Child and adolescent mental disorders module - evidence profile CAMH1: Pharmacological and psychological interventions for children with ADHD

WHO mhGAP guideline update: Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders

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Contents

Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders, available at: https://www.who.int/publications/i/item/9789240084278

1. Background

Attention-deficit hyperactivity disorder (ADHD) is an issue for child mental health of global import. One of the most common behavioural disorders, global estimates of community prevalence based on an overview of systematic reviews suggested an average of 5% in children.[1] Population-based estimates from the US suggest cross-sectional (as opposed to lifetime) prevalence of parent-reported diagnoses of 8.4% in children aged 2 to 17 years.[2] A more recent meta-analysis of prevalence estimates in sub-Saharan Africa generated a pooled prevalence of 7.5%.[3] The long-term sequelae of ADHD have important implications for young people's life chances, including lower earnings and increased risk of unemployment, and for health systems, with substantially greater health care costs across a range of categories.[1] Meta-analysis of long-term epidemiological studies indicates that adults who experienced ADHD in childhood or adolescence had higher rates of substance and alcohol use disorders and of antisocial behaviours (specifically, criminal activities).[4]

The purpose of this report is to describe the results of a systematic review of reviews to support the mhGAP guideline on children with ADHD, specifically the following question:

What is the effectiveness and safety of pharmacological and psychosocial intervention for children with a diagnosis of ADHD?

The evidence identification strategy sought to locate systematic review-level evidence, with a focus in the first instance on identifying relevant systematic reviews published in the last two years (i.e. from 2020 onwards).

As a result of discussions with the guideline secretariat, we took the decision to focus only on systematic reviews of pharmacological interventions contained in the PICO question. This was because updating of guidelines relating to psychotherapeutic and other psychosocial approaches was determined to be less of a priority than identifying relevant evidence in respect of pharmacological interventions. Thus, at full-text stage, we focused only on systematic reviews of pharmacological interventions.

2. Methodology

2.1. PICO question

We initially sought to address the following PICO questions.

- Population: Children with ADHD
- Interventions: Pharmacological interventions (atomoxetine, methylphenidate, dexamphetamine), psychosocial (e.g. cognitive behavioural therapy (CBT), interpersonal psychotherapy (IPT))
- Comparison: Placebo, head to head comparison
- Outcomes:
    - Critical: symptom reduction, adverse effects
    - Important: family/school functioning, treatment satisfaction, physical health

As described above, we ultimately sought to include only evidence relating to pharmacological interventions, specifically with regard to the three compounds (atomoxetine, methylphenidate, dexamphetamine) described above.

2.2. Search strategy

We undertook primary searches of MEDLINE, Embase and PsycInfo on 6 January 2022, with follow-up searches of Scopus, CINAHL, Global Index Medicus, Cochrane Database, PROSPERO and Open Science Framework on 9 March 2022. Search strings are provided in Appendix A. We have included terms for population, condition, intervention and study type and in the first instance applied a time filter from 2016. We have not set restrictions for language or publication type.

Inclusion criteria were aligned with the population, interventions, comparators and outcomes for this question. We included:

- systematic reviews, as defined by the DARE criteria,
- addressing the effectiveness of pharmacological (atomoxetine, methylphenidate, dexamphetamine),
- for children aged 0 to 18 years with a diagnosis of ADHD, and
- where at least one outcome of symptom reduction, adverse effects, family or school functioning, treatment satisfaction or physical health is synthesized.

In the first instance, we restricted our analysis to systematic reviews published from 2020 onwards, but undertook a search for systematic reviews published in the preceding five years.

The DARE criteria for a systematic review specified that a systematic review should meet the first three criteria and at least one of the last two criteria from the following:

1. Were inclusion/exclusion criteria reported?
2. Was the search adequate?
3. Were the included studies synthesized?
4. Was the quality of the included studies assessed?
5. Are sufficient details about the individual included studies presented?

2.3. Data collection and analysis

Selection was managed in Endnote. Deduplicated records were filtered through a validated classifier. This classifier estimates the probability that an individual record is a systematic review. Records scoring 0% to 19% were screened once for eligibility, while records scoring 20% and above were screened in duplicate and independently for eligibility. Remaining records were then screened at full text against the

inclusion criteria in duplicate and independently, initially focusing on those published in the last two years (from 2020). Reasons for exclusion of full-text records were recorded.

The flow of articles throughout the search was depicted with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram, which includes the number of excluded articles and the reasons for any exclusions at the full-text screening stage.

2.4. Selection and coding of identified records

Were multiple reviews to have been included, selected reviews would have been extracted in duplicate and independently to capture key domains of systematic review methods used, PICOs analysed and descriptive characteristics of the included evidence.

2.5. Quality assessment

Included reviews were mapped against the interventions and outcomes synthesized, and appraised using AMSTAR-2. Where more than one review existed for a given intervention-outcome combination, the highest-quality and most recent review would have preferred for inclusion in evidence profiles.

2.6. Analysis of subgroups or subsets

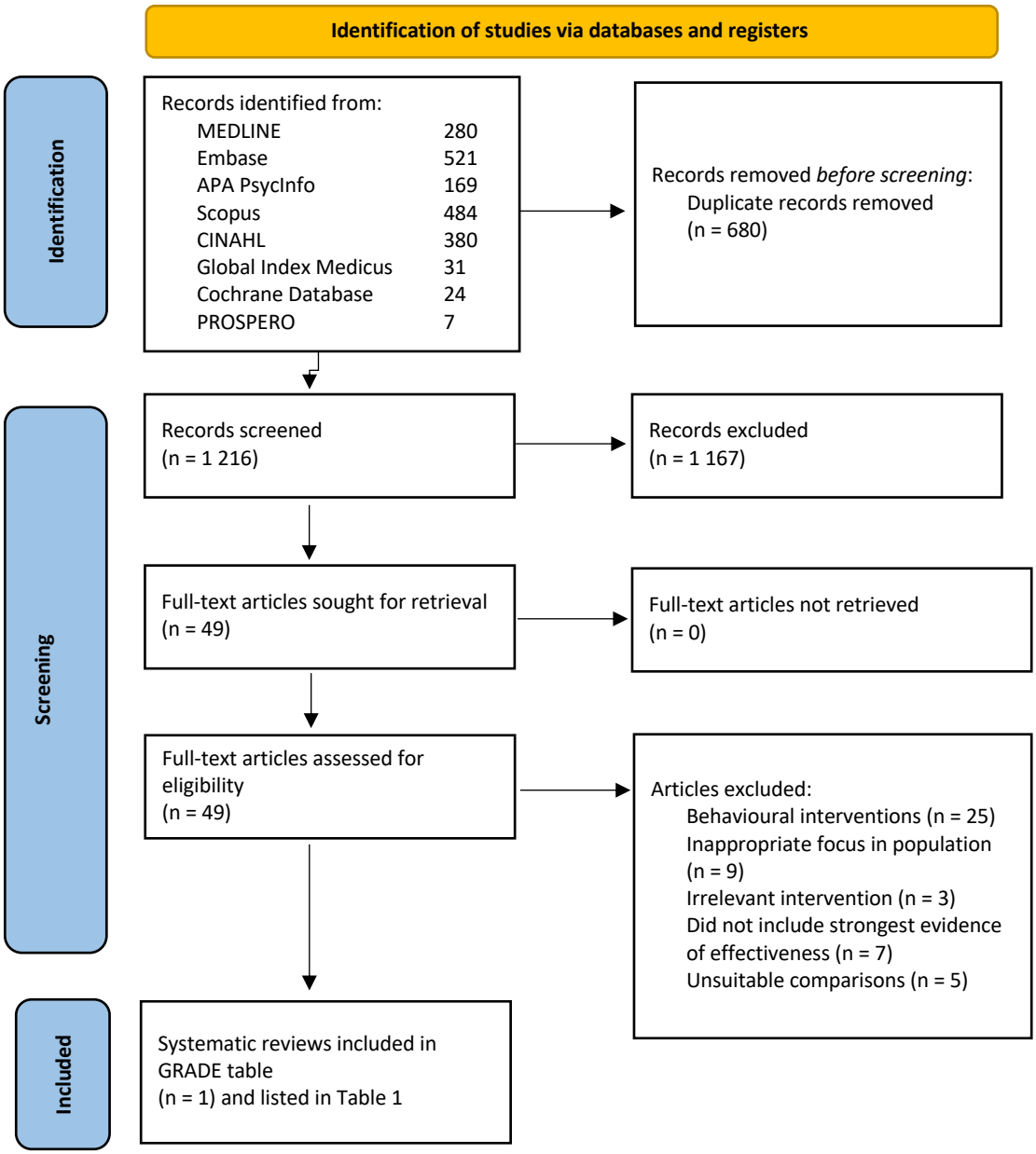
No analysis of subgroups was anticipated or undertaken.

