ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

PHARMACOLOGIC TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN ADULTS

FINAL SYSTEMATIC REVIEW REPORT

December 2015

Conflict of Interest Statement

No study members report any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock options, expert testimony, grants or patents received or pending, or royalties) that may present a potential conflict of interest in the Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder (ADHD) in Adults Drug Class Review.

Acknowledgments

The Ontario Drug Policy Research Network (ODPRN) is funded by grants from the Ontario Ministry of Health and Long-term Care (MOHLTC) Health System Research Fund. The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources and supporting organizations.

Study Team

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Note

Some details are censored in this report so as not to preclude publication. Publications (when available) and/or final unpublished reports will be available on the ODPRN website (www.odprn.ca).

Table of Exhibits

Key points

Efficacy

- Most of the pharmacotherapies were associated with a significant improvement in patient-reported clinical response relative to placebo. Extended-release dexmethylphenidate (standard dose) was associated with improved clinical response relative to most other therapies, and modafinil (high dose) was associated with worse clinical response than all other therapies.
- Mixed amphetamine salt, atomoxetine (standard dose), lisdexamfetamine, osmotic-release oral system (OROS) methylphenidate (standard dose), and immediate-release methylphenidate (high dose) were associated with improved observer-reported clinical response relative to placebo. High-dose mixed amphetamine salt was better than most other pharmacotherapies at improving observer-reported clinical response.
- The proportion of participants who achieved clinical response varied depending on whether a patient-reported or observer-reported scale was used. In general, standard-dose atomoxetine was better than most other pharmacotherapies in the patient-reported assessment of clinical response. In the observer-reported assessment, several pharmacotherapies were associated with better response compared with placebo, but there were few significant differences among the treatments.
- Standard-dose atomoxetine and high-dose mixed amphetamine salts were associated with significant improvements in quality of life relative to placebo. There were no significant differences among the pharmacotherapies.
- There were no significant differences in executive function between any of the pharmacotherapies and placebo or among the pharmacotherapies.

Safety

- Compared with placebo, standard doses of mixed amphetamine salts, atomoxetine, OROS methylphenidate, long-acting methylphenidate, and modafinil were associated with higher odds of withdrawal due to an adverse event. High doses of mixed amphetamine salts, lisdexamfetamine, OROS methylphenidate, and modafinil had higher odds of withdrawal compared with placebo. There were few significant differences among the pharmacotherapies.
- There were no significant differences in serious adverse events between any of the ADHD pharmacotherapies and placebo. Comparison among the pharmacotherapies was not possible for this outcome.
- Compared with placebo, atomoxetine (standard and high doses) and OROS methylphenidate (standard dose) were associated with higher odds of all-cause treatment discontinuation. Mixed amphetamine salts (high dose) and extended-release methylphenidate (standard dose) had lower odds of discontinuation relative to placebo. High-dose mixed amphetamine salts and standard-dose extended release methylphenidate were associated with a lower odds of treatment discontinuation compared with most other pharmacotherapies.
- One trial reported 1 case of suspected stroke in the mixed amphetamine salt group; no strokes

were reported in the placebo group.

- Two studies reported hospitalizations during the study period: 2 patients in the extended-release methylphenidate group and 1 patient in the mixed amphetamine salts group; no hospitalizations were reported in the placebo arms of either study.
- No trial reported myocardial infarction, cardiovascular death, or emergency room visits during the study period.

Exhibit 1: Comparison of standard-dose ADHD treatments relative to placebo for efficacy outcomes*

Treatment	Mean difference (95% CrI)				Odds ratio (95% CrI)	
	Clinical response, continuous				Clinical responder, dichotomous	
	Self-reported (CAARS)	Observer-reported (CAARS)	Quality of life (AAQoL)	Executive function (SDS)	Self-reported	Observer-reported
Mixed amphetamine salts, extended-release	—	**-18.03 (-31.54, -5.81)**	—	—	—	2.33 (0.44,11.88)
Atomoxetine	**-4.57 (-6.51, -2.90)**	**-4.16 (-6.85, -1.59)**	**4.27 (1.35, 8.76)**	-2.08 (-27.31, 22.61)	**20.20 (3.49, 164.90)**	**3.46 (1.47,8.85)**
Bupropion, sustained release	-1.75 (-6.98, 3.30)	-4.81 (-15.26, 5.84)	—	-2.97 (-27.86, 21.81)	1.16 (0.33, 3.85)	1.73 (0.53, 5.81)
Bupropion, extended release	—	—	—	—	—	—
Clonidine, immediate release	—	—	—	—	—	—
Clonidine, extended release	—	—	—	—	—	—
Dexmethylphenidate, immediate release	—	—	—	—	—	—
Dexmethylphenidate, extended release	**-15.94 (-21.39, -10.58)**	-7.02 (-16.79, 3.00)	—	—	—	2.39 (0.38, 14.18)
Dextroamphetamine, immediate release	-4.22 (-10.39, 2.16)	-1.28 (-13.73, 11.25)	—	—	1.75 (0.43, 7.03)	–
Dextroamphetamine, sustained release	—	—	—	—	—	—
Guanfacine, immediate release	**-8.43 (-16.56, -0.71)**	—	—	—	—	—
Guanfacine, extended release	—	—	—	—	—	—
Lisdexamfetamine	—	**-7.89 (-13.38, -2.46)**	7.11 (-1.22,15.44)	—	—	**5.79 (2.01, 16.41)**
Methamphetamine	—	—	—	—	—	—
Methylphenidate, OROS	**-4.88 (-7.33, -2.84)**	**-3.52 (-6.85, -0.18)**	1.59 (-4.18, 7.19)	-6.73 (-24.76, 10.52)	**6.45 (1.33, 38.53)**	**3.79 (1.74, 8.81)**
Methylphenidate, extended-release oral capsule	—	—	—	–	—	—
Methylphenidate extended-release oral tablet	—	-5.15 (-14.81, 4.36)	—	—	—	2.03 (0.35, 11.65)
Methylphenidate chewable/oral solution	—	–	—	—	—	—
Methylphenidate, immediate-release	-0.80 (-5.53, 4.02)	-4.83 (-10.73, 1.11)	—	2.12 (-15.46, 19.68)	1.49 (0.18,11.02)	1.41 (0.43, 4.31)
Methylphenidate long-acting	**-6.37 (-10.80, -1.86)**	-4.62 (-14.35, 5.13)	—	-1.90 (-26.36, 23.11)	—	2.46 (0.42, 14.01)
Methylphenidate, multi-layer release	—	—	—	—	—	—
Methylphenidate,	—	-5.62	—	—	0.74	1.17

