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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Guanfacine Hydrochloride Extended-Release for Attention Deficit Hyperactivity Disorder: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Context and Policy Issues

Attention-deficit/hyperactivity disorder (ADHD) is the most commonly diagnosed childhood behavioural disorder.[1] According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), ADHD is defined as a "persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent and severe than is typically observed in individuals at a comparable developmental level."[2] Symptoms of this disorder can affect children's cognitive, academic, behavioural, emotional, and social functioning.[3] As a result, treatment of ADHD can include behavioural and school-based interventions, medication, patient and education programs and psychological interventions. For children and adolescents who meet diagnostic criteria for ADHD in accordance with DSM-IV,[2] medication in combination with behavioural and psychological interventions is recommended.[3]

According to the Canadian ADHD Resource Alliance clinical practice guideline, psychostimulants, such as methylphenidate, amphetamines, and lisdexamfetamine, are considered first-line treatment for ADHD in children and adolescents.[1] Nonstimulants, such as atomoxetine and guanfacine, are an emerging class of medication for children and adolescents who show a fair response to psychostimulants or experience adverse effects with them, as monotherapy or adjunctive therapy.[1] Atomoxetine is a selective norepinephrine reuptake inhibitor and currently indicated for the treatment of ADHD in children six years of age and older, teenagers, and adults.[1]

Guanfacine hydrochloride extended-release (GXR; brand name: Intuniv XR) is currently indicated as monotherapy for the treatment of ADHD in children aged six to 12 years, as well as adjunctive therapy to psychostimulants for the treatment of ADHD in children aged six to 12 years with a suboptimal response to psychostimulants.[4] Guanfacine hydrochloride is a selective alpha$_{2A}$-adrenergic receptor agonist. Its mechanism of action in ADHD is not fully known; however, the drug appears to work on certain receptors in the prefrontal cortex, an area of the brain where behaviours such as inattention and impulsiveness are thought to be controlled.[1] According to previous literature, the safety profile of GXR is characterized by undesirable side-effects such as (orthostatic) hypotension, bradycardia, sedation, fatigue, and headache.[1] These unwanted effects have been shown to be very common and have the potential to limit tolerability. Discontinuation effects with this drug have also been known to occur, particularly after abrupt cessation of treatment, with symptoms of rebound hypertension and tachycardia.[4]

In 2014, this drug was reviewed under the Common Drug Review (CDR) process at CADTH, as an option for either monotherapy or adjunctive therapy to psychostimulants for the treatment of ADHD for children aged six to 12 years.[5] A systematic review was conducted with included seven double-blind, placebo-controlled RCTs of children with ADHD as monotherapy.[5] In addition, the manufacturer submitted two cost-utility analyses (one for monotherapy and one for adjunctive therapy) for children aged six to 12 with ADHD.

The Canadian Drug Expert Committee (CDEC) issued a recommendation on September 2014 that GXR not be listed.[6] The reasons provided for the recommendation was firstly,

that there was "insufficient evidence from randomized controlled trials (RCTs) to assess the comparative clinical benefit of GXR as monotherapy relative to other less costly treatments for ADHD";[6] and secondly, that "evidence for the use of GXR as adjunctive therapy in ADHD was limited to one RCT[7] that was only eight weeks in duration."[6] Although CDEC noted "there is an absence of treatments approved for use as adjunctive therapy in ADHD, the single included study provided insufficient evidence to adequately assess the overall and longer-term clinical benefit of GXR in this patient population."[6]

Since this time, GXR's role in ADHD therapy has continued to be studied. The aim of this review is to assist decision-makers and prescribers by evaluating the recently published evidence on the clinical effectiveness and cost-effectiveness of GXR for the treatment children and adolescents with ADHD. Clinical guidelines will also be examined.

Research Questions

1. What is the clinical effectiveness of guanfacine hydrochloride extended-release tablets for the treatment of children and adolescents with attention deficit hyperactivity disorder?
2. What is the cost-effectiveness of guanfacine hydrochloride extended-release tablets for treatment of children and adolescents with attention deficit hyperactivity disorder?
3. What are the evidence-based guidelines regarding the use of guanfacine hydrochloride extended-release tablets for the treatment of children and adolescents with attention deficit hyperactivity disorder?

Key Findings

Since the previous recommendations issued by the Canadian Drug Expert Committee (CDEC) on September 2014, four systematic reviews (including pairwise meta-analyses and network meta-analyses of direct and indirect evidence), one randomized controlled trial, and one guideline have been published regarding the use of guanfacine hydrochloride extended-release (GXR) for the treatment of attention deficit-hyperactivity disorder (ADHD) in children and adolescents.

All included studies reported significant improvements in subjective ADHD rating scales as well as scales in executive function when using GXR compared to placebo for treatment in children and adolescents with ADHD. This demonstrates improvements not only in ADHD symptoms but on social functioning, which is also integral to ADHD management. No studies were found which provided direct evidence comparing GXR to active treatments; however, four studies with indirect analyses were included which allowed comparisons to be made. There were no significant differences between GXR and active ADHD treatments; however, it was concluded that GXR may have a moderate effect on efficacy compared to active treatments. These clinical studies may further support evidence of the use of GXR in children with ADHD who are inadequately controlled with methylphenidate or an amphetamine.

All systematic reviews found that when GXR was compared to placebo, there was a significantly higher incidence of discontinuations due to treatment-emergent adverse events. Four systematic reviews also found a higher incidence of discontinuations due to treatment-emergent adverse events when GXR was compared against other active

treatments via direct and indirect comparisons. The most commonly reported adverse effects have been reported as abdominal pain, fatigue, and headaches.

One included guideline issued a recommendation based on moderate quality evidence on the use of GXR as monotherapy or in combination with a psychostimulant for the management of oppositional behavior in children and adolescents with ADHD, with or without oppositional defiant disorder.

However, the robustness of evidence included in this report for the use of GXR as monotherapy relative to other treatments for ADHD was low, and no relevant economic evaluations were identified. Several gaps in the evidence identified by CDEC in 2014 are remaining, such as the long-term efficacy and safety of GXR as adjunctive therapy to psychostimulants in children with ADHD.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Ovid Medline, Ovid Embase, PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases and a focused Internet search. No methodological filters were applied to limit retrieval by publication type. The search was limited to English language documents published between January 1, 2013 and February 5, 2018.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Children and adolescents aged 6 to 17 years with ADHD
Intervention	Guanfacine hydrochloride extended-release tablets (Intuniv XR) - As adjunctive therapy to psychostimulants (4mg maximum daily dose of guanfacine hydrochloride) - As monotherapy for patients intolerant to psychostimulants (7mg maximum daily dose of guanfacine hydrochloride)
Comparator	- Amphetamines (immediate or sustained release: lisdexamfetamine dimesylate, amphetamine mixed salts, dextroamphetamine) - Methylphenidate (immediate or sustained release) - Atomoxetine - Clonidine - Atypical antipsychotics (aripiprazole, clozapine, ziprasidone, risperidone, quetiapine, olanzapine, asenapine, and paliperidone), with or without adjunctive psychostimulants - Placebo or no treatment

Outcomes	Q1: Clinical benefits and harms: - Behavioural, functional, developmental, or cognitive outcomes assessed by validated scales (e.g., BRIEF-P, ADHD-RS IV, CGI-S, CGI-I) - Health-related quality of life - Harms outcomes: SAEs, discontinuations due to TEAEs, mortality, AEs, and AEs of particular interest (hypotension, cardiovascular AEs, etc.) Q2: Cost-effectiveness outcomes (ex. ICER/ICUR, cost per QALY or other health benefit) Q3: Recommendations for use
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, economic evaluations, guidelines

ADHD= attention deficit-hyperactivity disorder; ADHD-RS IV = ADHD Rating Scale IV; AE = adverse event; BRIEF-P = Behavioural Rating Inventory of Executive Function (parent form); CGI-I = Clinical Global Impressions – Improvement scale; CGI-S = Clinical Global Impressions – Severity of Illness scale; ICER= incremental cost-effectiveness ratio; ICUR= incremental cost-utility ratio; QALY = quality-adjusted life years; SAE= serious adverse events; TEAE = treatment emergent adverse event.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2013.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using the AMSTAR2 tool,[8] randomized studies were critically appraised using the Downs and Black checklist,[9] economic studies were assessed using the Drummond checklist,[10] and guidelines were assessed with the AGREE II instrument.[11] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 217 citations were identified in the literature search. Following screening of titles and abstracts, 177 citations were excluded and 40 potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 38 publications were excluded for various reasons, while six publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Four systematic reviews (SRs) with meta-analyses (MAs) and network meta-analyses (NMAs),[12-15] one randomized controlled trial (RCT),[16] and one evidence-based guideline[17] were identified.

