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Guanfacine for Autism Spectrum Disorder, Attention-Deficit/ Hyperactivity Disorder, and/or Oppositional Defiance Disorder

Rapid Review

CADTH

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Abbreviations

ASD	autism spectrum disorder
ADHD	Attention-deficit/ hyperactive disorder
ADHD-RS	ADHD rating scale
BRIEF-A	Behavioural Rating Inventory of Executive Function–Adult
BRIEF-P	Behavioural Rating Inventory of Executive Function–Parent
CGI-I	Clinical Global Impressions-Improvement
CGI-S	Clinical Global Impressions-Severity of Illness
CSSRS	Columbia Suicide Severity Rating Scale
DSM	Diagnostic and Statistical Manual
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HTA	health technology assessment
ICD	International Classification of Disease
MD	mean difference
ODD	oppositional defiance disorder
OR	odds ratio
RCT	randomized controlled trial
YGTSS	Yale Global Tic Severity Scale

Key Messages

- This review identified 4 relevant systematic reviews, 2 randomized controlled trials and 1 guideline since 2017.
- The systematic reviews and trials suggest that guanfacine is more clinically effective than placebo for improving symptoms of attention-deficit/ hyperactive disorder, however it may be associated with increased adverse events such as abdominal pain and fatigue.
- There is some suggestion from 2 systematic reviews that guanfacine may be equally effective as other psychostimulants or non-psychostimulants, with the potential for more greater side effects, but the evidence is highly uncertain.
- The included guideline has a strong recommendation to offer guanfacine for use in children and adolescents when psychostimulants have failed, or they are not tolerable.
- No evidence was identified on the cost-effectiveness of guanfacine relative to psychostimulants, non-psychostimulants or placebo that met the inclusion criteria.

Context and Policy Issues

Attention-deficit/hyperactivity disorder (ADHD) is 1 of the most commonly diagnosed childhood conditions.[1] Autism spectrum disorder (ASD) and oppositional defiance disorder (ODD) are related to ADHD with symptomatic overlap. Symptoms that can be present in all the conditions include hyperactivity, impulsivity, behavioural issues, and inattention. Hyperactivity is more common in young children; this may evolve into impulsivity in adolescence and remain as such throughout the life course. Inattention is often diagnosed later[2] and can remain in adulthood.[3] The symptoms can affect academics, social skills, and occupational performance. While difficulty keeping up with school and making friends may start in childhood, forgetfulness, prioritization, and difficulty organizing tasks can continue to inhibit executive function as an adult.[3]

Pharmacological treatment for these conditions includes psychostimulant (simply called stimulant) medications most commonly as a first option, and non-stimulant medications as alternatives. Stimulant medications increase the brain activity of producing dopamine and norepinephrine while the mechanism of non-stimulant medications can vary.[4] Selective norepinephrine reuptake inhibitors such as atomoxetine prevent reuptake of the same neurotransmitters, thus increasing concentrations. In contrast, alpha-2-agonists such as guanfacine and clonidine may mimic the effects of the neurotransmitters though their exact mechanism of action is unknown.[4] While stimulants are usually the first line treatment, non-stimulant medications can be more desirable in some situations.[5] They may be indicated when stimulant medications worsen co-occurring tic disorders, the person has a background of substance use, or have other intolerable side effects. In addition, symptoms may not always respond to stimulants necessitating trials with other options.[5]

Among the non-psychostimulants, guanfacine hydrochloride (used herein interchangeably with guanfacine) is an emerging and important choice to control ADHD, ASD, and ODD symptoms, but evidence is limited. The aim of this review is to summarize the evidence regarding the clinical and cost-effectiveness of guanfacine compared to stimulants and non-stimulants drugs for ADHD, autism spectrum disorder and ODD, as well as the evidence-based guidelines.

Research Questions

1. What is the clinical effectiveness of guanfacine versus psychostimulant drugs for attention-deficit/ hyperactivity disorder, autism spectrum disorder, and oppositional defiance disorder?
2. What is the clinical effectiveness of guanfacine versus other non-psychostimulant drugs for attention-deficit/hyperactivity disorder, autism spectrum disorder, and oppositional defiance disorder?
3. What is the clinical effectiveness of guanfacine versus placebo or no therapy for attention-deficit/hyperactivity disorder, autism spectrum disorder, and oppositional defiance disorder?
4. What is the cost-effectiveness of guanfacine versus psychostimulant drugs for attention-deficit/hyperactivity disorder, autism spectrum disorder, and oppositional defiance disorder?
5. What is the cost-effectiveness of guanfacine versus other non-psychostimulant drugs for attention-deficit/hyperactivity disorder, autism spectrum disorder, and oppositional defiance disorder?
6. What is the cost-effectiveness of guanfacine versus placebo or no therapy for attention-deficit/hyperactivity disorder, autism spectrum disorder, and oppositional defiance disorder?
7. What are the evidence-based guidelines regarding the use of guanfacine for attention-deficit/hyperactivity disorder, autism spectrum disorder, and oppositional defiance disorder?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, Embase, PsycINFO, the Cochrane Library, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was guanfacine. Search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or network meta-analyses, randomized controlled trials (RCTs), controlled clinical trials, guidelines, or economic studies. Comments, newspaper articles, editorials, conference abstracts and letters were excluded. Where possible, retrieval was limited to the human population. The search was completed on May 31, 2022 and limited to English language documents published since January 1, 2017.

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.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published before 2017. Systematic reviews in which all relevant studies were captured in other more recent or more comprehensive systematic reviews were excluded.[6-14] Primary studies retrieved by the search were excluded if they were captured in 1 or more included systematic reviews.[15] Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[16] for systematic reviews, the "Questionnaire to assess the relevance and credibility of a network meta-analysis"[17] for network meta-analyses, the Downs and Black checklist[18] for randomized and non-randomized studies, and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument[19] for guidelines. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Table 1: Selection Criteria

Criteria	Description
Population	People with attention-deficit/hyperactivity disorder, autism spectrum disorder and/or oppositional defiance disorder
Intervention	Guanfacine
Comparator	Q1 to Q4. Psychostimulant drugs e.g., short-acting or extended-release amphetamines (including lisdexamfetamine dimesylate, amphetamine, mixed salts, dextroamphetamine), methylphenidate (short acting or extended release), atypical antipsychotics (aripiprazole, clozapine, ziprasidone, risperidone, quetiapine, olanzapine, asenapine, and paliperidone). Q2 to Q5. Non-psychostimulant drugs, i.e., atomoxetine or clonidine (either with or without adjunctive psychostimulants). Q3 to Q6. Placebo and/or no treatment. Q7. Not applicable.
Outcomes	Q1 to Q3: Clinical effectiveness 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; safety e.g., harms, AEs (including AEs of particular interest e.g., hypotension, cardiovascular AEs, etc.), SAEs, discontinuations due to TEAEs, mortality. Q4 to Q6: Cost-effectiveness e.g., ICER/ICUR, cost per QALY or other health benefit. Q7: Evidence-based recommendations.
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, economic evaluations, evidence-based guidelines.

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-year; SAE = serious adverse event; TEAE = treatment emergent adverse event.

Summary of Evidence

Quantity of Research Available

A total of 274 citations were identified in the literature search. Following screening of titles and abstracts, 231 citations were excluded and 43 potentially relevant reports from the electronic search were retrieved for full-text review. 18 potentially relevant publications were retrieved from the grey literature search for full-text review. Of the 61 potentially relevant articles, 54 publications were excluded for various reasons, while 7 publications met the inclusion criteria and were included in this report. These comprised 4 systematic reviews, 2 randomized controlled trials (RCTs), and 1 evidence-based guideline. There were no economic evaluations that met the inclusion criteria. Appendix 1 presents the PRISMA[20] flow chart of the study selection.

Additional references of potential interest are provided in Appendix 7. The overlap of primary studies in the included systematic review is available in Appendix 5.