Treatment	Mean difference (95% CrI)				Odds ratio (95% CrI)	
	Clinical response, continuous				Clinical responder, dichotomous	
	Self-reported (CAARS)	Observer-reported (CAARS)	Quality of life (AAQoL)	Executive function (SDS)	Self-reported	Observer-reported
sustained release		(-13.17, 2.22)			(0.26, 2.24)	(0.19, 7.65)
Modafinil	0.45 (-4.60, 5.56)	-0.22 (-9.95, 9.58)	-0.27 (-8.55, 8.03)	—	1.77 (0.41, 7.46)	1.04 (0.17, 5.96)

Note: AAQoL = Adult ADHD Quality of Life, CAARS = Conners' Adult ADHD Rating Scale, CrI = credible interval, OROS = osmotic-release oral system, SDS = Sheehan Disability Scale.
*Data for continuous outcomes were analyzed using standardized mean differences; results were converted to mean difference using a common scale.

Exhibit 2: Comparison of standard-dose ADHD treatments relative to placebo for safety outcomes

	Odds ratio (95% credible interval)*		
	Withdrawals due to adverse events	Serious adverse events†	All-cause treatment discontinuation
Mixed amphetamine salts, extended release	**4.83 (1.48, 17.10)**	Not estimable	0.70 (0.33, 1.41)
Atomoxetine	**3.09 (2.25, 4.35)**	1.56 (0.40, 6.02)	**1.37 (1.14, 1.61)**
Bupropion, sustained release	0.74 (0.19, 3.13)	–	1.29 (0.40, 4.10)
Bupropion, extended release	–	–	–
Clonidine, immediate release	–	–	–
Clonidine, extended release	–	–	–
Dexmethylphenidate, immediate release	–	–	–
Dexmethylphenidate, extended release	1.55 (0.48, 6.06)	1.64 (0.08, 34.62)	0.83 (0.36, 2.02)
Dextroamphetamine, immediate release	1.85 (0.26, 16.65)	–	2.16 (0.65, 8.20)
Dextroamphetamine, sustained release	–	–	–
Guanfacine, immediate release	–	–	–
Guanfacine, extended release	–	–	–
Lisdexamfetamine	2.58 (0.85, 9.76)	0.80 (0.03, 19.78)	0.75 (0.44, 1.30)
Methamphetamine	–	–	–
Methylphenidate, osmotic-release oral system	**4.02 (2.32, 7.34)**	2.41 (0.78, 7.41)	**1.44 (1.05, 1.96)**
Methylphenidate, extended release oral capsule	–	–	–
Methylphenidate	1.59 (0.67, 4.13)	–	**0.40 (0.22, 0.72)**

	Odds ratio (95% credible interval)*		
	Withdrawals due to adverse events	Serious adverse events†	All-cause treatment discontinuation
extended-release oral tablet			
Methylphenidate chewable or oral solution	–	–	–
Methylphenidate, immediate-release	3.28 (0.56, 22.72)	–	2.37 (0.79, 7.32)
Methylphenidate long-acting	**7.40 (2.34, 34.16)**	0.77 (0.20, 3.02)	1.44 (0.81, 2.62)
Methylphenidate, multi-layer release	–	–	–
Methylphenidate, sustained release	0.86 (0.03, 37.90)	–	0.94 (0.41, 2.06)
Modafinil	**3.97 (1.43, 12.38)**	–	1.84 (0.94, 3.75)

*Unless otherwise stated.
†Odds ratio (95% confidence interval).

Exhibit 3: Summary table for efficacy outcomes for ADHD pharmacotherapies approved for ADHD treatment in Canada.* Pharmacotherapy in the row header is significantly better than the pharmacotherapies listed under each outcome

Pharmacotherapy	Short form	Dose category	Clinical response assessed using continuous measure		Proportion of patients with clinical response		Quality of life	Executive function
			Patient-reported	Observer-reported	Patient-reported	Observer-reported		
Mixed amphetamine salts, extended release	MAS-XR	Standard	—	Placebo ATX-STD MPH-OROS-STD	—	NS	—	—
		High	—	Placebo ATX-STD DEX-IR-STD LIS-DEX-STD/HD MPH-OROS-STD/HD MPH-SR-STD MPH-IR-STD	—	Placebo MPH-SR-HD	Placebo	NS
Atomoxetine	ATX	Standard	Placebo MPH-SR-HD	Placebo	Placebo ATX-HD MPH-IR-STD MPH-SR-STD/HD	Placebo	Placebo	NS
		High	—	NS	NS	NS	NS	—
Dextroamphetamine, immediate release	DEX-IR	Standard	NS	NS	NS	—	—	—
		High	—	—	—	—	—	—
Dextroamphetamine, sustained release	DEX-SR	Standard	—	—	—	—	—	—
		High	—	—	—	—	—	—
Guanfacine, extended release	GUAN-ER	Standard	—	—	—	—	—	—
		High	—	—	—	—	—	—
Lisdexamfetamine	LIS-DEX	Standard	—	Placebo	—	Placebo MPH-SR-HD	NS	—
		High	—	Placebo	—	Placebo	—	—
Methylphenidate, osmotic-release oral system	MPH-OROS	Standard	Placebo MPH-SR-STD	Placebo	Placebo MPH-SR-STD/HD	Placebo	NS	NS
		High	NS	MPH-IR-HD	Placebo MPH-SR-STD/HD	NS	—	—
Methylphenidate, immediate release	MPH-IR	Standard	NS	Placebo	—	NS	—	NS
		High	Placebo MPH-SR-HD	MPH-IR-STD	—	Placebo	—	—
Methylphenidate, multilayer-release	MPH-MR	High	—	—	—	—	—	—
		Standard	—	—	—	—	—	—
Methylphenidate, sustained release	MPH-SR	Standard	—	NS	NS	NS	—	—
		High	NS	—	NS	NS	—	—

Note: HD = high dose, STD= standard dose, NS = not significantly different compared to other treatments in this table.
— indicates pharmacotherapies not included in the network.
*Does not contain all pharmacotherapies included in the systematic review and network meta-analysis. Only select pharmacotherapies approved for ADHD treatment in Canada are presented in this table.

