

Reimbursement Review

Guanfacine Hydrochloride Extended Release

Requester: Public drug programs

Therapeutic area: Attention-deficit/hyperactivity disorder

Summary

What Is Attention-Deficit/Hyperactivity Disorder?

- Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder most commonly identified in children and adolescents that often continues into adulthood. It is an impairment of the ability to regulate attention or focus. ADHD can present differently in different people. Some symptoms may include forgetfulness, impulsivity, disorganization, distracted behaviour, and restlessness. People with ADHD can also experience emotional dysregulation. These factors may contribute to learning challenges, problems with self-esteem, and difficulties with relationships.
- In Canada, the prevalence of ADHD in children and adolescents combined is estimated to range from 2.6% to 8.6%.¹ The prevalence is thought to be higher in males (range, 3.7% to 13.3%) than in females (range, 1.5% to 7.0%).¹

What Are the Treatment Goals and Current Treatment Options for ADHD?

- The treatment goals for children and adolescents with ADHD are to reduce hyperactivity, impulsivity (including aggressive impulsive actions), inattention, oppositional behaviours, and emotional dysregulation to improve their development (e.g., learning, social development, cognitive outcomes, and health-related quality of life [HRQoL]).
- Methylphenidate and dextroamphetamine (or mixed amphetamine salts) preparations are common psychostimulant (PST) medications used as first-line treatment to target symptoms.
- However, PST treatment is not helpful to all patients, particularly those with certain medical conditions. This includes those who cannot tolerate PSTs due to their adverse effects; those whose disease does not have a clinical response to PSTs; those for whom optimized PST use results in only a partial disease response; and those whose families may feel strongly that PST medications are not a good option for them.
- Guanfacine hydrochloride extended release (GXR), a nonstimulant medication, could be used as a second-line treatment as monotherapy or as adjunctive therapy to a PST for patients whose disease responds suboptimally to PSTs alone.

Summary

What Is GXR and Why Did Canada's Drug Agency Conduct This Review?

- GXR, an alpha-2a agonist, is available as an oral tablet. Health Canada has approved GXR as monotherapy for the treatment of ADHD in children and adolescents aged 6 years to 17 years, and as adjunctive therapy to PSTs for the treatment of ADHD in children and adolescents aged 6 years to 17 years, with a sub-optimal response to PSTs.
- In 2015, the Canadian Drug Expert Committee recommended that GXR not be listed for the treatment of ADHD in children aged 6 years to 12 years as monotherapy (due to insufficient evidence to assess the comparative clinical benefit of GXR as monotherapy relative to other less costly treatments) or as adjunctive therapy (due to limited evidence from 1 randomized controlled trial [RCT] of only 9 weeks' duration).
- At the request of the participating public drug programs in 2025, Canada's Drug Agency (CDA-AMC) reviewed GXR used as monotherapy and as an adjunctive therapy to a PST to inform a recommendation on whether it should be reimbursed for the treatment of ADHD in children and adolescents aged 6 years to 17 years.

How Did CDA-AMC Evaluate GXR?

- CDA-AMC reviewed the clinical evidence on the beneficial and harmful effects of GXR and compared its costs versus those of other treatments used in Canada for ADHD in children and adolescents aged 6 years to 17 years. PSTs (e.g., amphetamine and methylphenidate, both short- and long-acting formulations) and other nonstimulants (e.g., atomoxetine and clonidine) were considered relevant treatments to compare with GXR.
- The clinical evidence was identified through systematic searches for available studies. The objectives of this review are 2-fold: to review the benefits and harms of GXR as monotherapy and to review the benefits and harms of GXR as adjunctive therapy to a PST. For the use of GXR as monotherapy, evidence from indirect treatment comparisons was sought due to limited direct evidence for GXR and active comparators found during evidence scoping.
- The review received no inputs from patient groups, clinician groups, or industry.
- Two clinical experts in the diagnosis and management of children and adolescents with ADHD were consulted as part of the review process, with representation from Ontario and British Columbia.

Summary

What Were the Findings?

CDA-AMC reviewed the following clinical evidence:

- 1 systematic review with network meta-analysis (NMA) comparing monotherapy oral medications (i.e., amphetamines, methylphenidate, modafinil, atomoxetine, clonidine, guanfacine, or bupropion) and placebo for the treatment of ADHD in children and adolescents
- 3 long-term extension (LTE) studies of GXR as monotherapy (1 of which also included evidence for GXR as an adjunctive therapy to a PST) for the treatment of ADHD in children and adolescents
- 2 RCTs with 4 reports comparing GXR versus placebo as adjunctive therapy to a PST for the treatment of ADHD in children and adolescents.

Clinical Evidence of Monotherapy

- NMA results showed:
 - GXR may result in decreases in ADHD core symptoms and an increase in clinical global functioning rated by clinicians compared with placebo.
 - Compared with amphetamines, GXR may result in an increase (i.e., less improvement) in ADHD core symptoms and a decrease (i.e., less improvement) in clinical global functioning as rated by clinicians.
 - Compared with atomoxetine or methylphenidate, GXR may result in little to no difference in ADHD core symptoms and an uncertainty in clinical global functioning as rated by clinicians.
 - The effects of GXR compared with clonidine on the improvement of ADHD core symptoms and clinical global functioning are uncertain.
 - GXR may result in an increase in study discontinuations due to adverse events (AEs) compared with placebo, but the effect of GXR compared with active comparators is very uncertain.
 - GXR may result in smaller decreases in weight compared with amphetamines, atomoxetine, or methylphenidate. The effect of GXR on weight compared with placebo or clonidine is uncertain.
 - GXR may result in a decrease in systolic blood pressure, but little to no difference in diastolic blood pressure compared with placebo.
 - In the absence of evidence, the effects of GXR compared with placebo or active comparators for other AEs, illness severity, or HRQoL are not known.
 - Limitations of the NMA included the potential for intransitivity (differences in patient and study characteristics across comparisons in the network), which would bias the effect estimates, affect study-

Summary

level risks of bias, and result in imprecision in the effect estimates. Evidence of all comparisons to active treatments were of low or very low certainty. The NMA also risks being out of date, resulting in risk of bias due to missing evidence in the synthesis.

- LTE studies showed:
 - Patients treated with GXR in 3 LTE studies for 24 months experienced clinically important decreases in ADHD core symptoms (3 studies), decreases in illness severity (2 studies), and clinically important improvements in psychosocial aspects of HRQoL (2 studies).
 - Somnolence, headache, fatigue, upper respiratory tract infection, sedation, dizziness, abdominal pain, insomnia, and irritability are common AEs associated with GXR use.
 - Although changes in vital signs, blood pressure, and cardiovascular events were not commonly observed in long-term treatment with GXR, these potential harms should be closely monitored as per suggestion of the clinical experts.
 - Due to the single-arm design of the LTE studies, it is uncertain to what extent the observed effects can be attributed to GXR. Other limitations include risk of bias in the measurement of the outcomes and due to missing outcomes data. The studies could not inform about the long-term effects of GXR relative to active comparators used in clinical practice.

Economic Evidence of Monotherapy

- Reimbursing GXR as monotherapy for the treatment of ADHD in children and adolescents aged 6 years to 17 years is expected to increase costs to public drug programs.

Clinical Evidence of Adjunctive Therapy

- Evidence from 2 RCTs comparing GXR + PST therapy versus placebo plus PST therapy suggests GXR + PST treatment may result in greater improvement in ADHD core symptoms in children and adolescents.
- GXR adjunctive therapy may also improve executive function (1 RCT), severity of illness (2 RCTs), clinical global functioning (2 RCTs), overall psychopathology (1 RCT), disease response and remission (1 RCT), and ADHD symptomatology and functioning (1 RCT) in children and adolescents.
- Common AEs such as headache, abdominal pain, fatigue, somnolence, dizziness, insomnia, and affective lability occurred more frequently in the GXR + PST group than in the placebo plus PST group.

Summary

- The findings were limited by short-term follow-up and various sources of bias. Long-term follow-up of a single-arm adjunctive therapy in a small subgroup suggested that the long-term safety and efficacy of GXR adjunctive therapy were consistent with the findings from short-term blinded studies. Due to the single-arm design of the LTE study, it is uncertain to what extent the observed effects can be attributed to GXR + PST therapy.

Economic Evidence of Adjunctive Therapy

- Reimbursing GXR as adjunctive therapy to a PST for the treatment of ADHD in children and adolescents aged 6 years to 17 years is expected to increase costs to public drug programs.

Table of Contents

Abbreviations.....	9
Background.....	11
Introduction	11
Disease Background.....	12
Current Management	13
Unmet Needs and Existing Challenges	14
Considerations for Using the Drug Under Review	14
Clinical Review	16
Methods	16
Clinical Evidence.....	17
Evidence on Monotherapy	18
Discussion.....	35
Conclusion	37
Economic Review of Monotherapy.....	38
Methods	38
Conclusion	39
Clinical Review of Adjunctive Therapy.....	39
Clinical Evidence.....	39
Evidence From RCTs on Adjunctive Therapy.....	39
Discussion.....	55
Conclusion	57
Economic Review of Adjunctive Therapy	57
Methods	57
Conclusion	58
References	59

List of Tables

Table 1: Information on the Drug Under Review and on the CDA-AMC Review	11
Table 2: Eligibility Criteria	17
Table 3: Number of Studies Contributing to the Comparisons and Statistical Heterogeneity in the Pairwise Comparisons of GXR Vs. Placebo.....	23
Table 4: Summary of NMA Results for Efficacy Outcomes at Time Points Closest to 12 Weeks of Guanfacine Vs. Comparator	26
Table 5: Summary of NMA Results for Harm Outcomes at Time Points Closest to 12 Weeks of Guanfacine Vs. Comparator.....	26
Table 6: Description of LTE Studies.....	28
Table 7: Patient Disposition in LTE Studies	30
Table 8: Baseline Characteristics of Patients in LTE Studies	30
Table 9: Efficacy Outcomes in LTE Studies.....	33
Table 10: Characteristics of Included Randomized Controlled Trials for GXR as Adjunctive Therapy	40
Table 11: Patient Disposition of GXR as Adjunctive Therapy Studies	43
Table 12: Baseline Characteristics of Included Studies for GXR as Adjunctive Therapy	44
Table 13: Summary of Key Efficacy Results of Included Studies for GXR as Adjunctive Therapy.....	48
Table 14: Patient Disposition in LTE Study on GXR as Adjunctive Therapy.....	53
Table 15: Baseline Characteristics of Patients in LTE Study on GXR as Adjunctive Therapy.....	53

Abbreviations

ADHD	attention-deficit/hyperactivity disorder
ADHD RS-IV	ADHD Rating Scale–IV
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
BRIEF-P	Behavior Rating Inventory of Executive Function–Preschool
BSFQ	Before School Functioning Questionnaire
CDA-AMC	Canada’s Drug Agency
CGI-I	Clinical Global Impressions–Improvement
CGI-P	Conners Global Index–Parent
CGI-S	Clinical Global Impressions–Severity of Illness
CHQ-PF50	Child Health Questionnaire–Parent Form 50
CI	confidence interval
CPRS-R	Conners Parent Rating Scale–Revised
CR	controlled release
DSM	<i>Diagnostic and Statistical Manual of Mental Disorders</i>
ECG	electrocardiogram
FMEC	Formulary Management Expert Committee
GIR	guanfacine hydrochloride immediate release
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GXR	guanfacine hydrochloride extended release
HRQoL	health-related quality of life
ITC	indirect treatment comparison
LOCF	last observation carried forward
LTE	long-term extension
MID	minimal important difference
NMA	network meta-analysis
PGA	Parents’ Global Assessment
PST	psychostimulant
RCT	randomized controlled trial
RoB	Risk of Bias
ROBIS	Risk of Bias in Systematic Reviews
RoB NMA	Risk of Bias in Network Meta-Analysis

SD	standard deviation
SMD	standardized mean difference
SR	systematic review
TEAE	treatment emergent adverse event
XR	extended release

Background

Introduction

The clinical review has 2 objectives. The first objective is to review and critically appraise the evidence on the beneficial and harmful effects of guanfacine hydrochloride extended release (GXR) oral tablets (1 mg, 2 mg, 3 mg, or 4 mg) as monotherapy in the treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents aged 6 years to 17 years. The second objective is to review and critically appraise the evidence on the beneficial and harmful effects of GXR as adjunctive therapy to a psychostimulant (PST) for the treatment of ADHD in children and adolescents, aged 6 years to 17 years, whose disease has responded suboptimally to PSTs.

The focus will be placed on comparing GXR, as monotherapy or as adjunctive therapy, to relevant comparators in clinical practice in Canada and on identifying gaps in the current evidence, outlined in [Table 1](#). The economic review consists of a cost comparison of GXR versus relevant comparators for the same population. The comparators considered relevant to this review were active monotherapies, including amphetamines (long acting or short acting), methylphenidate (long acting or short acting), atomoxetine, and clonidine.

Table 1: Information on the Drug Under Review and on the CDA-AMC Review

Item	Description
Information on the drug under review	
Drug	GXR tablets, 1 mg, 2 mg, 3 mg, 4 mg administered orally
Relevant Health Canada indication	- GXR as monotherapy for the treatment of ADHD in children and adolescents aged 6 to 17 years - GXR as adjunctive therapy to psychostimulants for the treatment of ADHD in children and adolescents, aged 6 to 17 years, with a sub-optimal response to psychostimulants
Mechanism of action	Guanfacine is a selective alpha2a-adrenergic receptor agonist. The mechanism of action of guanfacine in ADHD is not known. ²
Recommended dosage	- Starting dose for both monotherapy and adjunctive therapy: 1 mg, taken orally once a day (morning or evening) - Adjusted dose (depending on clinical response and tolerability): in increments of no more than 1 mg per week up to a maximum daily dose of 4 mg (6 to 12 years) or 7 mg (13 to 17 years), for monotherapy and up to a maximum daily dose of 4 mg for adjunctive therapy to psychostimulants
Data protection status	Data protection expired on January 5th, 2022
Status of generic drugs / biosimilars	Four (4) generics available (2 approved, 2 marketed) and 2 (2) generic submissions registered with HC as of 2023-09 date
Information on the CDA-AMC review	
Requester	Public drug programs: Ontario and British Columbia
Indication under consideration for reimbursement	Same as Health Canada indication

ADHD = attention-deficit/hyperactivity disorder; CDA-AMC = Canada's Drug Agency; GXR = guanfacine hydrochloride extended release; HC = Health Canada.

Context for the Review

A previous CADTH reimbursement review published in 2015 reviewed the clinical evidence of GXR for the treatment of ADHD in children (aged 6 years to 12 years) as monotherapy and as adjunctive therapy to PSTs.³

For monotherapy, 6 phase III randomized controlled trials (RCTs) and 1 phase II RCT were included. All compared GXR with placebo. Of the included studies, 1 phase III RCT had an atomoxetine arm to provide reference data versus placebo. This study was not designed to compare GXR with atomoxetine. Two open-label long-term extension (LTE) studies were identified and summarized in the Appendix of the previous CADTH review.³

For adjunctive therapy, 1 RCT was included that compared GXR given in the morning versus GXR given in the evening with placebo in children with ADHD whose disease had responded suboptimally to PSTs.

Based on the evidence available at that time, the Canadian Drug Expert Committee recommended that GXR not be listed as monotherapy due to insufficient evidence from RCTs to assess the comparative clinical benefit of GXR relative to other less costly treatments for ADHD. The Canadian Drug Expert Committee also recommended that GXR not be listed as adjunctive therapy due to insufficient evidence to adequately assess the overall and longer-term clinical benefit of GXR in this patient population.

Sources of Information

The contents of the clinical review are informed by studies identified through systematic literature searches and input received from interested parties.

Calls for patient group, clinician group, and industry input are issued for each Non-Sponsored Reimbursement Review. However, no responses to the calls were received.

The drug programs provide input on each drug being reviewed through the reimbursement review process by identifying issues that may affect their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted for this review are summarized and provided to the expert committee in a separate document.

Each review team includes at least 1 clinical expert with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process. Two clinical specialists with expertise in the diagnosis and management of children and adolescents with ADHD participated as part of the review team, with representation from Ontario and British Columbia.

Disease Background

In the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*, ADHD is defined with 3 subtypes (i.e., predominantly inattentive, predominantly hyperactive-impulsive, and combined).⁴ Patients with predominantly inattentive subtype mainly have inattention symptoms, such as difficulty focusing, organizing tasks, or following instructions, without substantial hyperactivity-impulsivity.⁴ Those with the predominantly hyperactive-impulsive subtype exhibit excessive hyperactivity and impulsivity, such as

fidgiting, difficulty waiting their turn, or interrupting others.⁴ The combined subtype has symptoms of both other subtypes.⁴

ADHD is 1 of the most common neurodevelopmental disorders of childhood worldwide.¹ Its prevalence among children across provinces in Canada is approximately 1.1% for preschoolers (aged 3 years to 5 years) and 4.1% for school-aged children (aged 6 years to 9 years).^{1,5} For children and adolescents combined, estimates range from 2.6% to 8.6%.¹ With respect to sex, prevalence estimates for females range from 1.5% to 7.0% and estimates for males range from 3.7% to 13.3%.¹

Current Management

Treatment Goals

Patient Group Input

No patient group provided input.

Clinician Input

The clinical experts consulted for this review stated that goals for the treatment of ADHD in children and adolescents are to reduce hyperactivity, impulsivity (including aggressive impulsive actions), inattention, oppositional behaviours, and emotional dysregulation. The overarching goal of treatment in children with ADHD is to improve their development (e.g., learning, social development, cognitive outcomes, and quality of life). As a result, treatment goals would include improved relationships with family, peers, and teachers; improved academic output and grades; improved ability to follow directions at home and at school; improved ability to cooperate with others in social situations; and improved self-regulation.

