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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Guanfacine Hydrochloride Extended-Release for the Treatment of Attention Deficit Hyperactivity Disorder in Adults: 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.

Abbreviations

ADHD	attention deficit hyperactivity disorder
ADHD-RS	Attention Deficit Hyperactivity Disorder – Rating Scale
CGI-S	Clinical Global Impression – Severity
GXR	guanfacine hydrochloride extended-release
NICE	National Institute for Health and Care Excellence
RCT	randomized controlled trial

Context and Policy Issues

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurobehavioural disorders in children and adolescents, and it can also persist into, or begin in, adulthood;[1] the estimated prevalence of ADHD in adults is 5.0% worldwide.[2] The etiology of ADHD is complex, and is believed to have a neurochemical basis involving an imbalance of the neurotransmitters dopamine and norepinephrine in the prefrontal cortex.[3] In adults, ADHD is characterized by symptoms of inattention, impulsivity, restlessness, impairment in executive function, and emotional dysregulation, which result in functional impairment.[1] The cost associated with ADHD across all ages is estimated to exceed $7 billion each year in Canada, including costs due to healthcare and education, lost productivity, justice and corrections, and social services and labour (e.g., increased costs to welfare, disability, and unemployment).[4] ADHD can have a negative impact on the quality of life of affected individuals and ADHD poses a substantial financial burden to the health care system.[3,4]

Treatment for ADHD can include pharmacotherapy, behavioural therapy, or their combination.[3] With respect to pharmacotherapy, stimulants (methylphenidate and amphetamines) are considered first-line treatments in adults, because they have been shown to have the greatest effectiveness, safety, and tolerability.[5,6] However, stimulants may not be effective in up to 30% of patients,[3] may be associated with adverse side-effects, and may create risk for dependency or diversion.[5,7] Non-stimulant medications can therefore be used as an adjunctive therapy or as a monotherapy alternative in patients with sub-optimal responses to, or intolerable side-effects from, stimulants.[6] In children and adolescents with ADHD, alpha-2 adrenergic agonists, such as guanfacine hydrochloride, have been shown to be effective as a non-stimulant monotherapy or adjunctive therapy to psychostimulants, but it is unclear whether the treatment effects would be similar in adult populations.[8]

Guanfacine hydrochloride extended-release (GXR; brand name: Intuniv XR) is currently indicated for patients with ADHD who are 6 to 17 years of age,[6] and CADTH has previously reviewed the evidence for the clinical and cost-effectiveness of GXR in this population.[9] At present, use of GXR for ADHD in adults is considered “off-label” and this is reflected in current prescribing practices. For instance, in the second quarter of 2014, of the greater than 900,000 prescriptions dispensed for adult ADHD in Canada, only approximately 0.3% were for GXR.[10] It is important to determine whether sufficient clinical and cost-effectiveness have been demonstrated to warrant the use of GXR for the treatment of ADHD in the adult population.

The purpose of this report is to examine the clinical effectiveness, cost-effectiveness, and evidence-based guidelines regarding the use of GXR for the treatment of adults with ADHD.

Research Questions

1. What is the clinical effectiveness of guanfacine hydrochloride extended-release tablets for the treatment of adults with attention deficit hyperactivity disorder?
2. What is the cost-effectiveness of guanfacine hydrochloride extended-release tablets for treatment of adults 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 adults with attention deficit hyperactivity disorder?

Key Findings

Limited evidence from a single randomized controlled trial suggested that guanfacine hydrochloride extended-release (GXR) was safe and well-tolerated when added to an existing psychostimulant treatment for adults with attention deficit hyperactivity disorder (ADHD). However, GXR did not differ from placebo with respect to clinical effectiveness. No evidence for the cost-effectiveness of GXR for the treatment of adults with ADHD was identified. One evidence-based guideline from the United Kingdom was identified that provides recommendations regarding the use of GXR in the management of ADHD in adults. Based on predominantly low- to moderate-quality evidence, the guideline provides a strong recommendation against the use of guanfacine (immediate or extended-release preparation not specified) in adults without advice from a tertiary ADHD service. Further, if a person taking guanfacine experiences sustained orthostatic hypotension or fainting episodes, the guideline recommends reducing the dose or switching to another ADHD medication.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, OVID Medline, Embase, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit retrieval to publication type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2013 and August 8, 2018.