3. Results

3.1. Systematic reviews identified by the search process

A total of 1216 deduplicated records were identified from database searches. As described in Figure 1, 49 records published in the last two years were considered for full-text inclusion. Of these, 44 records were excluded due to focusing on behavioural interventions, due to an inappropriate focus in population (e.g. co-occurring substance use disorder and ADHD), due to an irrelevant intervention (e.g. acupuncture), or due to review designs that blended a range of evidence sources (e.g. single-arm designs, non-randomized studies) that are not strongest for addressing effectiveness questions. A subsequent set of five reviews[5-9] were deemed potentially included, but were ultimately excluded. These are discussed below.

Fig. 1. PRISMA flowchart for identification of included reviews



3.1.1 Reviews included in GRADE tables

Upon considering reviews published not in the last two years but included in our search, we identified the "best and most recent" review of Cortese 2018.[10] This review clearly mapped onto relevant outcome domains; included appropriate comparisons between pharmacological interventions drawing on best available evidence; and was considered to be of very high quality. This review was used to create all relevant GRADE tables in this report, as reflected in Table 1.

Table 1. PICO table

Intervention/ Comparison	Outcomes	Systematic reviews (Name, Year)	Justification/Explanation for systematic review
Pharmacological therapies for ADHD	Symptom reduction	Cortese 2018	This reviews presented evidence on clinician-rated symptom reduction as an outcome.
	Adverse effects	Cortese 2018	This review presented evidence on tolerability (discontinuation due to adverse effects) as an outcome.
	Family/school functioning	Cortese 2018	This review presented evidence on teacher-rated symptom reduction as an outcome
	Physical health	Cortese 2018	This review presented evidence on weight as a physical health-related outcome.
	Treatment satisfaction	No review found	This outcome was not represented in any included systematic reviews.

3.1.2. Reviews excluded in GRADE tables

Of the five reviews published in the last two years that were deemed potentially included, none were ultimately included as they did not present suitable or sufficient comparisons for analysis, or did not draw on trial-level data to a direct enough degree to support GRADE assessments for the evidence.

- One review[7] focused only on headache as an adverse effect as a comorbidity in ADHD medication. This review did not address relevant outcomes directly enough to be included.
- Another two reviews[5,9] were structured as overviews of reviews. One[5] focused on methylphenidate alone and was primarily descriptive, without any pooled effects. The other[9] was transdiagnostic in nature, covering a range of psychiatric conditions. Again, no pooling was undertaken.
- A further review[8] focused on dose-response effects in methylphenidate only.
- A final review[6] analysed most relevant outcome domains and included all appropriate pharmacological interventions. However, this review combined pharmacological interventions into classes that did not permit disambiguation of effects; combined outcome domains into categories that did not map onto included PICO domains; and used a statistical procedure to pool effects that created serious doubts about the applicability of findings to the GRADE process.

3.2. Narrative description of studies that contributed to GRADE analysis

The abstract of the included systematic review is reproduced in Box 1.

Box 1. Abstract of the included systematic review

Background

The benefits and safety of medications for attention-deficit hyperactivity disorder (ADHD) remain controversial, and guidelines are inconsistent on which medications are preferred across different age groups. We aimed to estimate the comparative efficacy and tolerability of oral medications for ADHD in children, adolescents, and adults.

Methods

We did a literature search for published and unpublished double-blind randomized controlled trials comparing amphetamines (including lisdexamfetamine), atomoxetine, bupropion, clonidine, guanfacine, methylphenidate, and modafinil with each other or placebo. We systematically contacted study authors and drug manufacturers for additional information. Primary outcomes were efficacy (change in severity of ADHD core symptoms based on teachers' and clinicians' ratings) and tolerability (proportion of patients who dropped out of studies because of side-effects) at timepoints closest to 12 weeks, 26 weeks, and 52 weeks. We estimated summary odds ratios (ORs) and standardized mean differences (SMDs) using pairwise and network meta-analysis with random effects. We assessed the risk of bias of individual studies with the Cochrane risk of bias tool and confidence of estimates with the Grading of Recommendations Assessment, Development, and Evaluation approach for network meta-analyses. This study is registered with PROSPERO, number CRD42014008976.

Findings

133 double-blind randomized controlled trials (81 in children and adolescents, 51 in adults, and one in both) were included. The analysis of efficacy closest to 12 weeks was based on 10 068 children and adolescents and 8131 adults; the analysis of tolerability was based on 11 018 children and adolescents and 5362 adults. The confidence of estimates varied from high or moderate (for some comparisons) to low or very low (for most indirect comparisons). For ADHD core symptoms rated by clinicians in children and adolescents closest to 12 weeks, all included drugs were superior to placebo (e.g. SMD −1,02, 95% CI: −1,19 to −0,85 for amphetamines, −0.78, −0,93 to −0,62 for methylphenidate, −0,56, −0,66 to −0,45 for atomoxetine). By contrast, for available comparisons based on teachers' ratings, only methylphenidate (SMD −0,82, 95% CI: −1,16 to −0,48) and modafinil (−0,76, −1,15 to −0,37) were more efficacious than placebo. In adults (clinicians' ratings), amphetamines (SMD −0,79, 95% CI: −0,99 to −0,58), methylphenidate (−0,49, −0,64 to −0,35), bupropion (−0,46, −0,85 to −0,07), and atomoxetine (−0,45, −0,58 to −0,32), but not modafinil (0,16,

−0,28 to 0,59), were better than placebo. With respect to tolerability, amphetamines were inferior to placebo in both children and adolescents (odds ratio [OR] 2,30, 95% CI: 1,36 – 3,89) and adults (3,26, 1,54 – 6,92); guanfacine was inferior to placebo in children and adolescents only (2,64, 1,20 – 5,81); and atomoxetine (2,33, 1,28 – 4,25), methylphenidate (2,39, 1,40 – 4,08), and modafinil (4,01, 1,42 – 11,33) were less well tolerated than placebo in adults only. In head-to-head comparisons, only differences in efficacy (clinicians' ratings) were found, favouring amphetamines over modafinil, atomoxetine, and methylphenidate in both children and adolescents (SMDs −0,46 to −0,24) and adults (−0,94 to −0,29). We did not find sufficient data for the 26-week and 52-week timepoints.

Interpretation

Our findings represent the most comprehensive available evidence base to inform patients, families, clinicians, guideline developers, and policymakers on the choice of ADHD medications across age groups. Taking into account both efficacy and safety, evidence from this meta-analysis supports methylphenidate in children and adolescents, and amphetamines in adults, as preferred first-choice medications for the short-term treatment of ADHD. New research should be funded urgently to assess long-term effects of these drugs.

The summary of the independent appraisal of the included systematic review using AMSTAR-2 is included in Table 2. Given the results of the appraisal, we considered that the appropriate rating for the review is **high confidence** in the overall results.