Summary of Study Characteristics

Study Design

All 4 systematic reviews had broader search inclusion criteria than relevant to this report. Two included systematic reviews, 1 with 203 eligible RCTs,[21] and the other with 8 eligible RCTs,[22] had 1 relevant RCT each reporting about guanfacine. Both these systematic reviews included only double-blinded RCTs. Another systematic review included 12 RCTs related to guanfacine out of 133 studies; open or blinded RCTs were eligible.[23] The final systematic review included 13 out of 73 studies pertaining to guanfacine.[24] It was not specified whether the included RCTs were blinded.[24] The systematic reviews included articles from 1980 to November 2021,[21] database inception to April 2021,[23] from database inception to September 2017,[22] and to up to March 29, 2017.[24]

The systematic reviews had some overlap. The only guanfacine study in Osland, 2018[22] was also included in Cortese, 2018,[23] which included 12 RCTs. However, the systematic review by Osland, 2018[22] was retained because it reported outcomes related to tic disorders not reported by Cortese et al.[23] Seven primary studies overlapped between Luan, 2017[24] and Cortese, 2018[23](Appendix 5).

Of the RCTs, 1 was a multi-centre double-blinded design with 201 participants, where patients were randomized to receive either guanfacine or placebo.[25] The other trial was a crossover design with a 10-day washout period, meaning, the participants (40 in total) switched from their initial treatment assignment to the alternative (guanfacine or placebo) after allowing 10 days for the effect of the first to wane.[26] The participants received concurrent treatment with a psychostimulant.[26]

The guideline was developed by the UK's National Institute for Health and Care Excellence (NICE).[27] The guidelines identified evidence through a systematic search of multiple electronic databases. The quality of the evidence was rated according to Grading of Recommendations, Assessment, Development and Evaluations (GRADE). The final recommendations adopted a language-based rating system, where "should offer" and "do not offer" reflect the recommendations with highest level of confidence, while "should consider and should not consider" reflect a lower level of confidence.

Country of Origin

The systematic reviews originated from the UK,[22,23] Germany[21] and China.[24] One RCT was conducted at 71 Japanese centres between October 2016 and July 2017[25] while the other RCT was conducted at a single centre in Canada though the study period was not specified.[26] The guideline was developed by the NICE in the UK.[27]

Patient Population

One systematic review included children and adults (analyzed separately) diagnosed with ASD using at least Diagnostic and Statistical Manual (DSM)-III or other validated diagnostic tools.[21] Two systematic reviews included individuals diagnosed with ADHD.[23,24] One systematic review, included children and adults diagnosed with primary ADHD according to DSM-III, DSM-III-R, DSM-IV(TR), DSM-5, International Classification of Disease (ICD)-9, or ICD-10.[23] The other systematic review included only children aged 6 to 18 with a DSM-IV diagnosis of ADHD.[24] Another systematic review also included only children 18 or younger with a diagnoses of both ADHD and a chronic tic disorder.[22] In the systematic reviews without age restriction, the studies pertaining to guanfacine were done in children only.[21,23]

One of the RCTs was conducted in children aged 6 to 12 years with a primary diagnosis of predominantly inattentive, hyperactive or impulsive, or combined subtype based on DSM-IV diagnosis of ADHD. The children had to be taking a stable methylphenidate or amphetamine (stimulant) regimen for at least 30 days with ongoing executive function difficulties.[26] The other trial was done in adults at least 18 years old, with a DSM-V diagnoses of ADHD).[25]

The guideline targeted health care professionals, commissioners, people with ADHD as well as families and carers.[27]

Interventions and Comparators

Interventions

The systematic reviews included a variety of pharmacological interventions, though only analyses related to guanfacine were considered for this review. One systematic review included dietary-supplements in addition to medications, except for those given in combination with behavioural interventions or risperidone.[21] Findings comparing guanfacine to dietary-supplements were not included in this review. Another systematic review specified amphetamines, atomoxetine, bupropion, clonidine, guanfacine, methylphenidate and modafinil given as oral therapy, alone or in combination with other drugs.[23] One systematic review included any pharmacological treatment for ADHD given orally alone or in combination with another drug,[22] while the another systematic review included atomoxetine, bupropion, clonidine, guanfacine, methylphenidate and lisdexamfetamine.[24] Two studies specified the minimum duration of treatment as 7 days,[21,23] while another specified 3 weeks.[24]

In 1 RCT, the intervention was guanfacine titrated from 2 mg per day to 4 mg to 6 mg per day over 5 weeks to optimize the dose. This period was followed by a 5-week maintenance on the same dose, then tapering over 2 weeks.[25] In the crossover RCT, guanfacine was initiated at 1 mg per day and optimized over 4 weeks to a maximum of 4 mg per day. The optimization was followed by an 8-week maintenance period, then tapering over 11 days and a 10-day washout period.[26]

The guideline considered various pharmacological treatment though in this review only recommendations pertaining to guanfacine were included.[27]

Comparators

Two systematic reviews included placebo-controlled studies only,[21,22] and 2 systematic reviews included studies with placebo or other drugs as comparators.[23,24] In 2 systematic reviews, the duration of treatment had to be at least 7 days,[21,23] while in another the minimum study duration had to be 3 weeks.[24]

Both RCTs were placebo-controlled studies.[25,26]

Outcomes

All the systematic reviews reported change in ADHD symptoms outcomes, assessed by any validated scales and reported the finding using standardized mean difference (SMD).[22-24] However, 1 systematic reviews specified only accepting the ADHD Rating Scale (ADHD-RS).[24] Where included, parent, teacher and clinician ratings were analyzed separately.[21-23] In the systematic review involving people with ASD, changes in repetitive behaviour, and social communication difficulties were reported as additional outcomes.[21]

Two systematic reviews with network meta-analysis reported SMD and 95% confidence intervals (CIs) based on the different scales.[21,23] However, 1 systematic review limited meta-analysis to studies with a common scale, and reported a mean difference (MD) and 95% CI in the change in ADHD-RS.[24] The systematic review of studies involving with people with ADHD and a chronic tic disorder reported tic severity using any valid scale such as the YGTSS total tic score as additional an outcome.[22] Two systematic reviews measured clinical global functioning as secondary outcomes using the Clinical Global Impression- Improvement (CGI-I) tool.[21,23] All reviews collected safety information, e.g., the number of adverse events.

The 2 RCTs had different primary outcomes. One used only the Behaviour Rating Inventory of Executive Function–Parent (BRIEF-P) score at all visits outside of the maintenance period.[26] Secondary outcomes included changes in total score on the ADHD-RS-IV, Clinical Global Impression-Severity of illness (CGI-S), and the CGI-I. The other RCT[25] used the change in baseline score on the Japanese version of the ADHD-RS-IV with adult prompts. Secondary outcomes included the change from baseline in ADHD-RS-IV subscale, and Behaviour Rating Inventory of Executive Function - Adult Version (BRIEF-A) scores for executive function. Safety outcomes in both trials included adverse events, vital sign measurements, physical examinations (weight and height).[25,26] The Japanese trial additionally collected electrocardiogram parameters, while the Canadian study also measured safety using the used the Columbia Suicide Severity Rating Scale (CSSRS), which asks a series of 'yes' or 'no' questions to assess suicide risk.[26]

The included guideline's major outcomes were quality of life, ADHD symptoms, and the CGI-I scale. In addition, it collected information on serious adverse events, behavioural and functional outcomes, emotional dysregulation, academic outcomes, substance use and self-harm where available.

Details on the included measurement scales used to assess the outcomes are available in Appendix 6.

