

Review of Clinical Outcome Assessments in Pediatric Attention-Deficit/Hyperactivity Disorder

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Purpose: Various clinical outcome assessments (COAs) are used in clinical research to assess and monitor treatment efficacy in pediatric attention-deficit/hyperactivity disorder (ADHD) trials. It is unclear whether the concepts assessed are those that are important to patients and their caregivers. The concepts measured by commonly used COAs in this population have not been explicitly compared.

Methods: We conducted reviews of the qualitative literature to extract information on pediatric ADHD-related concepts reported by pediatric patients, parents, and teachers. Using these concepts, we developed a conceptual framework of pediatric ADHD using both the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) criteria and the additional symptoms and behavioral impacts identified in the literature. We searched for COAs that have been used in pediatric ADHD research and mapped their items based on their conceptual underpinning.

Results: Of the 27 COAs found in the empirical literature, 4 COAs assessed only DSM symptoms. The most comprehensive coverage of our conceptual framework was seen in the Swanson, Nolan, and Pelham Rating Scale–DSM-IV (SNAP-IV). Eighteen COAs were used in at least 1 clinical trial: ADHD-Rating Scale-IV (ADHD-RS-IV) was used most often (n=77), followed by SNAP-IV (n=50), Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale (SKAMP; n=31), Weiss Functional Impairment Rating Scale (WFIRS; n=24), and Vanderbilt ADHD Diagnostic Rating Scale (VADRS; n=15).

Conclusion: We identified symptoms and behavioral impacts from qualitative studies in pediatric ADHD that are not included in DSM-based criteria. Most COAs used in pediatric ADHD clinical trials measure only those symptoms listed in the DSM. While these COAs can measure symptom severity, they may not assess the full range of symptoms and impacts important to patients and their caregivers. Future research is needed to measure all concepts important to patients and caregivers within ADHD clinical trials.

Keywords: clinical outcome assessment, attention-deficit/hyperactivity disorder, children, adolescents, pediatrics, assessment scales, efficacy

Introduction

Attention-deficit/hyperactivity disorder (ADHD), a neurodevelopmental condition affecting both children and adults, comprises behavioral symptoms and attentional dysregulation (eg, inattentiveness, impulsivity, overactivity).¹ The prevalence of ADHD in the United States is about 6.1 million among children ages 2–17 years.² ADHD is a lifelong and impairing disorder, resulting in significant challenges to

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educational and vocational attainment as well as increased risks for negative physical, psychosocial, and financial outcomes, particularly when untreated.³

Although effective interventions for ADHD exist – including stimulant and nonstimulant medications and nonpharmacologic therapies^{4,5} – evaluation of treatment response can be difficult because of the subjectivity of ADHD symptoms.⁶ Outcome measures in clinical trials for ADHD treatments are often rating instruments based on symptom criteria defined by the *Diagnostic and Statistical Manual of Mental Disorders* (DSM).⁷ The symptoms of ADHD listed in both the Fourth and Fifth Editions (DSM-IV and DSM-5, respectively) are the same; changes between the 2 diagnostic editions were limited to additional examples of symptom manifestations, criteria for age of onset, and minor wording changes (eg, ADHD “types” in the DSM-IV are called “presentations” in the DSM-5).⁸ However, individuals with ADHD are typically referred for evaluation and treatment because of dysfunction in social, emotional, familial, academic, and/or occupational roles rather than ADHD symptoms alone.⁹ Therefore, it is necessary to evaluate treatment benefits beyond symptom reduction by using additional clinical outcome assessments (COAs).

COAs, as defined by the US Food & Drug Administration (FDA), are measures that “describe or reflect how a patient feels, functions, or survives.”¹⁰ COAs include outcome measures that are patient-reported, observer-reported, or clinician-reported as well as performance outcome measures.¹⁰ COA-based outcomes may be influenced by personal choices, judgment, and motivation.¹¹ They should measure treatment benefit on meaningful aspects of how a patient functions, feels, or survives in his/her life.¹¹ As such, the improvement of the concept(s) measured should be meaningful to the patient in his/her usual or typical life (outside of the clinical trial setting).¹¹

Despite a need to assess outcomes meaningful to pediatric patients with ADHD and their caregivers, there has not yet been a formal evaluation of the relevance of concepts measured by COAs commonly used within clinical trials in ADHD. Whether these COAs measure meaningful aspects of pediatric patients’ and their caregivers’ typical lives has also not been examined. In addition, the degree to which COAs used in pediatric ADHD clinical trials to support label claims capture the concepts important to patients has not been examined. The aim of this literature review is to: 1) identify concepts that are important to pediatric patients with ADHD and their caregivers; 2) identify COAs that

have been used in pediatric ADHD research and explore the extent to which they align with the identified concepts; and 3) identify the COAs and their frequency of use in clinical trials, including those that have undergone regulatory review to support product label claims.

Methods

We performed separate literature reviews to address 3 questions:

1. What concepts should be assessed by pediatric ADHD COAs?
2. How well are these concepts measured by existing COAs used to assess ADHD symptoms and impacts in children/adolescents?
3. Which COAs are currently used in pediatric ADHD clinical trials, including those that support label claims and have been reviewed by regulatory bodies?

After applying the search strategy, article filtering was conducted in 2 stages: first, on a title/abstract level, followed by a full-text level review of articles retained after the first filtering. We extracted data on the population, methods, and patient- or caregiver-reported concepts from the full-text articles. Each article was analyzed by one reviewer, and the resulting data were assessed by a second reviewer. If any aspect of the data was unclear, both reviewers reassessed the article. For each of the concepts that required additional review, the reviewers discussed the concept until a consensus was reached.

Literature Review of ADHD Concepts

Two searches were conducted in PubMed to identify publications reporting qualitative research on the symptoms or impacts of ADHD in pediatric patients. Search terms for both searches included “quality of life” or “burden” to capture multiple aspects of the ADHD experience. The first search was conducted to assess the experience of ADHD from the perspective of the patient, using the search terms “ADD OR ADHD” AND “Qualitative OR interview OR focus group” AND “Quality of life OR burden.” Results were limited to human studies published in English from 2000 through 2018 and to patients ≤18 years of age. The second literature search explored the experience of ADHD from the viewpoint of the parent, caregiver, or teacher. This search included the terms “ADD OR ADHD” AND “Qualitative OR interview OR focus group” AND “Quality of life OR burden” AND

“Parent OR caregiver OR teacher.” Results were limited to human studies published in English from 2000 through 2018.

Concepts reported by patients and their caregivers were analyzed and organized into a conceptual framework¹² to describe the experience of ADHD, including symptoms and impacts. The identified concepts were then compared with concepts from each pediatric ADHD COA. COAs were assessed to understand how well each captured the experience of ADHD.

The conceptual framework was first organized according to concepts underlying DSM diagnostic criteria for ADHD,¹ including: 1) predominantly inattentive; and 2) predominantly hyperactive/impulsive. Concepts that did not fit within DSM criteria were listed as additional behavioral symptoms or as specific to certain concepts within those categories. A final category of general functional impacts was also created to capture impacts that applied to ADHD more broadly.

Literature Review of Existing ADHD COAs and the Concepts They Measure

A search was conducted in PubMed to identify COAs used in ADHD research. Search terms included “Attention deficit disorder with hyperactivity” [MeSH Major Topic] AND “Patient-reported outcome [Title/Abstract] OR scale [Title/Abstract] OR instrument [Title/Abstract] OR questionnaire [Title/Abstract]” AND “Symptom OR impact OR quality of life.” We limited the search to articles in the English language published within the last 10 years. We extracted specific COA names from the abstracts and then assessed each COA for its relevance to pediatric ADHD. We also examined information about each COA’s development, psychometrics, and interpretation when available.

Literature Review of COAs Used in Clinical Trials and COAs Used to Support Labeling Claims

We conducted a search on ClinicalTrials.gov to identify and review COAs currently used in clinical trials for pediatric ADHD. Individual searches were conducted for each of the COAs identified through the literature review to document their use as outcome measures in clinical trials. We extracted the endpoints (primary, secondary, and exploratory) derived from these COAs.

To ascertain which COAs have been used to make label claims, we examined the medical reviews and product labels for pediatric ADHD medications approved in

the past 10 years by the FDA or the European Medicines Agency (EMA). We assessed the reviews and labels of each medication for information about the use of COAs in clinical trials.

Results

ADHD Concepts from the Perspective of Pediatric Patients and Their Caregivers

The initial stage of the literature search yielded 130 articles. After excluding articles deemed to be out of scope, 5 articles were included in our analysis (Figure 1).