Exhibit 4: Summary table for safety outcomes for ADHD pharmacotherapies approved for ADHD treatment in Canada.* Pharmacotherapy in the row header is significantly better than the pharmacotherapies listed under each outcome

Pharmacotherapy	Short form	Dose category	Withdrawals due to adverse events†	Serious adverse events‡	All-cause treatment discontinuation†
Placebo	—	—	MAS-XR-STD/HD ATX-STD LIS-DEX-HD MPH-OROS-STD/HD	NS	ATX-STD/HD MPH-OROS-STD
Mixed amphetamine salts, extended release	MAS-XR	Standard	NS	§	ATX-HD
		High	NS	NS	ATX-STD/HD MPH-OROS-STD/HD MPH-IR-STD
Atomoxetine	ATX	Standard	NS	NS	NS
		High	¶	NS	Placebo DEX-IR-STD LIS-DEX-STD
Dextroamphetamine, immediate release	DEX-IR	Standard	NS	—	ATX-HD
		High	—	—	—
Dextroamphet-amine, sustained release	DEX-SR	Standard	—	—	—
		High	—	—	—
Guanfacine, extended release	GUAN-ER	Standard	—	—	—
		High	—	—	—
Lisdexamfetamine	LIS-DEX	Standard	NS	NS	ATX-STD/HD MPH-OROS-STD
		High	NS	NS	NS
Methylphenidate, osmotic-release oral system	MPH-OROS	Standard	NS	NS	NS
		High	NS	§	NS
Methylphenidate, immediate release	MPH-IR	Standard	NS	—	NS
		High	¶	—	NS
Methylphenidate, multilayer-release	MPH-MR	Standard	—	—	—
		High	—	—	—
Methylphenidate, sustained release	MPH-SR	Standard	NS	—	NS
		High	¶	—	NS

Note: HD = high dose, NS = not significantly different compared to other treatments in this table, STD = standard dose.
*Does not contain all pharmacotherapies included in the systematic review and network meta-analysis. Only select pharmacotherapies approved for ADHD treatment in Canada are presented in this table.
†Based on network meta-analysis
‡Based on meta-analysis: comparison is relative to placebo (no comparison between individual treatments).
§Data not estimable owing to zero events in both groups.
¶Estimates were not robust owing to zero event counts for the treatment or placebo arm.

Methods

The strategy for building and analyzing the evidence base for the efficacy and safety of pharmacotherapies for adults with ADHD consists of two fundamental steps:

1. Update of an existing, high-quality systematic review
   In order to meet the rigorous timelines of the review process, we performed an update of a comprehensive, well-conducted, recent evidence synthesis that met the population, intervention, and comparator requirements (Exhibit 5) (1). We performed a new literature search to capture studies published from the date of the last literature search (week 4, June 2011) to present, with retrospective overlap of 12 months.

2. A Bayesian network meta-analysis of randomized evidence
   Bayesian network meta-analyses (NMA) were performed for outcomes with sufficient data to derive robust and consistent network models. The methods and procedures to be followed are those developed by the Canadian Collaboration for Drug Safety, Effectiveness and Network Meta-Analysis (ccNMA), funded by the Drug Safety and Effectiveness Network (DSEN) of the Canadian Institute of Health Research. If more than one scale was used to assess a specific outcome, the scale used to assess the primary outcome was chosen for analysis.

A protocol was developed using guidance from the PRISMA Statement (2) and following the methods and procedures outlined in the Cochrane Handbook for Systematic Reviews for Interventions.(3) The protocol was peer-reviewed by experts in pharmacology, statistics, and systematic review methodology. The protocol was registered in the Prospero database (no. CRD42015026049).

Electronic search strategies were based on the strategy included in the 2011 DERP report on pharmacologic treatments for ADHD(4). Enhancements to this strategy were developed and tested through an iterative process by an experienced medical information specialist in consultation with the review team. The database searches were executed on 27 Apr 2015. Using the OVID platform, we searched Ovid MEDLINE®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, Embase, and PsycINFO. We also searched the CENTRAL database using Cochrane Library on Wiley. Strategies used a combination of controlled vocabulary (e.g., attention deficit disorder with hyperactivity, bupropion, methylphenidate) and keywords (e.g., ADHD, Adderall, Ritalin). Vocabulary and syntax were adjusted across databases. Searches on all relevant drugs were updated from January 2011 except for buproprion, for which there was no date restriction. A validated randomized controlled trial filter was applied and animal-only and opinion-pieces were removed from the results. Grey literature was sought using CADTH's Grey Matters Light (www.cadth.ca/sites/default/files/is/cadth_Handout_greymatters_light_e.pdf). We also looked for trials using ClinicalTrials.gov and the International Clinical Trials Registry Platform.

Studies were eligible for inclusion in the systematic review if they satisfied the PICO criteria, including the study designs of interest (Exhibit 5).

Exhibit 5: Population, intervention, comparator, outcome, study design (PICOS) criteria

Title	Title
Population	Adult (age ≥ 18 years) outpatients with attention deficit disorders (attention deficit disorder or attention deficit hyperactivity disorder)
Interventions	Pharmacotherapies listed in Exhibit 6
Comparators	Placebo or pharmacotherapy listed in Exhibit 6 (to same pharmacotherapy [e.g., different dose or duration] or to each other)
Outcomes (efficacy)	• Clinical response • Quality of life • Executive function • Driving behavior (narrative summary)
Outcomes (safety)	• Withdrawals due to adverse effects • Treatment discontinuations • Serious adverse effects • Cardiovascular events, including outpatient myocardial infarction, stroke, unexpected cardiac death • Hospitalization • Emergency room visits
Study design	Randomized controlled trials (including crossover trials)
Exclusions	• Non-English articles • Non-human studies • Studies published only in abstract form

