Arcieri R, Germinario EA, Bonati M, et al. Cardiovascular measures in children and adolescents with attention-deficit/hyperactivity disorder who are new users of methylphenidate and atomoxetine. J Child Adolesc Psychopharmacol 2012;22(6):423-431. PMID: 23362511.

Arnold LE, Disilvestro RA, Bozzolo D, et al. Zinc for attention-deficit/hyperactivity disorder: placebo-controlled double-blind pilot trial alone and combined with amphetamine. J Child Adolesc Psychopharmacol 2011;21(1):1-19. PMID: 21309695.

Bai GN, Wang YF, Yang L, et al. Effectiveness of a focused, brief psychoeducation program for parents of ADHD children: Improvement of medication adherence and symptoms. Neuropsychiatric Disease and Treatment 2015;11:2721-2735.

Banaschewski T, Johnson M, Lecendreux M, et al. Health-related quality of life and functional outcomes from a randomized-withdrawal study of long-term lisdexamfetamine dimesylate treatment in children and adolescents with attention-deficit/hyperactivity disorder. CNS Drugs 2014;28(12):1191-203. PMID: 25139785.

Barragan E, Breuer D and Dopfner M. Efficacy and Safety of Omega-3/6 Fatty Acids, Methylphenidate, and a Combined Treatment in Children With ADHD. J Atten Disord 2014. PMID: 24464327.

Beck SJ, Hanson CA, Puffenberger SS, et al. A controlled trial of working memory training for children and adolescents with ADHD. J Clin Child Adolesc Psychol 2010;39(6):825-36. PMID: 21058129.

Berger I and Goldzweig G. Objective measures of attention-deficit/hyperactivity disorder: a pilot study. Isr Med Assoc J 2010;12(9):531-5. PMID: 21287795.

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Bloch Y, Fixman M, Maoz H, et al. Can computerized cognitive tests assist in the clinical diagnosis of attention-deficit hyperactivity disorder?. J Neuropsychiatry Clin Neurosci 2012;24(1):111-4. PMID: 22450621.

Boyer BE, Geurts HM, Prins PJ, et al. Two novel CBTs for adolescents with ADHD: the value of planning skills. Eur Child Adolesc Psychiatry 2015;24(9):1075-90. PMID: 25549767.

Bunte TL, Schoemaker K, Hessen DJ, et al. Clinical usefulness of the Kiddie-Disruptive Behavior Disorder Schedule in the diagnosis of DBD and ADHD in preschool children. J Abnorm Child Psychol 2013;41(5):681-90. PMID: 23474833.

Carballo JJ, Rodriguez-Blanco L, Garcia-Nieto R, et al. Screening for the ADHD Phenotype Using the Strengths and Difficulties Questionnaire in a Clinical Sample of Newly Referred Children and Adolescents. J Atten Disord 2014. PMID: 25515677.

Castro-Cabrera P, Gomez-Garcia J, Restrepo F, et al. Evaluation of feature extraction techniques on event-related potentials for detection of attention-deficit/hyperactivity disorder. Conf Proc IEEE Eng Med Biol Soc 2010;2010:851-4. PMID: 21096317.

Caudal F. New marker using bioimpedance technology in screening for attention deficit/hyperactivity disorder (ADHD) in children as an adjunct to conventional diagnostic methods. Psychol Res Behav Manag 2011;4:113-7. PMID: 22114541.

Çetin FH, Taş Torun Y and Işik Taner Y. Atomoxetine versus OROS methylphenidate in attention deficit hyperactivity disorder: A six-month follow up study for efficacy and adverse effects. Turkiye Klinikleri Journal of Medical Sciences 2015;35(2):88-96.

Chacko A, Bedard AC, Marks DJ, et al. A randomized clinical trial of Cogmed Working Memory Training in school-age children with ADHD: a replication in a diverse sample using a control condition. J Child Psychol Psychiatry 2014;55(3):247-55. PMID: 24117656.

Chacko A, Wymbs BT, Wymbs FA, et al. Enhancing traditional behavioral parent training for single mothers of children with ADHD. J Clin Child Adolesc Psychol 2009;38(2):206-18. PMID: 19283599.

Clemow DB, Mason OW, Sarkis EH, et al. Atomoxetine monotherapy compared with combination therapy for the treatment of ADHD: a retrospective chart review study. Expert Rev Neurother 2015;:1-14. PMID: 26488905.

Cortese S, Panei P, Arcieri R, et al. Safety of Methylphenidate and Atomoxetine in Children with Attention-Deficit/Hyperactivity Disorder (ADHD): Data from the Italian National ADHD Registry. CNS Drugs 2015;29(10):865-77. PMID: 26293742.

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dosReis S, Barksdale CL, Sherman A, et al. Stigmatizing experiences of parents of children with a new diagnosis of ADHD. Psychiatric Services 2010;61(8):811-816. PMID: 2010-16657-009.

Dovis S, Van der Oord S, Wiers RW, et al. Improving executive functioning in children with ADHD: training multiple executive functions within the context of a computer game. a randomized double-blind placebo controlled trial. PLoS One 2015;10(4):e0121651. PMID: 25844638.

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Egeland J, Aarlien AK and Saunes BK. Few effects of far transfer of working memory training in ADHD: a randomized controlled trial. PLoS One 2013;8(10):e75660. PMID: 24124503.

Ercan ES, Ardic UA, Kutlu A, et al. No beneficial effects of adding parent training to methylphenidate treatment for ADHD + ODD/CD children: a 1-year prospective follow-up study. J Atten Disord 2014;18(2):145-57. PMID: 22522574.

Evans SW, Langberg JM, Schultz BK, et al. Evaluation of a School-Based Treatment Program for Young Adolescents With ADHD. Journal of Consulting and Clinical Psychology 2015.

Ferrin M and Vance A. Examination of neurological subtle signs in ADHD as a clinical tool for the diagnosis and their relationship to spatial working memory. J Child Psychol Psychiatry 2012;53(4):390-400. PMID: 22141455.

Ferrin M, Moreno-Granados JM, Salcedo-Marin MD, et al. Evaluation of a psychoeducation programme for parents of children and adolescents with ADHD: immediate and long-term effects using a blind randomized controlled trial. Eur Child Adolesc Psychiatry 2014;23(8):637-47. PMID: 24292412.

Ferrin M, Perez-Ayala V, El-Abd S, et al. A Randomized Controlled Trial Evaluating the Efficacy of a Psychoeducation Program for Families of Children and Adolescents With ADHD in the United Kingdom: Results After a 6-Month Follow-Up. J Atten Disord 2016. PMID: 26838557.

Findling RL, Adeyi B, Chen G, et al. Clinical response and symptomatic remission in children treated with lisdexamfetamine dimesylate for attention-deficit/hyperactivity disorder. CNS Spectrums 2010;15(9):559-568.

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Hong SS and Cho SH. Treating attention deficit hyperactivity disorder with acupuncture: A randomized controlled trial. European Journal of Integrative Medicine 2015.

Huang YH, Chung CY, Ou HY, et al. Treatment effects of combining social skill training and parent training in Taiwanese children with attention deficit hyperactivity disorder. Journal of the Formosan Medical Association 2015;114(3):260-267.

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Katz M, Levine AA, Kol-Degani H, et al. A compound herbal preparation (CHP) in the treatment of children with ADHD: a randomized controlled trial. J Atten Disord 2010;14(3):281-91. PMID: 20228219.

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Kim JW, Lee J, Kim BN, et al. Theta-phase gamma-amplitude coupling as a neurophysiological marker of attention deficit/hyperactivity disorder in children. Neurosci Lett 2015;603:25-30. PMID: 26170246.

Klenberg L, Jamsa S, Hayrinen T, et al. The Attention and Executive Function Rating Inventory (ATTEX): Psychometric properties and clinical utility in diagnosing ADHD subtypes. Scand J Psychol 2010;51(5):439-448. PMID: 20338019.

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Liechti MD, Valko L, Muller UC, et al. Diagnostic value of resting electroencephalogram in attention-deficit/hyperactivity disorder across the lifespan. Brain Topogr 2013;26(1):135-51. PMID: 23053601.

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Martin-Martinez D, Casaseca-de-la-Higuera P, Alberola-Lopez S, et al. Nonlinear analysis of actigraphic signals for the assessment of the attention-deficit/hyperactivity disorder (ADHD). Med Eng Phys 2012;34(9):1317-29. PMID: 22297088.

Mautone JA, Marshall SA, Sharman J, et al. Development of a Family-School Intervention for Young Children With Attention Deficit Hyperactivity Disorder. School Psych Rev 2012;41(4):447-466. PMID: 24353368.

Milte CM, Parletta N, Buckley JD, et al. Eicosapentaenoic and docosahexaenoic acids, cognition, and behavior in children with attention-deficit/hyperactivity disorder: a randomized controlled trial. Nutrition 2012;28(6):670-7. PMID: 22541055.

Mohammadpour N, Jazayeri S, Tehrani-Doost M, et al. Effect of vitamin D supplementation as adjunctive therapy to methylphenidate on ADHD symptoms: A randomized, double blind, placebo-controlled trial. Nutr Neurosci 2016:1-8. PMID: 27924679.

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Moreno-García I, Delgado-Pardoa G, de Reya CC-V, et al. Neurofeedback, pharmacological treatment and behavioral therapy in hyperactivity: Multilevel analysis of treatment effects on electroencephalography. International Journal of Clinical and Health Psychology 2015;15(3):217-225. PMID: 2015-48012-005.

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Ostberg M and Rydell AM. An efficacy study of a combined parent and teacher management training programme for children with ADHD. Nord J Psychiatry 2012;66(2):123-30. PMID: 22150634.

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Park J, Kim C, Ahn JH, et al. Clinical Use of Continuous Performance Tests to Diagnose Children With ADHD. J Atten Disord 2016. PMID: 27412120.

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Pfiffner LJ, Hinshaw SP, Owens E, et al. A two-site randomized clinical trial of integrated psychosocial treatment for ADHD-inattentive type. J Consult Clin Psychol 2014;82(6):1115-27. PMID: 24865871.

Power TJ, Mautone JA, Soffer SL, et al. A family-school intervention for children with ADHD: results of a randomized clinical trial. J Consult Clin Psychol 2012;80(4):611-23. PMID: 22506793.

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Sibley MH, Graziano PA, Kuriyan AB, et al. Parent-teen behavior therapy + motivational interviewing for adolescents with ADHD. J Consult Clin Psychol 2016;84(8):699-712. PMID: 27077693.

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Webster-Stratton CH, Reid MJ and Beauchaine T. Combining parent and child training for young children with ADHD. J Clin Child Adolesc Psychol 2011;40(2):191-203. PMID: 21391017.

Widenhorn-Muller K, Schwanda S, Scholz E, et al. Effect of supplementation with long-chain omega-3 polyunsaturated fatty acids on behavior and cognition in children with attention deficit/hyperactivity disorder (ADHD): a randomized placebo-controlled intervention trial. Prostaglandins Leukot Essent Fatty Acids 2014;91(1-2):49-60. PMID: 24958525.

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Zhang H, Du M and Zhuang S. Impact of long-term treatment of methylphenidate on height and weight of school age children with ADHD. Neuropediatrics 2010;41(2):55-9. PMID: 20799150.

Appendix D. List of Excluded Studies

All studies listed below were reviewed in their full-text version and excluded for the reasons cited. Reasons for exclusion signify only the usefulness of the articles for this study and are not intended as criticisms of the articles.

Not a Full Publication or Full Text Not Available

Ang A, Hillhouse M, Jenkins J, et al. Methylphenidate for methamphetamine use disorders in participants with and without ADHD. Drug and Alcohol Dependence 2015;156:e7.

Bakhshayesh AR, Esser G and Wyschkon A. Effectiveness of EEG-biofeedback in the treatment of attention deficit/hyperactivity disorder. Psychological Research 2010;13(1):7-29.

Bilder RM, Loo S, McGough JJ, et al. Cognitive effects of stimulant, guanfacine, and combined treatment in child and adolescent attention-deficit/hyperactivity disorder. Biological Psychiatry 2016;79(9):158S.

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Appendix E. Key to Included Primary and Companion Articles

*The companion article marked with an asterisk did not individually meet criteria for inclusion but was considered for supplemental information (e.g., methods data pertinent to an included study).

Table E-1. Key to included primary and companion articles

Study Designation	Primary Abstracted Article	Companion Articles
CATTS (Children's ADHD Telemental Health Treatment Study)	Myers, 2015[1]	None
INCA (Impact of Nutrition on Children with ADHD)	Pelsser, 2011[2]	None
MTA (Multimodal Treatment Study)	Molina, 2009[3]	Vitiello, 2012[4] *MTA Cooperative Group, 1999[5]
SOSTRA (SOcial Skills TRaining Attachment)	Storebo, 2012[6]	None
None	Abikoff, 2015[7]	None
None	Abikoff, 2013[8]	None
None	Anand, 2016[9]	None
None	Arcieri, 2012[10]	None
None	Arnold, 2011[11]	None
None	Bai, 2015[12]	None
None	Banaschewski, 2014[13]	None
None	Barragan, 2014[14]	None
None	Beck, 2010[15]	None
None	Berger, 2010[16]	None
None	Bink, 2015[17]	None
None	Bloch, 2012[18]	None
None	Boyer, 2015[19]	Boyer, 2015[20]
None	Bunte, 2013[21]	Bunte, 2013[22]
None	Carballo, 2014[23]	None
None	Castro-Cabrera, 2010[24]	None
None	Caudal, 2011[25]	None
None	Cetin, 2015[26]	None
None	Chacko, 2014[27]	None
None	Chacko, 2009[28]	None
None	Clemow, 2015[29]	None
None	Cortese, 2015[30]	None
None	Didoni, 2011[31]	None
None	dosReis, 2010[32]	None
None	Dovis, 2015[33]	None
None	Duric, 2012[34]	Duric, 2014[35]
None	Dutta, 2012[36]	None
None	Egeland, 2013[37]	Hovik, 2013[38]
None	Ercan, 2014[39]	None
None	Evans, 2016[40]	None
None	Ferrin, 2016[41]	None
None	Ferrin, 2014[42]	None
None	Ferrin, 2012[43]	None
None	Findling, 2010[44]	None

Study Designation	Primary Abstracted Article	Companion Articles
None	Gelade, 2016[45]	None
None	Gevensleben, 2009[46]	Wangler, 2011[47] Gevensleben, 2010[48]
None	Gonzalez, 2013[49]	None
None	Gustafsson, 2010[50]	None
None	Hahn-Markowitz, 2016[51]	None
None	Hammerness, 2012[52]	None
None	Hariri, 2012[53]	None
None	Hiscock, 2015[54]	Papadopoulos, 2015[55]
None	Hong, 2015[56]	None
None	Huang, 2015[57]	None
None	Johnson, 2009[58]	Johnson, 2012[59]
None	Katz, 2010[60]	None
None	Kim, 2015[61]	None
None	Kim, 2015[62]	None
None	Klenberg, 2010[63]	None
None	Li, 2011[64]	None
None	Liechti, 2013[65]	None
None	Manor, 2012[66]	Manor, 2013[67]
None	Markovska-Simoska, 2016[68]	None
None	Martin-Martinez, 2012[69]	None
None	Mautone, 2012[70]	None
None	Milte, 2012[71]	Milte, 2015[72]
None	Mohammadi, 2012[73]	Mostafavi, 2012[74]
None	Mohammadpour, 2016[75]	None
None	Moreno-Garcia, 2015[76]	None
None	Newcorn, 2016[77]	None
None	Oberai, 2013[78]	None
None	Ogrim, 2012[79]	None
None	Ohan, 2011[80]	None
None	Ostberg, 2012[81]	None
None	Pane, 2010[82]	None
None	Park, 2016[83]	None
None	Pfiffner, 2014[84]	None
None	Power, 2012[85]	None
None	Raz, 2009[86]	None
None	Salehi, 2010[87]	None
None	Sallee, 2009[88]	None
None	Sayer, 2016[89]	None
None	Shakibaei, 2015[90]	None
None	Sibley, 2016[91]	None
None	Soliva, 2010[92]	None
None	Steiner, 2014[93]	Steiner, 2014[94]
None	Thorell, 2010[95]	None
None	Tobaiqy, 2011[96]	None
None	Trzepacz, 2011[97]	None
None	van der Donk, 2015[98]	None
None	van Dongen-Boomsma, 2014[99]	None
None	Vidal, 2015[100]	None
None	Webster-Stratton, 2011[101]	None
None	Widenhorn-Muller, 2014[102]	None
None	Zelnik, 2012[103]	None
None	Zhang, 2010[104]	None

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Appendix F. Characteristics of Included Studies

Appendix Table F-1. Characteristics of included studies for KQ 1

Study	Study Design Geographic Location N Completed	Mean Age (Years unless specified)	Gold Standard	Diagnostic Tools	Outcomes (Subgroups analyzed)	Quality
Berger, 2010[1]	Observational Middle East 58	ADHD: 9.86 (SD 1.89) Non-ADHD: 10.50 (SD 1.81)	A neurologic examination, the completion of DSM-based questionnaires by parents and teachers, and neuropsychologic evaluation confirmed the diagnosis.	Continuous Performance Functions Tests TOVA Conners CPT TOVA + Conner's CPT	Overall accuracy Sensitivity False negative	Fair
Bloch, 2012[2]	Observational Middle East 34	Total pop.: 11.5, Min. age: 7 Max. age: 17	Consensus achieved on a structured interview by a psychologist using DSM-IV based assessment and a clinical interview by child and adolescent psychiatrist .	CANTAB TOVA (Test of Variable of Attention)	Sensitivity Specificity False positive False negative	Fair
Bunte, 2013[3]	Observational UK/Europe 251	ADHD: 54.7 months (SD: 8.8) Non-ADHD: 53.1 months (SD: 8.4)	Clinical interview with psychiatrist and psychologist who agreed on diagnosis using K-DBDS semi-structured DSM-4 interview.	Disruptive Behavior Diagnostic Observation Schedule (DB-DOS) Kiddie-Disruptive Behavior Disorder Schedule (K-DBDS)	Sensitivity Specificity AUC (Comorbidity)	Fair
Carballo, 2014[4]	Observational UK/Europe 523	Min. age: 3 Max. age: 17	Positive ADHD diagnosis based exclusively on the ADHD RS-IV which assesses DSM-IV-TR ADHD symptoms.	SDQ	Sensitivity Specificity (ADHD presentation)	Poor
Castro-Cabrera, 2010[5]	Observational Latin America 46	Min. age: 4 Max. age: 15	Medical diagnostic was determined by neurophysiological evaluation based on clinical criteria of DSM IV.	Event-Related Potentials (ERPs)	Overall accuracy Sensitivity Specificity AUC	Fair
Caudal, 2011[6]	Observational UK/Europe 112	ADHD: 8.00 Non-ADHD: 8.70	Children diagnosed with ADHD according to the DSM-IV and further examinations.	Electro-interstitial scans (EIS)	Sensitivity Specificity	Fair
dosReis, 2010[7]	Observational USA 48	Total: 8.8 (SD 2.30)	Unclear/NR	Unclear/NR	Labeling/Stigma	Good