The second stage of the first literature search yielded 69 articles. After excluding articles that were out of scope or had incomplete information, 5 articles were included in our analysis (Figure 2).

Three articles were captured in both search strategies and reported perspectives from both the patients and caregivers (eg, both children and their teachers provided information), and thus these articles were included in both reviews. In all, 7 unique full-text articles were reviewed (Table 1). Studies were conducted across the United States, the United Kingdom, Canada, Puerto Rico, and South Africa.

The conceptual framework was developed using the concepts identified from the literature searches (Table 2). The final conceptual framework comprised 4 areas: symptoms of ADHD as listed in the DSM, additional behavioral symptoms not in the DSM, specific impacts of ADHD symptoms (eg, task-level functioning), and general impacts of ADHD (eg, overall functioning in broad domains such as self-esteem and socialization).

Existing ADHD COAs and the Concepts Assessed

A total of 483 articles were identified through the PubMed search for COAs. After excluding abstracts that were not relevant to pediatric ADHD or did not report the use of any COAs, 344 full-text articles were reviewed and 177 unique COAs were identified (Figure 3). After excluding those that were not relevant to the symptoms or impacts of pediatric ADHD, those that were not written in English, and those that could not be identified, 27 COAs remained. (See Supplemental Table 1 for a listing of identified measures.) Of the 27 relevant COAs, 12 were easily and fully accessible (ie, the full COA was available for review) and were mapped onto the conceptual framework.

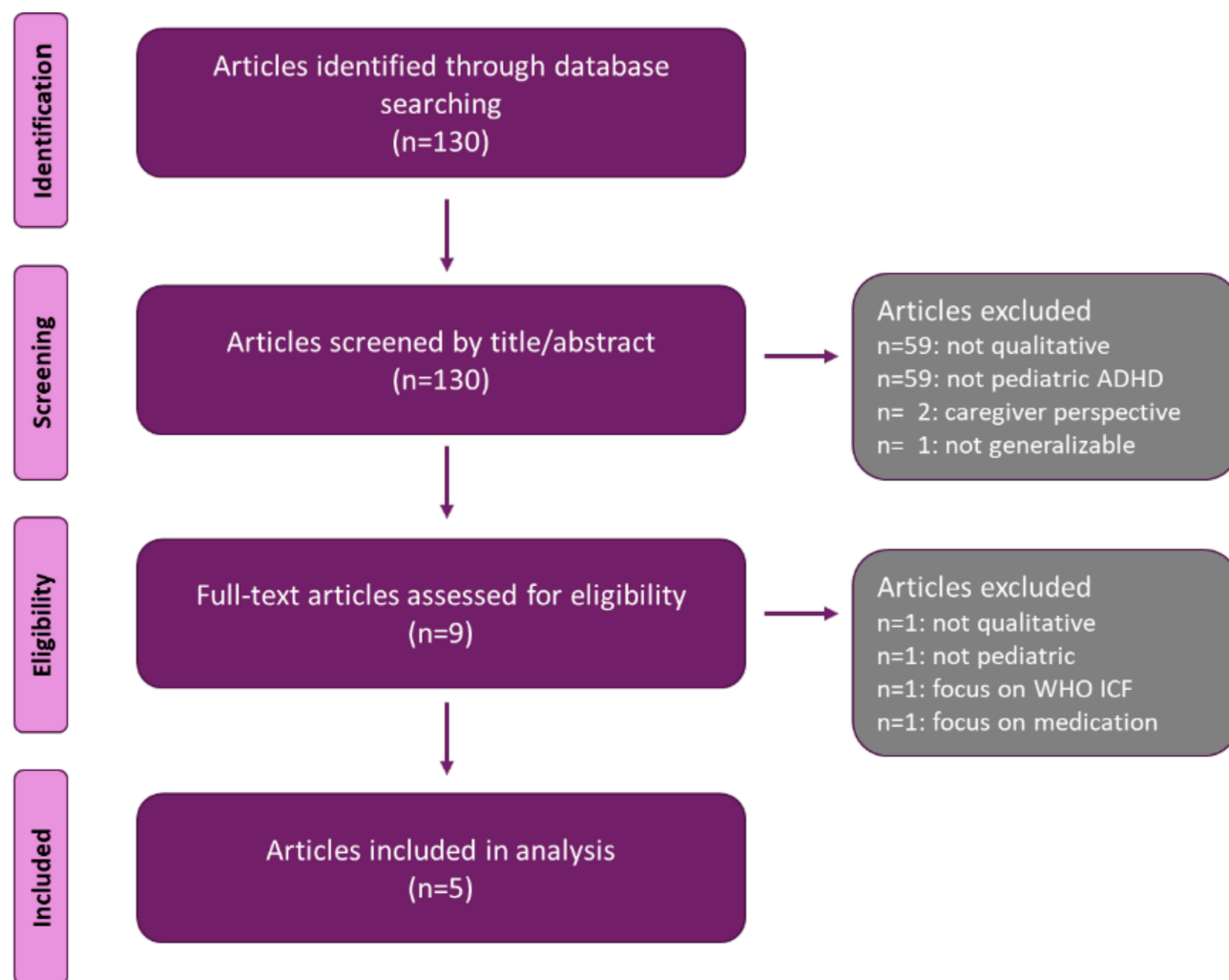


Figure 1 Literature review of ADHD concepts (patient perspective).

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ICF, International Classification of Functioning, Disability, and Health; WHO, World Health Organization.

The identified COAs differed in their scope and content; some strictly assessed DSM criteria while others also covered additional behavioral symptoms and impacts.

COAs Evaluating DSM Symptoms

We identified 4 of 12 COAs that assessed only the 18 DSM symptoms of ADHD: ADHD Current Symptoms Scale (ADHD CSS),²⁰ ADHD Rating Scale–DSM-5 (ADHD-RS-5),²¹ the Adult ADHD Self-Report Scale–Adolescent Edition (ASRS-Adolescent),²² and the Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN) Rating Scale.²³

ADHD Current Symptoms Scale (ADHD CSS)

The ADHD CSS,²⁰ also known as the Barkley Current Symptoms Scale, is both a self-report and parent-report measure of current ADHD symptoms. Each item provides

4 answer choices about experienced/observed behaviors: never or rarely, sometimes, often, and very often.

ADHD Rating Scale–DSM-5 (ADHD-RS-5)

The ADHD Rating Scale–DSM-IV (ADHD-RS-IV) and the updated version based on the DSM-5 (ADHD-RS-5)²¹ both measure the frequency of ADHD symptoms. Although the ADHD-RS-IV is more frequently cited in the literature than the ADHD-RS-5 because of the publication dates of the studies (ie, DSM-5 was released in 2013), the ADHD-RS-5 was used for this review because the purpose of the ADHD-RS-5 is to supersede the ADHD-RS-IV. The ADHD-RS-5 includes separate scales for children and adolescents in both the home (parent-report) and the school (teacher-report) setting. There are 4 answer choices for each item, ranging from 0 to 3. Depending on the phrasing of the question, these scores