Current Treatment Options

Treatment of ADHD in children and adolescents involves a multifaceted approach that may include medication (PSTs, nonstimulants) and behavioural therapy. Types of behavioural therapy included parental training in behavioural therapy and behavioural therapy with children. The clinical experts indicated that methylphenidate and dextroamphetamine (or mixed amphetamine salts) preparations are the commonly prescribed PST medications used in first-line treatment to target symptoms. However, these medications do not address the underlying neurologic process or its development. The clinical experts mentioned that a combination of medication and behavioural therapy can be helpful for some patients with mild to moderate cases. The clinical experts also prescribe some nonstimulants such as clonidine or atomoxetine to reduce inattention or hyperactivity. However, clonidine is seldomly used to treat ADHD due to its side effects (e.g., sedation, dizziness, and low blood pressure). Second-generation (atypical) antipsychotics might be used to achieve clinical stability (e.g., aggressive impulsivity).

The *Canadian ADHD Practice Guidelines (4.1 Edition)*⁶ recommend long-acting PSTs as first-line treatment drugs. An adequate trial of both classes of long-acting PSTs (methylphenidate and amphetamines) is recommended before engaging in a trial of a second-line treatment. The guidelines recommend atomoxetine, GXR, and short- or intermediate-acting PSTs as second-line treatment drugs, which can be used for patients who experience substantial side effects, whose disease has responded suboptimally with first-line

medications, who do not have access to first-line medications, or who have contraindications to stimulant medications.⁶

The *Canadian ADHD Practice Guidelines (4.1 Edition)*⁶ recommend that nonstimulants, including GXR, may be used in combination with first-line drugs (i.e., long-acting PSTs) as a potential augmentation for patients whose disease responds suboptimally to first-line treatments.

Utilization data for guanfacine and other drugs for ADHD are presented in Appendix 1 in the Supplemental Material on the [project landing page](#).

Unmet Needs and Existing Challenges

Current Treatment Options

Patient Group Input

No patient group provided input.

Clinician Input

The clinical experts indicated that currently available treatment with PSTs is not helpful to patients with certain medical conditions (e.g., arrhythmias, family histories of certain cardiac issues), those who cannot tolerate PSTs due to adverse effects (e.g., behavioural activation, appetite suppression, sleep disturbances, anxiety), those whose disease does not respond clinically to PSTs, those for whom optimized PST use results in only a partial disease response, and those whose families may feel that PST medications are stigmatizing or that treatment with a PST is not a good option for them. The clinical experts also noted that many of the nonmedication therapies are not easily accessible, because of either long wait-lists or the high cost of private care not covered by provincial insurance.

The clinical experts identified the need to find alternative treatments with better side effect profiles to improve tolerability, adherence, and convenience. Treatments with once daily dosing are greatly needed for patients with impaired executive functions (e.g., organizing tasks, remembering things) and disorganization in ADHD. Treatments are also needed to better address the nondiagnostic symptoms of ADHD, including emotional dysregulation and aggressive behaviours.

Considerations for Using the Drug Under Review

Contents within this section have been informed by input from the clinical experts consulted for the purpose of this review. The following has been summarized by the review team.

Place in Therapy

According to the clinical experts, GXR monotherapy is likely to be used in patients with comorbid conditions that pose contraindications to PSTs, those whose disease had no clinical response to PSTs, or those who could not tolerate any dose or type of PST medication.

The clinical experts believed that GXR would be used as adjunctive therapy to a PST for patients whose disease responded suboptimally to clinically optimized PSTs, or when they could not tolerate a higher dose of PSTs needed to obtain a good treatment effect.

The clinical experts suggested that clinicians should have the option to prescribe GXR before patients start PSTs in rare cases and when there is little opportunity for behavioural therapy and/or access to individualized educational programs. The clinical experts also suggested the use of GXR would reduce the costs of using long-acting stimulants, reduce the use of atypical antipsychotics, cut down costs for acute hospitalizations, decrease visits to child psychiatrists with subspecialized practices, and help decrease polypharmacy in specific populations such as individuals with autism or complex neurodevelopmental disorders who have comorbid ADHD. However, no evidence was provided to support these assertions.

Patient Population

The clinical experts explained that there is little way to predict whether a patient's disease will respond to any 1 psychiatric medication versus another. Choices are usually made on a case-by-case basis, with clinical reasoning as to which medication should be used first for a particular patient. It is important to have alternative treatment options with unique mechanisms of action and better side effect profiles.

The clinical experts indicated that patients who are best suited to GXR include those who do not tolerate PST adverse effects, those whose disease had incomplete response to PSTs, those who do not want to take a PST, those who need 24-hour coverage (both at school and after school hours) and cannot tolerate adverse effects of PSTs for their ADHD symptoms, and those who have emotional reactivity or dysregulation and/or severely disruptive behaviours. Most importantly, GXR is indicated when irritability and reactive aggression are prominent aspects of the clinical picture.

Assessing the Response to Treatment

The clinical experts discussed that the outcomes assessed in clinical practice are quite different than those used in clinical trials, which are usually confined to symptoms that comprise diagnostic criteria. In clinical practice, clinicians look at attainment of developmental milestones, school performance, overall functioning, better sleep and mood, and improvement in major clinical symptoms, such as irritability, emotional and behavioural dysregulation, aggression, oppositional behaviours, social struggles, mood, and anxiety. Parents and clinicians can develop a checklist for target symptoms and/or develop clear objectives or treatment targets for improved outcomes relevant to the individual child.

Discontinuing Treatment

The clinical experts suggested that GXR should be discontinued if benefits are not clear and/or there are prominent adverse effects such as drowsiness, headaches, or blood pressure issues. Treatment could also be discontinued if a patient's symptoms dissipate with age; the question of whether medication is still needed to treat ADHD is often considered when children reach adolescence.

Prescribing Considerations

The clinical experts commented that administration of GXR as monotherapy or as adjunctive therapy to a PST can be initiated in any outpatient setting and does not require a specialist. A primary care clinician familiar with the diagnosis and treatment of ADHD can prescribe GXR. However, if the diagnosis in question is complicated by other factors, or if standard dosages are not tolerated or are ineffective, then a specialist consultation is indicated.

Additional Considerations

One clinical expert commented that GXR is more effective in clinical practice than guanfacine hydrochloride immediate release (GIR) due to better adherence and tolerance. According to the clinical expert, GIR causes drowsiness more often than GXR. However, no evidence was provided to support these assertions. GIR is used to treat high blood pressure and not ADHD in clinical practice.

Clinical Review

Methods

The review team conducted literature searches to identify primary studies and systematic reviews (SRs) (with or without meta-analyses) of GXR as monotherapy and GXR as adjunctive therapy to a PST for the treatment of ADHD in children and adolescents. Studies were selected according to the eligibility criteria presented in [Table 2](#).

Two literature searches were conducted. The first search was conducted to identify indirect treatment comparison (ITC) evidence for GXR used as monotherapy due to the lack of direct evidence comparing GXR and active comparators found during evidence scoping. The second literature search was conducted to identify primary studies for GXR as monotherapy and GXR as adjunctive therapy to a PST. LTE studies of RCTs meeting the eligibility criteria were also eligible for inclusion.

ITCs meeting the criteria presented in [Table 2](#) (other than for study design) were considered for eligibility. When multiple eligible ITCs with overlapping primary studies were identified, we selected the most relevant studies for inclusion in this report by balancing comprehensiveness, relevance, recency, and methodological quality (assessed via A MeaSurement Tool to Assess systematic Reviews 2 [AMSTAR 2])⁷ informed by an evidence-based decision tool.⁸

Relevant comparators included treatments used in clinical practice in Canada for the patient population being considered. In the absence of direct evidence for GXR monotherapy compared with any active comparator, placebo-controlled studies were also considered eligible. Clinical expert inputs were considered when selecting outcomes (and follow-up times) for review. Selected outcomes are those considered relevant to expert committee deliberations. The risk of bias for each network meta-analysis (NMA) included was appraised using the following tools: Risk of Bias in Systematic Reviews (ROBIS) for SR-level assessment⁹ and Risk of Bias in Network Meta-Analysis (RoB NMA) for NMA-level assessment.¹⁰ The risk of bias of included RCTs was appraised using the revised Cochrane Risk of Bias tool for randomized trials (RoB 2).¹¹ The risk of bias appraisal for included single-arm studies was guided by principles outlined in the European Medicines Agency's reflection paper on single-arm trials.¹² When interpreting standardized mean differences (SMDs), we used Cohen guidance for effect sizes (i.e., 0.2 suggests a small effect, 0.5 suggests a moderate effect, and 0.8 suggests a large effect). We classified SMDs smaller than 0.2 as suggesting little to no difference.

Detailed methods for literature searches, study selection, data extraction, and risk of bias appraisal are provided in Appendix 1 and Appendix 2 in the Supplemental Material.

Table 2: Eligibility Criteria

Criterion	Description
Population	Children and adolescents aged 6 years to 17 years with ADHD
Intervention	Guanfacine hydrochloride extended-release tablets, oral • As monotherapy • As adjunctive therapy to a PST
Comparator	• Placebo • Long-acting PSTs ◦ Amphetamine (Adderall sustained release, Vyvanse, Dexedrine Spansule) ◦ Methylphenidate (Biphentin, Concerta, Focquest, Ritalin sustained release) • Short-acting PSTs ◦ Amphetamine (Dexedrine tablet) ◦ Methylphenidate (Ritalin) • Nonstimulants (atomoxetine, clonidine)
Outcomes	Clinical effectiveness outcomes • Change in severity of ADHD core symptoms assessed by clinicians, teachers, or parents (e.g., ADHD Rating Scale–IV, BRIEF-P) • Severity of illness (CGI-S) • Global Improvement (CGI-I) Patient-reported outcomes • HRQoL Safety outcomes • AEs • Serious AEs • Treatment discontinuation due to AEs • Notable harms (i.e., dizziness, dry mouth, fatigue, headache, irritability, gastrointestinal symptoms, ECG changes, arrhythmia events, cardiac events, change in blood pressure, change in heart rate, syncope, appetite suppression, weight change) • Mortality
Study design	Published RCTs, SRs ^a of RCTs

ADHD = attention-deficit/hyperactivity disorder; AE = adverse event; BRIEF-P = Behavior Rating Inventory of Executive Function–Preschool Version; CGI-I = Clinical Global Impressions–Improvement; CGI-S = Clinical Global Impressions–Severity of Illness; ECG = electrocardiogram; HRQoL = health-related quality of life; PST = psychostimulant; RCT = randomized controlled trial; SR = systematic review.

^aTo be considered an SR, the review must report a research question, the sources searched and a reproducible search strategy, inclusion and exclusion criteria, screening methods, critical appraisals of the included studies, and information about analysis and synthesis that allows for reproducibility of the results.¹³

Clinical Evidence

From the search for ITCs, the review team identified 210 unique records via the searches of databases, of which 203 were excluded by title and abstract. The review team screened 7 records by full text and included 1 SR with NMA. All SRs that were excluded were those whose primary studies overlapped with the included SR and were lower in methodological quality. Table 2 and Table 3 of Appendix 3 in the Supplemental

Material outline our assessment of the comprehensiveness, recency, relevance, and methodological quality of the overlapping candidate SRs with NMA. Aligned with these assessments, we chose the SR with NMA by Cortese et al. (2018)¹⁴ for presentation within this report as we judged it to provide the best balance of these criteria.

From the search for primary studies, the review team identified 251 unique records via the database searches, of which 242 were excluded by title and abstract. The review team screened 9 records by full text and included 7 reports consisting of 3 LTE studies¹⁵⁻¹⁷ of GXR as monotherapy (1 of which also included evidence for GXR as an adjunctive therapy to a PST) and 2 RCTs with 4 reports¹⁸⁻²¹ on GXR as an adjunctive therapy to a PST. The literature search identified no new primary studies on GXR used as monotherapy published since the search conducted for the included SR with NMA by Cortese et al. (2018).¹⁴

A list of included studies (Table 8) and a list of excluded studies with reasons for exclusion (Table 9) are provided in Appendix 4 in the Supplemental Material.

Evidence on Monotherapy

Summary of Available Evidence

Description of Indirect Comparisons

The SR with NMA by Cortese et al. (2018)¹⁴ aimed to estimate the comparative efficacy, acceptability, and tolerability of oral medications as monotherapy for ADHD in children, adolescents, and adults. Data from children and adolescents in this SR¹⁴ were analyzed separately from those of adults.

Study Selection and Review Methods

The study protocol was registered with PROSPERO and published.²² The literature searches were conducted in multiple electronic databases (including MEDLINE and Embase), grey literature sources, and trial registries from the date of database inception to April 7, 2017, with no language restrictions. These were supplemented with hand searches of FDA, European Medicines Agency, and drug manufacturer websites; reference lists of relevant SRs and guidelines; and communication with study authors and drug manufacturers for unpublished information. The authors of the SR¹⁴ did not restrict the search by ADHD subtype or presentation, sex, IQ, socioeconomic status, or comorbidities (except for those needing concomitant pharmacotherapy).

The authors included double-blind RCTs of at least 1 week's duration that enrolled children and adolescents (≥ 5 years to < 18 years) with a primary diagnosis of ADHD according to the *DSM*, including the *Third Edition (DSM-III)*; the *Third Edition, Revised (DSM-III-R)*; the *Fourth Edition, Text Revision (DSM-IV[TR])*; or the *Fifth Edition (DSM-5)*; or according to the International Classification of Diseases (Ninth Revision or 10th Revision). Studies were included if they assessed the following medications as oral monotherapy, compared with each other or with placebo: amphetamines (including lisdexamfetamine), atomoxetine, bupropion, clonidine, guanfacine, methylphenidate (including dexamethylphenidate), or modafinil. The primary outcomes were the severity of ADHD symptoms (based on clinicians' and teachers' ratings) and study discontinuation

due to AEs. Secondary outcomes included the severity of ADHD symptoms based on parents' ratings, change in Clinical Global Impression–Improvement (CGI-I) scores (clinicians' ratings), acceptability (study withdrawal for any reason), change in weight, and change in blood pressure. These outcomes were assessed at the times closest to 12 weeks (primary end point), 26 weeks, and 52 weeks.

Quasi-RCTs and studies using Latin square approach without adequate randomization were excluded. Open-label or single-blind RCTs, long-term studies using a maintenance design, N-of-1 trials, and studies with enrichment designs were excluded.

Study selection was conducted independently by 3 investigators. Data were independently extracted by at least 2 investigators. The risk of bias of the included primary studies was assessed using the Cochrane RoB tool (v. 2011).²³ Risk of bias was assessed at the study level by 3 investigators and double-checked by 2 review authors. The certainty of evidence was assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) with support of the CINeMA web application for the primary outcomes. Considerations for the overall certainty of evidence included study limitations (risk of bias), imprecision, inconsistency (heterogeneity and incoherence), indirectness, and publication bias.

ITC Analysis Methods

The authors of the SR¹⁴ first performed pairwise meta-analyses for all outcomes and comparisons at every available time point, using a random-effects model. Statistical heterogeneity within each pairwise comparison was assessed by calculating the I-squared statistic and its 95% confidence interval (CI). Second, an NMA was conducted within a frequentist framework. Statistical heterogeneity in the network was assessed via the common tau-squared statistic. Loop-specific and node-splitting approaches and a design-by-treatment model were used to evaluate local and global incoherence, respectively. Transitivity was assessed by comparing study characteristics across the included RCTs. Further, subgroup and sensitivity analyses were planned to assess the effects of treatment effect modifiers and study design differences (study duration, sex, age, psychiatric comorbidities, IQ, crossover design, medication status, industry sponsorship, inequalities in doses, risk of bias, and data imputation). Amphetamines and lisdexamfetamine were combined in the same node, and GXR and GIR were lumped within the same node.

The primary analysis was restricted to studies using medications within the therapeutic range as per FDA recommendations. The effects of different dose regimens were investigated in 2 sets of sensitivity analyses. First, studies that did not use FDA-licensed doses were excluded. Second, studies in which the dose ranges used were recommended in national or international guidelines or formularies but differed from FDA recommendations were included. Finally, post hoc analyses were conducted to investigate possible differences between lisdexamfetamine and other amphetamines, because lisdexamfetamine is metabolized differently than other amphetamines.

The authors of the SR¹⁴ examined the risk of publication bias by plotting a comparison-adjusted funnel plot of all trials comparing at least 1 treatment versus placebo.

Summary of Included Studies

The SR¹⁴ included 82 trials involving children and adolescents (N = 14,346) in the NMA. The included studies were double-blind RCTs (parallel group and crossover with washout).

The mean age ranged from 8.1 years to 14.8 years. ADHD core symptoms were measured by various scales and subscales. The authors of the SR¹⁴ selected only validated scales that measure exclusively the same 3 symptoms (i.e., inattention, hyperactivity, and impulsivity). The included studies enrolled patients with various comorbidities (e.g., aggression or defiance, major depressive disorder, conduct disorder, oppositional defiant disorder, substance use disorder, tic disorders, obsessive-compulsive disorder, or generalized anxiety disorder). The proportions of patients presenting with such comorbidities varied across the included studies. Participant medication status at baseline and sex differences varied across studies. The characteristics of the included SR¹⁴ and additional eligibility criteria are presented in Table 11 and Table 12 of Appendix 5 in the Supplemental Material, respectively.

The risk of bias of the primary studies included in the SR¹⁴ was rated overall low in 23.5% of included studies, unclear in 65.4%, and high in 11.1% by the SR authors. The medications investigated included amphetamines (including lisdexamfetamine), atomoxetine, bupropion, clonidine, guanfacine, and methylphenidate (including dextromethylphenidate). There were 11 trials of guanfacine, of which 9 used GXR and 2 used GIR. The doses of GXR or GIR started at 1 mg and reached up to 4 mg maximum daily. Methylphenidates and dextroamphetamines used included different formulations (e.g., intermediate acting, long acting, oral solution, or chewable tablets) and different starting doses. Study duration ranged from 2 weeks to 18 weeks for all included studies and from 4 weeks to 13 weeks for GXR studies.