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	Adults (aged ≥18) with attention deficit hyperactivity disorder
Intervention	Guanfacine hydrochloride extended-release tablets (Intuniv XR) – As adjunctive therapy to psychostimulants – As monotherapy for patients intolerant to psychostimulants
Comparator	– Amphetamines (e.g., lisdexamfetamine dimesylate, amphetamine mixed salts, dextroamphetamine) – Methylphenidate – Atomoxetine – Bupropion – Clonidine – Tricyclic antidepressants (e.g., desipramine and imipramine) – Atypical antipsychotics (e.g., aripiprazole, clozapine, ziprasidone, risperidone, quetiapine, olanzapine, asenapine, and paliperidone), with or without adjunctive psychostimulants – Placebo – No treatment
Outcomes	Q1: Clinical benefits and harms (e.g., 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, adverse events [e.g., hypotension, cardiovascular events], discontinuations due to treatment emergent adverse event, mortality, risk for abuse, misuse, and diversion) Q2: Cost-effectiveness Q3: Evidence-based guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, and guidelines

ADHD-RS IV = Attention Deficit Hyperactivity Disorder Rating Scale IV; 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.

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. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included randomized study was critically appraised using the Downs and Black checklist,[11] and the guideline was assessed with the AGREE II instrument.[12] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

Summary of Evidence

Quantity of Research Available

A total of 148 citations were identified in the literature search. Following screening of titles and abstracts, 138 citations were excluded and 10 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search. Of these potentially relevant articles, nine publications were excluded for various reasons. One review was excluded due to unclear methodology; in this review, a single potentially relevant study was identified but no data were provided.[13] Two publications (one randomized controlled trial[8] and one evidence-based guideline[14]) met the inclusion criteria and were included in this report. Appendix 1

presents 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

One double-blind, placebo-controlled, randomized controlled trial (RCT) was identified regarding the clinical effectiveness of GXR for the treatment of adults with ADHD.[8]

No studies that concerned the cost-effectiveness of GXR for the treatment of adults with ADHD were identified.

One evidence-based guideline was identified regarding the use of GXR for the treatment of adults with ADHD.[14] The guideline was developed by the National Institute for Health and Care Excellence (NICE), and was informed by systematic reviews of clinical evidence (that included blinded RCTs and systematic reviews of RCTs) and cost-effectiveness analyses, together with consideration of the values and preferences of committee members and patients, equality issues, and recommendations in other guidelines.[15,16] The quality of the evidence was rated using an adaptation of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.[15] Recommendations were consensus-based, and were rated as "strong" or "weak" based on the balance of benefits and harms, cost-effectiveness, and patient preferences.[15]

Country of Origin

The RCT was conducted in the United States,[8] and the evidence-based guideline was developed by NICE in the United Kingdom.[14,15]

Patient Population

The RCT included adults (age ≥18 years) with ADHD (as specified in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition – Text Revision) and a sub-optimal response to a stimulant-only treatment program.[8] A "sub-optimal response" was defined by the patient's dissatisfaction with clinical progress, by objective scores on scales assessing current ADHD symptoms (score of ≥28 on the ADHD – Rating Scale; ADHD-RS), or clinical impressions (score of ≥4 on the Clinical Global Impression – Severity; CGI-S).

The guideline applies to children (< 5 years of age), young people (ages 5 to 18) and adults (>18 years) with ADHD, with specific recommendations stratified by age groups.[14] The intended users are healthcare professionals, commissioners and providers, and people with ADHD, their families, and carers.

Interventions and Comparators

In the RCT, patients continued their existing psychostimulant treatment regimen (identified in Table 2), and were randomized to either GXR or placebo.[8] GXR was started at 1 mg and the dose was titrated up to 6 mg over eight weeks for each individual patient based on tolerance and response. The placebo was administered according to the same dosing schedule. After 10 weeks of treatment, GXR or placebo treatments were discontinued over a two week period (presumably to avoid problems with abrupt discontinuation).