Exhibit 6: Interventions of interest

Active ingredient(s)	Abbreviation	Common name	Trade Name	Format
Amphetamine mixture*	MAS-XR	Mixed amphetamine salts XR	Adderall XR	Extended-release oral capsule
Atomoxetine hydrochloride	ATX	Atomoxetine	Strattera	Oral capsule
Bupropion hydrochloride	Bup-SR	Sustained-release bupropion	Wellbutrin SR	Oral tablet
	Bup-ER	Extended-release bupropion	Wellbutrin XL	Oral tablet
Clonidine hydrochloride	CLON-IR	Immediate-release clonidine	Catapres	Oral tablet
	CLON-ER	Extended-release clonidine	Kapvay	Extended-release oral tablet
Dexmethylphenidate hydrochloride	DEX-MPH-IR	Immediate-release dexmethylphenidate	Focalin	Oral tablet
	DEX-MPH-ER	Extended-release dexmethylphenidate	Focalin XR	Extended-release oral capsule
Dextroamphetamine sulfate	DEX-IR	Immediate-release dextroamphetamine	Dexedrine	Oral tablet
	DEX-SR	Sustained-release dextroamphetamine	Dexedrine Spansule	Sustained-release oral capsule
Guanfacine hydrochloride	GUAN-IR	Immediate-release guanfacine	Tenex	Oral tablet
	GUAN-ER	Extended-release guanfacine	Intuniv SR	Extended-release oral tablet
Lisdexamfetamine dimesylate	LIS-DEX	Lisdexamfetamine	Vyvanse	Oral capsule
Methamphetamine hydrochloride	MET	Methamphetamine	Desoxyn	Oral tablet
Methylphenidate hydrochloride	MPH-OROS	Methylphenidate osmotic-release oral system	Concerta	Extended-release oral tablet
	MPH-CD	Methylphenidate CD	Metadate CD	Extended-release oral capsule
	MPH-ER	Methylphenidate ER	Metadate ER	Extended-release oral tablet
	MPH-CTS	Methylphenidate chewable or solution	Methylin	Oral chewable tablet or solution
	MPH-IR	Immediate-release methylphenidate	Ritalin	Oral tablet
	MPH-LAC	Methylphenidate long-acting	Ritalin LA	Extended-release oral capsule
	MPH-MR	Multilayer-release methylphenidate	Biphentin	Extended-release oral capsule
	MPH-SR	Methylphenidate sustained-release	Ritalin SR	Extended-release oral tablet
Modafinil	MODA	Modafinil	Provigil	Oral tablet
			Alertec[b]	Oral tablet

*Amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, dextroamphetamine sulfate.

Doses of each ADHD pharmacotherapy used in the randomized controlled trials (RCTs) were categorized as low, standard, or high (Exhibit 7), based on an approved or standard range of doses for ADHD treatment. Standard doses were based on Health Canada-approved monographs if available. For treatments not approved in Canada or used off-label, standard doses were based on the US Food and Drug Administration monographs or were established in consultation with ODPRN staff.

Exhibit 7: Dose categorization of ADHD treatments

Common name	Standard dose for ADHD treatment*	Comments
Mixed amphetamine salts XR	10–30 mg/d	
Atomoxetine	40–100 mg/d	
Sustained-release bupropion	200–300 mg/d	Not approved in Canada or US for ADHD
Extended-release bupropion	200–300 mg/d	Not approved in Canada or US for ADHD
Immediate-release clonidine	> 45 kg: 0.1–0.4mg	Not approved in Canada or US for ADHD
Extended-release clonidine	0.1–0.4 mg/d	Based on US FDA label (not approved in Canada)
Immediate-release dexmethylphenidate	5–20 mg/d	Based on US FDA label (not approved in Canada)
Extended-release dexmethylphenidate	10–40 mg/d	Based on US FDA label (not approved in Canada)
Immediate-release dextroamphetamine	10–60 mg/d	Based on US FDA label. Canada monograph does not provide dosage information for adults
Sustained-release dextroamphetamine	10–60 mg/d	Based on US FDA label. Canada monograph does not provide dosage information for adults
Immediate-release guanfacine	—	Not approved in Canada or US for ADHD
Extended-release guanfacine	1–7 mg/d	Not indicated for use in adults in Canada. FDA: 1-7 mg/d (does not specify adults or children)
Lisdexamfetamine	20–60 mg/d	
Methamphetamine hydrochloride	5–25 mg/d	Based on US FDA label (not approved in Canada)
Methylphenidate osmotic-release oral system	18–72 mg/d	
Methylphenidate CD	20–60 mg/d	Based on US FDA label (not approved in Canada)
Methylphenidate ER	10–60 mg/d	Not approved in Canada, and FDA monograph not available
Methylphenidate chewable or oral solution	10–60 mg/d	Based on US FDA label for chewable tablets (not approved in CAN). Oral solution not listed on Health Canada or FDA website.
Immediate-release methylphenidate	10–60 mg/d	
Methylphenidate long-acting	10–80 mg/d	Not approved in Canada. Dose based on

Common name	Standard dose for ADHD treatment*	Comments
		Anon Drugs for ADHD. Medical Letter March 2015;57:37-40
Multilayer-release methylphenidate	10–80 mg/d	
Methylphenidate sustained-release	10–60 mg/d	
Modafinil	100–400 mg/d	Not approved in Canada or US for ADHD; Dose range from Lexicomp
*Based on Health Canada monograph, unless otherwise stated. Standard doses for treatments not approved for ADHD were based on consultation with ODPRN staff.		

Results

Characteristics of the included studies

A total of 71 primary reports (in 110 publications) that met the PICO statement were identified in the systematic review (Exhibit 8). One report corresponded to a ClinicalTrials.gov record (NCT01863459) for an in-progress trial. Two publications each reported the results of two trials (5, 6). In total, 73 randomized controlled trials were included, reported in 110 publications.

Of the included RCTs, 49 involved a parallel-group design, while 24 involved a crossover design. Twenty-three of the 24 crossover trials reported a washout period (ranging from 4 to 7 days) between treatment periods. The treatment period of all included studies ranged from 2 weeks to 1.5 years; the majority of studies involved treatment for 4 to 12 weeks.

Of the included trials, 65 reported at least one outcome of interest. Of these, 39 were funded solely by pharmaceutical corporations. Most were conducted in the United States.

All of the included studies required participants to have a clinical diagnosis of ADHD. Most studies included participants with a diagnosis of ADHD based on either the 3rd or 4th edition of the *Diagnostic Statistical Manual for Mental Disorders.* Other scales used for diagnosis or screening included the following: ADHD-Rating Scale-IV; ADHD Investigator Symptom Ratings Scale; Adult Clinical Diagnostic Scale; the Attention-deficit Scales for Adults; Conners' Adult ADHD Diagnostic Interview for DSM-IV; Conners' Adult Rating Scale – Screening Version; Utah Criteria; and Wender-Reimherr Adult Attention Deficit Disorder Scale.