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

Summary of Critical Appraisal

All 4 systematic reviews had clear research questions and Population, Intervention, Comparator, Outcome (PICO) criteria.[21-24] They all searched at least 7 databases for relevant studies, with 3 systematic reviews using supplemental search methods such as handsearching reference lists,[21-23] thus, limiting the potential of missing pertinent studies. Risk of bias in studies was assessed using the Cochrane risk of bias tool.[21-24] The systematic reviews handled primary studies rated as having high risk of bias in different ways. One systematic review downgraded the overall evidence quality,[22] while 2 others conducted sensitivity analyses these studies in meta-analyses.[21,23] One systematic review did not present the results of study bias analysis, making it challenging to understand the quality of evidence. This was also the only review that did not provide an overall assessment of evidence quality challenging the interpretation of the findings.[24]

Three of the systematic reviews conducted random effects pairwise and network meta-analyses.[21,23,24] They all compared effect estimates derived from the network versus pairwise analysis, which helps to demonstrate the robustness of the analysis.[21,23,24] Three systematic reviews also assessed study heterogeneity,[21,23,24] though 2 of these did not discuss the findings or implications.[23,24] Two systematic reviews conducted additional sensitivity analyses to ensure robustness of effects against common issues such as different study baseline characteristics and the impact of excluding studies with high risk of bias.[21,23] The third systematic review did not conduct sensitivity analysis.[24]

Both included RCTs had clear research questions and inclusion criteria.[25,26] Computerized software was used for treatment assignment and randomization, and both studies had adequate power to detect treatment effects. One study described using sealed envelopes and identical tables for treatment and placebo to maintain blinding,[25] while the other trial did not provide specifics of the randomization, making it less clear whether blinding was adequately achieved.[26] The study arms were balanced in 1 study,[26] while in the other, the treatment group was younger than the placebo group (i.e., age less than 30 years was 47% in the treatment group compared to 39% in placebo group). There was no apparent adjustment for this imbalance, meaning it is unclear if age may have driven some of the observed effects.[25] Both RCTs were funded by a grant from Shire, the drug manufacturer of guanfacine, raising concerns of conflict of interest.[25,26]

The overall quality of the included guideline was high.[27] The intended users and target population, scope and purpose were clear, and the methodology for the literature review followed systematic approaches. Members of the committee to develop the guideline had a variety of backgrounds which would bring different perspectives. Where there were conflicts of interests, committee members withdrew from certain discussions. The guideline was also subjected to an online consultation period, which solicited comments from stakeholders on the draft recommendations that were incorporated as appropriate. The limitations of the guideline included lack of clarity on the process of developing the draft recommendations given the evidence, as well as no formal external peer review. There was however an online feedback period open to the public and invited stakeholders.

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

Summary of Findings

Clinical Effectiveness of Guanfacine Versus Psychostimulant Drugs

Two systematic reviews compared the effectiveness of guanfacine to psychostimulant drugs.[23,24] Guanfacine was not significantly different than methylphenidate in clinician-rated symptoms, parent-rated symptoms, or teacher-rated symptoms.[23] from indirect comparisons. Similarly, guanfacine was not significantly different than methylphenidate on the ADHD-RS in both network meta-analysis and pairwise comparisons.[24]

Indirect comparison in 1 systematic review found that amphetamines were superior to guanfacine to improve ADHD symptoms as rated by both clinicians and parents.[23] Amphetamines were also associated with greater positive response on the CGI-I.[23] However, another systematic review did not find a statistically significant difference in its indirect comparison of guanfacine to lisdexamphetamine to improve ADHD symptoms.[24] No direct evidence for this drug comparison was available.

In terms of safety, the tolerability of guanfacine was similar to methylphenidate and amphetamines in 1 systematic review.[23] However, another systematic review found that guanfacine was associated with greater odds of withdrawals due to adverse events compared to methylphenidate.[24] The systematic review also found that compared to lisdexamphetamine, the odds were higher with guanfacine for withdrawal due to lack of efficacy and increased abdominal pain.[24]

Clinical Effectiveness of Guanfacine Versus Non-Psychostimulant Drugs

Three systematic reviews had quantitative comparisons of the efficacy of guanfacine and atomoxetine. Guanfacine was potentially inferior to atomoxetine in 1 systematic review of people with ASD though finding bordered on being statistically insignificant in an indirect comparison.[21] Two other systematic reviews did not find a statistically significant difference between guanfacine and atomoxetine in indirect comparisons of clinician, teacher or parent ratings,[23] or both indirect and direct comparisons on the ADHD-RS.[24]

In indirect comparisons, 2 reviews did not find statistically significant differences between guanfacine and clonidine on clinician or teacher ratings of ADHD symptoms,[23] or on the ADHD-RS.[24] Guanfacine was also not associated with statistically significant differences to ADHD symptoms compared to bupropion or modafinil in an indirect comparison in 1 systematic review.[23]

One systematic review found that guanfacine was associated with greater improvement to ADHD symptoms compared (indirectly) to 15 different medications among patients with ASD, including riluzole and fluoxetine.[21] This same review did not find any statistically significant differences in repetitive behaviours or socio-communication difficulties in indirect comparisons to 21 medications.

In terms of safety and side effects, 1 systematic review found no significant differences in tolerance, or the occurrence of any adverse event compared to atomoxetine among people with ASD.[21] However another systematic review found higher odds of withdrawals due to adverse events associated with guanfacine compared to atomoxetine,[24] as well as increased likelihood of nausea.[24]

Guanfacine was also associated with more adverse events compared to sapropterin, dimethylglycine and sertraline in the review of people with ASD.[21]

Clinical Effectiveness of Guanfacine Versus Placebo or No Therapy

Guanfacine was consistently found to be more effective than placebo to improve ADHD symptoms in the systematic reviews and clinical trials.[21-26] Direct and indirect comparisons of guanfacine to placebo were reported in the reviews that conducted network meta-analysis.

Guanfacine was also associated with greater odds of positive response than placebo on the CGI-I in 2 systematic reviews.[21,23] and 1 RCT.[26] The assessment scales were however inconsistent. For example, guanfacine was associated with a greater improvement to symptoms than placebo based on clinician ratings though not in the teacher or parent-rated scales.[23] In 1 systematic review without meta-analysis that assessed the reduction in tic symptoms using the YGTSS total tic score, the treatment with guanfacine was associated with greater symptoms reduction than placebo.[22]

In the 1 systematic review among people with ASD, the effect of guanfacine was not statistically significantly better than placebo for improving socio-communication difficulties or repetitive behaviours[21]

In addition to symptoms, guanfacine was more effective to improve executive function than placebo in both the clinical trials. In 1 RCT in children, BRIEF-P scores improved more in the guanfacine group than the placebo group.[26] Similarly, the RCT in adults found statistically significant improvements on the Inhibit, Initiate, and Plan/Organize dimensions of the BRIEF-A scales, but not the other dimensions.[25]

On safety, guanfacine was associated with statistically significantly increased odds of sedation,[21] fatigue,[24] abdominal pain,[24] total adverse events,[21] and dropouts due to adverse events[23,24] compared to placebo. One systematic review found no statistically significant difference in laboratory test results, weight, or cardiovascular tests though 1 person dropped out of the study due to sedation.[22] In 1 RCT in adults, 19.8% (n = 19) of adverse events led to discontinuation in the guanfacine versus 3% (n = 3) in the placebo group, while 81% (n = 82) versus 62% (n = 62) experienced an adverse event in the guanfacine versus placebo group, respectively.[25] In the RCT among children, adverse event were 41 (87%) in the guanfacine group and 41 (85%) placebo group. Further, no participant demonstrated suicide risk using the CSSRS while in the treatment arm.[26]

Cost-Effectiveness of Guanfacine Versus Psychostimulant Drugs

There were no studies identified that met the inclusion criteria available, therefore, no summary can be provided.

Cost-Effectiveness of Guanfacine Versus Non-Psychostimulant Drugs

There were no studies identified that met the inclusion criteria, therefore, no summary can be provided.

Cost-Effectiveness of Guanfacine Versus Placebo or No Therapy

There were no studies identified that met the inclusion criteria, therefore, no summary can be provided.

Evidence-Based Guidelines Regarding the Use of Guanfacine

The 1 included guideline[27] recommended offering (i.e., based on strongest evidence) atomoxetine or guanfacine to children aged 5 years and over and young people only if they

cannot tolerate methylphenidate or lisdexamfetamine, or their symptoms have not responded to these stimulants. Further, they recommended considering (i.e., based on weaker evidence) changing from a stimulant medication to guanfacine in children aged 5 years and older if they have stimulant-related tics. Finally, they recommended not to offer (i.e., strongest evidence) guanfacine for adults without consulting a tertiary ADHD service.

Appendix 4 presents the main study findings and authors' conclusions.

Limitations

The main limitation is that the evidence is based on a lot of indirectness and uncertainty in the head-to-head comparisons, limiting the confidence in comparisons of guanfacine versus other non-psychostimulants and stimulant medications. The systematic reviews as well as the included studies were generally of sufficient quality. However, the quantity of primary studies with head-to-head comparisons and in subpopulations is limited. One systematic review concluded that the evidence quality for the guanfacine comparisons was moderate versus placebo, low versus atomoxetine and very for comparisons to clonidine, methylphenidate and modafinil.'[23] Two other systematic reviews concluded that the quality of evidence was low for the ASD population due to indirectness and imprecision,[21] and very low for children with ADHD and tics.[22]

Also, only 1 study was conducted in adults, only 1 study was completed in Canada, and there were no studies that explicitly discussed people with ODD. Therefore, the generalizability of the findings to the general Canadian population with ADHD, ASD and ODD is unclear.