Study	Study Design Geographic Location N Completed	Mean Age (Years unless specified)	Gold Standard	Diagnostic Tools	Outcomes (Subgroups analyzed)	Quality
Ferrin, 2012[8]	Observational Australia/NZ 1,185	ADHD: 131.44 months (SD 38.93 months) Non-ADHD: 133.16 months (SD 27.95 months)	ADHD status was categorically defined by the semistructured clinical interview of their parent's K–SADS–PL, and dimensionally by the Conners Global Index (CGI). The K-SADS-PL is a semi-structured diagnostic interview designed to assess current and past episodes of psychopathology in children and adolescents according to DSM-IV criteria.	Neurological subtle signs (NSS)	Overall accuracy AUC (Age)	Fair
Gonzalez, 2013[9]	Observational UK/Europe 43	Min. age: 4 Max. age: 15	Physical examination, clinical interview and a structured checklist covering DSM-IV and ICD-10 criteria.	EEG IM generalized EEG IM beta band	Overall accuracy Sensitivity Specificity	Fair
Kim, 2015[10]	Observational Asia 157	ADHD: 10.16 (SD 1.90) Non-ADHD: 9.62 (SD 1.72)	ADHD Diagnosis was based on a Korean version of the Diagnostic Interview Schedule for Children Version IV (DISC-IV) and the diagnoses were confirmed by multiple child and adolescent psychiatrists. The DISC-IV uses diagnostic criteria as specified in DSM-IV.	EEG-TGC EEG Delta Wave EEG Theta/beta ratio IVA CPT commission error IVA CPT omission error	Overall accuracy Sensitivity Specificity	Fair
Kim, 2015[11]	Observational Asia 97	ADHD: 9.25 (SD 1.63) Non-ADHD: 9.56 (SD 1.98)	ADHD Diagnosis was based on a Korean version of the Diagnostic Interview Schedule for Children Version IV (DISC-IV) and the diagnoses were confirmed by multiple child and adolescent psychiatrists. The DISC-IV uses diagnostic criteria as specified in DSM-IV.	EEG Theta Wave EEG Delta Wave EEG Theta/beta ratio IVA CPT commission error IVA CPT omission error	Overall accuracy Sensitivity Specificity	Fair
Klenberg, 2010[12]	Observational UK/Europe 916	ADHD: 10.10 (SD 2.40) Non-ADHD: 10.70 (SD 2.50)	Diagnoses were based on structured interviews of parents and children and a parent rating scale (ADHD RS-IV: Home Version) and teacher reports from school.	Attention and Executive Function Rating Inventory (ATTEX)	Overall accuracy Sensitivity Specificity AUC	Good

Study	Study Design Geographic Location N Completed	Mean Age (Years unless specified)	Gold Standard	Diagnostic Tools	Outcomes (Subgroups analyzed)	Quality
Liechti, 2013[13]	Observational UK/Europe 62	ADHD: 11.1 (SD 2.10) Non-ADHD: 11.2 (SD 2.10)	Children with ADHD combined subtype (DSM-IV), aged 8–16 years, were diagnosed using the semi-structured clinical diagnostic interview PACS (parental account of children's symptoms); plus Conners teacher rating scale—revised	EEG + Event Related Potentials (ERPs)	Overall accuracy Sensitivity Specificity	Fair
Markovska-Simoska, 2016 [14]	Observational Latin America 120	ADHD: 9 (SD 2.44)	Team of neuropsychologist, pediatrician and clinical psychologist. Also used Conners rating scale.	EEG TBR Cz EEG absolute theta Cz EEG absolute beta Cz EEG relative theta Cz EEG relative beta Cz	Diagnostic accuracy	Fair
Martin-Martinez, 2012[15]	Observational UK/Europe 63	Total pop.: 6	Case group was diagnosed as having the combined kind of ADHD according to the DSM-IV criteria	Actigraphy - PCA1 [Px00(15 min, D) + Pz22(1 min, FR) + Py01(15 min, AA)]	Overall accuracy Sensitivity Specificity AUC	Poor
Ogrim, 2012[16]	Observational UK/Europe 101	Total pop.: 11 (SD 3.00)	All diagnoses were according to DSM IV-TR and accepted clinical guidelines. A senior neuropsychologist (GO) was responsible for diagnostic conclusions after discussions in the team, which included a pediatrician and a clinical psychologist.	EEG Theta EEG Theta/beta ratio Visual CPT omission error	Overall accuracy	Fair
Ohan, 2011[17]	Observational Canada 56	Not Reported	Not Applicable	Not Applicable	Labeling/Stigma	Good
Park, 2016 [18]	Observational Asia 114	ADHD: 7.6 (SD 1.5)	DSM-4 criteria and Korean version of the K-SADS-PL-K	Advanced Test of Attention, Any Item with SD >1 Advanced Test of Attention, Any Item with SD >1.5 Advanced Test of Attention, Any Item with SD >12	Diagnostic Accuracy	Fair

Study	Study Design Geographic Location N Completed	Mean Age (Years unless specified)	Gold Standard	Diagnostic Tools	Outcomes (Subgroups analyzed)	Quality
Soliva, 2010[19]	Observational UK/Europe 78	ADHD: 10.90 (SD 2.83) Non-ADHD: 11.46 (SD 2.86)	ADHD subjects were diagnosed by a team consisting of a psychologist and a psychiatrist. Scoring was based on parent and teacher rating scales, as well as a semi-structured clinical interview, which systematically reviewed DSM-IV-TR criteria for ADHD, oppositional-defiant disorder, conduct disorder, and depressive and anxiety disorders (DICA-IV).	MRI of Caudate Body Volume	Overall accuracy Sensitivity Specificity (Sex and ADHD presentation)	Fair
Thorell, 2010[20]	Observational UK/Europe 45	Unclear/NR	Children met the symptom criteria, the age of onset criterion (i.e., < 7 years) the pervasiveness criterion (symptoms present in two settings), and the duration criterion (> 6 months) for ADHD according to DSM-IV. Subjects saw a child psychologist and if deemed "at risk" they were given scales to confirm diagnosis.	Childhood Executive Function Inventory (CHEXI)- Parent rating inhibition subscale	Overall accuracy Sensitivity Specificity	Fair
Zelnik, 2012[21]	Observational Middle East 230	Total pop.: 10 (SD 2.70)	Clinical diagnostic work-up included a family interview about the behavioral and neurodevelopmental history of the child, neurological evaluation and observation at the physician's office, utilization of the DSM-IV diagnostic criteria, and employment of the Conners Rating Scales.	TOVA (Test of Variable of Attention)	Sensitivity Specificity False positive False negative	Fair

Abbreviations: ADHD=attention deficit hyperactivity disorder; AUC=area under the curve; DISC-IV=Diagnostic Interview Schedule for Children Version IV; DSM= Diagnostic and Statistical Manual of Mental Disorders; EEG=electroencephalograph; K-DBDS= Kiddie Disruptive Behavior Disorder Schedule; MRI=magnetic resonance imaging; NR=not reported; SD=standard deviation; TBR=theta/beta ratio

Appendix Table F-2. Characteristics of included studies for KQ 2

Study	Study Design Geographic Location N Completed	Percent ADHD Subtype[a]	Mean Age (Years unless specified)	Interventions	Outcomes (Subgroups analyzed)	Quality
Abikoff, 2013[22]	RCT USA 151	Inattentive: 49.4% Combined: 38.9%	Arm 1: 9.06 (SD: 0.91) Arm 2: 9.01 (SD: 0.79) Arm 3: 9.15 (SD: 0.76)	Organizational Skills Training (teaching children new organizational tools and routines) vs. Performance based intervention precluding skill without organizational skills training vs. Waitlist control	Academic performance	Good
Abikoff, 2015[23]	RCT USA 164	Inattentive: 15.3% Hyperactive: 33.7% Combined: 50.9%	Total: 3.57 (SD: 0.5)	New Forest Parenting Package (home-based intervention) vs. Helping the noncompliant child (clinic-based parenting intervention) vs. Waitlist control	Behavior changes	Good
Anand, 2016[24]	RCT Asia 50	Unclear/NR	Unclear/NR	Dietary supplements vs. Atomoxetine	Changes in standardized symptom scores	Good
Arcieri, 2012[25]	Observational UK/Europe 751	Inattentive: 6% Hyperactive: 4% Combined: 90%	Arm 1: 10.41 (SD: 2.62) Arm 2: 10.82 (SD: 2.81) Arm 3: 10.56 (SD: 2.55)	Registry with patients on methylphenidate vs. Registry with patients on strattera vs. In registry taking both methylphenidate and strattera	Cardiac arrhythmias; Elevated blood pressure	Poor
Arnold, 2011[26]	RCT USA 52	Inattentive: 29.1%, 15%, 50% Combined: 70.8%, 85%	Arm 1: 10.24 (SD: 2.69) Arm 2: 9.61 (SD: 3.36) Arm 3: 8.89 (SD: 2.31)	Zinc 15mg once daily vs. Zinc 15mg twice daily vs. Placebo	Changes in standardized symptom scores; Behavior changes; Changes in appetite; Suicide ideation; Sleep disturbance; Tics or other movement disorders; Gastrointestinal symptoms	Fair

Study	Study Design Geographic Location N Completed	Percent ADHD Subtype[a]	Mean Age (Years unless specified)	Interventions	Outcomes (Subgroups analyzed)	Quality
Bai, 2015[27]	RCT Asia 89	Unclear/NR	Arm 1: 9.3 (SD: 2.8) Arm 2: 9.6 (SD: 2.9)	Planned behavior psychoeducation program for parents vs. General clinical counseling for parents, without psychoeducation	Changes in standardized symptom scores; Acceptability of treatment	Good
Banaschewski, 2014[28]	RCT USA, UK/Europe 73	Unclear/NR	Total: 11.1 (SD: 2.59)	Randomized to Lisdexamfetamine dimesylate (LDX) after 52 weeks of being on the drug (vs. withdrawal on placebo--see below) vs. Randomized to placebo after 52 weeks of being on LDX.	Quality of peer relationships; Risk-taking behaviors	Poor
Barragan, 2014[29]	RCT Latin America 69	Unclear/NR	Total: 8.27 (SD: 1.74)	Methylphenidate (maximum 1 mg/kg/day) vs. Methylphenidate (maximum 1 mg/kg/day and omega 3/6 fatty acid supplementation (6 capsules/day) vs. Omega 3/6 fatty acid supplementation (6 capsules/day)	Changes in appetite; Behavior changes; Sleep disturbance; Gastrointestinal symptoms; Changes in standardized symptom scores	Poor
Beck, 2010[30]	Observational USA 51	Inattentive: 71% Hyperactive: 0% Combined: 29%	Total: 11.75	Computer-based working memory intervention vs. Waitlist control	Changes in standardized symptom scores	Fair
Bink, 2015[31]	RCT UK/Europe 71	Unclear/NR	Arm 1: 16.1 (SD: 3.3) Arm 2: 16.2 (SD: 3.4)	Neurofeedback (NF) plus treatment as usual. NF training over about 25 wks, with 2-3 training sessions/wk. Participants offered 40 training sessions of 30 minutes. Mean # of sessions was 37 (minimum 19). Theta/sensorimotor rhythm training was applied. vs. Treatment as usual	Changes in standardized symptom scores	Good
Boyer, 2015[32]	RCT UK/Europe 136	Inattentive: 74.7%, 65.8% Hyperactive: 7.2%, 2.6% Combined: 18.1%, 31.6%	Arm 1: 14.4 (SD: 1.2) Arm 2: 14.4 (SD: 1.3)	CBT with an aim to improve planning skills vs. Solution-focused CBT without an aim to improve planning skills	Depression or anxiety; Changes in standardized symptom scores	Fair

Study	Study Design Geographic Location N Completed	Percent ADHD Subtype[a]	Mean Age (Years unless specified)	Interventions	Outcomes (Subgroups analyzed)	Quality
Çetin, 2015[33]	RCT Middle East 120	Inattentive: 12.5% Combined: 87.5%	Arm 1: 9.55 (SD: 2.71) Arm 2: 9.95 (SD: 2.02)	Atomoxetine (ATX) vs. Osmotic release oral system methylphenidate (OROS-MPH)	Changes in standardized symptom scores	Fair
Chacko, 2014[34]	RCT USA 73	Inattentive: 34%, 41% Combined: 66%, 59%	Arm 1: 8.4 (SD: 1.4) Arm 2: 8.4 (SD: 1.3)	Cogmed working memory training with difficulty titrated to a user's ability vs. "Placebo" cogmed working memory training with difficulty not titrated to a user's ability	Changes in standardized symptom scores; Academic performance	Good
Chacko, 2009[35]	RCT USA 118; 115 follow-up	Unclear/NR	Arm 1: 7.36 (SD: 1.86) Arm 2: 8.17 (SD: 2.42) Arm 3: 8.02 (SD: 2.15)	Strategies to Enhance Positive Parenting (STEPP) program (a manualized, behavioral parent training program for single mothers) with concurrent group social skills program for children vs. Behavioral parent training program with concurrent group social skills program for children vs. Waitlist control	Changes in standardized symptom scores; Acceptability of treatment	Good
Clemow, 2015[36]	Observational USA 71	Inattentive: 48.1%, 51.9% Combined: 26%, 38.9%	Arm 1: 24.0 (SD: 15.3) Arm 2: 26.2 (SD: 15.2)	First prescribed atomoxetine (ATX) and not switched or the monotherapy portion of time spent by those prescribed ATX with another ADHD drug and then was switched to ATX only. vs. First prescribed ATX with another drug and did not switch or the combination portion of time spent by those who were first prescribed ATX and then had another ADHD prescribed.	Changes in standardized symptom scores	Poor
Cortese, 2015[37]	Observational UK/Europe 2411	Inattentive: 11.5%, 11.9% Hyperactive: 2.4%, 5.2% Combined: 85.9%, 82.7%	Arm 1: 10.55 (SD: 2.75) Arm 2: 10.87 (SD: 2.84)	Methylphenidate immediate release, at a dosage of 0.3-0.6 mg/kg/dose/day, in 2-3 doses/day vs. Atomoxetine, starting with 0.5mg/kg daily for at least 7 days, then increasing up to 1.2mg/kg/day	Cardiac arrhythmias	Good

Study	Study Design Geographic Location N Completed	Percent ADHD Subtype[a]	Mean Age (Years unless specified)	Interventions	Outcomes (Subgroups analyzed)	Quality
Didoni, 2011[38]	Observational UK/Europe 229	Inattentive: 11.7%, 14.5% Hyperactive: 8.8%, 6.2% Combined: 79.4%, 70.1%	Arm 1: 10.7 (SD: 2.7) Arm 2: 11 (SD: 2.7)	Methylphenidate vs. Strattera	Acceptability of treatment; Changes in appetite; Behavior changes; Sleep disturbance; Increased heart rate; Gastrointestinal symptoms; Tics or other movement disorders	Fair
Dovis, 2015[39]	RCT UK/Europe 89	Combined: 0%, 100%, 100%	Arm 1: 10.6 (SD: 1.4) Arm 2: 10.3 (SD: 1.3) Arm 3: 10.5 (SD: 1.3)	"Braingame Brian" (computerized, home-based executive functioning training) vs. Braingame Brian in training mode and the working memory task in placebo mode vs. All tasks in training mode (overall easier)	Behavior changes	Good
Duric, 2012[40]	RCT UK/Europe 91	Inattentive: 5.4% Hyperactive: 15.4% Combined: 79.1%	Arm 1: 10.9 (SD: 2.4) Arm 2: 11.2 (SD: 2.8) Arm 3: 11.4 (SD: 3.1)	MPH (dose not reported) vs. MPH + Neurofeedback vs. Neurofeedback	Changes in standardized symptom scores	Poor
Dutta, 2012[41]	RCT Asia 86	Unclear/NR	Arm 1: 8 (SD: 1.12) Arm 2: 9.1 (SD: 1.1)	Memomet syrup (Bacopa monniera 125 mg, Convulvulus pleuricaulis 100 mg, Centella asiatica 100 mg) vs. Placebo	Changes in standardized symptom scores	Good
Egeland, 2013[42]	RCT UK/Europe 67	Unclear/NR	Arm 1: 10.5 (SD: 0.7) Arm 2: 10.3 (SD: 0.8)	Cogmed robomemo program vs. Waitlist control	Changes in standardized symptom scores	Good
Ercan, 2014[43]	Observational UK/Europe 45	Combined: 100%	Arm 1: 9.23 (SD: 2) Arm 2: 8.7 (SD: 1.7)	MPH+11 months of parent training vs. MPH (Usual care)	Changes in standardized symptom scores	Fair

Study	Study Design Geographic Location N Completed	Percent ADHD Subtype[a]	Mean Age (Years unless specified)	Interventions	Outcomes (Subgroups analyzed)	Quality
Evans, 2016[44]	RCT USA 312	Combined: 49.1%, 50%, 47.1%	Arm 1: 12.1 (SD: 0.9) Arm 2: 12.1 (SD: 0.9) Arm 3: 12.2 (SD: 1.0)	Challenging Horizons Program-After School (CHP-AS) program (organization, social functioning, and academic study skills training) vs. Challenging Horizons Program Mentoring Version (students paired with a mentor who delivered a subset of the CHP-AS interventions during school) vs. Usual care	Functional impairment; Academic performance	Fair
Ferrin, 2014[45]	RCT UK/Europe 76	Combined: 72.1%, 81.1%	Arm 1: 11.25 (SD: 2.96) Arm 2: 9.94 (SD: 3.04)	Psychoeducational program vs. Parent support group	Changes in standardized symptom scores	Good
Ferring, 2016[46]	RCT UK/Europe 62	Combined: 60.0%, 79.41%	Arm 1: 10.86 (SD 3.04) Arm 2: 10.56 (SD 3.20)	Psychosocial interventions vs. Usual care	Changes in standardized symptom scores	Good
Findling, 2010[47]	RCT USA 230	Combined: 96%	Min. age: 8.7 Max. age: 9.4	Lisdexamfetamine dimesylate (LDX) 30mg/day vs. Lisdexamfetamine dimesylate (LDX) 50mg/day vs. Lisdexamfetamine dimesylate (LDX) 70mg/day vs. Placebo	Changes in standardized symptom scores	Fair
Gelade, 2016[48]	RCT UK/Europe 103	Unclear/NR	Unclear/NR	Biofeedback or neurofeedback vs. Methylphenidate vs. Exercise	Sleep disturbance; Behavior changes	Good
Gevensleben, 2009[49]	RCT UK/Europe 94	Inattentive: 33.8%, 22.8% Combined: 66.1%, 77.1%	Arm 1: 9.10 (SD: 1.3) Arm 2: 9.4 (SD: 1.2)	Neurofeedback vs. Attention skills training	Changes in standardized symptom scores; Acceptability of treatment	Good

Study	Study Design Geographic Location N Completed	Percent ADHD Subtype[a]	Mean Age (Years unless specified)	Interventions	Outcomes (Subgroups analyzed)	Quality
Gustafsson, 2010[50]	RCT UK/Europe 82	Unclear/NR	Min. age: 7 Max. age: 12	Omega-3 fatty acid supplementation (eicosapentaenoic acid 500 mg daily) vs. Placebo	Changes in standardized symptom scores	Good
Hahn-Markowitz, 2016[51]	RCT Middle East 99	Inattentive: 43%, 55% Hyperactive: 4%, 6% Combined: 54%, 40%	Arm 1: 8.4 (SD 0.9) Arm 2: 8.6 (SD 0.8)	Cognitive training therapies vs. Waitlist	Changes in standardized symptom scores	Good
Hammerness, 2012[52]	Observational USA 115	Unclear/NR	Arm 1: 15.5 (SD: 1.7) Arm 2: 14.9 (SD: 3.4 Arm 3: 15.7 (SD: 2.7) Arm 4: 14.8 (SD: 2.9)	Clinical Trial Participant on MPH vs. Non-clinical trial participants on medication vs. Non-clinical trial participants not on medication vs. Non ADHD Group	Substance abuse	Fair
Hariri, 2012[53]	RCT Middle East 103	Unclear/NR	Arm 1: 7.9 (SD: 1.53) Arm 2: 7.9 (SD: 1.45)	Omega-3 fatty acid supplementation (900 mg daily) vs. Placebo	Changes in standardized symptom scores	Poor
Hiscock, 2015[54]	RCT Australia/NZ 196	Unclear/NR	Arm 1: 10.3 (SD: 1.8) Arm 2: 9.9 (SD: 2.1) Arm 3: 10.3 (SD: 1.7) Arm 4: 9.8 (SD: 2.0)	Sleep hygiene vs. Usual care	Changes in standardized symptom scores; Depression or anxiety; Workforce participation; Sleep disturbance (Comorbidity)	Good
Hong, 2015[55]	RCT Asia 48	Unclear/NR	Arm 1: 10.87 (SD 2.86) Arm 2: 11.11 (SD 2.79)	Acupuncture vs. Usual care	Changes in standardized symptom scores	Fair