Critical Appraisal of ITC

Table 4 and Table 5 of Appendix 3 in the Supplemental Material present the results of the ROBIS assessment and the RoB NMA assessment, respectively. All 3 domains (i.e., study eligibility criteria, identification and selection of the studies, and data collection and study appraisal) in the ROBIS assessment were judged as being of low concern. Of the 3 domains (i.e., interventions and network geometry, effect modifiers, and statistical synthesis) in the RoB NMA assessment, the first 2 were judged as having low risk of bias, while there were some concerns regarding the risk of bias in statistical synthesis. There were also important limitations to the analyses that preclude strong conclusions from the NMA, as described in the following paragraphs.

The SR¹⁴ clearly described the eligibility criteria for the types of participants, interventions, comparators, outcomes, and study design. The authors adhered to the preplanned methods and analyses, and all changes were appropriately justified, so there is a low risk of bias due to selective reporting. The literature search was adequately comprehensive; however, it risks being out of date (with April 7, 2017, the date the literature was last searched). Although our screening for primary studies did not identify any new studies of GXR monotherapy, it is unclear how much newer evidence of other comparators relevant to the NMA is missing. As such, there are concerns for risk of bias due to missing evidence, although the presence, direction, and extent of potential bias cannot be confirmed. Methods for study selection, data extraction, risk of bias, and certainty of evidence appraisal were sufficient to minimize the risks of bias and error in these processes.

However, a limitation is that the risk of bias was appraised at the study level, rather than at the level of the reported effects. This methodology ignores that risk of bias can vary depending on the effect estimate being evaluated, particularly for such domains as performance, detection, attrition, and reporting bias. As such, the risk of bias reported by the authors for each study may not universally apply to all outcomes investigated in the SR.¹⁴ According to the authors, most included studies were at high or unclear risk of bias, and due to the paucity of data they were unable to conduct sensitivity analyses with these studies removed from the analyses. As such, the impact of these studies on the results is unknown; however, the presence of these studies was accounted for in the certainty of evidence appraisals conducted by the authors. To reduce the risk of biased estimates, the authors excluded many studies, including open-label or single-blinded RCTs. It is unclear how the exclusion of these studies could have affected the NMA results.

There is some uncertainty as to whether the transitivity assumption (i.e., that patients in the included trials could be jointly randomized) underlying the NMA was upheld. If not upheld, the resulting treatment effect estimates would be biased. The authors compared potential treatment effect modifiers (e.g., age, sex, medication status, comorbidities) and study designs (e.g., length of follow-up, drug dosage) across included trials, and subgroup or sensitivity analyses were taken to investigate any potential intransitivity. However, not all planned sensitivity analyses could be undertaken due to a paucity of data. Further, the authors did not provide a justification for the patient and study characteristics investigated, so it is unclear whether their analyses accounted for all potential treatment effect modifiers. Across studies, reporting of potential treatment effect modifiers was often incomplete, precluding a comprehensive appraisal of similarity.

The networks were connected mostly through placebo. There were few closed loops in the networks, limiting the assessment of incoherence, the statistical manifestation of intransitivity. Furthermore, GXR was only linked to placebo in the network; therefore, the comparisons of GXR with active comparators relied entirely on indirect evidence. The authors of the SR¹⁴ suggested there was no evidence of disagreement between direct and indirect evidence for primary outcomes, as the test of global inconsistency did not show any statistically significant difference. However, this test usually has low power, so the absence of statistically significant incoherence cannot rule out the potential for incoherence.²⁴

I-squared statistic values suggested substantial statistical heterogeneity in multiple pairwise meta-analyses, and the patient population included patients from different age groups (children versus adolescents) and of different sexes (female versus male), who had different previous exposure and responses to ADHD medications. However, according to the authors, subgroup analyses to investigate possible sources of heterogeneity were not possible due to a scarcity of data. Further, the I-squared statistic alone is insufficient to inform a robust appraisal of the true variability in study effects, as small studies may have variable point estimates but wide, overlapping 95% CIs (potentially resulting in a low I-squared statistic in the presence of important inconsistency) whereas large studies may present a consistent clinical message but have narrower 95% CIs (potentially resulting in a high I-squared statistic in the absence of important inconsistency).²⁵ Forest plots for the pairwise meta-analyses were not reported, preventing a more nuanced appraisal. Therefore, whether statistical heterogeneity had any implications in terms of clinical heterogeneity and the validity of the results was unclear.

The SR¹⁴ included 9 RCTs with GXR and 2 RCTs with GIR, which were pooled into a single guanfacine node. Subgroup or sensitivity analyses to separate those who received GIR and those who received GXR were not performed, suggesting that the findings may not totally reflect the effect of GXR. The clinical experts commented that GIR may cause drowsiness more often than GXR, leading to lower adherence; therefore, combining the data for participants who received GIR or GXR into a single node could have affected efficacy and tolerability outcomes. Moreover, drugs of the same class but at different dose regimens, or lisdexamfetamine and other amphetamines, were pooled into single nodes.

The results of the NMA for primary outcomes closest to 12 weeks were shown. However, analyses of outcomes over a longer term (i.e., 26 weeks and 52 weeks, as planned) were not possible due to a scarcity of data. Thus, the findings can inform only the short-term effect of GXR treatment for ADHD. Further, although the time point closest to 12 weeks was selected, there was heterogeneity in the length of the trials, with some as short as 1 week in duration. It is unclear whether it was appropriate to combine data from trials with such variation in the time point of outcome assessment.¹⁴

Missing dichotomous outcome data were managed according to the intention-to-treat principle, and it was assumed that participants who dropped out after randomization had a negative outcome. Missing continuous outcome data were analyzed using last observation carried forward (LOCF) to the final assessment. If LOCF data were not reported, missing data were analyzed using what the authors describe as “a validated method”; however, the specific method was not reported. The LOCF method assumes no change in the results for an outcome from the time when the data were missing, forward. This assumption is unlikely to accurately reflect the trajectory of the outcomes.

The results showed the absence of asymmetry in all funnel plots, suggesting no potential publication bias. However, the possibility of missing information could not be ruled out, as many studies were excluded by the authors in an effort to adhere to the assumption of transitivity and reduce the risk of biased estimates.

Results of the GRADE assessments showed that the certainty of evidence for primary outcomes was low or very low in all relevant comparisons to active treatments. The certainty of evidence was commonly reduced due to study-level risk of bias and imprecision in the effect estimates (i.e., wide 95% CIs, often including the potential that either GXR or the treatment to which it was being compared could be favoured). As such, conclusions from the NMA are limited as the estimated effects may deviate to an important degree from the true effects.

The authors of the SR¹⁴ included studies that used different rating scales to assess the core symptoms of ADHD, and the effect estimates were presented as SMDs. Thus, it is difficult to interpret the clinical meaningfulness of any reported differences. For simplicity, we used Cohen guidance for effect sizes when interpreting SMDs, with 0.2 indicating a small effect, 0.5 indicating a medium effect, and 0.8 or greater indicating a large effect;²⁶ however, whether these thresholds align with patient-important effects is uncertain. For binary outcomes (i.e., CGI-I and treatment discontinuations due to AEs) only relative between-group effect estimates such as odds ratios were reported, precluding any interpretation of the magnitude (and clinical importance) of the estimated effects.

The authors of the SR¹⁴ excluded studies assessing the efficacy of multimodal treatments (including the combination of ADHD drug[s] plus psychotherapy), studies that included patients whose disease was considered to be “resistant” to a previous ADHD drug, and studies that included patients with comorbid disorders that were treated with a medication other than an ADHD drug. As such, the results may not be generalizable to these groups.

Although the NMA reported results for most outcomes considered important to interest holders, severity of illness and health-related quality of life (HRQoL) were not investigated. As such, no conclusions can be drawn for the effect of GXR relative to active comparators or placebo on patients’ overall severity of illness or HRQoL.

Efficacy and Harms Results of ITCs

The number of studies contributing to the networks for relevant outcomes, the number of studies contributing to pairwise comparisons of GXR versus placebo, and the statistical heterogeneity (I-squared) of the pairwise comparisons are reported in [Table 3](#).

Table 3: Number of Studies Contributing to the Comparisons and Statistical Heterogeneity in the Pairwise Comparisons of GXR Vs. Placebo

Outcome	Number of studies contributing to the network	Pairwise comparisons of GXR vs. placebo	
		Number of studies	I-squared (%)
Overall change in ADHD core symptoms – clinicians’ ratings	54	7	63.3
Overall change in ADHD core symptoms – teachers’ ratings	16	1	NA
Overall change in ADHD core symptoms – parents’ ratings	NR	NR	NR
CGI-I – clinicians’ ratings	40	8	34.3
Discontinuation due to AEs	67	7	41.9
Weight change	57	7	0.0
Blood pressure change	55	8	25.4

ADHD = attention-deficit/hyperactivity disorder; AE = adverse event; CGI-I = Clinical Global Impressions–Improvement; GXR = guanfacine hydrochloride extended release; NA = not applicable; NR = not reported; vs. = versus.

Key results of the NMA for relevant outcome comparisons are presented in [Table 4](#) and [Table 5](#). The certainty of evidence as assessed by the authors for each primary outcome is also provided. Comparisons of NMA and direct pairwise meta-analysis results of efficacy and safety outcomes are presented in Tables 13 to 20 of Appendix 5 in the Supplemental Material. NMA results of GXR compared with active comparators for systolic blood pressure and diastolic blood pressure were not available (unknown reasons).

ADHD Core Symptoms Rated by Clinicians

- Compared with placebo, GXR likely results in a decrease (or greater improvement) in core symptoms (moderate certainty due to risk of bias).

- Compared with atomoxetine, GXR may result in little to no difference in core symptoms (low certainty due to risk of bias and imprecision).
- Compared with methylphenidate, GXR may result in little to no difference in core symptoms (low certainty due to risk of bias and imprecision).
- Compared with amphetamines, GXR may result in an increase (or less improvement) in core symptoms (low certainty due to risk of bias and imprecision).
- The evidence is very uncertain about the effect of GXR compared with clonidine (very low certainty due to risk of bias and imprecision).
- The results of sensitivity analyses excluding trials with treatment duration less than 2 weeks, with an overall high risk of bias, in which all patients had psychiatric or neurologic comorbidities, and for which the imputation of missing data was required, and excluding nonsponsored trials or trials with unfair dose comparisons, were consistent with the base case results (Table 21 of Appendix 5 in the Supplemental Material).

ADHD Core Symptoms Rated by Teachers

- The evidence is very uncertain about the effect of GXR on core symptoms compared with placebo, atomoxetine, or methylphenidate (very low certainty due to risk of bias, indirectness, and/or imprecision).
- There is no evidence to inform the effect of GXR on core symptoms compared with amphetamines or clonidine.

ADHD Core Symptoms Rated by Parents

- The certainty of evidence was not assessed by the authors of the SR. The information necessary to inform a robust certainty of evidence appraisal by the Canada's Drug Agency (CDA-AMC) review team was unavailable.
- Compared with amphetamines, GXR may result in an increase (or less improvement) in core symptoms.
- The effect of GXR compared with placebo and atomoxetine is uncertain. Although the point estimate favoured atomoxetine compared with GXR, the estimate was imprecise (the 95% CI included the potential that either treatment being compared could be favoured).
- Compared with methylphenidate, GXR may result in an increase (or less improvement) in core symptoms; however, the estimate was imprecise (the 95% CI included the possibility of little to no difference).
- There is no evidence to inform the effect of GXR compared with clonidine.

Severity of Illness

- Severity of illness was not assessed in the NMA.

Clinical Global Functioning Measured by CGI-I Scores

- The certainty of evidence was not assessed by the authors of the SR. The information necessary to inform a robust certainty of evidence appraisal by the CDA-AMC review team was unavailable. As only relative effects were reported, the clinical relevance of the estimated effects could not be determined.
- Compared with placebo, GXR may result in an increase in clinical global functioning (i.e., GXR favoured over placebo).
- Compared with amphetamines, GXR may result in a decrease (i.e., less improvement) in clinical global functioning (i.e., amphetamines favoured over GXR).
- The effect of GXR compared with atomoxetine, clonidine, or methylphenidate is uncertain. Although the point estimates favoured GXR compared with atomoxetine or clonidine and favoured methylphenidate compared with GXR, the estimates were imprecise (the 95% CIs included the potential that either treatment being compared could be favoured).

Health-Related Quality of Life

- HRQoL was not assessed in the NMA.

Treatment Discontinuations Due to AEs

- Compared with placebo, GXR may result in an increase in AEs (low certainty due to risk of bias and imprecision).
- The evidence is very uncertain about the effect of GXR on AEs compared with amphetamines, atomoxetine, clonidine, or methylphenidate (very low certainty due to risk of bias and imprecision).

Change in Weight

- The certainty of evidence was not assessed by the authors of the SR. The information necessary to inform a robust certainty of evidence appraisal by the CDA-AMC review team was unavailable.
- The effect of GXR compared with placebo and clonidine is uncertain. Although the point estimates suggest little to no difference in effects on weight, the estimates were imprecise (the 95% CIs included the potential that either treatment being compared could be favoured).
- Compared with amphetamines, atomoxetine, or methylphenidate, GXR may result in smaller decreases in weight.

Change in Blood Pressure

- Results of pairwise meta-analysis suggested that GXR may result in a decrease in systolic blood pressure compared with placebo (SMD = -0.24; 95% CI, -0.40 to -0.08). GXR may result in little to no difference in diastolic blood pressure compared with placebo (SMD = -0.18; 95% CI, -0.36 to -0.00). Comparisons with relevant active comparators were unavailable (unknown reasons).

Table 4: Summary of NMA Results for Efficacy Outcomes at Time Points Closest to 12 Weeks of Guanfacine Vs. Comparator

Comparator	ADHD core symptoms, clinicians' ratings, SMD (95% CI); GRADE certainty	ADHD core symptoms, teachers' ratings, SMD (95% CI); GRADE certainty	ADHD core symptoms, parents' ratings, SMD (95% CI)	CGI-I, OR (95% CI)
Placebo	-0.67 (-0.85 to -0.50); moderate	-0.63 (-1.62 to 0.35); very low	-0.23 (-0.90 to 0.45)	3.63 (2.36 to 5.57)
Amphetamines	0.35 (0.10 to 0.59); low	NR	0.85 (0.12 to 1.58)	0.47 (0.27 to 0.81)
Atomoxetine	-0.11 (-0.32 to 0.09); low	-0.31 (-1.42 to 0.79); very low	0.37 (-0.31 to 1.06)	1.59 (0.82 to 3.13)
Clonidine	0.03 (-0.46 to 0.53); very low	NR	NR	1.30 (0.39 to 4.35)
Methylphenidate	0.11 (-0.13 to 0.34); low	0.18 (-0.86 to 1.22); very low	0.61 (-0.07 to 1.29)	0.65 (0.38 to 1.12)

ADHD = attention-deficit/hyperactivity disorder; CI = confidence interval; CGI-I = Clinical Global Impression–Improvement; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; GXR = guanfacine hydrochloride extended release; NMA = network meta-analysis; NR = not reported; OR = odds ratio; SMD = standardized mean difference; vs. = versus.

Notes: For SMDs, negative values favour GXR, while positive values favour comparators.

For ORs, values > 1 favour GXR and values < 1 favour comparators.

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Table 5: Summary of NMA Results for Harm Outcomes at Time Points Closest to 12 Weeks of Guanfacine Vs. Comparator

Comparator	Treatment discontinuation due to AEs, OR (95% CI); GRADE certainty	Change in body weight, SMD (95% CI)
Placebo	2.64 (1.20 to 5.81); low	0.09 (-0.42 to 0.60)
Amphetamines	1.15 (0.46 to 2.86); very low	0.80 (0.13 to 1.48)
Atomoxetine	1.75 (0.68 to 4.55); very low	0.94 (0.33 to 1.54)
Clonidine	0.58 (0.08 to 4.17); very low	-0.01 (-1.19 to 1.17)
Methylphenidate	1.83 (0.74 to 4.57); very low	0.86 (0.26 to 1.47)

AE = adverse event; CI = confidence interval; GRADE = Grading of Recommendations Assessment, Development and Evaluation; GXR = guanfacine hydrochloride extended release; NMA = network meta-analysis; OR = odds ratio; SMD = standardized mean difference; vs. = versus.

Notes: For SMDs, negative values indicate a greater decrease in weight with GXR compared with comparators while positive values indicate a smaller decrease in weight with GXR compared with comparators.

For ORs, values > 1 favour the comparators (fewer harms compared with GXR) and values < 1 favour GXR (fewer harms compared with the comparators).

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LTE Studies on Monotherapy

Description of Studies

Three LTE studies¹⁵⁻¹⁷ have been summarized to provide evidence regarding the long-term safety and efficacy of GXR in children and adolescents with ADHD ([Table 6](#)). Two^{15,16} of those studies had been

summarized in the previous CADTH reimbursement review.³ All LTE studies were 2-year single-arm open-label studies, which were conducted to further assess the long-term safety and efficacy of GXR. Patients enrolled in these LTE studies¹⁵⁻¹⁷ were previously exposed to GXR in antecedent studies. All phase III antecedent studies (i.e., SPD503-301, SPD503-304, SPD503-316, and SPD503-315) were included in the previous CADTH reimbursement review.³

Of note, 1 of the antecedent studies in the study by Sallee et al. (2009)¹⁶ was a phase II open-label, uncontrolled 9-week study to assess the safety of GXR administered adjunctively with PSTs for children and adolescents with ADHD, and whose disease had responded suboptimally to a PST. The long-term results of this subgroup (N = 54) are presented in the long-term evidence for adjunctive therapy.