All four SRs only included information from RCTs.[12,13,15,18] The SRs included reported results of a conventional, pairwise MA to provide direct comparisons, followed by a NMA used to show the combination of direct and indirect evidence.[12,13,15,18] For two included NMAs,[12,13] a ranking preference was provided for all interventions in the form of a surface of cumulative ranking curve area (SUCRA).[12,13]

The included RCT was a short-term, double-blind, placebo-controlled trial.[16] This RCT was a crossover design, where patients were randomized to either GXR or placebo in the first eight weeks, and then the other treatment for the subsequent eight weeks.[16] The total duration of this study was about 20 weeks, including three weeks of follow-up and a 10 day washout period in between treatments.[16]

One clinical practice guideline met selection criteria (Appendix 2, Table A3).[17] This guideline was developed in 2015 by a multi-disciplinary group of healthcare practitioners in Canada working with an ADHD population. The development of this guideline utilized the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which is partly based on the quality of evidence, but is conceptually distinct and determined separately by considering several other factors. This process consisted of defining clinical questions, specifying patient-important outcomes, conducting a systematic review of published and unpublished studies which are systematic reviews and RCTs, and have included outcomes on oppositional behavior, conduct problems or aggression, as well as a placebo phase or group. A multi-disciplinary group would then provide a rating for the quality of the evidence, and decide on the direction and strength of recommendations.[17]

Country of Origin

There were four SRs with MAs and NMAs included in this report, two of which were conducted in China.[12,13] One SR was conducted in Spain,[15] and one was conducted in Switzerland.[18] The included RCT took place in Canada.[16]

One guideline was included in this analysis, which was a guideline published in the Canadian Journal of Psychiatry by a multidisciplinary group of health professionals in Canada.[17]

Patient Population

Four SRs with MAs and NMAs were conducted, all of which selected children and adolescents with a diagnosis of ADHD.[12,13,15,18] Two of these SRs included children and adolescents aged 6 to 17 years of age,[13,18] one included children and adolescents between 4 and 18 years of age,[12] and one included children and adolescents under 18 years of age.[15] Three of these studies required patients to have been diagnosed in accordance with the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).[12,13,18] It is unclear whether there was any discrimination based on ADHD subtype. One of the included SRs had broader criteria which allowed patients who had been diagnosed in accordance with the International Classification of Diseases (ICD) of any or all ADHD subtype(s).[15]

One RCT included children between the ages of 6 and 12 years.[16] This RCT required patients to meet DSM-IV-TR criteria for a primary diagnosis of ADHD, with sub-optimal executive function.[16] Sub-optimal executive function was defined as having a *t*-score of at least 65 on the Behavioural Rating Inventory of Executive Function – Parent form (BRIEF-P). In addition, this RCT studied use of GXR as an adjunct to psychostimulant therapy in patients with ADHD,[16] therefore requiring the patients to be currently treated with a stable

regimen of psychostimulant (methylphenidate or amphetamine).[16] With regard to previous ADHD medications, it was required that patients be receiving a stable dose of psychostimulant for a period of at least 30 days prior to enrollment, and that the stimulant was confirmed to be optimized by the investigator.[16]

One guideline met inclusion criteria which was a Canadian in origin.[17] Recommendations were issued by a multi-disciplinary panel of Canadian healthcare professionals. The target population in this guideline was children and adolescents with ADHD, oppositional defiant disorder or conduct disorder requiring management for disruptive and aggressive behavior.[17]

Interventions and Comparators

Within the NMAs included, all were designed to compare pharmacological interventions for ADHD.[12,13,15,18] The pharmacological interventions for ADHD were compared against one another in all of these studies, by either direct or indirect comparison depending on studies included.[12,13,15,18] The pharmacological interventions included in all studies were: placebo, guanfacine extended-release (GXR), methylphenidate (MPH), lisdexamfetamine dimesylate (LDX) and atomoxetine (ATX).[12,13,15,18] One study specifically examined MPH immediate-release and MPH extended release as separate interventions.[18] In terms of pairwise MAs, all of the SRs compared GXR as monotherapy against placebo,[12,13,15,18] and one of these analyses additionally compared GXR against ATX, as well as MPH.[13] Indirect analyses were used by the NMAs to compare GXR to MPH,[12,13,15,18] LDX,[12,13,15,18] clonidine,[12,13,15] and ATX.[12,13,15,18] Dosing of medication was not captured in these studies.[12,13,15,18]

The included RCT directly compared GXR to placebo.[7] This study included a dose optimization phase, where GXR was initiated at 1 mg per day, and increased in 1 mg weekly increments until an optimal dose was established, which is in line with the product monograph.[4] A maximum dose of 4 mg was established for all patients, of which was a study with a patient population of children aged 6 to 12 years.[16]

The included guideline focused specifically on pharmacotherapeutic interventions for disruptive and aggressive behaviours in children and adolescents with ADHD, opposition defiant disorder or conduct disorder.[17] These interventions included psychostimulants such as MPH and amphetamines, ATX, GXR, clonidine, risperidone, quetiapine and haloperidol.[17]

Outcomes

The main outcomes reported in the SRs and RCT included:

- ADHD Rating Scale–IV (ADHD-RS-IV) score:[16,18] a tool consisting of 18 items designed to reflect current symptoms of ADHD based on DSM-IV criteria.[1] Each item is scored from a range of 0 (no symptoms) to 3 (severe) symptoms with total scores ranging from 0 to 54. These items maybe grouped into two subscales: hyperactivity/impulsivity and inattentiveness.[1,2,5] While there is no consensus on what constitutes a minimally clinically important difference (MCID), previous CADTH drug reviews have used a range of 5.2-7.7 for the ADHD-RS score difference between treatment options and placebo, or a ≥30% score difference.[5]
- ADHD Rating Scale (ADHD-RS) score:[12,13,15] a tool consisting of 18 items designed to reflect symptoms of ADHD just as ADHD-RS-IV above; however, it is based on DSM criteria.[2] The numerical value at the end of ADHD-RS represents the DSM version that

was used when determining the categories of symptoms associated with ADHD. Three included SRs did not impose restrictions on studies examining ADHD-RS of a specific numerical value.[1]

- Clinical Global Impression–Improvement (CGI-I) score:[16,18,19] a 7-point scale ranging from 1 (very much improved) to 7 (very much worse) which assesses worsening or improvement from baseline, and permits a global evaluation of improvement.[1] Previous CADTH drug reviews have suggested an MCID of 1 or 2 with respect to CGI-I outcomes.[5]
- Clinical Global Impression–Severity (CGI-S) score:[16,18] a 7-point scale ranging from 1 (normal, no symptoms) to 7 (among the most extremely ill subjects, very severe symptoms), and it permits a global evaluation of the subject's severity.[1,5] Previous CADTH drug reviews have suggested an MCID of 1 or 2 with respect to CGI-S outcomes.[5]
- Treatment response (efficacy):[15] the proportion of patients who displayed improvements in ADHD symptoms or global functioning on standardized rating scales such as "much improved" or "very much improved" on the CGI (≤ 2), or a reduction of at least 25% from the baseline score on the ADHD-RS.[15]
- BRIEF-P[16]: an 86-item questionnaire completed by parents which assesses executive function behaviours at home or at school. T-scores, which are transformations of raw scale scores, are used to interpret the child's level of executive functioning. A t-score at or above 65 is considered clinically significant.[1] A clear definition of MCID for this scale has not been established.
- Treatment-emergent adverse events (TEAEs)[13,16]
- All-cause discontinuation[13,15,18]
- Discontinuation due to TEAEs[12,13,18]
- Columbia-suicide severity rating scale (C-SSRS)[16]

The included RCT evaluated symptomatic and syndromal remission based on the ADHD-RS-IV and CGI rating scales.[7] Symptomatic remission was an exploratory outcome measured in this study, defined as an ADHD-RS-IV total score ≤ 18, and syndromal remission was defined as a CGI-S score ≤ 2 in addition to an ADHD-RS-IV total score ≤ 18.[7]

Summary of Critical Appraisal

The strengths and limitations of the included reports are summarized in Appendix 3.