The total number of randomized participants in each study ranged from 17 to 725. Participants were both treatment naïve and experienced; most studies required a washout period if ADHD pharmacotherapy had been used before enrollment (duration of washout period varied by route of administration).

In general, the mean age of most studies was between 30 and 40 years of age (54 studies). Four trials involved participants with a mean age of less than 30 years (5, 7, 8), and six involved participants with a mean age over 40 years (6, 9-13). No study had a mean age above 45 years of age; however, one study did not report the mean age of participants (14).

One study (14), allocated participants to receive dextroamphetamine, paroxetine, both, or placebo, as well as “problem-focused” therapy, which provided education about ADHD, support to establish coping strategies, and assistance with understanding how to optimize strategies to moderates the deficits associated with ADHD. The authors comment that this therapy was more helpful than they had anticipated, and because their power calculations did not take this effect into account, their ability to detect differences between drug treatment groups was minimized. As such, we did not include the results of this study in our analyses.

One study (15) initiated treatment with standard formulation methylphenidate but switched participants in the active treatment group to sustained-release methylphenidate, if tolerated. Because the author’s intent was to move all participants to the sustained-release formula, we have grouped all data for this trial with sustained-release methylphenidate. The proportion of participants on each formulation at the end of treatment was not reported.

No studies were located involving clonidine (immediate- or extended-release), immediate-release dexmethylphenidate, sustained-release dextroamphetamine, extended-release guanfacine, methamphetamine, extended-release oral capsule methylphenidate, chewable tablet or oral solution methylphenidate, or multilayer-release methylphenidate.

Exhibit 8: Summary of randomized controlled trial* characteristics

Trial Characteristic	Category	No. of included studies
Publication status	Literature sources	110
	Unique RCTs	73
	Protocols	2
	ClinicalTrials.gov records	1
Country†	Canada	3
	US	49
	Non-NA	16
Study design	Parallel	49
	Cross-over	24
Sponsors	Pharmaceutical	39
	Non-Pharmaceutical	15
	Mixed	6
	Not reported	5
Publication year	--	1985–2014
No. randomized‡	--	17–725

*Includes trials that reported at least one outcome of interest.
†If study location was not reported, country is based on affiliation of the first author.
‡Does not include participants randomized to arms involving treatments not of interest.

Efficacy

Network meta-analyses were conducted for 3 efficacy outcomes (clinical response, executive function, quality of life) and 2 safety outcomes (treatment discontinuation, withdrawal due to adverse

events). One safety outcome (serious adverse events) was analyzed by pair-wise meta-analysis. The choice of outcomes for network meta-analysis was based the sufficiency of the data available to derive robust and consistent network models. For clinical response, data were analyzed separately for patient- and observer-reported response. Data for clinical response were analyzed both as continuous values and as percentage of responders, as defined in the primary publication.

Clinical response

Reported on a continuous scale

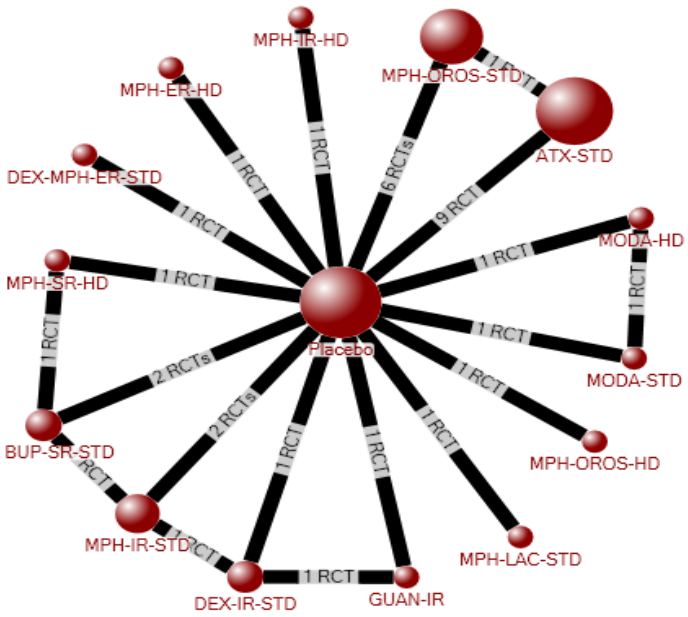
Patient-reported response

In total, 27 RCTs (26 publications) assessed patient-reported clinical response to ADHD treatment (6, 9-11, 16-37). Of these, two did not provide sufficient data for inclusion (17, 32).

Of the included trials, 15 trials used the Conners' Adult ADHD Rating Scale (6, 9, 19, 21, 22, 25, 28-31, 33-36), 6 used the Adult ADHD Self-Report Scale (16, 18, 23, 24, 27, 37), 2 used the ADHD Rating Scale (20, 26), and 1 trial each used the ADHD Behaviour Checklist (10) and the Attention Deficit Scales for Adults (11). For all scales, a lower score indicates improvement.

The evidence network for patient-reported clinical response included 25 RCTs involving a total of 4575 participants.

Exhibit 9: Evidence network, patient-reported clinical response



Compared with placebo, most of the treatments improved patient-reported clinical response (Exhibit 10). High-dose modafinil was associated with significantly worse patient-reported clinical response relative to placebo.

In the head-to-head comparison, standard-dose extended-release dexmethylphenidate was significantly better than most other pharmacotherapies, and high-dose modafinil was significantly worse than all other treatments.

Exhibit 10: Patient-reported clinical response — standardized mean differences (95% credible interval) for head-to-head comparisons of ADHD treatments