Study	Study Design Geographic Location N Completed	Percent ADHD Subtype[a]	Mean Age (Years unless specified)	Interventions	Outcomes (Subgroups analyzed)	Quality
Huang, 2015[56]	RCT Asia 97	Inattentive: 13.3%, 25% Combined: 86.7%, 75%	Arm 1: 8.2 (SD: 0.9) Arm 2: 8.5 (SD: 0.9)	Behavioral based social skill training for patients and parallel parent group sessions vs. Group therapy for motivation and treatment per their usual care	Changes in standardized symptom scores	Fair
Johnson, 2009[57]	RCT UK/Europe 59	Inattentive: 24%, 29% Hyperactive: 0%, 0% Combined: 25%, 21%	Arm 1: 11.8 (SD: 2.14) Arm 2: 12.2 (SD: 2.19)	Omega-3/6 fatty acid supplementation (792 mg daily) vs. Placebo	Changes in standardized symptom scores; Functional impairment	Good
Katz, 2010[58]	RCT Middle East 92	Unclear/NR	Arm 1: 9.72 (SD: 1.58) Arm 2: 9.20 (SD: 1.82)	Patented herbal preparation vs. Placebo	Motor vehicle collisions; Changes in appetite; Gastrointestinal symptoms; Sleep disturbance; Mood disorders	Fair
Li, 2011[59]	RCT Asia 69	Unclear/NR	Arm 1: 9.3 (SD: 1.8) Arm 2: 9.2 (SD: 2.2)	Methylphenidate 1 mg/kg/day vs. Ningdong granule (a traditional Chinese medicine preparation)	Chemical leukoderma; Changes in standardized symptom scores; Gastrointestinal symptoms; Sleep disturbance; Behavior changes; Changes in appetite	Good

Study	Study Design Geographic Location N Completed	Percent ADHD Subtype[a]	Mean Age (Years unless specified)	Interventions	Outcomes (Subgroups analyzed)	Quality
Manor , 2012[60]	RCT Middle East 162	Inattentive: 31%, 34% Hyperactive: 3%, 0% Combined: 66%, 65.9%	Arm 1: 9.2 (SD: 2.0) Arm 2: 9.2 (SD: 1.8)	PS-Omega 3 vs. Placebo	Chemical leukoderma; Changes in standardized symptom scores; Elevated blood pressure; Increased heart rate; Weight decrease; Growth suppression; Sleep disturbance; Behavior changes; Changes in appetite; Gastrointestinal symptoms; Tics or other movement disorders; Personality change	Good
Mautone, 2012[61]	RCT USA 53	Inattentive: 10.3%, 15.6% Hyperactive: 27.6%, 28.1% Combined: 62.1%, 56.3%	Unclear NR	Family-School Success—Early, Elementary (school-based intervention) vs. Parent support and education program	Academic performance	Fair
Milte, 2012[62]	RCT Australia/NZ 70	Unclear/NR	Arm 1: 8.77 (SD: 1.76) Arm 2: 8.89 (SD: 1.6) Arm 3: 9.14 (SD: 2.03)	Fish oil rich in the omega-3 fatty acid, eicosapentaenoic acid vs. Fish oil rich in the omega-3 fatty acid, docosahexaenoiacid vs. Safflower oil	Changes in standardized symptom scores	Good

Study	Study Design Geographic Location N Completed	Percent ADHD Subtype[a]	Mean Age (Years unless specified)	Interventions	Outcomes (Subgroups analyzed)	Quality
Mohammadi, 2012[63]	RCT Middle East 50	Combined: 100%	Arm 1 Median: 9.57 (SD: 1.65) Arm 2 Median: 8.83 (SD: 1.82)	MPH + melatonin vs. MPH+placebo	Changes in standardized symptom scores; Sleep disturbance; Changes in appetite; Weight decrease; Gastrointestinal symptoms; Behavior changes; Tics or other movement disorders	Fair
Mohammadpour, 2016[64]	RCT Middle East 54	Unclear/NR	Arm 1: 7.70 (SD 1.77) Arm 2: 8.03 (SD 1.44)	Dietary supplements vs. Placebo	Changes in standardized symptom scores, Behavior changes	Fair
Molina, 2009[65]	RCT USA 346 at 10-year follow-up; 436 at 8-year follow-up	Unclear/NR	Total: 16.8 (SD: 1.0)	Medication Management vs. Behavioral training(parent group, parent individual, classroom (student), and teacher sessions) vs. Combination: Medication management and Behavioral training vs. Usual care	Aggression; Incarceration; Depression or anxiety; Academic performance; Motor vehicle collisions; Elevated blood pressure; Increased heart rate	Fair
Moreno-García, 2015[66]	RCT UK/Europe 57	Inattentive: 42.1 %, 42.1%, 57.9% Hyperactive: 21.05%, 15.78%, 15.78% Combined: 36.84%, 42.10%, 26.31%	Arm 1: 9.21 (SD: 1.9) Arm 2: 9.21 (SD: 2.2) Arm 3: 8.11 (SD: 1.3)	Neurofeedback vs. Standard Pharmacological Treatment vs. Behavioral Treatment	Changes in standardized symptom scores	Fair

Study	Study Design Geographic Location N Completed	Percent ADHD Subtype[a]	Mean Age (Years unless specified)	Interventions	Outcomes (Subgroups analyzed)	Quality
Myers, 2015[67]	RCT USA NR	Inattentive: 82.8%, 82.1% Hyperactive: 66.6%, 58% Combined: 60.3%, 51.8%	Arm 1: 9.2 (SD: 2) Arm 2: 9.3 (SD: 2)	6 telehealth sessions using both synchronous and asynchronous technologies vs. Single consultation with a tele-psychiatrist	Behavior changes	Fair
Newcorn, 2016[68]	RCT USA, Canada, UK/Europe 129	Inattentive: 12.7%, 11.4% Hyperactive: 2.5%, 5.1% Combined: 84.7%, 83.5%	Arm 1: 10.7 (SD 2.64) Arm 2: 11.0 (SD 2.69)	Psychosocial interactions vs. Usual care	Changes in standardized symptom scores	Fair
Oberai, 2013[69]	RCT Asia 54	Unclear/NR	Arm 1: 8.6 (SD: 2.2) Arm 2: 9.9 (SD: 2.8)	Homeopathy vs. Placebo	Behavior changes	Fair
Ostberg, 2012[70]	RCT UK/Europe 61	Unclear/NR	Arm 1: 11.1 (SD: 2.1) Arm 2: 10.8 (SD: 1.8)	Barkley Parent + Teacher behavioral intervention vs. Waitlist control	Changes in standardized symptom scores	Good
Pane, 2010[71]	Observational UK/Europe 1424	Inattentive: 11.7% Hyperactive: 5% Combined: 83.3%	Median: 10.8 Min. age: 6 Max. age: 18	Atomoxetine vs. Methylphenidate	Suicide ideation; Conduction abnormalities; Tics or other movement disorders; Changes in appetite; Gastrointestinal symptoms; Elevated blood pressure	Fair

Study	Study Design Geographic Location N Completed	Percent ADHD Subtype[a]	Mean Age (Years unless specified)	Interventions	Outcomes (Subgroups analyzed)	Quality
Pelsser, 2011[72]	RCT UK/Europe 100 analyzed in first phase	Inattentive: 6%, 6% Hyperactive: 12%, 6% Combined: 82%, 88%	Arm 1: 6.8 (SD: 1.3) Arm 2: 7.0 (SD: 1.3)	Restricted elimination diet vs. No elimination diet	Changes in standardized symptom scores (ADHD Presentation)	Good
Pfiffner, 2014[73]	RCT USA 195	Inattentive: 100%	Arm 1: 8.8 (SD: 1.2) Arm 2: 8.7 (SD: 1.2) Arm 3: 8.4 (SD: 1.1)	Child Life and Attention Skills Treatment for children and parents vs. Child Life and Attention Skills Treatment—parents group component only vs. Usual care	Changes in standardized symptom scores; Functional impairment	Good
Power, 2012[74]	RCT USA 181	Inattentive: 55%, 48.5% Combined: 45%, 51.5%	Unclear NR	Family-School Success—Early, Elementary (school-based intervention) vs. Parent support and education program	Changes in standardized symptom scores; Academic performance	Fair
Raz, 2009[75]	RCT Middle East 63	Inattentive: 94%, 94% Hyperactive: 44%, 47%	Arm 1: 10.46 (SD: 1.42) Arm 2: 10.51 (SD: 1.47)	Omega-3 fatty acid supplementation vs. Placebo	Changes in standardized symptom scores	Fair
Salehi, 2010[76]	RCT Middle East 46	Unclear/NR	Arm 1: 9.12 (SD: 1.61) Arm 2: 9.61 (SD: 2.26)	Ginkgo biloba vs. MPH (up to 30 mg/day)	Changes in standardized symptom scores; Changes in appetite; Depression or anxiety; Sleep disturbance; Weight decrease	Good

Study	Study Design Geographic Location N Completed	Percent ADHD Subtype[a]	Mean Age (Years unless specified)	Interventions	Outcomes (Subgroups analyzed)	Quality
Sallee, 2009[77]	RCT Unclear/NR 60	Inattentive: 23.9% Hyperactive: 3.1% Combined: 73%	Total: 10.7 (SD: 2.6)	Guanfacine XR 1 mg/day with or without amphetamine or MPH vs. Guanfacine XR 2 mg/day with or without amphetamine or MPH vs. Guanfacine XR 3 mg/day with or without amphetamine or MPH vs. Guanfacine XR 4 mg/day with or without amphetamine or MPH	Changes in standardized symptom scores	Poor
Sayer, 2016[78]	RCT USA NR	Unclear/NR	Total: 10.2 (SD 2.1)	Guanfacine immediate release Vs. Dexmethylphenidate Vs. Dexmethylphenidate, guanfacine immediate release	Increased heart rate	Good
Shakibaei, 2015[79]	RCT Middle East 60	Unclear/NR	Arm 1: 7.83 (SD: 1.12) Arm 2: 8.41 (SD: 1.40)	Methylphenidate and Ginkgo Biloba vs. Methylphenidate and placebo	Behavior changes	Good
Sibley, 2016[80]	RCT USA 109	Unclear/NR	Arm 1: 12.65 (SD: 0.85) Arm 2: 12.85 (SD 0.87)	Behavioral interventions, mindfulness-based therapies, and parent behavior training vs. Usual care	Changes in standardized symptom scores; Academic performance	Fair
Steiner, 2014[81]	RCT USA 98	Unclear/NR	Arm 1: 8.4 (SD: 1.1) Arm 2: 8.9 (SD: 1.0) Arm 3: 8.4 (SD: 1.1)	Neurofeedback vs. Cognitive Training vs. Waitlist control	Changes in standardized symptom scores	Good
Storebo, 2012[82]	RCT UK/Europe 55	Inattentive: 35.7%, 22.2% Hyperactive: 0%, 7.4% Combined: 31.4%, 59.2%	Arm 1: 10.6 (SD: 1.29) Arm 2: 10.2 (SD: 1.34)	Social Skills Group vs. Usual care	Academic performance	Good

Study	Study Design Geographic Location N Completed	Percent ADHD Subtype[a]	Mean Age (Years unless specified)	Interventions	Outcomes (Subgroups analyzed)	Quality
Tobaiqy, 2011[83]	Observational UK/Europe 200	Unclear/NR	Max. age: 16	No arms. Questionnaire administered to elicit retrospective data to assess self-reported AEs for many different drugs used for ADHD.	Changes in standardized symptom scores	Fair
Trzepacz, 2011[84]	RCT UK/Europe, Australia/NZ 394	Inattentive: 23.1%, 19.4% Hyperactive: 4.6%, 5.3% Combined: 7.1%, 75.2%	Arm 1 Median: 10.6 (SD: 2.3) Arm 2 Median: 10.2 (SD: 2.2)	12 month follow up on atomoxetine after 3 month initial trial vs. 12 month follow up on placebo after 3 month initial trial	Growth suppression; Changes in appetite; Gastrointestinal symptoms	Fair
van der Donk, 2015[85]	RCT UK/Europe 100	Inattentive: 30%, 20% Combined: 58%, 70%	Arm 1: 9.8 (SD: 1.3) Arm 2: 10.0 (SD: 1.3)	Cogmed Working Memory Training vs. Paying Attention in Class (experimental, combined working memory and compensatory training)	Changes in standardized symptom scores	Fair
van Dongen-Boomsma, 2014[86]	RCT UK/Europe 47	Inattentive: 7.7%, 9.5% Hyperactive: 11.5%, 33.3% Combined: 80.8%, 57.1%	Arm 1: 6.5 (SD: 0.6) Arm 2: 6.6 (SD: 0.7)	Cogmed training program vs. Cogmed training program without adjustment to patient skill level (control group)	Changes in standardized symptom scores	Good
Vidal, 2015[87]	RCT UK/Europe 89	Inattentive: 35.6%, 0% Hyperactive: 1.7%, 41.6% Combined: 62.7%, 58.3%	Arm 1: 17.47 (SD: 1.88) Arm 2: 16.9 (SD: 1.75)	CBT vs. Usual care	Behavior changes	Good
Webster-Stratton, 2011[88]	RCT USA 94	Unclear/NR	Arm 1: 64.1 months (SD: 11.3) Arm 2: 64.4 months (SD: 10.6)	Increadible Years Program (a parent training intervention) vs. Waitlist control	Changes in standardized symptom scores	Fair
Widenhorn-Muller, 2014[89]	RCT UK/Europe 95	Inattentive: 54.7% Hyperactive: 2.1% Combined: 43.2%	Arm 1: 8.90 (SD: 1.48) Arm 2: 8.92 (SD: 1.24)	Omega-3 fatty acid supplementation (720 mg daily) plus 15 mg vitamin E vs. Placebo	Changes in standardized symptom scores	Fair

Study	Study Design Geographic Location N Completed	Percent ADHD Subtype[a]	Mean Age (Years unless specified)	Interventions	Outcomes (Subgroups analyzed)	Quality
Zhang, 2010[90]	Observational Asia 175	Inattentive: 16.4%, 24.1% Hyperactive: 8.9%, 27.6% Combined: 74.7%, 48.3%	Arm 1: 7.42 Min. age: 6.0 Max. age: 9.8 Arm 2: 8.35 Min. age: 6.0 Max. age: 12.5	Methylphenidate, 10-20 mg/d, 0.27-0.64 mg/kg for about 40 wks/yr (they also took a drug holiday). vs. Control	Growth suppression	Poor

[a]Multiple values are listed for percent female and age in instances where baseline data is reported by study arm rather than for the total population.
Abbreviations: ADHD=attention deficit hyperactivity disorder; AE=adverse events; ATX=atomoxetine; CBT=cognitive behavioral therapy; MPH=methylphenidate; NF=neurofeedback; NR=not reported; RCT=randomized controlled trial; SD=standard deviation; XR=extended release

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Appendix G. Overview of Included Studies

Table G-1. Overview of included studies in KQ 1

Study descriptions	Number of studies
Overview of all studies	
Single center	20[1-20]
Multiple centers	1[21]
Primary care setting	5[3,7,11,15,18]
Specialty practice	12[1,2,4,8-10,12,14-16,18,19]
Community setting	3[3,15,21]
School setting	5[6,11,19-21]
Unclear or unknown location	3[5,13,17]
Asia	3[1,7,16]
Australia/NZ	1[2]
Canada	1[20]
Latin America	2[6,17]
Middle East	3[8-10]
United States	1[18]
UK/Europe	10[3-5,11-15,19,21]
Government funding	4[1-3,18]
Non-government/non-industry funding	4[6,16,17,19]
Combination of funding sources:	
Government/non-government	2[4,5]
Government/industry	1[21]
Unclear/NR	10[7-15,20]
Good quality	3[18-20]
Fair quality	16[1-3,6-17,21]
Poor quality	2[4,5]
Studies examining diagnostic accuracy	
Gold standard based on DSM-IV diagnostic criteria:	
ADHD-Rating Scale	2[4,19]
Conners Teacher Rating Scale	2[9,21]
K-DBDS	1[11]
K-SADS-PL	2[2,16]
Disc-IV	2[1,7]
DICA-IV	1[14]
Structured checklist	1[3]
Specific ratings scales not reported (included mixture of parent/teacher scales, clinical evaluations, and various DSM-IV criteria checklists)	8[5,6,8,10,12,13,15,17]
Diagnosis confirmed by specialist	13[1,3,6-12,14,16,17,19]
Diagnosis confirmed by other care provider	1[12]
Unclear validation of diagnosis	7[2-5,13,15,21]
Subgroups	
Age	1[2]
Sex	1[14]
ADHD subtype	2[4,14]
Comorbidity	1[11]

Table G-2. Overview of included studies in KQ 2

Study descriptions	Number of studies
Overview of all studies	
Single center	36[22-57]
Multiple centers	31[58-88]
NR or unclear	2[89,90]
Primary care setting	9[23-25,30,52,57,63,69,81]
Specialty practice	41[22,26-28,32-35,37-42,44,46-51,53,56,58-60,62,64,66,72,73,75-78,80,82,83,86-88]
Community setting	1[43]
School setting	4[45,65,68,85]
Other location	5[54,61,67,79,86]
Specialty practice/school setting	1[64]
Specialty practice/other location	1[55]
Unclear	9[29,31,36,70,71,74,84,89,90]
Asia	8[22-26,54,57,58]
Australia/NZ	2[59,60]
Latin America	1[27]
Middle East	10[28-34,61,87,88]
United States	19[35-43,55,62-69,85]
UK/Europe	25[44-53,56,71-82,89,90]
UK/Europe and United States	2[70,86]
UK/Europe and Australia/NZ	1[83]
Unclear	1[84]
Government funding	30[30,37,38,40,42,45-48,50-52,55,56,58-60,63-68,72-74,78,81,85,89]
Industry	9[27,31,35,62,69,70,83,84,86]
Non-government/non-industry funding	8[24,28,33,53,54,87,88,90]
Combination of funding sources:	
Industry/government/non-government	1[23]
Non-government/industry	1[80]
Government/non-government	2[43,79]
Unclear/NR	18[22,25,26,29,32,34,36,39,41,44,49,57,61,71,75-77,82]
Good quality	32[23,25,28,31,33,37,38,43,47-49,51,53,55-60,64-66,71,75,76,78-82,87,90]
Fair quality	30[24,26,30,32,34-36,39-42,44-46,52,54,61,63,67-69,72-74,77,83,85,86,88]
Poor quality	7[22,27,29,62,70,84,89]

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Appendix H. Data Tables

Table H-1. Diagnostic accuracy of included studies with subjects ages 6 and under

Quality (Study)[a] N Subjects Diagnostic Tool(s)	Gold Standard	Overall Accuracy	AUC	Sensitivity	Specificity	PPV	NPV
Observational assessment studies							
Fair quality (Bunte, 2013[1,2]) 178 subjects (120 ADHD, 58 non-ADHD) 1. Disruptive Behavior – Diagnostic Observation Schedule	Clinical interview with psychiatrist and psychologist who agreed on diagnosis using K-DBDS semi-structured DSM-4 interview		92%	87%	79%		
Executive function studies							
Fair quality (Thorell, 2010[3]) 52 subjects (22 ADHD, 30 non-ADHD) 1. Childhood Executive Function Inventory– Parent rating inhibition subscale	Children met the symptom criteria, the age of onset criterion (i.e., <7 years) the pervasiveness criterion (symptoms present in two settings), and the duration criterion (>6 months) for ADHD according to DSM-IV. Subjects saw a child psychologist and if deemed "at risk" they were given scales to confirm diagnosis.	93.3%		93.3%	93.3%		
Standardized questionnaire studies							
Fair quality (Bunte, 2013[1,2]) Subgroup = ADHD subtypes 168 subjects (110 ADHD HI, 58 non-ADHD) 1. Kiddie-Disruptive Behavior Disorder Schedule (K-DBDS) – specific coding method	Clinical interview with psychiatrist and psychologist who agreed on diagnosis using K-DBDS semi-structured DSM-4 interview		98% (ADHD-HI)	77% (ADHD-HI)	98% (ADHD-HI)		

[a] See Methods section "Quality Assessment of Individual Studies" for definitions of quality assessment ratings.