Finally, the included RCTs were both funded by Shire, the manufacturer of Intuniv, creating a potential conflict of interest and uncertainty about editorial independence regarding the interpretation of findings.

Conclusions and Implications for Decision- or Policy-Making

This rapid review report included 4 systematic reviews, 2 RCTs and 1 evidence-based guideline. It adds to the current evidence base by synthesizing current evidence for clinical effectiveness and guidelines pertaining to using guanfacine for ADHD, ASD and ODD. The evidence suggests that guanfacine is generally more effective than placebo to improve ADHD symptoms among those with ADHD or ASD,[21-26] but with a higher potential for adverse events. Three systematic review found limited evidence of a significant difference in effectiveness between guanfacine and psychostimulants or non-psychostimulants,[21,23,24] but there may be greater risk of adverse events such as increased fatigue and abdominal pain.[24] The available 2018 guidelines by NICE is in line with these findings, only suggesting guanfacine if children cannot tolerate or do not respond to psychostimulants.[27] The evidence among adults with ADHD was limited to 1 clinical trial which found guanfacine was more effective than placebo to improve ADHD symptoms.[25]

Compared to a previous CADTH report on the same topic,[28] this review expands the research questions to more precisely compare guanfacine to psychostimulants and non-psychostimulants. Further, it includes 3 systematic reviews and 2 new RCTs, and a guideline that were unavailable in the previous report. The NICE guidelines identified in the current review recommended guanfacine in situations of intolerability or non-response.[27] However, this review aligns with the previous 1 in finding that the comparisons between guanfacine and other drugs for ADHD and related conditions are largely based on indirect evidence.

There is limit evidence about using guanfacine to treat ADHD, autism spectrum disorder, and oppositional defiance disorder in adults. Further, there was no evidence related to using guanfacine in people with ODD, indicating that the generalizability of the findings to this group is unknown. Also, due to the lack of evidence on cost-effectiveness, health care resource utilization studies may be useful to understand cost implications.[29] There is a need for studies comparing guanfacine to other medications in adult populations and people with ODD, and for evaluating the comparative cost-effectiveness analyses of the treatments.

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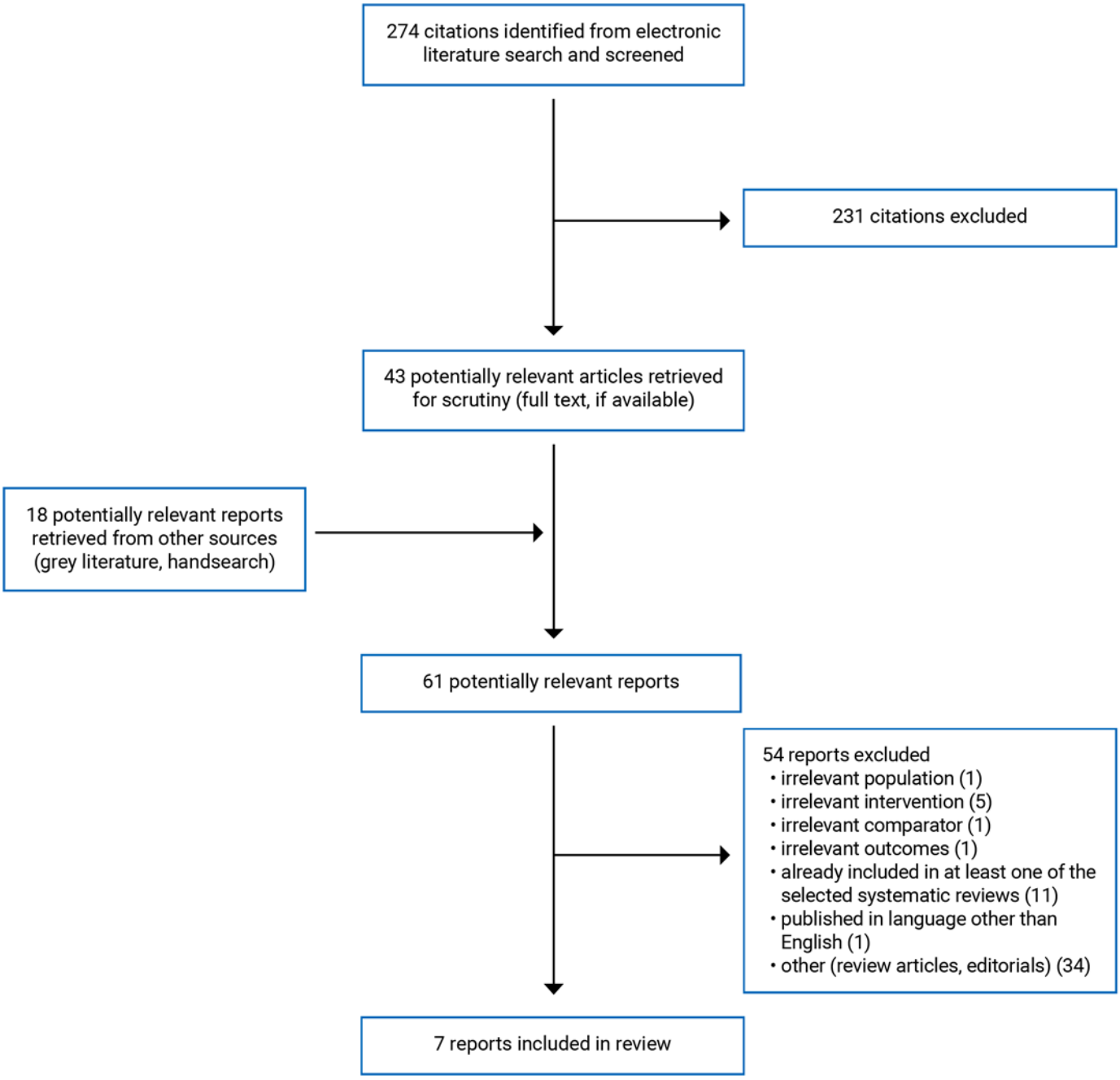
Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Note that this appendix has not been copy-edited.

Table 2: Characteristics of Included Systematic Reviews and Network Meta-Analyses

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow up
Siafis, 2022,[21] Germany Funding: Innovative Medicines Initiative 2 Joint Undertaking under Grant Agreement No. 777394 for the project AIMS2-TRIALS	Systematic review with network meta-analysis 203 placebo-controlled, parallel RCTs (open or blinded) One relevant RCT related to guanfacine	Children or adults (age unspecified) with a diagnosis of ASD (at least DSM-III) and/or validated diagnostic tools	Intervention: Any pharmacological or dietary supplement interventions for ASD Comparator: Placebo	Primary outcomes: • Social communication difficulties • Repetitive behaviours • ASD core symptoms Secondary outcomes: • Adverse events and behaviours, e.g., sedation and anxiety • Positive response on CGI-I • ADHD symptoms Follow up: Minimum duration 7 days
Cortese, 2018.[23] UK Funding: Stichting Eunethydis (European Network for Hyperkinetic Disorders), and the UK National Institute for Health Research Oxford Health Biomedical Research Centre.	Systematic review with network meta-analysis 133 double-blind RCTs with at least 1 week duration 12 relevant RCTs related to guanfacine	Children (aged ≥ 5 years and < 12 years), adolescents (aged ≥ 12 years and < 18 years), or adults (≥ 18 years) with a primary diagnosis of ADHD (DSM-III, DSM-III-R, DSM-IV(TR), DSM-5, ICD-9, or ICD-10).	Intervention: Amphetamines atomoxetine, bupropion, clonidine, guanfacine, methylphenidate and modafinil given as oral therapy. Comparator: Any placebo or other drug	Primary outcomes: • ADHD symptoms using any valid scale • Tolerability: discontinuation due to side effects Secondary outcomes: • Parent's rating on symptoms • CGI-I • Adverse events/ discontinuation due to any reason • Weight and blood pressure Follow up: 12 weeks
Osland, 2018,[22] Cochrane Collaboration, UK Funding: Internal sources (of support) • Department of Clinical	Systematic review 8 double-blind RCTs of any pharmacological treatment for ADHD in children with comorbid tic disorders One relevant RCT	Children 18 years or younger with a clinical diagnosis of ADHD and a chronic tic disorder (Tourette syndrome, chronic motor tic disorder, or chronic vocal tic disorder).	Intervention: Any pharmacological oral treatment for ADHD taken alone or in combination with another drug Comparator: Placebo	Primary outcome: • ADHD symptoms using any valid scale • Tic severity using any valid scale Secondary outcomes: Adverse effects

