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NON-STIMULANTS FOR THE TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Atomoxetine (Strattera)
Clonidine ER (Kapvay)
Guanfacine ER (Intuniv)
Viloxazine ER (Qelbree)

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Drug Regimen Review Center

Monet Luloh, PharmD, Clinical Pharmacist
Valerie Gonzales, PharmD, Clinical Pharmacist
Lauren Heath, PharmD, MS, BCACP, Clinical Pharmacist
Kristin Knippenberg, MFA, Administrator and Editor
Jacob Crook, MS, Data Analyst
Joanne LaFleur, PharmD, MSPH, Director

University of Utah College of Pharmacy, Drug Regimen Review Center
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CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

AAP	American Academy of Pediatrics
ADHD	Attention-deficit/hyperactivity disorder
ADHD-RS-IV	ADHD Rating Scale, version IV
AEs	Adverse events
ASD	Autism spectrum disorder
AV	Atrioventricular
CADDRA	Canadian ADHD Resource Alliance
CDC	Centers for Disease Control and Prevention
CGI-I	Clinical Global Impression-Improvement
CNS	Central nervous system
CPS	Canadian Paediatric Society
CYP	Cytochrome
DDIs	Drug-drug interactions
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DUR	Drug Utilization Review
ER	Extended-release
FDA	US Food and Drug Administration
IR	Immediate-release
MAOI	Monoamine oxidase inhibitor
NE	Norepinephrine
NICE	National Institute for Health and Care Excellence
NMAs	Network meta-analyses
NRI	Norepinephrine reuptake inhibitor
P&T	Pharmacy & Therapeutics
PTBM	Parent training in behavior management
RCTs	Randomized controlled trials
SDBP	Society for Developmental and Behavioral Pediatrics
SNRIs	Serotonin-norepinephrine reuptake inhibitors
SRs	Systematic reviews
SUD	Substance use disorder
TEAEs	Treatment-emergent adverse events
US	United States
WFIRS-P	Weiss Functional Impairment Rating Scale-Parent Report

EXECUTIVE SUMMARY

Background:

Attention-deficit/hyperactivity disorder (ADHD) is a chronic neurodevelopmental disorder,[1] often manifesting during childhood.[2-6] It is characterized by behavioral symptoms of impulsivity, hyperactivity, and/or inattentiveness.[2,4,6-9] ADHD often occurs with other comorbid conditions (eg, anxiety, depression, oppositional defiant disorder, autism spectrum disorder [ASD], conduct disorder).[7-10]

This report reviews 4 agents for the treatment of ADHD symptoms, listed below, which are approved by the United States (US) Food and Drug Administration (FDA)[11-14]:

i. 2 oral extended-release (ER), centrally-acting alpha-2 agonists: clonidine ER (Kapvay) and guanfacine ER (Intuniv)
ii. 2 oral norepinephrine reuptake inhibitors (NRIs): atomoxetine (Strattera) and viloxazine ER (Qelbree)

These dosage forms are indicated only for the treatment of ADHD.[11-14] While immediate-release (IR) preparations of clonidine and guanfacine are available in the US, they are not FDA-approved for the treatment of ADHD.[15] Viloxazine ER was the most recent non-stimulant to be FDA-approved (2021).[12] Clonidine ER and guanfacine ER are approved for use either as monotherapy or as adjuncts to stimulants[13,14]; viloxazine ER and atomoxetine are labeled without specifying whether they are to be used as monotherapy or concomitantly with stimulants.[11,12]

Viloxazine ER is indicated for patients ≥6 years of age, including adults.[12] Although atomoxetine, clonidine ER, and guanfacine ER are indicated without an explicit FDA-approved age for use,[11,13,14] none of the phase 3 clinical trials were conducted in pediatric patients <6 years of age; clonidine ER and guanfacine ER were studied in pediatric patients 6−17 years of age,[13,14] and atomoxetine was studied in pediatric patients ≥6 years of age and adults.[11]

These oral agents are available as either capsules (ie, atomoxetine, viloxazine ER) or tablets (ie, guanfacine ER, clonidine ER).[11-14] Atomoxetine capsules are intended to be consumed whole and should not be opened[11]; whereas viloxazine ER capsules may be opened and sprinkled over soft foods.[12] Except for guanfacine ER, all non-stimulants may be taken with or without food.[11-13] Guanfacine ER should not be taken with high-fat meals due to the potential for increased drug concentrations.[14]

The frequency of administration for all of these products is once daily, except for clonidine ER dosages exceeding 0.1 mg, which should be taken in 2 divided doses.[11-14] After initiating one of these non-stimulants, it may take up to a couple of weeks before the patient notices a reduction in ADHD symptoms.[15-17]

Guideline recommendations:

Recently published clinical practice guidelines for the treatment of ADHD include the Canadian ADHD Resource Alliance (CADDRA),[3] the 2020 guideline by the Society for Developmental and Behavioral Pediatrics (SDBP),[18] the 2019 guideline by the American Academy of Pediatrics (AAP),[6] and the 2018 guideline by the National Institute for Health and Care Excellence (NICE),[19] among others.[1,20,21] The

majority of these guidelines focus on the management of ADHD in children and adolescents,[3,6,18,20,21] with only a couple pertaining to adults.[1,3,19]

Guidelines list stimulants (eg, amphetamines, methylphenidate), usually long-acting, as the first-line pharmacologic treatment for ADHD.[1,3,6,18-20] Stimulants are favored over non-stimulants as initial pharmacotherapy for most patients due to the increased effectiveness and more robust evidence base.[1,3,6,21] Patients who are unresponsive to an initial stimulant are recommended to switch to another guideline-recommended stimulant, preferably in another stimulant class, before proceeding to non-stimulants.[3,19,20]

Non-stimulants are typically used when stimulants are unavailable, not tolerated, contraindicated (including because of a high likelihood of abuse), or with a lack of symptomatic improvement after an adequate trial of stimulants.[3,21] The preferred initial non-stimulant varies by guideline, with most recommending atomoxetine, guanfacine (IR or ER), or both[1,3,6,18-20]; however, guidelines indicate a preference for atomoxetine over guanfacine in adults (the use of clonidine in adults is not addressed).[1,19] The AAP (2019) guideline points out that clonidine ER has the least evidence supporting its use for ADHD in pediatric patients compared to atomoxetine and guanfacine ER, but the guideline does not make a formal recommendation preferring one agent over another.[6] Reviewed guidelines predate market approval of the newest non-stimulant, viloxazine ER; therefore, none provide recommendations for its use.

Non-stimulant treatment may also be preferred for treating ADHD in the presence of comorbidities that may be exacerbated by traditional stimulants.[22] For example, atomoxetine may be preferred with comorbid anxiety,[1] and clonidine or guanfacine (as alternative first-line agents) may be preferred with comorbid tic disorders, if tics are the predominant cause of impairment.[18]

Head-to-head comparisons:

We conducted a literature search for systematic reviews (SRs) of randomized controlled trials (RCTs) in Embase, Ovid Medline, and Epistemonikos to identify direct head-to-head comparative evidence between the non-stimulants addressed in this review. To supplement the SR evidence, we also searched Ovid Medline and Embase for individual RCTs published from 2017 to present.

Only 1 relevant head-to-head RCT was found, with a comparison between guanfacine ER and atomoxetine. No direct head-to-head evidence was identified for clonidine or viloxazine versus any other FDA-approved non-stimulant for ADHD.[23-28]

Guanfacine ER vs atomoxetine: The identified RCT primarily compared guanfacine ER to placebo among children and adolescents (6−17 years of age; N=338) with ADHD, but also included an atomoxetine study arm as a reference agent.[29] The statistical comparison between guanfacine ER and atomoxetine was prespecified for the primary efficacy outcome (change in the prescriber-rated ADHD Rating Scale, version IV [ADHD-RS-IV] from baseline to visit 15 [10 weeks for children aged 6−12 years, or 13 weeks for adolescents aged 13−17 years]).[29]

ADHD symptoms improved significantly with guanfacine ER (1−4 mg/day for children 6−12 years; 1−7 mg/day for adolescents 13−17 years) compared to atomoxetine (10–100 mg/day) at visit 15 (difference from atomoxetine: −5.1; *p=0.001*).[29]

In terms of drug-specific adverse events (AEs), the percentages of somnolence (43.9% vs 17.9%), headache (26.3% vs 19.6%), and fatigue (25.4% vs 21.4%) were numerically higher with guanfacine ER compared to atomoxetine, respectively.[29] However, percentages of nausea (26.8% vs 15.8%), vomiting (16.1% vs 5.3%), and decreased appetite (27.7% vs 13.2%) were numerically higher among participants treated with atomoxetine compared to guanfacine ER, respectively.[29]

Contraindications, and safety warnings and precautions:

Clonidine ER, guanfacine ER, and atomoxetine are contraindicated in patients with prior hypersensitivity reactions to an active ingredient or any excipient.[11,13,14] Due to the risk of hypertensive crisis, viloxazine ER and atomoxetine are contraindicated in patients who are taking a monoamine oxidase inhibitor (MAOI), or who discontinued an MAOI within the previous 14 days.[11,12] Viloxazine ER is also contraindicated in patients taking sensitive or narrow therapeutic window CYP1A2 substrates.[12] Unique contraindications to atomoxetine include patients with narrow-angle glaucoma, pheochromocytoma or a history of the condition, and severe cardiac or vascular disorders that are expected to worsen with elevations in heart rate or blood pressure.[11]

Of the reviewed FDA-approved non-stimulants, only the NRIs carry **black box warnings**. The viloxazine ER label warns of an increased risk of suicidal thoughts and behaviors in pediatric and adult patients.[12] Similarly, atomoxetine's label warns of the potential for suicidal ideation in children and adolescents.[11]

Other labeled warnings and precautions for both atomoxetine and viloxazine ER include the following[11,12]:

- Recommendation to screen all patients for bipolar disorder, including risk factors, before starting treatment due to the potential to cause mixed or manic episodes in those with underlying bipolar disorder
- Potential to cause elevations in heart rate and blood pressure

Labeled warnings and precautions for both clonidine ER and guanfacine ER include the following[13,14]:

- Elevated risk of hypotension, bradycardia, and syncope
- Risk of rebound hypertension with abrupt discontinuation
- Recommendation to frequently monitor and slowly titrate to an optimal dose in patients receiving other sympatholytic agents or who have cardiac conduction abnormalities

Viloxazine ER, clonidine ER, and guanfacine ER also include warnings for somnolence; patients are advised to avoid tasks that require mental alertness (eg, driving) until they are aware of how the medication may affect them.[12-14] The potential for additive sedative effects with concomitant use of CNS depressants (eg, benzodiazepines) should also be considered before using with clonidine ER or guanfacine ER.[13,14] Both atomoxetine and clonidine ER also have a labeled warning for allergic reactions.[11,13]

Other warnings and precautions specific to atomoxetine include the potential for new, emergent psychotic or manic symptoms in individuals without a history of associated psychiatric conditions; rare cases of severe liver injury; a recommendation to generally avoid use in patients with serious cardiac abnormalities; a recommendation to monitor for new or worsening hostility or aggression; the potential for urinary retention or hesitancy, or priapism; a recommendation to monitor pediatric patients for

weight and height changes during treatment; and lastly, a recommendation that dose adjustments may be required when used in combination with potent CYP2D6 inhibitors or in individuals who are poor metabolizers of CYP2D6.[11]

In contrast to stimulants, the reviewed non-stimulants have no known abuse potential, cause little to no physical dependence, and are not controlled substances.[11,13,14,30]

Summary:

Non-stimulants are typically recommended as second-line agents, after stimulants, for the treatment of ADHD.[1,3,6,18-20] The guidelines vary as to which non-stimulants are preferred, with most recommending atomoxetine, guanfacine (IR or ER), or both.[1,3,6,18-20] In adults, guidelines indicate a preference for atomoxetine over guanfacine (the use of clonidine in adults is not addressed).[1,19] A non-stimulant may be preferred when stimulant misuse or diversion is suspected,[6,20] in patients with certain comorbid conditions that may be exacerbated by stimulants,[1,18] or in patients with contraindications or poor tolerance of stimulants.[22]

The reviewed guidelines predate the regulatory approval of the newest FDA-approved non-stimulant, viloxazine ER; therefore, none commented on its use.

No direct head-to-head evidence was identified for clonidine or viloxazine versus any other FDA-approved non-stimulant for the treatment of ADHD.[23-28] Evidence from 1 RCT showed greater improvements in ADHD symptoms (as measured by the ADHD-RS-IV score) with guanfacine ER compared to atomoxetine in pediatric patients (6–17 years of age) with ADHD after 10 or 13 weeks of therapy.[29]

The safety profile of the reviewed non-stimulants generally varies based on drug class.

Utah Medicaid Preferred Drug List (PDL) considerations:

Considerations for the Utah Medicaid PDL, include the following:

A. Although stimulants (eg, amphetamines, methylphenidate) are recommended as first-line agents,[1,3,6,18-20] consider including at least 1 non-stimulant FDA-approved for treating ADHD in children and adults, particularly atomoxetine or viloxazine ER for adults, as preferred on the PDL.
    a. A non-stimulant may be preferred when stimulant misuse or diversion is suspected.[6,20]
        i. The non-controlled substances atomoxetine, viloxazine ER, clonidine ER, and guanfacine ER have no known abuse potential and little to no physical dependence.[11,13,14,30]
    b. A non-stimulant may be preferred with certain comorbidities, such as those that may be exacerbated by traditional stimulants.[22]
        i. Atomoxetine may be preferred with comorbid anxiety,[1] and clonidine or guanfacine (as alternative first-line agents) may be preferred with comorbid tic disorders, if tics are the predominant cause of impairment.[18]
    c. Different preferred non-stimulants may be selected for adult or pediatric patients. Some products (clonidine ER and guanfacine ER) lack adult trials; only atomoxetine and viloxazine ER have been studied in both populations.

1.0 INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a chronic, neurodevelopmental disorder characterized by persistent behavioral symptoms of impulsivity, hyperactivity, and/or inattentiveness for ≥6 months.[2,4,9] Depending on the core symptomatology, manifestations of ADHD include difficulty maintaining concentration, unnecessary risk-taking, or excessive physical activity or talking.[9] ADHD is often recognized during childhood,[2] with the majority of affected children continuing to experience symptoms into adolescence and adulthood.[3,4,6] Children and adolescents with ADHD tend to have school-related issues, suffer from peer rejection, and have a higher tendency for injury or accidents and substance abuse.[8] The risk of developing substance use disorder (SUD), as well as becoming incarcerated, increases with the presence of certain comorbid disorders (ie, antisocial personality disorder in adults, conduct disorder in adolescents).[8,9] Adults with ADHD often have poor employment stability due to unsatisfactory job performance, poor attendance, and a greater risk of interpersonal conflict.[9]

The two types of medications approved by the United States (US) Food and Drug Administration (FDA) for the treatment of ADHD include: central nervous system (CNS) stimulants* and non-stimulants.[31] Non-stimulant options may offer several advantages to individuals with ADHD over traditional CNS stimulants[17,32]:

- No associated abuse potential
- May be used in patients with a history of stimulant failure
- Mitigates the concern about possible long-term adverse effects (AEs) of stimulant therapy on developing children
- May be used in cases where a stimulant is contraindicated due to a medical condition, pharmacologic agent, or both

The 4 FDA-approved non-stimulants include the extended-release (ER) formulations of the centrally-acting alpha-2 agonists, guanfacine (Intuniv) and clonidine (Kapvay), and the norepinephrine reuptake inhibitors (NRIs), viloxazine ER (Qelbree) and atomoxetine (Strattera).[11-14,17] The first non-stimulant, atomoxetine, was FDA-approved in 2002, followed by approval of the other agents.[11,31,33,34] Viloxazine ER was the most recent non-stimulant to be FDA-approved in 2021.[12] While the immediate-release (IR) formulation of viloxazine is available in Europe for the treatment of depression, it has never been marketed in the US.[17,35] A generic equivalent is available for each non-stimulant, except for viloxazine ER.[36]

Each of these non-stimulants were studied in pediatric patients as young as 6 years of age, with atomoxetine and viloxazine ER also studied in adults.[11-14,17] While clonidine ER and guanfacine ER have proven efficacy to treat ADHD in pediatric patients (aged 6−17 years of age),[13,14] less is known about their use in adults.[5] With respect to the labeled indication, only viloxazine ER is specifically approved for patients ≥6 years of age[12]; atomoxetine, clonidine ER, and guanfacine ER are indicated without an explicit FDA-approved age for use.[11,13,14] Guanfacine ER and clonidine ER are approved for use either as

* Refer to our 2019 Utah Medicaid Pharmacy & Therapeutics report for details on FDA-approved CNS stimulants for the treatment of ADHD, available at: https://medicaid.utah.gov/pharmacy/pt-committee/.

monotherapy or as adjuncts to stimulants, whereas viloxazine ER and atomoxetine are labeled without specifying whether they are to be used as monotherapy or concomitantly with stimulants.[11-14]

These oral non-stimulants are available as either a capsule (ie, atomoxetine, viloxazine ER) or a tablet (ie, guanfacine ER, clonidine ER).[11-14] Atomoxetine capsules are intended to be consumed whole and should not be opened,[11] whereas viloxazine ER capsules may be opened and sprinkled over soft foods.[12] This administration method may be beneficial for individuals (eg, older adults, young children) who are unable to swallow whole capsules or tablets. While clonidine and guanfacine are also formulated as IR preparations,[15] only the ER tablets are FDA-approved for the treatment of ADHD.[13,14] Prior to the FDA-approval of the ER preparations of guanfacine and clonidine, the IR formulations were used off-label; however, concerns arising from tolerability (eg, sedation) and frequent daily dosing prompted longer-acting formulations to be developed.[17] With ER preparations of clonidine and guanfacine specifically approved for the treatment of ADHD, it is not recommended to use the IR products, according to expert opinion.[15]

The recommended initial and maintenance dosing for each agent varies according to patient-specific factors. For example, the dosing of atomoxetine and guanfacine ER is weight based, viloxazine ER dosing varies by age, and clonidine ER dosing is based on therapeutic response.[11-14] The frequency of administration for all of these products is once daily, except for clonidine ER dosages exceeding 0.1 mg, which should be taken in 2 divided doses.[11-14]

The objective of this report is to review the place-in therapy for these 4 FDA-approved non-stimulants (listed in **Table 1**) according to recent clinical guidelines, labeled safety information, and key differences between each of these agents based on head-to-head comparative evidence. According to the Preferred Drug List (PDL), published January 1, 2023, the preferred non-stimulant product by Utah Medicaid is atomoxetine (generic). Non-preferred agents are viloxazine ER (brand Qelbree) and the brand of atomoxetine, Strattera. Generic clonidine IR, as tablets, is available open access and is on the mandatory 3-month (ie 90 day) supply list. Clonidine ER, including the brand product Kapvay, is not listed on the PDL. Additionally, guanfacine ER and IR formulations are not listed on the PDL.