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

Table H-2. Diagnostic accuracy of included studies with subjects ages 7-17

Quality (Study)[a] N Subjects Diagnostic Tool(s)	Gold Standard	Overall Accuracy	AUC	Sensitivity	Specificity	PPV	NPV
Biometric devices							
Poor quality (Martin-Martinez, 2012[4]) 63 subjects (31 ADHD, 32 non-ADHD) 1. Actigraphy-PCA1 [Px00(15 min, D) + Pz22 (1 min, FR) + Py01 (15 min, AA)]	Case group was diagnosed as having the combined kind of ADHD according to the DSM-IV criteria	90.48%	94.96%	96.77%	84.38%		
EEG and imaging studies							
Fair quality (Markovska-Simoska, 2016[5]) 60 subjects (30 ADHD, 30 non-ADHD) 1. EEG Theta-Beta Ratio 2. EEG absolute theta 3. EEG absolute beta 4. EEG relative theta 5. EEG relative beta	Team of neuropsychologist, pediatrician and clinical psychologist. Also used Conners rating scale			58.6% 100% 86.2% 68.6% 0%	92.2% 71.1% 34.4% 60.0% 100%		
Fair quality (Gonzalez, 2013[6]) 43 subjects (22 ADHD, 21 non-ADHD) 1. EEG IM generalized 2. EEG IM beta band	Physical examination, clinical interview and a structured checklist covering DSM-IV and ICD-10 criteria	86.7% 74.4%		81.80% 63.60%	90.50% 90.50%		

Quality (Study)[a] N Subjects Diagnostic Tool(s)	Gold Standard	Overall Accuracy	AUC	Sensitivity	Specificity	PPV	NPV
Fair quality (Liechti, 2013[7]) 62 subjects (32 ADHD, 30 non-ADHD) 1. EEG + event-related potentials–including all stepwise variables	Children with ADHD combined subtype (DSM-IV), aged 8–16 years, were diagnosed using the semi-structured clinical diagnostic interview PACS (parental account of children's symptoms; plus Conners teacher rating scale—revised	72.6%		71.9%	73.3%		
Fair quality (Castro-Cabrera, 2010[8]) 46 subjects (23 ADHD, 23 non-ADHD) 1. Event-related potentials–best combination of features	Medical diagnostic was determined by neurophysiological evaluation based on clinical criteria of DSM IV	91.3%	94%	96%	87%		
Fair quality (Soliva, 2010[9]) Subgroup = ADHD subtypes 78 subjects (39 ADHD, 39 non-ADHD) 1. MRI of caudate body volume	ADHD subjects were diagnosed by a team consisting of a psychologist and a psychiatrist. Scoring was based on parent and teacher rating scales, as well as a semi-structured clinical interview, which systematically reviewed DSM-IV-TR criteria for ADHD, oppositional-defiant disorder, conduct disorder, and depressive and anxiety disorders (DICA-IV).	84%		60.0%	95.0%		
EEG, imaging, and CPT studies							

Quality (Study)[a] N Subjects Diagnostic Tool(s)	Gold Standard	Overall Accuracy	AUC	Sensitivity	Specificity	PPV	NPV
Fair quality (Kim, 2015[10]) 97 subjects (53 ADHD, 44 non-ADHD) 1. EEG theta-phase gamma-amplitude coupling 2. EEG delta wave 3. EEG theta/beta ratio 4. IVA CPT commission error 5. IVA CPT omission error	ADHD Diagnosis was based on a Korean version of the Diagnostic Interview Schedule for Children Version IV (DISC-IV) and the diagnoses were confirmed by multiple child and adolescent psychiatrists. The DISC-IV uses diagnostic criteria as specified in DSM-IV.	71.1% 63.3% 58.7% 75.3% 68.1%		60% 56% 49% 66% 58%	23% 27% 30% 18% 27%		
Fair quality (Kim, 2015[11]) 157 subjects (85 ADHD, 72 non-ADHD) 1. EEG delta wave 2. EEG theta wave 3. EEG theta/beta ratio 4. IVA CPT commission error 5. IVA CPT omission error	ADHD Diagnosis was based on a Korean version of the Diagnostic Interview Schedule for Children Version IV (DISC-IV) and the diagnoses were confirmed by multiple child and adolescent psychiatrists. The DISC-IV uses diagnostic criteria as specified in DSM-IV.	60.8% 56.4% 45.7% 82.1% 78.6%		60.1% 48.2% 47.1% 68.1% 64.7%	43.0% 40.5% 49.4% 9.54% 13.7%		
Fair quality (Ogrim, 2012[12]) 101 subjects (62 ADHD, 39 non-ADHD) 1. EEG theta 2. EEG theta/beta ratio 3. Visual CPT omission error	All diagnoses were according to DSM IV-TR and accepted clinical guidelines. A senior neuropsychologist (GO) was responsible for diagnostic conclusions after discussions in the team, which included a pediatrician and a clinical psychologist.	63% 58% 85%					
CPT studies							
Fair quality (Park, 2016[13]) Subgroups = ADHD subtype 114 subjects (79 ADHD, 35 non-ADHD) 1. Advanced Test of Attention	DSM-4 criteria and Korean version of the K-SADS-PL-K	72.8%		84.8%	45.7%	77.9%	57.1%

Quality (Study)[a] N Subjects Diagnostic Tool(s)	Gold Standard	Overall Accuracy	AUC	Sensitivity	Specificity	PPV	NPV
Fair quality (Zelnik, 2012[14]) 230 subjects (179 ADHD, 51 non-ADHD) 1. TOVA (Test of Variables of Attention)	Clinical diagnostic work-up included a family interview about the behavioral and neurodevelopmental history of the child, neurological evaluation and observation at the physician's office, utilization of the DSM-IV diagnostic criteria, and employment of the Conners Rating Scales			91.1%	21.6%	80.3%	40.7%
Fair quality (Berger, 2010[15]) 58 subjects (45 ADHD, 13 non-ADHD) 1. Continuous performance functions tests (CPT) 2. TOVA 3. Conners CPT 4. TOVA + Conners CPT	A neurologic examination, the completion of DSM-based questionnaires by parents and teachers, and neuropsychologic evaluation confirmed the diagnosis	94.8% – – –		100% 75% 52% 64%			
CPT and executive function studies							
Fair quality (Bloch, 2012[16]) 34 subjects (27 ADHD, 7 non-ADHD) 1. Cambridge Neuropsychological Testing Automated Battery 2. TOVA	Consensus achieved on a structured interview by a psychologist using DSM-IV based assessment and a clinical interview by child and adolescent psychiatrist			57%-71% 63%	7%-22% 85%	94%	37%
Executive function studies							
Good quality (Klenberg, 2010[17]) Subgroups = sex & ADHD subtype 916 subjects (215 ADHD, 701 non-ADHD) 1. Attention and Executive Function Rating Inventory	Diagnoses were based on structured interviews of parents and children and a parent rating scale (ADHD RS-IV: Home Version) and teacher reports from school	91% (boys) 93% (girls)	87% subtype	85% (boys) 83% (girls) 81% (subtype)	84% (boys) 85% (girls) 76% (subtype)		

Quality (Study)[a] N Subjects Diagnostic Tool(s)	Gold Standard	Overall Accuracy	AUC	Sensitivity	Specificity	PPV	NPV
Biometric devices							
Fair quality (Caudal, 2011[18]) 112 subjects (52 ADHD, 60 non-ADHD) 1. Electro-interstitial scans	Children diagnosed with ADHD according to the DSM-IV and further examinations			80%	98%		
Observational assessment studies							
Fair quality (Ferrin, 2012[19]) Subgroup = age 1185 subjects (1055 ADHD, 130 non-ADHD) 1. Neurological subtle signs	ADHD status was categorically defined by the semistructured clinical interview of their parent's K–SADS–PL, and dimensionally by the Conners' Global Index (CGI). The K-SADS-PL is a semi-structured diagnostic interview designed to assess current and past episodes of psychopathology in children and adolescents according to DSM-IV criteria.	84%	90.3% (<13 year) 77.9% (≥13 year)				
Poor quality (Carballo, 2014[20]) Subgroup = ADHD subtypes 523 subjects (283 ADHD, 240 non-ADHD) 1. Strengths and Difficulties Questionnaire	Positive ADHD diagnosis based exclusively on the ADHD RS-IV which assesses DSM-IV-TR ADHD symptoms			38.3% (ADHD) 84% (ADHD-C) 25% (ADHD-I) 77.8% (ADHD-HI)	66.7% (ADHD) 60.0% (ADHD-C) 75.0% (ADHD-I) 66.7% (ADHD-HI)		

[a] See Methods section "Quality Assessment of Individual Studies" for definitions of quality assessment ratings.

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

Table H-3. Adverse events reported in Italian National ADHD Registry

Reported Adverse Event of Interest	Atomoxetine (%)	Methylphenidate (%)
Cortese, 2015[21]	N=753	N=1350
GI effects	1.3	0.4
Eating disorders	1.5	0.7
Suicidal Ideation	0.7	0
Sleep disorders	0.4	.07
Mood disorders	0.5	0.07
Tachycardia	0.5	0.1
Didoni, 2011[22]	N=96	N=34
Decreased appetite	16	15
Irritability	9	0
Tachycardia	8	0
Unstable mood	7	0
Insomnia	3	3
Tics	2	3
Abdominal pain	3	0
Dyspepsia	3	0
Epigastralgia	8	0
Pane, 2010[23]	N=781	N=643
Suicidal ideation	0.4	0
ECG abnormality	1	0.9
Tics	0	0.2
Decreased appetite	0.3	0.3
GI disease	0.9	0
Increased blood pressure	0.1	0.2

Abbreviations: ECG=electrocardiogram; GI=gastrointestinal

Table H-4. Rates of adverse events

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

Table H-5. Findings on pharmacologic versus nonpharmacologic interventions for ADHD

Study (Companion) N Quality[a] Design Age Category[b]	Type of ADHD Diagnosis Criteria Age range in years % Male	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison
Academic performance						
Molina, 2009[24] (Vitiello, 2012[25]) 579 Fair RCT b	Combined Type DSM-IV 7.0-9.9 years 80% Male	Medication management	Behavioral training (parent group, parent individual, classroom (student), and teacher sessions) Combination: Medication management and Behavioral training Usual care	8 years	WIAT reading Mean = 96.1 (SD = 14.2) p=.8541 WIAT math = 91.5 (SD = 14.8) p=.5156 GPA = 2.79 (SD = .57) p=.3354	WIAT reading Mean = 96.2 (SD = 13.2) WIAT math = 96 (SD = 17) GPA = 2.83 (SD = .56) WIAT reading Mean = 94.7 (SD = 14.5) WIAT math = 94.7 (SD = 17.4) GPA = 2.7 (SD = 0.56) WIAT reading Mean = 95.6 (SD = 13.4) WIAT math = 95.7 (SD = 15.9) GPA = 2.71 (SD = 0.59)
Aggression						
Molina, 2009[24] (Vitiello, 2012[25]) 579 Fair RCT b	Combined Type DSM-IV 7.0-9.9 years 80% Male	Medication management	Behavioral training (parent group, parent individual, classroom (student), and teacher sessions) Combination: Medication management and Behavioral training Usual care	8 years	Aggression conduct parent measure rated 1 (never) to 4 (often) Mean = 1.17 (SD = .22) p=.4511	Aggression conduct parent measure rated 1 (never) to 4 (often) Mean = 1.13 (SD = .17) Aggression conduct parent measure rated 1 (never) to 4 (often) Mean = 1.15 (SD = .24) Aggression conduct parent measure rated 1 (never) to 4 (often) Mean = 1.15 (SD = .23)

Study (Companion) N Quality[a] Design Age Category[b]	Type of ADHD Diagnosis Criteria Age range in years % Male	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison
Behavior changes						
Gelade, 2016[26] 112 Good RCT b	Combined Type DSM-IV-TR 9.63 years (SD1.76) 76% Male	Neurofeedback training	MPH	12 weeks	SWAN-Inattention (parent) Mean = -0.32 (95% CI: -0.53, -0.10) SWAN-Hyperactivity/Impulsiveness (parent) Mean = -0.29 (95% CI: -0.50, -0.07) SWAN-Inattention (teacher) Mean = -0.10 (95% CI: -0.31, -0.11) SWAN-Hyperactivity/Impulsiveness (teacher) Mean = -0.03 (95% CI: -0.28, 0.23)	SWAN-Inattention (parent) Mean = -0.78 (95%CI: -1.03 to -0.53) SWAN-Hyperactivity/Impulsiveness (parent) Mean = -0.52 (95% CI: -0.74 to -0.30) SWAN-Inattention (teacher) Mean = -0.95 (95% CI: -1.23 to -0.68) SWAN-Hyperactivity/Impulsiveness (teacher) Mean = -0.70 (95% CI: -1.05 to -0.34)
Barragan, 2014[27] 90 Poor RCT b	Any subtype DSM-IV-TR 6-12 years 67.0% Male	MPH (maximum 1 mg/kg/day)	Omega-3/6 fatty acid supplementation (6 capsules/day) MPH (maximum 1 mg/kg/day and omega-3/6 fatty acid supplementation (6 capsules/day)	1 year	Irritability by the end of the study period (clinical assessment) % patients with outcome = 23.33	Irritability by the end of the study period (clinical assessment) % patients with outcome = 0 Irritability by the end of the study period % patients with outcome = 0
Li, 2011[28] 72 Good RCT b	NR DSM-IV 6-13 years 65.3% Male	MPH 1 mg/kg/day	Ningdong granule (a traditional Chinese medicine preparation)	8 weeks	Anxiety # patients with outcome = 5	Anxiety # patients with outcome = 1
Changes in appetite						
Barragan, 2014[27] 90 Poor RCT b	Any subtype DSM-IV-TR 6-12 years 67.0% Male	MPH (maximum 1 mg/kg/day)	Omega-3/6 fatty acid supplementation (6 capsules/day) MPH (maximum 1 mg/kg/day and omega-3/6 fatty acid supplementation (6 capsules/day)	1 year	Appetite suppression by the end of the study period % patients with outcome = 70	Appetite suppression by the end of the study period % patients with outcome = 33.3 Appetite suppression by the end of the study period % patients with outcome = 6.7
Li, 2011[28] 72 Good RCT b	NR DSM-IV 6-13 years 65.3% Male	MPH 1 mg/kg/day	Ningdong granule (a traditional Chinese medicine preparation)	8 weeks	Decreased appetite # patients with outcome = 13 Increased appetite # patients with outcome = 4	Decreased appetite # patients with outcome = 1 Increased appetite # patients with outcome = 5

Study (Companion) N Quality[a] Design Age Category[b]	Type of ADHD Diagnosis Criteria Age range in years % Male	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison
Salehi, 2010[29] 50 Good RCT b	Combined Type DSM-IV-TR 6-14 years 78% Male	MPH (up to 30 mg/day)	Ginkgo biloba	6 weeks	Decreased appetite # patients with outcome = 5	Decreased appetite # patients with outcome = 19
Changes in standardized symptom scores						
Barragan, 2014[27] 90 Poor RCT b	Any subtype DSM-IV-TR 6-12 years 67.0% Male	MPH (maximum 1 mg/kg/day)	Omega-3/6 fatty acid supplementation (6 capsules/day) MPH (maximum 1 mg/kg/day and omega-3/6 fatty acid supplementation (6 capsules/day)	1 year	ADHD-RS total score – 6 month Mean = 25.43 (SD = 4.84) ADHD-RS inattention – 6 months Mean = 11.73 (SD = 1.78) ADHD- RS hyperactivity – 6 months Mean = 13.7 (SD = 3.71) ADHD- RS – total – 12 month Mean = 25.83 (SD = 4.67) ADHD-RS inattention – 12 month Mean = 12.03 (SD = 1.71) ADHD-RS hyperactive – 12 month Mean = 13.8 (SD = 3.68)	ADHD-RS total score – 6 month Mean = 28.17 (SD = 7.92) ADHD-RS inattention – 6 months Mean = 12.33 (SD = 2.83) ADHD-RS hyperactivity – 6 months Mean = 15.83 (SD = 5.78) ADHD-RS – total – 12 month Mean = 27.77 (SD = 7.84) ADHD-RS inattention – 12 month Mean = 12.17 (SD = 2.7) ADHD-RS hyperactive – 12 month Mean = 15.6 (SD = 5.68) ADHD-RS total score – 6 month Mean = 25.5 (SD = 5.01) ADHD-RS inattention – 6 months Mean = 11.7 (SD = 2.17) ADHD-RS hyperactivity – 6 months Mean = 13.8 (SD = 3.28) ADHD-RS – total – 12 month Mean = 24.33 (SD = 5.09) ADHD-RS inattention – 12 month Mean = 11.3 (SD = 1.95) ADHD-RS hyperactive – 12 month Mean = 13.03 (SD = 3.44)
Duric 2012[30] (Duric, 2014[31]) 91 Poor RCT b	Attention and Hyperactive ICD-10 Diagnosis Criteria 6-18 years 80% Male	MPH (dose not reported) MPH + Neurofeedback	Neurofeedback	10 weeks	Total: Barkley Rating Scale for parent's Mean w/in group change = 7.9 95% CI = 4.5-11.4 p=0.31	Total: Barkley Rating Scale for parent's Mean w/in group change = 8.6 95% CI = 5.0-12.2

Study (Companion) N Quality[a] Design Age Category[b]	Type of ADHD Diagnosis Criteria Age range in years % Male	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison
Li, 2011[28] 72 Good RCT b	NR DSM-IV 6-13 years 65.3% Male	MPH 1 mg/kg/day	Ningdong granule (a traditional Chinese medicine preparation)	8 weeks	ADHD-RS Parent Mean w/in group change = 13.3 (SD = 3.2)	ADHD-RS Parent Mean w/in group change = 14.1 (SD = 2.9)
Salehi, 2010[29] 50 Good RCT b	Combined Type DSM-IV-TR 6-14 years 78% Male	MPH (up to 30 mg/day)	Ginkgo biloba	6 weeks	Parent ADHD Rating Scale-IV Mean = 26 (13,38) p<0.01 Teacher ADHD Rating Scale-IV Mean = 25 (15,35) p<0.001	Parent ADHD Rating Scale-IV Mean = 16 (5, 27) Teacher ADHD Rating Scale-IV Mean = 11 (4, 20)
Moreno-Garcia, 2015[32] 57 Fair RCT b	Combined, Inattentive and Hyperactive/Impulsive DSM-V 7-14 years 77.2% Male	Standard Pharmacological Treatment	Neurofeedback Behavioral treatment	20 weeks	Integrated Visual and Auditory Continuous Performance Test (IVA/CPT) – Full Scale Attention Mean = 2.1 (SD = 16.88) p=.002 p=0.013	Integrated Visual and Auditory Continuous Performance Test (IVA/CPT) – Full Scale Attention Mean = -28.57 (SD = 11.67) Integrated Visual and Auditory Continuous Performance Test (IVA/CPT) – Full Scale Attention Mean = -3.88 (SD = 16.24)
Chemical leukoderma						
Li, 2011[28] 72 Good RCT b	NR DSM-IV 6-13 years 65.3% Male	MPH 1 mg/kg/day	Ningdong granule (a traditional Chinese medicine preparation)	8 weeks	ADHD-RS Teacher Mean w/in group change = 12.3 (SD = 3.1)	ADHD-RS Teacher Mean w/in group change = 13.9 (SD = 2.3)
Depression or anxiety						
Salehi, 2010[29] 50 Good RCT b	Combined Type DSM-IV-TR 6-14 years 78% Male	MPH (up to 30 mg/day)	Ginkgo biloba	6 weeks	Sadness # patients with outcome = 2 Anxiety # patients with outcome = 7	Sadness # patients with outcome = 7 Anxiety # patients with outcome = 9