The objective of all 3 LTE studies¹⁵⁻¹⁷ was to assess the long-term safety and efficacy of GXR for the treatment of children (aged 6 years to 12 years) and adolescents (aged 13 years to 17 years) with ADHD. The maximum dose of GXR in all 3 LTE studies¹⁵⁻¹⁷ was 4 mg/day. In the study by Huss et al. (2018),¹⁷ the maximum permitted dose for adolescents was 7 mg/day. Eligible patients in all 3 LTE studies¹⁵⁻¹⁷ must not have had any clinically important AEs that would preclude further exposure to GXR. There were some weight restrictions applied to eligible patients.

For the long-term safety of GXR, all 3 LTE studies¹⁵⁻¹⁷ assessed AEs, vital signs, laboratory test results, electrocardiogram (ECG) parameters, and growth (i.e., height and weight).

For efficacy outcomes, all 3 LTE studies¹⁵⁻¹⁷ measured the change from baseline in severity of ADHD core symptoms using the ADHD Rating Scale–IV (ADHD RS-IV). The ADHD RS-IV consists of 18 items, each scored from 0 (no symptoms) to 3 (severe symptoms). The total score ranges from 0 to 54, with higher scores indicating more severe symptoms. The estimated minimal important difference (MID) for a within-group reduction in symptoms ranges between a 25% to 30% reduction in total score from baseline.²⁷ The estimated between-treatment MID ranges from 5.2 points to 7.7 points.²⁸

Two LTE studies by Biederman et al. (2008)¹⁵ and Sallee et al. (2009)¹⁶ also evaluated patients' behavioural improvement using the Parents' Global Assessment (PGA) scale and the Child Health Questionnaire–Parent Form 50 (CHQ-PF50). The PGA is a 7-point scale that ranges from “very much improved” to “very much worse.” The MID for the PGA has not been estimated. The CHQ-PF50, a 50-item parent-rated questionnaire divided into 14 domains (scales), has been used to measure HRQoL (i.e., physical well-being and psychosocial well-being) in children and adolescents. Scores for individual scales are transformed to a scale from 0 to 100, with higher scores representing better physical well-being and psychosocial well-being. A 5-point within-group change has been suggested as a useful threshold for detecting clinically or socially meaningful changes.¹⁵

Two LTE studies by Sallee et al. (2009)¹⁶ and Huss et al. (2018)¹⁷ assessed clinical global functioning using the CGI-I scale. The CGI-I is a 7-point clinician's rating scale, ranging from 1 (very much improved) to 7 (very much worse). The within-group MID is estimated to be a change of 1 point on a 7-point scale.²⁹

The LTE study by Sallee et al. (2009)¹⁶ assessed a cross-section of ADHD-related symptoms and behaviours using the Conners Parent Rating Scale–Revised (CPRS-R) short form, while the LTE study

by Huss et al. (2018),¹⁷ assessed the severity of illness using the Clinical Global Impressions–Severity of Illness (CGI-S) scale. The CPRS-R is a 27-item parent-rated questionnaire containing 4 subscales (i.e., oppositional, cognitive problems, hyperactivity, ADHD index). Each item is rated from 0 to 3. Total scores range from 0 to 81, with higher scores representing more symptoms. The MID for CPRS-R has not been estimated. The CGI-S clinician’s rating is a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). The MID for a within-group change is similar to that of CGI-I.²⁹

The descriptions of the outcome measures and the estimated MID are presented in Table 10 of Appendix 4 in the Supplemental Material.

Details of concomitant medications used by patients during the study were not reported in 2 included LTE studies,^{15,17} or in the monotherapy subgroup in the study by Sallee et al. (2009).¹⁶

Table 6: Description of LTE Studies

Category	Biederman et al. (2008) ¹⁵	Sallee et al. (2009) ¹⁶	Huss et al. (2018) ¹⁷
Antecedent studies	A phase III, multicentre, double-blind, placebo-controlled, fixed-dosage escalation study (SPD503-301) ³⁰	• A phase III, multicentre, double-blind, placebo-controlled, dose-ranging, forced-dose titration study (SPD503-304)³¹ • A phase II open-label, uncontrolled study to assess the safety of coadministration of GXR with psychostimulants (clinical trial NCT00151996)	• A phase III, randomized, double-blind, multicentre, placebo-controlled, dose optimization study (SPD503-316)³² • A phase III, double-blind, placebo-controlled, randomized-withdrawal study (SPD503-315)³³
Objective	Assessment of long-term safety and efficacy of GXR	Assessment of long-term safety and efficacy of GXR	Assessment of long-term safety and efficacy of GXR
Doses of GXR	2 mg/day to 4 mg/day	1 mg/day to 4 mg/day	1 mg/day to 4 mg/day for children (aged 6 years to 12 years) and 1 mg/day to 7 mg/day for adolescents (aged 13 years to 17 years)
Duration of treatment	Up to 24 months	Up to 24 months	Up to 24 months
Inclusion criteria	• Completed treatment at least 2 weeks in antecedent study • Children (aged 6 years to 12 years) and adolescents (aged 13 years to 17 years) • No clinically important AEs	• Totally completed treatment in antecedent studies • Children (aged 6 years to 12 years) and adolescents (aged 13 years to 17 years) • No AEs that would preclude further exposure to GXR • Weight > 55 lbs in 1 antecedent study and > 65 lbs in the other	• Totally completed treatment in antecedent studies • Children (aged 6 years to 12 years) and adolescents (aged 13 years to 17 years) • Blood pressure lower than the 95th percentile for age, sex, and height

Category	Biederman et al. (2008) ¹⁵	Sallee et al. (2009) ¹⁶	Huss et al. (2018) ¹⁷
Exclusion criteria	• Uncontrolled comorbid psychiatric diagnosis (except ODD) • Weight < 25 kg • Morbid obesity, hypertension, hypotension, and cardiac problems • Tic disorder, family history of Tourette disorder	• Uncontrolled comorbid psychiatric diagnosis (except ODD) • BMI ≥ 35 • A specific cardiac condition • Hypotension or hypertension	• Any current comorbid psychiatric diagnosis (except ODD) • BMI > 95th percentile • Weight: < 25 kg for children aged 6 years to 12 years; < 34 kg for adolescents aged 13 years and older • A specific cardiac condition • Hypotension or hypertension
Safety outcomes	• AEs • Laboratory test results • Vital signs • Height and weight • ECG parameters	• AEs • Vital signs • Height and weight • Laboratory test results • ECG parameters	• TEAEs • Vital signs • ECG parameters • Growth (height and weight, BMI)
Efficacy outcomes (outcome measures)	• ADHD core symptoms (ADHD RS-IV [total score and subscale scores]) • Child's behavioural improvement (PGA scale) • Physical and psychosocial well-being (CHQ-PF50)	• ADHD core symptoms (ADHD RS-IV [total score]) • Clinical global functioning (CGI-I) • Child's behavioural improvement (PGA) • Physical and psychosocial well-being (CHQ-PF50) • ADHD-related symptoms and problem behaviours (CPRS-R short form)	• ADHD core symptoms (ADHD RS-IV [total score and subscale scores]) • Severity of illness (CGI-S) • Clinical global functioning (CGI-I)

ADHD = attention-deficit/hyperactivity disorder; ADHD RS-IV = ADHD Rating Scale–IV; AE = adverse event; BMI = body mass index; CGI-I = Clinical Global Impressions–Improvement; CGI-S = Clinical Global Impressions–Severity of Illness; CHQ-PF50 = Child Health Questionnaire–Parent Form 50; CPRS-R = Conners Parent Rating Scale–Revised; ECG = electrocardiogram; GXR = guanfacine hydrochloride extended release; LTE = long-term extension; ODD = oppositional defiant disorder; PGA = Parents' Global Assessment; TEAE = treatment emergent adverse event.

Patient Disposition

Patient dispositions in included LTE studies¹⁵⁻¹⁷ are presented in [Table 7](#).

In all 3 studies,¹⁵⁻¹⁷ nearly 100% of enrolled patients received at least 1 dose of GXR and were included in the safety population. Most patients in the studies by Biederman et al. (2008)¹⁵ and Sallee et al. (2009)¹⁶ terminated the study early; approximately one-third of patients terminated the study early in the study by Huss et al. (2018).¹⁷ Reasons for early termination included withdrawal by participants, loss of follow-up, protocol violation, AEs, and lack of efficacy.

Table 7: Patient Disposition in LTE Studies

Category	Biederman et al. (2008) ¹⁵	Sallee et al. (2009) ¹⁶ (monotherapy)	Huss et al. (2018) ¹⁷
Total enrolled, n	240	208	215
Received at least 1 dose of guanfacine (safety population), n (%)	240 (100)	204 (98)	214 (99.5)
Completed study, n (%)	42 (17.5)	38 (18.3)	133 (61.9)
Early termination, n (%)	198 (82.5)	171 (82.2)	81 (37.7)
Withdrawal by participant	67 (33.8)	58 (27.9)	37 (45.7)
Loss of follow-up	36 (18.2)	28 (13.5)	5 (6.2)
Protocol violation	11 (5.6)	NR	1 (1.2)
Adverse event	52 (26.3)	28 (13.5)	7 (8.6)
Lack of efficacy	25 (12.6)	26 (12.5)	19 (23.5)
Other	7 (3.5)	31 (14.9)	12 (14.8)
Full analysis set,^a n (%)	228 (95)	204 (98)	209 (97)

LTE = long-term extension; NR = not reported.

^aThe full analysis set included all patients with an efficacy assessment from baseline in the antecedent study and at least 1 primary efficacy measurement recorded after the baseline of the current study.

Baseline Characteristics

Baseline characteristics of patients in the LTE studies¹⁵⁻¹⁷ are presented in [Table 8](#). Across studies, most patients (range, 61% to 78%) were aged 6 years to 12 years. There were more males (range, 72% to 77%) than females (range, 23% to 28%). Most patients (range, 73% to 83%) had the combined ADHD subtype. The mean age since diagnosis ranged from 2.2 years to 3.1 years across studies.

Table 8: Baseline Characteristics of Patients in LTE Studies

Characteristic	Biederman et al. (2008) ¹⁵ (N = 240)	Sallee et al. (2009) ¹⁶ (N = 206) (monotherapy)	Huss et al. (2018) ¹⁷ (N = 214)
Age (years)			
Mean (SD)	10.5 (2.6)	10.6 (2.7)	11.7 (2.8)
6 to 12, n (%)	188 (78.3)	151 (73.3)	131 (61.2)
13 to 17, n (%)	52 (21.7)	55 (26.7)	83 (38.8)
Sex, n (%)			
Female	56 (23.3)	58 (28.2)	56 (26.2)
Male	184 (76.7)	148 (71.8)	158 (73.8)
Weight (lb)			
Mean (SD)	96.8 (36.3)	95.4 (34.0)	100.2 (31.9)
Height (in)			

Characteristic	Biederman et al. (2008) ¹⁵ (N = 240)	Sallee et al. (2009) ¹⁶ (N = 206) (monotherapy)	Huss et al. (2018) ¹⁷ (N = 214)
Mean (SD)	57.1 (7.9)	57.1 (5.9)	59.6 (6.2)
ADHD subtype, n (%)			
Inattentive	63 (26.3)	51 (24.8)	20 (9.3)
Hyperactive	3 (1.3)	5 (2.4)	16 (7.5)
Combined	174 (72.5)	150 (72.8)	178 (83.2)
Years since ADHD diagnosis			
Mean (SD)	2.3 (2.9)	2.2 (2.8)	3.1 (2.9)
ADHD RS-IV total score at baseline (FAS)^a			
Mean (SD)	37.4 (9.4)	40.6 (8.5)	36.7 (10.4)

ADHD = attention-deficit/hyperactivity disorder; ADHD RS-IV = ADHD Rating Scale–IV; FAS = full analysis set; GXR = guanfacine hydrochloride extended release; LTE = long-term extension; SD = standard deviation.

^aFAS was defined as all enrolled patients who received at least 1 dose of GXR.

Critical Appraisal

Internal Validity

Major limitations of these LTE studies¹⁵⁻¹⁷ included considerations related study design (e.g., open label, no control group) and conduct (e.g., amounts and handling of missing data), limiting their usefulness for informing the long-term safety or efficacy of GXR. However, long-term placebo-controlled studies are often not possible from an ethical perspective.

The lack of a comparator precludes causal inferences, as it is not possible to infer to which degree observed effects can be attributed to GXR as opposed to placebo effects and/or the natural history of the disease. In all studies, there was risk of bias in the measurement of efficacy outcomes and subjective harms due to the open-label design such that participants, investigators, and outcome assessors were aware of the treatment. The potential bias would likely favour GXR for efficacy outcomes and may have resulted in the overreporting of known harms. The risk of bias may be less for objective harms, such as changes in vital signs.

Across the 3 LTE studies,¹⁵⁻¹⁷ 38% to 83% of patients withdrew early from the studies, with common reasons including AEs, lack of efficacy, and withdrawal of consent. Missing outcomes data were handled using the LOCF method in all studies. This method assumes that the result for the outcome remains constant from the time of the last assessment, forward, which is unlikely to reflect the true trajectory of the outcome. As such, for all outcomes measured in the 3 LTE studies there is high risk of bias due to missing outcomes data.

All 3 LTE studies¹⁵⁻¹⁷ reported the availability of predetermined protocols; however, only the study by Huss et al. (2018)¹⁷ provided adequate information (ClinicalTrials.gov identifier: NCT01500694) to access the protocol. As such, the potential for risk of bias in the selection of the reported results (whereby results may have been selected for reporting based on their magnitude, direction, and/or statistical significance) is uncertain for the studies by Biederman et al. (2008),¹⁵ and Sallee et al. (2009).¹⁶ Results were reported

per the protocol in the study by Huss et al. (2018),¹⁷ so there is a low risk of bias in the selection of the reported results.

Statistical analyses in the assessment of ADHD RS-IV scores and its subscale scores were performed without adjusting for multiplicity. As such, there is an increased risk of false-positive results (type I errors).

Multiple outcome measures used to assess the efficacy of GXR included the ADHD RS-IV, CGI-I, CGI-S, PGA, CHQ-PF50, and CPRS-R. The unavailability of the MIDs of some measures (i.e., CPRS-R and PGA) and the measurement properties (i.e., validity, reliability, and responsiveness to change) of these scales among children and adolescents with ADHD limited the estimation of the clinical relevance of the observed effects.

External Validity

Patients were selected according to various inclusion and exclusion criteria that may have resulted a population that was not truly reflective of the real-world population in clinical practice. Patients were excluded if they had morbid obesity or weighed less than 25 kg based on indicated criteria or if they had comorbid conditions such as uncontrolled psychiatric diagnosis (except ODD), hypertension, hypotension, or specific cardiac conditions. It was unclear whether the results can be generalized to these patients and whether these patients can be treated with GXR in clinical practice.

Only patients who participated in the antecedent RCTs without experiencing any clinically important AEs that would preclude further exposure to GXR were eligible for enrolment in the LTE studies.¹⁵⁻¹⁷ As such, the included patients are those who were able to tolerate GXR and stayed on treatment long enough to participate in the LTE studies. The studies by Biederman et al. (2008)¹⁵ and by Sallee et al. (2009)¹⁶ took place entirely at sites in the US, whereas the study by Huss et al. (2018)¹⁷ took place entirely at sites in Europe. Due to potential differences in the standard of care at the study sites, it is unclear whether the results are generalizable to Canada. Further, the studies took place between 2003 and 2015 (i.e., 10 years to 22 years before the time of this review). Given that standards of care may have changed during this time, there is uncertainty as to whether the results could be generalized to present-day clinical practice. Given the single-arm design, the LTE studies¹⁵⁻¹⁷ do not allow for any conclusions to be drawn regarding the long-term efficacy and harms of GXR relative to other active comparators used in clinical practice.

Results

Efficacy

Details of efficacy results of the LTE studies¹⁵⁻¹⁷ are presented in [Table 9](#). Due to the single-arm design of the LTE studies, the extent to which the observed effects can be attributed to GXR is unknown.

ADHD Core Symptoms

- There was a decrease in mean ADHD RS-IV total scores at 24 months in all 3 studies.¹⁵⁻¹⁷ The studies by Biederman et al. (2008)¹⁵ and Huss et al. (2018)¹⁷ also reported mean decreases in hyperactivity/impulsivity and inattentiveness domains. Decreases in mean total scores (approximately

50% decrease) surpassed the estimated MID (25% to 30% reduction in total score) in all 3 studies.¹⁵⁻¹⁷

- In the study by Sallee et al. (2009),¹⁶ there was a decrease in mean CPRS-R score. In the absence of an estimated MID, the clinical meaningfulness of the decrease is uncertain.

Global Improvement

- In the studies by Biederman et al. (2008)¹⁵ and Sallee et al. (2009),¹⁶ more than half of patients were classified as “much” or “very much” improved on the PGA scale.
- In the studies by Sallee et al. (2009)¹⁶ and Huss et al. (2018),¹⁷ approximately half of patients were classified as “much” or “very much” improved on the CGI-I scale.

Health-Related Quality of Life

- In the studies by Biederman et al. (2008)¹⁵ and Sallee et al. (2009),¹⁶ the authors reported improved psychosocial summary scores on the CHQ-PF50. Only the study by Sallee et al. (2009),¹⁶ provided sufficient information to inform the clinical meaningfulness of the effect, which exceeded the literature-based MID estimate (5 points). Insufficient data were reported for the physical summary scores to inform a conclusion.