The guideline considered aspects of the diagnosis and management of ADHD, including several pharmacological treatments (e.g., methylphenidate, amphetamines, tricyclic antidepressants, and alpha-2 adrenergic agonists).[16] With respect to clinical and cost-effectiveness of pharmacotherapy specifically, eligible comparators were: placebo, one medication compared with another, or class versus class comparisons.[16]

Outcomes

In the RCT, the primary outcomes of interest were the ADHD–RS score (as a measure of current ADHD symptoms) and the CGI–S score (as a measure of clinical impressions).[8] Secondary outcomes were heart rate, systolic and diastolic blood pressure, adverse events (tolerability and safety), and scores on the following measurement scales: the Arizona Sexual Experience Questionnaire, the Fatigue Symptom Inventory, the Pittsburgh Sleep Quality Index, the Hamilton Anxiety Inventory, and the Hamilton Depression Rating Scale.[8]

The outcomes of interest in the guidelines were clinical effectiveness and safety (including quality of life, ADHD symptoms, CGI–S score, adverse events, functional measures, emotional dysregulation, substance use, and self-harm), cost-effectiveness, and resource use.[14-16]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Randomized Controlled Trial

The RCT was generally well-conducted and reported; the study objective, inclusion and exclusion criteria, included patients, comparator, and main outcomes (including consideration of adverse events) were clearly described.[8] The intervention was well-described, including the dose titration schedule, except that the dose frequency (presumably per day) was not explicitly stated. Participants were randomly assigned to treatment groups using randomization software, and participants, the principal investigator, and study coordinator were blinded to treatment assignment. No patients were lost to follow-up, and compliance with the interventions was monitored (mean compliance ranged from 98% to 100% across the treatment duration). The primary limitation was that all participants had additional clinical observation (i.e., beyond that which would normally be expected in clinical practice), which may have contributed to performance bias. Similarly, participants were recruited via convenience sample from local advertisements and the clinic's patient population, and participants may represent a highly-motivated subset of patients who may be more likely to reinterpret their symptoms favourably while under more frequent observation. In addition, the methods of measuring heart rate and blood pressure (secondary outcomes) were not described, and details regarding the validity of outcomes and the minimal clinically important differences were not provided. Lastly, a power calculation was not performed, and *P*-values were only reported for a subset of all statistical tests that were conducted. It is therefore not clear if the differences reported are clinically meaningful or if the study was adequately powered to identify differences.

Guideline

The NICE guideline was methodologically rigorous and of high quality.[14-16] The guideline had a clearly defined scope and purpose, stakeholder involvement, rigour of development, consideration of applicability, and evidence of editorial independence. An assessment tool

to evaluate whether practice is in line with the recommendations in the guideline was provided,[17] however, specific monitoring and/or auditing criteria were not explicit. Barriers and facilitators to guideline application were described with the supporting evidence,[16] but were not explicitly linked to the specific recommendations.[14]

Summary of Findings

Rapid Response reports are organized so that the evidence for each research question is presented separately. A detailed summary of study findings and guideline recommendations is provided in Appendix 4.

Clinical Effectiveness of Guanfacine Hydrochloride Extended-Release for the Treatment of ADHD in Adults

One RCT was identified that provided evidence on the clinical effectiveness of GXR compared with placebo, in combination with existing psychostimulants, for the treatment of adults with ADHD.[8] After 10 weeks of treatment, there was no significant difference between GXR and placebo groups in current ADHD symptoms, clinical impressions, vital signs (heart rate and blood pressure), tolerability (sexual function, sleep quality, and symptoms or anxiety or depression), or safety (adverse events). All adverse events were considered minor (e.g., fatigue, dry mouth, irritability, headache, and increased appetite), and no participants discontinued treatment due to adverse events. Pooled across groups, significant improvements in several outcomes were observed from baseline to the end of 10 weeks of treatment (i.e., improvements in ADHD symptoms, clinical impressions, sleep quality, anxiety symptoms, and depression symptoms).