Systematic Reviews (SR) and Network Meta-analyses (NMA)

The quality of SR with NMAs included in this review was variable. Three studies clearly identified the population, intervention, comparator and outcomes of interest.[12,13,18] Three studies stated the review question, search strategy, inclusion and exclusion criteria in the study protocol.[12,13,18] In addition, in four studies,[12,13,15,18] any plan for investigating heterogeneity was outlined in the protocol. In three studies,[12,13,18] a comprehensive literature search strategy was provided. In four studies,[12,13,15,18] the review authors justified combining the data in an MA or NMA, and used appropriate weighted technique to combine

study results while adjusting for heterogeneity. In three studies,[13,15,18] the potential impact of risk of bias in individual studies and evidence synthesis was assessed, and in two studies,[13,15] the authors accounted for risk of bias when discussing the results. In three studies,[12,15,18] heterogeneity observed was discussed. One study[18] was funded by Shire Development, the manufacturer of Intuniv XR (GXR).[8]

All of SRs with NMAs included used scales which can be subjective, such as the ADHD-RS-IV scale, CGI-I, or CGI-S scale, which may lead to under or over-reporting. This may also cause participants in these scales (i.e., physicians or parents) to become prone to "halo" effects in the act of reporting. Although a combination of these scales can reduce subjectivity, there is still an opportunity for bias.[12-15]

RCTs

The included RCT had objectives and selection criteria stated clearly.[16] Patient characteristics, interventions and outcomes were well-described, and randomization was conducted in a double-blind fashion via an interactive web system.[16] Patients received treatment with GXR for 8 weeks, which may not be long enough to fully measure the effectiveness of GXR as an adjunctive therapy for children with ADHD on a background of psychostimulant therapy. There was an 11 day weaning period, which is shorter than previous studies of GXR, which have typically tapered over a two week period.[7,19-21] This study had a cross-over design, with patients initially assigned to either GXR or placebo for the first phase, and then patients received the other treatment for the second phase. This design was advantageous given the complex patient population, who were children with ADHD with suboptimal executive function, and concurrently receiving a stable dose of stimulant. Therefore, this design could limit between-group variability, since each patient provides results for each treatment. This patient population was also clinically relevant in that it represents an identified unmet need for treatment by CDEC in their recommendation.[6] Although there was a 10-day washout period after the 11-day weaning period, the risk of carry-over effects from treatment cannot be overlooked, especially with a drug that is known to be associated with withdrawal.[4] Finally, there was a risk for a patient's concurrent psychostimulant therapy to become a confounder if a patient improves adherence to their psychostimulant medication in this particular trial.[16]

With respect to the outcomes outlined in this study, the included RCT focused on a primary outcome of BRIEF-P, which is a functional measurement.[16] ADHD-RS-IV was also studied, as well as other functional measurements, such as CGI-I and CGI-S scores. The functional measurements in this study can demonstrate an improvement in social and executive functioning in school, family and social situations as well, which is an integral part of the ADHD diagnosis.

Guidelines

The included guideline was developed by an expert committee based on a systematic review process which was well described in a previous publication.[22] The objectives, clinical questions and the population for whom the guidance was intended for were all well-described. Recommendations were presented clearly Although attempts to account for bias were made in rating evidence quality, many studies included in the guidelines were industry funded.[17] Additionally, three of twelve expert committee members acknowledged receipt of funding from industry, all of whom had received funding from Shire.[17] These guidelines were externally reviewed by members of the Canadian Paediatric Society, and the Centre for ADHD Awareness Canada. In addition, these guidelines were reviewed by

parents of children and adolescents with ADHD, oppositional defiant disorder, or conduct disorder. This feedback was received by the expert committee and incorporated into the final document. There was no description provided on further updating or auditing of these guidelines after publication.[17,17]

Summary of Findings

The overall findings are summarized below and detailed findings from the individual studies are provided in Appendix 5.

What is the clinical effectiveness of guanfacine hydrochloride extended-release tablets for the treatment of children and adolescents with attention deficit hyperactivity disorder?

Efficacy

Among the four NMAs included,[12,13,15,18] a significant improvement was found in two studies when directly comparing GXR against placebo for its effect on ADHD-RS as weighted mean difference from placebo.[12,18] One NMA which used a primary outcome of treatment response, defined as either a reduction of ≥ 25% from baseline in ADHD-RS or a significant improvement from baseline in a CGI score, also found a significant improvement comparing GXR to placebo (OR 0.79 [95%CI 0.54-1.14]). The remaining NMA did not find a significant improvement in ADHD-RS from baseline when directly compared to placebo [OR 5.56 (95%CI -2.84, 13.96)];[13] however, when GXR and placebo were indirectly compared in this study, a significant improvement in this outcome was found [OR -6.58 (95%CI -10.58, -2.32)].[13]

The four NMAs included attempted to compare efficacy outcomes of GXR to alternative pharmacologic options for ADHD.[12,13,15,18] GXR was not found to perform significantly better than any other active treatment options for any of these outcomes, including ADHD-RS, or functional scales.[12,13,18] When LDX was included as an indirect comparison, it was found to be the most efficacious medication for ADHD, in both baseline to endpoint ADHD-RS,[12,13] or ADHD-RS-IV total score[18] change in children and adolescents. Using indirect comparisons, two NMAs found LDX to have a significantly higher efficacy rate compared to GXR when using ADHD-RS as an outcome.[12,13] This seems to correlate with the results obtained in another NMA, which found a much higher probability of LDX being the most efficacious treatment option (99.96%) compared to GXR, ATX and MPH-ER, which had the probability of being the most efficacious outcome, with a percentage of <1%.[18] Similar results were also found in this study for CGI-I, where the probability of LDX being the most efficacious drug was 96.21% for this outcome.[18] This meta-analysis attempted to draw a comparison in ADHD-RS between GXR and ATX and found the probability of GXR having a greater efficacy than ATX for this outcome to be between 81.19 and 97.86%; however, the confidence intervals for this probability overlapped, meaning that this result did not represent a significant difference.[18]

With respect to the included RCT, it compared the use of GXR to placebo.[16] This RCT evaluated the change from baseline to eight weeks for ADHD-RS-IV,[16] and found a significant improvement in ADHD-RS for GXR when being compared to placebo. This study saw a decrease in ADHD-RS-IV total score from baseline to end of treatment.[16]

In addition to the ADHD symptom rating scale (ADHD-RS-IV), all NMAs included a functional measure (such as CGI), which demonstrated improvement not only in ADHD symptoms but also on social functioning, which is also integral to ADHD management.[16] The RCT used a functional measure BRIEF-P as its primary outcome.[16] The results for this

outcome showed a significant improvement in this score for between the GXR arm relative to placebo [least squares (LS) mean difference from NOVA model= -3.0, 95%CI (-5.9, -0.2), p-value= 0.0392, intention-to-treat (ITT) population]. This RCT also found significant improvements comparing GXR and placebo in other functional scales for ADHD, which were CGI-I and CGI-S.[7,16] For CGI-S, the LS mean difference from NOVA model between GXR and placebo was -0.9, 95%CI (-1.4, -0.4) with a p-value of 0.0007, and for CGI-I, the LS mean difference from NOVA model between GXR and placebo was -0.7, 95%CI (-1.2, -0.3) with a p-value of 0.003, in the ITT population.[16] Lastly, this study found that for the subpopulation of patients who had ≥30% improvement of ADHD-RS-IV while on GXR, a significant difference was detected for the BRIEF-P score [LS mean difference= -7.6, 95% CI (-11.1, -4.1), p-value=0.0002].[16]