Table 9: Efficacy Outcomes in LTE Studies

Efficacy measure	Biederman et al. (2008) ¹⁵ (N = 227)	Sallee et al. (2009) ¹⁶ (N = 206) (monotherapy)	Huss et al. (2018) ¹⁷ (N = 214)
Mean change in ADHD RS-IV scores, ^a from baseline to end point ^b	Total score: -18.1 (SD = 13.0); P < 0.001	Total score: -21.2 (SD = 13.9); P < 0.001	Total score: -19.8 (SEM = 0.84); P < 0.0001
	Hyperactivity/impulsivity: -8.5 (SD = 6.8); P < 0.001	NR	Hyperactivity/impulsivity: -10.1 (SEM = 0.44); P < 0.0001
	Inattentiveness: -9.5 (SD = 7.6); P < 0.001	NR	Inattentiveness: -9.8 (SEM = 0.47); P < 0.0001
Proportions of participants whose PGA scores ^c at end point were rated “much” or “very much” improved from baseline ^b	Total: 58.6% (95 of 162) • Aged 6 years to 12 years: 57.3% (71 of 124) • Aged ≥ 13 years: 63.2% (24 of 38)	Total: 59.7% (126 of 211) ^d	NR
Mean change in CHQ-PF50 scores, ^e from baseline to end point ^b	• Physical summary scores: No statistically significant change (data not reported) • Psychosocial summary scores: improved (data NR)	• Physical summary scores: No statistically significant change (data not reported) ^d • Psychosocial summary scores: improved (mean difference = 9.2 [SD = 11.9]; P < 0.001)	NR

Efficacy measure	Biederman et al. (2008) ¹⁵ (N = 227)	Sallee et al. (2009) ¹⁶ (N = 206) (monotherapy)	Huss et al. (2018) ¹⁷ (N = 214)
Proportions of participants whose CGI-I scale scores ^f at end point were rated “very much” or “much” improved from baseline ^b	NR	Total: 58.1% (123 of 211) ^d • Very much improved: 29.3% (62 of 211) • Much improved: 28.8% (61 of 211)	Total: 46.4% (96 of 207)
Mean change in CPRS-R scores, ^g from baseline to end point ^b	NR	-18.2; ^d P < 0.001	NR

ADHD = attention-deficit/hyperactivity disorder; ADHD RS-IV = ADHD Rating Scale–IV; CHQ-PF50 = Child Health Questionnaire–Parent Form 50; CGI-I = Clinical Global Impressions–Improvement; CPRS-R = Conners Parent Rating Scale–Revised; GXR = guanfacine hydrochloride extended release; LTE = long-term extension; NR = not reported; PGA = Parent Global Assessment; SD = standard deviation; SEM = standard error of the mean.

Notes: In all 3 LTE studies, a sample size calculation was not necessary because of a single-arm open-label study design with no a priori hypothesis.

Efficacy analyses were performed for the intention-to-treat population, defined as all patients with an efficacy assessment from baseline in the antecedent study and at least 1 primary efficacy measurement recorded after the baseline of the current study.

Safety analyses were based on reports obtained in the safety population, defined as all patients who received at least 1 dose of GXR. Missing data were handled using the last observation carried forward.

^aADHD RS-IV is an 18-item rating scale, the first 9 items assess inattentive symptoms and the last 9 items assess hyperactive-impulsive symptoms. Scoring is based on a 4-point Likert-type severity scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe.

^bThe time from baseline to study end point was 24 months.

^cPGA scores capture parents' impressions of changes in their child's behaviour from baseline on a 7-point scale that ranges from “very much improved” to “very much worse” (1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse).

^dMeasured using the overall treatment group (those receiving monotherapy or adjunctive therapy).

^eCHQ-PF50 measures physical and psychosocial well-being in pediatric subjects. It has 50 items divided into 14 domains. Scaling of items is done by Likert-type scale with higher scores indicating better or more positive health states. The questionnaire yields 2 main summary scores: Physical Well-Being and Psychosocial Well-Being. Final scores range from 0 to 100, with higher scores indicating better physical and psychosocial well-being.

^fIn the CGI-I scale, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse.

^gThe CPRS-R was completed by parents and contained 4 subscales (i.e., oppositional, cognitive problems, hyperactivity, ADHD index). The CPRS-R evaluations were designed to permit an analysis of the duration of effect of GXR throughout the day by assessing scores at 12, 14, and 24 hours postdose. Parents answered 27 questions regarding their child's behaviour immediately preceding the assessment times. Responses to each question are scored from 0 to 3 (0 = not true at all, 1 = just a little true, 2 = pretty much true, 3 = very much true). Lower scores represent fewer symptoms.

Harms

Details of harms results of the LTE studies¹⁵⁻¹⁷ are presented in Table 22 of Appendix 6 in the Supplemental Material.

- More than 80% of patients in each of the 3 LTE studies¹⁵⁻¹⁷ had at least 1 treatment emergent AE (TEAE).
- The proportions of patients with 1 or more TEAE leading to treatment discontinuation were 21.7%,¹⁵ 13.6%,¹⁶ and 3.3%¹⁷ in the 3 LTE studies. In the study by Biederman et al. (2008),¹⁵ TEAEs leading to treatment discontinuation were somnolence (9 patients, 3.8%), weight increase (7 patients, 2.9%), fatigue (5 patients, 2.1%), abnormal ECG results (2 patients, 0.8%), hypotension (4 patients, 1.7%), and syncope (1 patient, 0.4%). The study by Huss et al. (2018)¹⁷ reported that TEAEs leading to early treatment discontinuation in 7 patients (3.3%) included somnolence, aggression, first-degree atrioventricular block, dizziness, cannabis use, and increase in weight. The study by Sallee et al. (2009)¹⁶ did not report the types of common TEAEs leading to treatment discontinuation.

- The proportion of patients with 1 or more serious TEAEs in the LTE studies¹⁵⁻¹⁷ ranged between 3.8% and 6.2%. The study by Biederman et al. (2008)¹⁵ found that 9 patients (3.8%) reported 11 serious TEAEs, including 1 event of orthostatic hypotension and 2 events of syncope (other events were not reported). The study by Sallee et al. (2009)¹⁶ reported that 16 patients (6.2%) experienced 22 serious TEAEs, including syncope (5 events) and head injury, loss of consciousness, and suicidal ideation (2 events each). In the study by Huss et al. (2018),¹⁷ 10 patients (4.7%) had a total of 13 serious TEAEs, including aggression, appendicitis, concussion, gastroenteritis, limb fractures, postprocedural hemorrhage, stomatitis, and testicular torsion.
- TEAEs occurred in $\geq 5\%$ of patients in the LTE studies¹⁵⁻¹⁷ and included somnolence, headache, sedation, dizziness, fatigue, pyrexia, lethargy, upper abdominal pain, vomiting, nausea, diarrhea, upper respiratory tract infection, weight increase, irritability, insomnia, cough, pharyngitis, nasopharyngitis, nasal congestion, rhinitis, and oropharyngeal pain.
- There were no deaths reported in the 3 included LTE studies.¹⁵⁻¹⁷
- In the study by Sallee et al. (2009),¹⁶ 28 patients (10.8%) had new, abnormal ECG results at end point, but only 2 were considered clinically significant by the investigators.
- There were changes in vital signs (e.g., heart rate, systolic blood pressure, diastolic blood pressure), weight, and height reported in the 3 LTE studies;¹⁵⁻¹⁷ however, their clinical significance was unclear.

Discussion

Efficacy

From the NMA

Overall, the evidence from the NMA suggests that GXR may result in a decrease in ADHD core symptoms and an increase in clinical global functioning as rated by clinicians compared with placebo. These findings were in line with the previous CADTH reimbursement review.³ Compared with amphetamines, GXR may result in an increase (i.e., less improvement) in ADHD core symptoms and a decrease (i.e., less improvement) in clinical global functioning as rated by clinicians. In other words, GXR may be less effective than amphetamines and more effective than placebo. Compared with atomoxetine or methylphenidate, GXR may result in little to no difference in ADHD core symptoms; the evidence for the effect of GXR compared with clonidine for this outcome is very uncertain. The effect of GXR on clinical global functioning compared with atomoxetine, methylphenidate, or clonidine is very uncertain. GXR may result in an increase in treatment discontinuations due to AEs compared with placebo; the evidence for the effect of GXR compared with amphetamines, atomoxetine, clonidine, or methylphenidate for this outcome is very uncertain. HRQoL and AEs were not assessed in the NMA. As such, the effect of GXR on HRQoL compared with other active comparators used in clinical practice is unknown.

Although the included SR¹³ was generally methodologically robust, it has limitations that prevent us from drawing strong conclusions from the analyses. First, when interpreting the results from the NMA, it is important to consider the potential for bias due to missing evidence. The date the literature was last searched was April 7, 2017, and it is uncertain how many relevant studies may have been published since this date.

Whether analyses including all evidence published to date would have yielded different results is unknown. There was also uncertainty as to whether the transitivity assumption underlying the NMA was upheld, as there were differences across trials in patient characteristics and study design. As no studies directly comparing GXR with other active comparators were identified, all results relevant to this review rely on indirect evidence. The certainty of evidence for most comparisons and outcomes relevant to this review was low or very low, commonly due to risk of bias in the included studies and imprecision in the effect estimates. As such, there is substantial uncertainty in the results and the true effects may differ to an important degree from the estimated effects. As the NMA authors pooled data from continuous outcome measures using SMDs and only relative effect estimates were reported for binary end points, it is not possible to confidently make conclusions on the clinical importance of the estimated effects. Further, the NMA pooled results closest to 12 weeks, and insufficient data were available from the primary studies for longer follow-up times. As such, the long-term efficacy and harms of GXR compared with other drugs used in clinical practice are not known.

Despite the aforementioned limitations of the NMA and the very low certainty of evidence due to risk of bias, indirectness, and/or imprecision, GXR monotherapy can be potentially used for treatment of ADHD in children and adolescents.

From the LTE Studies

Children and adolescents treated with GXR for 24 months in 3 LTE studies showed improvements in ADHD core symptoms. Important limitations of the LTE studies included the single-arm design (which precludes attributing the observed effects to GXR), risk of bias due to missing outcome data, and risk of bias in the measurement of the outcomes due to the open-label design. As such, these studies were severely limited in their ability to inform the long-term effects of GXR, and they cannot inform the effects of GXR relative to any active comparator used in clinical practice. These LTE studies have potentially limited external validity in certain patient groups, such as those with a diagnosis of minimal brain dysfunction, with uncontrolled comorbid disorders, with specific cardiac conditions, with disease that is stable or resistant to previous ADHD treatment, who weigh less than 25 kg or have morbid obesity, and with unstable vital signs.

Harms

From the ITC Study

GXR was less well tolerated than placebo, while the evidence for comparisons in tolerability between GXR and active comparators (i.e., amphetamines, atomoxetine, clonidine, or methylphenidate) was very uncertain. The presence of 2 studies using GIR among the 11 studies of guanfacine included in the SR¹⁴ may affect the tolerability outcome, as the clinical experts commented that GIR may cause drowsiness more often than GXR, leading to lower adherence. However, no evidence was provided to support these assertions. GXR may result in smaller decreases in weight compared with some active comparators (i.e., amphetamines, atomoxetine, or methylphenidate) and a decrease in blood pressure compared with placebo. The clinical experts discussed that weight change associated with GXR may not be a harm, but rather a result of stabilization in health overall. Harms outcomes such as AEs, serious AEs, and notable harms were not considered in the SR.¹⁴ As such, no conclusion can be drawn about the harms of GXR relative to those of other active treatments from this NMA.¹⁴

From LTE Studies

Across the 3 LTE studies more than 80% of patients experienced 1 or more AE. Serious AEs were infrequent (occurring in $\leq 6\%$ of participants) in all studies. Three to 22% of patients discontinued the study treatment due to a TEAE across studies. Somnolence, headache, sedation, dizziness, fatigue, pyrexia, lethargy, upper abdominal pain, vomiting, nausea, diarrhea, upper respiratory tract infection, weight increase, irritability, insomnia, cough, pharyngitis, nasopharyngitis, nasal congestion, rhinitis, and oropharyngeal pain were the common reported TEAEs. There were no deaths and no major changes in vital signs, cardiovascular events, weight, or height. Although changes in vital signs, blood pressure, and cardiovascular events were not commonly observed in long-term treatment with GXR, these potential harms should be closely monitored as per suggestion of the clinical experts. Indeed, there were patients across the studies who withdrew from treatment due to somnolence, weight increase, fatigue, abnormal ECG results, hypotension, or syncope.

Conclusion

Evidence from an SR with NMA¹⁴ suggests that GXR used as monotherapy for the treatment of children and adolescents with ADHD likely results in greater improvements in ADHD core symptoms as assessed by clinicians compared with placebo. GXR may result in less improvement in ADHD core symptoms compared with amphetamines, with little to no difference compared with atomoxetine or methylphenidate. The effect of GXR compared with clonidine on ADHD core symptoms is very uncertain. For clinical global improvement scores rated by clinicians, GXR may result in an increase (i.e., more improvement) compared with placebo, but a decrease (i.e., less improvement) compared with amphetamines. The effect of GXR on clinical global improvement relative to other treatment options, such as atomoxetine, clonidine, or methylphenidate, is very uncertain. GXR may result in an increase in study withdrawals due to AEs compared with placebo; however, the effect of GXR on study withdrawals compared with amphetamines, atomoxetine, clonidine, or methylphenidate is very uncertain. Results from the NMA suggested that GXR may result in smaller decreases in weight compared with amphetamines, atomoxetine, or methylphenidate. The effect of GXR compared with placebo and clonidine on weight is very uncertain. In the absence of evidence, the effects of GXR compared with placebo or active comparators on AEs, illness severity, and HRQoL are not known.

Important limitations of the NMA included the potential for intransitivity, which would bias the treatment effects, contribute to study-level risks of bias, and lead to imprecision in the effect estimates. As such, evidence for all comparisons to active treatments used in clinical practice were of low or very low certainty. The NMA is also at risk of being out of date, resulting in risk of bias due to missing evidence in the synthesis. The magnitude and direction of the potential bias cannot be predicted.

Evidence from 3 LTE studies¹⁵⁻¹⁷ suggests that patients exposed to GXR for 24 months may experience clinically important decreases in ADHD core symptoms, decreases in the severity of illness, and clinically important improvements in psychosocial aspects of HRQoL. Somnolence, headache, fatigue, and sedation were the most common TEAEs. Important limitations of the LTE studies included the single-arm design, which precludes attributing the observed effects to GXR; risk of bias due to missing outcome data; risk of bias in the measurement of the outcomes due to the open-label design; and potentially limited external

validity. As such, these studies were limited in their ability to inform the long-term effects of GXR and cannot inform the effects of GXR relative to any active comparator used in clinical practice.

The findings in this review did not address the question of whether GXR monotherapy should be used to treat patients who could not receive PSTs for various reasons including intolerance, lack of clinical response, or due to personal choice, as per suggestion by the clinical experts.

Economic Review of Monotherapy

Methods

The economic review consisted of a cost comparison for GXR as monotherapy for the treatment of ADHD in children and adolescents aged 6 years to 17 years compared with long-acting PSTs (methylphenidate controlled release [CR], methylphenidate extended release [XR], amphetamine XR, or lisdexamfetamine) or nonstimulants (atomoxetine or clonidine).

Based on public list prices, GXR as monotherapy is expected to have a per patient cost of \$927 per year for children (aged 6 years to 12 years of age) and \$1,732 for adolescents (aged 13 years to 17 years) (refer to Appendix 9 in the Supplemental Material). Comparators are expected to have per patient costs per year between \$44 (clonidine) and \$856 (methylphenidate CR) for children, and between \$89 (clonidine) and \$856 (methylphenidate CR) for adolescents. Therefore, the incremental cost of GXR per patient per year varies between \$71 (versus methylphenidate CR) and \$883 (versus clonidine) for children, and between \$876 (versus methylphenidate CR) and \$1,643 (versus clonidine) for adolescents. As such, the reimbursement of GXR as monotherapy for the treatment of ADHD in children and adolescents aged 6 years to 17 years is expected to increase overall drug acquisition costs. Additional items for consideration are provided in the following bullets:

- According to the clinical review, evidence from included studies suggests that the comparative effectiveness of GXR as monotherapy varies among its comparators, with an increase in ADHD core symptoms and a decrease (i.e., less improvement) in clinical global functioning compared to amphetamines; little to no difference in ADHD core symptoms and an uncertainty in clinical global functioning compared to atomoxetine or methylphenidate; and uncertain benefit compared to clonidine.
- As of September 2025, Health Canada had reviewed 4 generic versions of GXR (2 are marketed and 2 are approved), and 2 are currently under review at Health Canada.
- According to the clinical experts consulted for this review, GXR as monotherapy is expected to have similar treatment-related health care resource use compared with other treatments available in Canada.
- GXR as monotherapy was previously reviewed by CDA-AMC in 2015 for the treatment of ADHD in children aged 6 years to 12 years, and it received a “do not reimburse” recommendation. As of

September 2025, there are no other drugs under review by CDA-AMC for children and adolescents with ADHD.

- No cost-effectiveness studies for GXR as monotherapy conducted in Canada were identified based on a literature search conducted on April 28, 2025, with alerts maintained until the Formulary Management Expert Committee (FMEC) meeting on November 20, 2025.

Conclusion

The reimbursement of GXR as monotherapy for the treatment of ADHD in children and adolescents aged 6 years to 17 years is expected to increase overall drug acquisition costs. Based on the clinical review conclusions, compared to amphetamines GXR may result in an increase in ADHD core symptoms and a decrease (i.e., less improvement) in clinical global improvement scores; compared to atomoxetine or methylphenidate there is little to no difference in ADHD core symptoms and uncertain benefit in clinical global improvement scores; compared to clonidine the benefits in ADHD core symptoms and clinical global improvement scores are uncertain.

Given that GXR as monotherapy is associated with increased drug acquisition costs and uncertain clinical benefit, reimbursement of GXR as monotherapy will add costs to the public health care system with uncertain benefit.