Table 1 provides specific details about the labeled indications, dosing recommendations, and available formulations for the FDA-approved non-stimulant agents.

Table 1. FDA-Approved Non-Stimulants for ADHD[11-14]

Generic Name **Brand** (approval year), Dosage Form/Strength	**Labeled Indication**	**Frequency of Administration**	**Discontinuation Taper?**	**Dosing Recommendations**
Atomoxetine[a] **Strattera** (2002)[11] Oral Capsule: 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, 100 mg	Treatment of ADHD	Once daily[b]	No	**Pediatrics weighing ≤70 kg:** Initial dose: 0.5 mg/kg daily; Target dose: 1.2 mg/kg daily; Max dose: 1.4 mg/kg daily Increase the initial dose to the target dose after at least 3 days **Pediatrics weighing >70 kg and adults:** Initial dose: 40 mg daily; Target dose: 80 mg daily; Max dose: 100 mg Increase the initial dose to the target dose after at least 3 days. Based on response, the dose may be adjusted up to 100 mg after 2–4 weeks **HI:** Reduce the initial and maintenance dosages by 50% for moderate impairment and 25% for severe impairment **CYP2D6 poor metabolizers or strong inhibitors:** Only increase to the target dose if symptoms continue to persist for 4 weeks and the initial dose is tolerated
Clonidine hydrochloride[c] **Kapvay** (2010)[13] ER Oral Tablet: 0.1 mg	Treatment of ADHD as monotherapy or adjunctively with stimulants	Twice daily (for dosages >0.1 mg)	Yes; ≤0.1 mg every 3–7 days	Initial dose: 0.1 mg taken at bedtime Dose should be up-titrated weekly, at increments of 0.1 mg, until a therapeutic response is attained Total dose: 0.1–0.4 mg daily; evenly split among the morning and bedtime dose, or a higher split dose taken at bedtime • Ex: total daily dose = 0.3 mg; 0.1 mg in the morning + 0.2 mg at bedtime Max dose: 0.4 mg daily **RI:** Dose should be tailored based on the extent of impairment; monitor for signs of bradycardia and hypotension

[a] *To determine the effectiveness of the agent to treat ADHD, it was studied in adults and pediatric patients (6–18 years of age)*

[b] *May be administered as a single dose in the morning, or evenly split into 2 doses that are given in the morning and late afternoon/early evening*

[c] *To determine the effectiveness of the agent to treat ADHD, it was only studied in pediatric patients (6–17 years of age)*

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CYP, cytochrome P450; eGFR, estimated glomerular filtration rate; ER, extended-release; FDA, US Food and Drug Administration; HI, hepatic impairment; hrs, hours; RI, renal impairment

Table 1. FDA-Approved Non-Stimulants for ADHD[11-14]

Generic Name **Brand** (approval year), Dosage Form/Strength	**Labeled Indication**	**Frequency of Administration**	**Discontinuation Taper?**	**Dosing Recommendations**
Guanfacine[c] **Intuniv** (2009)[14] ER Oral Tablet: 1 mg, 2 mg, 3 mg, 4 mg	Treatment of ADHD as monotherapy or adjunctively with stimulants	Once daily	Yes; ≤1 mg every 3–7 days	Initial dose: 1 mg daily; Target dose: 1–7 mg daily, depending on weight • 25–33.9 kg: 2–3 mg daily • 34–41.4 kg: 2–4 mg daily • 41.5–49.4 kg: 3–5 mg daily • 49.5–58.4 kg: 3–6 mg daily • 58.5–91 kg: 4–7 mg daily • >91 kg: 5–7 mg daily Initial dose should be up-titrated weekly, at increments of ≤1 mg, to the target dose based on tolerability and treatment response Max dose for children 6–12 years of age: 4 mg daily Max dose for children 13–17 years of age: 7 mg daily **HI/RI:** Dose may need to be lowered in patients with significant impairment
Viloxazine **Qelbree** (2021)[12] ER Oral Capsule: 100 mg, 150 mg, 200 mg	Treatment of ADHD in patients ≥6 years of age	Once daily	No	**Pediatrics aged 6–11 years:** Initial dose: 100 mg daily; Max dose: 400 mg daily Dose may be up-titrated weekly, at increments of 100 mg, based on tolerability and treatment response **Pediatrics aged 12–17 years and adults:** Initial dose: 200 mg daily Dose may be up-titrated weekly, at increments of 200 mg, based on tolerability and treatment response Max dose for children 12–17 years of age: 400 mg daily Max dose for adults: 600 mg daily **RI:** Initial (100 mg) and maximum (200 mg) doses are reduced for patients with severe impairment (eGFR <30 mL/min/1.73m^2); may be up-titrated weekly, at increments of 50–100 mg

[a] To determine the effectiveness of the agent to treat ADHD, it was studied in adults and pediatric patients (6–18 years of age)

[b] May be administered as a single dose in the morning, or evenly split into 2 doses that are given in the morning and late afternoon/early evening

[c] To determine the effectiveness of the agent to treat ADHD, it was only studied in pediatric patients (6–17 years of age)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CYP, cytochrome P450; eGFR, estimated glomerular filtration rate; ER, extended-release; FDA, US Food and Drug Administration; HI, hepatic impairment; hrs, hours; RI, renal impairment

2.0 METHODS

2.1 Systematic literature search

Systematic literature searches, comprising of controlled vocabulary and keyword phrases, were executed in 3 bibliographic databases (Embase, Ovid Medline, and Epistemonikos). Ovid Medline and Epistemonikos were searched from 2017 to present (ie, November 2022) for systematic reviews (SRs) of randomized controlled trials (RCTs). Based on the robust literature search for head-to-head evidence from 2 SRs published in 2018,[23,26] the SR search in Embase was restricted from 2019 to 2022. In order to identify SRs of RCTs, our search in Ovid Medline contained a combination of methodological filters that were independently derived and obtained from McMaster University.[37] Additionally, SR filters were used in the other two databases: a website-embedded filter in Epistemonikos and an independently derived filter in Embase. To supplement the SR evidence, we also performed systematic searches for head-to-head RCTs in Embase and Ovid Medline. In both databases, we used a Cochrane Collaboration Handbook filter[38] to identify RCTs. Embase searches were restricted to English and excluded conference abstracts. Details of the search strategies, including terms and controlled vocabulary are available in **Appendix A**.

Our previously completed 2019 Pharmacy & Therapeutics (P&T)[39] and 2020 Drug Utilization Review (DUR)[40,41] reports on CNS stimulants for the treatment of ADHD among children, adolescents, and adults were reviewed for relevant guidelines.

The following websites were also screened for additional information:

1. To identify relevant guidelines recently published in the last 5 years (2017–2022) regarding the management of ADHD, the following organizational websites were searched: American Academy of Pediatrics (AAP), Society for Developmental and Behavioral Pediatrics (SDBP), National Institute for Health and Care Excellence (NICE), Canadian ADHD Resource Alliance (CADDRA), and the Canadian Paediatric Society (CPS).
2. Product labeling (ie, package inserts) was obtained from the Drugs@FDA website: https://www.accessdata.fda.gov/scripts/cder/daf/.
3. Evidence-based drug information websites: UpToDate (https://www.uptodate.com/contents/search) and Lexicomp (https://online.lexi.com/).

2.2 Screening

To evaluate inclusion eligibility of titles and abstracts, two reviewers independently screened all citations. Conflicts regarding eligibility were resolved by consensus. The full texts were retrieved for citations that received 2 votes for inclusion. The definitive decision for inclusion was made by the lead author based upon full text review. Additionally, the lead author screened references from identified articles for other relevant information. **Figure 1** in **Appendix B** shows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart[42] for the literature review process.

2.3 Inclusion and exclusion criteria

SRs and individual RCTs, as well as network meta-analyses (NMAs) with direct head-to-head efficacy or safety comparisons among the FDA-approved ADHD non-stimulants (refer to **Table 1**) were included.

Excluded references met one or more of the following criteria:

- Review articles that did not use a methodology consist with SRs
- SRs or RCTs that compared FDA-approved non-stimulants only to placebo or an uninterested active comparator (eg, stimulants)
- NMAs including only indirect comparisons
- Studies among patient populations without diagnosed ADHD
- Observational studies, pharmacokinetic studies, cost-effectiveness analyses studies, post hoc analyses studies, pharmacodynamic studies, study protocols

Appendix C contains a list of excluded references from the full-text screening process.

3.0 DISEASE OVERVIEW

ADHD is a chronic neurodevelopmental disorder,[1] often manifesting during childhood.[2-6] The terminology used for the disorder we now refer to as ADHD has undergone several revisions since it was first introduced in 1968 as a 'hyperkinetic reaction in childhood'.[3,43] In 1980, the nosology was re-conceptualized to Attention Deficit Disorder,[3,43] and lastly, updated to the current term, ADHD, in 1987.[43]

ADHD is often characterized by behavioral symptoms of impulsivity, hyperactivity, and/or inattentiveness that are expressed in a recognizable, persistent pattern, resulting in daily functional or developmental impairment in academic/occupational and/or social activities.[2,4,6-9] While children tend to have periodic behavioral issues,[4] the core symptoms of ADHD are persistent, and tend to be uncharacteristic based on the child's stage of development and age.[8] Behavioral symptoms of inattention include difficulty maintaining concentration, inability to complete tasks at work, home, or school, easily distracted, and presence of organizational issues.[9] Hyperactivity refers to excessive physical movement (eg, fidgeting, running, climbing), often occurring at socially-deemed inappropriate times, or excessive talking. Hyperactivity-related symptoms can vary with age; adults often express restlessness or "on the go" features.[9] Impulsive behavioral symptoms are characterized as sudden thoughtless actions, often manifesting as social invasiveness (eg, interrupting others during conversation) and/or making significant decisions without considering the consequences (eg, unnecessary risk-taking).[4,9] The clinical presentation of ADHD depends on the patient's predominant symptomatology[4,6]: patients can largely have inattentive symptoms; or hyperactivity/impulsivity symptoms; or an equal combination of inattentive and hyperactivity/impulsivity symptoms. Notably, the presenting symptomatology, and therefore, clinical presentation not only changes over time,[44] but also varies with age.[2,7,45] Adults with ADHD tend to experience fewer symptoms of hyperactivity/impulsivity[2,9] and express overt emotional dysregulation (up 70% of cases)[46] relative to affected children.[7,45] It is estimated that >50% of children and adolescents with ADHD have persistent symptoms as adults.[3] Predictive factors for ADHD persistence into adulthood include combined presentation of inattentive and hyperactivity/impulsivity symptoms, greater symptom severity, and the presence of comorbid conditions (eg, depression, parental antisocial personality disorder, or parental anxiety).[7,8]

In the US, ADHD is the most commonly diagnosed mental disorder among school-aged children (3−17 years of age), with an higher estimated prevalence than anxiety, behavioral issues, and depression.[47]

According to the Centers for Disease Control and Prevention (CDC), approximately 6 million children (9.8%) had a current or previous diagnosis of ADHD, with the greatest prevalence among those 12−17 years of age.[10] In Utah, the estimated prevalence of ADHD among children aged 3−17 years is 10%, according to parent-reported data from the 2016−2019 National Survey of Children's Health.[48] A greater prevalence exists in certain pediatric populations, including children in the foster care or correctional systems.[9] Existing data indicates that the prevalence is lower in older populations, but continues to persist into adulthood.[4-6] According to the National Comorbidity Survey (2001−2003), the prevalence of ADHD is 4.4% among the US adult population (18−44 years of age).[49] Among older adults, the estimated general prevalence is approximately 3%.[3]

ADHD poses a significant economic burden to the US healthcare system due to the high prevalence and chronic symptomatology.[50] The yearly societal costs of ADHD in children and adolescents is estimated to be about $38−72 billion,[50,51] and $105−194 billion in adults.[51,52] The highest expense categories among pediatric patients were education and healthcare; whereas adults tended to incur higher costs from loss of productivity and income.[52] An additional contributor to ADHD-related expenses may include comorbid conditions.

3.1 ADHD comorbidities

Children, adolescents, and adults with ADHD often have at least one comorbid condition, usually neurodevelopmental or psychiatric in origin.[7-10] Among children with ADHD, approximately 50% to 90% have at least one other comorbidity,[3] with the most common being a behavioral or conduct issue (eg, oppositional defiant disorder, conduct disorder), anxiety disorders (eg, obsessive compulsive disorder, anxiety), depression, or autism spectrum disorder (ASD).[8,10] Adults with ADHD are more likely to have co-occurring mood disorders (eg, bipolar disorder), anxiety, and SUD.[3,7] Other conditions that occur among individuals with ADHD include epilepsy, tic disorders, learning disabilities, and sleep disorders (eg, insomnia).[6,9,53] Comorbidities can increase symptom severity, alter the clinical presentation of ADHD, and substantially worsen functionality.[8] ADHD in the presence of other comorbid conditions is often referred to as 'complex ADHD', although this term can also be applied to other circumstances (eg, unclear diagnosis, treatment failure).[6,18]

3.2 Etiology and risk factors

Although genetics appear to have a predominant role in the development of ADHD, the exact etiology and risk factors are undetermined.[3,4] Based on twin studies, the heritability of ADHD is estimated to be 76%,[7,54] with the heritable risk among first-degree relatives estimated to be 30% to 40%.[3] Other factors that possibly contribute to the heterogeneous etiology include environmental exposures (eg, cigarette smoke, lead, organophosphate pesticides) in childhood or pregnancy, traumatic brain injury, premature delivery, alcohol/tobacco use during pregnancy, and low birth weight (<2.5 kg).[3,4,8,9,54]

4.0 DIAGNOSIS AND MANAGEMENT

The diagnosis of ADHD is based on the fulfillment of Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria, as determined by a physician specialized in psychiatry (ie, psychologist, psychiatrist), primary care (eg, pediatrician), or other qualified field.[19,44] Therefore, appropriate diagnosis does not rely on a particular laboratory test.[9,44] According to the DSM-5 ADHD

diagnostic criteria, symptoms must be present for ≥6 months, are uncharacteristic for the patient's stage of development, and negatively affect function or development in academic/occupational, and/or social activities.[9] To obtain a diagnosis of ADHD, children (≤16 years of age) must have 6 or more symptoms of hyperactivity/impulsivity and/or inattention, and adults (≥17 years of age) are required to have 5 or more symptoms.[9] In addition, other criteria are required to be met such as having a symptomatic presentation before 12 years of age, and symptoms occurring in multiple settings (eg, school, home, work).[9] The American Academy of Pediatrics (AAP) recommends diagnosing children who are at least 4 years of age presenting with behavioral or academic issues and core ADHD symptoms (ie, hyperactivity/impulsivity, or inattention); ADHD symptoms should be present in more than one setting and confirmed from individuals involved in the child's life (eg, teachers, parents) [Grade B; strong recommendation].[6] Notably, the diagnosis of ADHD in very young children (<4 years) is difficult to establish because it is challenging to distinguish normative behaviors from indicative ADHD symptoms.[9,55] **Table 2** outlines the DSM-5 diagnostic criteria for ADHD in children, adolescents, and adults, and provides examples of symptoms, categorized based on inattention or hyperactivity/impulsivity.