Safety

TEAEs were measured in three of the included studies, which seemed to agree with what is already known of GXR.[13,16] In the meta-analysis included, significant results were obtained concerning its ability to cause adverse effects when comparing GXR to placebo (abdominal pain: OR=2.04, 95%CI: 1.37, 3.13; fatigue: OR=2.70, 95%CI: 1.89, 3.85).[13] When examining adverse effects in a Bayesian model for refined indirect comparisons, results presented further reinforced initial estimates.[13] GXR as well as ATX presented a higher morbidity of abdominal pain when compared to placebo (ATX: OR=1.80, 95%CI: 1.40, 2.36; GXR: OR=2.18, 95%CI: 1.55, 3.19). Similarly, ATX and GXR presented significantly more fatigue than placebo (ATX: OR=2.48, 95%CI: 1.55, 4.14; GXR: OR=4.22, 95%CI 2.56, 7.54).[13] When observing the probability of best treatments derived from SUCRA for this study, ATX and GXR were associated with the worst evaluation in the morbidity of adverse events.[13] This incidence of TEAEs were similar to the results in one included RCT,[16] where 41/47 (87%) of patients on GXR and 41/48 (85%) of patients on placebo reported TEAEs.[16] In both these cases, the most commonly reported TEAE was headaches for both groups, followed by abdominal pain and fatigue in patients while taking GXR.[16]

Among the meta-analyses included, four reported all-cause discontinuation of GXR,[12,13,15,18] and three reported discontinuation due to TEAE as pictured in Table 2.[12,13,15,18] When examining pair-wise meta-analysis, two studies found GXR to be was significantly higher when compared to placebo for all-cause discontinuation.[12,15] It was mentioned in one of these studies that the GXR had a higher likelihood of producing withdrawal symptoms due to adverse effects compared to placebo (OR=3.09; 95%CI 1.80, 5.28).[12] When examining studies which provided indirect comparisons, one study found a significant increased risk of all-cause discontinuation of GXR relative to placebo.[15] Results of both pair-wise and indirect comparisons of discontinuation due to adverse effects displayed a significant increase relative to placebo.[12,13,18]

Table 2: Direct and Indirect Comparisons of Harms Outcomes for GXR vs placebo[a]

Studies	GXR vs Placebo, direct comparison OR (95% confidence interval)	GXR vs Placebo, indirect comparison OR (95% confidence interval)
All-cause discontinuation		
Luan, 2017[13]	0.90 (0.77, 1.05)	0.83 (0.63, 1.09)
Catala-Lopez, 2017[15]	**0.77 (0.61, 0.98)**	**3.29 (2.27, 4.82)**
Li, 2017[12]	**0.82 (0.70, 0.97)**	0.83 (0.61, 1.12)
Joseph, 2017[18]	0.82 (0.58, 1.18)	NR

Studies	GXR vs Placebo, direct comparison OR (95% confidence interval)	GXR vs Placebo, indirect comparison OR (95% confidence interval)
Discontinuation due to TEAE		
Luan, 2017[13]	**2.94 (1.41, 5.88)**	**3.39 (1.93, 6.30)**
Li, 2017[12]	**3.09 (1.80, 5.28)**	**3.95 (2.34, 7.30)**
Joseph[18]	**4.49 (2.10, 8.81)**	NR

GXR= guanfacine extended-release; NR= not reported; OR= odds ratio; TEAE= treatment-emergent adverse events.

[a]Results which are bolded indicate statistical significance.

What is the cost-effectiveness of guanfacine hydrochloride extended-release tablets for the treatment of children and adolescents with attention deficit hyperactivity disorder?

There were no studies found which met the inclusion criteria outlined for this report.

What are the evidence-based guidelines regarding the use of guanfacine hydrochloride extended-release tablets for the treatment of children and adolescents with attention deficit hyperactivity disorder?

One Canadian national guideline was found which issued recommendations based on moderate quality evidence for the use of GXR in managing oppositional behavior in children and adolescents with ADHD, with or without oppositional defiant disorder (ODD).[17] The indication for its use would be for the treatment of functionally disabling oppositional behavior in children and adolescents with ADHD who have done poorly (regarding response or tolerability) with adequate psychostimulant trials. GXR was recommended to be offered as monotherapy or in combination with a psychostimulant, depending on the clinical circumstances. GXR monotherapy was only recommended to be considered when psychostimulants have provided minimal benefit or caused intolerable adverse effects.[17] Combination therapy was also considered indicated when psychostimulants have provided clinically meaningful benefit and are well-tolerated, but significant behavioural challenges remain. With respect to age group, the guideline noted that GXR has been found to be superior to placebo in children but not in adolescents, but that that it is unknown whether the same differential effect by age group would be seen when treating oppositional behavior.[17]

This guideline also cautioned the side effect burden with this medication to be moderate, and that missed doses or abrupt discontinuation can cause rebound tachycardia and hypertension, therefore the potential for nonadherence should be considered.[17]

No additional guidelines published from January 2013 to February 2018 were found which issue recommendations for the use of GXR in the treatment of ADHD.

Limitations

Firstly, no cost-effectiveness studies were identified which met the inclusion criteria outlined in this report. Previous studies of GXR identified in the CDEC report identified key limitations,[6] including resource utilization costs and short treatment duration, which may have been able to be addressed in a long-term cost-effectiveness or cost-utility study. In addition to this, there were no health technology assessments which met criteria for inclusion in this report, which would have provided better context when making policy or coverage decisions.

Secondly, there was an unmet need identified in the CDEC recommendation for patients with ADHD requiring adjunctive therapy. GXR was not listed for this indication due to the fact that its "available evidence was limited to a single, short-term RCT",[6] The RCT included in this report did study GXR as adjuvant therapy with a stable dose of psychostimulants; however, it was over the same duration as the previous RCT included (eight weeks).[16] Unfortunately, the four SRs with NMAs included in this report included RCTs that examined the use of GXR as monotherapy in the treatment of children and adolescents with ADHD.[12-15] Due to the establishment of psychostimulants as first-line therapy, an analysis of GXR solely used as adjuvant therapy in the management of ADHD would be appropriate, considering the current unmet need amongst medications for ADHD, and the contrast GXR would provide in children and adolescents with ADHD on high doses of stimulants.

Finally, outlined in the CDEC recommendation was a need for an assessment of "comparative clinical benefit for GXR relative to other less costly treatments for ADHD".[6] Unfortunately, there have been no head-to-head studies which were found in this report which directly compared GXR against active treatment used in the management of ADHD.

Conclusions and Implications for Decision or Policy Making

Since the previous recommendations issued by CDEC, one additional RCT has been published using GXR as adjunctive therapy to psychostimulants, contributing available evidence to an area of ADHD management for which there is an unmet need. This RCT may also further support evidence of its use in children with ADHD who are inadequately controlled with methylphenidate or an amphetamine. CDEC had also previously noted that there is insufficient evidence of GXR use to support a recommendation in this area. This RCT was designed as a double-blind, cross-over study with concealed allocation, with a similar duration of treatment and placebo (8 weeks) to previous studies of GXR as adjunctive treatment,[7] however results of this study are limited by a small sample size, and short weaning period.

In addition, CDEC noted an absence of direct evidence comparing GXR with other active treatments. There were no new studies identified which addressed this concern; however there were a few indirect analyses which compared GXR with other pharmacological treatments. In terms of efficacy, GXR did not perform significantly better than any other pharmacological treatments for ADHD.[12-15] With respect to harms, significant increases in discontinuation due to TEAEs were found when comparing GXR to placebo via direct and indirect comparisons.[12,13,18] Most commonly reported adverse effects have been reported as abdominal pain, fatigue, and headaches.[13] One NMA compiled a SUCRA ranking of current ADHD therapies and found GXR to have a moderate ranking in efficacy, but was associated with the worst evaluation in the morbidity of adverse events.[13]

There were no identified economic evaluations which met inclusion criteria for this report; however, results from a recently published cost analysis study indicated that use of GXR as monotherapy or in combination in children and adolescents with ADHD may result in higher total all-cause and ADHD-related healthcare costs. These results should be interpreted with caution however, due to significant limitations in this study design.[23] There was also one recently published cost-effectiveness study which included GXR and clonidine in one arm compared to atypical antipsychotics. Results from this study suggest that the use of GXR or clonidine in children and adolescents with ADHD who have failed stimulant therapy is more cost-effective than the use of atypical antipsychotics.[24]