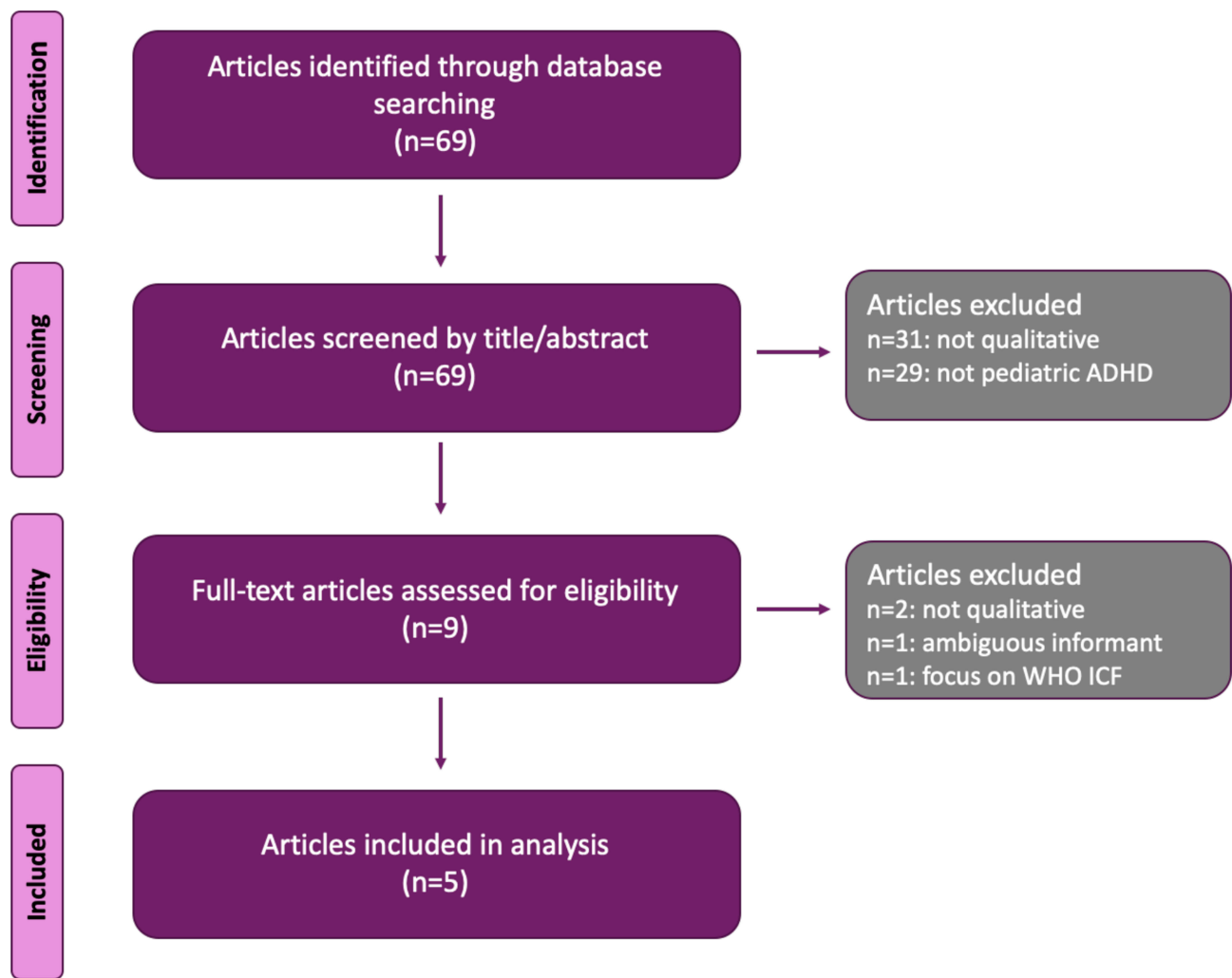


Figure 2 Literature review of ADHD concepts (parent, caregiver, or teacher perspective).

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ICF, International Classification of Functioning, Disability, and Health; WHO, World Health Organization.

are described as never or rarely, sometimes, often, and very often, or as no problem, minor problem, moderate problem, and severe problem.

Adult ADHD Self-Report Scale–Adolescent Edition (ASRS-Adolescent)

The ASRS-Adolescent²² is a self-report measure of current ADHD symptoms. It is typically used in adults but has also been used in adolescent populations. Item responses include never, rarely, sometimes, often, and very often.

Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN) Rating Scale

Lastly, the SWAN²³ is a self-, observer- (parent or teacher), or clinician-reported scale to assess ADHD symptom severity. Unlike the other 3 COAs that assess DSM symptoms, the SWAN uses positively worded scale items (eg, “Gives close

attention to detail” rather than “Struggles to give attention to detail”). In addition to assessing DSM criteria, it also asks the rater to consider the child’s behavior in comparison with other children. Item responses include far below average, below average, slightly below average, average, slightly above average, above average, and far above average.

COAs Evaluating Additional Concepts

Eight of 12 measures assessed symptoms and impacts not included in the DSM. These COAs include items referring to specific behavioral symptoms and/or specific or general impacts related to the ADHD subtypes. Some of these measures also included items measuring symptom criteria from the DSM, to varying degrees. Where available, we collected information on the item generation process, item reduction process, classical test theory criteria, responsiveness criteria, and Rasch measurement theory criteria.

Table 1 Full-Text Articles from Literature Review of ADHD Concepts

Authors	Objective	Population	Methods	Patient Concepts	Caregiver Concepts**
Bussing et al ¹³	To understand the perceptions of adolescents, parents, health-care providers, and teachers toward ADHD treatments, including willingness to use different treatment methods and potential negative effects*	<ul style="list-style-type: none"> Adolescent participants identified as ADHD high-risk (previously diagnosed, suspected of having ADHD, or having obtained elevated ADHD behavior ratings from parent/teacher) (n=148) Parents of elementary school students (n=161) Teachers randomly selected from a North Florida school district (n=122) 	<p>Participants were asked one open-ended question: "What other undesirable effects are you concerned about?" All responses were transcribed</p>	<ul style="list-style-type: none"> Dislike for both short- and long-acting medications <ul style="list-style-type: none"> Described as "burdensome" Short-acting Tx (more frequent dosing) associated with stigma/feelings of embarrassment – leads to lower self-esteem Tx side effects: loss of appetite, weight loss, lack of energy, sleeping problems, depression, irritability Behavior therapy/psychotherapy seen as ineffective, costly, and stigmatizing 	<ul style="list-style-type: none"> Believe medication should be combined with other interventions Short-acting Tx disruptive of academics/learning Short-acting Tx linked to emotional side effects such as sadness and irritability Tx side effects: loss of appetite, weight loss, lack of energy, sleeping problems, depression, irritability Behavior therapy/psychotherapy seen as ineffective, costly, and stigmatizing
Chavez et al ¹⁴	To collect adolescents' assessments of domains important to their QoL in order to develop a Spanish mental health QoL instrument	60 Latino adolescents (ages 12–18) with diagnoses of either ADHD, CD, ODD, GAD, or MDD. Participants were referred by clinicians in the San Juan metropolitan area.	<ul style="list-style-type: none"> Individual semistructured interviews (n=40) 3 focus groups (n=20) were conducted with a different cohort of participants (ie, not those who had been previously interviewed) 	<ul style="list-style-type: none"> Top 10 concepts for good QoL: 1) to feel able to accomplish goals; 2) to have a good attitude towards others; 3) to get good grades; 4) to respect others/not offend others; 5) to pay attention/concentrate at school; 6) to do things/participate in activities with others; 7) to behave well with others/not be rude; 8) to avoid looking for or getting in trouble; 9) to be healthy/to have good physical health; and 10) to not do things in a rush/to do them slowly Socialization=most prevalent focus group theme Being able to practice sports was most important for good QoL in interviews Believed not having a mental health condition would improve QoL 	N/A

Dewey et al ¹⁵	To investigate HRQoL and peer relationships in adolescents with DCD and ADHD	44 adolescents in Canada (aged 11–18) recruited from a cohort study examining genetics and neurobiology of motor and attention problems <ul style="list-style-type: none"> • ADHD only: n=9 • DCD only: n=9 • ADHD+DCD: n=10 Normally developing: n=19	Semistructured interviews exploring various aspects of HRQoL	<ul style="list-style-type: none"> • Most participants in ADHD-only group reported only enjoying nonsedentary activities (eg playing sports, dancing, swimming) • Close friends were a good source of support for all participants • ADHD participants reported feeling alone, lonely, ignored, left out, or marginalized (as compared with typically developing peers) 	N/A
Hareendran et al ¹⁶	To describe the experience of living with ADHD from the perspective of adolescents and their caregivers, for use in the creation of a new self-report instrument	<ul style="list-style-type: none"> • 3 teachers who had worked with students with ADHD • 60 adolescents (aged 13–17) with a clinician-confirmed diagnosis of ADHD <ul style="list-style-type: none"> ◦ No other Axis I or II conditions (per DSM-IV) ◦ Stable off medication for 1 week (if stimulant)–4 weeks (if non-stimulant) or on medication for at least 4 weeks • 60 primary caregivers (age 18+) of an adolescent with ADHD 	<ul style="list-style-type: none"> • Individual interviews with teachers • Individual interviews with adolescents • Individual interviews with caregivers • Interviews with adolescents and caregivers together (questions were addressed to adolescents first, then to caregivers to provide additional detail) 	<ul style="list-style-type: none"> • Difficulties with everyday activities that require attention <ul style="list-style-type: none"> ◦ School: classroom learning and extracurricular activities ◦ Home: early morning tasks, household chores, homework ◦ Leisure: hobbies, sports, part-time or voluntary work • Difficulties interacting with family, friends, and authority figures (teachers, coaches, team leaders) • Stress around social interactions and performing tasks <ul style="list-style-type: none"> ◦ High levels of effort needed to accomplish tasks, manage behavior, or engage in conversations • Problems regulating emotions • Medication helped to retain focus 	<p>Teacher interviews:</p> <ul style="list-style-type: none"> • Difficulty settling in class • Disruptive of classroom • Inability to follow instructions • Disrespectful/argumentative • Caregiver interviews • Caregivers supported difficulties reported by adolescents • Need to be reminded multiple times to complete tasks (eg, homework, chores) • Difficulty with afterschool activities (quality and consistency of activities) • Lack of motivation • Frequent procrastination • Difficulties with communication and frequent arguments about poor performance or neglecting to do tasks

(Continued)

Table 1 (Continued).