Study (Companion) N Quality[a] Design Age Category[b]	Type of ADHD Diagnosis Criteria Age range in years % Male	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison
Molina, 2009[24] (Vitiello, 2012[25]) 579 Fair RCT b	Combined Type DSM-IV 7.0-9.9 years 80% Male	Medication management	Behavioral training (parent group, parent individual, classroom (student), and teacher sessions) Combination: Medication management and Behavioral training Usual care	8 years	Depression (CDI) Mean = 5.78 (SD = 7.84) Anxiety (MASC) Mean = 77.7 (SD = 14.9)	Depression (CDI) Mean = 7.84 (SD = 7.24) Anxiety (MASC) Mean = 82.8 (SD = 16.7) Depression (CDI) Mean = 8 (SD = 7.66) Anxiety (MASC) Mean = 84.1 (SD = 18.3) Depression (CDI) Mean = 7.19 (SD = 7.73) Anxiety (MASC) Mean = 85.8 (SD = 19.7)
Elevated blood pressure						
Molina, 2009[24] (Vitiello, 2012[25]) 579 Fair RCT b	Combined Type DSM-IV 7.0-9.9 years 80% Male	Medication management	Behavioral training (parent group, parent individual, classroom (student), and teacher sessions) Combination: Medication management and Behavioral training Usual care	8 years	SBP at 14 months Mean = 102.4 (SD = 9.7) DBP at 14 months Mean = 67.6 (SD = 9.6)	SBP at 14 months Mean = 103.2 (SD = 10.3) DBP at 14 months Mean = 68.9 (SD = 9.1) SBP at 14 months Mean = 102.6 (SD = 10.2) DBP at 14 months Mean = 66.5 (SD = 10.4) SBP at 14 months Mean = 104.1 (SD = 10.6) DBP at 14 months Mean = 67.8 (SD = 8.8)

Study (Companion) N Quality[a] Design Age Category[b]	Type of ADHD Diagnosis Criteria Age range in years % Male	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison
Functional impairment						
Barragan, 2014[27] 90 Poor RCT b	Any subtype DSM-IV-TR 6-12 years 67.0% Male	MPH (maximum 1 mg/kg/day)	Omega-3/6 fatty acid supplementation (6 capsules/day) MPH (maximum 1 mg/kg/day and omega-3/6 fatty acid supplementation (6 capsules/day)	1 year	CGI-severity – parents- 6 months Mean = 4 (SD = 0.98) CGI-clinician – 6 months Mean = 4 (SD = 1.08) CGI-parent – 12 month Mean = 4.1 (SD = 1.06) CGI-clinician – 12 month Mean = 4.1 (SD = 1.06)	CGI-severity – parents- 6 months Mean = 3.97 (SD = 1.33) CGI-clinician – 6 months Mean = 4.1 (SD = 1.32) CGI-parent – 12 month Mean = 3.7 (SD = 1.51) CGI-clinician – 12 month Mean = 3.7 (SD = 1.51) CGI-severity – parents- 6 months Mean = 3.23 (SD = 0.866) CGI-clinician – 6 months Mean = 3.23 (SD = 0.86) CGI-parent – 12 month Mean = 3.63 (SD = 0.85) CGI-clinician – 12 month Mean = 3.63 (SD = 0.85)
Gastrointestinal symptoms						
Barragan, 2014[27] 90 Poor RCT b	Any subtype DSM-IV-TR 6-12 years 67.0% Male	MPH (maximum 1 mg/kg/day)	Omega-3/6 fatty acid supplementation (6 capsules/day) MPH (maximum 1 mg/kg/day and omega-3/6 fatty acid supplementation (6 capsules/day)	1 year	Dyspepsia by the end of the study period % patients with outcome = 0	Dyspepsia by the end of the study period % patients with outcome = 0 Dyspepsia by the end of the study period % patients with outcome = 40
Li, 2011[28] 72 Good RCT b	NR DSM-IV 6-13 years 65.3% Male	MPH 1 mg/kg/day	Ningdong granule (a traditional Chinese medicine preparation)	8 weeks	Nausea # patients with outcome = 16 Stomach pain # patients with outcome = 12	Nausea # patients with outcome = 2 Stomach pain # patients with outcome = 2
Incarceration						

Study (Companion) N Quality[a] Design Age Category[b]	Type of ADHD Diagnosis Criteria Age range in years % Male	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison
Molina, 2009[24] (Vitiello, 2012[25]) 579 Fair RCT b	Combined Type DSM-IV 7.0-9.9 years 80% Male	Medication management	Behavioral training (parent group, parent individual, classroom (student), and teacher sessions) Combination: Medication management and Behavioral training Usual care	8 years	Arrested once % patients with outcome = 22.4 p=.735 Arrested 2 or more times % patients with outcome = 10.3 p=.735	Arrested once % patients with outcome = 17.4 Arrested 2 or more times % patients with outcome = 7.8 Arrested once % patients with outcome = 18.9 Arrested 2 or more times % patients with outcome = 5.7 Arrested once % patients with outcome = 22.9 Arrested 2 or more times % patients with outcome = 7.8
Increased heart rate						
Molina, 2009[24] (Vitiello, 2012[25]) 579 Fair RCT b	Combined Type DSM-IV 7.0-9.9 years 80% Male	Medication management	Behavioral training (parent group, parent individual, classroom (student), and teacher sessions) Combination: Medication management and Behavioral training Usual care	14 months	Heart rate at 14 months Mean = 84.2 (SD = 12.4) Incidence of Tachycardia at 14 months % patients with outcome = .8	Heart rate at 14 months Mean = 79.1 (SD = 12) Incidence of Tachycardia at 14 months % patients with outcome = .8 Heart rate at 14 months Mean = 84.6 (SD = 12.2) Incidence of Tachycardia at 14 months % patients with outcome = 2.2 Heart rate at 14 months Mean = 78.9 (SD = 12.9) Incidence of Tachycardia at 14 months % patients with outcome = 2.5

Study (Companion) N Quality[a] Design Age Category[b]	Type of ADHD Diagnosis Criteria Age range in years % Male	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison
Motor vehicle collisions						
Molina, 2009[24] (Vitiello, 2012[25]) 579 Fair RCT b	Combined Type DSM-IV 7.0-9.9 years 80% Male	Medication management	Behavioral training (parent group, parent individual, classroom (student), and teacher sessions) Combination: Medication management and Behavioral training Usual care	8 years	Accidents, citations, ticket % patients with outcome = 28.6	Accidents, citations, ticket % patients with outcome = 19.7 Accidents, citations, ticket % patients with outcome = 19 Accidents, citations, ticket % patients with outcome = 21.5
Sleep disturbance						
Barragan, 2014[27] 90 Poor RCT b	Any subtype DSM-IV-TR 6-12 years 67.0% Male	MPH (maximum 1 mg/kg/day)	Omega-3/6 fatty acid supplementation (6 capsules/day) MPH (maximum 1 mg/kg/day and omega-3/6 fatty acid supplementation (6 capsules/day)	1 year	Insomnia by the end of the study period % patients with outcome = 20	Insomnia by the end of the study period % patients with outcome = 0 Insomnia by the end of the study period % patients with outcome = 0
Gelade, 2016[26] 112 Good RCT b	Combined Type DSM-IV-TR 9.63 years (SD1.76) 76% Male	Neurofeedback training	MPH	12 weeks	SDSC Mean = -2.16 (95% CI: -4.82, 0.51)	SDSC Mean = -0.54 (95% CI: -2.90, 1.81)
Li, 2011[28] 72 Good RCT b	NR DSM-IV 6-13 years 65.3% Male	MPH 1 mg/kg/day	Ningdong granule (a traditional Chinese medicine preparation)	8 weeks	Trouble falling asleep # patients with outcome = 9 Hypersomnia # patients with outcome = 0	Trouble falling asleep # patients with outcome = 1 Hypersomnia # patients with outcome = 6
Salehi, 2010[29] 50 Good RCT b	Combined Type DSM-IV-TR 6-14 years 78% Male	MPH (up to 30 mg/day)	Ginkgo biloba	6 weeks	Insomnia # patients with outcome = 3	Insomnia # patients with outcome = 12

Study (Companion) N Quality[a] Design Age Category[b]	Type of ADHD Diagnosis Criteria Age range in years % Male	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison
Weight decrease						
Salehi, 2010[29] 50 Good RCT b	Combined Type DSM-IV-TR 6-14 years 78% Male	MPH (up to 30 mg/day)	Ginkgo biloba	6 weeks	Weight loss # patients with outcome = 3	Weight loss # patients with outcome = 8

[a] See Methods section "Quality Assessment of Individual Studies" for definitions of quality assessment ratings.
[b] Age categories: a = children aged ≤6 years, b = children aged 7-17, c = children of all ages ≤17.
Abbreviations: CDI=Children's Depression Inventory; DSM=Diagnostic and Statistical Manual of Mental Disorders; MASC=Multidimensional Anxiety Scale for Children; MPH=methylphenidate; WIAT=Wechsler Individual Achievement Test

Table H-6. Summary of adverse effects

Adverse Effect	Findings
Physical	
Weight loss[29]	12.0% (n=3) receiving gingko biloba and 32.0% (n=8) receiving MPH
Gastrointestinal	
Nausea[27,28]	5.6% (n=2) receiving NDG and 44.4% (n=16) receiving MPH
	20%(n=6) receiving MPH alone
Dyspepsia[27]	40% (n=9) receiving omega-3/6 alone after 1 month of treatment
Stomach pain[28,29]	5.6% (n=2) receiving NDG and 33.3% (n=12) receiving MPH
	12.0% (n=3) receiving gingko biloba and 20.0% (n=5) receiving MPH
Sleep	
Insomnia[27,29]	20% (n=6) receiving MPH alone
	12.0% (n=3) receiving gingko biloba and 48.0% (n=12) receiving MPH
Hypersomnia[28]	16.7% (n=5) receiving NDG and 0 receiving MPH
Trouble falling asleep[28]	2.8% (n=1) receiving NDG and 13.9% (n=5) receiving MPH
Appetite	
Suppression[27]	70% (n=21) receiving MPH alone, 6.7% (n=2) receiving omega-3/6 alone, and 33.3% (n=10) receiving combined
Decreased[28,29]	2.8% (n=1) receiving NDG and 36.1% (n=13) receiving MPH
	20.0% (n=5) receiving gingko biloba and 76.0% (n=19) receiving MPH
Increased[28]	13.9% (n=5) receiving NDG and 11.1% (n=4) receiving MPH

Abbreviations: MPH=methylphenidate, NDG=ningdong granule

Table H-7. Findings on neurofeedback interventions for ADHD

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Acceptability of treatment						
Gevensleben, 2009[33] (Gevensleben, 2010[34] Wangler, 2011[35]) 102 Good RCT b	Neuro-feedback training	Attention skills training	2 months	Effectiveness of treatment Mean = 3.19 (SD = .82) Parent rated motivation of their children to participate in treatment Mean = .64 (SD = .77)	Effectiveness of treatment Mean = 3.13 (SD = .90) Parent rated motivation of their children to participate in treatment Mean = .56 (SD = 1.13)	p=.77 p = .71
Behavior changes						
Gelade, 2016[26] 103 Good RCT b	Neuro-feedback training	Physical activity	12 weeks	SWAN-Inattention (parent) Mean = -0.32 (95% CI: -0.53, -0.10 SWAN-Hyperactivity/Impulsiveness (parent) Mean = -0.29 (95% CI: -0.50, -0.07) SWAN-Inattention (teacher) Mean = -0.10 (95% CI: -0.31, -0.11) SWAN-Hyperactivity/Impulsiveness (teacher) Mean = -0.03 (95% CI: -0.28, 0.23)	SWAN-Inattention (parent) Mean = -0.17 (95%CI: -0.37, 0.02) SWAN-Hyperactivity/Impulsiveness (parent) Mean = -0.21 (95% CI: -0.41, -0.01) SWAN-Inattention (teacher) Mean = -0.05 (95% CI: -0.23, -0.12) SWAN-Hyperactivity/Impulsiveness (teacher) Mean = -0.02 (95% CI: -0.18, 0.13)	NS NS NS NS

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Changes in standardized symptom scores						
Bink, 2015[36] 90 Good RCT b	Neuro-feedback plus treatment as usual	Treatment as usual	0 months baseline 6 months	ADHD-RS Inattention Mean=4.4 (SD=2.49) ADHD-RS Hyperactivity/inattention Mean=3.44 (SD=2.12) Youth Self Report Total score Mean=48.5 (SD=22.01) CBCL Total score Mean=60.81 (SD=28.57) ADHD-RS Inattention Mean=2.84 (SD=2.59) ADHD-RS Hyperactivity/inattention Mean=2.36 (SD=2.16) Youth Self Report Total score Mean= 40.43 (SD=18.24) CBCL Total score Mean= 53.35 (SD= 27.55)	ADHD-RS Inattention Mean=5.27 (SD=2.16) ADHD-RS Hyperactivity/inattention Mean=3.27 (SD=2.01) Youth Self Report Total score Mean=52.58 (SD=18.89) CBCL Total score Mean=63.77 (SD=27) ADHD-RS Inattention Mean=3.62 (SD=2.45) ADHD-RS Hyperactivity/inattention Mean=2.38 (SD=2.14) Youth Self Report Total score Mean= 46.12 (SD=20.17) CBCL Total score Mean=52.81 (SD=30.28)	NS
Gevensleben, 2009[33] (Gevensleben, 2010[34] Wangler, 2011[35]) 102 Good RCT b	Neuro-feedback training	Attention skills training	2 months	German ADHD rating scale Mean within group change = -.39 (SD = .37)	German ADHD rating scale Mean within group change = -.1 (SD = .44)	p<.005

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Moreno-Garcia, 2015[32] 57 Fair RCT b	Neuro-feedback	Standard Pharmacological Treatment Behavioral Treatment	NR	Integrated Visual and Auditory Continuous Performance Test – Full Scale Attention Mean = 2.1 (SD = 16.88)	Integrated Visual and Auditory Continuous Performance Test – Full Scale Attention Mean = 28.57 (SD = 11.67) Changes in standardized symptom scores Integrated Visual and Auditory Continuous Performance Test – Full Scale Attention Mean = 3.88 (SD = 16.24)	 p =.002 p =.013
Steiner, 2014[37] (Steiner, 2014[38]) 104 Good RCT b	Neuro-feedback	Cognitive training Control		Conner 3 Parent Inattention Within-group effect size = -0.8 Conners 3 Parent Executive Functioning Within-group effect size = -0.49 Conners 3 Parent Global Index Within-group effect size = -0.37 Conners 3 Teacher Inattention Within-group effect size = -0.25	Conner 3 Parent Inattention Within-group effect size = -0.46 Conners 3 Parent Executive Functioning Within-group effect size -0.12 Conners 3 Parent Global Index Within-group effect size = -0.09 Conners 3 Teacher Inattention Within-group effect size = -0.24 Conner 3 Parent Inattention Within-group effect size = -0.15 Conners 3 Parent Executive Functioning Within-group effect size = -0.09 Conners 3 Parent Global Index Within-group effect size = -0.05 Conners 3 Teacher Inattention Within-group effect size =0	 p<.05 p<.001 p<.001 p<.001
Sleep disturbance						
Gelade, 2016[26] 103 Good RCT b	Neuro-feedback training	Physical activity	12 weeks	SDSC Mean = -2.16 (95% CI: -4.82, 0.51)	SDSC Mean = -1.03 (95% CI: -2.86, 0.80)	NS

[a] See Methods section "Quality Assessment of Individual Studies" for definitions of quality assessment ratings.
[b] Age categories: a = children aged ≤6 years, b = children aged 7-17, c = children of all ages ≤17.
Abbreviations: ADHD=attention deficit hyperactivity disorder; CBCL=Child Behavior Checklist; RS=rating scale; SD=standard deviation

Table H-8. Findings on cognitive training interventions for ADHD

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Academic performance						
Chacko, 2014[39] 85 Good RCT b	Cogmed working memory training with difficulty titrated to a user's ability	"Placebo" Cogmed working memory training with difficulty <u>not</u> titrated to a user's ability	3 weeks post	WRAT-4 – word reading WRAT-4 Sentence completion WRAT-4 Math computation WRAT-4 Spelling		Treatment effect = -2.72 (SE = 5.5) p = -.5 Treatment effect = 5.6 (SE = 4.7) p = .23 Treatment effect = 5.22 (SE = 5.21) p = .31 Treatment effect = 1.28 (SE = 6.17) p = .83
Acceptability of treatment						
Gevensleben,2009[33] (Gevensleben, 2010[34] Wangler, 2011[35]) 102 Good RCT b	Neurofeedback training	Attention skills training	2 months	Effectiveness of treatment Mean = 3.19 (SD = .82) Parent-rated motivation of their children to participate in treatment Mean = .64 (SD = .77)	Effectiveness of treatment Mean = 3.13 (SD = .90) Parent-rated motivation of their children to participate in treatment Mean = .56 (SD = 1.13)	P= .77 P= .71

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Behavior changes						
Dovis, 2015[40] 89 Good RCT b	Braingame Brian (computerized, home-based executive functioning training)	Braingame Brian in training mode and the working memory task in placebo mode All tasks in training mode (overall easier)	3 months	Parent DBDRS Inattention Mean=12.9 (SD=4.1) P-DBDRS Hyperactivity/Impulsivity Mean = 12.6 (SD = 6.4) Teacher DBDRS Inattention Mean = 12.2 (SD = 5.8) Teacher DBDRS Hyperactivity/Impulsivity Mean = 9.3 (SD = 4.9)	Parent DBDRS Inattention Mean = 14.6 (SD = 5.3) P-DBDRS Hyperactivity/Impulsivity Mean = 13 (SD = 5.1) Teacher DBDRS Inattention Mean = 13.3 (SD = 6.6) Teacher DBDRS Hyperactivity/Impulsivity Mean = 11.5 (SD = 7) Parent DBDRS Inattention Mean = 14.1 (SD = 4.7) P-DBDRS Hyperactivity/Impulsivity Mean = 12.5 (SD = 5.7) Teacher DBDRS Inattention Mean = 11.3 (SD = 5.1) Teacher DBDRS Hyperactivity/Impulsivity Mean = 6 (SD = 9.1)	NS NS NS NS NS NS NS NS
Changes in standardized symptom scores						
Chacko, 2014[39] 85 Good RCT b	Cogmed working memory training with difficulty titrated to a user's ability	"Placebo" Cogmed working memory training with difficulty <u>not</u> titrated to a user's ability	3 weeks post	Parent Disruptive Behavior Disorder Rating Scale – Inattention symptoms Parent Disruptive Behavior Disorder Rating Scale – Hyperactive symptoms Teacher Disruptive Behavior Disorder Rating Scale – Inattention symptoms Teacher Disruptive Behavior Disorder Rating Scale – Hyperactive		Treatment effect = 1.98 (SE = 1.17) p = .2 Treatment effect = 1.88 (SE = 1.15) p = .2 Treatment effect = 1.84 (SE = 1.49) p = .22 Treatment effect = 1.94 (SE = 1.54) p = .21

