Updated 2018 NICE guideline on pharmacological treatments for people with ADHD: a critical look

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ABSTRACT
The National Institute for Health and Care Excellence (NICE) recently updated its guideline on pharmacological treatments for attention deficit hyperactivity disorder (ADHD). The guideline builds on evidence reviews with serious methodological limitations concerning multiplicity, imprecision, selective reporting, and short-term data. Strong clinical practice recommendations for methylphenidate and lisdexamfetamine are informed by GRADE-evaluated, low-quality studies and subjective value judgements. This article critically discusses the updated NICE guideline on pharmacological treatments for ADHD and proposes concrete solutions to address the issues at hand.

**KEYWORDS**

National Institute for Health and Care Excellence, attention deficit hyperactivity disorder, pharmacology, stimulant, methylphenidate, amphetamine, atomoxetine
INTRODUCTION

In March 2018, the National Institute for Health and Care Excellence (NICE) updated its guideline (NG87) on diagnosing and managing attention deficit hyperactivity disorder (ADHD), and its evidence-base on the efficacy and safety of pharmacological treatments for ADHD. The guideline currently recommends short- and long-acting methylphenidate as the first-line pharmacological treatment for children over five, adolescents, and adults with ADHD, and lisdexamfetamine for adults only (recommendations under section 1.7). Practicing physicians are advised to consider dexamfetamine and atomoxetine if their first-line prescriptions generate adverse events or bring about little symptom reduction in patients. NICE states that methylphenidate and lisdexamfetamine show clinically important benefits for ADHD, compared to placebo and other drugs (p. 47).

ADHD is a neurodevelopmental disorder characterised by excessive hyperactivity, impulsivity, and inattention. The condition is associated with increased risk of substance-use disorder, accidents, academic failure, criminality, death, and other adverse health outcomes. Targeted treatment options for ADHD are lacking and its genetic and environmental causes remain largely unknown.

We previously authored five Cochrane systematic reviews on the clinical efficacy and adverse events of methylphenidate and amphetamines for children, adolescents, and adults with ADHD. All of the published reviews concluded that the GRADE evidence quality (i.e., the confidence in the treatment estimates) was low to very low, advising readers to cautiously interpret the results. The methodology and conclusions from the published Cochrane reviews contrast markedly from the updated NICE evidence-base and recommendations.
According to the NICE manual, recommendations should be informed by the best available evidence, but if the evidence is unsubstantial and biased, committee members are often required to make subjective value judgements upon recommending treatments. This is why guidelines can be controversial, why they should be critically evaluated, and arguably why patients, clinicians, and decision-makers should be explicitly informed on the certainty behind each recommendation they read. Building on the methods and findings from the previous Cochrane reviews, this paper critically discusses the NICE evidence-base and recommendations on pharmacological treatments for ADHD, and proposes specific steps to improve the way NICE synthesises and communicates evidence to care providers and receivers.

**SELECTIVE REPORTING**

The updated NICE recommendations on pharmacological interventions were based on clinical- and economic evidence reviews on effectiveness and adverse events, the clinical experience of appointed committee members (e.g., specialists, generalists, and care providers), and drug licencing regulations (p. 47). NICE evidence reviews are similar to regular systematic reviews, and they include study protocols to outline review scopes. The protocols in the updated reviews were not published a priori or registered on PROSPERO (the International prospective register of systematic reviews), as the guideline developers indicated themselves (Appendices A). All systematic review authors are strongly advised against this because it limits consistency, accountability, and transparency, and inflates the risk of a range of biases, including selective reporting bias. We see no reason why systematic reviews by clinical guidelines should be exempt from such standards, and we encourage NICE to prospectively register its protocols in the future.
NICE excluded unpublished data and open-label trials from the evidence reviews.\textsuperscript{2,3} When systematic reviews exclude unpublished data, valuable clinical information is often lost,\textsuperscript{25} and meta-analytic estimates are more prone to bias.\textsuperscript{26} In addition, NICE included double-blinded clinical trials only, but this does not guarantee unbiased blinding procedures. Adverse events and certain behavioural effects are more frequent in pharmacological treatments for ADHD than placebo interventions in clinical trials,\textsuperscript{10,13} which increases the risk of de-blinding in study participants.\textsuperscript{27} De-blinding could have affected the subjective and regulatory efficacy outcomes reported by NICE, such as ADHD symptom severity and quality of life. The selection of outcomes by NICE is worthy of critique in itself: For patients and clinicians, outcomes related to crime, substance-use, accidents, academic functioning, and death could be more meaningful than symptom severity and life quality.\textsuperscript{5–8}