Authors	Objective	Population	Methods	Patient Concepts	Caregiver Concepts**
Laugesen et al ¹⁷	A systematic review of the qualitative literature to identify and synthesize reported experiences of parenting a child with ADHD	<p>21 published research articles that:</p> <ul style="list-style-type: none"> • Employed qualitative methods • Focused on parents or primary caregivers of children (ages 5–18) with a diagnosis of ADHD • Reported on the parenting experience or effect of ADHD on family life 	<ul style="list-style-type: none"> • An exhaustive search was conducted in MedNar, ProQuest, PubMed, Embase, PsycINFO, and CINAHL • Data were extracted and synthesized using the Qualitative Assessment and Review Instrument • The 129 main study findings were combined into 15 categories 	<ul style="list-style-type: none"> • N/A 	<ul style="list-style-type: none"> • Living with a child with ADHD described as disruptive and burdensome • Need to be “on duty around the clock” • Feel inadequate/unable to help child • Must have advocacy skills to help/protect child • Isolation/lack of understanding from friends, family, etc. • Avoid social events because of child's disruptive behavior • Everyday battles to get ready for school, finish homework, go to bed on time, etc. • Difficulty getting child to obey commands/have to try different motivational techniques • Acceptance of diagnosis leads to happier experiences

Lloyd et al ¹⁸	To understand impact of ADHD on HRQoL from the perspective of adolescent patients and their caregivers	<ul style="list-style-type: none"> • 20 adolescents (aged 11–16) with ADHD who had received at least 1 month of medication or therapy-based treatment within the past year • 17 parents or caregivers of children with ADHD who had held the role of primary caregiver for at least 5 years 	<ul style="list-style-type: none"> • Semistructured interviews regarding ADHD impact on HRQoL • 9 interviews conducted with adolescent and caregiver together • All other interviews conducted individually 	<ul style="list-style-type: none"> • Positive attitudes toward physical education/activities (eg, swimming and climbing) <ul style="list-style-type: none"> ◦ Physical activity improved mood and concentration • Clumsy and accident-prone (including injury) • Difficulty settling at night/falling asleep • Poor concentration, easily distracted, forgetful, poor listening, planning, and organizational skills • School difficulties including problems with written work and making simple mistakes, difficulty organizing themselves, and difficulty completing homework • Social skills underdeveloped <ul style="list-style-type: none"> ◦ Reported having only a few friends/feeling lonely ◦ Excluded from clubs for hyperactive/impulsive behavior • Teased/bullied by peers 	<ul style="list-style-type: none"> • Easily provoked to anger • Become annoyed and frustrated with those around them • Often lack self-confidence or self-esteem
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Table 1 (Continued).

Authors	Objective	Population	Methods	Patient Concepts	Caregiver Concepts**
Mofokeng et al ¹⁹	To explore the experiences of parents living with a child with ADHD	<ul style="list-style-type: none"> Parents (n=10) of children ages 6–12 who were assessed by a psychiatrist and diagnosed with ADHD, per DSM-IV criteria 	<ul style="list-style-type: none"> Unstructured interviews starting with one open-ended question: "What are your experiences as a parent living with a child diagnosed with ADHD?" Interviews were supplemented by interviewers' field notes Open-ended probe questions were asked following responses 	<ul style="list-style-type: none"> N/A 	<ul style="list-style-type: none"> Living with a child with ADHD/dealing with ADHD behavior described as demanding, stressful, and burdensome Caregiving associated with feelings of frustration, sadness, helplessness, depression, and anger Child's behavior affects family functioning and relationships with siblings and peers Child often rejected/stigmatized, causes family to experience social isolation Struggle with educational system (eg, negative reports, lack of understanding from teachers, difficulty finding an appropriate school) Negatively impacts caregiver's job performance/ability to work Strategies for managing behavior include channeling energy, time outs, withdrawing privileges, and monitoring/routine

Notes: *Did not distinguish between patient- and caregiver-reported concepts. **Caregiver perspectives as to impact of their child's ADHD on their own lives is recorded but not relevant to the aims of this review.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CD, conduct disorder; DCD, developmental coordination disorder; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; GAD, generalized anxiety disorder; HRQoL, health-related quality of life; MDD, major depressive disorder; N/A, not available; ODD, oppositional-defiant disorder; Tx, treatment; QoL, quality of life.

Table 2 Conceptual Framework: Impacts on Pediatric Patients with ADHD

DSM	Additional Behavioral Symptoms*	Specific Impacts	General Impacts
Inattention <ul style="list-style-type: none"> Often fails to give close attention to detail or makes mistakes Often has difficulty sustaining attention in tasks or activities Often does not seem to listen when spoken to directly Often does not follow through on instructions and fails to finish school-work or workplace duties Often has difficulty organizing tasks and activities Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort Often loses things necessary for tasks or activities Is easily distracted by extraneous stimuli Is often forgetful in daily activities 		<ul style="list-style-type: none"> Needs reminders to perform activities (eg, brush teeth, do homework) Poor performance on/neglecting to do tasks 	<ul style="list-style-type: none"> Poor academic performance Difficulty communicating Difficulty in social situations/poor relationships with others (eg, family members, isolated from others) Low self-confidence and self-esteem
Hyperactivity/impulsivity <ul style="list-style-type: none"> Often fidgets with or taps hands and feet or squirms in seat Often leaves seat in situations when remaining in seat is expected Often runs and climbs in situations where inappropriate Often unable to play or engage in leisure activities quietly Is often “on the go,” acting as if “driven by a motor” Often talks excessively Often blurts out answers before a question has been completed Often has difficulty waiting their turn Often interrupts or intrudes on others 	<ul style="list-style-type: none"> Easy to anger Frustration Difficulty regulating emotion Disrespectful/argumentative Clumsy/accident-prone 	<ul style="list-style-type: none"> Disruptions in class Getting to school on time Difficulty settling down (eg, in class, to sleep) 	

Note: *Additional behavioral symptoms not included in DSM criteria for ADHD.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; DSM, *Diagnostic and Statistical Manual of Mental Disorders*.

The ADHD Functional Impairment Questionnaire (ADHD-FX)

The ADHD-FX is a 32-item, observer-reported measure of the level of functional impairment a child experiences related to his or her ADHD.²⁴ Response options include not at all, a little, quite a bit, a lot, and do not know. As shown in Table 3, the scale assesses 3 DSM inattention symptoms and 3 hyperactivity/impulsivity symptoms as well as a few specific and general impacts. It has demonstrated adequate reliability and convergent and divergent validity.²⁵

ADHD Impact Module–Child (AIM-C)

The AIM-C is a parent-completed measure of the impact of ADHD on a child's functioning and at-home quality of life.⁴² The scale is divided into 2 sections: Child Scale and Home Scale. The Child Scale consists of 8 items and measures the child's well-being, including emotional functioning and school performance. The Home Scale has 10 items and measures the impact of the child's ADHD on family life. The AIM-C also includes general questions regarding the child's treatment history and other demographic