Clinical Review of Adjunctive Therapy

Clinical Evidence

From the search for primary studies, 2 RCTs with 4 reports¹⁸⁻²¹ on adjunctive therapy of GXR to PSTs were identified and included in the review. We also included evidence from an LTE study.¹⁶

Evidence From RCTs on Adjunctive Therapy

Description of Studies

Study Characteristics

In addition to the pivotal study by Willens et al. (2012)¹⁹ that was included in the previous CADTH reimbursement review,³ a double-blind placebo-controlled crossover trial by van Stralen (2020)¹⁸ was identified and included in the current review. Two additional reports of the study by Willens et al. (2012),¹⁹ conducted by Cutler et al. (2014)²⁰ and Wilens et al. (2017),²¹ were also identified and included in this review. These reported post hoc analysis and analysis of secondary end points, respectively, using the data of the pivotal study.¹⁹

Characteristics and eligibility criteria of the included studies¹⁸⁻²¹ are summarized in [Table 10](#). Additional eligibility criteria of the included studies by van Stralen (2020)¹⁸ and Willens et al. (2012)¹⁹ are presented in Table 23 of Appendix 7 in the Supplemental Material.

The study by van Stralen (2020)¹⁸ was a single-centre, randomized, double-blind, 2-period crossover study that evaluated GXR in children (aged 6 years to 12 years) with ADHD. Patients continued to take their PSTs and were randomly assigned at baseline to receive GXR or placebo. The primary efficacy outcome measure was the Behavior Rating Inventory of Executive Function–Preschool Version (BRIEF-P), a 90-item questionnaire completed by parents. Secondary efficacy outcome measures included ADHD RS-IV, CGI-S, and CGI-I scores. Safety measures included AEs, vital signs, ECGs, and laboratory test evaluations.

The study by Wilens et al. (2012)¹⁹ was a multicentre, 9-week, double-blind, placebo-controlled, dose optimization study. The study population consisted of children and adolescents (aged 6 years to 17 years) with ADHD whose disease had responded suboptimally to a PST alone. Patients continued their stable dose of PST given in the morning and were randomized to receive GXR in the morning (GXR AM), GXR in the evening (GXR PM), or placebo. The primary efficacy end point was the change in severity of ADHD core symptoms assessed using the 18-item ADHD RS-IV. Secondary efficacy end points included changes in CGI-S and CGI-I scores. Safety measures included AEs, vital signs, ECGs, and laboratory test evaluations.

Cutler et al. (2014)²⁰ conducted post hoc analyses using data from the study by Wilens et al. (2012).¹⁹ The authors assessed whether GXR adjunctive to a PST resulted in greater response and remission rates than placebo plus PST. Response was defined as at least a 40% to 50% reduction in ADHD RS-IV total scores. Symptomatic remission was defined as an ADHD RS-IV total score of at most 18 points. Syndromal remission was defined as participants having a score of at most 2 (borderline ill or normal) on the CGI-S scale in addition to achieving symptomatic remission.

Wilens et al. (2017)²¹ described secondary assessments using data from the study by Wilens et al. (2012).¹⁹ The authors examined whether GXR adjunctive to a PST resulted in significant benefit over placebo plus PST on the Conners Global Index–Parent (CGI-P). CGI-P scores were measured in the morning (before leaving for school) and evening (before bedtime). The Before School Functioning Questionnaire (BSFQ) was evaluated following the use of GXR or placebo as adjunctive treatment to a PST for ADHD.

The summary of those outcome measures and their MIDs (wherever available) are presented in Table 10 of Appendix 4 in the Supplemental Material.

Table 10: Characteristics of Included Randomized Controlled Trials for GXR as Adjunctive Therapy

Study name, design, and sample size	Key inclusion criteria	Key exclusion criteria	Intervention and comparator	Relevant outcome measures
Van Stralen (2020) ¹⁸ Single-centre (Ottawa, Canada), double-blind placebo-controlled crossover trial N = 50	- Children (aged 6 years to 12 years) with a primary diagnosis of ADHD (assessed using the ADHD RS-IV) - Treated with a stable stimulant	- Comorbid psychiatric diagnosis (except oppositional defiant disorder) - Clinically significant medical illness - Known personal history or presence	GXR vs. placebo - Sequence 1: GXR followed by placebo - Sequence 2: Placebo followed by GXR GXR: started at 1 mg/day and increased	Primary end point: Expression of executive function (BRIEF-P)^a completed by a parent or legally authorized representative Secondary end points:

Study name, design, and sample size	Key inclusion criteria	Key exclusion criteria	Intervention and comparator	Relevant outcome measures
	(methylphenidate or amphetamine) regimen and presented with suboptimal executive function (a T score ≥ 65 on the BRIEF-P) • Had a stable dose of stimulant for a period of at least 30 days before enrolment	of structural cardiac abnormalities • Cardiovascular or cerebrovascular disease • Serious heart rhythm abnormalities, syncope, tachycardia, or cardiac conduction problem • Known renal or hepatic insufficiency	weekly in 1 mg/day increments to a maximum of 4 mg/day Treatment duration: 12 weeks (4 weeks of optimization, 8 weeks of maintenance) Tapered off GXR or placebo over 11 days at the end of each phase with a further 10-day washout	• ADHD RS-IV ^b • CGI-S ^c • CGI-I ^d • AEs • Vital signs, findings from physical examinations, clinical laboratory evaluations, and ECGs
Wilens et al. (2012) ¹⁹ (post hoc analyses and analyses of secondary outcomes: Cutler et al. [2014] ²⁰ and Wilens et al. [2017] ²¹) Multicentre (59 sites in the US), double-blind, placebo-controlled, parallel, 1:1:1 ratio, dose optimization trial N = 461	• Children and adolescents (6 to 17 years) with a primary diagnosis of ADHD (assessed using ADHD RS-IV and K-SADS-PL) • With a suboptimal response to an extended-release oral preparation of methylphenidate or amphetamine • Had at least 4 weeks of a stable dose of treatment with an extended-release PST with improvement but continued mild to moderate symptoms of ADHD (ADHD RS-IV total score of ≥ 24 and CGI-S ≥ 3)	• Any current, controlled or uncontrolled comorbid psychiatric diagnosis (except oppositional defiant disorder), including any severe comorbid Axis II disorders or severe Axis I disorders	• GXR AM + PST (N = 150) • GXR PM + PST (N = 152) • Placebo plus PST (N = 153) Treatment duration: 9 weeks (5 weeks of optimization, 3 weeks of maintenance, and 1 week of tapering) PSTs: amphetamine, lisdexamfetamine, methylphenidate, dexamethylphenidate, or FDA-approved generic equivalents	Primary end point: • ADHD RS-IV, ^b clinicians' ratings (mean change) Secondary end points: • CGI-S ^c • CGI-I ^d • CGI-P ^g • BSFQ ^h • AEs • Vital signs, findings from physical examinations, clinical laboratory test evaluations, and ECG Post hoc analyses: • ADHD RS-IV, ^a clinicians' ratings (response, ^e remission ^f)

ADHD = attention-deficit/hyperactivity disorder; ADHD RS-IV = ADHD Rating Scale–IV; AE = adverse event; BRIEF-P = Behavioural Rating Inventory of Executive Function–Preschool Version; BSFQ = Before School Functioning Questionnaire; CGI-I = Clinical Global Impression–Improvement; CGI-P = Conners Global Index–Parent; CGI-S = Clinical Global Impression–Severity of Illness; ECG = electrocardiogram; GXR = guanfacine hydrochloride extended release; GXR AM = guanfacine hydrochloride extended release administered in the morning; GXR PM = guanfacine hydrochloride extended release administered in the evening; K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia–Present and Lifetime; PST = psychostimulant; vs. = versus.

^aA 90-item questionnaire designed to measure real-world expression of executive function. The overall score on BRIEF-P is called Global Executive Composite. T scores ≥ 65 indicate clinically significant levels of difficulties.

^bADHD RS-IV is an 18-item rating scale. The first 9 items assess inattentive symptoms and the last 9 items assess hyperactive-impulsive symptoms. Scoring is based on a 4-point Likert-type severity scale: 0 = none, 1 = mild, 2 = moderate, and 3 = severe.

^cA 7-point scale ranging from 1 (not at all ill) to 7 (among the most extremely ill patients).

^dA 7-point scale ranging from 1 (very much improved) to 7 (very much worse).

^eAt least a 40% to 50% reduction in ADHD RS-IV score.

^fADHD RS-IV total score ≤ 18 .

^aA short, 10-item measure used to assess the overall psychopathology of children and adolescents, particularly those with ADHD or other behavioural challenges, from a parent's perspective. T scores < 60 indicate no significant concern; T scores between 60 and 69 indicate possible emotional, behavioural, or academic problems, potentially related to ADHD; T scores ≥ 70 indicate the possibility of severe ADHD symptoms or other substantial emotional, behavioural, or academic problems.

^bA 20-item parent-rated questionnaire used to assess ADHD symptomatology and functioning on a severity scale of 0 to 3 (0 = none, 1 = mild, 2 = moderate, and 3 = severe), focusing primarily on early morning, before school activities. There is also a 14-item self-reported section that is split into 2 subscales (7 items each), Feelings and Behaviours, and assesses how the child felt, their relationship with parents and siblings, their success with morning activities or problems, and whether the child was proud of themselves over the past week during the hours of 6:00 a.m. through 9:00 a.m. The self-report question scores range from 0 = no to 2 = a lot.

Sources: Van Stralen (2020)¹⁸ and Wilens et al. (2012).¹⁹

Statistical Testing and Analysis Populations

The study by van Stralen (2020)¹⁸ required a total of 40 patients to achieve approximately 80% power at a 2-sided 0.05 significance level if the true difference between treatments was 6.5 units for the primary end point, assuming a standard deviation (SD) of 10. The authors estimated that a minimum of 55 patients were required to ensure 40 completed the study, with an assumption of a 10% screen failure rate and a 20% discontinuation rate. Analyses were undertaken via analysis of variance (ANOVA) with treatment, period, and sequence as the fixed effects and patients nested within sequence as a random effect. All randomized patients who received at least 1 dose of study medication were included in the safety population. Similarly, all randomized patients who received at least 1 dose of study medication and completed at least 1 nonbaseline BRIEF-P questionnaire during either periods 1 or 2 were included in the intention-to-treat population.

The study by Wilens et al. (2012)¹⁹ targeted a total of 441 patients, with approximately 399 needed to complete the study (133 per group) to achieve approximately 90% power at a 2-sided 0.05 significance level to detect an effect size of 0.4 for the primary end point, assuming an SD of 10. The efficacy and safety analyses were performed using the full analysis set and safety population, respectively. The full analysis set consisted of patients who received at least 1 dose of study medication and completed at least 1 nonbaseline primary outcome assessment. Patients in the safety population were those who received at least 1 dose of study medication. The primary efficacy analysis was performed on the change from baseline to end of treatment in ADHD RS-IV total score, using an analysis of covariance (ANCOVA) model. Multiplicity adjustment was applied to control the false-positive error rate for the primary efficacy variable at 0.05 (2-sided). The ADHD RS-IV inattention and hyperactivity/impulsivity subscale scores were analyzed using an ANCOVA model that included treatment group (the effect of interest), PST type (the blocking factor, amphetamine, or methylphenidate), and the corresponding baseline score (the covariate). CGI-S and CGI-I results were analyzed using Cochran–Mantel–Haenszel tests stratified by PST type (amphetamine or methylphenidate) for each visit after baseline and for each end point.

Patient Disposition

Patient disposition of the included studies of GXR adjunctive therapy to PST is presented in [Table 11](#).

Of the 50 patients randomized in the study by van Stralen (2020),¹⁸ a total of 39 patients (78.0%) completed the study, consisting of 19 patients (76.0%) in the GXR–placebo group and 20 patients (80.0%) in the placebo–GXR group. More patients in the placebo–GXR group withdrew (16%) compared with the GXR–placebo group (4%) due to AEs. Other reasons for discontinuation from the study that occurred in the total population included protocol violation (1 patient), refused further participation (1 patient), and lack of efficacy (4 patients). The safety and full analysis set populations consisted of 49 patients.

Of the 461 patients randomized in the study by Wilens et al.(2012)¹⁹ (154 in the GXR AM + PST group, 153 in the GXR PM + PST group, and 154 in the placebo plus PST group), the safety and full analysis set populations included 455 patients (150 in the GXR AM + PST group, 152 in the GXR PM + PST group, and 153 in the placebo plus PST group). Overall, 378 (82%) patients completed the study, and 83 patients discontinued from the study (33 in the GXR AM + PST group, 25 in the GXR PM + PST group, and 25 in the placebo plus PST group). More patients in the GXR groups discontinued from the study due to AEs and protocol violations, although the numbers were small across all groups. The numbers of patients who discontinued due to other reasons such as refused further participation, loss of follow-up, or lack of efficacy appeared to be similar across groups.

Table 11: Patient Disposition of GXR as Adjunctive Therapy Studies

Variable	Van Stralen (2020) ¹⁸		Wilens et al. (2012) ¹⁹		
	GXR–placebo	Placebo–GXR	GXR AM + PST	GXR PM + PST	Placebo plus PST
Screened, N	25	25	154	153	154
Randomized, N (%)	25 (100)	25 (100)	154 (100)	153 (100)	154 (100)
Discontinued, n (%)	6 (24)	5 (20)	33 (21.4)	25 (16.3)	25 (16.2)
Adverse events	1 (4)	4 (16)	4 (2.6)	6 (3.9)	1 (0.6)
Protocol violation	1 (2.0)		8 (5.2)	6 (3.9)	3 (1.9)
Refused further participation	1 (2.0)		7 (4.5)	8 (5.2)	11 (7.1)
Loss of follow-up	NR		9 (5.8)	3 (2.0)	5 (3.2)
Lack of efficacy	4 (8.0)		3 (1.9)	2 (1.3)	5 (3.2)
Other	NR		2 (1.3)	0	0
FAS, N (%)	GXR: 49 (98) Placebo: 49 (98)		150 (97.4)	152 (99.3)	153 (99.4)
Safety, N (%)	GXR: 49 (98) Placebo: 49 (98)		150 (97.4)	152 (99.3)	153 (99.4)

FAS = full analysis set; GXR AM = guanfacine hydrochloride extended release administered in the morning; GXR PM = guanfacine hydrochloride extended release administered in the evening; NR = not reported; PST = psychostimulant.

Baseline Characteristics

Patient baseline characteristics of the included studies^{18,19} for adjunctive therapy are summarized in [Table 12](#).

The mean ages of patients in the study by van Stralen (2020)¹⁸ were 9.4 years (SD = 1.6 years) and 9.0 years (SD = 1.4 years) in the GXR–placebo sequence and placebo–GXR sequence, respectively. The mean ages of patients in the study by Wilens et al. (2012)¹⁹ were 11.0 years (SD = 2.6 years), 10.6 years (SD = 2.3 years), and 10.8 years (SD = 2.3 years) in the GXR AM + PST group, GXR PM + PST group, and placebo plus PST group, respectively. In both studies,^{18,19} there were more males than females. Patients in both studies^{18,19} had similar mean ADHD RS-IV total scores at baseline, which was approximately 37.0 points.

Table 12: Baseline Characteristics of Included Studies for GXR as Adjunctive Therapy

Characteristic	Van Stralen (2020) ¹⁸		Wilens et al. (2012) ¹⁹		
	GXR–placebo (N = 25)	Placebo–GXR (N = 25)	Placebo plus PST (n = 153)	GXR AM + PST (n = 150)	GXR PM + PST (n = 152)
Age (years)					
Mean (SD)	9.4 (1.6)	9.0 (1.4)	10.8 (2.3)	11.0 (2.6)	10.6 (2.3)
6 years to 12 years, n (%)	25 (100)	25 (100)	123 (80.4)	114 (76.0)	124 (81.6)
13 years to 17 years, n (%)	NA	NA	30 (19.6)	36 (24.0)	28 (18.4)
Sex, n (%)					
Female	3 (12)	5 (20)	41 (26.8)	42 (28.0)	46 (30.3)
Male	22 (88)	20 (80)	112 (73.2)	108 (72.0)	106 (69.7)
Weight (lb)					
Mean (SD)	67.8 (19.8)	62.9 (17.8)	89.1 (27.9)	90.8 (29.7)	85.4 (26.5)
ADHD RS-IV total score					
Mean (SD)	37.0 (7.8)	35.6 (8.3)	37.7 (7.8)	37.6 (8.1)	37.0 (7.7)
CGI-S score					
Mean (SD)	4.8 (0.5)	4.8 (0.6)	NR	NR	NR
BRIEF-P total score					
Mean (SD)	75.4 (6.2)	74.0 (5.8)	NR	NR	NR

ADHD = attention-deficit/hyperactivity disorder; ADHD RS-IV = ADHD Rating Scale–IV; BRIEF-P = Behavioural Rating Inventory of Executive Function–Preschool Version; CGI-S = Clinical Global Impressions–Severity of Illness; GXR AM = guanfacine hydrochloride extended release administered in the morning; GXR PM = guanfacine hydrochloride extended release administered in the evening; NR = not reported; PST = psychostimulant; SD = standard deviation.

Treatment Exposure and Concomitant Medications

In both studies,^{18,19} patients continued to receive a stable dose of PST, which was confirmed to be optimized by the investigator during the study. Doses of PSTs and concomitant therapies were not reported.

In the study by van Stralen (2020),¹⁸ adherence to GXR was 100%, while adherence to the placebo was 95.8%. In this study, the mean optimized doses for GXR in the 2 sequences of crossover periods (GXR followed by placebo, and placebo followed by GXR) were 3.4 mg and 3.9 mg, respectively.

In the study by Wilens et al. (2012), adherence rates for GXR, as measured by tablet counts, were 97.2% in the GXR AM group and 98.5% in the GXR PM group. Adherence rates to PSTs, as assessed by asking patients if they had missed any doses, ranged from 95.3% to 97.4%.