Cost-Effectiveness of Guanfacine Hydrochloride Extended-Release for the Treatment of ADHD in Adults

No relevant evidence regarding the cost-effectiveness of GXR for the treatment of adults with ADHD was identified; therefore, no summary can be provided.

Guidelines for Guanfacine Hydrochloride Extended-Release for the Treatment of ADHD in Adults

One evidence-based guideline, produced by NICE in the United Kingdom, was identified that provides recommendations for the management of ADHD in adults, including GXR.[14] With respect to GXR, the guideline strongly recommends against offering guanfacine (immediate or extended-release preparation not specified) to adults without advice from a tertiary ADHD service (i.e., specialized care). In addition, if a person taking guanfacine experiences sustained orthostatic hypotension or fainting episodes, the guideline recommends reducing the dose or switching to another ADHD medication (however, the strength of this recommendation was unclear, and this recommendation was not for adults specifically). The quality of the evidence supporting the recommendations specific to guanfacine in adults ranged from “very low” to “high”.[16]

Limitations

The main limitation of this review is the paucity of available evidence. No evidence was identified regarding the cost-effectiveness of GXR for the treatment of adults with ADHD, and a single RCT (with 13 patients per group) was identified regarding the clinical effectiveness of GXR, in combination with psychostimulant medication, in this population.[8] No evidence was identified regarding the clinical effectiveness of GXR as a monotherapy, or in comparison to psychostimulants or other treatment options such as atomoxetine,

clonidine, or tricyclic antidepressants. Lastly, the single evidence-based guideline provides recommendations based on limited evidence of varied quality.[14]

Conclusions and Implications for Decision or Policy Making

This report identified limited evidence on the clinical effectiveness of GXR for the treatment of ADHD in adults, and an evidence-based guideline regarding the use of GXR in this population. No evidence was identified for the cost-effectiveness of GXR in the treatment of adults with ADHD.

With respect to the clinical effectiveness of treatment, evidence from the single RCT (N = 26) demonstrated that GXR (individually titrated to up to 6 mg, in combination with existing psychostimulant treatment) was safe and well-tolerated in adults with ADHD who had demonstrated a sub-optimal response to stimulant-only treatment.[8] However, GXR did not differ from placebo in terms of clinical effectiveness, safety, or tolerability. When results were pooled across GXR and placebo groups, overall improvements in ADHD symptoms, clinical impressions, sleep quality, anxiety symptoms, and depression symptoms, were demonstrated after 10 weeks of treatment.

A single evidence-based guideline was identified that provides recommendations regarding the use of GXR for treatment of adults with ADHD.[14] Based on predominantly low- to moderate-quality evidence, the guideline strongly recommends against offering guanfacine (immediate or extended-release preparation not specified) to adults without advice from a tertiary ADHD service. Further, if a person taking guanfacine experiences sustained orthostatic hypotension or fainting episodes, the guideline recommends reducing the dose or switching to another ADHD medication.

Additional research is required to more definitively determine the clinical effectiveness of GXR, and to discern the cost-effectiveness of GXR, for the treatment of adults with ADHD.