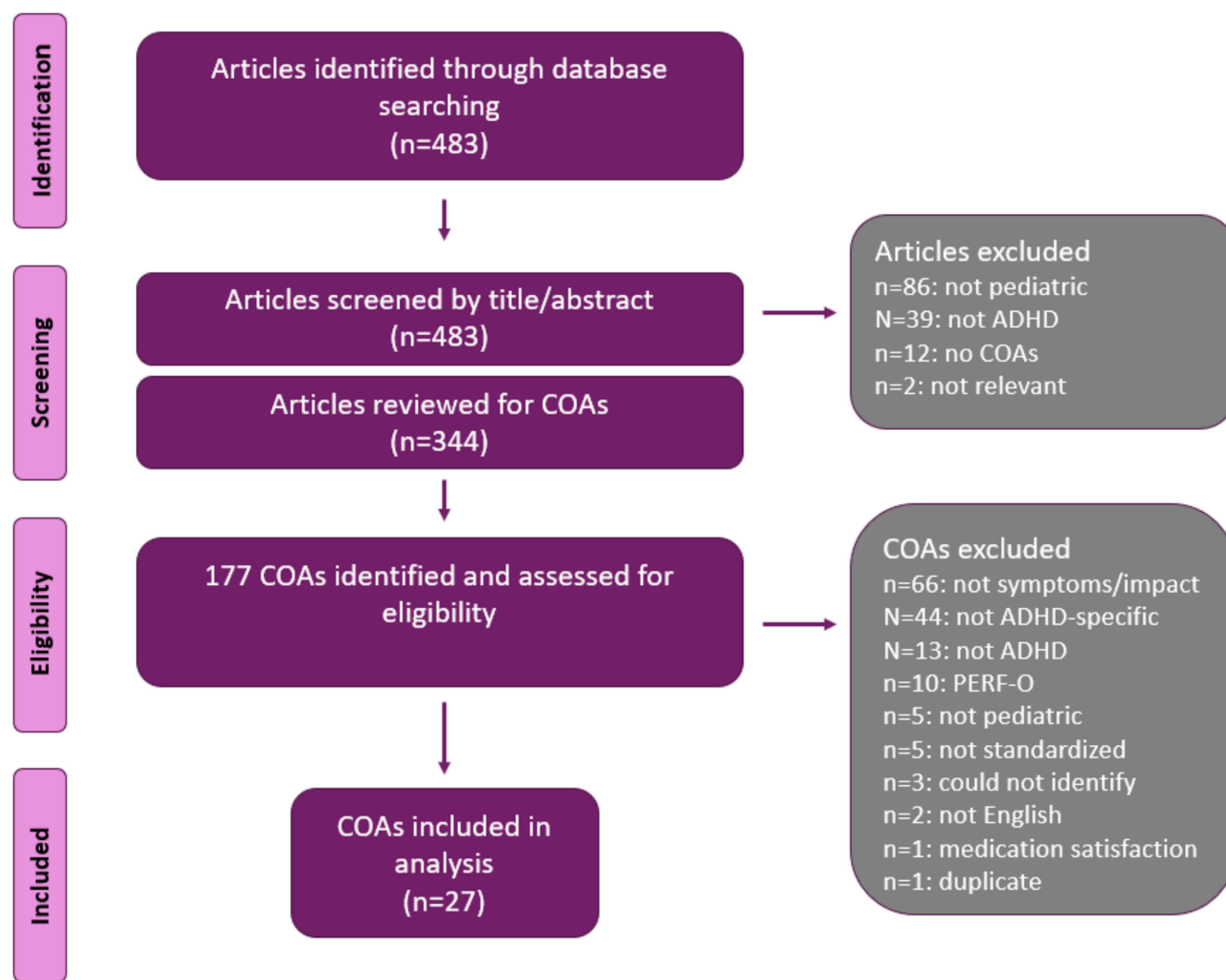


Figure 3 Search of existing ADHD COAs.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; COAs, clinical outcome assessments; PERF-O, performance outcome measures.

information. Items were generated using patient input and literature reviews and were refined with additional patient and expert input. Mean scores have been shown to be significantly worse for children with ADHD-combined subtype than for those with ADHD-inattention subtype.²⁶ Items on the AIM-C have little conceptual coverage of ADHD symptoms as listed in the DSM (Table 3).

Day Profile of ADHD Symptoms (DAYAS)

The DAYAS scale is a parent- or teacher-completed form (DAYAS-P and DAYAS-T, respectively) that measures the intensity of ADHD symptoms and problematic behaviors.²⁷ The measure consists of 17 (DAYAS-P) or 15 (DAYAS-T) items. Answer choices are not at all, just a little, pretty much, and very much. Information about the original item generation was not reported, but patient input was used to reduce the number of items included in the final scale. As

shown in Table 3, it provides better coverage of DSM symptoms than the ADHD-FX and AIM-C but is not comprehensive. In addition to nondiagnostic behavioral symptoms, the DAYAS addresses impairment in social relationships but not in other general or specific areas.

Impairment Rating Scale (IRS)

The IRS is a parent- or teacher-completed measure of child functioning across multiple clinically relevant domains: peer, sibling, parent, teacher, academics, self-esteem, classroom/family, and global.²⁸ The IRS Parent consists of 8 items and the IRS Teacher has 7 items. Items are scored on a 7-point scale ranging from no problem (definitely does not need treatment or special services) to extreme problem (definitely needs treatment or special services). Each item on the IRS also includes a space for the respondent to provide an open-ended written answer. It

Table 3 Mapping of Pediatric ADHD COAs Onto the Pediatric ADHD Conceptual Framework

Measure	DSM Symptoms Assessed	Additional Behavioral Symptoms Not Assessed in DSM Criteria for ADHD	Specific Impacts Assessed	General Impacts Assessed	Benefits
ADHD-FX ²⁴	Inattention <ul style="list-style-type: none"> • Often does not seem to listen when spoken to directly • Often does not follow through on instructions and fails to finish schoolwork or workplace duties • Often has difficulty organizing tasks and activities Hyperactivity/impulsivity <ul style="list-style-type: none"> • Often leaves seat in situations when remaining in seat is expected • Often runs and climbs in situations where inappropriate • Often interrupts or intrudes on others 	Difficulty regulating emotion Disrespectful/argumentative	Needs reminders Disruptions in class	Difficulty in social situations/poor relationships with others	Addresses some nondiagnostic behavioral symptoms Addresses some functional impairment Has established reliability and validity
AIM-C ⁴²	Inattention <ul style="list-style-type: none"> • Often does not follow through on instructions and fails to finish schoolwork or workplace duties Hyperactivity/impulsivity <ul style="list-style-type: none"> • Often leaves seat in situations when remaining in seat is expected • Often runs and climbs in situations where inappropriate 	N/A	Getting to school on time	Poor academic performance Difficulty in social situations/poor relationships with others	Includes items on the child's treatment history and other demographics Has established reliability and validity Addresses some functional impairment
DAYAS ²⁷	Inattention <ul style="list-style-type: none"> • Often fails to give close attention to detail or makes mistakes • Often has difficulty sustaining attention in tasks or activities • Often does not seem to listen when spoken to directly • Is easily distracted by extraneous stimuli Hyperactivity/impulsivity <ul style="list-style-type: none"> • Often fidgets with or taps hands and feet or squirms in seat • Often runs and climbs in situations where inappropriate • Is often "on the go," acting as if "driven by a motor" • Often has difficulty waiting their turn • Often interrupts or intrudes on others 	Easy to anger Frustration Difficulty regulating emotion Disrespectful/argumentative	N/A	Difficulty in social situations/poor relationships with others	Has established reliability and validity Addresses many DSM-5 symptoms of both ADHD subtypes Addresses some functional impairment Assesses intensity of symptoms and behaviors

(Continued)

Table 3 (Continued).

Measure	DSM Symptoms Assessed	Additional Behavioral Symptoms Not Assessed in DSM Criteria for ADHD	Specific Impacts Assessed	General Impacts Assessed	Benefits
IRS ²⁸	N/A	N/A	Disruptions in class	Poor academic performance Difficulty in social situations/poor relationships with others Low self-confidence and self-esteem	Has established validity Addresses some functional impairment
SKAMP ^{30,31}	Inattention <ul style="list-style-type: none"> • Often has difficulty sustaining attention in tasks or activities • Often does not follow through on instructions and fails to finish schoolwork or workplace duties • Often has difficulty organizing tasks and activities • Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort Hyperactivity/impulsivity <ul style="list-style-type: none"> • Often leaves seat in situations when remaining in seat is expected • Often talks excessively • Often blurts out answers before question has been completed • Often has difficulty waiting their turn 	Disrespectful/argumentative	N/A	Difficulty in social situations/poor relationships with others	Has been used extensively in clinical trials in a laboratory classroom Addresses some functional impairment

SNAP-IV ^{3,4}	<p>Inattention</p> <ul style="list-style-type: none"> • Often fails to give close attention to detail or makes mistakes • Often has difficulty sustaining attention in tasks or activities • Often does not seem to listen when spoken to directly • Often does not follow through on instructions and fails to finish schoolwork or workplace duties • Often has difficulty organizing tasks and activities • Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort • Often loses things necessary for tasks or activities • Is easily distracted by extraneous stimuli • Is often forgetful in daily activities <p>Hyperactivity/impulsivity</p> <ul style="list-style-type: none"> • Often fidgets with or taps hands and feet or squirms in seat • Often leaves seat in situations when remaining in seat is expected • Often runs and climbs in situations where inappropriate • Often unable to play or engage in leisure activities quietly • Is often "on the go," acting as if "driven by a motor" • Often talks excessively • Often blurts out answers before question has been completed • Often has difficulty waiting their turn • Often interrupts or intrudes on others 	<p>Easy to anger</p> <p>Frustration</p> <p>Difficulty regulating emotion</p> <p>Disrespectful/argumentative</p>	<p>Poor performance on/neglecting to do tasks</p> <p>Disruptions in class</p> <p>Difficulty settling down (eg, in class, to sleep)</p>	<p>Poor academic performance</p> <p>Difficulty communicating</p> <p>Difficulty in social situations/poor relationships with others</p> <p>Low self-confidence and self-esteem</p>	<p>Includes items to address oppositional defiant disorder</p> <p>Has established reliability and validity</p> <p>Addresses all 18 DSM-5 symptoms of both subtypes of ADHD</p> <p>Addresses several nondiagnostic behavioral symptoms</p> <p>Addresses many specific and general functional impairments</p>
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(Continued)

Table 3 (Continued).