Table 2. Independent appraisal of the included review

Domain	Score
Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes
Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
Did the review authors use a comprehensive literature search strategy?	Yes
Did the review authors perform study selection in duplicate?	Yes
Did the review authors perform data extraction in duplicate?	Yes
Did the review authors provide a list of excluded studies and justify the exclusions?	Yes
Did the review authors describe the included studies in adequate detail?	Yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
Did the review authors report on the sources of funding for the studies included in the review?	Yes
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

The PICO listed five outcomes.

- To assess symptom reduction, we used continuous estimates of clinician-rated symptom reduction.
- To assess family/school functioning, we used continuous estimates of teacher-rated symptom reduction, and rated estimates down by one level for indirectness.
- To assess adverse effects, we used tolerability (discontinuation due to adverse events), and rated estimates down by one level for indirectness.
- To assess physical health, we used weight change.
- No data were available to assess treatment satisfaction.

We were informed by GRADE tables prepared by the review authors for many of the tables presented below; specifically for symptom reduction, school functioning and tolerability analyses.

Finally, where comparator group risks are cited for analyses relating to tolerability, these are estimated from the median comparator group risk in the arm-level data for included trials.
Because the included review used network meta-analyses, comparisons drew on both direct and indirect evidence. Comparisons for methylphenidate vs placebo are presented in Table 1; for atomoxetine vs placebo in Table 2; for amphetamines vs placebo in Table 3; for atomoxetine vs methylphenidate in Table 4; for amphetamines vs methylphenidate in Table 5; and for amphetamines vs atomoxetine in Table 6.

The final summary of findings table is reported in Table 7.

3.3. Grading the Evidence

Table 1. GRADE assessment: methylphenidate vs placebo for children and young people with ADHD

Certainty assessment							Comparator group risk	Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)	Absolute (95% CI)		
Symptom reduction (clinician-rated, follow-up closest to 12 weeks)											
9	randomized trials	serious[a]	not serious	not serious	not serious	none	SMD 0.78 SD lower (95% CI: 0.62 - 0.93 lower)			⨁⨁⨁◯ Moderate	CRITICAL
School functioning (ADHD symptoms [teacher-rated], follow-up closest to 12 weeks)											
5	randomized trials	serious[a]	not serious	very serious[b,c]	not serious	none	SMD 0.82 SD lower (95% CI: 0.48 - 1.16 lower)			⨁◯◯◯ Very low	IMPORTANT
Adverse events (Discontinuation due to adverse events, follow-up closest to 12 weeks)											
22	randomized trials	serious[a]	not serious	serious[c]	very serious[d]	none	1.1%	**OR 1.44** (0.92 - 2.31)	**5 more per 1000** (from 1 fewer to 14 more)	⨁◯◯◯ Very low	CRITICAL
Weight (kg, follow-up closest to 12 weeks)											
12	randomized trials	serious[a]	serious[e]	not serious	not serious	none	SMD 0.77 SD lower (95% CI: 0.45 - 1.09 lower)			⨁⨁◯◯ Low	IMPORTANT

CI: confidence interval; **OR:** odds ratio; **SMD:** standardized mean difference

a. Downgraded as > 50% of evidence was from studies at moderate risk of bias

b. More than 50% of the contribution from comparisons with partial indirectness

c. Outcome is an indirect measure of the true domain

d. Very serious imprecision as 95% CI includes null effect, including potential reversal

e. Serious inconsistency due to high between-study variance parameter

Table 2. GRADE assessment: atomoxetine vs placebo for children and young people with ADHD

Certainty assessment							Comparator group risk	Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)	Absolute (95% CI)		
Symptom reduction (clinician-rated, follow-up closest to 12 weeks)											
21	randomized trials	serious[a]	not serious	not serious	not serious	none	SMD 0.56 SD lower (95% CI: 0.45 - 0.66 lower)			⊕⊕⊕◯ Moderate	CRITICAL
School functioning (ADHD symptoms [teacher-rated], follow-up closest to 12 weeks)											
3	randomized trials	serious[a]	not serious	very serious[b,c]	very serious[d]	none	SMD 0.32 SD lower (95% CI: 0.82 lower - 0.18 higher)			⊕◯◯◯ Very low	IMPORTANT
Adverse events (Discontinuation due to adverse sevents, follow-up closest to 12 weeks)											
13	randomized trials	serious[a]	not serious	serious[b]	very serious[e]	none	1.1%	**OR 1.49** (0.84 - 2.64)	**5 more per 1000** (from 2 fewer to 18 more)	⊕◯◯◯ Very low	CRITICAL
Weight (kg, follow-up closest to 12 weeks)											
13	randomized trials	serious[a]	serious[f]	not serious	not serious	none	SMD 0.84 lower (95% CI: 0.52 - 1.16 lower)			⊕⊕◯◯ Low	IMPORTANT

CI: confidence interval; **OR:** odds ratio; **SMD:** standardized mean difference

a. Downgraded as > 50% of evidence was from studies at moderate risk of bias

b. Downgraded as this is an indirect measure of the outcome domain

c. Downgraded as > 50% contribution from comparisons with partial indirectness

d. Very serious imprecision as 95% CI crossed null effect, including potential harm

e. Very serious imprecision as 95% CI crossed null effect, including potential reversal

f. Serious inconsistency due to high between-study variance parameter

Table 3. GRADE assessment: amphetamines vs placebo for children and young people with ADHD

Certainty assessment							Comparator group risk	Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)	Absolute (95% CI)		
Symptom reduction (clinician-rated, follow-up closest to 12 weeks)											
6	randomized trials	serious[a]	not serious	not serious	not serious	none	SMD 1.02 SD lower (95% CI: 1.19 - 0.85 lower)			⨁⨁⨁◯ Moderate	CRITICAL
School functioning (ADHD symptoms [teacher-rated], follow-up closest to 12 weeks)											
0							Outcomes were not reported for this comparison and domain.			-	IMPORTANT
Adverse events (Discontinuation due to adverse sevents, follow-up closest to 12 weeks)											
9	randomized trials	serious[a]	not serious	serious[b]	not serious	none	1.1%	**OR 2.30** (1.36 - 3.89)	**14 more per 1000** (from 4 more to 30 more)	⨁⨁◯◯ Low	CRITICAL
Weight (kg, follow-up closest to 12 weeks)											
6	randomized trials	serious[a]	serious[c]	not serious	not serious	none	SMD 0.71 SD lower (95% CI: 0.27 lower - 1.15 lower)			⨁⨁◯◯ Low	IMPORTANT

CI: confidence interval; **OR:** odds ratio; **SMD:** standardized mean difference

a. Downgraded as > 50% of evidence was from studies at moderate risk of bias

b. Outcome is an indirect measure of the true domain

c. Serious inconsistency due to high between-study variance parameter

Table 4. GRADE assessment: atomoxetine vs methylphenidate for children and young people with ADHD

Certainty assessment							Comparator group risk	Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)	Absolute (95% CI)		
Symptom reduction (clinician-rated, follow-up closest to 12 weeks)											
3	randomized trials	serious[a]	not serious	not serious	serious[b]	none	SMD 0.22 SD higher (95% CI: 0.05 - 0.39 higher)			⊕⊕◯◯ Low	CRITICAL
School functioning (ADHD symptoms [teacher-rated], follow-up closest to 12 weeks)											
0	randomized trials	serious[a]	not serious	serious[c]	very serious[d]	none	SMD 0.50 SD higher (95% CI: 0.11 lower - 1.10 higher)			⊕◯◯◯ Very low	IMPORTANT
Adverse events (Discontinuation due to adverse sevents, follow-up closest to 12 weeks)											
4	randomized trials	serious[a]	not serious	serious[c]	extremely serious[e]	none	2.9%	**OR 1.04** (0.55 - 1.94)	**1 more per 1000** (from 13 fewer to 26 more)	⊕◯◯◯ Very low	CRITICAL
Weight (kg, follow-up closest to 12 weeks)											
3	randomized trials	serious[a]	serious[f]	not serious	extremely serious[e]	none	SMD 0.07 SD lower (95% CI: 0.49 lower - 0.35 higher)			⊕◯◯◯ Very low	IMPORTANT

