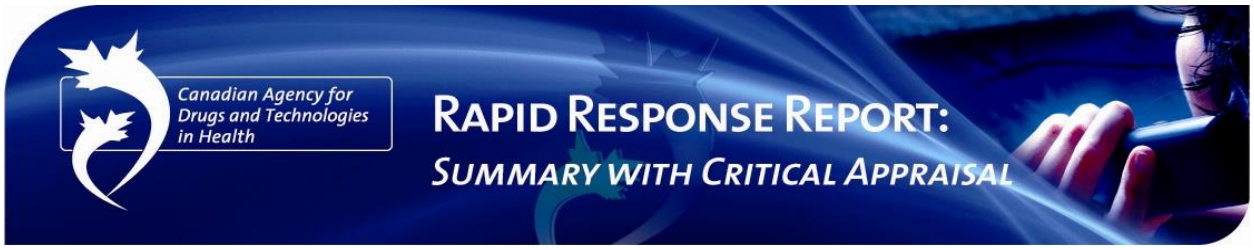


TITLE: Attention-Deficit/Hyperactivity Disorder Medication Switching for Patients with Aggression or Mood Changes Secondary to Current Medication: A Review of Clinical Effectiveness and Guidelines

DATE: 14 September 2015

CONTEXT AND POLICY ISSUES

Attention-deficit/hyperactivity disorder (ADHD) is a common neuropsychiatric disorder that affects an estimated 4.4% of adults[1] and 5% to 8% of school-aged children[2] in the United States. ADHD is characterized by hyperactivity, impulsivity, difficulty with organization and sustaining focus, and emotional control impairments.[3,4] The recommended first-line treatment for school-aged children and adults with ADHD is pharmacological management with psychostimulants, such as methylphenidate and dextroamphetamine.[5,6] However, aggression and mood changes are possible adverse events associated with these stimulants and patients and clinicians should be mindful of their appearance or worsening upon treatment.[7,8] Therefore, alternative pharmacological treatment options are required for patients who experience behavioural and mood changes following treatment with stimulants to address these adverse events while still effectively managing the core symptoms of ADHD.

The purpose of this report is to identify the clinical effectiveness, safety, and evidence-based guidelines regarding switching medications in patients with ADHD who experience aggression or mood changes secondary to treatment with common first-line pharmacological treatments.

RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of switching to another ADHD medication for patients who experience aggression or mood changes secondary to therapy with methylphenidate immediate-release (IR), methylphenidate sustained-release (SR), dextroamphetamine IR, or dextroamphetamine SR?

2. What are the evidence-based guidelines regarding switching to another ADHD medication for patients who experience aggression or mood changes secondary to therapy with methylphenidate IR, methylphenidate SR, dextroamphetamine IR, or dextroamphetamine SR?

KEY FINDINGS

No evidence regarding the clinical effectiveness or safety of switching ADHD medications following stimulant-related aggression or mood changes was identified. One evidence-based guideline suggested switching to atomoxetine in this clinical situation, however, the evidence for this recommendation was limited.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD), PsycINFO, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and August 14, 2015.

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

Selection Criteria and Methods

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

Table 1: Selection Criteria

Population	Patients with ADHD experiencing aggression or mood changes secondary to therapy with one of: • methylphenidate IR • methylphenidate SR • dextroamphetamine IR • dextroamphetamine SR
Intervention	Switching to other ADHD medications available in Canada: • amphetamine mixed salts • lisdexamfetamine • methylphenidate ER • atomoxetine • guanfacine ER
Comparator	Remaining on treatment with methylphenidate IR, methylphenidate SR, dextroamphetamine IR, or dextroamphetamine SR; Switching to a different ADHD medication available in Canada (e.g., patients switched to atomoxetine compared with patients switched to guanfacine ER)

Table 1: Selection Criteria	
Outcomes	Q1: Decrease or elimination of aggression or mood changes secondary to therapy Q2: Evidence-based guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines

ADHD = attention-deficit/hyperactivity disorder; ER = extended-release; IR = immediate-release; SR = sustained-release.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, guidelines with no methodology provided, or were published prior to 2010.