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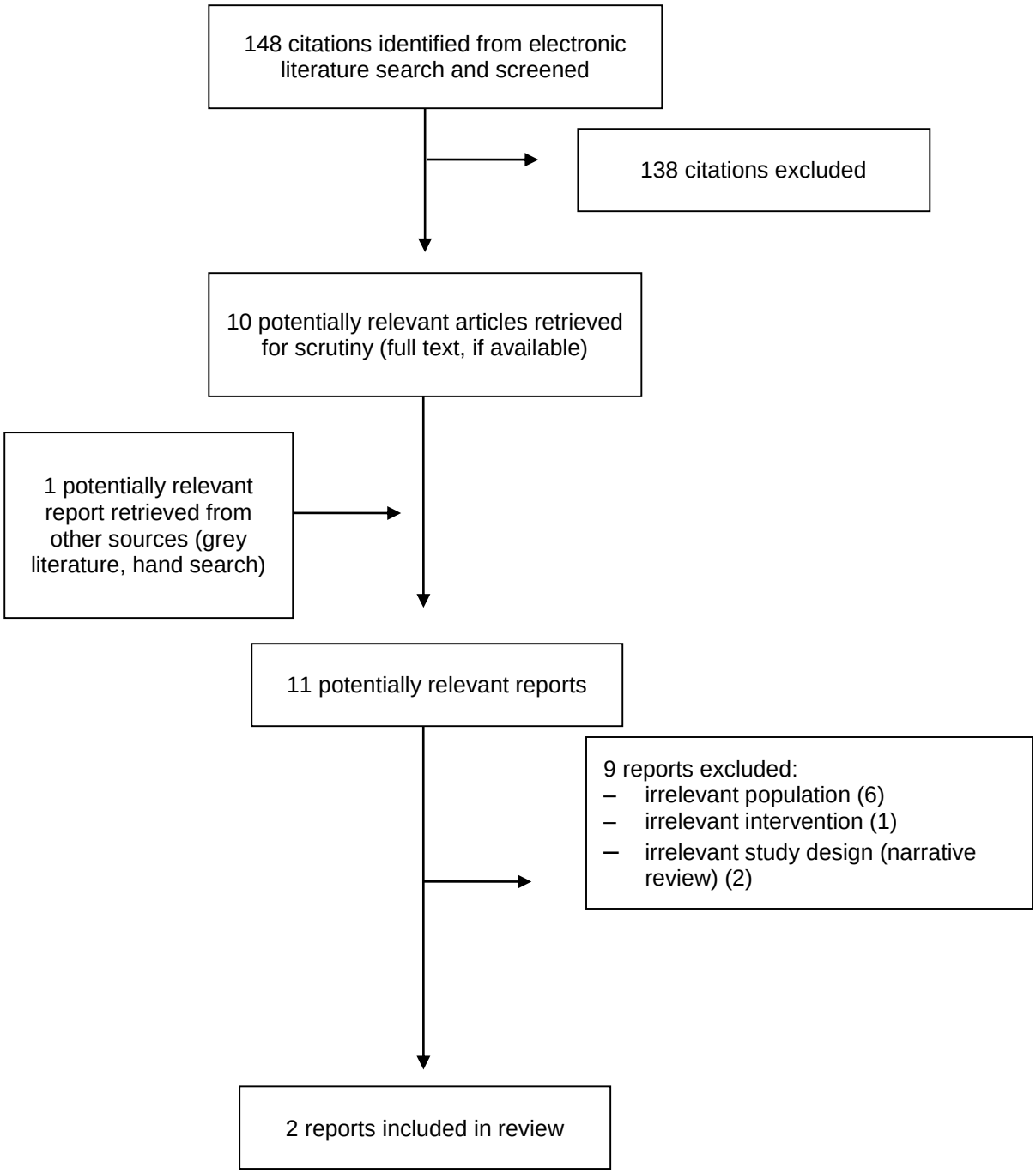
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of the Included Primary Clinical Study

Study Citation, Country	Study Design	Population Characteristics	Intervention	Comparator	Clinical Outcomes, Length of Follow-Up
Butterfield et al. 2016[8] **United States**	Randomized Controlled Trial	Adults with ADHD and a sub-optimal response to a stimulant-only treatment program N = 26 Mean age ± SD = 37.5 ± 12.2 y (range 19 to 62 y) Current primary medications were: Vyvanse (n = 9), Adderall XR (n = 8), Adderall (n = 6), Ritalin (n = 2), Concerta (n = 1)	In addition to existing psychostimulant treatment regimen: GXR; started with 1 mg and titrated to optimal dose based on tolerance and response (up to 6 mg) over 8 weeks (for a total of 10 weeks of treatment), followed by 2 weeks dose discontinuation	In addition to existing psychostimulant treatment regimen: Placebo; same dosing schedule as with GXR	*Primary outcomes:* ADHD – RS (measure of current symptoms), CGI – S (measure of clinical impressions) *Secondary outcomes:* HR, SBP, DBP, ASEX, FSI, PSQI, HAM – A, HAM – D, adverse events (tolerability and safety) *Length of follow-up:* 12 weeks