CI: confidence interval; **OR:** odds ratio; **SMD:** standardized mean difference

a. Downgraded as > 50% of evidence was from studies at moderate risk of bias
b. Serious imprecision as 95% crossed on MID (0.2 SD)
c. Downgraded as this measure is indirect for the outcome domain
d. Very serious imprecision as 95% CI includes null effect and some possibility of harm
e. Extremely serious imprecision as 95% CI includes MID on both sides of the null effect
f. Serious inconsistency due to high between-study variance parameter

Table 5. GRADE assessment: amphetamines vs methylphenidate for children and young people with ADHD

Certainty assessment							Comparator group risk	Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)	Absolute (95% CI)		
Symptom reduction (clinician-rated, follow-up closest to 12 weeks)											
3	randomized trials	serious[a]	not serious	not serious	serious[b]	none	SMD 0.24 SD lower (95% CI: 0.44 - 0.05 lower)			⊕⊕◯◯ Low	CRITICAL
ADHD symptoms (teacher-rated) (follow-up: range 1 weeks to 18 weeks											
0							Outcomes were not reported for this comparison and domain.			-	IMPORTANT
Adverse events (Discontinuation due to adverse sevents, follow-up closest to 12 weeks)											
6	randomized trials	serious[a]	not serious	serious[c]	very serious[d]	none	2.9%	**OR 1.60** (0.94 - 2.73)	**17 more per 1000** (from 2 fewer to 46 more)	⊕◯◯◯ Very low	CRITICAL
Weight (kg, follow-up closest to 12 weeks)											
3	randomized trials	serious[a]	serious[e]	not serious	extremely serious[e]	none	SMD 0.06 SD higher (95% CI: 0.43 lower - 0.55 higher)			⊕◯◯◯ Very low	IMPORTANT

CI: confidence interval; **OR:** odds ratio; **SMD:** standardized mean difference

a. Downgraded as > 50% of evidence was from studies at moderate risk of bias

b. Serious imprecision as 95% CIs crossed one MID (0.2 SD)

c. Outcome is an indirect measure of the true domain

d. Very serious imprecision as 95% CI includes null effect

e. Serious inconsistency due to high between-study variance parameter

Table 6. GRADE assessment: amphetamines vs atomoxetine for children and young people with ADHD

Certainty assessment							Comparator group risk	Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)	Absolute (95% CI)		
Symptom reduction (clinician-rated, follow-up closest to 12 weeks)											
1	randomized trials	serious[a]	not serious	not serious	serious[b]	none	SMD 0.46 SD lower (95% CI: 0.65 - 0.27 lower)			⨁⨁◯◯ Low	CRITICAL
School functioning (ADHD symptoms [teacher-rated], follow-up closest to 12 weeks)											
0							Outcomes were not reported for this comparison and domain.			-	IMPORTANT
Adverse events (Discontinuation due to adverse sevents, follow-up closest to 12 weeks)											
1	randomized trials	serious[a]	not serious	serious[c]	extremely serious[d]	none	3.2%	**OR 1.54** (0.79 - 3.01)	**16 more per 1000** (from 7 fewer to 58 more)	⨁◯◯◯ Very low	CRITICAL
Weight (kg, follow-up closest to 12 weeks)											
0	randomized trials	serious[a]	serious[e]	not serious	extremely serious[e]	none	SMD 0.13 SD higher (95% CI: 0.40 lower - 0.67 higher)			⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval; **OR:** odds ratio; **SMD:** standardized mean difference

a. Downgraded as more than 50% of evidence was from studies at moderate risk of bias

b. Serious imprecision as 95% CI crossed one MID (0.2 SD)

c. Outcome is an indirect measure of the true domain

d. Extremely serious imprecision as 95% CI includes MID on both sides of the null effect

e. Serious inconsistency due to high between-study variance parameter

4. From Evidence to Recommendations

4.1. Summary of findings

Table 7. Summary of findings table based on Cortese 2018[10]

GRADE Table	Outcome	Number of Studies	Effects	Certainty of Evidence
Table 1. GRADE assessment: methylphenidate vs placebo for children and young people with ADHD	Symptom reduction	9	SMD 0.78 lower (95% CI: 0.62 - 0.93 lower)	⊕⊕⊕◯ MODERATE Due to serious risk of bias.
	School functioning	5	SMD 0.82 SD lower (95% CI: 0.48 - 1.16 lower)	⊕◯◯◯ VERY LOW Due to serious risk of bias. Due to very serious indirectness.
	Adverse events	22	5 more per 1000 discontinue (95% CI: 1 fewer - 14 more per 1000 discontinue)	⊕◯◯◯ VERY LOW Due to serious risk of bias. Due to serious indirectness. Due to very serious imprecision.
	Weight (kg)	12	SMD 0.77 SD lower (95% CI: 0.45 - 1.09 lower)	⊕⊕◯◯ LOW Due to serious risk of bias. Due to serious inconsistency.
Table 2. GRADE assessment: atomoxetine vs placebo for children and young people with ADHD	• Symptom reduction	• 21	• SMD 0.56 SD lower (95% CI: 0.45 - 0.66 lower)	⊕⊕⊕◯ MODERATE Due to serious risk of bias.
	School functioning	3	SMD 0.32 SD lower (95% CI: 0.82 lower - 0.18 higher)	⊕◯◯◯ VERY LOW Due to serious risk of bias. Due to very serious indirectness. Due to very serious imprecision.

GRADE Table	Outcome	Number of Studies	Effects	Certainty of Evidence
GRADE Table	**Outcome**	**Number of Studies**	**Effects**	**Certainty of Evidence**
	Adverse events	13	5 more per 1000 discontinue (95% CI: 2 fewer - 18 more per 1000 discontinue)	⊕◯◯◯ VERY LOW Due to serious risk of bias. Due to serious indirectness. Due to very serious imprecision.
	Weight (kg)	13	SMD 0.84 lower (95% CI: 0.52 - 1.16 lower)	⊕⊕◯◯ LOW Due to serious risk of bias. Due to serious inconsistency.
Table 3. GRADE assessment: amphetamines vs placebo for children and young people with ADHD	Symptom reduction	6	SMD 1.02 SD lower (95% CI: 1.19 - 0.85 lower)	⊕⊕⊕◯ MODERATE Due to serious risk of bias.
	School functioning	0	No findings were reported for this outcome.	No rating
	Adverse events	9	14 more per 1000 discontinue (95% CI: 4 - 30 more per 1000 discontinue)	⊕⊕◯◯ LOW Due to serious risk of bias. Due to serious indirectness.
	Weight (kg)	6	SMD 0.71 SD lower (95% CI: 0.27 lower - 1.15 lower)	⊕⊕◯◯ LOW Due to serious risk of bias. Due to serious inconsistency.
Table 4. GRADE assessment: atomoxetine vs methylphenidate for children and young people with ADHD	Symptom reduction	3	SMD 0.22 SD higher (95% CI: 0.05 - 0.39 higher)	⊕⊕◯◯ LOW Due to serious risk of bias. Due to serious imprecision.
	School functioning	0 (all estimates indirect)	SMD 0.50 SD higher (95% CI: 0.11 lower - 1.10 higher)	⊕◯◯◯ VERY LOW Due to serious risk of bias. Due to serious indirectness.

GRADE Table	Outcome	Number of Studies	Effects	Certainty of Evidence
				Due to very serious imprecision.