Critical Appraisal of Individual Studies

The included guideline was assessed with the Appraisal of Guidelines for Research & Evaluation II (AGREE II) instrument.[9] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 526 citations were identified in the literature search. Following screening of titles and abstracts, 470 citations were excluded and 56 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 57 publications were excluded for various reasons; one publication met the inclusion criteria and was included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest that examine changes in aggression and mood in an alternate population, and a guideline with unclear methodology are provided in Appendix 2. Appendices 3, 4, and 5 list the study characteristics, critical appraisal, and study results, respectively.

Summary of Study Characteristics

Study Design

One evidence-based guideline on the diagnosis and management of ADHD from the National Institute of Health and Care Excellence (NICE) in the United Kingdom (UK) was identified. A Guideline Development Group (GDG) was formed to establish the scope and clinical questions to be addressed by the guideline; research questions were developed using a modified nominal group technique. Systematic literature searches were performed for research questions related to diagnosis and interventions, and both published and unpublished data were considered, where appropriate. The quality of the evidence was evaluated according to a rating scheme and evidence summaries were provided to the GDG to support drafting of recommendations. The review process for questions with a good evidence base was reported to be variable and

dependent on the clinical question. The GDG followed an informal consensus process to answer the clinical questions that lacked high-quality supporting evidence.

Patient Population

The population of interest for the guideline is children (aged 3 to 18 years, both pre-school and school-aged), and adults with a diagnosis of ADHD with or without comorbidities.

Interventions and Comparators

This guideline addresses several interventions, including pre-diagnostic and diagnostic measures as well as pharmacologic and non-pharmacologic treatment options for children and adults with ADHD that are available in the UK. The interventions relevant to this report include pharmacologic management of ADHD with methylphenidate, dextroamphetamine (also known as dexamfetamine in the UK), and atomoxetine. Study selection for the guideline was not limited by drug formulation; IR and ER preparations of methylphenidate and dextroamphetamine met inclusion criteria.

Outcomes

Outcomes in studies informing the pharmacological management of ADHD section in the guideline include: improvement on ADHD symptoms and behavioural problems (measured by teacher-rated and parent-rated tools), clinician-rated clinical improvement, adverse events, and study withdrawal. Outcomes addressed by the overall guideline that are relevant to this report include: clinical effectiveness and ADHD symptoms, behavioural and emotional outcomes, non-response to treatment, and adverse effects of treatment.

Summary of Critical Appraisal

The NICE guideline was of high quality overall. The objectives, research questions, population, interventions, and outcomes considered were all clearly described. The guideline development group was comprehensive and representative of the relevant clinical areas, and clear conflict of interest declarations were provided for each member. Input from patients and caregivers was also sought during guideline development. A systematic literature search was performed for the pharmacological treatment section of the guideline that is relevant to this report, and clear study inclusion and exclusion criteria were provided. The data were described in tables with the associated quality of evidence rating provided; however, there was no explicit link between the evidence identified during this search and the specific recommendations; this made it difficult to identify the process by which each recommendation was formed (informal consensus or otherwise). Furthermore, ratings for the strength of recommendations were not provided, which further separates the recommendations and the quality of the supporting evidence. Recommendations were easily identifiable and peer reviewed before publication, though in some cases they were vague; some recommendations offered potential treatment strategies for patients who were “unresponsive” or “intolerant” to treatment without elaborating on which specific clinical outcomes this represented. The benefits and harms of treatment, resource implications, and implementation strategies were considered in this guideline.

Summary of Findings

What is the clinical effectiveness and safety of switching to another ADHD medication for patients who experience aggression or mood changes secondary to therapy with methylphenidate IR, methylphenidate SR, dextroamphetamine IR, or dextroamphetamine SR?