A differential diagnosis is especially important because other disorders (eg, sleep disorders, depression, anxiety) often have related symptoms, or are often co-occuring.[8,44] Conditions that may be misdiagnosed as ADHD include learning disorders, sleep disorders, oppositional defiant disorder, anxiety disorders, intellectual disability, language disorder, and ASD, among others; but these conditions can also be comorbid with ADHD.[8] AAP (2019) recommends that all children and adolescents be screened for emotional, behavioral, developmental, and physical comorbid conditions when determining an ADHD diagnosis [Grade B; strong recommendation].[6]

Standardized rating scales may be used to supplement the initial diagnosis of ADHD to determine associated symptoms or comorbidities,[6] but used solely, are inefficient to establish an ADHD diagnosis due to the overlapping symptomatology with other conditions.[3,8,19] These rating scales include the ADHD Rating Scale-IV (ADHD-RS-IV) and the Conner's Comprehensive Behavior Rating Scale, which have been validated in preschool-aged children.[8] Other rating scales include the SNAP-IV Teacher and Parent Rating Scale, the Adult ADHD Self-Rating Scale, and the Vanderbilt ADHD Diagnostic Rating Scale.[2,3]

Based on results from a 2014 national survey, the average age of ADHD diagnosis among children was 7 years; with nearly 33% diagnosed prior to 6 years of age.[6] Among school-aged children and adolescents, males are roughly two-to-three times more likely to be diagnosed with ADHD relative to females, potentially due to the recognizable hyperactive and disruptive behaviors, especially observed in young boys.[3,6] Therefore, young females are often under-diagnosed, but the discrepancy between sexes begins to diminish near adulthood.[3] While ADHD can be diagnosed in adults who did not manifest the disorder during childhood,[7] it is estimated that ≥50% of children and adolescents diagnosed during youth will have significant ADHD symptoms that continue to persist into adulthood.[3]

Table 2. Diagnostic Criteria for ADHD in Children, Adolescents, and Adults, According to DSM-5-TR[9]

Age, Number of Required Symptoms	Symptoms of Inattention	Symptoms of Hyperactivity/Impulsivity	Other Diagnostic Requirements
Children and adolescents (≤16 years of age): ≥6 symptoms[a] Adolescents and adults (≥17 years of age): ≥5 symptoms[a]	• Fails to observe details, or makes inattentive mistakes • Struggles to maintain concentration on tasks (eg, conversations, reading) • Appears to not be listening when directly spoken to • Fails to complete tasks at home, school, or work • Organizational issues (eg, poor time management, disorganized work or belongings) • Averse to tasks that require persistent mental effort • Misplaces necessary objects (eg, school materials, wallet, keys) • Easily distracted • Forgets daily activities (eg, errands, paying bills, chores)	• Fidgets or wiggles when seated • Restlessness (climbs or runs at inappropriate times) • Struggles to remain seated when it is expected behavior (eg, classroom, workplace) • Fails to quietly participate in leisure activities • "On the go" (eg, others feel the person is hard to keep up with; trouble being stationary for extended periods) • Talks excessively or speaks at an inappropriate time (eg, finishes others' sentences) • Struggles with waiting for their turn • Infringes or disturbs others (eg, may invade conversations or personal space, or use others' belongings without permission)	• Several symptoms were exhibited before 12 years of age • Symptoms occur in ≥2 settings (eg, school, work, home) • Symptoms negatively impact social, occupational, or academic functioning • No other explanatory psychiatric disorder exists for the presenting symptoms

[a] *Symptoms (either classified as inattention, hyperactivity/impulsivity, or a mixture of both) should persist for at least 6 months, and are uncharacteristic for the patient's stage of development*

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; DSM-5-TR, Diagnostic and Statistical Manual of Mental Disorders, 5th edition, text revision

5.0 CLINICAL PRACTICE GUIDELINE RECOMMENDATIONS

Recent clinical guidelines for the treatment of ADHD include the 2020 guideline by the Canadian ADHD Resource Alliance (CADDRA),[3] the 2020 guideline by the Society for Developmental and Behavioral Pediatrics (SDBP),[18] the 2019 guideline by the American Academy of Pediatrics (AAP),[6] and the 2018 guideline by the National Institute for Health and Care Excellence (NICE),[19] among others.[1,20,21] The majority of these guidelines focus on the management of ADHD in children and adolescents,[3,6,18,20,21] with only a couple pertaining to adults.[1,3,19] Guideline recommendations for specific agents may differ due to differences in national regulatory approval or availability. For example, clonidine ER (Kapvay) is not available in Canada, United Kingdom, or Europe[56-58]; therefore, recommendations made by guidelines originating in those countries refer only to the IR formulation, or simply "clonidine."[1,3,19,21] All of the reviewed guidelines predate regulatory approval of the newest non-stimulant, viloxazine ER, so this agent is not included in any of the guideline recommendations. **Table 3** highlights the country/region of origin and target population for the most current ADHD guidelines.

Table 3. Summary of the Country of Origin and Target Population of Reviewed ADHD Guidelines

Sponsoring Organization (Year)	Country or Region of Origin					Target Population	
	United States	Canada	United Kingdom	Europe	International	Pediatric Patients (<18 years of age)	Adults (≥18 years of age)
CADDRA (2020)[3]		✓				✓	✓
SDBP (2020)[18]	✓					✓[a]	
ICASA (2020)[20]					✓	✓[b]	
AAP (2019)[6]	✓					✓	
ENAA; NDAL of the EPA (2019)[1]				✓			✓
NICE (2018)[19]			✓			✓	✓
CPS (2018)[21]		✓				✓	

[a] *This guideline applies to pediatric patients through 18 years of age*

[b] *This guideline applies to adolescents only*

Abbreviations: AAP, American Academy of Pediatrics; ADHD, attention-deficit/hyperactivity disorder; CADDRA, Canadian ADHD Resource Alliance; CPS, Canadian Paediatric Society; ENAA, European Network Adult ADHD; EPA, European Psychiatric Association; NDAL, Neurodevelopmental Disorders Across the Lifespan; NICE, National Institute for Health and Care Excellence; SDBP, Society for Developmental and Behavioral Pediatrics

The goal of ADHD treatment is to alleviate symptoms and improve functionality and emotional lability, resulting in better occupational/academic performance.[59] Most guidelines promote a multimodal, evidence-based treatment approach, consisting of psychosocial interventions (eg, parent training in behavior management [PTBM], cognitive behavioral therapy, behavioral interventions, psychoeducation) in addition to pharmacotherapy, especially in the presence of comorbidities or

complex ADHD[†].[1,3,6,18,20,21] Behavioral and/or educational interventions (eg, behavioral peer or classroom interventions, behavioral parent training) are usually recommended as the initial treatment approach, especially in younger children.[6,19] Pharmacologic management, prescribed by a healthcare provider with ADHD expertise,[19] is typically reserved for patients ≥6 years of age (or ≥5 years of age in the 2018 NICE guideline)[3,6,19,21] but may be considered for preschool-aged children with significant impairment despite the use of non-pharmacologic interventions.[6,60] Methylphenidate is the preferred first-line stimulant in preschool-aged children.[6,18]

Guidelines generally prefer long-acting stimulants as first-line pharmacotherapy.[1,3,6,18-20] Long-acting stimulants are preferred to shorter-acting stimulants due to the lower abuse liability, improved patient adherence, and prevention of rebound symptoms.[1,3] Guidelines favor stimulants over non-stimulants as initial pharmacotherapy for most patients due to the increased effectiveness and more robust evidence base.[1,3,6,21] Patients who are unresponsive to an initial stimulant are recommended to switch to another guideline-recommended stimulant, preferably in another stimulant class, before proceeding to non-stimulants.[3,19,20] CADDRA (2020) is unique in recommending short-/intermediate-acting stimulants as second-line pharmacotherapy.[3]

Non-stimulants are typically used when stimulants are unavailable, in patients who are intolerant or contraindicated to stimulants (including because of a high likelihood of abuse), or in patients who fail to have symptomatic improvement after an adequate trial of stimulants.[3,21] The preferred initial non-stimulant varies by guideline, with most recommending atomoxetine, guanfacine (IR or ER), or both.[1,3,6,18-20]

- In adults, atomoxetine tends to be recommended over guanfacine due to the greater amount of supportive evidence in this population.[1] Furthermore, the NICE guideline recommends atomoxetine in adults, but also states that guanfacine should not be offered to adults until after consulting a tertiary ADHD service.[19]
    - The use of clonidine in adults is not addressed by these guidelines.[1,19]
- Notably, only the AAP (2019) guideline specifically mentions clonidine ER, with no reference to the IR formulation.[6]
    - Additionally, the AAP guideline points out that clonidine ER has the least evidence supporting its use for ADHD in pediatric patients compared to atomoxetine and guanfacine ER, but the guideline does not make a formal recommendation preferring one agent over another.[6]
- The CADDRA guideline recommends clonidine as a third-line pharmacologic option, after second-line agents such as guanfacine ER, atomoxetine, or psychostimulants, potentially due to ADHD being an off-label indication; CADDRA recommends reserving clonidine for treatment-resistant cases.[3]

[†] Complex ADHD is defined as having any of the following: (1) initial symptoms or signs of impairment present at <4 years of age or >12 years of age; (2) comorbidities, including neurodevelopmental disorders (eg, autism spectrum disorder, intellectual disability, tic disorders), learning disorders, psychiatric disorders (eg, anxiety, depression, conduct disorder), chronic medical conditions (eg, cancer, epilepsy), genetic disorders, or other complex psychosocial issues (eg, childhood trauma); (3) "Moderate to severe functional impairments in important aspects of daily living (eg, relationships with family and peers, activities of daily living)" (page S39)[18]; (4) primary care physician is uncertain of the diagnosis; or (5) the patient has experienced treatment failure or it is unclear how to proceed with treatment.

Aside from non-responsiveness, the reasons why a non-stimulant may be preferred over a stimulant vary. Concerning adverse effects (AEs) associated with stimulant therapy, especially among children, may prompt switching to a non-stimulant option.[22] Such AEs include increased blood pressure or heart rate, decreased appetite, insomnia, weight loss, and behavioral changes (eg, irritability, dysphoria).[15,61] A non-stimulant may be preferred when stimulant misuse or diversion (ie, using an agent outside of its intended medical purpose) is suspected.[6,20] For patients with ADHD and SUD, guidelines tend to recommend offering a non-stimulant, or more specifically atomoxetine, or a stimulant with lower abuse liability (eg, ER or transdermal preparations).[18,21]

Non-stimulants can also be used adjunctively with stimulants to augment ADHD treatment. Adjunctive therapy may be considered for patients who are unable to tolerate the adverse effects of stimulants at recommended doses, therefore requiring a lower stimulant dose, or in patients who have responded inadequately to stimulant monotherapy.[3,6] In the US, clonidine ER and guanfacine ER are FDA-approved as adjuncts to stimulants.[13,14] While atomoxetine can also be used adjunctively with stimulants,[3] limited evidence supports its use in this manner.[6]

The presence of neurodevelopmental or other common comorbidities (eg, ASD, anxiety) with ADHD does not tend to alter the second-line non-stimulant recommendation of most guidelines, due to the paucity of available evidence.[18] However, non-stimulants may be preferred in the presence of comorbidities that may be exacerbated by traditional stimulants.[22] For example, atomoxetine may be preferred with comorbid anxiety.[1] Although stimulants can still be used as a first-line option, clonidine or guanfacine (as alternative first-line agents) may be preferred with comorbid tic disorders, if tics are the predominant cause of impairment.[18]

In general, guidelines recommend initiating pharmacologic agents at a low dosage and up-titrating based on the desired response and/or tolerability, or until the maximum recommended dose is reached.[3,6,19]

- Relative to ADHD patients without comorbid SUD, higher doses of stimulants may be required in ADHD patients with SUD in order to achieve the desired therapeutic effect on symptom reduction and decreased substance use.[1,20]
- For treatment-resistant patients, CADDRA (2020) comments that exceeding the recommended maximum dosage of pharmacologic agents can be considered as a third-line approach, with additional caution, and only if other agents have failed at the recommended dosage.[3] If this therapeutic approach is considered, or medications are used in an "off-label" manner,[19] the patient should be referred to an ADHD specialist.[3]
- NICE (2018) recommends that patients who do not adequately respond to treatment with ≥1 stimulant and 1 non-stimulant should be referred to a tertiary service or receive a second opinion.[19]

Table 4 summarizes treatment recommendations from guidelines published within the past 5 years for the management of ADHD.

Table 4. Summary of Clinical Practice Guideline Recommendations for the Treatment of ADHD[1,3,6,18-21]

Guideline **(Sponsoring Organization; Year)**	**Recommendations (LOE; Strength of Recommendation, if applicable)**[a]
Canadian ADHD Practice Guidelines, Edition 4.1 **(CADDRA; 2020)**[3]	Pharmacologic recommendations pertain to patients who are **at least 6 years of age**. The guideline advises the use of medications in accordance with their respective age of approval. If pharmacologic treatment is required before the age of 6, it should be conducted "within the context of specialized care." (page 55)[3] First-line pharmacologic treatment: • A trial of a long-acting psychostimulant from either class (amphetamines or methylphenidate) is recommended Adjunctive pharmacologic treatment: • Non-stimulants may be used adjunctively with first-line stimulants in patients who have an inadequate response to first-line agents alone ○ In Canada, **atomoxetine** and **guanfacine ER** may be used as adjunctive therapy; however, only guanfacine ER is approved for this indication. Second-line pharmacologic treatment: • Recommended second-line agents are **guanfacine ER** (only in children 6–17)**, atomoxetine**, and short-/intermediate-acting psychostimulants (eg, methylphenidate, dextroamphetamine); may be used when a first-line agent is contraindicated, unavailable, or an inadequate response is achieved or significant adverse effects are experienced Third-line pharmacologic treatment: • Recommended third-line agents are off-label use of **clonidine**[b], bupropion, imipramine, desipramine, and modafinil • Typically reserved for treatment-resistant cases • Can consider exceeding maximum recommended dosages of ADHD medications once other options at the recommended dosage have failed, but this approach should be used cautiously
Society for Developmental and Behavioral Pediatrics Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents with Complex Attention-Deficit/Hyperactivity Disorder **(SDBP; 2020)**[18]	According to the complementary treatment algorithms, pharmacologic agents are routinely recommended in children **6 years of age and older**, but may be considered for preschool-aged children (between 3 and 6 years of age) with significant impairment despite the use of psychosocial interventions.[60] • When beginning treatment, psychoeducation and evidence-based behavioral and educational interventions (eg, behavioral peer interventions, behavioral parent training) are recommended for all pediatric patients with complex ADHD (Grade B; strong recommendation) • While non-pharmacologic interventions are the mainstay of treating complex ADHD, these interventions are often used with pharmacotherapy. Techniques for self-management, skill acquisition, and preventing negative consequences (eg, behavioral issues, suicidal ideation, poor academic performance) should be aimed at improving functionality, not only symptoms (Grade C to B; recommendation) First-line pharmacologic treatment: • Generally, stimulants (ie, amphetamine or methylphenidate) at the lowest feasible dose[60] ○ Methylphenidate is preferred in preschool-aged children; **clonidine**[c] and **guanfacine**[c] are alternative options, but have limited evidence[60] • Stimulants are recommended for patients with ADHD and an intellectual disability • **Clonidine**[c] or **guanfacine**[c] may be used as alternative first-line pharmacologic options among patients with ADHD and comorbid tic disorders, if the tics are the predominant cause of impairment Second-line pharmacologic treatment: • Given the paucity of available evidence, non-stimulants (ie, **atomoxetine, clonidine**[c]**, guanfacine**[c]) tend to be recommended as second-line agents for patients with ADHD and comorbid autism spectrum disorder Additional considerations: • For patients with ADHD and SUD, **atomoxetine** or a stimulant with lower abuse liability (eg, ER or transdermal preparations) should be considered • **Atomoxetine** can be considered as a therapeutic option among patients with ADHD and a learning disorder or internalizing disorder (ie, depression, anxiety), but the evidence is more supportive for the use of stimulants • Patients should have regular follow-up during the course of their lifespan, especially during periods of academic transitions (eg, middle to high school) (Grade B; strong recommendation)