One included guideline recommended the use of GXR as monotherapy or in combination with a psychostimulant for the management of oppositional behavior in children and adolescents with ADHD, with or without oppositional defiant disorder. The multi-disciplinary expert committee regarded the quality of evidence for this recommendation to be moderate, and the magnitude of benefit to range from small to moderate. It also noted the side effect burden to be moderate, and concluded that the strength of this recommendation was conditional, in favour.[17]

In conclusion, this report is limited in its ability to answer gaps in therapy which were identified in the previous CDEC report.[6] The robustness of evidence included in this report for the use of GXR as monotherapy relative to other treatments for ADHD is low. Furthermore, there were no economic evaluations identified to provide further context on resource utilization attributable to GXR treatment and consideration of less costly comparators, elements of which were lacking in the previous CDR report for GXR.[5] There have been encouraging results found in an RCT which adds to the existing body of literature examining the use of GXR as adjunctive therapy to psychostimulants in children, an area of which there are a limited number of treatments approved for use. However, the duration of this study, (8 weeks) was the same as a previous study evaluated by CDEC, where it was deemed as an insufficient length of time. Also, long-term efficacy of this drug is still unknown. There was a significant increase in incidence of discontinuations found due to adverse effects with GXR, relative to active comparators as well as placebo. Furthermore, there continues to be a lack of long-term safety data associated with the use of this drug.

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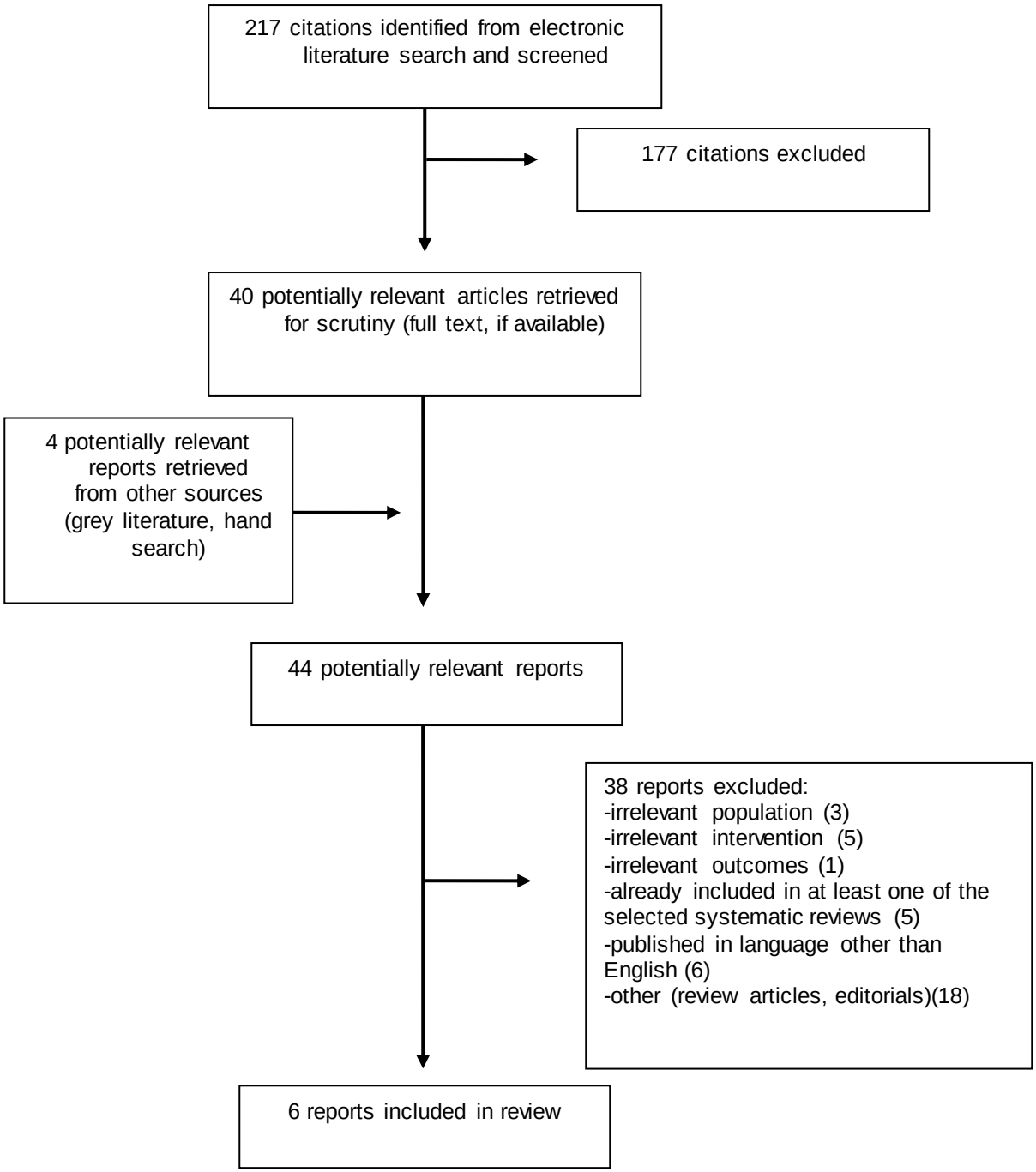
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 3: Characteristics of Included Systematic reviews (with Pairwise Meta-Analyses and Network Meta-Analyses)

First Author, Publication, Year, Country	Types and numbers of primary studies included	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-Up
Luan, 2017[13] **China**	Total primary studies: N=73; 13 with a GXR comparison All RCTs	Children and adolescents (6-17 years old) diagnosed with ADHD in accordance with DSM-IV criteria	GXR	Placebo (direct, 11 studies), ATX (direct, 1 study), MPH (indirect), LDX (indirect), clonidine (indirect)	ADHD-RS; all-cause discontinuation; discontinuation due to TEAEs; discontinuation due to lack of efficacy; nausea; abdominal pain; fatigue
Catala-Lopez, 2017[15] **Spain**	Total primary studies: N=190; 10 with a GXR comparison All RCTs	Children and adolescents (under 18 years of age) with a diagnosis of ADHD in accordance with DSM-IV criteria or the ICD of any/all ADHD sub-types	GXR	Placebo, MPH, ATX, clonidine, LDX	Treatment response (efficacy), all-cause discontinuation
Li, 2017[12] **China**	Total primary studies: N=62; 11 with a GXR comparison All RCTs	Children and adolescents (4-17 years old) diagnosed with ADHD in accordance with DSM-IV criteria	GXR	Placebo, MPH, LDX, clonidine, ATX	Mean difference in ADHD-RS scores, discontinuation due to adverse events
Joseph, 2017[18] **Switzerland**	Total primary studies: N=36; 6 with a GXR comparison All RCTs	Children and adolescents (6-17 years old) diagnosed with ADHD using DSM-IV criteria	GXR	LDX, ATX, MPH-ER, MPH-IR	ADHD-RS-IV scores; CGI-I score; all-cause discontinuation; discontinuation due to adverse effects

ADHD= attention deficit hyperactivity disorder; ADHD-RS= attention deficit hyperactivity disorder rating scale; ATX= atomoxetine; CGI-I= Clinical Global Impression-Improvement; DSM-IV= Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; ICD= International Classification of Diseases; GXR= guanfacine extended-release; LDX= lisdexamfetamine dimesylate; MPH= methylphenidate; MPH-ER= methylphenidate extended-release; MPH-IR= methylphenidate immediate-release; RCT = randomized controlled trial; TEAE= treatment-emergent adverse event.