No relevant health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, or non-randomized studies regarding the clinical effectiveness and safety of switching ADHD medications in the event of aggression or mood changes were identified; therefore, no summary can be provided.

What are the evidence-based guidelines regarding switching to another ADHD medication for patients who experience aggression or mood changes secondary to therapy with methylphenidate IR, methylphenidate SR, dextroamphetamine IR, or dextroamphetamine SR?

One NICE guideline on the diagnosis and management of ADHD in children and adults was identified that suggests switching to atomoxetine to address anxiety symptoms related to stimulant use, particularly for adults with a history of anxiety. The evidence base supporting this specific recommendation was unclear as the recommendation was not referenced, and no further detail on suggested dosing was provided.

Limitations

The main limitation of the identified guideline from NICE is that there is an unclear link between specific studies and the recommendations that were developed, making it difficult to understand whether each recommendation is strictly evidence-based, based on good practice and clinical judgment, or both. Furthermore, the recommendation of interest to this report does not specify suggested dosing for atomoxtine in the event of a medication switch. In addition, no recommendations were made regarding other agents for ADHD that are available in Canada, such as amphetamine mixed salts or guanfacine ER.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

No evidence regarding the clinical effectiveness and safety of switching ADHD medications following aggression or mood changes on methylphenidate IR or SR, or dextroamphetamine IR or SR, was identified. One guideline from NICE on the diagnosis and management of ADHD was identified that suggests that patients who experience anxiety symptoms secondary to treatment with stimulants may benefit from switching to atomoxetine. However, the specific studies that lead to the development of this recommendation were not clearly presented within the guideline. This guideline used an informal consensus process for recommendations related to clinical questions that did not have a wide evidence base, which may have been the method employed in this case. However, this is not certain as a systematic literature search was performed regarding the clinical effectiveness of various pharmacological agents.

The NICE recommendation is generally consistent with the clinical practice guideline with unclear methodology produced by the Canadian ADHD Resource Alliance (CADDRA; Appendix 2).[10] The CADDRA guideline suggests that patients who experience intolerable side effects from treatment can be switched to another medication, and gives suggested regimens for switches from one class of stimulant to another, and from stimulants to atomoxetine or guanfacine. However, the CADDRA guideline development methodology was not provided and no comment

can be made on the quality of the supporting evidence; recommendations should be interpreted with caution. Therefore, the preferred treatment option for ADHD medication switching due to behavioural or mood changes secondary to first-line treatment remains unclear.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

REFERENCES

1. Kessler RC, Adler L, Barkley R, Biederman J, Conners CK, Demler O, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatry [Internet]. 2006 Apr [cited 2015 Aug 20];163(4):716-23. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2859678

2. Arnold LE, Bozzolo DR, Hodgkins P, McKay M, Beckett-Thurman L, Greenbaum M, et al. Switching from oral extended-release methylphenidate to the methylphenidate transdermal system: continued attention-deficit/hyperactivity disorder symptom control and tolerability after abrupt conversion. Curr Med Res Opin [Internet]. 2010 Jan [cited 2015 Aug 20];26(1):129-37. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3875401/pdf/nihms511456.pdf

3. Adler LA, Alperin S, Leon T, Faraone S. Clinical effects of lisdexamfetamine and mixed amphetamine salts immediate release in adult ADHD: results of a crossover design clinical trial. Postgrad Med. 2014 Sep;126(5):17-24.