GRADE Table	Outcome	Number of Studies	Effects	Certainty of Evidence
	Adverse events	4	1 more per 1000 discontinue (95% CI: 13 fewer - 26 more per 1000 discontinue	⊕◯◯◯ VERY LOW Due to serious risk of bias. Due to serious indirectness. Due to extremely serious imprecision.
	Weight (kg)	3	SMD 0.07 SD lower (95% CI: 0.49 lower - 0.35 higher)	⊕◯◯◯ VERY LOW Due to serious risk of bias. Due to serious inconsistency. Due to extremely serious imprecision.
Table 5. GRADE assessment: amphetamines vs methylphenidate for children and young people with ADHD	Symptom reduction	3	SMD 0.24 SD lower (95% CI: 0.44 - 0.05 lower)	⊕⊕◯◯ LOW Due to serious risk of bias. Due to serious imprecision.
	School functioning	0	No findings were reported for this outcome.	No rating
	Adverse events	6	17 more per 1000 discontinue (95% CI: 2 fewer - 46 more per 1000 discontinue)	⊕◯◯◯ VERY LOW Due to serious risk of bias. Due to serious indirectness. Due to very serious imprecision.
	Weight (kg)	3	SMD 0.06 SD higher (95% CI: 0.43 lower - 0.55 higher)	⊕◯◯◯ VERY LOW Due to serious risk of bias. Due to serious inconsistency. Due to extremely serious imprecision.
Table 6. GRADE assessment: amphetamines vs atomoxetine for children and young people	Symptom reduction	1	SMD 0.46 SD lower (95% CI: 0.65 - 0.27 lower)	⊕⊕◯◯ LOW Due to serious risk of bias.

GRADE Table	Outcome	Number of Studies	Effects	Certainty of Evidence
with ADHD				Due to serious imprecision.
	School functioning	0	No findings were reported for this outcome.	No rating
GRADE Table	**Outcome**	**Number of Studies**	**Effects**	**Certainty of Evidence**
	Adverse events	1	16 more per 1000 discontinue (95% CI: 7 fewer - 58 more per 1000 discontinue)	⨁◯◯◯ VERY LOW Due to serious risk of bias. Due to serious indirectness. Due to extremely serious imprecision.
	Weight (kg)	0 (all estimates indirect)	SMD 0.13 SD higher (95% CI: 0.40 lower - 0.67 higher)	⨁◯◯◯ VERY LOW Due to serious risk of bias. Due to serious inconsistency. Due to extremely serious imprecision.

4.2. Evidence to decision

Table 10. Evidence to decision table

Please note * indicates evidence from overarching qualitative review by Gronholm et al, 2023.

Note: Evidence review teams to populate sections on: Priority of the problem; Desirable effects; Undesirable effects; Certainty of evidence and Balance of effects. Sections on Values; Resources required; Cost effectiveness; Health equity, Equality and non-discrimination; Feasibility and Human rights and sociocultural acceptability, will also be informed by overarching reviews conducted by the secretariat.

	CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Priority of the problem	Is the problem a priority? The more serious a problem is, the more likely it is that an option that addresses the problem should be a priority (e.g. diseases that are fatal or disabling are likely to be a higher priority than diseases that only cause minor distress). The more people who are affected, the more likely it is that an option that addresses the problem should be a priority.			
	• Are the consequences of the problem serious (that is, severe or important in terms of the potential benefits or savings)? • Is the problem urgent? • Is it a recognized priority (such as based on a political or policy decision)? [Not relevant when an individual patient perspective is taken]	☐ No ☐ Probably no ☐ Probably yes ☒ **Yes** ☐ Varies ☐ Don't know	Attention-deficit hyperactivity disorder (ADHD) is an issue for child mental health of global import. One of the most common behavioural disorders, global estimates of community prevalence based on an overview of systematic reviews suggested an average of 5% in children.[1] Population-based estimates from the US suggest cross-sectional (as opposed to lifetime) prevalence of parent-reported diagnoses of 8.4% in children aged 2 to 17 years.[2] A more recent meta-analysis of prevalence estimates in sub-Saharan Africa generated a pooled prevalence of 7.5%.[3] The long-term sequelae of ADHD have important implications for young people's life chances, including lower earnings and increased risk of unemployment, and for health care systems, with substantially greater health care costs across a range of categories.[1] Meta-analysis of long-term epidemiological studies indicates that adults who experienced ADHD in	

	CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			childhood or adolescence had higher rates of substance and alcohol use disorders and of antisocial behaviours (specifically, criminal activities).[4]	
Desirable Effects	How substantial are the desirable anticipated effects? The larger the benefit, the more likely it is that an option should be recommended.			
	• Judgements for each outcome for which there is a desirable effect • How substantial (large) are the desirable anticipated effects (including health and other benefits) of the option (taking into account the severity or importance of the desirable consequences and the number of people affected)?	☐ Trivial ☐ Small ☐ Moderate ☐ Large ☒ **Varies** ☐ Don't know	Desirable effects in comparisons against placebo are substantial for symptom reduction, but less substantial for school functioning and could not be judged for treatment satisfaction. For **symptom reduction**, a critical outcome, each of the three pharmacological interventions had a substantial and statistically significant impact, with confidence intervals that do not include the minimally important difference of 0.2 SD. However, for **school functioning**, an important outcome, only methylphenidate and atomoxetine were compared against placebo. Findings were substantial for methylphenidate, including a statistically and clinically significant estimate, but less so for atomoxetine, where confidence intervals included the point of null effect.	Mixed and indirect treatment comparisons for **symptom reduction** suggested that differences between treatments were statistically significant as well. Indirect treatment comparisons for atomoxetine and methylphenidate on **school functioning** were imprecise and did not suggest a significant difference.
Undesirable Effects	How substantial are the undesirable anticipated effects? The greater the harm, the less likely it is that an option should be recommended.			
	• Judgements for each outcome for which there is an undesirable effect • How substantial (large) are the undesirable anticipated effects (including harms to health and other harms) of the option (taking into account the severity or importance of the adverse effects and the number of people affected)?	☐ Large ☐ Moderate ☐ Small ☐ Trivial ☒ **Varies** ☐ Don't know	Estimates for **tolerability** were not significant for atomoxetine and methylphenidate vs placebo suggested an elevated risk of discontinuation, but were not significant. However, estimates for amphetamines vs placebo were significant, with the confidence interval excluding the minimally important difference.	Mixed and indirect treatment comparisons did not suggest significant differences between pharmacological interventions on **tolerability** or **weight**.

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			Estimates for **weight** were relatively uniform across pharmacological interventions, suggesting substantial weight loss beyond a minimally important difference.	
Certainty of evidence	What is the overall certainty of the evidence of effects? The less certain the evidence is for critical outcomes (those that are driving a recommendation), the less likely that an option should be recommended (or the more important it is likely to be to conduct a pilot study or impact evaluation, if it is recommended).			
	• What is the overall certainty of this evidence of effects, across all of the outcomes that are critical to making a decision? • See GRADE guidance regarding detailed judgements about the quality of evidence or certainty in estimates of effects	☐ Very low ☒ **Low** ☐ Moderate ☐ High ☐ No included studies	While evidence for comparisons against placebo is primarily moderate for the critical outcome of **symptom reduction**, it is primarily low or very low for **adverse events**. Evidence for important outcomes, where this is present, is low or very low. Again, no evidence was located for the outcome of **treatment satisfaction**.	Overall certainty for evidence from comparisons between pharmacological interventions is very low.
Values	Is there important uncertainty about or variability in how much people value the main outcomes? The more likely it is that differences in values would lead to different decisions, the less likely it is that there will be a consensus that an option is a priority (or the more important it is likely to be to obtain evidence of the values of those affected by the option). Values in this context refer to the relative importance of the outcomes of interest (how much people value each of those outcomes). These values are sometimes called "utility values".			
	• Is there important uncertainty about how much people value each of the main outcomes? • Is there important variability in how much people value each of the main outcomes?	☐ Important uncertainty or variability ☒ **Possibly important uncertainty or variability** ☐ Probably no important uncertainty or variability ☐ No important uncertainty or variability	• Improvements in children's social interaction and academic performance often prompted therapy continuation, however side effects such as weight loss, appetite suppression and sleep disturbances often resulted in treatment discontinuation (Ahmed et al 2017) • Parents started and continued use of pharmacotherapy due to its positive impact on child behaviour. • Young people identifying themselves as neurodiverse may not value symptoms reduction as treatment target.	

	CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Balance of effects	Does the balance between desirable and undesirable effects favour the intervention or the comparison? The larger the desirable effects in relation to the undesirable effects, taking into account the values of those affected (i.e. the relative value they attach to the desirable and undesirable outcomes) the more likely it is that an option should be recommended.			
	• Judgements regarding each of the four preceding criteria • To what extent do the following considerations influence the balance between the desirable and undesirable effects: - How much less people value outcomes that are in the future compared to outcomes that occur now (their discount rates)? - People's attitudes towards undesirable effects (how risk averse they are)? - People's attitudes towards desirable effects (how risk seeking they are)?	☐ Favours the comparison ☐ Probably favours the comparison ☐ Does not favour either the intervention or the comparison ☒ **Probably favours the intervention** ☐ Favours the intervention ☐ Varies ☐ Don't know	The balance between desirable and undesirable effects probably favours active pharmacological interventions given that evidence is strongest for the critical outcome of **symptom reduction**. This is in contrast to relatively lower certainty for other key outcomes considered here. It must be noted, however, that evidence for **treatment satisfaction** remains lacking.	
Resources required	How large are the resource requirements (costs)? The greater the cost, the less likely it is that an option should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.			
	• How large is the difference in each item of resource use for which fewer resources are required? • How large is the difference in each item of resource use for which more resources are required? • How large an investment of resources would the option require or save?	☐ Large costs ☐ Moderate costs ☐ Negligible costs and savings ☐ Moderate savings ☐ Large savings ☐ Varies ☒ **Don't know**	No review examining resources required was identified.	

	CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)?			
	• Have all-important items of resource use that may differ between the options being considered been identified? • How certain is the evidence of differences in resource use between the options being considered (see GRADE guidance regarding detailed judgements about the quality of evidence or certainty in estimates)? • How certain is the cost of the items of resource use that differ between the options being considered? • Is there important variability in the cost of the items of resource use that differ between the options being considered?	☐ Very low ☐ Low ☐ Moderate ☐ High ☒ **No included studies**	No review examining resources required was identified.	
Cost effectiveness	Does the cost-effectiveness of the intervention favour the intervention or the comparison? The greater the cost per unit of benefit, the less likely it is that an option should be a priority.			
	• Judgements regarding each of the six preceding criteria • Is the cost effectiveness ratio sensitive to one-way sensitivity analyses? • Is the cost effectiveness ratio sensitive to multivariable sensitivity analysis? • Is the economic evaluation on which the cost effectiveness estimate is based reliable? • Is the economic evaluation on which the cost effectiveness estimate is based applicable to the setting(s) of interest?	☐ Favours the comparison ☐ Probably favours the comparison ☐ Does not favour either the intervention or the comparison ☒ **Probably favours the intervention** ☐ Favours the intervention ☐ Varies ☐ No included studies	Different combinations of stimulant/non-stimulant medications for children with ADHD were reported to be cost-effective at willingness-to-pay thresholds reported in the original papers (Sampaio et al 2021).	

CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Health equity, equality and non-discrimination	What would be the impact on health equity, equality and non-discrimination? (WHO INTEGRATE) Health equity and equality reflect a concerted and sustained effort to improve health for individuals across all populations, and to reduce avoidable systematic differences in how health and its determinants are distributed. Equality is linked to the legal principle of non-discrimination, which is designed to ensure that individuals or population groups do not experience discrimination on the basis of their sex, age, ethnicity, culture or language, sexual orientation or gender identity, disability status, education, socioeconomic status, place of residence or any other characteristics. All recommendations should be in accordance with universal human rights standards and principles. The greater the likelihood that the intervention increases health equity and/or equality and that it reduces discrimination against any particular group, the greater the likelihood of a general recommendation in favour of this intervention.			
	• How are the condition and its determinants distributed across different population groups? Is the intervention likely to reduce or increase existing health inequalities and/or health inequities? Does the intervention prioritize and/or aid those furthest behind? • How are the benefits and harms of the intervention distributed across the population? Who carries the burden (e.g. all), who benefits (e.g. a very small sub-group)? • How affordable is the intervention for individuals, workplaces or communities? • How accessible - in terms of physical as well as informational access - is the intervention across different population groups? • Is there any suitable alternative to addressing the condition, does the intervention represent the only available option? Is this option proportionate to the need, and will it be subject to periodic review?	☐ Reduced ☐ Probably reduced ☐ Probably no impact ☐ Probably increased ☐ Increased ☐ Varies ☒ **Don't know**	Availability of methylphenidate and access to methylphenidate varies across countries and can be very limited in some low-income contexts. Methylphenidate is not in the WHO Essential Medicines List. Methylphenidate is reported to have lower pricing for generic versions in areas where unemployment rates are high (Chisholm-Burns det al 2017). Trends and patterns of methylphenidate among children reflect diagnostic patterns of ADHD which were largely shaped by socioeconomic status, cultural attitudes and gender (Jaber et al 2017). Data on overuse of methylphenidate is available from a few countries only. Toxicity as a result of overuse of methylphenidate has led to similar symptoms as amphetamine intoxication (Morton et al 2000). These symptoms include euphoria, confusion delirium, seizures and hallucination (Spiller et al 2013).	

	CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Feasibility	Is the intervention feasible to implement? The less feasible (capable of being accomplished or brought about) an option is, the less likely it is that it should be recommended (i.e. the more barriers there are that would be difficult to overcome).			
	• Can the option be accomplished or brought about? • Is the intervention or option sustainable? • Are there important barriers that are likely to limit the feasibility of implementing the intervention (option) or require consideration when implementing it?	☐ No ☐ Probably no ☒ **Probably yes** ☐ Yes ☐ Varies ☐ Don't know	There is limited information about the feasibility of prescribing methylphenidate in PHC. Prescriptions of methylphenidate in PHC has seen dispensing largely from pharmacies in South Africa (89.6%) (Truter I, 2005). In England, dispensing of drugs for ADHD in PHC saw an average increase of 11.07% per year (Hasan et al 2022). The importance of specialist involvement in the management of ADHD in PHC settings is recognized (Salt et al 2005). In low- and middle-income countries (LMICs), psychostimulants are less costly than atomoxetine and are more likely to be available in LMICs (Flisher et al 2010).	
Human rights and sociocultural acceptability	Is the intervention aligned with human rights principles and socioculturally acceptable? (WHO INTEGRATE) This criterion encompasses two distinct constructs: The first refers to an intervention's compliance with universal human rights standards and other considerations laid out in international human rights law beyond the right to health (as the right to health provides the basis of other criteria and sub-criteria in this framework). The second, sociocultural acceptability, is highly time-specific and context-specific and reflects the extent to which those implementing or benefiting from an intervention as well as other relevant stakeholder groups consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention. The greater the sociocultural acceptability of an intervention to all or most relevant stakeholders, the greater the likelihood of a general recommendation in favour of this intervention.			
	• Is the intervention in accordance with universal human rights standards and principles? • Is the intervention socioculturally acceptable to patients/beneficiaries as well as to those implementing it? To which extent do patients/beneficiaries value different non-health outcomes? • Is the intervention socioculturally acceptable to the public and other relevant stakeholder groups? Is the intervention sensitive to sex, age, ethnicity, culture or language, sexual orientation or gender identity, disability status, education,	☐ No ☐ Probably no ☐ Probably yes ☐ Yes ☒ **Varies** ☐ Don't know	Methylphenidate had better acceptability among children and adolescents than placebo (Cortese et al, 2017). No difference in acceptability could be found for atomoxetine and methylphenidate (Hanwella et al, 2011). Parent acceptability of methylphenidate had the least acceptability when compared to other treatment modalities, however an increase in acceptability among parents was	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	socioeconomic status, place of residence or any other relevant characteristics? • How does the intervention affect an individual's, population group's or organization's autonomy, i.e. their ability to make a competent, informed and voluntary decision? • How intrusive is the intervention, ranging from low intrusiveness (e.g. providing information) to intermediate intrusiveness (e.g. guiding choices) to high intrusiveness (e.g. restricting or eliminating choices)? Where applicable, are high intrusiveness and/or impacts on the privacy and dignity of concerned stakeholders justified?		seen when there was an increase in knowledge about ADHD (Liu et al, 1991).	