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow up
Neurosciences, University of Calgary, Canada. External sources • None, Other.	pertaining to guanfacine			Follow up: Guanfacine trial was 8 weeks long
Luan, 2017, 25 China, Funding: unclear	Systematic review 73 "mostly" RCTs with minimum 3-week duration 13 relevant studies of unclear design pertaining to guanfacine	Children and adolescents aged 6 to 18 years diagnosed with ADHD (DSM-IV).	Intervention: Atomoxetine, bupropion, clonidine, guanfacine, methylphenidate and lisdexamfetamine Comparator: Placebo or other drugs	Primary: efficacy measured by the ADHD-RS Secondary: All cause withdrawals, withdraw due to adverse event, withdrawal due to lack of efficacy, nausea, abdominal pain, or fatigue for tolerability Follow up: minimum 3 weeks duration

ADHD = attention-deficit/hyperactivity disorder; ADHD-RS = ADHD Rating Scale; ASD = Autism Spectrum Disorder; CGI-I = Clinical Global Impressions Scale-Improvement DSM = Diagnostic and Statistical Manual; ICD = International Classification of Disease; RCT = randomized controlled trial.

Table 3: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow up
Iwanami, 2020,[25] Japan, Funding: Shire International GmbH (manufacturer/licensee of Intuniv)	Phase 3, double-blind, placebo-controlled RCT	Japanese patients aged ≥ 18 years with ADHD (DSM-5)	Intervention: Guanfacine (n = 101) titrated from 2 mg per day to 4 to 6 mg per day (dose- optimization; 5 weeks), followed by 4 to 6 mg per day (dose-maintenance; 5 weeks), then tapered doses to 2 mg per day (2 weeks). Comparator: placebo (n = 100)	Primary Outcome: Change from baseline in total score on the Japanese version of the ADHD-RS-IV with adult prompts Secondary outcomes: Symptoms and improvement as measured by CGI-I, BRIEF-A, CAARS, CGI-S, AAQoL, PGI-I Safety outcomes: Adverse events, vital signs, body weight, ECG parameters, and clinical laboratory test values Length of follow up: 10 weeks

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow up
Van Stralen, 2020,[26] Canada, Funding: an investigator-initiated grant from Shire Canada Inc (manufacturer/licensee of Intuniv)	Single centre, double-blind placebo-controlled crossover trial	Children aged 6 to 12 years with: • primary diagnosis of predominantly inattentive, hyperactive/impulsive, or combined subtype of ADHD (DSM-IV) • treatment with a stable stimulant for at least 30 days (methylphenidate or amphetamine) • suboptimal executive function (a t score of ≥ 65 on the BRIEF-P).	Intervention: Guanfacine initiated at 1mg per day and optimized over 4 weeks to a maximum of 4 mg per day. 8-week maintenance period, then tapering over 11 days and a 10-day washout period. Comparator: Placebo	Primary outcome: Executive function measured by the BRIEF-P Secondary outcomes: ADHD symptoms and behaviours measured using ADHD-RS-IV, CGI-S, and the CGI-I. Safety outcomes: Adverse events, vital sign measurements, physical examinations (weight and height), and Columbia Suicide Severity Rating Scale Length of follow up: Final visit to measure outcomes at 21 days after the last visit (15 visits total, varying from 7 days to 8 weeks between visits with more frequent visits on visit 2 to 6 to optimize the dose, then 8 weeks to sustain the dose before tapering off)

AAQoL = adult attention-deficit hyperactivity disorder quality-of-life scale; ADHD = attention-deficit/hyperactivity disorder; ADHD-RS-IV = attention-deficit/hyperactivity disorder rating scale; BRIEF-A = Behaviour Rating Inventory of Executive Function–Adult Version; BRIEF-P = Behaviour Rating Inventory of Executive Function–Parent Version; CAARS = Conners' Adult ADHD Rating Scales, CGI-I = Clinical Global Impressions-Improvement; CGI-S = Clinical Global Impressions-Severity, DSM = Diagnostic and Statistical Manual; PGI-I = Patient Global Impressions-Improvement, RCT = randomized controlled trial.

Table 4: Characteristics of Included Guideline

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
NICE, 2018[27]						
Intended users: Health care professionals Commissioners and providers, People with ADHD, and their families and carers Target population: People with ADHD	Clinical and cost-effectiveness of pharmacolo-gical treatment	Quality of life, ADHD symptoms, CGI, serious adverse events, behavioural, functional, emotional dysregulation, academic outcomes, substance use and self-harm	• Systematic review of blinded RCTs and systematic reviews of RCTs was conducted with multiple database searches. • The evidence was up to date as of Dec 2021	Evidence was rated according to GRADE	Committee discussed evidence to arrive at recommendations, including the trade-off between benefits and harms, economic consideration and resources, and feasibility of the intervention	• Draft recommen-dations developed based on evidence and expert committee • Document posted for comment with registered stakeholders

ADHD = attention-deficit hyperactivity disorder; CGI = Clinical Global Impressions; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; NICE = The National Institute for Health and Care Excellence; RCT = randomized controlled trial.

Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

Table 5: Strengths and Limitations of Systematic Reviews and Network Meta-Analyses Using AMSTAR 2[16] and the ISPOR Questionnaire[17]

Strengths	Limitations
Siafis, 2022[21]	
• Clear PICO question, relevance and appropriate inclusion/ exclusion criteria related to this • Data were screened and extracted by at least 2 independent investigators, reducing risk of bias • Published a priori protocol, which helps prevents divergence when carrying out the research • Comprehensive database search with 7 databases, as well as hand searched reference lists and contacted study authors where necessary for additional information • Risk of study bias assessed using Cochrane risk of bias tool (rated low, moderate, high) • Quality of evidence assessed using GRADE • Strong statistical analyses: used random effects pairwise when incoherence detected, and network meta-analysis, used ITT data when available • Excluded studies with high risk of bias in randomization in the primary analysis • Assessment of transitivity and baseline imbalance: predefined list of potential-effect modifiers, examined distributions, used change scores instead of end points due to baseline differences in scales • Heterogeneity and network incoherence assessed • Provided network visualization, league table and pairwise comparisons	• Multiple doses of the same intervention were combined, with different follow up times tested only in sensitivity analyses (though this was robust) • Almost any scale was accepted but unclear whether their standardization was appropriate to provide exchangeable outcome measurement in the network meta-analysis
Cortese, 2018[23]	
• Clear PICO question and appropriate inclusion/exclusion criteria related to this • Data were screened and extracted by at least 2 independent investigators, reducing risk of bias • Visualizations of networks were provided • Comprehensive database search including 13 databases, handsearching reference lists and drug manufacturer websites limits the potential of missing important studies • Included trials were assessed using the Cochrane risk of bias tool: • Confidence in evidence measured using the GRADE approach for network meta-analysis	• Lack of discussion of heterogeneity between studies and implications for the analyses • Unclear comparability of the different scales used to assess ADHD symptoms

Strengths	Limitations
• Appropriate approach to pairwise and network meta-analysis: assessment of comparability of baseline population characteristics, and assessment of similarity of interventions and distribution of effect modifiers which showed robustness through subgroup/sensitivity analyses, use of random effects for statistical analysis • Provided list of excluded studies and reasons were in line with criteria	
Osland, 2018[22]	
• Clear PICO question and appropriate inclusion/exclusion criteria related to this • Searched 15 databases, trial registers and contacted experts for additional references • Two reviewers independently screened and selected studies, completed data extraction and assessed bias • Risk of bias assessment complete: Unclear risk of bias for random sequence generation, allocation concealment but low risk for blinding, attrition bias, or other bias • Used GRADE approach to assess the overall quality of evidence: Judged to be very low as there was only one small study • Appropriately no meta-analysis due to inconsistency across studies and lack of data availability	
Luan, 2017[24]	
• Clear PICO question • Risk of bias assessed using Cochrane tool • Publication bias assessed using funnel plots • Assessed for incoherence between direct/indirect estimates • Provide visualizations of networks for NMA • Assessed study heterogeneity	• Unclear inclusion and exclusion criteria (e.g., type of RCT unspecified) • Did not specify whether 2 independent investigators extracted the data • Limited database search of only 4 databases, without supplemental methods, as well as limited keywords • Do not discuss overall quality of evidence or implications • Do not conduct sensitivity analyses or discuss potential differences in study baseline characteristics or effect modifiers • Do not provide the results of the risk of bias analysis for each study • Do not discuss results of study heterogeneity analysis or implications • Funding statement is not available in the publication

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; ITT = Intention to treat; NMA = network meta-analysis; PICO = Population, Intervention, Comparator, Outcome; RCT = randomized controlled trial.