Table 4: Characteristics of Included Randomized Controlled Trials

First Author, Publication, Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Study Sample Size	Intervention(s)	Comparator(s)	Main Clinical Outcomes
van Stralen, 2018[16] **Canada**	Double-blind, randomized, placebo-controlled crossover trial (preceded by a 4 week dose optimization phase, followed by 11-day weaning) 16 weeks (8 weeks GXR; 8 weeks placebo) + 3 week follow-up	Children aged 6 to 12 years diagnosed with primary ADHD in accordance with DSM-IV-TR N= 25 per group (randomized to start with either GXR or placebo, 50 in total) ITT analysis	GXR (initiated at 1mg/day, increased in 1mg/week increments to a maximum 4mg/day)	Placebo	BRIEF-P (parent-completed); ADHD-RS-IV; CGI-S; CGI-I; TEAEs; C-SSRS

ADHD= attention deficit hyperactivity disorder; ADHD-RS-IV= attention deficit hyperactivity disorder rating scale IV; BRIEF-P= Behavioural rating inventory of executive function; CGI-I= Clinical global impression-improvement score; CGI-S= Clinical global impression-severity score; C-SSRs= Columbia-suicide severity rating scale; DSM-IV-TR= Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, text revision; GXR= guanfacine extended-release; TEAE= treatment-emergent adverse event

Table 5: Characteristics of Included Guidelines

Citation	Intended users/ Target population	Intervention and Practice Considered	Major Outcomes Considered	Evidence collection, selection and synthesis	Evidence Quality and Strength	Recommendations development and Evaluation
Gorman, 2015 Canada	Intended users: clinicians who provide care for children and adolescents with behavioural problems Target population: children and adolescents with ADHD, ODD or CD	Pharmaco-therapy for functionally disabling oppositional behaviour, conduct problems, and aggression in children and adolescents with ADHD, ODD or CD (including GXR)	Clinical efficacy and side effect burden for the treatment of oppositional behaviour, conduct problems and aggression	Multiple electronic database searches (updated to October 2013) without language restrictions or regard for publication status	Evidence rated according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) levels of evidence	Recommendations developed by an expert multidisciplinary consensus group comprising 12 members from across Canada; graded recommendations according to level of evidence upon which they were based, as well as considering perceived value and preferences of patients and families; guidelines were externally reviewed by members of the CPS, CACAP, and CADDAC

ADHD= attention deficit-hyperactivity disorder; CACAP= Canadian Academy of Child and Adolescent Psychiatry; CADDAC= Centre for ADHD Awareness Canada; CD= conduct disorder; CPS= Canadian Paediatric Society GXR= guanfacine extended-release; ODD= oppositional defiant disorder RCT = randomized controlled trial

Appendix 3: Critical Appraisal of Included Publications

Table 6: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 28

Strengths	Limitations
Luan 2017[13]	
- Population, research questions, inclusion criteria and outcomes of interest were clearly defined - Relevant comparators have been considered - Publication bias was investigated via funnel plot and likelihood and magnitude of impact was discussed - Risk of bias assessment was conducted at baseline - Graphic representation of evidence network provided	- Although heterogeneity was assessed in this study via I^2 and Cochran's Q, it was not discussed in the body of the report, and no subgroup analyses or meta-regression analyses with pre-specified co-variates were performed - Individual study results were not reported - Effect of age, use of combination ADHD medications on treatment effects were not reported
Catala-Lopez 2017[15]	
- Population, research questions, inclusion criteria and outcomes of interest were clearly defined in previously published protocol - Heterogeneity was assessed by I^2 index and Cochran's Q - Publication bias and risk of bias assessment was conducted at baseline - Sensitivity analyses were performed which excluded studies at an overall high risk of bias	- High degree of heterogeneity in trial design, patient population and outcome measurements - Individual study results were not reported - Treatment efficacy was reported as a composite outcome (defined as either a reduction of ≥25% from baseline in ADHD-RS or a significant improvement from baseline in a CGI score), which can reduce robustness of data
Li 2017[12]	
- Population, research question, inclusion/exclusion criteria and outcomes of interest were clearly defined - Relevant comparators were considered - High sample size (N=12,930) - Heterogeneity was assessed using I^2 and Q statistics - Graphic representation of evidence network provided	- Main efficacy outcome of interest was termed ADHD-RS, which was not specific to the edition of the scale, potentially increasing heterogeneity in the results - Results were subjective to the volume of literature available for pharmacotherapy options in ADHD management, this study noted a higher amount of data for ATX outcomes - No risk of bias or publication bias was assessed - Included RCTs were not assessed for blinding, concealment of treatment allocation, randomization or ITT analysis
Joseph 2017[16]	
- Research questions and inclusion criterial clearly defined - Sensitivity analyses were performed for each outcome to assess robustness of findings, which attempted to account for variations (ie statistical method to account for outcome heterogeneity (fixed vs random effects), study duration) - Heterogeneity was assessed using I^2 and Cochran's *Q* - Data extraction was performed in duplicate - Studies were assessed for blinding, concealment of treatment allocation, randomization, ITT analysis	- An investigation of publication bias was not carried out or discussed - Dosing was not evaluated, thus could not distinguish titration period - Research was funded by Shire Development, the manufacturer of Intuniv XR

ADHD=attention deficit hyperactivity disorder; ADHD-RS= attention deficit hyperactivity disorder rating scale; ATX= atomoxetine; CGI= Clinical Global Impression scale; ITT= intention-to-treat; RCT = randomized controlled trial; XR= extended-release

Table 7: Strengths and Limitations of Randomized Controlled Trials using Downs and Black[9]

Strengths	Limitations
van Stralen 2017[10]	
- Majority of patients included were male aged 6-12 years old, which is aligned with ADHD prevalence - Duration was 15 weeks (including a titration and weaning phase) - Cross-over design can limit between-patient variability - Patients were randomized in double-blind fashion in a 1:1 fashion via an interactive web randomization system	- Cross-over design risks carry-over effects from treatment due to insufficient wash-out - 39 patients (78%) completed the study, which is slightly lower than the 40 patients required to detect a treatment difference with a probability of 80% - Shorter dose-optimization phase than other RCTs

Table 8: Strengths and Limitations of Guidelines using AGREE II[11]

Strengths	Limitations
Gorman, 2015	
- Overall objective(s) of the guideline, target population, intended users and questions are specifically described - Guideline development group included a multidisciplinary team of clinical experts in this area, with views and preferences of the target population captured through the use of a survey - Systematic methods used to search evidence with search strategy provided, with methods provided - Recommendations are specific, clear, easily identifiable - Advice provided on applying recommendations to practice	- Three of the twelve consensus group members acknowledged receipt of funding from industry, all had received funding from manufacturer of GXR (Shire) - Although attempts to account for bias were made in rating evidence quality, many studies included in the guidelines were industry funded - Conduct problems and aggression was not evaluated for most studies including GXR