[a] *Refer to Appendix D for information regarding the recommendation strength and the LOE.*

[b] *Clonidine ER (Kapvay) is not available in Canada, United Kingdom, or Europe*[56-58]*; therefore, recommendations made by guidelines originating in those countries refer to the agent as "clonidine", indicating the immediate-release formulation.*

[c] *It is unclear whether this guideline is referring to the IR, ER, or both formulations of clonidine and guanfacine.*

Abbreviations: AAP, American Academy of Pediatrics; ADHD, attention-deficit/hyperactivity disorder; BMI, body mass index; CADDRA, Canadian ADHD Resource Alliance; CBT, cognitive behavioral therapy; CPS, Canadian Paediatric Society; ECG, electrocardiogram; ENAA, European Network Adult ADHD; EPA, European Psychiatric Association; ER, extended-release; FDA, US Food and Drug Administration; GRADE, Grading of Recommendations: Assessment, Development, and Evaluation; ICASA, International Collaboration on ADHD and Substance Abuse; LOE, level of evidence; NDAL, Neurodevelopmental Disorders Across the Lifespan (NDAL); NICE, National Institute for Health and Care Excellence; PTBM, parent training in behavior management; SDBP, Society for Developmental and Behavioral Pediatrics; SUD, substance use disorder

Table 4. Summary of Clinical Practice Guideline Recommendations for the Treatment of ADHD[1,3,6,18-21]

Guideline **(Sponsoring Organization; Year)**	**Recommendations (LOE; Strength of Recommendation, if applicable)**[a]
International Consensus Statement for the Screening, Diagnosis, and Treatment of Adolescents with Concurrent Attention-Deficit/Hyperactivity Disorder and Substance Use Disorder **(ICASA; 2020)**[20]	Due to the paucity of evidence available among adolescents with ADHD and SUD, treatment recommendations were primarily based on clinical studies among ADHD-affected adolescents without SUD and/or adults with ADHD and comorbid SUD. First-line pharmacologic treatment: long-acting stimulants (eg, lisdexamfetamine, methylphenidate, dexamphetamine) • Due to differences in inter-patient variability, it is recommended to try long-acting formulations of (lis)dexamphetamine, methylphenidate, and mixed amphetamine salts. Patients who may be unresponsive to one of the aforementioned stimulants at an appropriate dose should switch to the other stimulants that have yet to be tried. Second-line pharmacologic treatment: **atomoxetine**, **guanfacine ER**, or bupropion • A non-stimulant can be considered in the event stimulant misuse or diversion is suspected Adolescents with ADHD and comorbid SUD: • It is encouraged to start psychosocial (eg, psychoeducation, motivational interviewing, family therapy, CBT) and/or pharmacologic agents as soon as possible for the treatment of SUD ○ A combination of pharmacotherapy and psychosocial interventions are recommended for patients with co-existing SUD and moderate to severe ADHD ○ Even though an individual has a response to ADHD medications, additional CBT can be considered for adolescents who continue to have functional impairment • Ideally, for most patients, treatment should begin with abstaining or reducing/stabilizing the use of substances; but this should not be a reason to delay ADHD treatment Additional considerations: • Before starting stimulants, it is recommended to obtain an ECG "only in adolescents with ADHD and SUD who have a (family) history, symptoms or signs of cardiac disease, and/or who use a medication or illicit drug (eg, cocaine and amphetamine) that may increase cardiac risk." (page 229)[20] It is recommended to monitor heart rate and blood pressure in all patients with ADHD and SUD while they are being treated with ADHD medications ○ Patients taking stimulants or **atomoxetine** should be monitored for growth and weight changes
Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents **(AAP; 2019)**[6]	Children, preschool-aged (4–5 years): • As first-line treatment, evidence-based PTBM and/or behavioral classroom interventions are recommended, if available (Grade A; strong recommendation) • If symptoms do not improve and there is moderate-to-severe dysfunction despite using the aforementioned behavioral interventions, methylphenidate can be considered. If behavioral interventions are unavailable, a risk-benefit assessment should be conducted by the provider before starting pharmacologic treatment in children <6 years of age (Grade B; strong recommendation) Children, elementary and middle school-aged (6–12 years): • A multimodal approach should be used; behavioral interventions (ie, behavioral classroom intervention and/or PTBM [preferably both]) in combination with FDA-approved agents for the treatment of ADHD (Grade A; strong recommendation) ○ Strong evidence supports the use of stimulants, but less robust evidence for monotherapy of non-stimulants: **atomoxetine, guanfacine ER, and clonidine ER** (in descending order) Children and adolescents (aged 12–17 years): • FDA-approved agents (stimulants and non-stimulants) for the treatment of ADHD are recommended (Grade A; strong recommendation) • It is encouraged to also use "evidence-based training interventions and/or behavioral interventions as treatment of ADHD, if available" (page 6)[6] (Grade A; strong recommendation)
Updated European Consensus Statement on Diagnosis and Treatment of Adult ADHD **(ENAA, NDAL of the EPA; 2019)**[1]	Adults (aged 18 years and older): • As the first-line treatment approach, psychoeducation is recommended for patients, including their spouse First-line pharmacologic treatment: stimulants (eg, methylphenidate, dexamphetamine) • Long-acting formations are preferred due to improved patient compliance, decreased abuse liability, and prevention of rebound symptoms Second-line pharmacologic treatment: **atomoxetine** ○ **Atomoxetine** is preferred over **guanfacine** due to the limited evidence available regarding the use of guanfacine in the adult population

[a] *Refer to Appendix D for information regarding the recommendation strength and the LOE.*

[b] *Clonidine ER (Kapvay) is not available in Canada, United Kingdom, or Europe*[56-58]*; therefore, recommendations made by guidelines originating in those countries refer to the agent as "clonidine", indicating the immediate-release formulation.*

[c] *It is unclear whether this guideline is referring to the IR, ER, or both formulations of clonidine and guanfacine.*

Abbreviations: AAP, American Academy of Pediatrics; ADHD, attention-deficit/hyperactivity disorder; BMI, body mass index; CADDRA, Canadian ADHD Resource Alliance; CBT, cognitive behavioral therapy; CPS, Canadian Paediatric Society; ECG, electrocardiogram; ENAA, European Network Adult ADHD; EPA, European Psychiatric Association; ER, extended-release; FDA, US Food and Drug Administration; GRADE, Grading of Recommendations: Assessment, Development, and Evaluation; ICASA, International Collaboration on ADHD and Substance Abuse; LOE, level of evidence; NDAL, Neurodevelopmental Disorders Across the Lifespan (NDAL); NICE, National Institute for Health and Care Excellence; PTBM, parent training in behavior management; SDBP, Society for Developmental and Behavioral Pediatrics; SUD, substance use disorder

Table 4. Summary of Clinical Practice Guideline Recommendations for the Treatment of ADHD[1,3,6,18-21]

Guideline **(Sponsoring Organization; Year)**	**Recommendations (LOE; Strength of Recommendation, if applicable)**[a]
Attention Deficit Hyperactivity Disorder: Diagnosis and Management **(NICE; 2018)**[19]	Children (aged <5 years): • As first-line treatment, an ADHD-centered training program should be offered to parents or guardians • If the first-line approach fails to improve symptoms, including modifying environmental factors (eg, minimizing distractions, shorter break times), consult an ADHD specialist; pharmacologic treatment should not be offered without a second opinion Children and adolescents (aged ≥5 to ≤17 years): • ADHD-centered training program or support should be offered to parents or guardians, especially in the presence of comorbidities (ie, conduct disorder, oppositional defiant disorder) • Pharmacotherapy may be offered to children and adolescents who continue to have persisting symptoms and resulting impairment in ≥1 domain (eg, education, personal relationships) despite modifying environmental factors ○ First-line pharmacologic treatment: short- or long-acting methylphenidate ○ Patients who tried methylphenidate at an appropriate dosage for an adequate duration (ie, 6 weeks) without a significant reduction in symptoms/impairment, can consider switching to lisdexamfetamine ▪ Patients who respond to lisdexamfetamine but are unable to tolerate the "longer effect profile", can consider switching to dexamphetamine ○ Second-line pharmacologic treatment: **guanfacine** or **atomoxetine** can be offered to patients who: ▪ are intolerant to methylphenidate or lisdexamfetamine, or ▪ fail to have symptoms resolve after a 6-week trial of methylphenidate or lisdexamfetamine at recommended dosages, taking into account the utilization of other formulations • Even though an individual has responded to pharmacotherapy, targeted CBT can be considered for adolescents who continue to have persisting symptoms and resulting impairment in ≥1 domain Adults (≥18 years of age): • Pharmacotherapy may be offered to adults who continue to have persisting symptoms and resulting impairment in ≥1 domain (eg, education, personal relationships) despite modifying environmental factors ○ First-line pharmacologic treatment: methylphenidate or lisdexamfetamine ○ Patients who tried methylphenidate or lisdexamfetamine at an appropriate dosage for an adequate duration (ie, 6 weeks) without a significant reduction in symptoms/impairment, can consider switching to the other respective first-line agent ▪ Patients who respond to lisdexamfetamine but are unable to tolerate the "longer effect profile", can consider switching to dexamphetamine ○ Second-line pharmacologic treatment: **atomoxetine** can be offered to adults who: ▪ are intolerant to first-line agents (ie, methylphenidate, lisdexamfetamine), or ▪ fail to have symptoms resolve after a 6-week trial of methylphenidate or lisdexamfetamine at recommended dosages, taking into account the utilization of other formulations • A combination of pharmacologic and non-pharmacologic interventions can be considered for adults who respond to medication, but continue to have persisting symptoms and resulting impairment in ≥1 domain • Non-pharmacologic interventions (eg, ADHD-centered psychological support, CBT) can be considered for adults who have trouble with medication compliance, decide not to take pharmacologic agents, or were unable to tolerate or had a poor response to medication(s) Additional pharmacologic considerations: • Patients ≥5 years of age who do not adequately respond to treatment with ≥1 stimulant and 1 non-stimulant should be referred to a tertiary service or receive a second opinion • The following agents should only be used after consulting a tertiary ADHD service: ○ off-label use of **guanfacine** in adults ○ off-label use of **clonidine**[b] in children with ADHD and certain comorbidities (ie, rages, tics, sleep disturbances) ○ "atypical antipsychotics in addition to stimulants for people with ADHD and coexisting pervasive aggression, rages, or irritability" (page 28)[19] ○ Any pharmacologic agent not included in the guideline recommendations

[a] *Refer to Appendix D for information regarding the recommendation strength and the LOE.*

[b] *Clonidine ER (Kapvay) is not available in Canada, United Kingdom, or Europe*[56-58]*; therefore, recommendations made by guidelines originating in those countries refer to the agent as "clonidine", indicating the immediate-release formulation.*

[c] *It is unclear whether this guideline is referring to the IR, ER, or both formulations of clonidine and guanfacine.*

Abbreviations: AAP, American Academy of Pediatrics; ADHD, attention-deficit/hyperactivity disorder; BMI, body mass index; CADDRA, Canadian ADHD Resource Alliance; CBT, cognitive behavioral therapy; CPS, Canadian Paediatric Society; ECG, electrocardiogram; ENAA, European Network Adult ADHD; EPA, European Psychiatric Association; ER, extended-release; FDA, US Food and Drug Administration; GRADE, Grading of Recommendations: Assessment, Development, and Evaluation; ICASA, International Collaboration on ADHD and Substance Abuse; LOE, level of evidence; NDAL, Neurodevelopmental Disorders Across the Lifespan (NDAL); NICE, National Institute for Health and Care Excellence; PTBM, parent training in behavior management; SDBP, Society for Developmental and Behavioral Pediatrics; SUD, substance use disorder

Table 4. Summary of Clinical Practice Guideline Recommendations for the Treatment of ADHD[1,3,6,18-21]

Guideline **(Sponsoring Organization; Year)**	**Recommendations (LOE; Strength of Recommendation, if applicable)**[a]

ADHD in Children and Youth: Part 2–Treatment **(CPS; 2018)**[21]	**Pharmacotherapy is reserved for symptomatic (eg, inattention, hyperactive, impulsive) children ≥6 years of age**
	Children (aged <6 years):
	• Parent behavior training is recommended as first-line treatment for preschool-aged children with ADHD (not included in formalized recommendations)
	Children (aged ≥6 years):
	• First-line pharmacotherapy: a stimulant, either dextroamphetamine or methylphenidate preparations
	  ○ Before determining whether a patient is unresponsive or intolerant to stimulants, it is recommended to switch to a different preparation of dextroamphetamine or methylphenidate
	  ○ The long-acting formulations of stimulants, used with nonpharmacologic interventions, are recommended as first-line pharmacotherapy for the majority of ADHD-affected children and adolescents
	  ○ If a concern for stimulant-related cardiovascular adverse events exists, patients should receive an ECG or a specialized consultation prior to receiving stimulants; routine ECG screening before starting stimulants is not recommended
	  ○ All pediatric patients taking stimulants should have their growth parameters (eg, height, BMI, appetite) monitored
	• Second-line pharmacotherapy: **non-stimulants (ie, atomoxetine, guanfacine ER, clonidine[b])** are recommended when a patient is unresponsive, intolerant, or contraindicated to stimulants
	  ○ **Non-stimulants** or a long-acting stimulant with a lower abuse liability should be considered for pediatric patients who have ADHD and a history of SUD
	  ○ For patients taking **guanfacine ER** or **clonidine[b]**, blood pressure should be monitored prior to starting treatment, after escalating the dose, and occasionally during treatment. Patients and their caregivers should be advised to not suddenly discontinue these agents
	Additional considerations:
	• A multimodal treatment approach is recommended for children and adolescents with ADHD and other comorbid conditions
	• The treatment plan should be directed by individualized, shared-decision making goals for symptomatic management or improved functionality (eg, enhanced autonomy in performing tasks, decreasing distracting behaviors)
	• To monitor treatment response, standardized checklists should be used in ≥2 settings, including school

[a] *Refer to Appendix D for information regarding the recommendation strength and the LOE.*

[b] *Clonidine ER (Kapvay) is not available in Canada, United Kingdom, or Europe*[56-58]*; therefore, recommendations made by guidelines originating in those countries refer to the agent as "clonidine", indicating the immediate-release formulation.*

[c] *It is unclear whether this guideline is referring to the IR, ER, or both formulations of clonidine and guanfacine.*

Abbreviations: AAP, American Academy of Pediatrics; ADHD, attention-deficit/hyperactivity disorder; BMI, body mass index; CADDRA, Canadian ADHD Resource Alliance; CBT, cognitive behavioral therapy; CPS, Canadian Paediatric Society; ECG, electrocardiogram; ENAA, European Network Adult ADHD; EPA, European Psychiatric Association; ER, extended-release; FDA, US Food and Drug Administration; GRADE, Grading of Recommendations: Assessment, Development, and Evaluation; ICASA, International Collaboration on ADHD and Substance Abuse; LOE, level of evidence; NDAL, Neurodevelopmental Disorders Across the Lifespan (NDAL); NICE, National Institute for Health and Care Excellence; PTBM, parent training in behavior management; SDBP, Society for Developmental and Behavioral Pediatrics; SUD, substance use disorder

6.0 PHARMACOLOGY

The agents reviewed in this report modulate the physiologic mechanisms implicated in the manifestation of core ADHD symptoms (ie, hyperactivity/impulsivity, or inattention) originating in the prefrontal cortex.[11-14] The FDA-approved non-stimulants for ADHD are organized into 2 drug classes: selective norepinephrine reuptake inhibitors (atomoxetine and viloxazine ER)[11,12] and alpha-2 adrenergic agonists (clonidine ER and guanfacine ER).[13,14] The mechanism of action for each of these agents is provided in **Table 5**.