4. Katic A, Dirks B, Babcock T, Scheckner B, Adeyi B, Richards C, et al. Treatment outcomes with lisdexamfetamine dimesylate in children who have attention-deficit/hyperactivity disorder with emotional control impairments. J Child Adolesc Psychopharmacol [Internet]. 2013 Aug [cited 2015 Aug 28];23(6):386-93. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3749705

5. Guidelines and recommendations for ADHD in children and adolescents [Internet]. Ottawa: CADTH; 2011 Oct. [cited 2015 Sep 1]. (Summary of current evidence). Available from: https://www.cadth.ca/media/pdf/RC0290_ADHD_Children_Adolescents_overview.pdf?utm_source=ADHD_Summary_of_CE&utm_medium=db-pdf&utm_campaign=CMA_Ref-link_Nov18-11

6. National Collaborating Centre for Mental Health. Attention deficit hyperactivity disorder: Diagnosis and management of ADHD in children, young people and adults [Internet]. London: The British Psychological Society; 2009. [cited 2015 Aug 28]. (National Clinical Practice Guideline Number 72). Available from: http://www.nice.org.uk/guidance/cg72/evidence/cg72-attention-deficit-hyperactivity-disorder-adhd-full-guideline-2

7. Dexedrine® (dextroamphetamine sulfate) 5 mg tablets; 10mg and 15 mg spansules® [product monograph] [Internet]. Montreal: Paladin Labs; 2009 Feb 2. [cited 2015 Sep 1]. Available from: http://www.paladin-labs.com/pdf_files/Dexedrine.pdf

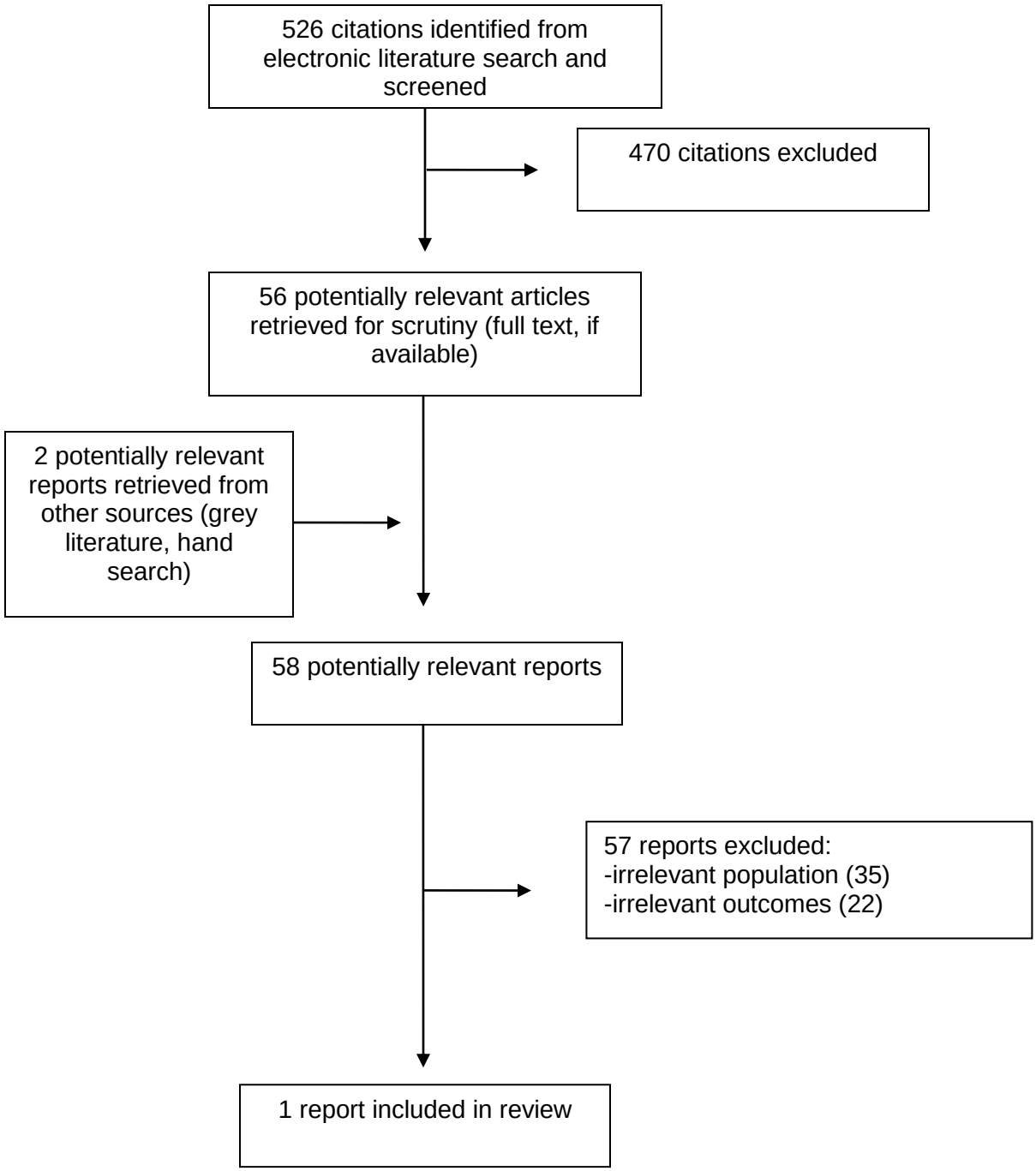
8. Ritalin® (methylphenidate hydrochloride) 10 mg and 20 mg tables Novartis standard. Ritalin® SR (methylphenidate hydrochloride extended-release tables) 20 mg tables Novartis standard [product monograph] [Internet]. Dorval (QC): Novartis Pharmaceuticals Canada; 2015 Feb 27. [cited 2015 Sep 1]. Available from: http://www.novartis.ca/en/products/pharmaceuticals/index.shtml