Appendix 4: Main Study Findings and Author's Conclusions

Table 9: Summary of Findings of Included Studies

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusion</th></tr>
<tr><td colspan="2">Luan 2017[13]</td></tr>
<tr><td>
Relative treatment effects of GXR vs active comparators in direct meta-analyses
<table>
<tr><th>Outcome</th><th>GXR vs Placebo</th><th>GXR vs. ATX</th><th>MPH vs GXR</th></tr>
<tr><td>ADHD-RS</td><td>5.56 (-2.84, 13.96)</td><td>-</td><td>-0.22 (-4.32, 3.88)</td></tr>
<tr><td>All-cause withdrawal</td><td>0.90 (0.77, 1.05)</td><td>1.02 (0.54, 1.89)</td><td>0.98 (0.35, 2.78)</td></tr>
<tr><td>Withdrawal due to adverse events</td><td>2.94 (1.41, 5.88)</td><td>1.75 (0.57, 5.26)</td><td>1.96 (0.17, 20.00)</td></tr>
<tr><td>Withdrawal due to lack of efficacy</td><td>0.41 (0.30, 0.56)</td><td>0.97 (0.27, 3.45)</td><td>0.49 (0.04, 5.56)</td></tr>
<tr><td>Nausea</td><td>1.27 (0.88, 1.85)</td><td>0.58 (0.31, 1.11)</td><td>0.67 (0.26, 1.69)</td></tr>
<tr><td>Abdominal pain</td><td>2.04 (1.37, 3.13)</td><td>0.75 (0.33, 1.67)</td><td>0.93 (0.45, 1.92)</td></tr>
<tr><td>Fatigue</td><td>2.70 (1.89, 3.85)</td><td>1.18 (0.65, 2.13)</td><td>0.22 (0.08, 0.63)</td></tr>
</table>
Odds Ratios for ADHD-RS of GXR vs active comparators in network meta-analyses
<table>
<tr><th>Active Comparators</th><th>Odds Ratios (95% CI)</th></tr>
<tr><td>ATX</td><td>0.19 (-4.59, 4.90)</td></tr>
<tr><td>Clonidine</td><td>1.53 (-9.85, 12.84)</td></tr>
<tr><td>LDX</td><td>3.80 (-2.80, 10.26)</td></tr>
<tr><td>MPH</td><td>0.63 (-4.47, 5.63)</td></tr>
<tr><td>Placebo</td><td>-6.58 (-10.58, -2.32)</td></tr>
</table>
Relative safety outcomes of GXR vs active comparators in network meta-analyses
<table>
<tr><th>Outcome</th><th>GXR vs Placebo</th><th>GXR vs. LDX</th></tr>
<tr><td>All-cause withdrawal</td><td>0.83 (0.63, 1.09)</td><td>1.34 (0.79, 2.23)</td></tr>
<tr><td>Withdrawal due to adverse events</td><td>3.39 (1.93, 6.30)</td><td>2.48 (0.94, 6.49)</td></tr>
<tr><td>Withdrawal due to lack of efficacy</td><td>0.37 (0.26, 0.54)</td><td>3.46 (1.70, 7.61)</td></tr>
</table>
Relative efficacy
- Comparing GXR versus placebo, significant results were obtained concerning its ability to cause adverse effects (abdominal pain, fatigue and withdrawal due to adverse events, but the change of withdrawal due to lack of efficacy was reduced
- Significant improvement was obtained on GXR comparison with placebo for ADHD-RS [MD=6.58, 95%CI CrI: 2.32-10.94]
- GXR did not perform significantly better than any other treatments with the exception of placebo
- Significant results were acquired when evaluating LDX with other drugs (except clonidine), including GXR: OR=0.29, 95%CrI: 0.13-0.59)
Adverse events
- For withdrawal due to an adverse event, GXR showed higher possibility vs placebo (OR=3.39, 95% CrI: 1.93-6.30); and GXR showed more association with adverse response which ahad led to withdrawal than ATX (OR=2.29, 95% CrI: 1.20-4.57), and MPH presented reduction vs GXR (OR=0.39, 95%CrI: 0.18-0.83)
- In results of withdrawals and adverse events, GXR was found to be significantly greater than ATX for all cause withdrawal [0.51 (0.26, 0.96)]; significantly greater than MPH for withdrawal due to adverse events [0.39 (0.18, 0.83)]; and significantly greater than LDX for withdrawal due to lack of efficacy [0.29 (0.13, 0.69)]
SUCRA ranking
- LDX and MPH were considered as a group with the best comprehensive ranking score, including efficacy and tolerability
- ATX and GXR had moderate rankings in efficacy, but were associated with the worst evaluation in the morbidity of adverse events
</td><td>"GXR is located at a moderate position under symptom improvement and withdrawal rate, which is consistent with existing evidence. However, the unsatisfying SUCRA ranking scores in nausea, abdominal pain and fatigue do not mean it is poorly tolerated or unsafe. GXR can be seen as a moderate choice in ADHD treatment."</td></tr>
</table>

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusion</th></tr>
<tr><td colspan="2">Catala-Lopez 2017[15]</td></tr>
<tr><td>Network meta-analysis for treatment response and all-cause discontinuation of GFX vs other treatments
<table>
<tr><th>Other Treatments</th><th>Treatment Response OR (95%CI)</th><th>All-cause discontinuation OR (95% CI)</th></tr>
<tr><td>Placebo</td><td>0.79 (0.54-1.14)*</td><td>3.29 (2.27-4.82)*</td></tr>
<tr><td>Methylphenidate</td><td>1.34 (0.86-2.07)</td><td>0.62 (0.40-0.98)*</td></tr>
<tr><td>Atomoxetine</td><td>0.92 (0.61-1.41)</td><td>0.91 (0.58-1.41)</td></tr>
<tr><td>Clonidine</td><td>1.99 (0.91-4.33)</td><td>0.83 (0.36-1.92)</td></tr>
</table></td><td>"Guanfacine seemed significantly more efficacious than placebo. Methylphenidate seemed more efficacious than atomoxetine and guanfacine."</td></tr>
<tr><td colspan="2">Li, 2017[12]</td></tr>
<tr><td>Pair-wise Meta-analysis results:
- ADHD-RS as primary outcome found a significant difference comparing GXR vs placebo : weighted mean difference= -0.60, 95%CI [-0.75, -0.44], tau^2= 0.02, I^2 46.9%
- GXR was found to have a higher likelihood of discontinuation due to adverse effect compared to placebo (OR=3.09, 95%CI [1.80, 5.28], tau^2=0.26, I^2=24.60%), and was higher in all-cause withdrawals compared to placebo (OR=0.82, 95%CI [0.70, 0.97], tau^2=0.05, I^2=38.9%)
- Regarding withdrawal due to lack of efficacy, GXR proved to have a better performance than placebo (OR 0.38, 95%CI [0.28, 0.51], tau^2=0, I^2=1%)
Network Meta-analysis results
Mean ADHD-RS total score decrease from baseline of GXR relative to other ADHD treatments
<table>
<tr><th>ADHD therapies</th><th>Mean decrease in total score vs GXR (95% CI)</th></tr>
<tr><td>Placebo</td><td>-7.58 (-10.22, -5.22)</td></tr>
<tr><td>ATX</td><td>-0.46 (-3.38, 2.28)</td></tr>
<tr><td>Clonidine</td><td>-1.15 (-6.47, 4.01)</td></tr>
<tr><td>LDX</td><td>6.71 (2.92, 10.34)</td></tr>
<tr><td>MPH</td><td>1.49 (-2.18, 5.01)</td></tr>
</table>
- LDX was shown to be the most efficient medication for ADHD, and had a significantly higher efficacy rate that GXR (mean difference: 6.7, 95%CI [2.9, 10.0])
- GXR as well as ATX had a relatively low probability of withdrawal (ATX: 22.83%, GXR: 28.00%)
Incidence of discontinuation due to TEAE of GXR relative to other ADHD treatments
<table>
<tr><th>ADHD therapies</th><th>Incidence of Discontinuation due to TEAE vs GXR (95% CI)</th></tr>
<tr><td>Placebo</td><td>3.95 (2.34, 7.30)</td></tr>
<tr><td>ATX</td><td>2.54 (1.38, 5.21)</td></tr>
<tr><td>Clonidine</td><td>1.60 (0.45, 6.51)</td></tr>
<tr><td>LDX</td><td>1.92 (0.86, 4.82)</td></tr>
<tr><td>MPH</td><td>3.33 (1.56, 7.82)</td></tr>
</table>
- Considering withdrawals due to adverse events, patients using GXR were more likely to suffer from severe adverse effects than if they were to take the other drugs (87.17% for cumulative ranking probabilities)
- ATX was considered the safest drug for ADHD based on the analysis, due to its lowest incidence rate of all-cause withdrawals as well as withdrawals due to lack of efficacy, although efficacy appears to be lower than GXR</td><td>"GXR is found to have a high efficacy when ADHD-RS is applied as a variable, among which LDX has the highest efficacy together with safety ranking in fourth place. The high incidence of withdrawals should be taken into consideration when BUP, clonidine, GXR and LDX are used on ADHD patients."</td></tr>
<tr><td colspan="2">Joseph 2017[18]</td></tr>
<tr><td>ADHD-RS-IV
- LDX demonstrated significantly better efficacy than other treatments in baseline to endpoint ADHD-RS-IV total score change in children and adolescents, with a 99.96% probability of being the most efficacious of all pharmacotherapies within the network</td><td>"This study found that LDX had greater efficacy than GXR, ATX and MPH in reducing symptoms in children and adolescents with</td></tr>
</table>

Main Study Findings	Author's Conclusion

- Among non-stimulants, the probability of GXR having greater efficacy than ATX ranged from 81.19 to 97.86%

Mean ADHD-RS-IV total score decrease from baseline relative to placebo

ADHD therapies	Total score decrease vs placebo (95% CI)	Probability of the treatment being most effective among all	Probability of GXR being more effective compared with each treatment
LDX	-14.98 (-12.80, -17.14)	99.96%	-
MPH-ER	-9.33 (-7.04, -11.63)	<1%	<1%
GXR	-8.68 (-6.72, -10.63)	<1%	93.91%
ATX	-6.88 (-5.49, -8.22)	<1%	33.04%