4.3. Summary of judgements

Table 11. Summary of judgements

Priority of the problem	- Don't know	- Varies		- No	- Probably No	- Probably Yes	✓ **Yes**
Desirable effects	- Don't know	✓ **Varies**		- Trivial	- Small	- Moderate	- Large
Undesirable effects	- Don't know	✓ **Varies**		- Large	- Moderate	- Small	- Trivial
Certainty of the evidence	- No included studies			- Very low	✓ **Low**	- Moderate	- High
Values				- Important uncertainty or variability	✓ **Possibly important uncertainty or variability**	- Probably no important uncertainty or variability	- No important uncertainty or variability
Balance of effects	- Don't know	- Varies	- Favours comparison	- Probably favours comparison	- Does not favour either	✓ **Probably favours intervention**	- Favours intervention
Resources required	✓ **Don't know**	- Varies	- Large costs	- Moderate costs	- Negligible costs or savings	- Moderate savings	- Large savings
Certainty of the evidence on required resources	✓ **No included studies**			- Very low	- Low	- Moderate	- High
Cost–effectiveness	- No included studies	- Varies	- Favours comparison	- Probably favours comparison	- Does not favour either	✓ **Probably favours intervention**	- Favours intervention
Equity, equality and non-discrimination	✓ **Don't know**	- Varies	- Reduced	Probably reduced	- Probably no impact	- Probably increased	- Increased
Feasibility	- Don't know	- Varies		- No	- Probably No	✓ **Probably Yes**	- Yes
Human rights and sociocultural acceptability	- Don't know	✓ **Varies**		- No	- Probably No	- Probably Yes	- Yes

✓Indicates category selected, -Indicates category not selected

5. References

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Yang K-H, Lane H-Y, Chang Y-C, Tzang R-F. Exploring the effects of pharmacological, psychosocial, and alternative/complementary interventions in children and adolescents with attention-deficit/hyperactivity disorder: Meta-regression approach. International Journal of Neuropsychopharmacology. 2021 2021;24(10):776-786. doi:https://dx.doi.org/10.1093/ijnp/pyab034

Appendix A. Search terms used to identify systematic reviews

Ovid MEDLINE(R) ALL <1946 to 05 January 2022>

1 (teen* or youth* or adolescen* or juvenile* or (young adj2 (adult* or person* or individual* or people* or population* or man or men or wom#n)) or youngster* or highschool* or college* or ((secondary or high*) adj2 (school* or education))).ti,ab. or adolescent/ or young adult/ 2982381
2 (child* or stepchild* or step-child* or kid or kids or girl or girls or boy or boys or teen* or youth* or youngster* or preschool* or pre-school* or kindergarten* or school* or juvenile* or minors or p?ediatric* or PICU).ti,ab. or exp child/ 2966443
3 (baby or babies or neonate* or neo-nate* or newborn* or new-born* or infant*).ti,ab. or infant/ or infant, newborn/ or infant, low birth weight/ or infant, small for gestational age/ or infant, very low birth weight/ or infant, extremely low birth weight/ or infant, postmature/ or infant, premature/ or infant, extremely premature/ 1429094
4 1 or 2 or 3 5184275
5 "attention deficit and disruptive behavior disorders"/ or attention deficit disorder with hyperactivity/ 33930
6 ("attention deficit" or ADHD or ADDH or (attention adj3 disorder*)).ti,ab. 39488
7 (hyperactiv* or "short attention" or (hyperkinetic adj disorder)).ti,ab. 64938
8 5 or 6 or 7 81062
9 Atomoxetine Hydrochloride/ 1282
10 exp Methylphenidate/ 7528
11 exp Dextroamphetamine/ 7111
12 (atomoxetine or methylphenidate or dexamphetamine or dextroamphetamine or ritalin).ti,ab. 9527
13 (dexmethylphenidate or lisdexamfetamine).ti,ab. 492
14 9 or 10 or 11 or 12 or 13 17497
15 exp Cognitive Behavioral Therapy/ 33007
16 Interpersonal Psychotherapy/ 66
17 ("interpersonal psychotherapy" or IPT).ti,ab. 3026
18 (CBT or "cognitive behavio?r*").ti,ab. 34109
19 exp Behavior Therapy/ 83297
20 ((psychosocial or psychological or psychotherap* or behavio?r* or multimodal or social) adj3 (treat* or therap* or interven* or program*)).ti,ab. 135222
21 (parent* adj2 (train* or interven* or educat* or program*)).ti,ab. 19438
22 15 or 16 or 17 or 18 or 19 or 20 or 21 216057
23 14 or 22 232617
24 meta-analysis.pt. 149964
25 meta-analysis/ or systematic review/ 253442
26 (meta analysis or search* or (systematic adj2 review*)).ti,ab. 694590
27 24 or 25 or 26 709989
28 4 and 8 and 23 and 27 649
29 limit 28 to yr="2016 -Current" 280

Embase <1974 to 05 January 2022>

1 (teen* or youth* or adolescen* or juvenile* or (young adj2 (adult* or person* or individual* or people* or population* or man or men or wom#n)) or youngster* or highschool* or college* or ((secondary or high*) adj2 (school* or education))).ti,ab. or adolescent/ or young adult/ 2534671
2 (child* or stepchild* or step-child* or kid or kids or girl or girls or boy or boys or teen* or youth* or youngster* or preschool* or pre-school* or kindergarten* or school* or juvenile* or minors or p?ediatric* or PICU).ti,ab. or exp child/ 3829058
3 (baby or babies or neonate* or neo-nate* or newborn* or new-born* or infant*).ti,ab. or exp infant/ 1318437
4 1 or 2 or 3 5193409

5 attention deficit disorder/ 68064
6 ("attention deficit" or ADHD or ADDH or (attention adj3 disorder*)).ti,ab. 55299
7 (hyperactiv* or "short attention" or (hyperkinetic adj disorder)).ti,ab. 86485
8 5 or 6 or 7 122825
9 atomoxetine/ 5806
10 methylphenidate/ or dexmethylphenidate/ 22710
11 dextroamphetamine/ or dexamphetamine/ or lisdexamfetamine/ 13672
12 (atomoxetine or methylphenidate or dexamphetamine or dextroamphetamine or ritalin).ti,ab. 12970
13 (dexmethylphenidate or lisdexamfetamine).ti,ab. 793
14 9 or 10 or 11 or 12 or 13 35717
15 exp cognitive behavioral therapy/ 18903
16 interpersonal psychotherapy/ 413
17 ("interpersonal psychotherapy" or IPT).ti,ab. 3945
18 (CBT or "cognitive behavio?r*").ti,ab. 48548
19 exp behavior therapy/ 64200
20 ((psychosocial or psychological or psychotherap* or behavio?r* or multimodal or social) adj3 (treat* or therap* or interven* or program*)).ti,ab. 184301
21 (parent* adj2 (train* or interven* or educat* or program*)).ti,ab. 24810
22 15 or 16 or 17 or 18 or 19 or 20 or 21 253290
23 14 or 22 286038
24 meta-analys:.mp. 362920
25 exp meta-analysis/ or "systematic review"/ 437931
26 (meta analysis or search* or (systematic adj2 review*)).ti,ab. 876065
27 24 or 25 or 26 997222
28 4 and 8 and 23 and 27 1235
29 limit 28 to yr="2016 -Current" 521