Table 6: Strengths and Limitations of Clinical Studies Using the Downs and Black Checklist[18]

Strengths	Limitations
Iwanami, 2020[25]	
• Clear research question, outcome measure clearly described • Specific inclusion and exclusion criteria that were appropriate to the research question • Allocation concealment done through computer generated random numbers, and blinding maintained through sealed envelopes and identical tablets for intervention and placebo • Description of power test suggests adequate power to detect an effect • Used an appropriate statistical model for repeat measures to analyze data, accounting for the repeat measures on patients • Overall, balanced baseline characteristics except for age: in the treatment group, 47% were less than 30 years old and 17% greater than 40 years, while the placebo group had 39% and 27% in these groups, respectively	• Not an intention-to-treat analysis, potentially biasing the effect upwards (included only those who had received at least one dose of medication or placebo and at least one measured outcome) • Assessed baseline differences using tests for statistical significance without correction for multiple testing • Characteristics of those who dropped out not presented • Did not adjust for the age imbalance between groups in primary analysis • Present several significance tests for each finding without correction for multiple testing • Funding was provided by Shire (drug manufacturer)
Van Stralen, 2020[26]	
• Allocation concealment and randomization: Treatment assignment was automatically provided by the Interactive Web Randomization System (IWRS). • Clear research question, outcome measure clearly described • Specific inclusion and exclusion criteria • Power calculation suggested adequate sample size to detect a treatment effect • Appropriate statistical analysis with a random effect to adjust for repeat measures on the same patients • Treatment arms were balanced, without statistical significance testing • Intention-to-treat analysis	• Exclusion criteria limit the generalizability, e.g., excluded anyone who had tried guanfacine in the past but failed to respond or suicide risk • Unclear basis for a 10-day washout period, and whether this would be long enough • Procedures to ensure blinding not described; unclear whether investigators and data analysts were actually blinded • Conducted additional exploratory analyses when correlation between treatment arms was detected, which suggested statistically significant differences remained in a subpopulation where scores were uncorrelated • Funding was provided by Shire (drug manufacturer)

Table 7: Strengths and Limitations of Guideline Using AGREE II[19]

Item	NICE27
Domain 1: Scope and Purpose	
1. The overall objective(s) of the guideline is (are) specifically described.	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes
Domain 2: Stakeholder Involvement	
4. The guideline development group includes individuals from all relevant professional groups.	Yes

Item	NICE27
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Unclear: The background of the commentors was not described
6. The target users of the guideline are clearly defined.	Yes
Domain 3: Rigour of Development	
7. Systematic methods were used to search for evidence.	Yes
8. The criteria for selecting the evidence are clearly described.	Yes
9. The strengths and limitations of the body of evidence are clearly described.	Yes
10. The methods for formulating the recommendations are clearly described.	No: While there were general processes described on the NICE website, the methods for formulating recommendations were vague
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	No: The evidence review was separate to the guideline, making the links difficult to specify
13. The guideline has been externally reviewed by experts before its publication.	No
14. A procedure for updating the guideline is provided.	Yes
Domain 4: Clarity of Presentation	
15. The recommendations are specific and unambiguous.	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes
17. Key recommendations are easily identifiable.	Yes
Domain 5: Applicability	
18. The guideline describes facilitators and barriers to its application.	Yes
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes
20. The potential resource implications of applying the recommendations have been considered.	Yes
21. The guideline presents monitoring and/or auditing criteria.	No
Domain 6: Editorial Independence	
22. The views of the funding body have not influenced the content of the guideline.	Yes
23. Competing interests of guideline development group members have been recorded and addressed.	Yes

AGREE II = Appraisal of Guidelines for Research and Evaluation II; NICE = The National Institute for Health and Care Excellence.

Appendix 4: Main Study Findings and Authors' Conclusions

Note that this appendix has not been copy-edited.

Table 8: Summary of Findings Included Systematic Reviews and Network Meta-Analyses

Main study findings	Authors' conclusion
Siafis, 2022[21]	
Network meta-analysis (other medication comparisons that were not statistically significant: mirtazapine, valproate, risperidone, aripiprazole, L1 to 79, atomoxetine, memantine, bumetanide, tideglusib, sapropterin, fluoxetine, n-acetylcysteine, sertraline, buspirone, citalopram, mecamylamine, lamotrigine, oxytocin, lurasidone, arbaclofen, simvastatin) Primary outcomes (ref: placebo), results from comparisons in network meta-analysis) Socio-communication difficulties: SMD (95% CI) = 0.04 (−0.46 to 0.54) Repetitive behaviours: SMD (95% CI) = 0.55 (−0.02 to 1.11) Secondary outcomes (ref: placebo (95% CI), results from comparisons in network meta-analysis unless otherwise specified) • Anxiety: 0.1046 [-0.5328; 0.7419] • Irritability (pairwise analysis): SMD (95% CI) = 0.50 [0.00, 1.01] • Positive response on CGI-I (pairwise analysis): OR = 9.67 [2.41, 38.71]) • Dropouts due to adverse events: OR (95% CI) = 11.0377 [0.5683; 214.3810] • Any adverse event: GUA vs placebo: OR (95% CI) = 17.94 [0.98, 329.56] (additional statistically significant findings: GUA vs sapropterin: OR (95% CI) = 36.2810 [1.5721; 837.2943], vs dimethylglycine: OR = 41.4027 [1.5146; 1131.7527]; vs sertraline: OR = 77.9412 [1.1250; 5399.8602]) • Dropouts for any reason: OR (95% CI) = 1.7500 [0.4413; 6.9396] (additional statistically significant findings: GUA vs risperidone: OR (95% CI) = 4.6461 [1.0565; 20.4326]) • Sedation (pairwise analysis): OR (95% CI) = 62.83 [12.84, 307.45] • ADHD symptoms: SMD = 1.39 [0.73, 2.05] (additional statistically significant findings: guanfacine vs ATX: 0.7454 [0.0014; 1.4895]; GUA vs riluzole: 1.0115 [0.1010; 1.9220]; GUA vs sapropterin: 1.0818 [0.1345; 2.0291]; GUA vs sertraline: 1.0956 [0.1503; 2.0408]; GUA vs amantadine 1.0970 [0.1183; 2.0758]; n-acetylcysteine 1.1733 [0.4029; 1.9437]; GUA vs arbaclofen 1.1908 [0.3772; 2.0045]; GUA vs fluoxetine 1.2042 [0.3888; 2.0195]; GUA vs mecamylamine 1.2698 [0.1031; 2.4364]; GUA vs bumetanide 1.2773 [0.4030; 2.1515]; GUA vs lurasidone 1.2908 [0.4683; 2.1132]; GUA vs	"Among ADHD medications, atomoxetine and guanfacine improved ADHD symptoms and potentially repetitive behaviors, but not social communication difficulties. Guanfacine was also associated with more adverse events and sedation." (p 9)