ADHD = attention deficit hyperactivity disorder; ADHD – RS = Attention Deficit Hyperactivity Disorder – Rating Scale; ASEX = Arizona Sexual Experience Questionnaire; CGI – S = Clinical Global Impression – Severity; DBP = diastolic blood pressure; FSI = Fatigue Symptom Inventory; GXR = guanfacine hydrochloride extended-release; HAM – A = Hamilton Anxiety Inventory; HAM – D = Hamilton Depression Rating Scale; HR = heart rate; PSQI = Pittsburgh Sleep Quality Index; SBP = systolic blood pressure; SD = standard deviation; y = years.

NOTE: The dosing schedule for GXR is assumed to be in mg per day, however this was not explicitly stated in the study.

Table 3: Characteristics of the Included Guideline

Target Population, Intended Users	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
National Institute for Health and Care Excellence[14,15]						
Target population: Children (<5 years of age), young people (ages 5 to 18), and adults (>18 years) with ADHD **Intended Users:** Healthcare professionals; commissioners and providers; people with ADHD, and their families and carers	Aspects of diagnosis and management (including several pharmacological treatments; e.g., methylphenidate, amphetamines, tricyclic antidepressants, and alpha-2 adrenergic agonists)	Clinical effectiveness and safety (including quality of life, ADHD symptoms, clinical global impressions scale, serious adverse events, functional measures, emotional dysregulation, substance use, self-harm), cost-effectiveness and resource use	Electronic database searches up to April 28, 2017, hand-searching of relevant papers, and nomination of additional studies by committee members; retrieved references screened in duplicate with committee input where consensus could not be reached; evidence tabulated and summarized in meta-analyses and narrative summaries; cost-effectiveness analyses for selected areas	Evidence rated using an adaptation of GRADE (ratings from "very low" to "high" quality)	Expert consensus based on: interpretation of the available evidence; balance of benefits, harms, and costs of different courses of action; values and preferences of committee members. If evidence was of poor quality, conflicting, or absent, the following were also considered: patient preferences, equality issues, recommendations in other guidelines. "Strong" recommendations made when benefits clearly outweighed harms and the intervention was likely to be cost-effective; "weak" recommendations made when there was a closer balance of benefits and harms and some patients would choose the intervention while others would not. Strength of recommendations not stated explicitly but "offer" and "consider" were used for strong and weak recommendations, respectively.	Six week public consultation, feedback and peer-review process

ADHD = attention deficit hyperactivity disorder; GRADE = Grading of Recommendations Assessment, Development and Evaluation.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Primary Clinical Study using the Downs and Black Checklist[11]

Strengths	Limitations
Butterfield et al. 2016[8]	
• Study objective clearly described • Patient inclusion and exclusion criteria provided • Characteristics of included patients clearly described • Comparator and main outcomes clearly described • Intervention was well-described, including the dose titration schedule, except that the dose frequency (presumably per day) was not explicitly stated • Main findings clearly described, including statistical estimates of variability • Adverse events associated with the intervention were considered • No patients lost to follow-up • Actual probability values (*P*-values) reported for some results • Staff, places, and facilities where the patients were treated were representative of the treatment of the majority of patients (with the exception of more frequent clinical observation) • Study participants, the principal investigator, and the study coordinator were blinded to treatment assignments • Retrospective analyses were conducted, but these were identified as such (*"further probing"*; p. 139) • Appropriate statistical tests used to assess outcomes • Compliance with the interventions was monitored and was reliable	• Participants were recruited via convenience sample *"from local advertisements and the clinic's existing patient population"* (p. 137) and may not represent all patients with ADHD and sub-optimal response to stimulant-only treatment • Method of measuring heart rate and blood pressure not described • Details regarding the validity of outcomes and the minimal clinically important differences were not provided • Patients had additional clinical observation (i.e., beyond that which would normally be expected in clinical practice) • No list of principal confounders or their distribution between groups (however, this is of minimal concern due to appropriate randomization) • *P*-values not reported for all statistical tests that were reported to be non-significant • Power calculation not performed

ADHD = attention deficit hyperactivity disorder.