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Egeland, 2013[41] (Hovik, 2013[42]) 75 Good RCT b	Cogmed RoboMemo program	Waitlist control	8 months	ADHD-RS Total Score Teacher Mean=20.1 (SD=9.8) ADHD-RS Parent Mean=27 (SD=11.5)	ADHD-RS Total Score Teacher Mean=22.6 (SD=12.3) ADHD-RS Parent Mean=28.1 (SD=11)	NS NS
Gevensleben, 2009[33] (Gevensleben, 2010[34] Wangler, 2011[35]) 102 Good RCT b	Neurofeedback Training	Attention skills training	1 month	German ADHD rating scale (FBB-HKS) Mean w/in group change = -.39 (SD = .37)	German ADHD rating scale (FBB-HKS) Mean w/in group change = -.1 (SD = .44)	P<.005
Steiner, 2014[37] (Steiner, 2014[38]) 104 Good RCT b	Neurofeedback	Cognitive training Waitlist control	5 months	Conner 3 Parent Inattention Within-group effect size = -0.8 Conners 3 Parent Executive Functioning Within-group effect size = -0.49 Conners 3 Parent Global Index Within-group effect size = -0.37 Conners 3 Teacher Inattention Within-group effect size = -0.25	Conner 3 Parent Inattention Within-group effect size = -0.46 Conners 3 Parent Executive Functioning Within-group effect size -0.12 Conners 3 Parent Global Index Within-group effect size = -0.09 Conners 3 Teacher Inattention Within-group effect size = 0.24 Conner 3 Parent Inattention Within-group effect size = -0.15 Conners 3 Parent Executive Functioning Within-group effect size = -0.09 Conners 3 Parent Global Index Within-group effect size = -0.05 Conners 3 Teacher Inattention Within-group effect size =0	p<.05 NS p<.05 p<.05 p<.001 p<.001 p<.001 NS

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
van Dongen-Boomsma, 2014[43] 51 Good RCT c	Cogmed training program	Cogmed training program without adjustment for patient skill level (control group)	5 weeks	ADHD-RS Total Investigator Score Mean=32.4 (SE=5.7) ADHD-RS Teacher Mean=27.5 (SE=10.1)	ADHD-RS Total Investigator Score Mean=30.3 (SE=7.4) ADHD-RS Teacher Mean=25.5 (SE=7.7)	NS NS

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Beck, 2010[44] 52 Fair Observational b	Computer-based working memory intervention	Waitlist control	Baseline/ 4-month follow-up	ADHD Index Parent Mean = 71.7 (SD = 8.82) / Mean = 62.78 (SD = 9.35) Conners Cognitive Problems/Inattention Parent Mean = 67.96 (SD = 9.55) / Mean = 59.89 (SD = 9.15) Conners Hyperactivity Parent Mean = 68.37 (SD = 15.98) / Mean = 59.59 (SD = 14.89) Conners Oppositional Parent Mean = 60 (SD = 13.34)/ Mean = 53.96 (SD = 9.67) Conners ADHD Index Teacher # patients with outcome = 60.78 (SD = 14.96) / # patients with outcome = 56.38 (SD = 13.28) Conners Cognitive Problems/Inattention Teacher Mean = 60.89 (SD = 10.58) / Mean = 57.5(SD = 7.91) Conners Hyperactivity Teacher Mean = 59.59 (SD = 15.17) / Mean = 56.31 (SD = 13.47) Conners Oppositional Teacher Mean = 56.52 (SD = 8.93) / Mean = 52.35 (SD = 10.12) BRIEF Metacognition Index Parent Mean = 72.96 (SD = 8.06)/ Mean = 64.19 (SD = 9.24) BRIEF Metacognition Index Teacher Mean = 67.96 (SD = 18.67) / Mean = 64.85 (SD = 16.35)	ADHD Index Parent Mean = 69.92 (SD = 7.86) / Mean = 67.33 (SD = 7.33) Conners Cognitive Problems/Inattention Parent Mean = 65.38 (SD = 9.22) / Mean = 64.75 (SD = 10.22) Conners Hyperactivity Parent Mean = 65.7 (SD = 16.5) / Mean = 62.75 (SD = 13.73) Conners Oppositional Parent Mean = 59.79 (SD = 12.17) / Mean = 57.5 (SD = 10.59) Conners ADHD Index Teacher # patients with outcome = 58.4 (SD = 11.4) / # patients with outcome = 56.52 (SD = 10.25) Conners Cognitive Problems/Inattention Teacher Mean = 56.24 (SD = 11.05) / Mean = 55.56 (SD = 10.26) Conners Hyperactivity Teacher Mean = 55.36 (SD = 13.2) / Mean = 55.64 (SD = 11.14) Conners Oppositional Teacher Mean = 52.92 (SD = 8.93) / Mean = 50.58 (SD = 8.71) BRIEF Metacognition Index Parent Mean = 71.38 (SD = 7.73) / Mean = 69.61 (SD = 7.19) BRIEF Metacognition Index Teacher Mean = 60.2 (SD = 13.04) / Mean = 60.79 (SD = 12.76)	p=.01 p<.01 p=.04 p=.10 p=.43 p=.23 p=.25 p=.59 p=.01 p=.22

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Van der Donk, 2015[45] 105 Fair RCT b	Cogmed Working Memory Training	Paying Attention in Class (experimental, combined working memory and compensatory training)	6 weeks 6 months	CBCL Attention Problems Scale CBCL Externalizing Problems Scale	CBCL Attention Problems Scale CBCL Externalizing Problems Scale	NR NR
Functional impairment						
van Dongen-Boomsma, 2014[43] 51 Good RCT c	Cogmed training program	Cogmed training program without adjustment for patient skill level (control group)	5 weeks	CGI-I # patients w/ outcome = 25	CGI-I # patients w/ outcome = 21	P=0.514

[a] See Methods section "Quality Assessment of Individual Studies" for definitions of quality assessment ratings.
[b] Age categories: a = children aged ≤6 years, b = children aged 7-17, c = children of all ages ≤17.
Abbreviations: ADHD=attention deficit hyperactivity disorder; BRIEF=Behavior Rating Inventory of Executive Function; CBCL= Child Behavior Checklist; DBDRS=Disruptive Behavior Disorder Rating Scale; SNAP=Swanson, Nolan and Pelham Revision

Table H-9. Findings on cognitive behavioral therapy interventions for ADHD

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Changes in standardized symptom scores						
Vidal, 2015[46] 119 Good RCT b	CBT	Usual care	12 weeks	ADHD-RS Adolescent Inattention Mean 10.14 (0.51) ADHD-RS Adolescent Impulsivity Mean 8.29 (0.7) ADHD-RS Parents Inattention 11.31 (0.58) ADHD RS Parents Impulsivity Mean 7.72 (0.77)	ADHD-RS Adolescent Inattention Mean 14.47 (0.5) ADHD-RS Adolescent Impulsivity Mean 11.72 (0.7) ADHD-RS Parents Inattention Mean 16.99 (0.6) ADHD RS Parents Impulsivity Mean 11.56 (0.78)	ES=8.57 (p<.001) ES=4.9 (p<.001) ES=9.62 (p<.001) ES=4.95 (p<.001)

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Boyer, 2015[47] (Boyer, 2015[48]) 159 Fair RCT b	CBT with an aim to improve planning skills	Solution-focused CBT without an aim to improve planning skills	3 months	ADHD symptom scale – combined inattentive and Hyperactivity/Impulsivity Mean = 18.66 (9.64) Disruptive Behavior Disorders – summarized ODD/CD subscales Mean = 5.84 (5.49)	ADHD symptom scale – combined inattentive and Hyperactivity/Impulsivity Mean = 19.99 (9.69) Disruptive Behavior Disorders – summarized ODD/CD subscales Mean = 5.99 (5.78)	
			12 months	ADHD symptom scale – combined inattentive and Hyperactivity/Impulsivity Mean = 18.41 (9.76) Disruptive Behavior Disorders – summarized ODD/CD subscales Mean = 4.74 (4.30)	ADHD symptom scale – combined inattentive and Hyperactivity/Impulsivity Mean = 20.02 (8.21) Disruptive Behavior Disorders – summarized ODD/CD subscales Mean = 4.55 (3.80)	p < .001 p < .001
Depression or anxiety						
Boyer, 2015[47] (Boyer, 2015[48]) 159 Fair RCT b	CBT with an aim to improve planning skills	Solution-focused CBT without an aim to improve planning skills	3 months	Child Depression Inventory Mean = 8.92 (6.82) Screen for Child Anxiety Related Emotional Disorders Mean = 20.49 (16.17)	Child Depression Inventory Mean = 9.21 (5.57) Screen for Child Anxiety Related Emotional Disorders Mean = 19.54 (18.17)	
			12 months	Child Depression Inventory Mean = 7.68 (5.10) Screen for Child Anxiety Related Emotional Disorders Mean = 18.86 (14.39)	Child Depression Inventory Mean = 8.48 (4.65) Screen for Child Anxiety Related Emotional Disorders Mean = 18.53 (16.17)	p < .001 p < .001
Functional impairment						
Vidal, 2015[46] 119 Good RCT b	CBT	Usual care	12 weeks	CGI-S Self Report Mean 2.9)0.12) CGI-S Clinician 2.86 (0.07)	CGI-S Self Report Mean 3.35 (0.12) CGI-S Clinician 3.4 (0.07)	ES=3.75 (p<.001) ES=7.71 (p<.001)

[a] See Methods section "Quality Assessment of Individual Studies" for definitions of quality assessment ratings.
[b] Age categories: a = children aged ≤6 years, b = children aged 7-17, c = children of all ages ≤17.
Abbreviation: CBT=cognitive behavioral therapy; CGI-S=Clinical Global Impression-Severity; ODD/CD=Oppositional defiant disorder/conduct disorder

Table H-10. Findings on child or parent training or behavioral interventions for ADHD

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Academic performance						
Abikoff, 2013[49] 180 Good RCT b	Organizational skills	Performance-based intervention precluding skill Waitlist	12 weeks	Academic Performance Rating Scale Mean=pre: 53.45; post: 62.16 (SD=pre: 10.34; post: 10.52) Academic Proficiency Scale Mean=pre: 16.39; post: 18.55 (SD=pre: 4.27; post: 4.26)	Academic Performance Rating Scale Mean=pre: 54.45; post: 63.96 (SD=pre: 11.12; post: 11.90) Academic Proficiency Scale Mean=pre: 17.08; post: 18.35 (SD=pre: 3.54; post: 3.89) Academic Performance Rating Scale Mean=pre: 54.06 ; post: 54.53 (SD=pre: 8.58; post: 9.74) Academic Proficiency Scale Mean=pre: 16.05 ; post: 16.63 (SD= pre: 3.22; post: 3.30)	NS NS
Storebo, 2012[50] 56 Good RCT b	Social skills group + medication management	Medication management (usual care)	3 months 6 months	Conners CBRS Academic Score Mean=20.13 (SD=15.15) Conners CBRS Academic Score Mean=21.04 (SD= 11.98); Between group MD: -0.48 (95% CI=-7.254 to 6.293)	Conners CBRS Academic Score Mean=17.88 (SD=10.11) Conners CBRS Academic Score Mean=21.52 (SD 12.56)	NS
Acceptability of treatment						
Chacko, 2009[51] 120 Good RCT c	**STEPP**	BPT program Waitlist	2.07 months	Parent Treatment Attitude Inventory-Satisfaction with Process Mean = 16.36 (SD = 2.03)	Parent Treatment Attitude Inventory- Satisfaction with Process Mean = 14.12 (SD = 2.09)	P<0.01
Changes in standardized symptom scores						
Bai, 2015[52] 89 Good RCT b	A psycho-education program based on the theory of planned behavior	General clinical counseling	3 months	ADHD-RS-IV Mean=33.7 (SD=5.4) (Baseline mean=49.9, SD 11.5)	ADHD-RS-IV Mean=45.1 (SD=7.9) (Baseline mean=48.1, SD 8.1)	P=.008

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Chacko, 2009[51] 120 Good RCT c	STEPP	BPT program	2.07 months	Disruptive Behavior Disorder scale-Inattentive Mean = 1.78 (SD = .63) Disruptive Behavior Disorder-Hyperactive/Impulsive: Mean = 1.69 (SD = .57) Treatment Attitude Inventory- Satisfaction with Outcome Mean = 24.18 (SD = 3.02)	Disruptive Behavior Disorder scale-Inattentive Mean = 1.67 (SD = .74) Disruptive Behavior Disorder-Hyperactive/Impulsive: Mean = 1.59 (SD = .70) Treatment Attitude Inventory- Satisfaction with Outcome Mean = 20.20 (SD = 2.35)	NR NR NR
		Waitlist			Disruptive Behavior Disorder scale-Inattentive Mean = 1.72 (SD = .65) Disruptive Behavior Disorder-Hyperactive/Impulsive: Mean = 1.72 (SD = .56)	NR NR
Ferrin, 2014[53] 81 Good RCT c	Psycho-educational program	Control	12 weeks 12 months	CPRS inattention -12 weeks Mean = 7.95 (SD = 3.84) p = .001 CPRS hyperactivity/impulsivity -12 weeks Mean = 6.74 (SD = 4.84) Conners parent rating scale – index Mean = 18.6 (SD = 8.66) Conners parent rating scale – opposition subscale Mean = 5.2 (SD = 4.06) Conners parent rating scale-inattention/cognition Mean = 8.26 (SD = 4.3) p = .032 Conners parent rating scale – hyperactivity/impulsivity Mean = 7.4 (SD = 4.84) CPRS index -12 weeks Mean = 16.8 (SD = 7.18) p = .001 CPRS opposition -12 weeks Mean = 4.95 (SD = 3.79)	CPRS inattention -12 weeks Mean = 11 (SD = 3.28) CPRS hyperactivity/impulsivity -12 weeks Mean = 8.45 (SD = 4) Conners parent rating scale – index Mean = 21.16 (SD = 7.08) Conners parent rating scale – opposition subscale Mean = 5.63 (SD = 3.86) Conners parent rating scale- inattention/cognition Mean = 10.41 (SD = 3.62) Conners parent rating scale – hyperactivity/impulsivity Mean = 8.47 (SD = 3.82) CPRS index -12 weeks Mean = 22.44 (SD = 6.13) CPRS opposition -12 weeks Mean = 6.18 (SD = 3.87)	P=0.001 NS NS NS P=0.0032 NS P=0.001 NS

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Hiscock, 2015[54] (Papadopoulos, 2015[55]) 244 Good RCT c	Sleep hygiene practices and standardized behavioral strategies	Children in the control group received usual clinical care	6 Months	ADHD rating scale IV-total symptoms (parent report) Mean = 28.4 (SD = 10.8) ADHD Rating Scale IV – Parent Report (Inattentive) Mean = 15.1 (SD = 6.0) ADHD Rating Scale IV – Parent Report (Hyperactivity/Impulsivity) Mean = 13.3 (SD = 6.0) ADHD rating scale IV Total Score (Teacher Report) Mean = 20.6 (SD = 11.6) ADHD Rating Scale IV: Teacher Report (Inattentive) Mean = 14.1 (SD = 6.9) ADHD Rating Scale IV: Teachers Report (Hyperactivity/Impulsivity) Mean = 8.4 (SD = 6.2)	ADHD rating scale IV-total symptoms (parent report) Mean = 33.8 (SD = 9.5) ADHD Rating Scale IV – Parent Report (Inattentive) Mean = 18.2 (SD = 4.8) ADHD Rating Scale IV – Parent Report (Hyperactivity/Impulsivity) Mean = 15.6 (SD = 5.8) ADHD rating scale IV Total Score (Teacher Report) Mean = 25.1 (SD = 12.6) ADHD Rating Scale IV: Teacher Report (Inattentive) Mean = 12.3 (SD = 6.9) ADHD Rating Scale IV: Teachers Report (Hyperactivity/Impulsivity) Mean = 10.9 (SD = 7.1)	P=0.004 P=0.001 P=0.04 P=0.31 P=0.59 P=0.19
Ostberg, 2012[56] 92 Good RCT b	Barkley based Parent + Teacher behavioral intervention	Waitlist	10 weeks 3 months	ADHD-C Parent Mean = 9.1 (SD = 4.5) ADHD-C Teacher Mean = 7.7 (SD = 6.3) ADHD-C Parent Mean = 7.7 (SD = 4.7) ADHD-C Teacher Mean = 7.7 (SD = 5.7)	ADHD-C Parent Mean = 9.8 (SD = 6) ADHD-C Teacher Mean = 9.4 (SD = 6.3) ADHD-C Parent Mean = 10.1 (SD = 5.3) ADHD-C Teacher Mean = 9.4 (SD = 5.4)	NS NS P<.05 NS

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Pfiffner, 2014[57] 199 Good RCT b	Child Life and Attention Skills Treatment	Parent group component only Evaluation and community care Parent group component only Evaluation and community care	10-13 weeks 5-7 months	Parent Child Symptom Inventory Mean=2.2 (SE=0.3) Child Symptom Inventory Mean=2.99 (SE=0.3) Parent Child symptom inventory Mean=2.2 (SE=0.3) Child symptom inventory Mean=3.7 (SE=0.4)	Parent Child Symptom Inventory Mean=3.2 (SE=0.3) Child Symptom Inventory Mean=4.2 (SE=0.3) Parent Child Symptom Inventory Mean=4.1 (SE=0.4) Child Symptom Inventory Mean=5 (SE=0.4) Parent Child Symptom Inventory Mean=3.2 (SE=0.3) Child Symptom Inventory Mean=4.2 (SE=0.4) Parent Child Symptom Inventory Mean=4.1 (SE=0.4) Child Symptom Inventory Mean=4.2 (SE=0.4) Parent Child Symptom Inventory Mean=4.1 (SE=0.4) Child Symptom Inventory Mean=4.2 (SE=0.4)	P=.001 P<0.001 NR NR NR NR P<0.001 P=0.396 NR
Ercan, 2014[58] 120 Fair Observational b	MPH+11 months of parent training	MPH (Usual care)	12 months	CPRS Mean w/in group change = 7.91 (SD = 6.9) CTRS–teacher Mean = 29.69 (SD = 15.03)	CPRS Mean w/in group change = 10.07 (SD = 5.74) CTRS–teacher Mean = 35.27 (SD = 13.47)	NS

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Huang, 2015[59] 97 Fair RCT b	Behavioral-based social skill training for patients and parallel parent group sessions	Group therapy for motivation and treatment per usual care, such as medication and counseling at the outpatient department	6 months	Change in Child Behavioral Checklist Withdrawn Subscale Mean= -.84 (SD=2.3) Change in CBCL Somatic Complaints Subscale Mean within group change= -.14 (SD=2.7) CBCL Change Anxious/Depressed Subscale Mean within group change= -2.19 (SD=4) CBCL Change Social Problems Subscale Mean within group change= -1.4 (SD=2.3) CBCL Change Thought Problems Subscale Mean within group change= -1.02 (SD=2.8) CBCL Change Attention Problems Subscale Mean within group change= -1.26 (SD=2.8) CBCL Change Delinquent Behavior Subscale Mean within group change= -.76 (SD=2.2) CBCL Change Aggressive Behavior Subscale Mean within group change= -4 (SD=7.1)	Change in Child Behavioral Checklist Withdrawn Subscale Mean= -.28 (SD=1.6) Change in CBCL Somatic Complaints Subscale Mean within group change= -1.42 (SD=3.7) CBCL Change Anxious/Depressed Subscale Mean within group change= -.89 (SD=3.7) CBCL Change Social Problems Subscale Mean within group change= -.92 (SD=2.2) CBCL Change Thought Problems Subscale Mean within group change= -1.06 (SD=2.1) CBCL Change Attention Problems Subscale Mean within group change= -1.772 (SD=3.2) CBCL Change Delinquent Behavior Subscale Mean within group change= -.6 (SD=1.9) CBCL Change Aggressive Behavior Subscale Mean within group change= -2.37 (SD=5.9)	P=0.84 P=0.14 P=0.79 P=0.57 P=0.60 P=0.04 P=0.91 P=0.94
Depression or anxiety						
Hiscock, 2015[54] (Papadopoulos, 2015[55]) 244 Good RCT c	Sleep hygiene practices and standardized behavioral strategies	Children in the control group received usual clinical care	6 Months	Depression or anxiety-Depression Anxiety Stress Scale Mean = 31.3 (SD = 23.6) Depression or anxiety-Parent mental health with the Depression Anxiety Stress Scale – Total score	Depression or anxiety-Depression Anxiety Stress Scale Mean = 33.9 (SD = 28.5)	P=0.55
Functional impairment						
Chacko, 2009[51] 120 Good RCT c	STEPP	BPT program Waitlist	2.07 months	Impairment Rating Scale (IRS)-Overall Mean = 3.31 (SD 1.41)	Impairment Rating Scale (IRS)-Overall Mean = 4.11 (SD 1.67) Impairment Rating Scale (IRS)- Overall Mean = 4.65 (SD 1.30)	P<.01 NR

