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

Background

The Patient-Centered Outcomes Research Institute (PCORI) is partnering with AHRQ to update a systematic evidence review on diagnosis and treatment for attention deficit hyperactivity disorder (ADHD) in children and adolescents. The American Academy of Pediatrics (AAP), the nominator of the 2018 AHRQ systematic review[1], will partner with PCORI in this endeavor with the hope that the results of the update will provide valuable insight for future guidelines for the diagnosis and treatment of ADHD.

ADHD is a chronic neurobehavioral disorder consisting of a pattern of inattention and/or hyperactivity, impulsivity, more frequent and severe than typically observed in individuals of comparable developmental levels; it is among the most common disorders of childhood[2]. Children with ADHD often present with a number of behavioral, social, and academic concerns. The effects of these concerns can be persistent, and most individuals experience appreciable symptoms into adulthood[3]. Early and effective treatment may be helpful in improving long-term outcomes[4].

Estimates of ADHD prevalence vary across diagnostic criteria, evaluation methods, and populations, with recent estimates indicating that 2% - 9.5% of school-aged children and adolescents have ADHD[4]. In the United States, a national survey conducted in 2016 found 9.4% of children aged 2 – 17 years had a diagnosis of ADHD[3]. ADHD is more prevalent among boys than girls[5], with boys more than twice as likely to receive an ADHD diagnosis[3]. Approximately one-third of children are diagnosed before 6 years of age, most frequently by their pediatrician or primary care provider[3]. ADHD is most common in non-Hispanic, white (10.75%) and Black (9.85%) children[6], but differences across race/ethnicity for diagnosis are generally thought to be an artefact of underdiagnosis and undertreatment of Black and Hispanic children [7, 8].

Management options for ADHD include pharmacologic and nonpharmacologic treatments, used alone or in combination[3]. Pharmacologic treatments include stimulant and nonstimulant medications, with methylphenidate (a stimulant) generally recommended as the first line option. Nonpharmacologic interventions for the treatment of ADHD encompass behavioral interventions, parent training, school-based interventions, social skills training, neurofeedback, physical activity, dietary interventions, vitamins and supplements, mindfulness, and other alternative therapies[4]. Children receiving treatment for ADHD should be monitored regularly by a primary care provider for adherence to treatment plan, response to treatment, and any adverse effects. The frequency of monitoring visits depends on the use of pharmacologic treatment and how well the child responds to the treatment plan[4].

The American Academy of Pediatrics (AAP) published a clinical practice guideline in 2019 on the diagnosis, evaluation, and treatment of ADHD in children and adolescents[3], which was informed by the 2018 AHRQ systematic review. Since then, findings from a large number of new trials have been released, particularly pertaining to the treatment of ADHD and focused on nonpharmacologic treatment. Consequently, AAP is interested in an update of the systematic

review of diagnosis and treatment for attention deficit hyperactivity disorder (ADHD) in children and adolescents.