Table 5. Mechanism of Action of FDA-Approved Non-stimulants for ADHD

Generic Name Brand Name	Proposed Pharmacology
Alpha-2 Agonists	
Clonidine hydrochloride **Kapvay**	Alpha-2 receptors in the brain stem are stimulated by clonidine, causing inhibitory neurons to be activated, and ultimately, a reduction in sympathetic outflow from the CNS.[13] This cascade of events results in decreased peripheral and renal vascular resistance, blood pressure, and heart rate. While the exact mechanism of action in the treatment of ADHD is unknown,[13] it is hypothesized that the reduced sympathetic outflow also alters subcortical activity in the prefrontal cortex.[15,61]
Guanfacine **Intuniv**	"By stimulating alpha$_{2a}$-adrenergic receptors, guanfacine reduces sympathetic nerve impulses from the vasomotor center to the heart and blood vessels." (page 15)[14] This causes a reduction in heart rate and peripheral vascular resistance. The exact mechanism of action in the treatment of ADHD is unknown,[14] but it is hypothesized that the selective binding of alpha$_{2a}$ receptors in the prefrontal cortex may affect ADHD symptoms.[62]
Norepinephrine Reuptake Inhibitors	
Atomoxetine **Strattera**	The exact mechanism of action in the treatment of ADHD is unknown.[11] However, it is hypothesized that the therapeutic effects may be due to the higher concentrations of NE and dopamine in the prefrontal cortex as a result of selectively inhibiting the pre-synaptic NET.[11,15,17]
Viloxazine **Qelbree**	While the exact mechanism of action in the treatment of ADHD is unknown, it is theorized that the beneficial effects are due to the inhibition of NE reuptake in the prefrontal cortex.[12,22] Although not considered the primary mechanism for alleviating ADHD symptoms,[17] viloxazine also stimulants serotonin (5-HT)$_{2C}$ receptors and antagonizes 5-HT$_{2B}$ receptors.[22,61]

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CNS, central nervous system; FDA, Food and Drug Administration; NE, norepinephrine; NET, norepinephrine transporter

The alpha-2 agonists (ie, clonidine ER and guanfacine ER) bind to alpha-2 receptors, which can result in antihypertensive effects;[13,14] these agents are also believed to alter activity in the prefrontal cortex, thereby reducing ADHD symptoms.[15,61] Clonidine produces its effects by non-selectively binding to alpha-2 receptors, whereas guanfacine selectively binds to alpha$_{2a}$ receptors.[13,14,63]

By selectively inhibiting the pre-synaptic NET in the prefrontal cortex, atomoxetine not only increases the concentrations of NE, but also dopamine in this region of the brain.[64] Therefore, atomoxetine does

not have an effect on dopamine in other regions of the brain such as the nucleus accumbens and stratum, resulting in a low potential for abuse.[15,17,64] Similar to atomoxetine, viloxazine ER also inhibits NE reuptake contributing to its use as a therapeutic option for ADHD.[12,17] Yet, a unique mechanism to viloxazine ER is its modulation of postsynaptic serotonin (5-HT) receptors, which may contribute to treatment response, especially among patients with comorbid depression and/or anxiety, but this has yet to be determined.[17,22,61]

Depending on the formulation of clonidine and guanfacine, the pharmacokinetic properties differ. For example, compared to the corresponding IR formulation of each agent, clonidine ER and guanfacine ER have a 50% and 60% lower peak plasma concentration, respectively.[13,65] Therefore, other products of clonidine and guanfacine, including the IR formulation should not be dose substituted on a milligram-per-milligram basis for the relative ER formulation due to differences in exposure.[13,14]

Atomoxetine is highly dependent on cytochrome (CYP) 2D6 metabolism.[11] A small proportion of the population (approximately 7% of Caucasians and 2% of African Americans) may have increased exposure to atomoxetine due to poor metabolic activity (referred to as poor metabolizers) via this enzymatic pathway.

While atomoxetine, clonidine ER, and viloxazine ER may be taken with or without food,[11-13] guanfacine ER is not recommended to be taken with a high-fat meal due to the potential for increased drug concentrations.[14] However, administering atomoxetine or viloxazine ER with a high-fat meal may delay the onset of effect.[11,12]

Table 6 summarizes key pharmacokinetic parameters of ADHD non-stimulants.

Table 6. Pharmacokinetic Parameters of FDA-Approved Non-stimulants for ADHD[11-14]

Generic Name **Brand Name** Formulation	T_{max} (hrs)	Half-life (hrs)	Metabolism	Excretion
Alpha-2 Agonists				
Clonidine hydrochloride **Kapvay** *Extended-release oral tablet*	7–8[65]	• 12–16 • Severe renal impairment: 41[a]	Extensively metabolized in the liver to inactive metabolites (approx. 50% of the absorbed dose)	Primarily excreted in the urine as unchanged (approx. 40–60% of the absorbed dose)
Guanfacine **Intuniv** *Extended-release oral tablet*	• Children and adolescents: ~5 • Adults: 4–8	• Children: 14.4[62] • Adolescents: 18[62] • Adults: 18 ± 4	Primarily via CYP3A4 (approx. 50% of the absorbed dose)	Primarily excreted in the urine as unchanged (approx. 50% of the absorbed dose)[62]
Norepinephrine Reuptake Inhibitors				
Atomoxetine **Strattera** *Oral capsule*	1–2; delayed by 3 hrs when taken with a high-fat meal	• ~5; PM: 21.6 • 4-hydroxyatomoxetine (active metabolite): 6–8 • N-desmethylatomoxetine (active metabolite): 6–8; PM: 34–40	• Primarily via CYP2D6 and glucuronidation • Active metabolites are formed: 4-hydroxyatomoxetine (equipotent activity) primarily via CYP2D6 and n-desmethylatomoxetine (limited activity) via CYP2C19	• Primarily excreted in the urine as glucuronidated 4-hydroxy metabolite (>80% of the dose), with <3% unchanged • Feces: <17% of the dose
Viloxazine **Qelbree** *Extended-release oral capsule*	~ 5 (ranged 3–9); delayed by 2 hrs when taken with a high-fat meal	7.02 ± 4.74	Primarily via UGT1A9, UGT2B15, and CYP2D6	• Primarily excreted in the urine (90% of the dose) • Feces: <1% of the dose

[a] *While studies of Kapvay among patients with renal impairment are lacking, it is presumed the findings will be similar to the immediate-release preparation.*

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; approx., approximately; FDA, US Food and Drug Administration; hrs, hours; PM, poor CYP2D6 metabolizers

7.0 DIRECT COMPARATIVE EVIDENCE

Literature searches for SRs of RCTs, and an supplemental search from 2017 to 2022 for individual RCTs with head-to-head direct comparisons between the non-stimulant agents for the treatment of ADHD yielded a total of 506 unique records. Only 1 RCT was identified that met inclusion criteria. This RCT primarily evaluated guanfacine ER to placebo among children and adolescents with ADHD, but also included an atomoxetine study arm as a reference agent.[29] No direct head-to-head evidence was identified for clonidine or viloxazine versus any other FDA-approved non-stimulant for the treatment of ADHD.[23-28] Refer to **Appendix B** for the PRISMA flow diagram of the publication screening process.

7.1 Guanfacine ER vs atomoxetine

Hervas et al (2014) conducted a phase III, double-blind, randomized, placebo-and active-controlled, multicenter, dose optimization study among children and adolescents (aged 6−17 years; N=338) with at least moderately severe ADHD[‡].[29] The study duration varied by age to allow an appropriate amount of time for all participants to titrate to the optimal daily dose of guanfacine ER (0.05−0.12 mg/kg): 10 weeks for children aged 6−12 years, or 13 weeks for adolescents aged 13−17 years. Participants were randomized to either guanfacine ER, atomoxetine, or placebo and were instructed to take the medication at the same time each day, and to avoid taking it with a high-fat meal.[29] It is likely that concomitant stimulant use was prohibited and, therefore, these agents were evaluated as monotherapy.

Comparing the efficacy of guanfacine ER to atomoxetine was not the purpose of this study; nevertheless, the comparison was still prespecified for the primary efficacy outcome.[29] The primary outcome evaluated ADHD symptom burden as measured by the change in the prescriber-rated ADHD Rating Scale, version IV (ADHD-RS-IV) from baseline to visit 15 (week 10 or 13 of treatment depending on the participant's age); with higher scores on this scale reflective of a greater symptom burden. Key secondary endpoints were the percentage of participants showing an improvement in the Clinical Global Impression-Improvement (CGI-I) rating scale and the Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P; family, school, and learning domains).[29]

Compared to placebo, both guanfacine ER and atomoxetine significantly improved the ADHD-RS-IV total score (difference from placebo: −8.9 and −3.8, respectively) from baseline to visit 15.[29] A significant difference was observed between active treatment arms; guanfacine ER significantly improved ADHD symptoms compared to atomoxetine at visit 15 (difference from atomoxetine: −5.1; *p=0.001*). However, this statistical comparison was not controlled for multiplicity.[29] A formal statistical test comparing guanfacine ER to atomoxetine for secondary efficacy outcomes was not reported. Both atomoxetine and guanfacine ER significantly outperformed placebo for change from baseline to visit 15 for improving CGI-I scores, and functional impairment in school and learning domains.[29] Improvements in the third functional impairment domain, family, were observed for both guanfacine ER and atomoxetine versus placebo, but the comparison was statistically significant only for guanfacine ER.[29] **Table 7** summarizes the efficacy results from this trial.

[‡] Defined as a total score of ≥32 on the ADHD Rating Scale, version IV and a score of ≥4 on the Clinical Global Impression-Severity rating scale at baseline

Table 7. Efficacy Outcomes from Hervas et al (2014)[29]

Efficacy Endpoint	Guanfacine ER (GXR)	Atomoxetine (ATX)	Placebo
ADHD-RS-IV mean change from baseline to visit 15[a] (least squares mean) – *primary endpoint*	−23.9	−18.8	−15.0
Difference from placebo (95% CI; p-value):	−8.9 (−11.9, −5.8; p<0.001)	−3.8 (−6.8, −0.7; p=0.017[b])	
Difference from atomoxetine (95% CI; p-value)	−5.1 (−8.2, −2.0; p=0.001)[b]		
CGI-I score of 1 ('very much improved') or 2 ('much improved') at visit 15[a] (% of participants)	67.9	56.3	44.1
Difference from placebo (95% CI; p-value):	23.7 (11.1, 36.4; p<0.001)	12.1 (−0.9, 25.1; p=0.024)	
WFIES-P mean change from baseline to visit 15[a] (least square mean) in school, learning domains[c]	–0.65	–0.6	–0.4
Difference from placebo (95% CI; p-value):	−0.22 (−0.36, −0.08; p=0.003)	−0.16 (−0.31, −0.02; p=0.026)	
WFIES-P mean change from baseline to visit 15[a] in family domain[c]	–0.6	–0.5	–0.4
Difference from placebo (95% CI; p-value):	−0.21 (−0.36, −0.06; p=0.006)	–0.09 (–0.24, –0.06; p=0.242)	

[a] *Visit 15 occurred at week 10 for children (6–12 years of age), and at week 13 for adolescents (13–17 years of age)*

[b] *Not controlled for multiplicity*

[c] *Note that these values are not exact and were estimated based on the information presented in Figure 4 of the publication*

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ADHD-RS-IV, ADHD Rating Scale, version IV; CGI-I, Clinical Global Impression-Improvement; CI, confidence interval; WFIRS-P, Weiss Functional Impairment Rating Scale-Parent Report

Regarding safety, a numerically greater percentage of participants in the guanfacine ER group (77.2%) experienced any adverse event (AE) compared to the proportion in other treatment arms (atomoxetine: 67.9%; placebo: 65.8%).[29] In addition, numerically more participants treated with guanfacine ER experienced severe treatment-emergent adverse events (TEAEs) and were more likely to discontinue the agent due to an AE. Participants receiving guanfacine ER had a mean reduction from baseline in blood pressure and heart rate, whereas atomoxetine-treated participants had a minor elevation. For both agents, the magnitude of changes in blood pressure and/or heart rate were consistent with the findings from previous studies. Numerically more participants in the atomoxetine group reported suicidal ideation[§] (n=3) as a TEAE based on the Columbia-suicide severity rating scale (C-SSRS) compared to the other treatment groups (guanfacine: n=2; placebo: n=2); no active suicides were reported during the study. The most common AEs reported among participants receiving guanfacine ER were headache, somnolence, and fatigue, whereas those receiving atomoxetine reported a higher incidence of nausea, vomiting, and decreased appetite.[29] **Table 8** summarizes the safety results from this trial.

[§] A positive suicidal ideation response was defined as answering 'yes' to any of the following: wishing to be dead, having non-specific active suicidal thoughts, or non-suicidal self-injurious behavior.

Table 8. Summary of the Safety Information from Hervas et al (2014)[29]

Safety Results		Guanfacine ER (N=114)	Atomoxetine (N=112)	Placebo (N=111)
Most frequently reported TEAEs[a] (≥15% in any treatment group; n, %)	Any TEAE[a]	88 (77.2%)	76 (67.9%)	73 (65.8%)
	Somnolence	50 (43.9%)	20 (17.9%)	16 (14.4%)
	Headache	30 (26.3%)	22 (19.6%)	27 (24.3%)
	Fatigue	29 (25.4%)	24 (21.4%)	20 (18.0%)
	Abdominal pain	19 (16.7%)	19 (17.0%)	20 (18.0%)
	Nausea	18 (15.8%)	30 (26.8%)	11 (9.9%)
	Decreased appetite	15 (13.2%)	31 (27.7%)	12 (10.8%)
	Vomiting	6 (5.3%)	18 (16.1%)	8 (7.2%)
	Dizziness	14 (12.3%)	17 (15.2%)	9 (8.1%)
TEAE[a] severity (n, %)	Mild	38 (33.3%)	46 (41.1%)	46 (41.4%)
	Moderate	42 (36.8%)	28 (25.0%)	24 (21.6%)
	Severe	8 (7.0%)	2 (1.8%)	3 (2.7%)
Other safety results (n, %)	Deaths	0 (0%)	0 (0%)	0 (0%)
	SAEs	2 (1.8%)	0 (0%)	1 (0.9%)
	Discontinued treatment due to AEs	9 (7.9%)	5 (4.5%)	1 (0.9%)

[a] An adverse events was considered a TEAE if it manifested or worsened during the time between the administration of the first treatment dose to three days after the treatment was discontinued

Abbreviations: AEs, adverse events; SAEs, serious adverse events; TEAEs, treatment-emergent adverse events

8.0 SPECIAL POPULATIONS

Table 9 summarizes details from the prescribing information for the use of atomoxetine, viloxazine ER, guanfacine ER, and clonidine ER among special populations, including renal/hepatic impairment. Please refer to the following subsections for additional details.

8.1 Pregnancy

Both of the alpha-2 agonists (guanfacine ER and clonidine ER) appear to be safe during pregnancy when used at recommended dosages based on observational data in pregnant women.[13,14] However, based on animal studies, clonidine ER has the potential to impair reproductive fertility at very high doses (10 and 40 times the MRHD); it is unclear whether this effect is observed at lower doses.[13] Prescribing information for viloxazine ER recommends to discontinue the agent when pregnancy is recognized due to the potential for maternal harm, unless the benefits of the medication outweigh the associated risks.[12] Additionally, given the paucity of human evidence for the use of atomoxetine during pregnancy, some experts recommend avoiding its use and switching to another agent.[1,66] When determining the best approach, it is important to consider the potential maternal and fetal risks caused by drug exposure with respect to abruptly interrupting treatment.[1] Patients taking any of these agents are encouraged to

report AEs related to drug exposure during pregnancy to a national registry (National Pregnancy Registry for ADHD Medications).[11-14]

8.2 Breastfeeding

When using atomoxetine, clonidine ER, guanfacine ER, or viloxazine ER during lactation, prescribing information recommends considering the potential risks on the nursing infant with respect to the maternal need for the medication.[11-14] Breastfed infants exposed to clonidine ER or guanfacine ER are recommended to be monitored for signs of hypotension and bradycardia (eg, sedation, poor feeding, fatigue).[13,14]

8.3 Pediatric population

All of the FDA-approved non-stimulants (ie, atomoxetine, viloxazine ER, clonidine ER, guanfacine ER) have been studied in pediatric patients (aged 6−17 years), but the effectiveness and safety of these agents has not been proven in clinical trials for pediatric patients younger than 6 years of age.[11-14] For guanfacine ER, maximum daily dosages exceeding 4 mg and 7 mg have not been evaluated in children older than 12 years of age and 17 years of age, respectively.[14] When using higher than recommended dosages of clonidine and guanfacine, juvenile animal studies suggest that these agents have the potential to cause delayed sexual maturation.[13,14] Additionally, delayed sexual development was observed among animal studies with atomoxetine, but the clinical significance to humans is unclear.[11] Pediatric patients treated with viloxazine ER are recommended to be monitored for weight changes, and the appearance of suicidal thoughts and behaviors.[12]

8.4 Older adults

The efficacy and safety of guanfacine ER and atomoxetine has not been evaluated in older adults,[11,14] and it is unclear whether clonidine ER has been evaluated in this patient population.[13] Additionally, clinical trials for viloxazine ER included an insufficient number of older adults (≥65 years of age) so it is unclear whether these individuals respond differently compared to younger individuals.[12]

Table 9. Recommendations for Use of FDA-Approved Non-Stimulants in Special Populations[11-14] [a]