Treatment	Placebo	ATX-STD	BUP-SR-STD	DEX-MPH-ER-STD	DEX-IR-STD	GUAN-IR	MPH-OROS-STD	MPH-OROS-HD	MPH-ER-HD	MPH-LAC-STD	MPH-IR-STD	MPH-IR-HD	MPH-SR-HD	MODA-STD	MODA-HD
ATX-STD	**-0.40 (-0.57, -0.26)**	—													
BUP-SR-STD	-0.15 (-0.61, 0.29)	0.25 (-0.23, 0.72)	—												
DEX-MPH-ER-STD	**-1.40 (-1.88, -0.93)**	**-1.00 (-1.49, -0.49)**	**-1.25 (-1.90, -0.58)**	—											
DEX-IR-STD	-0.37 (-0.91, 0.19)	0.03 (-0.52, 0.62)	-0.22 (-0.89, 0.49)	**1.03 (0.31, 1.76)**	—										
GUAN-IR	**-0.74 (-1.46, -0.06)**	-0.34 (-1.06, 0.37)	-0.59 (-1.40, 0.22)	0.66 (-0.21, 1.48)	-0.37 (-1.07, 0.33)	—									
MPH-OROS-STD	**-0.43 (-0.64, -0.25)**	-0.03 (-0.27, 0.21)	-0.28 (-0.77, 0.21)	**0.97 (0.44, 1.47)**	-0.06 (-0.67, 0.51)	0.31 (-0.41, 1.04)	—								
MPH-OROS-HD	-0.53 (-1.19, 0.09)	-0.12 (-0.80, 0.51)	-0.37 (-1.16, 0.40)	**0.87 (0.05, 1.65)**	-0.16 (-1.00, 0.67)	0.21 (-0.73, 1.16)	-0.10 (-0.78, 0.56)	—							
MPH-ER-HD	**-0.91 (-1.36, -0.44)**	**-0.51 (-0.98, 0.00)**	**-0.75 (-1.38, -0.09)**	0.49 (-0.17, 1.17)	-0.54 (-1.26, 0.17)	-0.17 (-0.99, 0.68)	-0.48 (-0.95, 0.04)	-0.38 (-1.15, 0.41)	—						
MPH-LAC-STD	**-0.56 (-0.95, -0.16)**	-0.16 (-0.57, 0.29)	-0.41 (-0.98, 0.21)	**0.84 (0.23, 1.47)**	-0.19 (-0.87, 0.48)	0.18 (-0.60, 1.00)	-0.13 (-0.54, 0.33)	-0.03 (-0.75, 0.74)	0.35 (-0.25, 0.95)	—					
MPH-IR-STD	-0.07 (-0.49, 0.35)	0.33 (-0.11, 0.78)	0.08 (-0.47, 0.64)	**1.33 (0.70, 1.97)**	0.30 (-0.25, 0.83)	0.67 (-0.07, 1.43)	0.36 (-0.09, 0.83)	0.46 (-0.28, 1.23)	**0.84 (0.23, 1.46)**	0.49 (-0.09, 1.07)	—				
MPH-IR-HD	**-0.66 (-1.23, -0.08)**	-0.26 (-0.84, 0.34)	-0.51 (-1.22, 0.23)	0.74 (-0.01, 1.48)	-0.29 (-1.07, 0.53)	0.08 (-0.81, 1.01)	-0.23 (-0.82, 0.39)	-0.14 (-0.96, 0.75)	0.24 (-0.48, 0.97)	-0.10 (-0.80, 0.58)	-0.59 (-1.31, 0.12)	—			
MPH-SR-HD	0.25 (-0.31, 0.79)	**0.65 (0.08, 1.22)**	0.40 (-0.15, 0.99)	**1.65 (0.91, 2.38)**	0.62 (-0.16, 1.38)	**0.99 (0.12, 1.88)**	**0.68 (0.10, 1.27)**	0.77 (-0.05, 1.62)	**1.15 (0.42, 1.86)**	**0.81 (0.13, 1.47)**	0.32 (-0.36, 0.99)	**0.91 (0.11, 1.71)**	—		

Treatment	Placebo	ATX-STD	BUP-SR-STD	DEX-MPH-ER-STD	DEX-IR-STD	GUAN-IR	MPH-OROS-STD	MPH-OROS-HD	MPH-ER-HD	MPH-LAC-STD	MPH-IR-STD	MPH-IR-HD	MPH-SR-HD	MODA-STD	MODA-HD
MODA-STD	0.04 (-0.40, 0.49)	0.44 (-0.02, 0.93)	0.19 (-0.42, 0.83)	**1.44 (0.79, 2.10)**	0.41 (-0.29, 1.11)	0.78 (-0.03, 1.61)	0.47 (0.00, 0.98)	0.57 (-0.18, 1.39)	**0.95 (0.31, 1.58)**	**0.60 (0.00, 1.19)**	0.11 (-0.48, 0.72)	0.70 (-0.01, 1.43)	-0.21 (-0.91, 0.51)	—	
MODA-HD	1.70 (1.23, 2.18)	2.10 (1.61, 2.61)	1.85 (1.22, 2.52)	3.10 (2.43, 3.79)	2.07 (1.35, 2.79)	2.44 (1.62, 3.30)	2.13 (1.63, 2.67)	2.23 (1.45, 3.05)	2.61 (1.95, 3.27)	2.26 (1.65, 2.89)	1.77 (1.13, 2.40)	2.36 (1.64, 3.10)	1.45 (0.73, 2.21)	1.66 (1.21, 2.11)	–

Observer-reported response

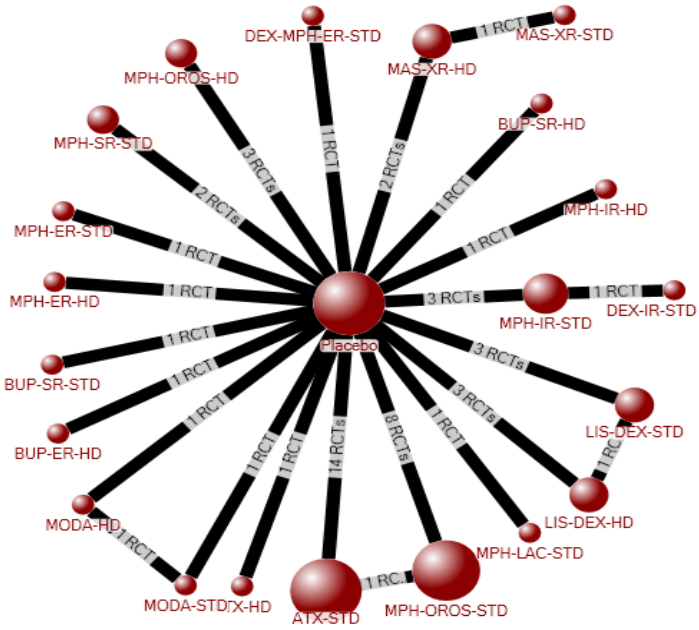
In total, 50 RCTs (49 publications) assessed observer-reported clinical response to ADHD treatment (6-8, 12, 13, 15-20, 22-26, 28-60). Of these, two did not provide sufficient data for inclusion (17, 26).