Table 5: Strengths and Limitations of Guideline using AGREE II[12]

Item	Guideline
	NICE[14,15]
Domain 1: Scope and Purpose	
1. The overall objective(s) of the guideline is (are) specifically described.	✓
2. The health question(s) covered by the guideline is (are) specifically described.	✓
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	✓
Domain 2: Stakeholder Involvement	
4. The guideline development group includes individuals from all relevant professional groups.	✓[18]
5. The views and preferences of the target population (patients, public, etc.) have been sought.	✓
6. The target users of the guideline are clearly defined.	✓
Domain 3: Rigour of Development	
7. Systematic methods were used to search for evidence.	✓
8. The criteria for selecting the evidence are clearly described.	✓
9. The strengths and limitations of the body of evidence are clearly described.	✓
10. The methods for formulating the recommendations are clearly described.	✓
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	✓
12. There is an explicit link between the recommendations and the supporting evidence.	✓
13. The guideline has been externally reviewed by experts prior to its publication.	✓
14. A procedure for updating the guideline is provided.	✓
Domain 4: Clarity of Presentation	
15. The recommendations are specific and unambiguous.	✓
16. The different options for management of the condition or health issue are clearly presented.	✓
17. Key recommendations are easily identifiable.	✓
Domain 5: Applicability	
18. The guideline describes facilitators and barriers to its application.	✓
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	✓
20. The potential resource implications of applying the recommendations have been considered.	✓
21. The guideline presents monitoring and/or auditing criteria.	X
Domain 6: Editorial Independence	
22. The views of the funding body have not influenced the content of the guideline.	✓
23. Competing interests of guideline development group members have been recorded and addressed.	✓

AGREE II = Appraisal of Guidelines for Research and Evaluation – II; NICE = National Institute for Health and Care Excellence; ✓ = yes; X = no or unclear.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings of the Included Primary Clinical Study

Main Study Findings	Authors' Conclusion
Butterfield et al. 2016[8]	
Primary Outcomes: • ADHD – RS and CGI – S were not significantly different between GXR and Placebo groups at baseline or after 10 weeks of treatment (all $P > 0.05$) • Pooled across groups, both the ADHD – RS and CGI – S improved significantly from baseline to 10 weeks of treatment (both $P < 0.001$) ADHD – RS (complete sample), mean ± SD: • Baseline: 35.58 ± 6.36 • After 10 wk treatment: 24.19 ± 9.86 • Improvement: 11.39, 95% CI, 8.10 to 14.67 CGI – S (complete sample), mean ± SD: • Baseline: 4.42 ± 0.58 • After 10 wk treatment: 3.50 ± 0.91 • Improvement: 0.93, 95% CI, 0.60 to 1.25 *Secondary Outcomes:* • HR, SBP and DBP were not significantly different between groups at baseline, after 10 wk treatment, or following 2 wk dose discontinuation • Pooled across groups, HR (beats per minute) increased significantly over the course of the trial ($P = 0.003$), mean ± SD: ○ Baseline: 77.58 ± 12.23 ○ After 10 wk treatment: 79.96 ± 11.76 ○ After 2 wk dose discontinuation: 84.15 ± 12.33 • The most common adverse events were (for GXR and Placebo, respectively): fatigue (30.8%, 61.5%), dry mouth (38.5%, 23.1%), irritability (15.4%, 23.1%), headache (15.4%, 23.1%) and increased appetite (7.7%, 15.4%) • There were no differences between groups in ASEX or FSI at baseline or after 10 weeks of treatment (all $P > 0.05$) • Pooled across groups, the PSQI, HAM – A and HAM – D improved significantly from baseline to 10 weeks of treatment (all $P < 0.05$) PSQI (complete sample), mean ± SD: • Baseline: 8.73 ± 4.35 • After 10 wk treatment: 6.35 ± 4.51 • Improvement: 2.39, 95% CI, 0.32 to 4.45 HAM – A (complete sample), mean ± SD: • Baseline: 11.23 ± 5.87	*"The treatments [GXR or placebo] did not differ in terms of their efficacy, safety, or tolerability."* p. 136 *"Significant adverse events were not encountered in this study, and no participants discontinued the study due to them."* p. 139 *"It may be that the additional clinical observation undergone by all participants was enough to improve their symptoms, but it may also be that the act of observation simply caused them to reinterpret their symptoms or change the way they reported them. At the very least, these results suggest that further research is necessary to explore this phenomenon, and they do indicate that [GXR] may be a safe and tolerable supplement to an existing psychostimulant treatment for adults with ADHD."* p. 140