9. Brouwers M, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in healthcare. CMAJ. 2010 Dec;182(18):E839-E842.

10. Canadian ADHD Resource Alliance (CADDRA). Canadian ADHD practice guidelines (CAP-guidelines) [Internet]. 3rd. Toronto: CADDRA; 2011. [cited 2015 Sep 1]. Available from: http://www.caddra.ca/pdfs/caddraGuidelines2011.pdf

11. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ [Internet]. 2004 Jun 19 [cited 2015 Aug 20];328(7454):1490. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC428525

APPENDIX 1: Selection of Studies



APPENDIX 2: Additional References of Potential Interest

Guidelines with No Methodology

Canadian ADHD Resource Alliance (CADDRA). Canadian ADHD practice guidelines (CAP-guidelines) [Internet]. 3rd. Toronto: CADDRA; 2011. [cited 2015 Sep 1]. Available from: http://www.caddra.ca/pdfs/caddraGuidelines2011.pdf

Alternate Population

No Aggression or Mood Changes Secondary to Therapy at Time of Medication Switch

Kim BN, Kim YN, Cheong US, Kim JW, Hwang JW, Shin MS, et al. Switching from methylphenidate-immediate release (MPH-IR) to methylphenidate-OROS (OROS-MPH): A multi-center, open-label study in Korea. Clin Psychopharmacol Neurosci [Internet]. 2011 Apr [cited 2015 Aug 20];9(1):29-35. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3568652

Mixed Population of Treatment-Naive Patients and Those Switching Medication

Sobanski E, Dopfner M, Ose C, Fischer R. A non-interventional study of extended-release methylphenidate in the routine treatment of adolescents with ADHD: effectiveness, safety and adherence to treatment. Atten Defic Hyperact Disord. 2013 Dec;5(4):387-95.