Measure	DSM Symptoms Assessed	Additional Behavioral Symptoms Not Assessed in DSM Criteria for ADHD	Specific Impacts Assessed	General Impacts Assessed	Benefits
VADRS ⁴⁰	<p>Inattention</p> <ul style="list-style-type: none"> • Often fails to give close attention to detail or makes mistakes • Often has difficulty sustaining attention in tasks or activities • Often does not seem to listen when spoken to directly • Often does not follow through on instructions and fails to finish schoolwork or workplace duties • Often has difficulty organizing tasks and activities • Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort • Often loses things necessary for tasks or activities • Is easily distracted by extraneous stimuli • Is often forgetful in daily activities <p>Hyperactivity/impulsivity</p> <ul style="list-style-type: none"> • Often fidgets with or taps hands and feet or squirms in seat • Often leaves seat in situations when remaining in seat is expected • Often runs and climbs in situations where inappropriate • Often unable to play or engage in leisure activities quietly • Is often "on the go," acting as if "driven by a motor" • Often talks excessively • Often blurts out answers before question has been completed • Often has difficulty waiting their turn • Often interrupts or intrudes on others 	<p>Easy to anger</p> <p>Frustration</p> <p>Disrespectful/argumentative</p>	<p>Disruptions in class</p>	<p>Poor academic performance</p> <p>Difficulty in social situations/poor relationships with others</p> <p>Low self-confidence and self-esteem</p>	<p>Includes items to address oppositional defiant disorder as well as depression and anxiety symptoms</p> <p>Has established reliability and validity</p> <p>Addresses all 18 DSM-5 symptoms of both ADHD subtypes</p> <p>Addresses several nondiagnostic behavioral symptoms</p> <p>Addresses several general functional impairments</p>

WFIRS ⁴¹ (Canadian ADHD Resource Alliance, 2011)	N/A	N/A	Needing reminders Disruptions in class Getting to school on time Difficulty settling down (eg, in class, to sleep)	Poor academic performance Difficulty in social situations/poor relationships with others Low self-confidence and self-esteem	Has established reliability and validity Addresses several specific and general functional impairments
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Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ADHD-FX, ADHD Functional Impairment Questionnaire; AIM-C, ADHD Impact Module-Child; DAYAS, Day Profile of ADHD Symptoms; DSM, Diagnostic and Statistical Manual of Mental Disorders; IRS, Impairment Rating Scale; N/A, not available; SKAMP, Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale; SNAP-IV, Swanson, Nolan, and Pelham Rating Scale-DSM-IV; VADRS, Vanderbilt ADHD Diagnostic Rating Scale; WFIRS, Weiss Functional Impairment Rating Scale.

is unclear what sources were used to generate the items on this scale. The IRS does not measure DSM symptoms or additional behavioral symptoms for either ADHD subtype. Items on the IRS assess only 1 specific impact of hyperactivity/impulsivity and 3 of the 4 identified general impacts of ADHD from the conceptual framework (Table 3).

Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale (SKAMP)

The SKAMP is a 13-item observer-rated measure of the child's impairment on various ADHD-related behaviors.²⁹⁻³³ It is used in laboratory classrooms and scored by trained observers. Responses are given on a 7-point scale, ranging from 0 (no impairment) to 6 (maximal impairment). The SKAMP measures some but not all DSM symptoms as well as some nondiagnostic behaviors and general impacts identified in the conceptual framework (Table 3).

Swanson, Nolan, and Pelham Rating Scale-DSM-IV (SNAP-IV)

The SNAP-IV³⁴ measures the child's problematic behavior. It is derived from the DSM-IV ADHD criteria and includes 10 questions assessing behaviors typical of oppositional defiant disorder (ODD), as the 2 disorders are often comorbid. Items on the scale were developed from the older SNAP questionnaire, with additional input from the Conners Index Questionnaire and the IOWA Conners Questionnaire. The scale must be completed by a parent or teacher and consists of 90 items in total. Item response choices include not at all, just a little, quite a bit, and very much. The SNAP-IV covers nearly all of the concepts included in the conceptual framework, including all DSM-specific symptoms for both ADHD subtypes, as well as many nondiagnostic behavioral symptoms and specific and general ADHD impacts (Table 3).

Vanderbilt ADHD Diagnostic Rating Scale (VADRS)

The VADRS is based on DSM-IV symptoms³⁵ and is used by teachers or parents to determine whether a child should be evaluated for a diagnosis of ADHD.³⁶ The latter half of the scale addresses the presence of ODD symptoms as well as symptoms of anxiety or depression. There are 45 items in total. The first 35 items are answered on a 4-point scale: never, occasionally, often, and very often. The remaining 10 items ask for a rating on a 5-point scale, from problematic to above average. The VADRS includes all 18 DSM-5 criteria for both subtypes of ADHD, numerous nondiagnostic

behavioral symptoms, one specific impact (ie, disruption in class), and several general impacts (Table 3).

Weiss Functional Impairment Rating Scale (WFIRS)

Finally, the WFIRS measures a child's functioning in a variety of domains, including family, school, social activity, and life skills.³⁷ Items on this parent- and self-report form were developed using a conceptual framework. There are 46 total items; item responses are never or not at all, sometimes or somewhat, often or much, very often or very much, and N/A (not applicable). The parent form may be used to differentiate 5-to-19-year-olds with and without ADHD based on functional impairment.³⁸ The WFIRS includes none of the DSM diagnostic criteria, nor does it focus on any nondiagnostic behavioral symptoms; rather, it includes items that address both the specific and general impacts listed in our conceptual framework (Table 3).

Conners Rating Scales, Third Edition (Conners 3)

Although not part of our mapping to the pediatric ADHD conceptual framework due to lack of access to the full COA, the Conners 3³⁹ is a commonly used measure in pediatric ADHD clinical trials (Table 6). This COA assesses ADHD symptoms and common comorbid conditions (eg, full criteria for DSM-IV conduct disorder and ODD; screening questions for anxiety and depression) in children and adolescents ages 6–18 years. It includes all 18 items of both subtypes of DSM-IV ADHD. Subscales also provide assessments of ADHD-related problems or areas of concern, including learning difficulties, problems with executive functioning, aggression, and peer and family relations. Versions are available for parents (Conners 3-P), teachers (Conners 3-T), and the child self-reports (Conners 3-SR) and come in both long and short forms.

COAs Used in Clinical Trials and Regulatory Labels

We searched ClinicalTrials.gov for each of the 27 COAs identified through the PubMed review. Eighteen of these COAs were used in at least one clinical trial as a primary or secondary endpoint. We extracted data on each study, including a description of the endpoint measured by the COA (Table 4). We did not include information on the informant completing the COA (ie, self, parent, or teacher), as it was not consistently reported on ClinicalTrials.gov.

We reviewed product labels of pediatric ADHD products approved by the FDA. Table 5 summarizes the COAs used in clinical trials that support FDA-approved product labels.

Table 6 summarizes the COAs identified through our literature search that were also used in clinical trials (from ClinicalTrials.gov) and regulatory information.

Discussion

A number of COAs are available to assess symptoms and impacts of pediatric ADHD, and some have been used to assess treatment benefits in clinical trials. The need to measure treatment benefits meaningful to the patient in his/her normal life within clinical trials has been increasingly recognized.^{4,9,11} However, there has not yet been a formal evaluation of whether the concepts measured by the various ADHD COAs are of relevance to pediatric patients with ADHD and/or their caregivers. In this review, we set out first to identify the conceptual areas of the ADHD experience important to pediatric patients and their caregivers based on existing qualitative research and then to evaluate the extent to which COAs used in pediatric ADHD research align with these identified concepts. Finally, we identified the subset of COAs that have been used in clinical trials, including those that have undergone regulatory review to support product label claims.