Of the included trials, 15 used the Conners' Adult ADHD Rating Scale (6, 8, 13, 19, 22, 23, 25, 28, 30, 33, 35, 38, 40, 44), 16 used the ADHD Rating Scale (7, 12, 20, 24, 34, 36, 39, 42, 43, 46, 51, 52, 54, 56, 58, 59), 8 used the Adult ADHD Investigator Symptom Rating Scale (16, 18, 37, 41, 47, 48, 50, 53), six used the Wender–Reimherr Adult Attention Deficit Disorder Scale (29, 31, 32, 45, 55, 57), and 1 each used the Physician's Global Rating Scale (60), the Clinical Global Impressions-Severity Scale (49), and the Targeted Adult Attention Deficit Disorder Scale (15).

The placebo arm of one trial was excluded because insufficient data were reported; the other two arms of this trial were included in the evidence network (52).

The evidence network for observer-reported clinical response included 48 RCTs involving a total of 3548 participants (Exhibit 11).

Exhibit 11: Evidence network, observer-reported clinical response



Compared with placebo, mixed amphetamine salt (standard and high dose), atomoxetine (standard dose), lisdexamfetamine (standard and high dose), OROS methylphenidate (standard dose), and immediate-release methylphenidate (high dose) were associated with significantly better observer-reported clinical response (Exhibit 12).

In the head-to-head comparison, mixed amphetamine salt (high dose) was significantly better than most other pharmacotherapies. There were few other significant differences between the treatments.

Exhibit 12: Observer-reported clinical response — standardized mean differences (95% credible interval) for head-to-head comparisons of ADHD treatments

Treatment	Placebo	MAS-XR-STD	MAS-XR-HD	ATX-STD	ATX-HD	BUP-SR-STD	BUP-SR-HD	BUP-ER-HD	DEX-MPH-ER-STD	DEX-IR-STD	LIS-DEX-STD	LIS-DEX-HD	MPH-OROS-STD	MPH-OROS-HD	MPH-ER-STD	MPH-ER-HD	MPH-IR-STD	MPH-IR-HD	MPH-SR-STD	MPH-LAC-STD	MODA-STD	MODA-HD
MAS-XR-STD	**-2.14 (-3.73, -0.69)**	—																				
MAS-XR-HD	**-2.28 (-3.32, -1.36)**	-0.14 (-1.30, 1.03)	—																			
ATX-STD	**-0.49 (-0.81, -0.19)**	**1.64 (0.16, 3.27)**	**1.78 (0.82, 2.86)**	—																		
ATX-HD	-0.99 (-2.21, 0.24)	1.15 (-0.74, 3.18)	1.29 (-0.20, 2.93)	-0.49 (-1.75, 0.78)	—																	
BUP-SR-STD	-0.57 (-1.81, 0.69)	1.57 (-0.30, 3.65)	**1.71 (0.20, 3.37)**	-0.08 (-1.34, 1.21)	0.42 (-1.32, 2.16)	—																
BUP-SR-HD	-0.89 (-2.19, 0.40)	1.25 (-0.69, 3.34)	1.39 (-0.17, 3.06)	-0.39 (-1.72, 0.94)	0.10 (-1.67, 1.87)	-0.32 (-2.09, 1.46)	—															
BUP-ER-HD	-0.81 (-1.98, 0.35)	1.33 (-0.51, 3.32)	**1.46 (0.00, 3.07)**	-0.32 (-1.53, 0.89)	0.17 (-1.51, 1.87)	-0.24 (-1.93, 1.46)	0.08 (-1.68, 1.84)	—														
DEX-MPH-ER-STD	-0.83 (-1.99, 0.35)	1.30 (-0.53, 3.30)	1.44 (-0.01, 3.05)	-0.34 (-1.54, 0.89)	0.15 (-1.53, 1.85)	-0.26 (-1.96, 1.43)	0.06 (-1.67, 1.79)	-0.02 (-1.67, 1.65)	—													
DEX-IR-STD	-0.15 (-1.63, 1.33)	1.98 (-0.05, 4.18)	**2.12 (0.46, 3.96)**	0.34 (-1.17, 1.85)	0.83 (-1.07, 2.74)	0.42 (-1.51, 2.35)	0.74 (-1.22, 2.69)	0.66 (-1.20, 2.56)	0.68 (-1.17, 2.54)	—												
LIS-DEX-STD	**-0.93 (-1.58, -0.29)**	1.20 (-0.38, 2.94)	**1.34 (0.24, 2.60)**	-0.44 (-1.16, 0.28)	0.05 (-1.34, 1.43)	-0.36 (-1.77, 1.04)	-0.05 (-1.50, 1.39)	-0.12 (-1.47, 1.23)	-0.10 (-1.45, 1.24)	-0.78 (-2.39, 0.82)	—											
LIS-DEX-HD	**-1.02 (-1.69, -0.33)**	1.12 (-0.47, 2.88)	**1.26 (0.15, 2.53)**	-0.52 (-1.27, 0.23)	-0.03 (-1.46, 1.37)	-0.45 (-1.87, 0.97)	-0.13 (-1.58, 1.35)	-0.20 (-1.56, 1.15)	-0.18 (-1.53, 1.15)	-0.86 (-2.47, 0.75)	-0.08 (-0.91, 0.75)	—										
MPH-OROS-STD	**-0.42 (-0.81, -0.02)**	**1.72 (0.22, 3.38)**	**1.86 (0.88, 3.00)**	0.08 (-0.41, 0.57)	0.57 (-0.72, 1.85)	0.15 (-1.15, 1.46)	0.47 (-0.88, 1.82)	0.39 (-0.84, 1.61)	0.41 (-0.82, 1.64)	-0.27 (-1.79, 1.27)	0.52 (-0.25, 1.28)	0.60 (-0.19, 1.39)	—									
MPH-OROS-HD	-0.80 (-1.63, 0.03)	1.33 (-0.30, 3.16)	**1.47 (0.26, 2.84)**	-0.31 (-1.19, 0.58)	0.18 (-1.30, 1.66)	-0.23 (-1.72, 1.25)	0.09 (-1.43, 1.60)	0.01 (-1.42, 1.43)	0.03 (-1.41, 1.45)	-0.65 (-2.35, 1.04)	0.13 (-0.91, 1.18)	0.21 (-0.85, 1.28)	-0.38 (-1.29, 0.53)	—								
MPH-ER-STD	-0.61 (-1.75, 0.52)	1.53 (-0.31, 3.48)	**1.67 (0.24, 3.24)**	-0.12 (-1.30, 1.07)	0.38 (-1.31, 2.06)	-0.04 (-1.72, 1.63)	0.28 (-1.45, 1.99)	0.20 (-1.43, 1.84)	0.22 (-1.39, 1.85)	-0.46 (-2.29, 1.40)	0.32 (-0.99, 1.62)	0.40 (-0.93, 1.73)	-0.19 (-1.40, 1.00)	0.19 (-1.22, 1.61)	—							
MPH-ER-HD	-0.83 (-2.01,	1.31 (-0.52,	**1.45 (0.02,**	-0.33 (-1.56,	0.16 (-1.53,	-0.26 (-1.95,	0.06 (-1.69,	-0.02 (-1.69,	0.01 (-1.67,	-0.68 (-2.55,	0.11 (-1.22,	0.19 (-1.17,	-0.41 (-1.64,	-0.02 (-1.46,	-0.22 (-1.87,	—						