Generic Name Brand Name	Pregnancy	Breastfeeding	Pediatrics	Renal or Hepatic Dysfunction
Clonidine hydrochloride **Kapvay**	• Human data does not indicate a risk of adverse maternal or fetal outcomes • Animal studies imply no developmental abnormalities at doses up to 3 times the MRHD	• Secreted in human milk • Consider risks vs benefits • Exposed infants should be monitored for sedation, tachypnea, fatigue, and poor feeding	• Established efficacy and safety in patients 6–17 years of age ○ Not evaluated in children <6 years of age • Juvenile animal studies suggest a delay in sexual maturation at doses of 3 times the MRHD	• Initial dose should be tailored based on the extent of impairment • Not required to administer an additional dose after hemodialysis • No dose adjustment for hepatic impairment
Guanfacine **Intuniv**	• Human data does not indicate a risk of adverse maternal or fetal outcomes • Animal studies showed no negative fetal outcomes at doses of 3 and 4 times the MRHD ○ Decreased fetal survival and maternal toxicity occurred at doses 13.5 the MRHD	• Unknown if secreted in human milk, but likely since it is present in animal milk • Consider risks vs benefits • Exposed infants should be monitored for sedation, fatigue, and poor feeding	• Established efficacy and safety in patients 6−17 years of age ○ Not evaluated in children <6 years of age • The following maximum daily dosages are recommended: ○ children (aged 6−12 years): 4 mg ○ adolescents (aged 13−17 years): 7 mg • Juvenile animal studies suggest a delay in sexual maturation at doses 2−3 times the MRHD	• Patients with significant renal or hepatic impairment may require a lower dosage
Atomoxetine **Strattera**	• Insufficient human data • Animal studies suggest fetal developmental abnormalities	• Unknown if secreted in human milk, but likely since it is present in animal milk • Consider risks vs benefits	• Consider risks vs benefits • Similar pharmacokinetic parameters to adults • Not evaluated in children <6 years of age	• Initial and maintenance dosages should be adjusted for patients with moderate or severe hepatic impairment

[a] Information is reported based on the product labeling (ie, package inserts)

[b] Prescribing information does not provided dosage adjustments for individuals with hepatic impairment

Abbreviations: eGFR, estimated glomerular filtration rate; MRHD, maximum recommended human dose

Table 9. Recommendations for Use of FDA-Approved Non-Stimulants in Special Populations[11-14] [a]

Generic Name Brand Name	Pregnancy	Breastfeeding	Pediatrics	Renal or Hepatic Dysfunction
			• Juvenile animal studies imply delayed sexual development, but the clinical significance to humans is unclear	○ Moderate impairment: decrease the normal dose by 50% ○ Severe impairment: decrease the normal dose by 25% • No dose adjustment for renal impairment
Viloxazine **Qelbree**	• Animal studies suggest maternal harm can occur • Recommend to discontinue during pregnancy, unless benefits outweigh the risks	• Unknown if secreted in human milk, but likely since it seems to be present in animal milk • Consider risks vs benefits	• Established efficacy and safety in patients 6–17 years of age ○ Not evaluated in children <6 years of age • Juvenile animal studies suggest weight changes can occur • Monitor for weight changes, suicidal thoughts and behavior	• Severe renal impairment (eGFR<30 mL/min/1.73m^2): adjust initial dose to 100 mg daily and the maximum dose to 200 mg daily • No dose adjustment for mild or moderate renal impairment • No dose adjustment for hepatic impairment[b]

[a] *Information is reported based on the product labeling (ie, package inserts)*

[b] *Prescribing information does not provided dosage adjustments for individuals with hepatic impairment*

Abbreviations: eGFR, estimated glomerular filtration rate; MRHD, maximum recommended human dose

9.0 SAFETY

9.1 Adverse events

Details about the commonly reported adverse events (AEs) are shown below for each of the reviewed agents according to the prescribing information. AEs for clonidine ER and guanfacine ER are separated according to use (ie, monotherapy, adjunctively with stimulants), while AEs for atomoxetine and viloxazine ER are separated according to the age of the studied population (ie, pediatric patients, adults).

Alpha-2 Agonists:

- Clonidine ER (AE≥5%; at least twice the placebo rate)[13]:
    - **Fixed-dose monotherapy:** somnolence, irritability, fatigue, nightmare, constipation, insomnia, dry mouth
    - **Adjunctively with stimulants:** somnolence, decreased appetite, fatigue, dizziness
- Guanfacine ER (AE≥5%; at least twice the placebo rate)[14]:
    - **Fixed-dose monotherapy:** somnolence, hypotension, nausea, fatigue, lethargy
    - **Flexible dose-optimization monotherapy:** somnolence, abdominal pain, hypotension, fatigue, insomnia, dizziness, irritability, nausea, vomiting, dry mouth, bradycardia
    - **Adjunctively with stimulants:** somnolence, insomnia, fatigue, abdominal pain, dizziness

Norepinephrine Reuptake Inhibitors (NRIs):

- Atomoxetine (AE≥5%; at least twice the placebo incidence)[11]:
    - **Children and adolescents:** somnolence, nausea, vomiting, decreased appetite, fatigue, abdominal pain
    - **Adults:** dry mouth, constipation, decreased appetite, nausea, erectile dysfunction, dizziness, urinary hesitation
- Viloxazine ER (AE≥5%; at least twice the placebo rate)[12]:
    - **Children and adolescents:** somnolence, fatigue, decreased appetite, nausea, vomiting, irritability, insomnia
    - **Adults:** headache, somnolence, insomnia, nausea, fatigue, dry mouth, decreased appetite, constipation

9.2 Contraindications

Clonidine ER, guanfacine ER, and atomoxetine should not be used in patients with prior hypersensitivity reactions (eg, angioedema, rash, urticaria, pruritus) to an active ingredient or any excipient.[11,13,14] Due to the risk of hypertensive crisis, viloxazine ER and atomoxetine are contraindicated in patients who are taking an monoamine oxidase inhibitor (MAOI), or who discontinued an MAOI within the previous 14 days.[11,12] Because viloxazine ER strongly inhibits CYP1A2,[12,22] this agent is also contraindicated in patients taking sensitive or narrow therapeutic window CYP1A2 substrates[12]; CYP1A2 substrates that are recommended to be avoided include melatonin,[61] tasimelteon, and duloxetine.[30,67] Unique contraindications to atomoxetine include patients with narrow-angle glaucoma,

pheochromocytoma or a history of the condition, and severe cardiac or vascular disorders that are expected to worsen with elevations in heart rate or blood pressure.[11]

9.3 Warnings and precautions

Of the reviewed FDA-approved non-stimulants, only the NRIs carry **black box warnings**. The viloxazine ER label warns of an increased risk of suicidal thoughts and behaviors in pediatric and adult patients.[12] Similarly, atomoxetine's label warns for the potential development of suicidal ideation in children and adolescents.[11] Patients taking either of these agents should be closely monitored for the emergence of concerning symptoms (eg, suicidality, behavioral changes) or clinical deterioration, especially within the first few months after starting the agent, or when the dosage is adjusted upwards or downwards.[11,12] If emergent suicidality or other indicative symptoms related to suicide develop, discontinuing the agent and switching to another regimen should be considered.[11,12]

The NRIs (ie, atomoxetine and viloxazine ER) also carry warnings for causing mixed or manic episodes in individuals with bipolar disorder; therefore all patients should be screened for this condition, including risk factors (eg, family history, depression) before starting treatment.[11,12]

Unique warnings and precautions that apply to the centrally-acting alpha-2 agonists (ie, clonidine ER, guanfacine ER) include the risk of rebound hypertension with abrupt discontinuation and the potential to exacerbate sinus node dysfunction and atrioventricular (AV) block due to the sympatholytic effects.[13,14] Patients receiving other sympatholytic agents or who have cardiac conduction abnormalities should be frequently monitored and slowly titrated to the optimal dose. When discontinuing either agent, it is recommended to incrementally taper the dose every 3 to 7 days to prevent rebound hypertension.[13,14]

All of the reviewed agents have the potential to affect blood pressure and heart rate. Clonidine ER and guanfacine ER may cause hypotension, bradycardia, or syncope, in a dose-dependent manner.[13,14] Therefore, it is recommended to gradually titrate and frequently monitor patients who are at an increased risk of hypotension, heart block, syncope, bradycardia, chronic renal failure, or other predisposed conditions. Patients likely to experience syncope should avoid overheating or becoming dehydrated.[13,14] In contrast, atomoxetine and viloxazine ER may increase blood pressure and heart rate.[11,12] Therefore, atomoxetine should be used cautiously in patients with tachycardia, hypertension, or cerebrovascular or cardiovascular disease.[11] Heart and blood pressure should be monitored before starting therapy, after increasing the dose, and occasionally during treatment[11-14]; notably, the dosages of these agents should be appropriately adjusted or used cautiously with antihypertensives.[11-14]

Other warnings and precautions are drug-specific (refer to **Table 10**). Viloxazine ER, clonidine ER, and guanfacine ER include a warning for somnolence; thereby, patients are advised to avoid tasks that require mental alertness (eg, driving) until they are aware of how the medication may affect them.[12-14] The potential for additive sedative effects with concomitant use of CNS depressants (eg, benzodiazepines, alcohol) should be consider before using with clonidine ER or guanfacine ER.[13,14]

Other warnings and precautions specific to atomoxetine include the potential for new, emergent psychotic or manic symptoms (eg, delusional thinking, hallucinations) in individuals without a history of associated psychiatric conditions; if this occurs, consider stopping the agent.[11] The agent should also be

discontinued and not restarted in patients who experience signs of severe liver injury (eg, jaundice, elevated liver enzymes). Patients starting atomoxetine should be monitored for new or worsening hostility or aggression. Due to the increased risk of serious cardiovascular events (eg, stroke, myocardial infarction, sudden death), avoiding the use of atomoxetine in adults with serious cardiac abnormalities should be considered. A more stern warning to generally avoid the use of atomoxetine applies to pediatric patients with pre-existing structural cardiac abnormalities or other serious cardiac issues. Before starting treatment with atomoxetine, individuals should undergo a history and physical exam to identify any cardiovascular conditions. Atomoxetine also has the potential to cause urinary retention or hesitation, and priapism; if priapism is suspected, it should be treated immediately. Pediatric patients treated with atomoxetine should be monitored for weight and height changes due to the potential for these parameters to fluctuate during treatment.[11]

In contrast to stimulants, these non-stimulants have no known abuse potential, cause little to no physical dependence, and are not controlled substances.[11,13,14,30]

Table 10 provides the contraindications, warnings, and precautions for these agents based on the product labeling.

Table 10. Contraindications, Warnings, and Precautions for FDA-Approved Non-Stimulants for ADHD[a]

Contraindications[11-14]
• Hypersensitivity to active ingredient or any excipient (CXR, GXR,ATX) • Currently taking or recently discontinued an MAOI within the previous 14 days (ATX, VLX) • Concomitant use of sensitive or narrow therapeutic CYP1A2 substrates (VLX) • Narrow angle glaucoma (ATX) • Pheochromocytoma or history of the condition (ATX) • Severe cardiac or vascular disorders that are expected to worsen with elevations in heart or blood pressure (ATX)
Warnings and Precautions[11-14]
Applies to NRI agents (ATX, VLX): • Potential to cause elevations in heart rate and blood pressure • Recommendation to screen all patients for bipolar disorder, including risk factors, before starting treatment **Applies to centrally-acting alpha-2 agonists** (GXR, CXR)**:** • Elevated risk of hypotension, bradycardia, and syncope • Risk of rebound hypertension with abrupt discontinuation • Recommendation to frequently monitor and slowly titrate to an optimal dose in patients receiving other sympatholytic agents or who have cardiac conduction abnormalities **Applies to certain agents:** • Increased risk of suicidal thoughts and behaviors (**BBW**; VLX) • Potential development of suicidal ideation in pediatric patients (**BBW**; ATX) • Severe liver injury (ATX) • Generally avoid use in patients with serious cardiac abnormalities (ATX) • New, emergent psychotic or manic symptoms (ATX) • Recommendation to monitor for new or worsening hostility or aggression (ATX)

Table 10. Contraindications, Warnings, and Precautions for FDA-Approved Non-Stimulants for ADHD[a]

Warnings and Precautions[11-14]
• Allergic reactions (ATX, CXR) • Potential to cause urinary retention or hesitancy, or priapism (ATX) • Recommendation to monitor pediatric patients for weight and height changes (ATX) • Dose may need to be adjusted when used in combination with potent CYP2D6 inhibitors or in individuals who are poor metabolizers of CYP2D6 (ATX) • Elevated risk of somnolence (VLX, GXR, CXR)

[a] Information is based on the contraindications, warnings and precautions as reported in the product labeling (ie, package inserts)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ATX, atomoxetine; BBW, black box warning; CYP, cytochrome P450; CXR, clonidine extended-release; FDA, US Food and Drug Administration; GXR, guanfacine extended-release; NRI, norepinephrine reuptake inhibitor; VLX, viloxazine extended-release

9.4 Drug-drug interactions

The reviewed agents have the potential to cause drug-drug interactions (DDIs).

- Atomoxetine and viloxazine ER can interact with MAOIs[11,12]
    - Coadministration or use within 14 days of an MAOI is contraindicated due to the potential for serious, and sometimes life-threatening, reactions (eg, hypertensive crisis).[11,12]
- For atomoxetine, the dose should be decreased when taken with CYP2D6 inhibitors (eg, fluoxetine, paroxetine) in patients who are extensive metabolizers. Also, this agent should be used carefully in patients receiving systemic (oral or intravenous) albuterol or other beta-2 agonists, antihypertensives, or pressors (eg, dobutamine, dopamine).[11]
    - When used with stimulants (ie, methylphenidate), atomoxetine did not produce additive cardiovascular effects.[11]
- Viloxazine ER is contraindicated in patients taking sensitive or narrow therapeutic window CYP1A2 substrates (eg, melatonin,[61] tasimelteon and duloxetine.[30,67]).[12] Additionally, combination use with *moderately* sensitive CYP1A2 substrates is recommended to be avoided, but if taken together, the dose of viloxazine ER should be reduced. Patients taking CYP2D6 or 3A4 substrates should be monitored for AEs, and the dose of the substrates should be adjusted accordingly.[12]
- Guanfacine ER is extensively metabolized by CYP3A4[14]:
    - The dose should be decreased by 50% when taken with strong or moderate CYP3A4 inhibitors (eg, fluconazole, ketoconazole)
    - The dose should be increased to up twice the recommended dose over 1 to 2 weeks when taken with strong or moderate CYP3A4 inducers (eg, efavirenz, rifampin)
- Clonidine ER may potentiate the effects of CNS depressants (eg, barbiturates, alcohol) and agents that modulate the sinus node or AV node conduction (eg, calcium channel blockers, digitalis, beta blockers); therefore, it is recommended to avoid the concomitant use of these agents.[13] Patients taking antihypertensives (may cause hypotension) or tricyclic antidepressants (may decrease clonidine's hypotensive effects) should have their blood pressure monitored and the dose adjusted accordingly.[13]

Table 11 shows the potential DDIs of these agents based on the product labeling.