• After 10 wk treatment: 7.19 ± 5.08 • Improvement: 4.04, 95% CI, 1.94 to 6.14 HAM – D (complete sample), mean ± SD: • Baseline: 7.65 ± 3.90 • After 10 wk treatment: 3.88 ± 3.79 • Improvement: 3.77, 95% CI, 1.94 to 6.14 *Other findings:* • Mean compliance from weeks 1 through 10 of treatment ranged from 98% to 100% (SD = 0 to 7%).	

ADHD = attention deficit hyperactivity disorder; ADHD – RS = Attention Deficit Hyperactivity Disorder – Rating Scale; ASEX = Arizona Sexual Experience Questionnaire; CGI – S = Clinical Global Impression – Severity; DBP = diastolic blood pressure; FSI = Fatigue Symptom Inventory; GXR = extended release guanfacine hydrochloride; HAM – A = Hamilton Anxiety Inventory; HAM – D = Hamilton Depression Rating Scale; HR = heart rate; PSQI = Pittsburgh Sleep Quality Index; SBP = systolic blood pressure; SD = standard deviation; wk = weeks.

Table 7: Summary of Recommendations in Included Guideline

Recommendations	Strength of Evidence and Recommendations
National Institute for Health and Care Excellence[14]	
"Further medication choices *1.7.17 Do not offer any of the following medication for ADHD without advice from a tertiary ADHD service:* • *Guanfacine for adults*[*] • *[…]* [*] *At the time of publication (March 2018), guanfacine did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information."* (p. 24 and 35)	**Strength of Evidence:** Not reported **Strength of Recommendation:** Not explicit, but the term "offer" was used which indicates a "strong" recommendation as per the guideline methods paper (p. 29).[15] **Further Rationale:** *"Because guanfacine is not licensed for use in adults and there was no evidence specifically supporting its use in this population, the committee recommended atomoxetine for adults with intolerance or a lack of response to stimulants."* (p. 47)[14]
"Cardiovascular *1.8.12 If a person taking guanfacine has sustained orthostatic hypotension or fainting episodes, reduce their dose or switch to another ADHD medication."* (p. 29)	**Strength of Evidence:** Not reported **Strength of Recommendation:** Not reported

ADHD = attention deficit hyperactivity disorder.

Note: The quality of the overall evidence for guanfacine (immediate or extended-release preparation not specified) was rated as "very low" to "high" (and was predominantly "low" to "moderate") in the supporting systematic review,[16] however the quality of the evidence supporting specific recommendations was not reported.

Appendix 5: Additional References of Potential Interest

Guidelines – Unclear Methodology

Canadian ADHD Resource Alliance (CADDRA). Canadian ADHD Practice Guidelines. 4th ed. 2018. https://www.caddra.ca/wp-content/uploads/CADDRA-Guidelines-4th-Edition_-Feb2018.pdf . Accessed August 10, 2018.

Herefordshire NHS. Guidelines for the Pharmacological Management of Attention Deficit Hyperactivity Disorder (ADHD) in Children, Young People and Adults. 2017. http://www.hpft.nhs.uk/media/2072/guidelines-for-the-pharmacological-management-of-adhd-july-2017.pdf . Accessed August 10, 2018.