CGI-I

- The best clinical response among all pharmacotherapies was highest for LDX with a point estimates of relative risk of 2.56 (95%CI 2.21, 2.91), followed by 2.13 (95%CI 1.70, 2.54) for MPH-ER, 1.94 (95%CI 1.59, 2.29) for GXR, 1.77 (95% CI 1.31, 2.26) for ATX and 1.62 (95%CI 1.05, 2.17) for MPH-IR (placebo relative risk was 0.31 (95%CI 0.28, 0.34))
- The probability of LDX being the most efficacious drug was 96.21% for this outcome

Odds ratios and relative risks for all-cause discontinuation vs placebo

Drug	Odds ratio (95%CI)	Relative risk (95% CI)	Treatment least likely to be discontinued (Probability, %)
GXR	0.82 (0.58, 1.18)	0.87 (0.66, 1.12)	<1%
LDX	0.58 (0.38, 0.88)	0.66 (0.46, 0.91)	3.41%
ATX	0.83 (0.63, 1.11)	0.88 (0.71, 1.08)	<1%
MPH-ER	0.43 (0.31, 0.62)	0.52 (0.38, 0.69)	19.25%
MPH-IR	0.35 (0.19, 0.61)	0.44 (0.25, 0.69)	77.23%

- Confidence intervals between GXR and ATX overlapped in their risk of discontinuation due to any cause

Discontinuation due to Adverse Events

- The relative risk estimates for adverse event-related discontinuation were 1.20 (95%CI 0.32, 3.06) for MPH-IR, 1.38 (95% CI 0.60, 2.68) for MPH-ER, 2.39 (95% CI 1.26, 4.11) for ATX, 3.11 (95% CI 1.20, 6.76) for LDX and 4.49 (95% CI 2.10, 8.81) for GXR (placebo relative risk was 0.02 (95%CI 0.01, 0.02))
- The probability of GXR being discontinued due to adverse events was highest among all treatments

ADHD, with no overlap in confidence intervals on the ADHD-RS-IV. Safety, as measured by all-cause and AE-related discontinuations, was slightly better for MPH relative to other therapies, but the sample sizes were relatively low and statistical uncertainty was high for this outcome. Further study with an updated network is warranted if additional direct or indirect evidence becomes available."

van Stralen, 2018[16]

- Of the 50 randomized patients, 39 patients (78%) completed the study (19 patients in the GXR-PLB sequence and 20 patients in the PLB-GXR sequence)
- A total of 40 patients were needed to complete this study with an 80% probability that a treatment difference to be detected.

Analysis of primary and secondary outcome measures in children with ADHD:

Efficacy Measure	GXR		Placebo		LS mean form NOVA model	p-value
	Baseline mean (SE)	End of treatment mean (SE)	Baseline mean (SE)	End of treatment mean (SE)		
BRIEF-P	71.2 (1.20)	64.3 (1.64)	72.8 (1.25)	67.4 (1.63)	-3.0	**0.0392***
ADHD-RS	34.1 (1.27)	22.9 (1.39)	35.5 (1.25)	30.1 (1.83)	-6.9	**<0.0001***
CGI-S	4.7 (0.09)	3.3 (0.20)	4.8 (0.08)	4.2 (0.16)	-0.9	**0.0007***
CGI-I		2.6		3.3	-0.7	**0.0030***

"The results of this study show that adjunctive administration of guanfacine extended-release, to a psychostimulant in patients with suboptimal response to psychostimulants improves executive function compared with psychostimulant with placebo."

Main Study Findings	Author's Conclusion
Adverse Effects - 41 (87%) of patients reported TEAEs when taking GXR and 41 (85%) reported TEAEs when taking placebo, majority of which were mild - Moderate TEAEs were sleep disorder (2% vs 2%), fatigue (2% vs 0%), somnolence (2%vs 0%), and depressed mood (2% vs 0%) in the GXR arm vs the placebo arm - No patients discontinued due to a TEAE in the GXR arm vs 8% in the placebo arm - A total 60% (28/47) patients in GXR arm vs 27% (13/48) in placebo arm reported at least one TEAE; somnolence was reported for 11% of patients in the GXR arm and 4% in the placebo arm, and was experienced for a median duration of 7 days vs 8.5 days	
Guidelines	
Gorman, 2015[17]	
- "GXR monotherapy should be considered when psychostimulants have provided minimal benefit or have caused intolerable adverse effects - When psychosocial therapy provides insufficient benefit, clinicians may offer GXR for the treatment of functionally disabling oppositional behaviour in children and adolescents with ADHD who have done poorly (regarding response or tolerability) with adequate psychostimulant trials - Conversely, combination treatment should be considered when psychostimulants have provided clinically meaningful benefit and are well tolerated, but significant behavioural challenges remain. Of note, in two studies that analyzed ADHD outcomes by age group, GXR was superior to placebo in children but not in adolescents it is unknown whether the same differential effect by age group would be found for oppositional behavior - The side effect burden of guanfacine is moderate, and missed doses or abrupt discontinuation can cause rebound tachycardia and hypertension, therefore the potential for medication nonadherence should be considered"	"GXR (monotherapy or in combination with a psychostimulant) for oppositional behavior in children and adolescents with ADHD, with or without oppositional defiant disorder - Quality of evidence: moderate - Magnitude of benefit: small to moderate - Side effect burden: moderate - Strength of recommendation: conditional, in favour"

ADHD=attention deficit hyperactivity disorder; ADHD-RS= attention deficit hyperactivity disorder rating scale; ADHD-RS-IV= attention deficit hyperactivity disorder rating scale IV; ATX= atomoxetine; BMI= body mass index; CGI-I= Clinical Global Impression –Improvement; CI= confidence interval; GXR= guanfacine extended release; LDX= lisdexamfetamine dimesylate; LS= least squares;MPH= methylphenidate; NA= not applicable; NR=not reported; OR= odds ratio; RCT = randomized controlled trial; SD= standard deviation; SE= standard error; SUCRA= surface under the cumulative ranking curve; TEAE= treatment-emergent adverse event; WFIRS-P= Weiss Functional Impairment Rating Scale- parent report.

Appendix 5: Additional References of Potential Interest

HTA analyses excluded based on language restrictions

INTUNIV (guanfacine), agoniste alpha adrénergique [Internet]. Paris: Haute Autorité de Santé; 2017. [cited 2018 Feb 23]. (Avis sur les médicaments). Available from: https://www.has-sante.fr/portail/jcms/c_2769369/fr/intuniv?xtmc=&xtcr=78

Intuniv® (guanfacine) [Internet]. Copenhagen: Danish Health Authority; 2016. [cited 2018 Feb 23]. Available from: https://www.sst.dk/en/rational-pharmacotherapy/reviews/intuniv-guanfacine

Institut national d'excellence en santé et en services sociaux (INESSS). Intuniv XRMC – trouble du déficit de l'attention avec ou sans hyperactivité [Internet]. Québec: INESSS; 2014 Feb. [cited 2018 Mar 7]. Available from: https://www.inesss.qc.ca/fileadmin/doc/INESSS/Inscription_medicaments/Avis_au_ministre/Fevrier_2014/Intuniv-XR_2014_02_CAV.pdf

HTA analyses excluded due to lack of systematic search

Committee for Medicinal Products for Human Use (CHMP). Assessment report: Intuniv (guanfacine) [Internet]. London (GB): European Medicines Agency; 2015 Feb 26. [cited 2018 Feb 23]. (European public assessment report). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003759/WC500195132.pdf

Guanfacine, 1mg, 2mg, 3mg and 4mg prolonged-release tablets (Intuniv®)[Internet]. Glasgow: Scottish Medicines Consortium; 2016 Jan 8 [cited 2018 Mar 7]. (SMC advice; no. 1123/16). Available from: http://www.scottishmedicines.org.uk/files/advice/guanfacine_hydrochloride_Intuniv_FINAL_January_2016_for_website.pdf

Guideline without recommendations specific to GXR

Attention deficit hyperactivity disorder: diagnosis and management [Internet]. London: National Institute for Health and Care Excellence; 2016 [cited 2018 Mar 7]. Available from: https://www.nice.org.uk/guidance/cg72

Note: to be updated in 2018