Critical Appraisal

Table 6 and Table 7 of Appendix 3 in the Supplemental Material present the risk of bias based on Cochrane RoB 2 assessments¹¹ of the 2 included studies.^{18,19}

Internal Validity

Van Stralen (2020)¹⁸

Randomization was conducted using a centralized Interactive Web Response System. Patient characteristics appeared to be balanced at baseline. However, the sample size was small and few baseline characteristics were reported, so the potential for prognostic imbalances between groups cannot be ruled out.

Additionally, while the trial was double-blinded and patients, care providers, investigators, and outcome assessors were masked to treatment allocation, it is unclear how the blinding and masked allocation were carried out. This limits our ability to judge the adequacy of blinding. Due to notable differences in efficacy and harms between GXR and placebo, it is possible that patients could have inferred their treatment assignment. If this were to have occurred, there would be bias in the measurement of the efficacy outcomes (as these were subjectively reported) and subjective harms. The overall risk of this bias cannot be confirmed.

Adherence to GXR was 96% in the GXR–placebo sequence and 100% in the placebo–GXR sequence. One patient discontinued due to a protocol violation, 1 withdrew consent, and 4 discontinued due to lack of efficacy, suggesting potential risk of bias due to deviations from the intended interventions.

An ANOVA with fixed effects (treatment, period, sequence) and a random effect (patients nested within sequence) was used for statistical analysis. Using the ANOVA modelling approach appropriately accounts for the crossover design by considering both between- and within-participant variability. To reduce the risk of carryover effects in the crossover design, the investigators included an 11-day taper and 10-day washout period to reduce this risk, equivalent to 16.7 times the half-life of GXR, which is about 17 hours (range, 10 hours to 30 hours).³⁴

Although the amounts of missing outcomes data in each treatment group were not reported, 22% of patients did not complete the study. The methods for handling missing data in the analyses were not reported by the authors. As such, there are concerns for risk of bias due to missing outcome data for all outcomes assessed. Data were analyzed in accordance with a prespecified plan, and the results being assessed were unlikely to have been selected due to favourable direction and/or magnitude of effect.

There are some concerns regarding the risk of bias in the measurement of outcomes. While the methods of measuring the outcomes were appropriate, clearly described, and similar between intervention groups, specific details about double-blinding were not provided. Although the trial registration noted that patients, care providers, investigators, and outcome assessors were masked to treatment allocation, it is unclear how the blinding was carried out and whether the outcome assessors could have been aware of the intervention received by study participants. Given that primary and outcomes were measured by subjective rating scales, the assessor's knowledge of group assignment could have influenced how the rating scales were reported or interpreted, leading to differential measurement bias between the 2 groups.

Multiple outcome measures used to assess the efficacy of GXR included BRIEF-P, ADHD RS-IV, CGI-I, and CGI-S. The unavailability of the MID of BRIEF-P scores and the measurement properties (i.e., validity, reliability, and responsiveness to change) of that scale among children and adolescents with ADHD limited the estimation of the clinical relevance of the observed effects.

There was no adjustment for multiple testing of the secondary outcomes, which means there is a higher probability of statistical significance by chance alone, increasing the risk a false-positive result (type I error).

Wilens et al. (2012)¹⁹

The study by Wilens et al. (2012)¹⁹ was a multicentre, double-blind, placebo-controlled trial, with an overall low risk of bias across all Cochrane RoB 2 domains, except there are some concerns about the risk of bias in the measurement of the outcome. Randomization was conducted using a 1:1:1 allocation stratified by age group and stimulant type, and the baseline characteristics of the treatment groups appeared to be balanced at baseline.

The adherence rates for GXR, as measured by tablet counts, were 97.2% for the GXR AM + PST group and 98.5% for the GXR PM + PST group. The adherence rates for PSTs ranged between 95.3% and 97.4%. Missing data for end points from dropout or for other reasons was not reported, nor were the methods for handling missing outcome data. As such, there is risk of bias due to missing outcome data for all outcomes assessed. Furthermore, validated and clinician-rated outcome measures (ADHD RS-IV, CGI-S, and CGI-I scores) were used consistently across sites. Although the study was reported to have been double-blind in design, the methods for blinding were not reported.

Multiple outcome measures used to assess the efficacy of GXR included ADHD RS-IV, CGI-I, CGI-S, CGI-P, and BSFQ scores. The unavailability of MIDs for some measures (i.e., CGI-P and BSFQ) and the measurement properties (i.e., validity, reliability, and responsiveness to change) of these scales among children and adolescents with ADHD limited the estimation of the clinical relevance of the observed effects.

To adjust for multiple comparisons and control the false-positive error rate at 0.05, the Dunnett procedure was applied. However, there was no control for multiple testing for the secondary outcomes, so there is an increased risk for type 1 errors (false-positive results) for results that are statistically significant. The study did not adequately describe how double-blinding was carried out, and it is unclear if the outcome assessors could have been aware of the intervention received by study participants. As such, there are some concerns in the risk of bias in measurement of the outcomes.

Data that produced the results in the published report were analyzed in accordance with a prespecified analysis plan. Analyses of response and remission of ADHD were undertaken post hoc. As such, it is possible that the results presented were among multiple analyses of the data, selected based on the direction and/or magnitude of effect.

External Validity

Van Stralen (2020)¹⁸

The study included a narrower population (children aged 6 years to 12 years) than listed in our inclusion criteria (children and adolescents aged 6 years to 17 years) from Canada. The findings in this study could be applicable to children aged 6 years to 12 years but may have limited generalizability to adolescents in Canada. Furthermore, participants in this study were mostly males, limiting its generalizability to female patients with ADHD.

Additionally, given the few baseline characteristics reported, it is difficult to determine the extent to which the patients enrolled were reflective of those seen in clinical practice in Canada. Finally, participants were recruited from 1 centre in Ottawa, which may limit broader generalization of the results to patients in Canada.

Wilens et al. (2012)¹⁹

The trial population included children and adolescents aged 6 years to 17 years across multiple sites in the US, which makes it applicable to the age range of the requested indication and to patients in Canada. However, the structured titration of GXR and close monitoring of patients may not be feasible in all environments, especially where frequent follow-up or child psychiatry services are limited.

Results

Efficacy

Results of efficacy outcomes are presented in [Table 13](#). The MID of the outcome measures for ADHD are presented in Table 10 of Appendix 4 in the Supplemental Material.

Study by van Stralen (2020)¹⁸

- There was improvement in the primary outcome measure in this study, the BRIEF-P Global Executive Composite score, in the GXR + PST group compared to the placebo plus PST group, after 12 weeks of treatment (least squares mean = -3.0; 95% CI, -5.9 to -0.2; P = 0.0392). In the absence of an estimated MID, the clinical importance of the difference is uncertain.
- Similar results of improvement were observed in the GXR + PST group compared to the placebo plus PST group with secondary outcome measures (ADHD RS-IV total score, CGI-S score, and CGI-I score). For ADHD RS-IV total scores, the difference between GXR + PST group and the placebo plus PST group met the estimated MID. For CGI-I and CGI-S scores, although within-group MIDs have been suggested (i.e., a change of 1 point on a 7-point scale), the clinical importance of the difference between groups is uncertain due to the absence of an estimated between-group MID.

Study by Wilens et al. (2012)¹⁹

- There was improvement in the primary outcome measure in this study, the ADHD RS-IV total score, in both GXR + PST groups compared to the placebo plus PST group after 9 weeks of treatment. Compared to the placebo plus PST group, the least squares means of -4.5 points (95% CI, -7.5 to -1.4; P = 0.002) in the GXR AM + PST group and -5.3 points (95% CI, -8.3 points to -2.3 points; P < 0.001) in the GXR PM + GST group barely met the between-treatment difference MID of 5.2 points to 7.7 points. However, the authors argued that, for an adjunctive therapy study in which patients had already experienced a reduction in ADHD symptoms while receiving a stimulant alone before entry, a 4-point difference in ADHD RS-IV total score between treatments could be considered representative of a clinically meaningful additional improvement.¹⁹
- Similar results of improvement in the GXR + PST group compared to the placebo plus PST group were observed with ADHD RS-IV inattention subscale scores and ADHD RS-IV hyperactivity/impulsivity subscale scores.

- Assessment using CGI-S scores, a secondary outcome measure, showed that patients in both the GXR AM and GXR PM groups were less severely ill than patients in the placebo group. However, only P values were reported. As such, the clinical meaningfulness of the differences is unknown. Similarly, more patients in both the GXR AM and GXR PM groups had improvement in CGI-I scores compared with placebo at the study end point.
- Secondary analyses of outcomes such as CGI-P morning assessment, CGI-P evening assessment, and BSFQ (parent-rated version) assessment showed that adjunctive GXR AM or GXR PM was associated with improvements in ADHD symptoms in both morning and evening compared with placebo.²¹ The participant-rated BSFQ did not show any improvement for either adjunctive GXR AM or GXR PM groups compared with placebo. For CGI-P, both adjunctive GXR AM and GXR PM groups showed consistent improvement from week 5 to the study end point compared with placebo. In the absence of estimated MIDs for the CGI-P and the BSFQ, the clinical importance of the differences is uncertain.
- Post hoc analyses outcomes such as response, symptomatic remission, and syndromal remission showed that higher proportions of patients in both GXR + PST groups achieved response and remission compared with those in the placebo plus PST group.²⁰

Table 13: Summary of Key Efficacy Results of Included Studies for GXR as Adjunctive Therapy

Variable	Van Stralen (2020) ¹⁸		Wilens et al. (2012) ¹⁹		
	GXR + PST (N = 50)	Placebo plus PST (N = 50)	GXR AM + PST (n = 150)	GXR PM + PST (n = 152)	Placebo plus PST (n = 153)
BRIEF-P (T scores ≥ 65 [clinically significant difficulties])					
Number of patients contributing to the analysis, n (%)	47 (94)	48 (96)	NA	NA	NA
Baseline score, mean (SE)	71.2 (1.20)	72.8 (1.25)	NA	NA	NA
End of treatment score, mean (SE)	64.3 (1.64)	67.4 (1.63)	NA	NA	NA
LS mean ^a (95% CI)	-3.0 (-5.9 to -0.2)	Reference	NA	NA	NA
P value	0.0392 ^b	Reference	NA	NA	NA
ADHD RS-IV, total score (0 [best] to 54 [worst])					
Number of patients contributing to the analysis, n (%)	47 (94)	48 (96)	150 (97.4)	152 (99.3)	153 (99.4)
Baseline score, mean (SE or SD)	34.1 (SE = 1.27)	35.5 (SE = 1.25)	37.6 (SD = 8.13)	37.0 (SD = 7.65)	37.7 (SD = 7.75)
End of treatment score, mean (SE or SD)	22.9 (SE = 1.39)	30.1 (SE = 1.83)	17.3 (SD = 12.86)	16.1 (SD = 11.84)	21.7 (SD = 12.98)

Variable	Van Stralen (2020) ¹⁸		Wilens et al. (2012) ¹⁹		
	GXR + PST (N = 50)	Placebo plus PST (N = 50)	GXR AM + PST (n = 150)	GXR PM + PST (n = 152)	Placebo plus PST (n = 153)
LS mean ^a (95% CI)	-6.9 (-9.8 to -4.0)	Reference	-4.5 (-7.5 to -1.4)	-5.3 (-8.3 to -2.3)	Reference
P value	< 0.0001 ^b	Reference	0.002 ^c	< 0.001 ^c	Reference
ADHD RS-IV, Inattention subscale (0 [best] to 27 [worst])					
Number of patients contributing to the analysis, n (%)	NR	NR	150 (97.4)	152 (99.3)	153 (99.4)
Baseline score, mean (SE or SD)	NR	NR	NR	NR	NR
End of treatment score, mean (SE or SD)	NR	NR	NR	NR	NR
LS mean ^a (95% CI)	NR	NR	-2.4 (-3.9 to -0.9)	-3.1 (-4.6 to -1.5)	Reference
P value	NR	NR	0.002 ^b	< 0.001 ^b	Reference
ADHD RS-IV, Hyperactivity/Impulsivity subscale (0 [best] to 27 [worst])					
Number of patients contributing to the analysis, n (%)	NR	NR	150 (97.4)	152 (99.3)	153 (99.4)
Baseline score, mean (SE or SD)	NR	NR	NR	NR	NR
End of treatment score, mean (SE or SD)	NR	NR	NR	NR	NR
LS mean ^a (95% CI)	NR	NR	-2.1 (-3.4 to -0.7)	-2.3 (-3.6 to -0.9)	Reference
P value	NR	NR	0.002 ^b	< 0.001 ^b	Reference
CGI-S (1 [normal] to 7 [extremely ill])					
Number of patients contributing to the analysis, n (%)	47 (94)	48 (96)	150 (97.4)	152 (99.3)	153 (99.4)
Baseline score, mean (SE)	4.7 (0.09)	4.8 (0.08)	NR	NR	NR
End of treatment score, mean (SE)	3.3 (0.20)	4.2 (0.16)	NR	NR	NR
LS mean ^a (95% CI)	-0.9 (-1.4 to -0.4)	Reference	NR	NR	NR
P value	0.0007 ^b	Reference	0.013 ^b	< 0.001 ^b	Reference

Variable	Van Stralen (2020) ¹⁸		Wilens et al. (2012) ¹⁹		
	GXR + PST (N = 50)	Placebo plus PST (N = 50)	GXR AM + PST (n = 150)	GXR PM + PST (n = 152)	Placebo plus PST (n = 153)
CGI-I (1 [very much improved] to 7 [very much worse])					
Number of patients contributing to the analysis, n (%)	47 (94)	48 (96)	150 (97.4)	152 (99.3)	153 (99.4)
Baseline score, mean (SE)	NR	NR	NR	NR	NR
End of treatment score, mean (SE)	2.6 (NR)	3.3 (NR)	NR	NR	NR
LS mean ^a (95% CI)	-0.7 (-1.2 to -0.3)	Reference	NR	NR	NR
Improvement ^d at study end point, n (%)	28 (57.4)	14 (27.7)	105 (70.5)	110 (74.3)	88 (57.9)
P value	NR	NR	0.024 ^b	0.003 ^b	Reference
Response (≥ 40% reduction in ADHD RS-IV total scores)					
Number of patients contributing to the analysis, n (%)	NA	NA	150 (97.4)	152 (99.3)	153 (99.4)
Number of patients achieving response, n (%)	NA	NA	105 (69.8)	107 (70.3)	89 (57.9)
P value	NA	NA	0.032 ^b	0.026 ^b	Reference
Response (≥ 50% reduction in ADHD RS-IV total scores)					
Number of patients contributing to the analysis, n (%)	NA	NA	150 (97.4)	152 (99.3)	153 (99.4)
Number of patients achieving response, n (%)	NA	NA	95 (63.1)	99 (64.9)	66 (43.4)
P value	NA	NA	< 0.001 ^b	< 0.001 ^b	Reference
Symptomatic remission (ADHD RS-IV total score ≤ 18)					
Number of patients contributing to the analysis, n (%)	NA	NA	150 (97.4)	152 (99.3)	153 (99.4)
Number of patients achieving symptomatic remission, n (%)	NA	NA	92 (61.1)	95 (62.2)	71 (46.1)
P value	NA	NA	0.01 ^b	0.005 ^b	Reference
Syndromal remission (CGI-S ≤ 2 and ADHD RS-IV ≤ 18)					
Number of patients contributing to the analysis, n (%)	NA	NA	150 (97.4)	152 (99.3)	153 (99.4)

Variable	Van Stralen (2020) ¹⁸		Wilens et al. (2012) ¹⁹		
	GXR + PST (N = 50)	Placebo plus PST (N = 50)	GXR AM + PST (n = 150)	GXR PM + PST (n = 152)	Placebo plus PST (n = 153)
Number of patients achieving syndromal remission, n (%)	NA	NA	60 (40.3)	71 (46.6)	45 (29.6)
P value	NA	NA	0.053 ^b	0.002 ^b	Reference
CGI-P morning assessment (0 [best] to 30 [worst])					
Number of patients contributing to the analysis, n (%)	NA	NA	150 (97.4)	152 (99.3)	153 (99.4)
Baseline CGI-P score (morning)	NA	NA	16.7 (6.13)	17.5 (6.60)	17.1 (6.67)
LS mean ^a (95% CI)	NA	NA	-1.7 (-3.2 to -0.3)	-2.6 (-4.0 to -1.1)	Reference
P value	NA	NA	0.019 ^b	< 0.001 ^b	Reference
CGI-P evening assessment (0 [best] to 30 [worst])					
Number of patients contributing to the analysis, n (%)	NA	NA	150 (97.4)	152 (99.3)	153 (99.4)
Baseline CGI-P score (evening)	NA	NA	17.7 (6.19)	17.8 (5.89)	18.2 (6.51)
LS mean ^a (95% CI)	NA	NA	-2.4 (-4.0 to -0.9)	-3.0 (-4.5 to -1.5)	Reference
P value	NA	NA	0.002 ^b	< 0.001 ^b	Reference
BSFQ – parent rated (0 [best] to 60 [worst])					
Number of patients contributing to the analysis, n (%)	NA	NA	150 (97.4)	152 (99.3)	153 (99.4)
LS mean ^b (95% CI)	NA	NA	-5.1 (NR)	-4.7 (NR)	Reference
P value	NA	NA	< 0.001 ^b	0.002	Reference
BSFQ – participant rated (0 [best] to 28 [worst])					
Number of patients contributing to the analysis, n (%)	NA	NA	150 (97.4)	152 (99.3)	153 (99.4)
Feeling score, LS mean ^b (95% CI)	NA	NA	-0.5 (-1.1 to 0.1)	-0.3 (-0.9 to 0.2)	Reference
P value	NA	NA	0.116 ^b	0.239 ^b	Reference
Behavioural score, LS mean ^b (95% CI)	NA	NA	-0.2 (-0.8 to 0.3)	-0.5 (-1.1 to 0.1)	Reference
P value	NA	NA	0.429 ^b	0.104 ^b	Reference

ADHD RS-IV = ADHD Rating Scale–IV; BRIEF-P = Behavioural Rating Inventory of Executive Function–Preschool Version; BSFQ = Before School Functioning Questionnaire; CGI-I = Clinical Global Impressions–Improvement; CGI-P = Conners Global Index–Parent; CGI-S = Clinical Global Impressions–Severity of Illness; CI =

confidence interval; GXR = guanfacine hydrochloride extended release; GXR AM = guanfacine hydrochloride extended release administered in the morning; GXR PM = guanfacine hydrochloride extended release administered in the evening; LS = least square; NA = not applicable; NR = not reported; PST = psychostimulant; SD = standard deviation; SE = standard error.