Draft Key Questions

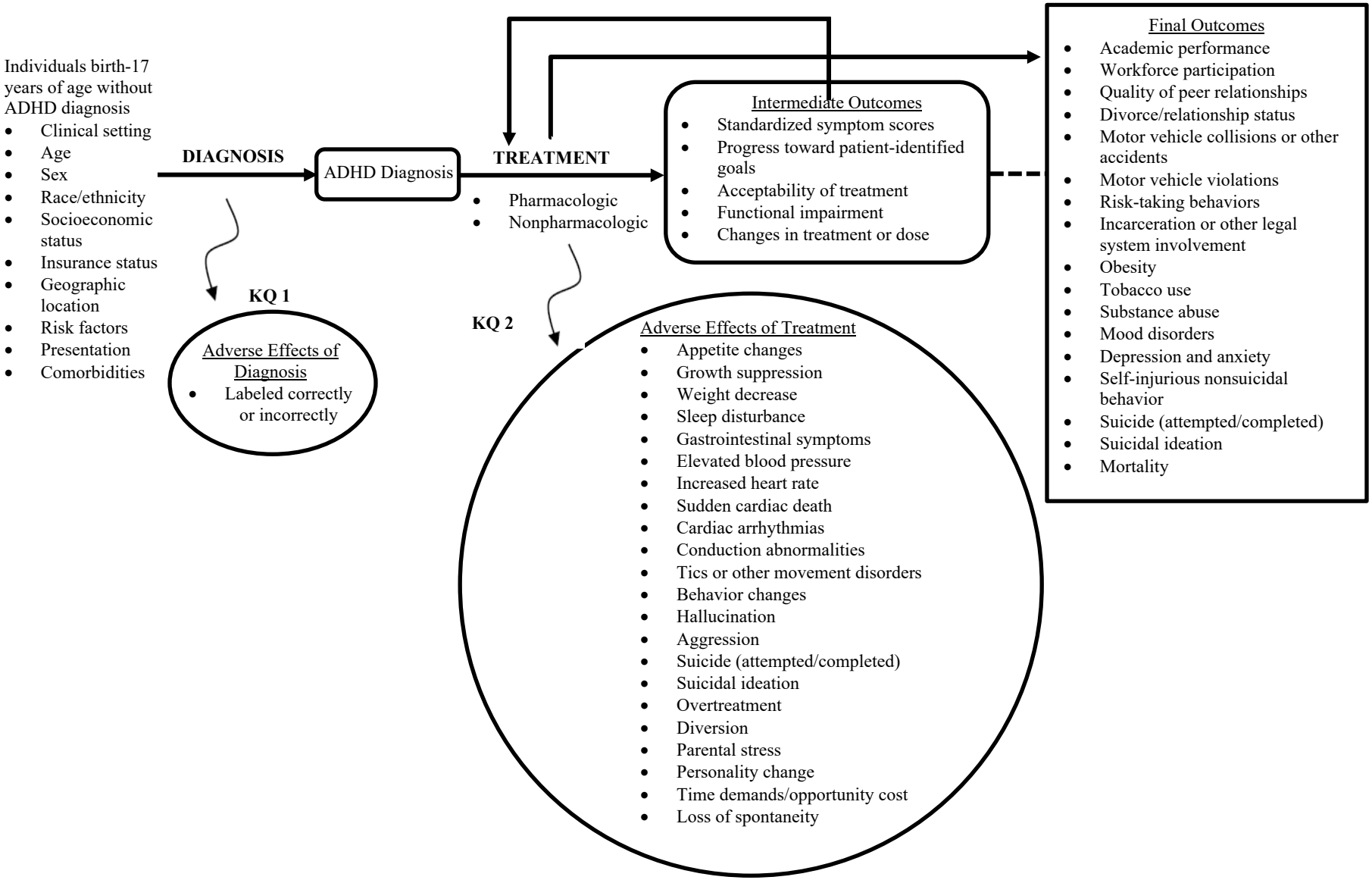
KQ1. For the diagnosis of ADHD:
a. What is the comparative diagnostic accuracy of approaches that can be used in the primary care practice setting or by specialists to diagnose ADHD among individuals younger than 7 years of age?
b. What is the comparative diagnostic accuracy of EEG, imaging, or approaches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

KQ2. What are the comparative safety and effectiveness of pharmacologic and/or nonpharmacologic treatments of ADHD in improving outcomes associated with ADHD? 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?

KQ3. 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)?

Draft Analytic Framework

Figure 1. Draft analytic framework for Attention Deficit Hyperactivity Disorder: Diagnosis and Treatment in Children and Adolescents



PICOTS

Table 1: PICOTS for Attention Deficit Hyperactivity Disorder: Diagnosis and Treatment in Children and Adolescents

PICOTS Element	Inclusion Criteria	Exclusion Criteria
Population	**KQ 1:** Individuals birth through 17 years of age without the diagnosis of ADHD, divided by sub-question 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.
	