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Pfiffner, 2014[57] 199 Good RCT b	Child Life and Attention Skills Treatment	Parent group component only Evaluation and community care Parent group component only Evaluation and community care	10-13 weeks 5-7 months	Parent CGI Mean=6 (SE=0.7) Teacher CGI Severity Mean=5.8 (SE=0.8) Parent CGI Mean=6 (SE=1) Teacher CGI-Severity Mean=3.4 (SE=0.2)	Parent CGI Mean=5.8 (SE=0.9) Teacher CGI Severity Mean=5.2 (SE=1) Parent CGI Mean=5 (SE=1) Teacher CGI Severity Mean=5 (SE=1.1) Parent CGI Mean=5.8 (SE=1) Teacher CGI-Severity Mean=3.5 (SE=0.2) Parent CGI Mean=5.3 (SE=0.23) Teacher CGI Severity Mean=3.6 (SE=0.2)	P=0.0 P=0.0 NR NR P=0.001 P=0.775 NR NR
Sleep disturbance						
Hiscock, 2015[54] (Papadopoulos, 2015[55]) 244 Good RCT c	Sleep hygiene practices and standardized behavioral strategies	Children in the control group received usual clinical care	6 Months	Sleep disturbance-Child Sleep Habits Questionnaire (CSHQ) Total Score Mean 53.2 (7.5)	Sleep disturbance-Child Sleep Habits Questionnaire (CSHQ) Total Score, Mean = 55.9 (8.8)	P<0.001

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Workforce participation						
Hiscock, 2015[54] (Papadopoulos, 2015[55]) 244 Good RCT c	Sleep hygiene practices and standardized behavioral strategies	Children in the control group received usual clinical care	3 months	Workforce participation-Days late for work Workforce participation-Missed days of work		P=0.02 P=0.03 (both non-parametric tests)

[a] See Methods section "Quality Assessment of Individual Studies" for definitions of quality assessment ratings.

[b] Age categories: a = children aged ≤6 years, b = children aged 7-17, c = children of all ages ≤17.

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

Table H-11. Findings on omega-3 fatty acid supplementation for ADHD

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Behavior changes						
Manor, 2012[60] (Manor, 2013[61]) 200 Good RCT b	Phospha-tidylserine enriched with omega-3 fatty acids	Placebo	15 weeks	Euphoric % patients with outcome = 38.9 Anxiety % patients with outcome = 45 Irritable % patients with outcome = 79.1 Prone Cry % patients with outcome = 62.7 Talk Less % patients with outcome = 31.8 Sad/Unhappy % patients with outcome = 40 Irritability % patients with outcome = 15.31	Euphoric % patients with outcome = 34.6 Anxiety % patients with outcome = 63.5 Irritable % patients with outcome = 84.6 Prone Cry % patients with outcome = 57.7 Talk Less % patients with outcome = 32.7 Sad/Unhappy % patients with outcome = 34 Irritability % patients with outcome = 11.63	NR NR NR NR NR NR NR
Changes in standardized symptom scores						
Anand, 2016[62] 50 Good RCT c	Polyunsaturated fatty acids (300 mg/d) plus atomoxetine (0.5 mg/kg/d)	Atomoxetine (0.5 mg/kg/d)	4 months	Conners Parent Rating Scale-Revised: Short Form Mean = 36.6 (SD = 2.21)	Conners Parent Rating Scale-Revised: Short Form Mean = 37.4 (SD = 2.18)	NS
Gustafsson, 2010[63] 109 Good RCT b	Omega-3 fatty acid supplemen-tation (eico-sapentaenoic acid 500mg daily)	Placebo	15 weeks	Total Conners Parent Rating Scale score Mean = 43.8 (SD = 18.6) Total Conners Rating Scale score Mean = 43.1 (SD = 18.8)	Total Conners Parent Rating Scale score Mean = 39.4 (SD = 18.4) Total Conners Rating Scale score Mean = 40.7 (SD = 17.9)	NS NS

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Johnson, 2009[64] (Johnson, 2012[65]) 75 Good RCT b	Omega-3/6 fatty acid supplemen-tation (792mg daily)	Placebo	3 months (double-blind phase)	ADHD Rating Scale Mean change = -3.78 (7.14)	ADHD Rating Scale Mean change = -1.65 (4.54)	NS
			6 months (open-label extension: continuous and naïve groups)	ADHD Rating Scale Mean change = -7.82 (8.07)	ADHD Rating Scale Mean change = -5.81 (7.16)	NS
Manor, 2012[60] (Manor, 2013[61]) 200 Good RCT b	Phospha-tidylserine enriched with omega-3 fatty acids	Placebo	15 weeks (treatment and placebo groups, N=162)	CRS-P PS-Omega-3 continuous (30 weeks) ADHD Index Mean = 64.05 (10.21)	CRS-P Placebo (weeks 1-15) ADHD Index Mean = 65.67 (12.79)	NS
				CRS-T PS-Omega-3 continuous (30 weeks) ADHD Index Mean= 62.35 (10.64)	CRS-T Placebo (weeks 1-15) ADHD Index Mean = 64.44 (10.07)	NS
			30 weeks (open-label extension: continuous and naïve groups, N=147)	CRS-P PS-Omega-3 continuous (30 weeks) ADHD Index Mean Change = -0.95 (7.91)	CRS-P PS-Omega-3 (weeks 15-30) ADHD Index Mean Change = -2.86 (8.51)	NS
				CRS-T PS-Omega-3 continuous (30 weeks) ADHD Index Mean Change = 0 (8.62)	CRS-T PS-Omega-3 (weeks 15-30) ADHD Index Mean Change = -1.72 (6.19)	NS
Milte, 2012[66] (Milte, 2015[67]) 90 Good RCT b	Fish oil rich in the omega-3 fatty acid, eico-sapentaenoic acid (EPA)	Fish oil rich in the omega-3 fatty acid, docosahexae noiacid (DHA) Placebo: Linoleic acid (LA)	4 months	Conners Parent Rating Scale ADHD total Mean between-group change (vs. placebo) = 1.56 (1.77)	Conners Parent Rating Scale ADHD total Mean between-group change (vs. placebo) = 1.64 (1.9)	NR EPA vs. placebo p=0.38 DHA vs. placebo p=0.39
Raz, 2009[68] 78 Fair RCT b	Omega-3 fatty acid supplemen-tation	Placebo	1.75 months	Conners-ADHD (Teacher) Mean = 3.64 (1.48)	Conners-ADHD (Teacher) Mean = 3.66 (1.12)	NS
				Conners Mood (Teacher) Mean = 2.76 (1.28)	Conners Mood (Teacher) Mean = 2.74 (1.30)	NS
				Conners Mood (Parent) Mean = 3.44 (1.42)	Conners Mood (Parent) Mean = 4.03 (1.25)	NS

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Widenhorn-Muller, 2014[69] 110 Fair RCT b	Omega-3 fatty acid supplementation (720 mg daily) plus 15 mg vitamin E	Placebo	4	CBCL total problems Mean = 62.36 (SE = 1.47) Teacher Report Form--total problems Mean = 55.8 (SE = 1.09)	CBCL total problems Mean = 60.15 (SE = 1.38) Teacher Report Form--total problems Mean = 56.82 (SE = 1.16)	P=0.98 P=0.62
Hariri, 2012[70] 120 Poor RCT b	Omega-3 fatty acid supplemen-tation (900 mg daily)	Placebo	8 weeks	Conners Abbreviated Mean = 21.03 (3.98)	Conners Abbreviated Mean = 24.02 (4.22)	P=0.251
Elevated blood pressure						
Manor, 2012[60] (Manor, 2013[61]) 200 Good RCT b	Phospha-tidylserine enriched with omega-3 fatty acids	Placebo	15 weeks	Systolic Mean = 103.6 (SD = 14.82) Diastolic Mean = 64.66 (SD = 11.39)	Systolic Mean = 100.25 (SD = 12.95) Diastolic Mean = 63.89 (SD = 10.28)	P=0.955 P=0.342
Functional impairment						
Johnson, 2009[64] (Johnson, 2012[65]) 75 Good RCT b	Omega-3/6 fatty acid supplementation (792 mg daily)	Placebo	3 months (double-blind phase) 6 months (open-label extension: continuous and naïve groups)	Clinical Global Impression score Mean change = -0.58 (0.87) Clinical Global Impression score Mean change = -1.24 (1.07)	Clinical Global Impression score Mean change = -0.13 (0.50) Clinical Global Impression score Mean change = -0.93 (0.92)	NS NS
Sleep disturbance						
Manor, 2012[60] (Manor, 2013[61]) 200 Good RCT b	Phospha-tidylserine enriched with omega-3 fatty acids	Placebo	15 weeks	Insomnia % patients with outcome = 38.2 Severe insomnia % patients with outcome = 2.04 Nightmares % patients with outcome = 29.1	Insomnia % patients with outcome = 53.9 Severe insomnia % patients with outcome = 6.98 Nightmares % patients with outcome = 34.6	NR NR NR

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Tics or other movement disorders						
Manor, 2012[60] (Manor, 2013[61]) 200 Good RCT b	Phospha-tidylserine enriched with omega-3 fatty acids	Placebo	15 weeks	Tics % patients with outcome = 22.7	Tics % patients with outcome = 32.7	NR
Gastrointestinal symptoms						
Manor, 2012[60] (Manor, 2013[61]) 200 Good RCT b	Phospha-tidylserine enriched with omega-3 fatty acids	Placebo	15 weeks	Stomachaches % patients with outcome = 39.5 Decreased appetite % patients with outcome = 32.7 Severely decreased appetite % patients with outcome = 4.08	Stomachaches % patients with outcome = 46.2 Decreased appetite % patients with outcome = 32.7 Severely decreased appetite % patients with outcome = 4.65	NR NR NR
Growth suppression						
Manor, 2012[60] (Manor, 2013[61]) 200 Good RCT b	Phospha-tidylserine enriched with omega-3 fatty acids	Placebo	15 weeks	Height in cm Mean = 135.25 (SD = 13.35)	Height in cm Mean = 136.77 (SD = 12.26)	P=0.196
Increased heart rate						
Manor, 2012[60] (Manor, 2013[61]) 200 Good RCT b	Phospha-tidylserine enriched with omega-3 fatty acids	Placebo	15 weeks	Increased Heart Rate Mean = 79.72 (SD = 12.03)	Increased Heart Rate Mean = 81.18 (SD = 13.24)	p=0.825
Personality change						
Manor, 2012[60] (Manor, 2013[61]) 200 Good RCT b	Phospha-tidylserine enriched with omega-3 fatty acids	Placebo	15 weeks	Uninterested % patients with outcome = 32.7	Uninterested % patients with outcome = 38	NR

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Weight decrease						
Manor, 2012[60] (Manor, 2013[61]) 200 Good RCT b	Phospha-tidylserine enriched with omega-3 fatty acids	Placebo	15 weeks	Weight (kg) Mean = 33.39 (SD = 10.61)	Weight (kg) Mean = 33.06 (SD = 8.42)	P=0.980

[a] See Methods section "Quality Assessment of Individual Studies" for definitions of quality assessment ratings.
[b] Age categories: a = children aged ≤6 years, b = children aged 7-17, c = children of all ages ≤17.
Abbreviations: ADHD=attention deficit hyperactivity disorder; CRS-P=Conners Rating Scale-Parent; CRS-T=Conners Rating Scale-Teacher; NR=not reported; SE=standard error; SD=standard deviation; RCT=randomized controlled trial

Table H-12. Findings on herbal interventions or dietary approaches for ADHD

Study N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Behavior changes						
Shakibaei, 2015[71] 66 Good RCT b	Methylphenidate and Ginkgo Biloba	Methylphenidate and placebo	6 weeks	Parent ADHD Rating Scale IV Inattention Mean = 13.58 (SD = 3.68) Parent ADHD Rating Scale IV Hyperactivity-Impulsivity Mean = 11.54 (SD = 4.42) Teacher ADHD Rating Scale IV Inattention Mean = 13.74 (SD = 4.04) Teacher ADHD Rating Scale IV Hyperactivity-Impulsivity Mean = 10.93 (SD = 4.06) Children's Global Assessment Scale (CGAS) Mean w/in group change = 8.92 (SD = 7.37)	Parent ADHD Rating Scale IV Inattention Mean = 14.34 (SD = 4.03) Parent ADHD Rating Scale IV Hyperactivity-Impulsivity Mean = 11.37 (SD = 4.11) Teacher ADHD Rating Scale IV Inattention Mean = 13.75 (SD = 3.85) Teacher ADHD Rating Scale IV Hyperactivity-Impulsivity Mean = 11.2 (SD = 4.43) CGSA Mean w/in group change = 8.51 (SD = 5.33)	P<.001 P=0.417 P=0.004 P=0.203 P=0.901

Study N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Arnold, 2011[72] 52 Fair RCT b	Zinc 15 mg once daily (> 8 weeks with amphetamine in all groups)	Zinc 15mg twice daily	8 weeks	Affective blunting # patients with outcome = 1	Affective blunting # patients with outcome = 0	NR
			>8 weeks	Affective blunting # patients with outcome = 4	Affective blunting # patients with outcome = 0	NR
			8 weeks	Anxiety # patients with outcome = 6	Anxiety # patients with outcome = 2	NR
			>8 weeks	Anxiety # patients with outcome = 9	Anxiety # patients with outcome = 3	NR
			8 weeks	Depression # patients with outcome = 7	Depression # patients with outcome = 2	NR
			>8 weeks	Depression # patients with outcome = 11	Depression # patients with outcome = 4	NR
			8 weeks	Irritability # patients with outcome = 9	Irritability # patients with outcome = 5	NR
			>8 weeks	Irritability # patients with outcome = 9	Irritability # patients with outcome = 6	NR
		Placebo	8 weeks		Affective blunting # patients with outcome = 1	NR
			>8 weeks		Affective blunting # patients with outcome = 6	NR
			8 weeks		Anxiety # patients with outcome = 6	NR
			>8 weeks		Anxiety # patients with outcome = 5	NR
			8 weeks		Depression # patients with outcome = 5	NR
			>8 weeks		Depression # patients with outcome = 9	NR
			8 weeks		Irritability # patients with outcome = 10	NR
			>8 weeks		Irritability # patients with outcome = 14	NR

Study N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Mohammadpour, 2016[73] 54 Fair RCT c	2000 IU Vitamin D plus MPH	Placebo Vitamin D plus MPH	2 days	WPREMB morning symptoms Mean = 2.76 (SD 2.2) WPREMB evening symptoms Mean = 8.32 (SD 3.9) WPREMB total score Mean = 11.08 (SD 5.5)	WPREMB morning symptoms Mean = 3.65 (SD 3.1) WPREMB evening symptoms Mean = 11.68 (SD 5.4) WPREMB total score Mean = 15.34 (SD 7.7)	NS Significant Significant
Changes in appetite						
Arnold, 2011[72] 52 Fair RCT b	Zinc 15 mg once daily (> 8 weeks with amphetamine in all groups)	Zinc 15mg twice daily Placebo	8 weeks >8 weeks 8 weeks >8 weeks	Changes in appetite # patients with outcome = 3 Changes in appetite # patients with outcome = 15	Changes in appetite # patients with outcome = 4 Changes in appetite # patients with outcome = 8 Changes in appetite # patients with outcome = 4 Changes in appetite # patients with outcome = 17	NR NR NR NR
Katz, 2010[74] 120 Fair RCT b	Patented herbal preparation	Placebo	0.5 months	Decreased appetite # patients with outcome = 1	Decreased appetite # patients with outcome = 2	NR
Changes in standardized symptom scores						
Dutta, 2012[75] 86 Good RCT b	Memomet syrup (Bacopa monniera 125 mg, Convulvulus pleuricaulis 100 mg, Centella asiatica 100 mg)	Placebo	4 months	Conners 10-point rating scale (hyperactivity) Mean Percent Change 48%	Conners 10-point rating scale (hyperactivity) Mean Percent Change 29%	Reported as significant in text

Study N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Pelsser, 2011[76] 100 Good RCT c	Restricted elimination diet	No elimination diet	5 weeks after intervention started	ADHD rating scale--Parental total score Mean 24.2 95% CI=19.5, 29.0	ADHD rating scale--Parental total score Mean 1.3 95% CI = 0.2, 2.5 Mean between group change = 23.7 95% CI = 18.6, 28.8	p<.0001
				ADHD rating scale, teacher total score Mean 14.3 95% CI=11.6, 17.1	ADHD rating scale, teacher total score Mean -0.4 95% CI=-1.7, 1.0 Mean between group change = 15.3 95% CI = 12.0, 18.6	p<.0001
				ADHD rating scale, Parent inattention score Mean 11.3 95% CI=8.9, 13.8	ADHD rating scale, Parent inattention score Mean 0.2 95% CI=-0.4, 0.8 Mean between group change = 11.8 95% CI = 9.1, 14.4	p<.0001
				ADHD rating scale, parent hyperactivity and impulsivity score Mean 12.9 95% CI 10.5, 15.3	ADHD rating scale, parent hyperactivity and impulsivity score Mean 0.3 95% CI=-0.6, 1.1 Mean between group change = 11.9 95% CI = 9.3, 14.5	p<.0001
				ADHD rating scale, Teacher hyperactivity and impulsivity score Mean 7.8 95% CI= 6.2, 9.5	ADHD rating scale, Teacher hyperactivity and impulsivity score Mean -0.6 95% CI=-1.4, 0.2 Mean between group change = 8.5 95% CI = 6.8, 10.3	p<.0001
				Abbreviated Conners' scale-Parent Mean 12.0 95% CI=9.4, 14.6	Abbreviated Conners' scale-Parent Mean 0.1 95% CI=-0.7, 0.8 Mean between group change = 11.8 95% CI = 9.2, 14.5	p<.0001
				Abbreviated Conners' scale-Teacher Mean 6.6 95% CI= 4.9, 8.4	Abbreviated Conners' scale-Teacher Mean -0.8 95% CI=-1.4, -0.3 Mean between group change = 7.5 95% CI = 5.9, 6.2	p<.0001
				ADHD Rating Scale "Behaviour scores" Total score Mean = 9.6 (SD = 6.9)	ADHD Rating Scale "Behaviour scores" Total score Mean = 46.9 (SD = 5.5)	
				ADHD Rating Scale "Behaviour scores" Inattention Mean = 4.1 (SD = 3.9)	ADHD Rating Scale "Behaviour scores" Inattention Mean= 23.4 (SD = 26.3)	
				ADHD Rating Scale Hyperactivity and Impulsivity Mean = 5.3 (SD = 3.9)	ADHD Rating Scale Hyperactivity and Impulsivity Mean = 24.1 (SD = 4.2)	p<.0001
				Abbreviated Conners Scale Mean = 5.9 (SD = 3.7)	Abbreviated Conners Scale Mean = 24 (SD = 3.7)	