APPENDIX 3: Characteristics of Included Publications

Table A1: Characteristics of the Included Guideline

NICE, 2013[6]		
Objectives	**Intended users/ Target population**	Intended users: Advanced practice nurses, dietitians, nurses, occupational therapists, patients, pharmacists, physician assistants, physicians, psychologists, non-physician behavioral health clinicians, social workers, students Target population: Children (aged 3 to 11 years), young people (aged 12 to 18 years), and adults with a diagnosis of ADHD and related diagnoses
	Intervention and Practice Considered	• Identification, pre-diagnostic intervention, and referral to secondary services • Diagnosis of ADHD • Post-diagnostic advice • Treatment for pre-school children • Treatment for school-age children and young people with ADHD and moderate impairment • Treatment for school-age children and young people with severe impairment and adults (including drug and non-drug interventions) • Monitoring side effects
	Major Outcomes Considered	• Sensitivity and specificity of diagnostic measures • Clinical effectiveness • ADHD symptoms • Conduct problems • Social skills • Emotional outcomes • Self-efficacy • Reading and mathematics attainment • Nonresponse to treatment • Adverse effects of stimulants • Cost-effectiveness
Methodology	**Evidence collection, Selection and Synthesis**	Hand-searches of published literature (primary and secondary sources), electronic database searches, searches for unpublished studies; Study selection in duplicate based on pre-specified eligibility criteria; Systematic reviews and meta-analyses performed and data presented in evidence tables
	Evidence Quality and Strength	Expert consensus and weighting according to the GRADE rating scheme:[11] • High – further research is very unlikely to change the confidence in the estimate of the effect

Table A1: Characteristics of the Included Guideline		
NICE, 2013[6]		
		• Moderate – further research is likely to have an important impact on the confidence in the estimate of the effect and may change the estimate • Low – further research is very likely to have an important impact on the confidence in the estimate of the effect and is likely to change the estimate • Very low – any estimate of effect is very uncertain
	Recommendations Development and Evaluation	Expert consensus and informal consensus
	Guideline Validation	External and internal peer review

ADHD = attention-deficit/hyperactivity disorder; GRADE = Grading of Recommendations: Assessment, Development, and Evaluation; NICE = National Institute for Health and Care Excellence.

APPENDIX 4: Critical Appraisal of Included Publications

Table A2: Strengths and Limitations of the Guideline using AGREE II[9]

Strengths	Limitations
NICE, 2013[6]	
• Guideline objectives and research questions are clearly described • Population to whom the guideline applies and intended users of the guideline are clearly described • Guideline development group includes individuals from all relevant professional groups • Input from patients and carers was sought during guideline development • Systematic literature search performed for guideline section on pharmacological treatment (multiple databases searched with search date ranges provided) • Clearly described inclusion and exclusion criteria for evidence selection • Quality of included studies provided in evidence tables • Informal and expert consensus processes well described • Health benefits and harms have been considered in formulation of recommendations • Guideline underwent external peer review prior to publication • General process for updating NICE guidelines is provided • Multiple management options addressed by the guideline • Recommendations are easily identifiable • Implementation strategy is provided with consideration of resource implications and auditing support • Conflict of interest declarations for each member of the guideline development group provided to manage potential conflicts	• No rating scheme for strength of the recommendations provided • Unclear which recommendations were the result of the informal consensus process • No explicit link between evidence summary and specific recommendations, particularly regarding the recommendation to switch from methylphenidate to atomoxetine • Recommendations overall somewhat ambiguous, especially when referring to patients who are “unresponsive or intolerant” to treatment

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

APPENDIX 5: Main Study Findings and Author's Conclusions

Table A3: Summary of Findings of the Included Guideline

Main Study Findings	Author's Conclusions
NICE, 2013[6]	
One RCT was identified in the literature search for the guideline that showed increased anxiety in adults treated with methylphenidate than with placebo. Two studies were identified for the guideline that compared methylphenidate and atomoxetine use in school-aged children; one showed no difference in clinical effectiveness between the two drugs, and the other showed greater clinical improvement in children who took osmotically-released methylphenidate than in those who took atomoxetine. The evidence source regarding reduction of anxiety with atomoxetine following methylphenidate treatment was unclear.	*"Anxiety symptoms, including panic, may be precipitated by stimulants, particularly in adults with a history of coexisting anxiety. Where this is an issue, lower doses of the stimulant and/or combined treatment with an antidepressant used to treat anxiety can be used; switching to atomoxetine may be effective."* Recommendation 10.18.11.15, page 313

NICE = National Institute for Health and Care Excellence; RCT = randomized controlled trial.