When identifying relevant studies, NICE evaluated five Cochrane reviews,\textsuperscript{11,28–31} out of which three were protocols.\textsuperscript{28–30} The two largest Cochrane reviews on the benefits and harms methylphenidate and amphetamines from 2015 and 2016 were not identified.\textsuperscript{10,13} Both of these were developed by our research groups and included markedly more studies than the NICE reviews. To illustrate, our review on methylphenidate versus placebo for children and adolescents\textsuperscript{13} aggregated data from 175 randomised clinical trials. NICE included 16 clinical trials on immediate- and osmotic-release methylphenidate versus placebo for the same population (section 1.1.3.4).\textsuperscript{2} Our review on amphetamines versus placebo for children and adolescents\textsuperscript{10} included 23 trials. NICE included one trial for the same study population (section 1.1.3.5).\textsuperscript{2}
Cochrane reviews have frequently been cited by NICE guidelines in the past,\textsuperscript{32} and we question how NICE did not systematically assess the best available evidence for ADHD management – one of the NICE's key principles.\textsuperscript{16} The exclusion of unpublished material and open-label trials also contributed to reduced information sizes (e.g., the meta-analytic sample size) and limited the representability of the NICE evidence-base. If NICE is concerned with systematic bias and inconsistency in such data, we recommend using appropriate subgroup and sensitivity analyses instead of simply excluding potentially valuable information. Future joint efforts and constructive dialogue between NICE and the Cochrane Collaboration would be valuable to ensure the use of appropriate methods for evidence synthesis.\textsuperscript{32}

**MULTIPLE COMPARISONS**

The NICE evidence review on clinical- and cost-efficacy\textsuperscript{2} reported on 17 primary- and 6 secondary outcomes and conducted 309 head-to-head and placebo-controlled meta-analyses on randomised clinical trials. The systematic review on harms\textsuperscript{3} reported on 16 primary outcomes (which were further stratified on trial duration) and conducted 174 meta-analyses. Apparently, no adjustment strategies for multiple comparisons were carried out. With this many outcomes and comparisons, the likelihood of finding false positive results at $p < 0.05$ (type I error) increases dramatically.\textsuperscript{33,34} Most of the comparisons on efficacy and harms contained only two clinical trials (appendices E).\textsuperscript{2,3} This also increases the risk of imprecise estimates with wide confidence intervals due to insufficient statistical power to detect true differences (type II errors), and the rates of random errors and false positives (type I errors) due to unequal distributions of prognostic factors despite randomisation procedures.\textsuperscript{33–36}
To prevent these issues, NICE could have combined the 15 out of 17 outcomes on ADHD symptomology in their effectiveness review\(^2\) into one meta-analytic estimate, and conducted subsequent subgroup and sensitivity analyses on the variations in ADHD outcomes, such as teacher-rated and observer-rated outcomes. This would have satisfied their review scope criteria while protecting against multiplicity and power issues in the main meta-analytic comparisons. NICE could also have adjusted the threshold for statistical significance in their reviews according to the number of primary outcomes, calculated required information sizes (i.e. the meta-analytic sample size) for each outcome, and applied sequential hypothesis testing techniques to their comparisons.\(^{33–36}\) A critique of the NICE guidance on bipolar disorder from 2016 highlighted similar issues,\(^{37}\) but NICE have not taken appropriate measures since. This is problematic, seeing how inappropriate controlling for multiplicity and power issues may greatly increase the likelihood of biased treatment recommendations, and serve as a fundamental error in the way NICE synthesises evidence across patient populations.

**GENERALISABILITY**

As a neuro-developmental condition, ADHD frequently affects people through childhood and into adulthood.\(^9\) However, the clinical trials in the NICE evidence reviews were short in duration, lasting usually under 12 weeks. This undermines the generalisability of the data. The short duration was the main rationale for not recommending pharmacological treatments as first-line treatments to children under five (p. 42).\(^{38}\) However, the data from all the other age groups in the NICE evidence-base presided from short-term trials too.\(^{2,3}\) It therefore appears inconsistent that the data from the short-term trials for children over five, adolescents, and adults are considered acceptable in terms of clinical relevance and generalizability, while the data from those under five is not. Also, the choice
to stratify all meta-analyses into groups of patients under five years and over seems arbitrary. The NICE committee for ADHD management does mention the lack of long-term evidence in their evidence review on pharmacological treatments (p. 157), but this issue is not sufficiently presented to readers in the actual guideline recommendations.