We found that most outcome measures used in ADHD studies are a reflection of DSM symptoms, a finding that extends those of previous literature reviews of outcome assessments in pediatric ADHD.^{7,9} Epstein and Weiss reviewed measures used to assess treatment response in individuals with ADHD across the life span.⁹ Although findings were not stratified into adults versus children/adolescents, the review reported that most studies assessing ADHD treatment effects used DSM-based symptom measures. The investigators also proposed that additional domains, including functional impairment, quality of life, adaptive life skills, and executive functioning, should be evaluated to determine treatment effect.⁹ Another literature review corroborated that DSM-based rating scales were most frequently used to measure treatment outcomes.⁷

Although DSM criteria measure symptom severity, they may not assess the full range of symptoms and/or impacts important to patients and their caregivers. Hence, relying on DSM-based outcome measures may result in a failure to assess treatment benefit in ADHD comprehensively. The American Academy of Pediatrics recommends

Table 4 Review of COAs in Clinical Trials

COA	Ages Included	Primary Endpoint (n)	Definition of Primary Endpoint	Secondary Endpoint (n)	Definition of Secondary Endpoint
ADHD-FX	5–12	1	<ul style="list-style-type: none"> ADHD impairment change 	0	N/A
ADHD-RS	3–29	55	<ul style="list-style-type: none"> Improvement of ADHD symptoms (investigator rated) Frequency of each ADHD symptom Number of participants with at least 70% reduction in ADHD symptoms Change from baseline Change in inattentive score (clinician-rated) Severity of total ADHD symptoms Screening for symptoms of ADHD in the preschool population 	22	<ul style="list-style-type: none"> Change from baseline ADHD symptoms Overall score Efficacy of stimulant treatment Effect of adjunct therapy on ADHD symptom control Severity of total symptoms Summed total score for “inattention, hyperactivity and impulsivity” and the subscores for “inattention” and for “hyperactivity and impulsivity”
AIM-C	6–12	0	N/A	3	<ul style="list-style-type: none"> Psychosocial functioning
ASRS	3–18	1	<ul style="list-style-type: none"> Not specified 	2	<ul style="list-style-type: none"> Evaluate ADHD symptoms that may influence treatment response and adherence “Four or more positive answers in Part A (6 questions) are indicative of ADHD symptoms”
Brown ADD Scale	6–18	0	N/A	2	<ul style="list-style-type: none"> Executive functioning
CGI-ADHD S	6–18	1	<ul style="list-style-type: none"> Not specified 	17	<ul style="list-style-type: none"> Change from baseline Compare morning vs evening dosing vs placebo “To compare the effects of atomoxetine and psychoeducation with those of placebo and psychoeducation at 10 weeks in patients with ADHD with regard to severity of illness and improvement”
Conners 3	3–18	32 (used as both primary and secondary in 9 studies)	<ul style="list-style-type: none"> ADHD characteristics Change in score Inattention, impulsivity, hyperactivity ratings Behavioral symptoms Improvement in efficacy and clinical improvement in the child Composite score ADHD symptoms ADHD behavioral symptoms Change in ADHD symptoms 	60 (used as both primary and secondary in 9 studies)	<ul style="list-style-type: none"> Change from baseline ADHD symptoms Validity of VADRS Improvement in ADHD symptoms Change in teacher-reported inattention and hyperactivity Duration of therapeutic response Comparison of scores in ORADUR® – methylphenidate vs placebo Social well-being and school parameters; self-esteem and behavior
Conners–Wells	6–17	0	N/A	1	<ul style="list-style-type: none"> ADHD symptoms and severity
DPREMB	6–17	2 (used as both primary and secondary in 2 studies)	<ul style="list-style-type: none"> Evening settling difficulties 	2 (used as both primary and secondary in 2 studies)	<ul style="list-style-type: none"> Morning behaviors

(Continued)

Table 4 (Continued).

COA	Ages Included	Primary Endpoint (n)	Definition of Primary Endpoint	Secondary Endpoint (n)	Definition of Secondary Endpoint
DAYAS	6–12	0	N/A	1	<ul style="list-style-type: none"> Adverse effects
FSI	3–10	0	N/A	2	<ul style="list-style-type: none"> Detection of family strain
FTF	7–15	0	N/A	2	<ul style="list-style-type: none"> Evaluation of development and behavior “To investigate if the results are modified by comorbid and/or developmental problems”
IRS	5–15	6 (used as both primary and secondary in 1 study)	<ul style="list-style-type: none"> Change from baseline in ADHD symptom impairment Change in score Teacher ratings of academic performance 	8 (used as both primary and secondary in 1 study)	<ul style="list-style-type: none"> Change in score Youth impairment
SKAMP	6–17	24 (used as both primary and secondary in 14 studies)	<ul style="list-style-type: none"> Change from predose in combined attention and deportment scores Change in deportment scores Onset of effect of Vyvanse Change from predose in combined score Change from baseline in ADHD symptoms Change in scores Change in combined scores Change from baseline Comparison following treatment between drug and placebo Change from baseline in ADHD symptoms 	21 (used as both primary and secondary in 14 studies)	<ul style="list-style-type: none"> Change from predose in separate attention and deportment scores Onset and duration of clinical effect Duration of effect of Vyvanse Change from predose in subscale scores Onset and duration of effect; average attention and deportment scores Mean combined score; change from baseline in subscale scores Functional impairment Efficacy measure Functional impairment of ADHD symptoms
SNAP-IV	5–20	28 (used as both primary and secondary in 6 studies)	<ul style="list-style-type: none"> ADHD symptoms Change from baseline Change in average parent-reported inattention and hyperactivity symptoms Change in score Diagnostic and severity measure Hyperactivity and impulsivity scores Inattention Necessary duration of treatment Teacher score in treatment group vs placebo 	28 (used as both primary and secondary in 6 studies)	<ul style="list-style-type: none"> ADHD symptoms Assess the efficacy of 810M (molindone) Change from baseline Remission rate Change in ADHD subscale scores Changes in scores for inattention, hyperactivity and total ADHD symptom severity Diagnostic and severity measure Effects on psychiatric state Hyperactivity and impulsivity Mean total score ODD symptoms Parent score in treatment group vs placebo
SWAN	6–17	3	<ul style="list-style-type: none"> Change from baseline Change in ADHD symptoms Improvement in behavior 	3	<ul style="list-style-type: none"> Change in ADHD symptoms Behavior

(Continued)

Table 4 (Continued).

COA	Ages Included	Primary Endpoint (n)	Definition of Primary Endpoint	Secondary Endpoint (n)	Definition of Secondary Endpoint
VADRS	5–18	12 (used as both primary and secondary in 2 studies)	<ul style="list-style-type: none"> • Total ADHD symptom score • Change in scores • Reliability of VADRS • Inattention and hyperactivity/impulsivity • Change in caregiver-rated symptoms 	5 (used as both primary and secondary in 2 studies)	<ul style="list-style-type: none"> • Change in score (teacher-rated) • Validity of VADRS • Parent-rated ADHD symptoms • Teacher report of ADHD symptoms
WFIRS	6–18	2 (used as both primary and secondary in 2 studies)	<ul style="list-style-type: none"> • Posttreatment functional impairment • Psychosocial functioning 	24 (used as both primary and secondary in 2 studies)	<ul style="list-style-type: none"> • Assess relationship between change in symptoms and change in functional outcomes • Assessment of symptoms • Change from baseline • Change in score • Degree to which behavior or emotional problems have impacted functioning • Examine psychometrics of French-language WFIRS • Change from randomization to the end of the randomized withdrawal period on WFIRS-P • Overall functioning • Validation of WFIRS-P

Abbreviations: ADD, attention-deficit disorder; ADHD, attention-deficit/hyperactivity disorder; ADHD CSS, ADHD Current Symptoms Scale; ADHD-FX, ADHD-Functional Impairment Questionnaire; ADHD-RS-IV, ADHD Rating Scale–DSM-IV; AIM-C, ADHD Impact Module–Child; ASRS, Adult ADHD Self-Report Scale–Adolescent Edition; CGI-ADHD S, Clinical Global Impressions–ADHD–Severity; DPREMB, Daily Parent Rating of Evening and Morning Behavior; DAYAS, Day Profile of ADHD Symptoms; FSI, Family Strain Index; FTF, Five to Fifteen; IRS, Impairment Rating Scale; N/A, not available; ODD, oppositional defiant disorder; SKAMP, Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale; SNAP-IV, Swanson, Nolan, and Pelham Rating Scale–DSM-IV; SWAN, strengths and weaknesses of ADHD symptoms and normal behavior; VADRS, Vanderbilt ADHD Diagnostic Rating Scale; WFIRS-P, Weiss Functional Impairment Rating Scale–Parent Form.

that patients' and families' perspectives be considered to sustain appropriate treatments and achieve long-term successful treatment outcomes.⁴ In contrast with previous literature reviews, our approach was to first determine symptoms and impacts important to the patient and caregiver (eg, teacher, parent) through a review of existing qualitative literature in order to construct a more comprehensive conceptual framework against which assessment tools could be mapped.