^aLS mean difference in the change from baseline at study end point.

^bVersus placebo, not adjusted for multiple testing.

^cVersus placebo, based on the Dunnett adjustment for multiplicity.

^dJudged as improved (including much or very much improved). On the CGI-I scale, 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse.

Although HRQoL was considered important to this review, it was not reported in the included studies.

Harms

Harms in the 2 included studies of GXR as adjunctive therapy are presented in Table 24 of Appendix 8 in the Supplemental Material.

- In both studies,^{18,19} most patients in the GXR + PST and placebo plus PST groups had at least 1 TEAE.
- In both studies,^{18,19} common TEAEs such as headache, abdominal pain, fatigue, somnolence, dizziness, and insomnia occurred more frequently in the GXR + PST groups compared to the placebo plus PST group.
- In both studies,^{18,19} few patients in the active treatment groups discontinued treatment due to AEs.
- In both studies,^{18,19} no deaths occurred during treatment.
- In the study by Wilens et al. (2012),¹⁹ GXR + PST compared with placebo plus PST was associated with decreases in heart rate, systolic blood pressure, and diastolic blood pressure.
- In the study by Wilens et al. (2012),¹⁹ there were no abnormal ECG results (no patients in any treatment groups met the outlier criteria of a corrected QT interval of ≥ 480 milliseconds calculated using the Fridericia formula or a corrected QT interval of ≥ 500 milliseconds calculated using the Bazett formula).
- In the study by Wilens et al. (2012),¹⁹ there were no notable differences in weight gain from baseline to end point between patients receiving GXR + PST and those receiving placebo plus PST.

LTE Study on Adjunctive Therapy

Description of Studies

As mentioned earlier in this report, the long-term study by Sallee et al. (2009)¹⁶ included patients from 2 antecedent studies, 1 of which was a phase II open-label, uncontrolled 9-week study to assess the safety of GXR administered concomitantly with a PST in children and adolescents with ADHD whose disease had responded suboptimally to a PST. Fifty-four patients from this antecedent study were included as a subgroup in the long-term study by Sallee et al. (2009),¹⁶ the results of which are presented here.

Similar to the monotherapy subgroup, patients in the adjunctive subgroup were maintained at their optimal dose until 24 months when GXR was tapered off by 1 mg/day decrements at weekly intervals. GXR was co-administered with the patients' same PST medication (amphetamine or methylphenidate) as provided in the antecedent study. Dosages of GXR or PSTs could be adjusted throughout the 24-month open-label period.

Patient Disposition

Patient disposition of the LTE in the adjunctive subgroup is presented in [Table 14](#).

The full analysis set comprised 53 patients (98.1% of patients enrolled) who received the drug and had at least 1 primary efficacy measurement after the baseline. Early termination from the study occurred in 31 of 54 patients (57.4%). As in the monotherapy subgroup, withdrawal by participant was the most frequent reason for discontinuation. Other reasons for early termination included loss of follow-up, AEs, and lack of efficacy.

Table 14: Patient Disposition in LTE Study on GXR as Adjunctive Therapy

Category	Sallee et al. (2009) ¹⁶ (Adjunctive therapy)
Total enrolled	54
Received at least 1 dose of guanfacine (safety population), n (%)	53 (98.1)
Completed study, n (%)	22 (40.7)
Early termination, n (%)	31 (57.4)
Withdrawal by participant	15 (28)
Loss of follow-up	9 (16.7)
Protocol violation	NR
Adverse event	3 (5.6)
Lack of efficacy	1 (1.9)
Other	3 (5.6)
Full analysis set, n (%)	53 (98.1)

GXR = guanfacine hydrochloride extended release; LTE = long-term extension; NR = not reported.

Baseline Characteristics

Baseline characteristics of patients in the adjunctive therapy subgroup are presented in [Table 15](#). Briefly, patients had a mean age of 11.2 years (SD = 1.8 years). Most patients were aged between 6 years and 12 years (75.5%) and there were more males (75.5%) than females (24.5%). Most patients had the combined ADHD subtype (73.6%) and the mean years since ADHD diagnosis was 4.0 years (SD = 2.6 years).

Table 15: Baseline Characteristics of Patients in LTE Study on GXR as Adjunctive Therapy

Characteristic	Sallee et al. (2009) ¹⁶ (N = 53)
Age (years)	
Mean (SD)	11.2 (1.8)
6 years to 12 years, n (%)	40 (75.5)
13 years to 17 years, n (%)	13 (24.5)
Sex, n (%)	

Characteristic	Sallee et al. (2009) ¹⁶ (N = 53)
Female	13 (24.5)
Male	40 (75.5)
Weight (lb)	
Mean (SD)	102.2 (29.8)
Height (in)	
Mean (SD)	59.2 (4.4)
ADHD subtype, n (%)	
Inattentive	11 (20.8)
Hyperactive	3 (5.7)
Combined	39 (73.6)
Years since ADHD diagnosis	
Mean (SD)	4.0 (2.6)
ADHD RS-IV total score at baseline (FAS)	
Mean (SD)	29.3 (10.9)

ADHD = attention-deficit/hyperactivity disorder; FAS = full analysis set; LTE = long-term extension; SD = standard deviation.

Critical Appraisal

The limitations of the study by Sallee et al. (2009)¹⁶ were previously described in the GXR monotherapy section of this report. In the adjunctive therapy subgroup analysis, the total patient population was very small (N = 53), limiting external validity. The lack of a comparator in the LTE study precludes causal conclusions. The open-label design of the study may be subject to risk of bias in the measurement of efficacy outcomes and subjective harms. There was a risk of bias due to missing outcomes data, as a large proportion of patients did not complete the trial. Missing outcomes data were handled using the LOCF approach, which assumes a constant outcome from the time of the last assessment forward, which is unlikely a reasonable reflection of the true trajectory of the outcome.

Results

Efficacy

- Long-term treatment with GXR adjunctive to PSTs resulted in improvements in ADHD core symptoms.
- The overall final mean score on the ADHD RS-IV at end point (24 months) was 13.2 (SD = 8.5). Thus, the mean change in ADHD RS-IV total score from baseline to end point was -16.1 (SD = 11.0). The change represented a reduction of more than 50% from the mean baseline score, which surpassed the MID for ADHD RS-IV (i.e., a 25% to 30% reduction in total score).

Harms

Details of harms results of the LTE study in the adjunctive subgroup are presented in Table 24 of Appendix 8 in the Supplemental Material.

- Eighty-seven percent of patients in the adjunctive therapy group had at least 1 TEAE.
- Three patients (5.7%) discontinued treatment due to TEAEs.
- Serious TEAEs were not reported.
- Common TEAEs occurring in 10% or more of patients included headache, upper respiratory tract infection, nasopharyngitis, pharyngitis, abdominal pain, decrease appetite, and irritability.
- There were no deaths reported.
- Other notable harms such as blood pressure changes, cardiac events, changes in appetite, and changes in weight or height were not reported. There was little change in heart rate from baseline to end point.

Discussion

Efficacy

Compared to the previous CADTH review,³ which included only 1 RCT investigating the efficacy and safety of GXR adjunctive to a PST versus GXR alone, evidence from this review was derived from 2 RCTs (1 of which was included in the previous reimbursement review). Two additional publications presenting analyses of secondary end points and post hoc analyses of the trial included in the previous reimbursement review were also included. We also included the results of an adjunctive therapy subgroup from an LTE study. The results may further support the potential effect of GXR as adjunctive treatment in patients whose disease had responded suboptimally to PSTs.

The results from the van Stralen (2020) and Wilens et al. (2012) RCTs^{18,19} suggested that short-term adjunctive administration of GXR to a PST in patients with suboptimal disease response to PSTs may reduce ADHD symptoms (ADHD RS-IV scores), improve executive function (BRIEF-P Global Executive Composite T scores), and improve Clinical Global Impression (CGI-S and CGI-I scores). Additionally, 2 reports^{20,21} of post hoc and secondary analyses using data from the study by Wilens et al. (2012)¹⁹ also suggested that GXR given as adjunctive therapy to a PST improved parent-rated CGI-P scores and early morning functional impairment (BSFQ scores) and increased disease response and remission over placebo with a PST. These benefits were observed when adjunctive administration of GXR was given either in the morning or evening.

In both studies,^{18,19} the reductions in ADHD symptoms at the end of treatment compared to placebo met the MID for ADHD RS-IV total score for adjunctive therapy (a 4-point difference) among patients who had already experienced reductions in ADHD symptoms while receiving a stimulant alone. In the study by Wilens et al. (2012),¹⁹ the mean ADHD RS-IV total scores at end point were less than 18 points in both GXR + PST groups. Posttreatment clinical interpretation of scores less than 18 points suggests that patients' disease responded well to treatment and symptoms were within the normal range.³⁵ For the CGI-I assessed in the study by Wilens et al. (2012),¹⁹ improvement judged as "much or very much improved" occurred in more than 70% of participants in both GXR + PST groups compared to 58% in the placebo plus PST group. A

similar observation was seen in the study by van Stralen (2020),¹⁸ in which 57.4% in the GXR + PST group showed improvement to a score of very much improved or improved compared to 27.7% in the placebo plus PST group. However, it is unclear whether the between-group differences are clinically relevant. A post hoc analysis study by Cutler et al. (2014)²⁰ and analyses of secondary end points by Wilens et al. (2017)²¹ also showed improvement in GXR + PST groups for various outcome measures such as disease response, disease remission, CGI-P scores, and BSFQ scores compared to the placebo plus PST group. In the absence of estimated MIDs for these outcomes, the clinically meaningful improvements are uncertain.

One of the methodological limitations of both included studies^{18,19} was the short treatment duration that limited conclusions regarding the efficacy and safety of long-term adjunctive therapy. Second, the crossover trial by van Stralen (2020)¹⁸ may be subject to carryover effect when analyzing the primary outcome measure. To minimize this limitation, the authors conducted the weaning for 11 days with a further a 10-day washout. This washout period may be sufficient to eliminate GXR in the system, as the half-life of GXR is 17 hours (range, 10 hours to 30 hours).³⁴ Third, although both studies were double-blinded, assessments of some outcome measures were done by parents (e.g., BRIEF-P, CGI-Parent, BSFQ). Parental completion of scales differs from children's perspectives because parents can be influenced by their expectations about treatment, and they tend to rate observable behaviours. To illustrate the differential end point effects based on the instrument rater, the BSFQ parent-rated items indicated a significant improvement in participants who received GXR + PST compared with placebo plus PST. In contrast, this improvement was not found in the BSFQ participant-rated items. Fourth, the placebo effect observed in both studies was relatively high: changes from baseline to end of treatment in the placebo groups were calculated to be 15% and 42% reductions in ADHD RS-IV total scores in the studies by van Stralen (2020)¹⁸ and Wilens et al. (2012),¹⁹ respectively. A placebo effect was also observed in the post hoc analysis study by Cutler et al. (2014)²⁰ and the secondary analysis study by Wilens et al. (2017)²¹ when assessing outcome measures such as disease response, disease remission, CGI-P scores, and BFSQ scores. The responses observed in the placebo plus PST groups were likely due to patients having improved adherence with their PSTs. The studies were not powered to detect differences between active treatment groups and the placebo plus PST group; therefore, a true placebo effect could not be derived. Indeed, 80% and 84% of patients in the placebo groups of the study by van Stralen (2020)¹⁸ and the study by Wilens et al. (2012),¹⁹ respectively, remained in the study to the end of treatment. However, adherence to PST before the onset of the study was not assessed. Fifth, although patients were required to receive a stable dose of PST that was confirmed to be optimized by the investigator, and they were required to manifest a certain disease response to PST before enrolment, neither study incorporated PST monotherapy optimization during the adjunctive therapy study, which may overestimate the efficacy evaluation of GXR.^{18,19} The disease response to PST monotherapy before the study was unknown.

Results of long-term treatment (2 years) with GXR adjunctive to PST showed improvement in ADHD core symptoms. Major limitations of this LTE subgroup of the study by Salle et al. (2009)¹⁶ included the single-arm design, small sample size, risk of bias in the measurement of outcomes due to the open-label design, and potentially limited external validity. As such, the long-term effects of GXR as adjunctive therapy remains inconclusive.

Despite these limitations, the treatment approach and the findings in both studies^{18,19} may be applicable to the Canadian setting, given that 1 study¹⁸ was conducted in 1 Canadian centre and the other study¹⁹ was conducted in the US. However, the inclusion and exclusion criteria in both studies created a select group of patients that may not be comparable to the real-world clinical population.

Harms

In both studies,^{18,19} most patients (about 80%) in both the GXR and placebo groups completed the study. In both studies,^{18,19} few patients discontinued treatment due to AEs. Common TEAEs reported in both adjunctive therapy RCTs^{18,19} that occurred more frequently in the GXR + PST group compared to the placebo plus PST group were headache, abdominal pain, fatigue, somnolence, dizziness, and insomnia. Some of these common TEAEs were also observed in long-term treatment (2 years) with GXR adjunctive to PST. However, due to the single-arm design of the LTE study, it was unclear if there were any synergistic effects in adjunctive GXR + PST. It was also difficult to determine which harms are associated with PSTs versus with GXR. In the study by Wilens et al. (2012),¹⁹ decreases in heart rate and blood pressure were observed in the GXR + PST groups compared to the placebo plus PST group, but no patients in any treatment groups had any cardiac events.

Conclusion

Evidence from a single-centre, double-blind, placebo-controlled crossover trial¹⁷ and a multicentre, double-blind, placebo-controlled trial¹⁸ suggested that the addition of GXR to optimized PST therapy is potentially effective. The long-term efficacy and safety of GXR as adjunctive therapy to PST remains to be determined.

Economic Review of Adjunctive Therapy

Methods

The economic review consisted of a cost comparison for GXR as adjunctive therapy to a PST (methylphenidate CR, methylphenidate XR, amphetamine XR, or lisdexamfetamine) for the treatment of ADHD in children and adolescents aged 6 years to 17 years compared with PSTs as monotherapy, atomoxetine, or clonidine.

Based on public list prices, GXR as adjunctive therapy is expected to have a per patient cost of \$927 per year for children (aged 6 years to 12 years) and adolescents (aged 13 years to 17 years) added to the costs of PSTs, which vary between \$330 (amphetamine XR) and \$856 (methylphenidate CR) (refer to Appendix 9 in the Supplemental Material). Clonidine and atomoxetine are expected to have per patient costs per year between \$44 and \$296 for children and between \$89 and \$565 for adolescents, respectively. When comparing GXR + PST with nonstimulant monotherapy in children, the incremental cost per patient per year ranged from \$961 (atomoxetine) to \$1,739 (clonidine); in adolescents, the incremental cost per patient per year ranged from \$692 (amphetamine) to \$1,694 (clonidine). As such, the reimbursement of GXR as adjunctive therapy for the treatment of ADHD in children and adolescents aged 6 years to 17 years

is expected to increase overall drug acquisition costs. Additional items for consideration are provided in the following bullets:

- According to the clinical review, evidence from clinical trials suggests GXR + PST may result in greater improvement in multiple clinical outcomes when compared to placebo plus PST and unknown benefit compared to atomoxetine or clonidine.
- As of September 2025, Health Canada had reviewed 4 generic versions of GXR (2 are marketed and 2 are approved), and 2 are currently under review at Health Canada.
- According to the clinical experts consulted for this review, GXR as adjunctive therapy is expected to have similar treatment-related health care resource use compared with other treatments available in Canada.
- GXR as adjunctive therapy to a PST was previously reviewed by CDA-AMC in 2015 for the treatment of ADHD in children aged 6 years to 12 years, and it received a “do not reimburse” recommendation. As of September 2025, there are no other drugs under review by CDA-AMC for children and adolescents with ADHD.
- One cost-effectiveness study conducted in Canada for GXR as adjunctive therapy was identified based on a literature search conducted on April 28, 2025, with alerts maintained until the FMEC meeting on November 20, 2025. The cost-utility analysis³⁶ was published in 2016 and was based on the pivotal trial by Wilens et al.,¹⁹ which compared GXR as an adjunctive therapy to a PST versus placebo plus PST. The study concluded that GXR + PST was more costly and more effective compared to placebo plus PST, with an incremental cost-effectiveness ratio of \$23,720 per quality-adjusted life-year gained from a public payer perspective; however, multiple limitations were identified that would prevent the generalizability of these findings to the context of this review. Additional information regarding this literature has been summarized in the Appendix 10 in the Supplemental Material.

Conclusion

The reimbursement of GXR as adjunctive therapy to a PST for the treatment of ADHD in children and adolescents aged 6 years to 17 years is expected to increase overall drug acquisition costs. Based on the clinical review conclusions, GXR as adjunctive therapy to a PST may improve multiple clinical outcomes when compared to placebo plus a PST, with unknown benefit when compared to atomoxetine or clonidine.

Given that GXR as adjunctive therapy to a PST is associated with increased drug acquisition costs and incremental clinical benefit, a cost-effectiveness analysis would be required to determine the cost-effectiveness of GXR relative to active comparators. A Canadian study concluded that GXR may be cost-effective when compared to PSTs as monotherapy; however, the results cannot be generalized to the context of this review; additionally, the cost-effectiveness of GXR compared to clonidine or atomoxetine were not assessed in the literature and could not be determined.

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