Study N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Arnold, 2011[72] 52 Fair RCT b	Zinc 15 mg once daily (> 8 weeks with amphetamine in all groups)	Zinc 15mg twice daily	8 weeks	SNAP parent DSM-IV ADHD symptoms Mean = 1.92 (SD = 0.54)	SNAP parent DSM-IV ADHD symptoms Mean = 1.47 (SD = 0.65)	NR
				CRS-parent Mean = 1.93 (SD = 0.49)	CRS-parent Mean = 1.62 (SD = 0.73)	NR
				CRS-Teacher * zinc vs. placebo Mean = 1.90 (0.67)	CRS-Teacher * zinc vs. placebo Mean = 1.71 (SD = 0.79)	NR
		Placebo			SNAP parent DSM-IV ADHD symptoms Mean = 1.9 (SD = 0.63)	NR
					CRS-parent Mean = 1.84 (0.56)	NR
		Zinc 15mg twice daily	10 weeks	SNAP parent DSM-IV ADHD symptoms Mean = 1.61 (SD = 0.52)	SNAP parent DSM-IV ADHD symptoms Mean = 1.26 (0.62)	NR
				CRS-parent Mean = 1.52 (SD = 0.52)	CRS-parent Mean = 1.21 (SD = 0.75)	NR
				CRS-Teacher * zinc vs. placebo Mean = 1.23 (SD = 0.58)	CRS-Teacher * zinc vs. placebo Mean = 1.40 (0.81)	NR
		Placebo			SNAP parent DSM-IV ADHD symptoms Mean = 1.47 (0.51)	NR
					CRS-parent Mean = 1.24 (0.5)	NR
		Zinc 15mg twice daily	13 weeks	SNAP parent DSM-IV ADHD symptoms Mean = 1.19 (0.56)	SNAP parent DSM-IV ADHD symptoms Mean = 0.67 (0.38)	NR
				CRS-parent Mean = 1.08 (SD = 0.45)	CRS-parent Mean = 0.81 (SD = 0.58)	NR
				CRS-Teacher * zinc vs. placebo Mean = 0.9 (SD = 0.65)	CRS-Teacher * zinc vs. placebo Mean = 0.63 (0.58)	NR
		Placebo			SNAP parent DSM-IV ADHD symptoms Mean = 1.01 (SD = 0.38)	NR
					CRS-parent Mean = 0.91 (0.43)	NR
		Zinc 15mg twice daily	21 weeks	SNAP parent DSM-IV ADHD symptoms Mean = .99 (SD = 0.52)	SNAP parent DSM-IV ADHD symptoms Mean = 0.67 (SD = 0.56)	
				CRS-parent Mean = .83 (SD = 0.47)	CRS-parent Mean = 0.8 (SD = 0.59)	
				CRS-Teacher * zinc vs. placebo Mean = 1.17 (SD = 0.53)	CRS-Teacher * zinc vs. placebo Mean = 0.94 (0.69)	
		Placebo			SNAP parent DSM-IV ADHD symptoms Mean = 0.82 (0.44)	
					CRS-parent Mean = 0.72 (0.52)	

Study N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Mohammadpour, 2016[73] 54 Fair RCT c	2000 IU Vitamin D plus MPH	Placebo Vitamin D plus MPH	2 days	CPRS Oppositional Mean = 55.28 (SD 11.6) CPRS Cognitive Mean = 56 (SD 11.8) CPRS Hyperactive Mean = 56.92 (SD 11.8) CPRS ADHD index Mean = 55.84 (SD 10.2) ADHD-RS, Inattentive Mean = 49.80 (SD 31.7) ADHD-RS, Hyperactive/Impulsive Mean = 69.40 (SD 22.4) ADHD-RS, Total score Mean = 60.44 (SD 22.1)	CPRS Oppositional Mean = 59.76 (SD 12.1) CPRS Cognitive Mean = 57.21 (SD 10.5) CPRS Hyperactive Mean = 59.79 (SD 12.4) CPRS ADHD index Mean = 56.79 (SD 9.6) ADHD-RS, Inattentive Mean = 61.37 (SD 29.5) ADHD-RS, Hyperactive/Impulsive Mean = 77.44 (SD 19.5) ADHD-RS, Total score Mean = 71.75 (SD 23.6)	NR NR NR NR NR NR NR
Gastrointestinal symptoms						
Arnold, 2011[72] 52 Fair RCT b	Zinc 15 mg once daily	Zinc 15mg twice daily Placebo	8 weeks >8 weeks 8 weeks >8 weeks	Stomachaches + other GI # patients with outcome = 11 Stomachaches + other GI # patients with outcome = 11	Stomachaches + other GI # patients with outcome = 4 Stomachaches + other GI # patients with outcome = 3 Stomachaches + other GI # patients with outcome = 18 Stomachaches + other GI # patients with outcome = 14	NR NR NR NR
Katz, 2010[74] 120 Fair RCT b	Patented herbal preparation	Placebo	0.5 months	GI discomfort # patients with outcome = 2	GI discomfort # patients with outcome = 3	NR
Mood disorders						
Katz, 2010[74] 120 Fair RCT b	Patented herbal preparation	Placebo	0.5 months	Emotional lability # patients with outcome = 2	Emotional lability # patients with outcome = 4	NR

Study N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Motor vehicle collisions						
Katz, 2010[74] 120 Fair RCT b	Patented herbal preparation	Placebo	0.5 months	Accidental injury # patients with outcome = 1	Accidental injury # patients with outcome = 2	NR
Sleep disturbance						
Arnold, 2011[72] 52 Fair RCT b	Zinc 15 mg once daily	Zinc 15mg twice daily	8 weeks >8 weeks	Sleep # patients with outcome = 0 Sleep # patients with outcome = 8	Sleep # patients with outcome = 1 Sleep # patients with outcome = 6	NR NR
		Placebo	8 weeks >8 weeks		Sleep # patients with outcome = 4 Sleep # patients with outcome = 16	NR NR
Katz, 2010[74] 120 Fair RCT b	Patented herbal preparation	Placebo	0.5 months	Sleep disturbance # patients with outcome = 1	Sleep disturbance # patients with outcome = 4	NR
Suicide ideation						
Arnold, 2011[72] 52 Fair RCT b	Zinc 15 mg once daily	Zinc 15mg twice daily	8 weeks >8 weeks	Harm to self or others # patients with outcome = 1 Harm to self or others # patients with outcome = 1	Harm to self or others # patients with outcome = 0 Harm to self or others # patients with outcome = 0	NR NR
		Placebo	8 weeks >8 weeks		Harm to self or others # patients with outcome = 0 Harm to self or others # patients with outcome = 0	NR NR

Study N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Tics or other movement disorders						
Arnold, 2011[72] 52 Fair RCT b	Zinc 15 mg once daily	Zinc 15mg twice daily Placebo	8 weeks >8 weeks 8 weeks >8 weeks	Stereotypical behaviors # patients with outcome = 3 Stereotypical behaviors # patients with outcome = 7	Stereotypical behaviors # patients with outcome = 1 Stereotypical behaviors # patients with outcome = 2 Stereotypical behaviors # patients with outcome = 5 Stereotypical behaviors # patients with outcome = 9	NR NR NR NR

[a] See Methods section "Quality Assessment of Individual Studies" for definitions of quality assessment ratings.
[b] Age categories: a = children aged ≤6 years, b = children aged 7-17, c = children of all ages ≤17.
Abbreviations: ADHD=attention deficit hyperactivity disorder; CRS=Conners Rating Scale; SNAP=Swanson, Nolan and Pelham Revision; WPREMB=Weekly Parent Ratings of Evening and Morning Behavior

Table H-13. Findings on other approaches for ADHD

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Academic performance						
Evans, 2016[77] 326 Fair RCT b	Challenging Horizons Program–after school version	Challenging Horizons Program–mentoring version Community Care	12 months	GPA Mean = 2.3	GPA Mean = 2.1 GPA Mean = 2.1	P= 0.146

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Mautone, 2012[78] 61 Fair RCT c	Family-School Success-Early Elementary	Coping with ADHD through Relationships and Education	12 weeks 2 months post-12 weeks	Academic Competence Evaluation Scales score Mean = 3.38 (SD = 0.57) ACES score Mean = 3.39 (SD = 0.48)	Academic Competence Evaluation Scales score Mean = 3.11 (SD = 0.5) ACES score Mean = 3.25 (SD = 0.66)	NR NR
Power, 2012[79] 199 Fair RCT b	Family School Success Therapy	Coping With ADHD Through Relationships and Education	3 months 6 months	Academic Performance Rating Scale Mean = 3.32 (SD = 0.65) Mean = 3.51 (SD = 0.64)	Academic Performance Rating Scale Mean = 3.2 (SD = 0.68) Mean = 3.36 (SD = 0.76)	NS NS
Behavior changes						

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Abikoff, 2015[80] 164 Good RCT a	New Forest Parenting Package	Helping the noncompliant child	6.8 months	Behavior changes-Conners Parent Rating Scale Revised Scale-Revised - Total Mean = 68.01 (SD = 11.69) Behavior changes-Conners Parent Rating Scale Revised Scale-Revised - Inattention Mean = 65.60 (SD 13.53) Behavior changes-Conners Parent Rating Scale Revised Scale-Revised - Hyperactivity Mean = 68.08 (SD 10.69) Behavior changes-Conners Teachers Rating Scale Revised Scale-Revised - Total Mean = 64.27 (SD = 12.27) Behavior changes-Conners Teacher Rating Scale Revised Scale-Revised - Inattention Mean = 61.39 (SD = 13.58) Behavior changes-Conners Teacher Rating Scale Revised Scale-Revised - Hyperactivity Mean = 64.25 (SD = 11.64)	Behavior changes-Conners Parent Rating Scale Revised Scale-Revised - Total Mean = 63.44 (SD = 10.13) Behavior changes-Conners Parent Rating Scale Revised Scale-Revised - Inattention Mean = 61.74 (SD 10.04) Behavior changes-Conners Parent Rating Scale Revised Scale-Revised - Hyperactivity Mean = 63.39 (SD 10.24) Behavior changes-Conners Teachers Rating Scale Revised Scale-Revised - Total Mean = 62.06 (SD = 11.39) Behavior changes-Conners Teacher Rating Scale Revised Scale-Revised - Inattention Mean = 60.48 (SD = 11.79) Behavior changes-Conners Teacher Rating Scale Revised Scale-Revised - Hyperactivity Mean = 62.01 (SD = 12.06)	NS NS NS NS NS NS
		Control			Behavior changes-Conners Parent Rating Scale Revised Scale-Revised - Total Mean = 76.44 (SD = 9.84) Behavior changes-Conners Parent Rating Scale Revised Scale-Revised - Inattention Mean = 75.31 (SD 10.38) Behavior changes-Conners Parent Rating Scale Revised Scale-Revised - Hyperactivity Mean = 74.45 (SD 10.67) Behavior changes-Conners Teachers Rating Scale Revised Scale-Revised - Total Mean = 70.65 (SD = 11.22) Behavior changes-Conners Parent Rating Scale Revised Scale-Revised - Inattention Mean = 68.22 (SD = 11.81) Behavior changes-Conners Parent Rating Scale Revised Scale-Revised - Hyperactivity Mean = 70.26 (SD = 11.98)	P=.001 P=.001 P=.001 NS NS NS

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Mohammadi, 2012[81] (Mostafavi, 2012[82]) 60 Fair RCT b	MPH + melatonin	MPH + placebo	8 weeks	Irritability # patients with outcome = 16 Sadness # patients with outcome = 10	Irritability # patients with outcome = 10 Sadness # patients with outcome = 2	NR NR
Myers, 2015[83] 223 Fair RCT c	Telemedicine	Usual Care + Consult	25 weeks	Behavior changes-Vanderbilt caregiver, meeting criteria for inattention Behavior changes-Vanderbilt caregiver, meeting criteria for hyperactivity Behavior changes-Vanderbilt caregiver, meeting criteria for Combined Behavior changes-Vanderbilt teacher, meeting criteria for inattention Behavior changes-Vanderbilt teacher, meeting criteria for hyperactivity Behavior changes-Vanderbilt teacher, meeting criteria for combined		P<.001 P=.02 P=.005 NS P=.02 P=.045

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Oberai, 2013[84] 61 Fair RCT b	Homeopathy	Placebo	6 weeks	CPRS-R Oppositional Mean = 56.4 (SD = 7) CPRS-R Cognition Problems Mean = 56.6 (SD = 7.4) CPRS-R Hyperactivity Mean = 63.7 (SD = 9.8) CPRS-R ADHD Index Mean = 58.2 (SD = 7.3)	CPRS-R Oppositional Mean = 63.2 (SD = 8.3) CPRS-R Cognition Problems Mean = 67.4 (SD = 5.4) CPRS-R Hyperactivity Mean = 78.3 (SD = 7.9) CPRS-R ADHD Index Mean = 68.3 (SD = 4.6)	NR NR NR NR
			12 weeks	CPRS-R Oppositional Mean =49.5 (9.5) CPRS-R Cognition Problems Mean = 50.7 (7.7) CPRS-R Hyperactivity Mean = 55.6 (11.9) CPRS-R ADHD Index Mean = 51.8 (9.1) Conners Parent Rating Scale – Revised Effect size = 0.22	CPRS-R Oppositional Mean = 66.2 (7.6) CPRS-R Cognition Problems Mean = 66.6 (6.2) CPRS-R Hyperactivity Mean = 78.2 (6.9) CPRS-R ADHD Index Mean = 68.4 (5)	P=.0001 P=.0001 P=.0001 P=.0001 P = 0.005
Changes in appetite						
Mohammadi, 2012[81] (Mostafavi[82]) 60 Fair RCT b	MPH + melatonin	MPH + placebo	8 weeks	Appetite score Mean = 13.26 Loss of appetite # patients with outcome = 14	Appetite score Mean = 12.33 Loss of appetite # patients with outcome = 11	P=0.755

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Changes in standardized symptom scores						
Hong, 2015[85] 48 Fair RCT b	Acupuncture	Waitlist control	1.5 months	ADHD-RS (Korean version) total score Mean = -4.91 (SD 10.50) ADHD-RS Inattention Mean w/in group change = -2.67 (SD 4.90) ADHD-RS Hyperactivity/Impulsivity Mean w/in group change = -2.26 (SD 5.50) Conners-RS Mean w/in group change = -2.51 (SD 4.95) CBCL total score Mean w/in group change = -7.79 (SD 16.69) CBCL-ADHD subscale Mean w/in group change = -1.38 (SD 3.54) CBCL-external subscale Mean w/in group change = -1.85 (SD 7.19)	ADHD-RS (Korean version) total score Mean = -4.00 (SD 11.00) ADHD-RS Inattention Mean w/in group change = -1.68 (SD 4.61) ADHD-RS Hyperactivity/Impulsivity Mean w/in group change = -2.84 (SD 4.00) Conners-RS Mean w/in group change = -1.78 (SD 4.14) CBCL total score Mean w/in group change = -3.00 (SD 25.00) CBCL-ADHD subscale Mean w/in group change = -0.64 (SD 4.36) CBCL-external subscale Mean w/in group change = -1.00 (SD 10.00)	0.561 0.250 0.956 0.385 0.393 0.247 0.632
Mohammadi, 2012[81] (Mostafavi, 2012[82]) 60 Fair RCT b	MPH + melatonin	MPH + placebo	8 weeks	ADHD RS attention score Mean = 11.11 ADHD-RS Hyperactivity score Mean = 11.62	ADHD RS attention score Mean = 11.29 ADHD-RS Hyperactivity score Mean = 10.96	P= 0.974 P= 0.720
Webster-Stratton, 2011[86] 99 Fair RCT c	Incredible Years Program	Waitlist	5 months	CBCL-mother Attention problems Mean = 65.8 (SD = 7) CBCL Father – Attention problems Mean = 64.8 (SD = 8.6)	CBCL-mother Attention problems Mean = 68.8 (SD = 9.6) CBCL Father – Attention problems Mean = 65.8 (SD = 10)	NS NS

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Functional impairment						
Evans, 2016[77] 326 Fair RCT b	Challenging Horizons Program–after school version	Challenging Horizons Program–mentoring version Community Care	6 months post-treatment	Impairment Rating Scale- Parent report; relation to children Mean = 1.76 (SD = 1.89) Impairment Rating Scale- Teacher report; Relation with peers Mean = 1.93 (SD = 1.91)	Impairment Rating Scale- Parent report; relation to children Mean = 1.67 (SD = 1.78) Impairment Rating Scale- Teacher report; Relation with peers Mean = 1.97 (SD = 1.83) Impairment Rating Scale- Parent report; relation to children Mean = 1.8 (SD = 1.69) Impairment Rating Scale- Teacher report; Relation with peers Mean = 1.72 (SD = 1.94)	NR NS NS
Hong, 2015[85] 48 Fair RCT b	Acupuncture	Waitlist control	1.5 months	CGI-S Mean w/in group change = -0.83 (SD 1.00)	CGI-S Mean w/in group change = 0.00 (SD 1.00)	0.012
Oberai, 2013[84] 61 Fair RCT b	Homeopathy	Placebo	6 weeks 12 weeks	CGI-SS Mean = 2.9 (SD = 0.7) Clinical Global Impression Severity Scale Mean = 2.5 (0.7)	CGI-SS Mean = 3.8 (SD = 0.6) Clinical Global Impression Severity Scale Mean = 4 (0.6)	NR P=.0001
Gastrointestinal symptoms						
Mohammadi, 2012[81] (Mostafavi, 2012[82]) 60 Fair RCT b	MPH + melatonin	MPH + placebo	8 weeks	Stomachache # patients with outcome = 9 Nausea and vomiting # patients with outcome = 3	Stomachache # patients with outcome = 5 Nausea and vomiting # patients with outcome = 3	NR NR

Study (Companion) N Quality[a] Design Age Category[b]	Intervention	Comparison	Follow-up Times	Findings–Intervention	Findings–Comparison	Between group P value
Sleep disturbance						
Mohammadi, 2012[81] (Mostafavi, 2012[82]) 60 Fair RCT b	MPH + melatonin	MPH + placebo	8 weeks	Mean sleep latency (min) Mean = 17.96 Total sleep (hour) Mean = 8.51 SDSC sleep score Mean = 41.3 Insomnia # patients with outcome = 8 Sleepiness # patients with outcome = 4	Mean sleep latency (min) Mean = 26.37 Total sleep (hour) Mean = 8.27 SDSC sleep score Mean = 45.5 Insomnia # patients with outcome = 8 Sleepiness # patients with outcome = 4	P=0.267 P= 0.197 P= 0.528 NR NR
Tics or other movement disorders						
Mohammadi, 2012[81] (Mostafavi, 2012[82]) 60 Fair RCT b	MPH + melatonin	MPH + placebo	8 weeks	Dyskinesias # patients with outcome = 0 Tics # patients with outcome = 1	Dyskinesias # patients with outcome = 2 Tics # patients with outcome = 1	NR NR
Weight decrease						
Mohammadi, 2012[81] (Mostafavi, 2012[82]) 60 Fair RCT b	MPH + melatonin	MPH + placebo	8 weeks	Weight loss # patients with outcome = 9	Weight loss # patients with outcome = 9	NR

[a] See Methods section "Quality Assessment of Individual Studies" for definitions of quality assessment ratings.
[b] Age categories: a = children aged ≤6 years, b = children aged 7-17, c = children of all ages ≤17.
Abbreviations: ADHD=attention deficit hyperactivity disorder; CBCL=Child Behavior Checklist; CGI-SS= Clinical Global Impression of Severity of Suicidality; CPRS=Conners Parent Rating Scale; GPA=grade point average; SDSC=Sleep Disturbance Scale for Children

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