	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]:
	  ○ Psychostimulants
	  ▪ Methylphenidate (MPH)
	  ▪ Dexmethylphenidate (D-TMP)
	  ▪ Dextroamphetamine (DEX)
	  ▪ Lisdexamfetamine (LDX)
	  ▪ Mixed amphetamine salts (MAS)
	  ▪ Amphetamine
	  ○ Tricyclic antidepressants
	  ▪ *Desipramine
	  ▪ *Nortriptyline
	  ○ Selective norepinephrine reuptake inhibitors
	  ▪ Atomoxetine (ATX)
		KQ 1: Validation studies or diagnosis conducted using a non-validated 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
	○ Alpha-2 agonists ▪ Clonidine (immediate and extended release) ▪ Guanfacine extended release (GXR) ▪ *Guanfacine immediate release (GIR) ○ 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 • Nonpharmacologic therapies considered include psychosocial interventions, behavioral interventions, cognitive behavioral therapy, digital gamified cognitive therapies, 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. Include the selection of scales/validated tools for monitoring of ADHD severity and treatment response along with forms of remote monitoring or telehealth strategies.	
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 different settings of follow-up.	**KQ 1:** Comparison to diagnosis with a nonvalidated instrument
Outcomes	**KQ1:** • Accuracy of diagnostic strategy, as measured by: ○ Diagnostic concordance of primary care provider with specialist ○ Inter-rater reliability ○ Internal consistency	

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	○ Test-retest ○ Sensitivity ○ Specificity ○ Positive predictive value ○ Negative predictive value ○ False positives ○ False negatives ○ Risk of missed condition that can appear as ADHD (i.e., misdiagnosis) • Labeling is any measure of stigma following diagnosis comparing those with and without ADHD. **KQ 2:** • Intermediate outcomes: ○ 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) ○ Acceptability of treatment ○ Functional impairment (assessed using the Clinical Global Impressions [CGI] scale of the Impairment Rating Scale [IRS]) • Final outcomes include: ○ 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) ○ Workforce participation ○ Quality of peer relationships ○ Divorce/relationship status ○ Motor vehicle collisions or other accidents ○ Motor vehicle violations ○ Risk-taking behaviors ○ Incarceration or other interactions with the legal system (juvenile detention, probation, court-mandated interventions, need for residential placement) ○ Obesity ○ Tobacco use ○ Substance abuse ○ Mood disorders ○ Depression or anxiety ○ Self-injurious nonsuicidal behavior ○ Suicide (attempted or completed)	

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	○ Suicidal ideation ○ Mortality • Adverse effects of treatment, including: ○ Changes in appetite ○ Growth suppression ○ Weight decrease ○ Sleep disturbance ○ Gastrointestinal symptoms ○ Elevated blood pressure ○ Increased heart rate ○ Risk of sudden cardiac death ○ Cardiac arrhythmias ○ Conduction abnormalities ○ Tics or other movement disorders ○ Behavior changes ○ Hallucination ○ Aggression ○ Suicide (attempted or completed) ○ Suicidal ideation ○ Overtreatment ○ Diversion of pharmacotherapy ○ Parental stress ○ Personality change ○ Time demands/opportunity cost ○ Loss of spontaneity ○ Chemical leukoderma ○ Priapism **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	
Setting	**KQ 1:** Primary or specialty care settings. **KQs 2 and 3:** Any (including remote monitoring and telehealth)	
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: ○ ≥20 subjects for KQs 1 and 3 ○ ≥50 subjects for KQ 2 (or 100 subjects for studies comparing two or more	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

PICOTS Element	Inclusion Criteria	Exclusion Criteria
	pharmacologic treatments approved by the FDA for the treatment of ADHD) • Observational studies with sample size: ○ ≥20 subjects for KQs 1 and 3 ○ ≥50 subjects for KQ 2 (or 100 subjects for studies comparing two or more pharmacologic treatments approved	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

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