Table 11. Drug-drug Interactions for FDA-Approved Non-Stimulants for ADHD[a]

Drug Interactions[11-14]
• Atomoxetine: MAOIs, CYP2D6 inhibitors (eg, fluoxetine, quinidine, paroxetine), antihypertensives, pressors (eg, dobutamine, dopamine) • Viloxazine ER: MAOIs, sensitive or narrow therapeutic window CYP1A2 substrates, moderately sensitive CYP1A2 substrates, CYP2D6 or CYP3A4 substrates • Guanfacine ER: Strong or moderate CYP3A4 inhibitors (eg, fluconazole, ketoconazole) or inducers (eg, efavirenz, rifampin) • Clonidine ER: CNS depressants (eg, barbiturates, alcohol), digitalis, beta blockers, calcium channel blockers, antihypertensives, tricyclic antidepressants

[a] Information is based on the drug-drug interactions as reported in the product labeling (ie, package inserts)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ATX, atomoxetine; CYP, cytochrome P450; CXR, clonidine extended-release; FDA, US Food and Drug Administration; GXR, guanfacine extended-release; VLX, viloxazine extended-release

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APPENDIX A – LITERATURE SEARCH STRATEGIES FOR SYSTEMATIC REVIEWS AND RANDOMIZED CONTROLLED TRIALS

Ovid Medline literature search strategies

Systematic reviews

Date of search: November 17, 2022
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to November 15, 2022>

1 "attention deficit and disruptive behavior disorders"/ or attention deficit disorder with hyperactivity/ or conduct disorder/ or child behavior disorders/ or hyperkinesis/ 60438

2 (ADDH or ADHD or "AD/HD" or ADD-H or HKD).ti,ab,kw,kf. 31059

3 ((attention$ or behav$) adj3 (defic$ or dysfunc$ or disorder$)).ti,ab,kw,kf. 76108

4 ((Hyperkin$ or hyperactiv$) adj2 (defic$ or dysfunc$ or disorder$)).ti,ab,kw,kf. 33538

5 1 or 2 or 3 or 4 112824

6 ((alpha-2 adj3 agonist$) or ((noradrenaline or norepinephrine) adj3 (inhibit$ or blocker$)) or nonstimulant* or non-stimulant*).ti,ab,kw,kf. 14673

7 Atomoxetine hydrochloride/ or Clonidine/ or Guanfacine/ or Viloxazine/ 15539

8 (atomoxetine or Strattera or clonidine or Kapvay or guanfacine or Intuniv or viloxazine or Qelbree or SPN-812 or SPN-809).ti,ab,kw,kf. 17742

9 6 or 7 or 8 32183

10 5 and 9 2495

11 (ADDH or ADHD or "AD/HD" or ADD-H or HKD).ti. 11769

12 ((attention$ or behav$) adj3 (defic$ or dysfunc$ or disorder$)).ti. 23255

13 ((Hyperkin$ or hyperactiv$) adj2 (defic$ or dysfunc$ or disorder$)).ti. 14020

14 11 or 12 or 13 33915

15 (drug$ or pharmacologic$ or pharmacother$ or medication$).ti. 575175

16 14 and 15 1810

17 10 or 16 3876

18 meta-analysis/ or (metaanaly$ or meta-analy$).ti,ab,kw,kf. or "Systematic Review"/ or ((systematic* adj3 review*) or (systematic* adj2 search*) or cochrane$ or (overview adj4 review)).ti,ab,kw,kf. or (cochrane$ or systematic review?).jw. 486245

19 (MEDLINE or Embase or PubMed or systematic review).tw. or meta analysis.pt. 454975

20 18 or 19 566200

21 17 and 20 384

22 limit 21 to yr="2017 - 2022" **155**

Randomized controlled trials

Date of search: November 29, 2022
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to November 28, 2022>

1 "attention deficit and disruptive behavior disorders"/ or attention deficit disorder with hyperactivity/ or conduct disorder/ or child behavior disorders/ or hyperkinesis/ 60488

2 (ADDH or ADHD or "AD/HD" or ADD-H or HKD).ti,ab,kw,kf. 31133

3 ((attention$ or behav$) adj3 (defic$ or dysfunc$ or disorder$)).ti,ab,kw,kf. 76274

4 ((Hyperkin$ or hyperactiv$) adj2 (defic$ or dysfunc$ or disorder$)).ti,ab,kw,kf. 33623

5 1 or 2 or 3 or 4 113014

6 Atomoxetine hydrochloride/ or Clonidine/ or Guanfacine/ or Viloxazine/ 15533

7 (atomoxetine or Strattera or clonidine or Kapvay or guanfacine or Intuniv or viloxazine or Qelbree or SPN-812 or SPN-809).ti,ab,kw,kf. 17752

8 6 or 7 21597

9 ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.) 1368708

10 5 and 8 and 9 624

11 limit 10 to yr="2017 -Current" **142**

Embase literature search strategies

Systematic reviews

Date of search: November 28, 2022

No.	Query	Results
#20	#19 AND (**2019**:py OR **2020**:py OR **2021**:py OR **2022**:py)	167
#19	#17 AND #18	710
#18	(**cochrane***:jt OR **'systematic review*'**:jt OR **'meta analysis'**/mj OR **'systematic review'**/exp OR ((**systematic** NEAR/3 **review**):ti,ab,kw) OR **'meta analys*'**:ti,ab,kw OR **metaanalys***:ti,ab,kw OR **search***:ti,ab OR **pubmed**:ab OR **embase**:ab OR **medline**:ab OR **cochrane**:ab OR ((**overview** NEAR/4 (**review** OR **reviews**)):ti)) NOT (**'conference abstract'**/it OR **'conference review'**/it) AND [english]/lim	828,046
#17	#10 OR #16	8,735
#16	#14 AND #15	2,482
#15	**drug***:ti OR **pharmacologic***:ti OR **pharmacother***:ti OR **medication***:ti	793,223
#14	#11 OR #12 OR #13	46,019
#13	((**hyperkin*** OR **hyperactiv***) NEAR/2 (**defic*** OR **dysfunc*** OR **disorder*** OR **syndrome***)):ti	18,100
#12	((**attention** OR **behav***) NEAR/3 (**defic*** OR **dysfunc*** OR **disorder*** OR **syndrome***)):ti	30,147
#11	**adhd**:ti OR **'ad/hd'**:ti OR **addh**:ti OR **'add h'**:ti OR **hkd**:ti	17,099
#10	#5 AND #9	7,118

	65,166
#9 **#6** OR **#7** OR **#8**	
	23,328
#8 **atomoxetine**:ti,ab,kw OR **strattera**:ti,ab,kw OR **clonidine**:ti,ab,kw OR **kapvay**:ti,ab,kw OR **guanfacine**:ti,ab,kw OR **intuniv**:ti,ab,kw OR **viloxazine**:ti,ab,kw OR **qelbree**:ti,ab,kw OR **'spn 812'**:ti,ab,kw OR **'spn 809'**:ti,ab,kw	
	51,927
#7 **'atomoxetine'**/de OR **'clonidine'**/de OR **'guanfacine'**/de OR **'viloxazine'**/de	
	14,340
#6 ((**'alpha 2'** NEAR/3 **agonist***):ti,ab,kw) OR (((**noradrenaline** OR **norepinephrine**) NEAR/3 (**inhibit*** OR **blocker***)):ti,ab,kw) OR **nonstimulant***:ti,ab,kw OR **'non stimulant*'**:ti,ab,kw	
	163,006
#5 **#1** OR **#2** OR **#3** OR **#4**	
	44,774
#4 ((**hyperkin*** OR **hyperactiv***) NEAR/2 (**defic*** OR **dysfunc*** OR **disorder*** OR **syndrome***)):ti,ab,kw	
	104,689
#3 ((**attention** OR **behav***) NEAR/3 (**defic*** OR **dysfunc*** OR **disorder*** OR **syndrome***)):ti,ab,kw	
	45,056
#2 **adhd**:ti,ab,kw OR **'ad/hd'**:ti,ab,kw OR **addh**:ti,ab,kw OR **'add h'**:ti,ab,kw OR **hkd**:ti,ab,kw	
	99,462
#1 **'attention deficit hyperactivity disorder'**/exp OR **'conduct disorder'**/exp OR **'hyperactivity'**/de OR **'hyperkinesia'**/exp	

Randomized controlled trials

Date of search: November 29, 2022

No. **Query**	**Results**
	331
#11 **#10** AND (**2017**:py OR **2018**:py OR **2019**:py OR **2020**:py OR **2021**:py OR **2022**:py)	
	1,565
#10 **#5** AND **#8** AND **#9**	
	2,271,212
#9	

('**crossover procedure**':de OR '**double-blind procedure**':de OR '**randomized controlled trial**':de OR '**single-blind procedure**':de OR **random***:de,ab,ti OR **factorial***:de,ab,ti OR **crossover***:de,ab,ti OR ((**cross** NEXT/1 **over***):de,ab,ti) OR **placebo***:de,ab,ti OR ((**doubl*** NEAR/1 **blind***):de,ab,ti) OR ((**singl*** NEAR/1 **blind***):de,ab,ti) OR **assign***:de,ab,ti OR **allocat***:de,ab,ti OR **volunteer***:de,ab,ti) NOT ('**conference abstract**'/it OR '**conference review**'/it) AND [english]/lim

53,927

#8

#**6** OR #**7**

23,328

#7

atomoxetine:ti,ab,kw OR **strattera**:ti,ab,kw OR **clonidine**:ti,ab,kw OR **kapvay**:ti,ab,kw OR **guanfacine**:ti,ab,kw OR **intuniv**:ti,ab,kw OR **viloxazine**:ti,ab,kw OR **qelbree**:ti,ab,kw OR '**spn 812**':ti,ab,kw OR '**spn 809**':ti,ab,kw

51,927

#6

'**atomoxetine**'/de OR '**clonidine**'/de OR '**guanfacine**'/de OR '**viloxazine**'/de

163,006

#5

#**1** OR #**2** OR #**3** OR #**4**

44,774

#4

((**hyperkin*** OR **hyperactiv***) NEAR/2 (**defic*** OR **dysfunc*** OR **disorder*** OR **syndrome***)):ti,ab,kw

104,689

#3

((**attention** OR **behav***) NEAR/3 (**defic*** OR **dysfunc*** OR **disorder*** OR **syndrome***)):ti,ab,kw

45,056

#2

adhd:ti,ab,kw OR '**ad/hd**':ti,ab,kw OR **addh**:ti,ab,kw OR '**add h**':ti,ab,kw OR **hkd**:ti,ab,kw

99,462

#1

'**attention deficit hyperactivity disorder**'/exp OR '**conduct disorder**'/exp OR '**hyperactivity**'/de OR '**hyperkinesia**'/exp

Epistemonikos literature search strategy

Systematic reviews

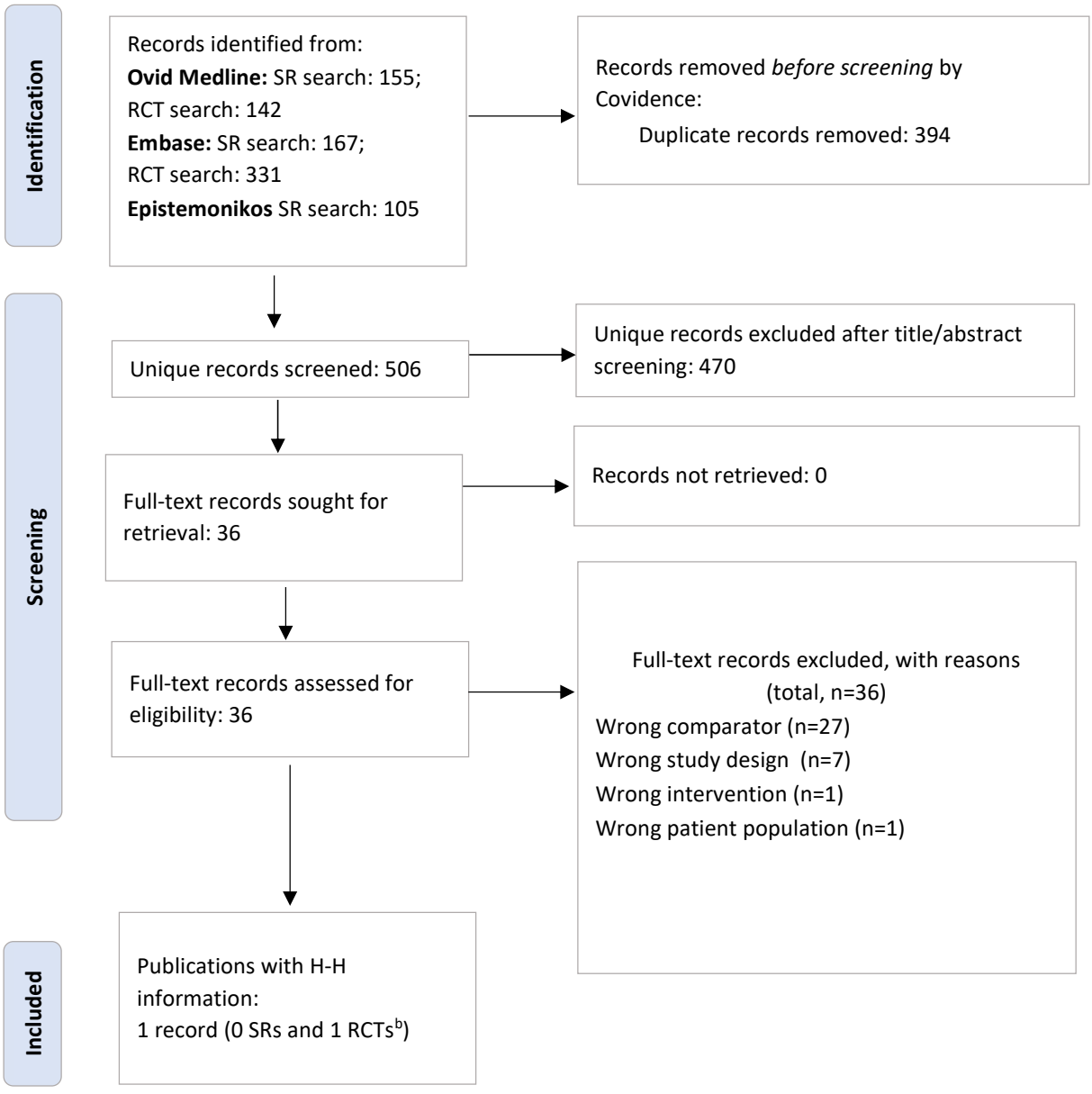
Date of search: November 17, 2022
Restricted years: 2017–2022

title:(("attention deficit" OR "attention-deficit" OR hyperkin* OR hyperactiv* OR ADHD OR HKD OR ADDH OR AD/HD OR ADD-H) AND (drug* OR pharmacologic* OR pharmacother* OR medication*)) OR (title:(("attention deficit" OR "attention-deficit" OR hyperkin* OR hyperactiv* OR ADHD OR HKD OR ADDH OR AD/HD OR ADD-H) AND (atomoxetine OR Strattera OR clonidine OR Kapvay OR guanfacine OR Intuniv OR viloxazine OR Qelbree OR SPN-812 OR SPN-809 OR "alpha-2 agonist*" OR "alpha 2 agonist*" OR "noradrenaline inhibit*" OR "noradrenaline blocker*" OR "norepinephrine inhibit*" OR "norepinephrine inhibit*" OR nonstimulant* OR non-stimulant*)) OR abstract:(("attention deficit" OR "attention-deficit" OR hyperkine* OR hyperactiv* OR ADHD OR HKD OR ADDH OR AD/HD OR ADD-H) AND (atomoxetine OR Strattera OR clonidine OR Kapvay OR guanfacine OR Intuniv OR viloxazine OR Qelbree OR SPN-812 OR SPN-809 OR "alpha-2 agonist*" OR "alpha 2 agonist*" OR "noradrenaline inhibit*" OR "noradrenaline blocker*" OR "norepinephrine inhibit*" OR "norepinephrine inhibit*" OR nonstimulant* OR non-stimulant*)))

APPENDIX B – SCREENING OF STUDIES

The flow chart below outlines our screening process for the results obtained from our literature searches, including the number of unique records excluded at the identification and screening phases.