In addition to DSM-defined symptoms, we identified many patient-, parent-, and teacher-reported concepts that may be important to consider when evaluating treatment benefits in pediatric ADHD. For the inattention subtype category of ADHD, we identified 5 additional concepts: poor listening, poor planning, frequently procrastinating, needing reminders to perform activities, and poor performance on/neglecting to do tasks. For the hyperactivity and Impulsivity subtype category, there were 8 additionally identified concepts: easy to anger, frustration, difficulty regulating emotion, disrespectful/argumentative, clumsy/accident-prone, disruptions in class, difficulty getting to school on time, and difficulty settling

down. Additional general impacts included poor academic performance, difficulty communicating, difficulty in social situations/poor relationships with others, and low self-confidence/self-esteem.

Our work on patient- and caregiver-reported ADHD concepts and the resulting conceptual framework based on these concepts (Table 1) is important because it elucidates the extent to which certain COAs accurately and thoroughly capture patient and caregiver experiences of ADHD, which may inform their potential use in clinical trials.

We found that some COAs were used as endpoints in the registration trials of currently marketed pediatric ADHD medications. Among DSM-based scales, the ADHD-RS-IV was most frequently used in pediatric ADHD clinical trials and was mentioned in 4 pediatric ADHD product labels. The SKAMP was also mentioned in many product labels ($n = 6$) and was used to assess outcomes in 31 clinical trials. The SKAMP may be preferred because it is a rating scale that is completed in a classroom setting;^{30,31} ADHD medications are often

Table 5 COAs Cited in Labels

FDA Label	Product
ADHD-RS-IV	Adezenys XR-ODT™ (amphetamine extended-release orally disintegrating tablets) Aptensio XR™ (methylphenidate hydrochloride extended-release) Intuniv® (guanfacine) Mydayis® (mixed salts of a single-entity amphetamine product) Quillivant XR® (methylphenidate hydrochloride)
SKAMP (although not noted in label, PERMP was collected and used to determine items on the SKAMP)	Adezenys XR-ODT™ (amphetamine extended-release orally disintegrating tablets) Aptensio XR™ (methylphenidate hydrochloride extended-release) Contempla XR-ODT (methylphenidate extended-release orally disintegrating tablets) DYANAVEL™ XR (amphetamine) Quillichew ER® (methylphenidate hydrochloride extended-release chewable tablets) Quillivant XR® (methylphenidate hydrochloride for extended release oral suspension)
PERMP	Adezenys XR-ODT™ (amphetamine extended-release orally disintegrating tablets) Mydayis® (mixed salts of a single-entity amphetamine product)
CGI-I	Mydayis® (mixed salts of a single-entity amphetamine product) Quillivant XR® (methylphenidate hydrochloride for extended-release oral suspension; secondary endpoint)
CGI-S	Quillivant XR® (methylphenidate hydrochloride for extended-release oral suspension; secondary endpoint)

Abbreviations: ADHD-RS-IV, ADHD Rating Scale–DSM IV; CGI-I, Clinical Global Impression of Improvement; CGI-S, Clinical Global Impression of Severity; COA, clinical outcome assessment; FDA, US Food & Drug Administration; PERMP, permanent product measure of performance; SKAMP, Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale.

designed to reduce symptoms during the school day or improve other activities that require focus and concentration that a parent may not be able to observe.⁴³ The SKAMP may have been used in clinical trials of ADHD medications, including registration trials, specifically to obtain evidence of these treatment benefits (ie, attention and behaviors in simulated academic settings, which may permit an understanding of time-course effects). The use of the ADHD-RS-IV or ADHD-RS-5 and the SKAMP in registration studies may suggest their acceptance by regulatory bodies.

Of the outcome measures we evaluated; the SNAP-IV appears to have the most comprehensive coverage of the concepts listed in our conceptual framework. The SNAP-IV not only assesses DSM symptoms but also most of the additional concepts identified in our framework (Table 3). Although the SNAP-IV was widely used in clinical trials (n=50), it has not been used in registration trials and it was not found in any product labels.

The FDA has published guidance on the use of COAs, which include patient- and observer-reported outcomes, as clinical trial efficacy endpoints to support labeling claims.^{10,12} Whether some of the COAs evaluated in this review meet the criteria stated in the FDA guidance will need to be further examined.

Limitations

Our study is limited by the use of publications instead of collecting data directly from patients and their caregivers. For example, we were not able to assess how questions were asked or the environment in which the qualitative studies were conducted. Instead, we assumed the studies used to form our conceptual framework were conducted with good qualitative methods. Our study also did not include a review of the psychometric properties of each COA, but rather aimed at assessing content validity from a patient-centric perspective.

Table 6 Efficacy COAs in Pediatric ADHD Used in Clinical Trials and Regulatory Information

COA Name and Completion	Number of Items	Coverage of DSM Concepts	Coverage of Other Concepts	Use in Clinical Trials (n) (January 2019)	Use in FDA Labels for Reviewed Drugs in Pediatric ADHD (n) (January 2019)
ADHD-FX	32	5/18	7/17	1	0
ADHD-RS-IV	18	18/18	0/17	77	4
AIM-C	47	3/18	3/17	3	0
ASRS	24	18/18	0/17	3	0
Brown ADD Scale	*	*	*	2	0
CGI-ADHD S	*	*	*	18	0
Conners 3	*	*	*	83	0
Conners–Wells	*	*	*	1	0
DPREMB	*	*	*	2	0
DAYAS	17	8/18	6/17	1	0
FSI	*	*	*	2	0
FTF	*	*	*	2	0
IRS	15	0/18	4/17	13	0
SKAMP	10	6/18	3/17	31	6
SNAP-IV	90	18/18	16/17	50	0
SWAN	30	18/18	0/17	6	0
Vanderbilt scale	43	18/18	9/17	15	0
WFIRS	50	0/18	7/17	24	0

Note: *Did not have full text of COA to review.

Abbreviations: ADD, attention-deficit disorder; ADHD, attention-deficit/hyperactivity disorder; ADHD CSS, ADHD Current Symptoms Scale; ADHD-FX, ADHD Functional Impairment Questionnaire; ADHD-RS-IV, ADHD Rating Scale–DSM-IV; AIM-C, ADHD Impact Module–Child; ASRS, Adult ADHD Self-Report Scale–Adolescent Edition; CGI-ADHD-S, Clinical Global Impressions–ADHD–Severity; COA, clinical outcome assessment; DPREMB, Daily Parent Rating of Evening and Morning Behavior; DAYAS, Day Profile of ADHD Symptoms; FSI, Family Strain Index; FTF, Five to Fifteen; IRS, Impairment Rating Scale; SKAMP, Swanson, Kotkin, Agler, M-Flynn, and Pelham Scale; SNAP-IV, Swanson, Nolan, and Pelham Rating Scale–DSM-IV; SWAN, Strengths and Weaknesses of ADHD Symptoms and Normal Behavior; WFIRS, Weiss Functional Impairment Rating Scale.

Conclusion

The need to measure treatment benefits meaningful to the patient in his/her usual or typical life has been increasingly recognized.^{4,9,11} A number of COAs are available to assess symptoms and/or impacts of pediatric ADHD, but the concepts they measure vary. In this review, we set out to first identify a conceptual framework of the ADHD experience important to pediatric patients and their caregivers based on existing qualitative research. We mapped the existing ADHD COAs used in pediatric ADHD research to the conceptual framework and summarized the extent to which these COAs align with the identified concepts. The registration trials of currently available pediatric ADHD medications frequently used ADHD-RS-IV or ADHD-RS-5 to assess DSM symptoms and the SKAMP, administered in the classroom to assess symptoms and functional impairments during the school day. Future research is needed to understand the best way to measure all concepts important to patients and caregivers within clinical trials in ADHD.

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