Main study findings	Authors' conclusion
tianeptine 1.3615 [0.0052; 2.7179]; GUA vs oxytocin 1.3963 [0.6399; 2.1527]; GUA vs simvastatin 1.6629 [0.6062; 2.7197]; GUA vs citalopram 1.5786 [0.7645; 2.3927]; GUA vs donepezil 1.7422 [0.7319; 2.7524]) Note: Confidence in evidence was low, due to concerns regarding the imprecision and more minor concerns regarding indirectness	
Cortese, 2018[23]	
Network Meta-analysis Primary outcomes: • ADHD symptoms- clinician rating (SMD (95% CI): findings < 0 favour the first drug): GUA vs placebo: −0.67 (−0.85, −0.50) (additional statistically significant findings: amphetamines vs guanfacine: −0.35 (−0.59, −0.10); no difference: ATX, BUP, Clonidine, MPH, MOD) • ADHD symptoms - teacher's rating (SMD (95% CI): findings < 0 favour the first drug): GUA vs placebo: −0.63 (−1.62,0.35) (no difference: ATX, BUP, MPH, MOD) Tolerability (OR (95% CI): findings > 1 mean the first drug is less tolerable): GUA vs placebo: 2.64 (1.20,5.81) (no difference: amphetamines, ATX, BUP, clonidine, MPH) Secondary outcomes • ADHD symptoms - parents' rating (SMD (95% CI): findings < 0 favour the first drug): GUA vs placebo:-0.23 (−0.90;0.45) (additional statistically significant findings: Amphetamines vs GUA: −0.85 (−1.58;-0.12); no difference: ATX, BUP, MPH, MOD) • CGI-I (OR (95% CI): findings > 1 favour more improvement with the first drug): GUA vs placebo: 3.63 (2.36;5.57) (additional statistically significant findings: Amphetamines vs GUA: 2.13 (1.24;3.66); no difference: ATX, MPH, MOD) Acceptability (OR (95% CI): findings > 1 mean lower acceptability for the first drug): GUA vs placebo: 0.81 (0.54,1.23) (no difference: amphetamines, ATX, BUP, Clonidine, MPH, MOD) • Weight (SMD (95% CI): findings < 0 mean the first drug was associated with a decrease in weight): GUA vs placebo: 0.09 (−0.42;0.60) (additional statistically significant findings: GUA vs MPH: 0.86 (0.26;1.47); GUA vs MOD: 1.02 (0.19;1.86); amphetamines vs GUA: 0.80 (−1.48;-0.13) ; ATX vs GUA: −0.94 (−1.54;-0.33); clonidine)	"In children and adolescents, all compounds were superior to placebo on the CGI-I scale" (p 733) "With respect to tolerability, in children, only amphetamines and guanfacine were less well tolerated than placebo."(p 734) "[Guanfacine] was not superior to placebo according to parents' ratings (SMD −0·23, 95% CI −0·90 to 0·45) (p 733) "With respect to ADHD core symptoms rated by clinicians in children and adolescents, all drugs were superior to placebo" (p 731)
Osland, 2018[22]	
Primary outcomes: • ADHD-RS completed by the teacher: guanfacine: 37.2 (SD 8.4) points at baseline, 23.6 (SD 13.6) points at end point; placebo: 34.4 (SD 9.3) points at baseline, 31.7 (SD 11.2) points at end point (P < 0.01) • YGTSS total tic score: guanfacine: 15.2 (SD 6.6) points at	"Methylphenidate, clonidine, guanfacine, desipramine, and atomoxetine appear to reduce ADHD symptoms in children with tics though the quality of the available evidence was low to very low. Although stimulants have not been shown to worsen tics in most people with tic disorders, they may, nonetheless, exacerbate tics in individual cases. In these instances,

Main study findings	Authors' conclusion
baseline, 10.7 (SD 7.0) points at end point; placebo: 15.4 (SD 7.0) points at baseline, 15.4 (SD 5.5) points at end point (P = 0.05). Secondary outcomes: • Adverse events: No statistically significant difference between groups	treatment with alpha agonists or atomoxetine may be an alternative." (p 2)
Luan, 2017[24]	
Network meta-analysis Primary outcome (ADHD-RS: value > 0 favours the first drug): GUA vs placebo: MD = 6.58 (2.32, 10.94) (no difference: ATX, CLON, MPH, LDX, MPH Secondary outcomes (95% credible interval) (all comparisons: ATX, CLON, MPH, LDX, MPH; no statistically significant difference unless otherwise noted): All cause withdrawal: GUA vs placebo: OR = 0.83 (0.63 to 1.09) Withdrawals due to adverse events: GUA vs placebo: OR = 3.39 (1.93 to 6.30) (additional: GUA vs ATX: OR = 2.29 (1.20, 4.57); GUA vs MPH: OR = 0.39 (0.18 to 0.83)) Withdrawal due to lack of efficacy: GUA vs placebo: OR = 0.37 (0.26 to 0.54) (additional: GUA vs LDX: OR = 3.46 (1.70 to 7.60) Nausea: GUA vs placebo: OR = 1.45 (0.83 to 2.64) (additional: GUA vs ATX: OR = = 0.51 (0.26 to 0.96)) Abdominal pain: GUA vs placebo: OR = 2.18 (1.55 to 3.19) (additional: GUA vs LDX: OR = 4.85 (2.25 to 10.1)) Fatigue: GUA vs placebo: OR = 4.22 (2.56 to 7.54) (additional: MPH vs GUA: OR = 0.19 (0.08 to 0.45))	"ATX and [GUA] are located at moderate positions under symptom improvement and rate of withdrawal. There are not significant differences in ADHD-RS when compared with another therapy, which indicated comparable efficacy. " (p. 11) "In summary, according to the results obtained from our NMA, the stimulants LDX and MPH are still highly recommended because they are highly efficacious and well tolerated by patients. Among the non-stimulants, CLON should be taken into consideration for its appreciable effectiveness and tolerability. ATX and [GUA] can be seen as moderate choices. We failed to evaluate BUP because of the lack of enhanced evidence." (p. 12)

ADHD = attention-deficit/hyperactivity disorder; ADHD-RS = ADHD Rating Scale; ATX = atomoxetine; BUP = bupropion; BSP = buspirone; CLON = clonidine; DEX = dexamphetamine; EDX = edivoxetine; GUA = guanfacine; LDX = lisdexamfetamine; MPH = methylphenidate; MAS = mixed amphetamine salts; MOD = modafinil; PDL = pindolol; OR = odds ratio; 95% CI = 95% confidence interval; RBX = reboxetine; SLG = selegiline; SD = standard deviation; SMD = standardized mean difference; MD = mean difference; VEN = venlafaxine; YGTSS = Yale Global tic Severity Scale.