Appendix B, Figure 1. PRISMA Flow Chart[a] for Literature Screening



[a] *Modified from Page et al. 2021*[42]

[b] *The one RCT was identified from the reference lists of screened SRs*

Abbreviations: H-H, head-to-head; RCT, randomized controlled trials; SR, systematic review

APPENDIX C – INCLUDED AND EXCLUDED REFERENCES

List of included references

Randomized controlled trials identified from screened systematic reviews:

1. Hervas A, Huss M, Johnson M, et al. Efficacy and safety of extended-release guanfacine hydrochloride in children and adolescents with attention-deficit/hyperactivity disorder: a randomized, controlled, phase III trial. *Eur Neuropsychopharmacol*. 2014;24(12):1861-1872. doi:10.1016/j.euroneuro.2014.09.014

List of excluded references

Wrong comparator:

1. Liu Q, Zhang H, Fang Q, Qin L. Comparative efficacy and safety of methylphenidate and atomoxetine for attention-deficit hyperactivity disorder in children and adolescents: Meta-analysis based on head-to-head trials. *J Clin Exp Neuropsychol*. 2017;39(9):854-865. doi:10.1080/13803395.2016.1273320
2. Chiu S, Campbell K. *Clonidine for the Treatment of Psychiatric Conditions and Symptoms: A Review of Clinical Effectiveness, Safety, and Guidelines*. Canadian Agency for Drugs and Technologies in Health; 2018: 22 pages. Last Updated February 21, 2018. Accessed November 22, 2022. Available at https://www.cadth.ca/sites/default/files/pdf/htis/2018/RC0961%20Clonidine%20Final.pdf
3. Solmi M, Fornaro M, Ostinelli EG, et al. Safety of 80 antidepressants, antipsychotics, anti-attention-deficit/hyperactivity medications and mood stabilizers in children and adolescents with psychiatric disorders: a large scale systematic meta-review of 78 adverse effects. *World Psychiatry*. 2020;19(2):214-232. doi:10.1002/wps.20765
4. De Crescenzo F, Cortese S, Adamo N, Janiri L. Pharmacological and non-pharmacological treatment of adults with ADHD: a meta-review. *Evid Based Ment Health*. 2017;20(1):4-11. doi:10.1136/eb-2016-102415
5. Khoodoruth MAS, Ouanes S, Khan YS. A systematic review of the use of atomoxetine for management of comorbid anxiety disorders in children and adolescents with attention-deficit hyperactivity disorder. *Res Dev Disabil*. 2022;128:104275. doi:10.1016/j.ridd.2022.104275
6. Osland ST, Steeves TD, Pringsheim T. Pharmacological treatment for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders. *Cochrane Database Syst Rev*. 2018;6(6):Cd007990. doi:10.1002/14651858.CD007990.pub3
7. Elliott J, Johnston A, Husereau D, et al. Pharmacologic treatment of attention deficit hyperactivity disorder in adults: A systematic review and network meta-analysis. *PLoS One*. 2020;15(10):e0240584. doi:10.1371/journal.pone.0240584
8. Rodrigues R, Lai MC, Beswick A, et al. Practitioner Review: Pharmacological treatment of attention-deficit/hyperactivity disorder symptoms in children and youth with autism spectrum disorder: a systematic review and meta-analysis. *J Child Psychol Psychiatry*. 2021;62(6):680-700. doi:10.1111/jcpp.13305

9. Cortese S, Adamo N, Del Giovane C, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. *Lancet Psychiatry*. 2018;5(9):727-738. doi:10.1016/s2215-0366(18)30269-4
10. Surman CBH, Walsh DM. Do Treatments for Adult ADHD Improve Emotional Behavior? A Systematic Review and Analysis. *J Atten Disord*. 2022;26(14):1822-1832. doi:10.1177/10870547221110926
11. Fu D, Wu DD, Guo HL, et al. The Mechanism, Clinical Efficacy, Safety, and Dosage Regimen of Atomoxetine for ADHD Therapy in Children: A Narrative Review. *Front Psychiatry*. 2021;12:780921. doi:10.3389/fpsyt.2021.780921
12. Nageye F, Cortese S. Beyond stimulants: a systematic review of randomised controlled trials assessing novel compounds for ADHD. *Expert Rev Neurother*. 2019;19(7):707-717. doi:10.1080/14737175.2019.1628640
13. Froehlich TE, Fogler J, Barbaresi WJ, Elsayed NA, Evans SW, Chan E. Using ADHD Medications to Treat Coexisting ADHD and Reading Disorders: A Systematic Review. *Clin Pharmacol Ther*. 2018;104(4):619-637. doi:10.1002/cpt.1192
14. Catalá-López F, Hutton B, Núñez-Beltrán A, et al. The pharmacological and non-pharmacological treatment of attention deficit hyperactivity disorder in children and adolescents: A systematic review with network meta-analyses of randomised trials. *PLoS One*. 2017;12(7):e0180355. doi:10.1371/journal.pone.0180355
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17. Li Y, Gao J, He S, Zhang Y, Wang Q. An Evaluation on the Efficacy and Safety of Treatments for Attention Deficit Hyperactivity Disorder in Children and Adolescents: a Comparison of Multiple Treatments. *Mol Neurobiol*. 2017;54(9):6655-6669. doi:10.1007/s12035-016-0179-6
18. Luan R, Mu Z, Yue F, He S. Efficacy and Tolerability of Different Interventions in Children and Adolescents with Attention Deficit Hyperactivity Disorder. *Front Psychiatry*. 2017;8:229. doi:10.3389/fpsyt.2017.00229
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21. Joseph A, Ayyagari R, Xie M, et al. Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison. *Eur Child Adolesc Psychiatry*. 2017;26(8):875-897. doi:10.1007/s00787-017-0962-6

22. Padilha S, Virtuoso S, Tonin FS, Borba HHL, Pontarolo R. Efficacy and safety of drugs for attention deficit hyperactivity disorder in children and adolescents: a network meta-analysis. *Eur Child Adolesc Psychiatry*. 2018;27(10):1335-1345. doi:10.1007/s00787-018-1125-0
23. Clavenna A, Bonati M. Pediatric pharmacoepidemiology - safety and effectiveness of medicines for ADHD. *Expert Opin Drug Saf*. 2017;16(12):1335-1345. doi:10.1080/14740338.2017.1389894
24. Miller J, Perera B, Shankar R. Clinical guidance on pharmacotherapy for the treatment of attention-deficit hyperactivity disorder (ADHD) for people with intellectual disability. *Expert Opin Pharmacother*. 2020;21(15):1897-1913. doi:10.1080/14656566.2020.1790524
25. Faraone SV, Banaschewski T, Coghill D, et al. The World Federation of ADHD International Consensus Statement: 208 Evidence-based conclusions about the disorder. *Neurosci Biobehav Rev*. 2021;128:789-818. doi:10.1016/j.neubiorev.2021.01.022
26. Balasundaram MK, Singh A. Viloxazine for attention-deficit hyperactivity disorder: a new formulation for a new indication. *Drugs & Therapy Perspectives*. 2022;38(2):77-83. doi:10.1007/s40267-022-00892-z.
27. Perugi G, Pallucchini A, Rizzato S, Pinzone V, De Rossi P. Current and emerging pharmacotherapy for the treatment of adult attention deficit hyperactivity disorder (ADHD). *Expert Opin Pharmacother*. 2019;20(12):1457-1470. doi:10.1080/14656566.2019.1618270

Wrong study design:

28. Brunkhorst-Kanaan N, Libutzki B, Reif A, Larsson H, McNeill RV, Kittel-Schneider S. ADHD and accidents over the life span - A systematic review. *Neurosci Biobehav Rev*. 2021;125:582-591. doi:10.1016/j.neubiorev.2021.02.002
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31. Pipe A, Ravindran N, Paric A, Patterson B, Van Ameringen M, Ravindran AV. Treatments for child and adolescent attention deficit hyperactivity disorder in low and middle-income countries: A narrative review. *Asian J Psychiatr*. 2022;76:103232. doi:10.1016/j.ajp.2022.103232
32. Auvin S, Wirrell E, Donald KA, et al. Systematic review of the screening, diagnosis, and management of ADHD in children with epilepsy. Consensus paper of the Task Force on Comorbidities of the ILAE Pediatric Commission. *Epilepsia*. 2018;59(10):1867-1880. doi:10.1111/epi.14549
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34. Elbe D. Switching from Clonidine Immediate-Release to Guanfacine Extended-Release. *J Can Acad Child Adolesc Psychiatry*. 2020;29(2):121-123.

Wrong intervention:

35. Santos GM, Santos EM, Mendes GD, Fragoso YD, Souza MR, Martimbianco ALC. A review of Cochrane reviews on pharmacological treatment for attention deficit hyperactivity disorder. *Dement Neuropsychol*. 2021;15(4):421-427. doi:10.1590/1980-57642021dn15-040001

Wrong patient population:

36. Williamson E, Sathe NA, Andrews JC, et al. *Medical Therapies for Children With Autism Spectrum Disorder—An Update*. Agency for Healthcare Research and Quality; 2017: 713 pages. Last Updated May 26, 2017. Accessed November 22, 2022. Available at https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/asd-medical_research-2017.pdf

APPENDIX D – GUIDELINE DEFINITIONS

Appendix D, Table 1. Definitions of Guideline Level of Evidence and Recommendation Strength

CADDRA; 2020[3]	
Recommendations provided by the guideline were not graded nor assigned an evidence rating, but were decided on a consensus-basis among multidisciplinary healthcare providers (eg, primary care physicians, psychiatrists, pediatricians).	
SDBP; 2020[18]	
Overall, the evidence strength of recommendations was based on the grading used in the 2011 AAP ADHD guideline,[68] as outlined below; and determined based on Panel consensus.	
Strong recommendation (Grade B)	Based on "high to moderately high quality of evidence and a preponderance of benefit over harm" (page S38)[18]
Recommendation (Grade C)	
Option Level	Based on "lower quality or limited evidence combined with the consensus expert opinion of the Panel" (page S38) [18] These recommendations may be considered based on the practitioner's clinical judgment and their knowledge of the patient's clinical scenario.
ICASA; 2020[20]	
Recommendations provided by the guideline were not graded nor assigned an evidence rating, but were decided based on expert consensus using a modified Delphi process among multidisciplinary healthcare providers (eg, psychiatrists, physicians specialized in addiction, pharmacists) from various countries. A 5-point scale was used to ascertain agreement among the group (1=majority disagree, to 5=strongly agree) for each statement, with 3 rounds of rating. For each round, a consensus was achieved when >95% of the group assigned a score of ≥3.	
AAP; 2019[6]	
Strong recommendation	Based on Level A evidence that clearly demonstrates the benefits or risks. Strong recommendations should be adhered to, "unless a clear and compelling rationale for an alternative approach is present." (page 4)[6]
Moderate recommendation	Based on Level B evidence that clearly demonstrates the benefits or risks.
Weak recommendation	Based on evidence with a low-quality rating (ie, level C or D), or higher quality evidence (ie, Level A, B, or C) suggesting a equipoise exists between the risks and benefits
Grade A	Level A studies (ie, well-designed and conducted trials, including meta-analyses and gold standard diagnostic studies
Grade B	Level B studies (ie, "Trials or diagnostic studies with minor limitations; consistent findings from multiple observational studies."[6 a]) or extrapolated from level A evidence

Abbreviations: AAP, American Academy of Pediatrics; ADHD, attention-deficit/hyperactivity disorder; CADDRA, Canadian ADHD Resource Alliance; ENAA, European Network Adult ADHD; EPA, European Psychiatric Association; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ICASA, International Collaboration on ADHD and Substance Abuse; NDAL, Neurodevelopmental Disorders Across the Lifespan; NICE, National Institute for Health and Care Excellence; RCTs, randomized controlled trials; SDBP, Society for Developmental and Behavioral Pediatrics

Appendix D, Table 1. Definitions of Guideline Level of Evidence and Recommendation Strength

Grade C	Level C studies (ie, "Single or few observational studies or multiple studies with inconsistent findings or major limitation."[6 a]) or extrapolated from level B or C evidence
Grade D	Level D studies (ie, "Expert opinion, case reports, reasoning from first principles."[6 a]) or inconclusive evidence of level A, B, C, or D
Level X	Not considered a formal evidence level, but was reserved for "exceptional situations in which validating studies cannot be performed, and there is a clear preponderance of benefit or harm."[6 a]
ENAA; NDAL of the EPA; 2019	
Statements were not graded nor assigned an evidence rating, but were decided on a consensus-basis among healthcare experts. The majority of authors that participated in forming the 2010 consensus statement on ADHD updated the previous statements for the 2019 iteration based on recent literature findings.	
NICE; 2018[19,69]	
To evaluate the evidence quality of included studies (eg, RCTs, non-randomized studies), a GRADE assessment was performed on the outcomes, which was used to determine whether an intervention was clinically significant.[69] Each outcome was evaluated on the following elements: risk of bias, inconsistency, indirectness, imprecision, publication bias, and other concerns (eg, conflicts of interest)	
High level of quality	"Further research is very unlikely to change our confidence in the estimate of effect."[69 b]
Moderate level of quality	"Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate."[69 b]
Low level of quality	"Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate."[69 b]
Very low level of quality	"Any estimate of effect is very uncertain."[69 b]
Strong recommendation	A strong recommendation was generally denoted by the word "offer." Strong recommendations apply to the majority of patients based on the evidence demonstrating the benefits clearly outweigh the risks, and the recommended action tends to be cost effective
Weaker recommendation	A weaker recommendation was generally denoted by the word "consider." The risks and benefits of the recommended action tends to be less clear for weaker recommendations.
CPS; 2018[21]	
Recommendations provided in the position statement were not graded nor assigned an evidence rating, but were "based on current guidelines, evidence from the literature, and expert consensus" (page 462)[21]	

[a] *Located in Figure 1 on page 4 of the 2019 AAP clinical practice guideline on ADHD[6]*

[b] *Located in Table 4 on page 21 of the supplemental material for the 2018 NICE guideline on the diagnosis and management of ADHD[69]*

Abbreviations: AAP, American Academy of Pediatrics; ADHD, attention-deficit/hyperactivity disorder; CADDRA, Canadian ADHD Resource Alliance; ENAA, European Network Adult ADHD; EPA, European Psychiatric Association; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ICASA, International Collaboration on ADHD and Substance Abuse; NDAL, Neurodevelopmental Disorders Across the Lifespan; NICE, National Institute for Health and Care Excellence; RCTs, randomized controlled trials; SDBP, Society for Developmental and Behavioral Pediatrics

APPENDIX E – EXPERT OPINION

In 2020, **Young et al** published an article providing practice recommendations from the United Kingdom for the management of children and adults with ADHD and comorbid ASD based on expert consensus.[2] Experts consisted of clinicians from various occupational fields (eg, pediatrics, psychiatry, social work, primary care, academic, speech therapy), with experience in managing patients with ASD and ADHD.[2] **Appendix E, Table 1** summarizes the key pharmacologic recommendations for patients with ADHD and comorbid ASD, which are discussed below.

In terms of managing these conditions, experts defer to guideline-recommended pharmacologic treatments for ADHD (**Table 4**) and ASD.[2] Authors note that there is no available evidence demonstrating effective pharmacologic options that address core symptoms of ASD; therefore, ADHD-indicated pharmacologic agents are to be used among individuals with ADHD as a unique condition or co-occurring with ASD, not for ASD alone.[2]

Experts recommend analyzing behavioral patterns and psychological/environmental interventions (eg, peer support groups, parent/guardian training programs, changing uncomfortable lighting, minimizing distracting noises) as first-line treatment in children with ADHD and ASD.[2] For children who are unresponsive to first-line non-pharmacologic interventions, pharmacologic agents for ADHD, either stimulants or non-stimulants, may be considered to help alleviate associated symptoms (eg, impulsivity, inattention, hyperactivity, emotional lability). After initial behavioral and environmental modification approaches, if children and adolescents with ASD have persistent and prominent irritability, second-generation antipsychotics (eg, aripiprazole, risperidone) can be used for a limited duration.[2]

In adults with ADHD and ASD, it is encouraged to not delay pharmacologic treatment based on the availability of psychological interventions, especially given that these specialized services for ADHD/ASD adults are often limited.[2] Consequently, pharmacologic agents, based on appropriateness, tend to be used before psychological management in adults. Notably, the use of pharmacologic agents for ADHD may enhance the benefit from psychological interventions and improve concentration.[2]

Given the potential for increased sensitivity to adverse effects and treatment resistance among this patient population, medications should be up-titrated at a slow rate and patients should be frequently monitored.[2] While these conditions tend to be lifelong,[3,5,6,21,70] experts encourage short-term use of pharmacotherapy, if feasible.[2] No particular agent is recommended over others, but medication selection may depend on patient-specific factors. For example, individuals with co-existing ASD may have trouble swallowing whole tablets, preferring the use of other formulations (eg, liquid) or agents that are able to be sprinkled.[2]

Caution should be taken when using stimulants in ADHD/ASD patients with prior cardiac issues or in older adults.[2] Furthermore, the use of pharmacologic agents, especially stimulants, during pregnancy is discouraged. Given that both ADHD and ASD are often associated with other comorbidities (eg, mood disorders, anxiety), clinicians should be diligent about other comorbid conditions and treat them appropriately.[2]

Appendix E, Table 1. Treatment Plan for Patients with ADHD and ASD, According to Expert Consensus

Children	Adults

First-line:
Psychological/environmental interventions and analyzing behavioral patterns (can use the Functional Behavioral Analysis)
Second-line:
Pharmacologic agents[a]:
• Agents for ADHD (stimulants or non-stimulants)
  ○ ADHD symptoms: impulsivity, inattention, hyperactivity, irritability, emotional lability, aggression
• Second-generation antipsychotics (eg, aripiprazole, risperidone)[b]
  ○ ASD symptoms: irritability
	First-line:
	• Psychological interventions (eg, CBT)
	• *Note:* pharmacologic treatment[a] for ADHD should not be delayed based on availability or completion of psychological interventions

Additional Considerations:

- The appropriate pharmacologic treatment should be prescribed to treat any comorbidities (eg, mood disorders, anxiety, sleep disturbances), if present
- Medications should be up-titrated at a slow rate and patients should be frequently monitored for adverse effects
- Patients with ASD may have trouble swallowing whole tablets, preferring the use of other formulations
- Caution should be taken when using stimulants in patients with prior cardiac issues or in older adults
- The use of pharmacologic agents, especially stimulants, during pregnancy is discouraged

[a] *Experts defer to following guideline-recommended pharmacologic treatments for ADHD and ASD*

[b] *May also be used in adolescents with ASD*

Abbreviations: ADHD, attention deficit/hyperactivity disorder; ASD, autism spectrum disorder; CBT, cognitive behavioral therapy