QUALITY AND RISK OF BIAS

For pharmacological efficacy, NICE assessed the GRADE evidence quality at moderate to low for all age ranges (section 1.3.1.2) and low to very low for the clinical trials on harms (section 1.9.1.2). The previously published Cochrane reviews on efficacy and adverse events for methylphenidate and amphetamines assessed the evidence quality at low to very low. NICE consistently graded studies with serious imprecision (e.g., studies with wide confidence intervals) at moderate evidence quality, a practice not endorsed by the previous Cochrane reviews nor GRADE. According to GRADE, it is crucial to downgrade the quality of critically imprecise estimates, and we encourage NICE to implement GRADE standards in future reviews.

Regardless of these differences, both NICE and the Cochrane studies were unanimous in finding widespread low-quality evidence. The majority of the clinical trials in the NICE reviews were subject to high risk of bias, with frequent methodological flaws such as incomplete outcome data, issues with blinding, and outcome reporting bias. Thus, the interpretability of the NICE evidence-base is systematically undermined. In the evidence review on efficacy, the NICE committee acknowledges the low quality of evidence (p.157), but the poor methodological quality does not seem to have affected the actual recommendations on pharmacological treatments for ADHD. Care providers and users would undoubtedly benefit from more transparent and vivid
indicators of the confidence behind each recommendation they read. The room for improvement here, is great.

VESTED INTERESTS

The NICE manual states that “guidance is developed by independent and unbiased Committees of experts” (p. 14). The committee for the updated ADHD guideline consisted of a chair, a clinical advisor, and 17 members, out of which 15 (78%) disclosed financial interests. The clinical advisor in the group disclosed 16 interests, and one committee member declared as many as 49 interests. NICE decided to act (i.e., excluding a member from discussions) on three conflicts out of the hundreds that were declared. The share amount of declarations calls into question the methods by which NICE employs to evaluate the independency of its committee members. Industry sponsorship leads to more favourable results and conclusions in systematic reviews, and it is of critical importance that institutions like NICE work to minimise its influence. At first glance, it does not seem as if the guideline for ADHD drug management has been developed by “independent and unbiased” committee members.

META-ANALYSES

The meta-analytic estimates in the review on clinical- and economic efficacy are often imprecise and hard to interpret. For instance, all the analyses on ADHD symptoms are stratified into teacher-, and investigator-rated symptoms, trial duration, subscales, and a multitude of rating scales. Some show borderline significant effects in favour of methylphenidate over placebo on ADHD total symptoms (-0.37; 95% CI -0.69 to -0.05; teacher-rated; SNAP-IV; 1 study) and others strong effects (-13.00; 95% CI -16.05 to -9.95; investigator-rated; ADHD-RS; 1 study). The few included
randomised trials in each analysis, the number of analyses, and the failure to convert scales to yield more precise estimates, all contribute less interpretable findings. All the observational economic evidence is challenging to interpret too, given how the 11 observational studies in the reviews on efficacy and harms\textsuperscript{2,3} were assessed at low-quality according to GRADE standards. Not surprisingly, the guideline committee members indicate how they had troubles evaluating all the different pairwise comparisons presented to them (p.157).\textsuperscript{2}

Non-randomised studies were not assessed in the evidence review on harms,\textsuperscript{3} even though they can have several advantages over randomised clinical trials for assessing adverse events. Non-randomised studies are often larger, involve a broader range of participants, reflect clinical practice more accurately, have longer follow-up periods, and cost less than randomised trials.\textsuperscript{44,45} Adverse events are often underreported and neglected in clinical trials,\textsuperscript{46} and issues with statistical power can lead to inflated type II errors and failure to detect important harms, such as accidents and death.\textsuperscript{7} NICE did not measure all-cause treatment discontinuation either, a measure of acceptability that weighs symptom improvement against safety. Had this outcome been included, the committee members would have discovered that methylphenidate,\textsuperscript{47} lisdexamfetamine,\textsuperscript{14} and atomoxetine\textsuperscript{48} do not show better acceptability than placebo in adults with ADHD.