Table 9: Summary of Findings of Included Primary Clinical Studies

Main study findings	Authors' conclusion
Iwanami, 2020[25]	
Primary outcome: ADHD-RS-IV total score: Change of −11.55 (1.10) vs −7.27 (1.07); MD = −4.28 (−6.67 to −1.88) in treatment vs placebo group respectively(P = 0.0005) **Secondary outcomes** (MD (95% CI): value < 0 favours GUA) ADHD-RS-IV inattention: MD = −2.51 (−4.16 to −0.85) (P = 0.0032) ADHD-RS-IV hyperactivity-impulsivity: MD = −1.74 (−2.84 to −0.64) (P = 0.0021) CAARS scores: • DSM-IV Total ADHD Symptoms: MD = −3.11 (−5.15 to −1.08) (P = 0.0029) • DSM-IV Inattentive Symptoms: MD = −1.89 (−3.31 to −0.47) (P = 0.0092) • DSM-IV Hyperactive/Impulsive Symptoms: MD = −1.18 (−2.09 to −0.26) P = 0.0118 AAQoL: no statistically significant changes in total score or sub-dimensions (life outlook, relationships, psychological health) except for life productivity (MD = 6.78 (1.86 to 11.71), P = 0.0072) BRIEF-A: statistically significant changes for Inhibit (MD = −2.91 (−5.30 to −0.52) 0.0173), Initiate (MD = −3.32 (−6.49 to −0.14)), Plan/Organize (MD = −3.76 (−6.85 to −0.67) P = 0.0174) but not Shift, Emotional Control, Self-Monitor, Behavioural Regulation Index, Working Memory, Task Monitor or Organization of Materials Metacognition Index: MD = −3.04 (−6.11 to 0.03) 0.0519 Global Executive Function Index: MD = −3.06 (−5.99 to −0.14) 0.0404 Safety outcomes: n = 82 (81%) in GUA vs n = 62 (62%) in placebo had adverse event, 19.8% lead to discontinuation in GUA group vs 3% in placebo group. 2% had severe in GUA group vs 0 in placebo group.	"The superiority of [guanfacine] compared with placebo was demonstrated for ADHD symptoms as measured by the ADHD-RS-IV and CAARS. Furthermore, the improvement in ADHD symptoms was associated with physician- and patient-rated clinical improvement (CGI-I and PGI-I) as well as patient-rated quality of life (life productivity on the AAQoL) and executive functioning (some BRIEF-A subscales). The most commonly observed [treatment related adverse events] were mild to moderate in severity and consistent with the known safety profile of GXR. The favorable benefit-risk profile of [guanfacine] in the treatment of ADHD was established in pediatric patients, and these results support its profile in adult patients." (p e7)
Van Stralen, 2020[26]	
Primary outcome: BRIEF-P: MD = −3.0, 95% CI [−5.9, −0.2]; p value = 0.0392 (change of −9.2% (SE = 2.11%) vs. −6.9% (SE = 1.94%) in the treatment vs placebo arm, respectively) **Secondary outcomes** (MD [95% CI]; negative MD favours GUA): • ADHD-RS-IV total score: MD = −6.9, 95% CI [−9.8, −4.0]; p value < 0.0001 • CGI-S: MD = −0.9 (1.4, −0.4); p value = 0.0007	"The results of this study show that adjunctive administration of the selective α2A-adrenoceptor agonist, [guanfacine], to a psychostimulant in patients with suboptimal response to psychostimulants improves executive function...This adjunct therapy also improved the ADHD symptom control as assessed by the ADHD-RS-IV and the CGI-I and CGI-S scales." (p 322)

Main study findings	Authors' conclusion
• CGI-I: MD = −0.7 (1.2, −0.3); p value = 0.0030 Safety outcomes: Any adverse event: n = 41 (87%) vs n = 41 (85%) in GUA vs placebo respectively. Headache most common (49% vs 33%) followed by abdominal pain (30% vs 10%) No "yes" responses to the CSSRS during the GUA arms of the study.	

AAQoL = adult attention-deficit/hyperactivity disorder quality-of-life scale; ADHD = attention-deficit/hyperactivity disorder; ADHD-RS-IV = ADHD Rating Scale IV; BRIEF-A = Behaviour Rating Inventory of Executive Function–Adult Version; BRIEF-P = Behavioural Rating Inventory of Executive Function; CAARS = Conners' Adult ADHD Rating Scales; CGI-S = Clinical Global Impressions of Severity of Illness; CGI-I = Clinical Global Impressions-Improvement; CSSRS = Columbia Suicide Severity Rating Scale; MD = mean difference.

Table 10: Summary of Recommendations in Included Guideline

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
NICE, 2018[27]	
"1.7.10 Offer atomoxetine or guanfacine to children aged 5 years and over and young people if: • they cannot tolerate methylphenidate or lisdexamfetamine or • their symptoms have not responded to separate 6-week trials of lisdexamfetamine and methylphenidate, having considered alternative preparations and adequate doses" (p 25) "1.7.17 Do not offer any of the following medication for ADHD without advice from a tertiary ADHD service: • guanfacine for adults (off-label use)" (p 26) "1.8.14 If tics are stimulant related, reduce the stimulant dose, or consider changing to guanfacine (in children aged 5 years and over and young people only)..." (p 31) Supporting evidence: "Atomoxetine and guanfacine were the non-stimulant drugs with the most convincing evidence. The committee noted that atomoxetine is more widely used and that there was stronger evidence for a benefit of atomoxetine compared with placebo than guanfacine compared with placebo." (p. 46)	The word 'offer': clear and strong evidence of benefit (1.7.10, 1.7.17) The word 'consider': evidence is less certain (1.8.14)

ADHD = attention-deficit/hyperactivity disorder; NICE = The National Institute for Health and Care Excellence.

Appendix 5: Overlap Between Included Systematic Reviews

Note that this appendix has not been copy-edited.

Table 11: Overlap in Relevant Primary Studies between Included Systematic Reviews

Primary study citation	Osland, 2018 [22]	Cortese, 2018 [23]	Luan, 2017[26]
Scahill L, et al. American Journal of Psychiatry 2001;158(7):1067 to 74.	Yes	Yes	—
Biederman J, et al. Pediatrics. 2008;121(1):e73 to 84.	—	Yes	Yes
Connor DF, et al. CNS Drugs. 2010;24(9):755 to 768.	—	Yes	Yes
Newcorn JH, et al. J Am Acad Child Adolesc Psychiatry. 2013;52(9):921 to 930.	—	Yes	Yes
Rugino TA. J Atten Disord. 2014.	—	Yes	Yes
Sallee FR, et al. J Am Acad Child Adolesc Psychiatry. 2009;48(2):155 to 165.	—	Yes	Yes
Hervas A, et al. Eur Neuropsychopharmacol. 2014;24(12):1861 to 1872.	—	Yes	Yes
Wilens TE, et al.J Am Acad Child Adolesc Psychiatry. 2015;54(11):916 to 925.e912.	—	Yes	Yes

Appendix 6: Details on included scales

Note that this appendix has not been copy-edited.

ADHD Rating Scale, ADHD Rating Scale IV (ADHD-RS)[24-26]: completed independently by a parent or teacher, and scored by a clinician. The scale consists of 2 subscales: inattention (9 items) and hyperactivity-impulsivity (9 items) for a total of 18 items. The total score can range from 0 to 54; a higher score means worse ADHD symptoms.

Behaviour Rating Inventory of Executive Function–Parent (BRIEF-P)[26]: an 86-item questionnaire completed by parents to assess executive function in children. Raw scores are transformed to T-scores of which above 65 is considered clinically significant.

Behaviour Rating Inventory of Executive Function - Adult Version (BRIEF-A)[25]: like the BRIEF-P but for adults, it includes 75 items to assess adult executive function behaviours.

Clinical Global Impressions- Severity of illness (CGI-S)[21,23,25,26]: Scale ranges from 1 (no symptoms) to 7 (very severe symptoms).

Clinical Global Impressions-Improvement (CGI-I)[21,23,25,26]: Scale ranges from 1 (most improvement) to 7 (least improvement): Three or less means improvement, 4 means no change, 5 to 7 means worse.

Yale Global Tic Severity Scale (YGTSS) total tic score[22]: tool to quantify the severity of tic symptoms in children aged 6 to 17. A higher score indicates more severe tics symptoms: the Total Tic Severity Score has a range of 0 to 50, and the Global Severity Score has a range of 0 to 100.

Appendix 7: References of Potential Interest

Note that this appendix has not been copy-edited.

Previous CADTH Reports

Harricharan S, Frey N. Intravenous acetaminophen for the management of short-term post-operative pain: a review of clinical effectiveness and cost-effectiveness. *(CADTH rapid response report: summary with critical appraisal)*. Ottawa (ON): CADTH; 2018: https://www.cadth.ca/sites/default/files/pdf/htis/2019/RC1023%20IV%20Acetaminophen%20v2%20Revised%20Final.pdf. Accessed 2022 June 5.

Additional References

American Academy of Neurology. Practice guideline recommendations summary: treatment of tics in people with Tourette Syndrome and chronic tic disorders. 2019; https://www.aan.com/Guidelines/Home/GuidelineDetail/958. Accessed 2022 June 5.

Molife C, Haynes VS, Nyhuis A, et al. Healthcare utilization and costs of children with attention deficit/hyperactivity disorder initiating atomoxetine versus extended-release guanfacine. *Curr Med Res Opin.* 2018;34(4):619-632. .PubMed

Newcorn JH, Huss M, Connor DF, Hervás A, Werner-Kiechle T, Robertson B. Efficacy of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder and comorbid oppositional defiant disorder. *J Dev Behav Pediatr.* 2020 Sep;41(7):565-570. .PubMed

United States Department of Veteran Affairs. Management of posttraumatic stress disorder and acute stress reaction 2017. (*VA/DoD Clinical Practice Guidelines)*. 2017; https://www.healthquality.va.gov/guidelines/MH/ptsd/. Accessed 2022 June 5.