APA PsycInfo <1806 to Week 4 December 2021>

1 (teen* or youth* or adolescen* or juvenile* or (young adj2 (adult* or person* or individual* or people* or population* or man or men or wom#n)) or youngster* or highschool* or college* or ((secondary or high*) adj2 (school* or education))).ti,ab. 629547
2 (child* or stepchild* or step-child* or kid or kids or girl or girls or boy or boys or teen* or youth* or youngster* or preschool* or pre-school* or kindergarten* or school* or juvenile* or minors or p?ediatric* or PICU).ti,ab. 1115193
3 (baby or babies or neonate* or neo-nate* or newborn* or new-born* or infant*).ti,ab. 103636
4 1 or 2 or 3 1418132
5 exp attention deficit disorder/ 29482
6 ("attention deficit" or ADHD or ADDH or (attention adj3 disorder*)).ti,ab. 39175
7 (hyperactiv* or "short attention" or (hyperkinetic adj disorder)).ti,ab. 43388
8 5 or 6 or 7 54033
9 atomoxetine/ 671
10 methylphenidate/ or dexmethylphenidate/ 3887
11 dextroamphetamine/ or dexamphetamine/ or lisdexamfetamine/ 2049
12 (atomoxetine or methylphenidate or dexamphetamine or dextroamphetamine or ritalin).ti,ab. 7612
13 (dexmethylphenidate or lisdexamfetamine).ti,ab. 268
14 9 or 10 or 11 or 12 or 13 8732
15 exp cognitive behavior therapy/ 24194
16 interpersonal psychotherapy/ 1452
17 ("interpersonal psychotherapy" or IPT).ti,ab. 1885
18 (CBT or "cognitive behavio?r*").ti,ab. 45996
19 exp behavior therapy/ 21995

20 ((psychosocial or psychological or psychotherap* or behavio?r* or multimodal or social) adj3 (treat* or therap* or interven* or program*)).ti,ab. 154737
21 (parent* adj2 (train* or interven* or educat* or program*)).ti,ab. 25734
22 15 or 16 or 17 or 18 or 19 or 20 or 21 200515
23 14 or 22 208668
24 (meta analysis or search* or (systematic adj2 review*)).ti,ab. 148215
25 meta analysis/ 5125
26 "systematic review"/ 672
27 24 or 25 or 26 149307
28 4 and 8 and 23 and 27 398
29 limit 28 to yr="2016 -Current" 169

CINAHL

Search Terms	Search Options	
S31	S11 AND S12 AND S18 AND S26 AND S30 Limiters - Published Date: 20160101-20221231	(380)
S30	S27 OR S28 OR S29	(635,230)
S29	TX meta analysis or search* or (systematic N2 review*)	View Results (635,230)
S28	(MH "Systematic Review")	View Results (107,699)
S27	(MH "Meta Analysis")	View Results (60,930)
S26	(S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25)	View Results (298,102)
S25	TX (parent* N3 (train* or interven* or educat* or program*))	View Results (61,798)
S24	TX (psychosocial or psychological or psychotherap* or behavior* or behaviour* or multimodal or social) N3 (treat* or therap* or interven* or program*)	View Results (233,898)
S23	(MH "Behavior Therapy+")	View Results (38,797)
S22	TX CBT or "cognitive behavior*" or "cognitive behaviour*"	View Results (47,648)
S21	TX "interpersonal psychotherapy" or IPT	View Results (2,916)
S20	(MH "Interpersonal Psychotherapy")	View Results (30)
S19	(MH "Cognitive Therapy+")	View Results (26,810)
S18	S13 OR S14 OR S15 OR S16 OR S17	View Results (9,542)
S17	TX dexmethylphenidate or lisdexamfetamine	View Results (763)

S16	TX atomoxetine or methylphenidate or dexamphetamine or dextroamphetamine or ritalin	View Results (9,312)
S15	(MH "Dextroamphetamine")	View Results (454)
S14	(MH "Methylphenidate")	View Results (2,572)
S13	(MH "Atomoxetine")	View Results (317)
S12	S8 OR S9 OR S10	View Results (57,671)
S11	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7	View Results (3,784,570)
S10	TX hyperactiv* or "short attention" or (hyperkinetic N1 disorder)	View Results (46,807)
S9	TX "attention deficit" or ADHD or ADDH or (attention N3 disorder*)	View Results (43,002)
S8	(MH "Attention Deficit Hyperactivity Disorder")	View Results (18,330)
S7	(MH "Infant+")	View Results (280,259)
S6	TX (baby or babies or neonate* or neo-nate* or newborn* or new-born* or infant*)	View Results (539,431)
S5	(MH "Child+")	View Results (725,319)
S4	TX (child* or stepchild* or step-child* or kid or kids or girl or girls or boy or boys or teen* or youth* or youngster* or preschool* or pre-school* or kindergarten* or school* or juvenile* or minors or pediatric* or paediatric* or PICU)	View Results (3,056,723)
S3	(MH "Young Adult")	View Results (276,471)
S2	(MH "Adolescence+")	View Results (575,935)
S1	TX (teen* or youth* or adolescen* or juvenile* or (young N2 (adult* or person* or individual* or people* or population* or man or men or women or woman)) or youngster* or highschool* or college* or ((secondary or high*) N2 (school* or education)))	View Results (2,028,320)

Global Index Medicus

tw:((tw:(adhd OR addh OR "attention deficit" OR "attention disorder" OR hyperactiv*)) AND (tw:(child* OR teen* OR adolescent* OR infant* OR young* OR school* OR paediatric* OR pediatric*)) AND (tw:(psycho* OR therap* OR atomoxetine OR methylphenidate OR dexamphetamine OR dextroamphetamine OR ritalin OR dexmethylphenidate OR lisdexamfetamine OR cbt))) AND (type_of_study:("qualitative_research" OR "guideline" OR "evaluation_studies" OR "systematic_reviews" OR "overview" OR "policy_brief" OR "health_economic_evaluation")) AND (year_cluster:[2016 TO 2022])

Scopus

((TITLE-ABS-KEY (teen* OR youth* OR adolescen* OR juvenile*)) OR (TITLE-ABS-KEY ((young W/2 (adult* OR person* OR individual* OR people* OR population* OR man OR men OR women OR woman)))) OR (TITLE-ABS-KEY (youngster* OR highschool* OR college*)) OR (TITLE-ABS-KEY ((secondary OR high*) W/2 (school* OR education))) OR (TITLE-ABS-KEY (child* OR stepchild* OR step-child* OR kid OR kids OR girl OR girls OR boy OR boys OR teen* OR youth* OR youngster* OR preschool* OR pre-school* OR kindergarten* OR school* OR juvenile* OR minors OR pediatric* OR paediatric* OR picu)) OR (TITLE-ABS-KEY (baby OR babies OR neonate* OR neo-nate* OR newborn* OR new-born* OR infant*))) AND ((TITLE-ABS-KEY ("attention deficit" OR adhd OR addh OR (attention W/3 disorder*))) OR (TITLE-ABS-KEY (hyperactiv* OR "short attention" OR (hyperkinetic W/1 disorder)))) AND ((TITLE-ABS-KEY (atomoxetine OR methylphenidate OR dexamphetamine OR dextroamphetamine OR ritalin OR dexmethylphenidate OR lisdexamfetamine)) OR (TITLE-ABS-KEY ("interpersonal psychotherapy" OR ipt OR cbt OR "cognitive behaviour*" OR "cognitive behavior*")) OR (TITLE-ABS-KEY ((psychosocial OR psychological OR psychotherap* OR behavior* OR behaviour* OR multimodal OR social) W/3 (treat* OR therap* OR interven* OR program*))) OR (TITLE-ABS-KEY (parent* W/2 (train* OR interven* OR .educat* OR program*)))) AND ((TITLE-ABS-KEY (meta AND analysis OR search*)) OR (TITLE-ABS-KEY (systematic W/2 review*))) AND (LIMIT-TO (PUBYEAR , 2022) OR LIMIT-TO (PUBYEAR , 2021) OR LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016))