We recently published a Cochrane systematic review on the adverse events of methylphenidate for children and adolescents with ADHD, assessing non-randomised studies only.\textsuperscript{12} 260 non-randomised studies were included, finding that the proportion of patients with any non-serious adverse events was 51·2\% (95\% CI 41·2\% to 61·1\%; 49 studies, 13 978 participants), and that the risk ratio for any serious adverse event was 1·36 (95\% CI 1·17 to 1·57; two studies; 72 005
participants) when compared to untreated controls. For placebo-controlled methylphenidate trials in children and adolescents, NICE found risk ratios on total adverse events of 1.95 (95% CI 1.11 to 3.43; one study; 69 participants) (appendix E.2.1), and 1.23 (95% CI 0.98 to 1.55; one study; 294 participants) (appendix E.2.2). These estimates are hard to interpret due to low information sizes, and they do not differentiate between serious and non-serious adverse events. Also, NICE indicated that there was a lack of consistent reporting on harms in the literature, with trials using conflicting methods to assess adverse events (section 1.9.1.2).3 Taking into account the short-term evidence on harms, efforts to precisely evaluate the ratio between benefits and harms of drug treatments remain a daunting task.

**STRONG RECOMMENDATIONS, LIMITED EVIDENCE**

The responsibility of NICE is both simple and noble: To provide guidance on promoting good health for preventing and treating disease.49 Much of their work is commendable, and we applaud many of the individual NICE recommendations on ADHD management, such as the need for thorough baseline assessments, appropriately qualified practitioners when prescribing medications, systematic monitoring of adverse events, and social support for patients.1 The heterogeneous nature and unclear etiological pathways of ADHD9 are also mentioned in their guideline, and they give recommendations for research, which is constructive. Other prominent guidelines on ADHD management, such as the guidance from the American Academy of Paediatrics,50 have not been updated in recent years, and NICE should also be acknowledged for leading the way here.

However, the updated NICE guideline on pharmacological treatments for ADHD is based on questionable methods for evidence synthesis and low-quality studies. Not once, in the widely
accessible document on ADHD diagnosis and management,¹ and on the affiliated guideline webpages,³⁸ does NICE mention the low quality of their evidence. The NICE Social Value Judgements policy⁴⁹ states that “NICE should not recommend an intervention (…) if there is no evidence, or not enough evidence, on which to make a clear decision” (p. 16). NICE nevertheless strongly recommends methylphenidate and amphetamine derivatives for children and adults (recommendation 1.1.13 and 1.5.15), indicating clear evidence of beneficial treatments, according to the NICE manual.¹⁶ The existence of such clear evidence is highly questionable.

If the magnitude of benefits and harms of an intervention is uncertain, strong recommendations for that intervention is clearly troublesome.⁵¹ NICE policy indicates that subjective value judgements may be sufficient for recommending treatments if good quality evidence is absent,⁴⁹ and committee member experience is indeed frequently mentioned upon explaining why the recommendations were made (p. 47).¹ But without rigorous empirical data, such qualitative recommendations appear unreliable and weak. Clinical guidelines should at minimum be transparent in communicating the flaws of their evidence-base to patients, practitioners, and decision-makers in a clear and concise manner.⁵²

Many guidelines use letters and symbols to communicate the strength of their evidence, but NICE, being one of the most respected guideline developers out there, does not. A consensus on how guidelines should optimise the way they communicate the certainty of recommendations to readers is clearly needed. Here, the visual system developed by the GRADE Working Group could serve as inspiration.⁵¹ GRADE offers symbolic representations to organisations wishing to adopt their system (see Fig 1 for an illustrated example), and we encourage NICE to consider their visual
Such changes would ensure transparency, methodological rigour, and ultimately facilitate improved clinical decision-making.

[Fig 1]

SEARCH STRATEGY AND SELECTION CRITERIA

Due to the narrative and critical nature of this Personal View, our search strategy and methods do not reflect the standards of systematic reviews. We retrieved articles up to XX.XX.18 from searches in MEDLINE Ovid, EMBASE Ovid and Google Scholar, using the key terms “The National Institute for Health and Care Excellence”, “attention deficit hyperactivity disorder”, “pharmacology”, “methylphenidate”, “amphetamine” and “atomoxetine”. We also traced cross-references from relevant literature and surveyed journals, such as the BMJ, The Lancet Psychiatry, JAMA Psychiatry and Cochrane Database of Systematic Reviews. All material from NICE was retrieved from their webpages on ADHD management.

CONTRIBUTIONS

CG and OJS had the initial idea for the study. EGF retrieved relevant literature and wrote multiple drafts including the final version. All authors commented, edited and made suggestions.

DECLARATION OF INTERESTS
CG, OJS, MZ, and ES have authored several of the Cochrane reviews on treatments for ADHD and have no commercial conflicts of interest. XC has authored two of the Cochrane reviews on treatments for ADHD and has no conflicts of interest to report.

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**FIGURE LEGEND**

**Fig 1:** Illustrated example of GRADE-inspired symbols used for NICE recommendations.