Treatment	Placebo	MAS-XR-STD	MAS-XR-HD	ATX-STD	ATX-HD	BUP-SR-STD	BUP-SR-HD	BUP-ER-HD	DEX-MPH-ER-STD	DEX-IR-STD	LIS-DEX-STD	LIS-DEX-HD	MPH-OROS-STD	MPH-OROS-HD	MPH-ER-STD	MPH-ER-HD	MPH-IR-STD	MPH-IR-HD	MPH-SR-STD	MPH-LAC-STD	MODA-STD	MODA-HD
	0.34)	3.32)	**3.05)**	0.88)	1.82)	1.47)	1.82)	1.64)	1.65)	1.21)	1.44)	1.56)	0.82)	1.39)	1.44)							
MPH-IR-STD	-0.57 (-1.27, 0.13)	1.56 (-0.05, 3.34)	**1.70 (0.57, 2.98)**	-0.08 (-0.84, 0.69)	0.41 (-1.00, 1.82)	0.00 (-1.42, 1.43)	0.32 (-1.15, 1.80)	0.24 (-1.13, 1.60)	0.26 (-1.12, 1.63)	-0.42 (-1.72, 0.89)	0.36 (-0.58, 1.32)	0.44 (-0.54, 1.42)	-0.15 (-0.96, 0.65)	0.23 (-0.85, 1.32)	0.04 (-1.29, 1.37)	0.25 (-1.10, 1.62)	—					
MPH-IR-HD	**-2.00 (-3.21, -0.79)**	0.13 (-1.74, 2.18)	0.27 (-1.22, 1.90)	**-1.51 (-2.75, -0.25)**	-1.02 (-2.70, 0.71)	-1.43 (-3.16, 0.29)	-1.12 (-2.90, 0.63)	-1.19 (-2.88, 0.51)	-1.17 (-2.86, 0.49)	-1.85 (-3.76, 0.03)	-1.07 (-2.45, 0.30)	-0.99 (-2.37, 0.42)	**-1.59 (-2.85, -0.32)**	-1.20 (-2.65, 0.26)	-1.39 (-3.06, 0.27)	-1.18 (-2.88, 0.54)	**-1.43 (-2.84, -0.04)**	—				
MPH-SR-STD	-0.67 (-1.56, 0.26)	1.47 (-0.23, 3.34)	**1.61 (0.34, 3.05)**	-0.17 (-1.13, 0.81)	0.32 (-1.20, 1.86)	-0.10 (-1.63, 1.45)	0.22 (-1.33, 1.81)	0.14 (-1.32, 1.64)	0.17 (-1.32, 1.65)	-0.51 (-2.25, 1.23)	0.27 (-0.84, 1.40)	0.35 (-0.78, 1.51)	-0.25 (-1.23, 0.76)	0.14 (-1.07, 1.38)	-0.06 (-1.50, 1.42)	0.16 (-1.30, 1.66)	-0.09 (-1.22, 1.06)	1.34 (-0.19, 2.87)	—			
MPH-LAC-STD	-0.55 (-1.70, 0.61)	1.59 (-0.23, 3.59)	**1.73 (0.32, 3.31)**	-0.05 (-1.23, 1.15)	0.44 (-1.23, 2.13)	0.02 (-1.67, 1.71)	0.34 (-1.38, 2.08)	0.26 (-1.36, 1.91)	0.28 (-1.35, 1.91)	-0.40 (-2.25, 1.45)	0.39 (-0.93, 1.71)	0.47 (-0.85, 1.81)	-0.13 (-1.33, 1.09)	0.26 (-1.17, 1.65)	0.06 (-1.56, 1.69)	0.28 (-1.35, 1.92)	0.03 (-1.31, 1.37)	1.46 (-0.21, 3.15)	0.12 (-1.34, 1.57)	—		
MODA-STD	-0.03 (-1.18, 1.13)	**2.11 (0.25, 4.12)**	**2.25 (0.80, 3.87)**	0.47 (-0.73, 1.67)	0.96 (-0.73, 2.65)	0.54 (-1.17, 2.26)	0.86 (-0.90, 2.58)	0.78 (-0.86, 2.44)	0.81 (-0.84, 2.45)	0.12 (-1.74, 2.01)	0.91 (-0.42, 2.25)	0.99 (-0.36, 2.34)	0.39 (-0.84, 1.62)	0.78 (-0.65, 2.20)	0.58 (-1.04, 2.22)	0.80 (-0.86, 2.43)	0.55 (-0.80, 1.90)	**1.98 (0.29, 3.66)**	0.64 (-0.85, 2.11)	0.52 (-1.10, 2.17)	—	
MODA-HD	0.07 (-1.10, 1.25)	**2.21 (0.36, 4.23)**	**2.35 (0.89, 3.95)**	0.57 (-0.65, 1.78)	1.06 (-0.63, 2.75)	0.64 (-1.07, 2.35)	0.96 (-0.79, 2.70)	0.88 (-0.77, 2.56)	0.91 (-0.74, 2.54)	0.22 (-1.66, 2.11)	1.01 (-0.32, 2.36)	1.09 (-0.26, 2.44)	0.49 (-0.74, 1.73)	0.88 (-0.56, 2.30)	0.68 (-0.95, 2.34)	0.90 (-0.76, 2.55)	0.65 (-0.71, 2.02)	**2.08 (0.41, 3.74)**	0.74 (-0.74, 2.22)	0.62 (-1.01, 2.26)	0.10 (-1.04, 1.25)	—

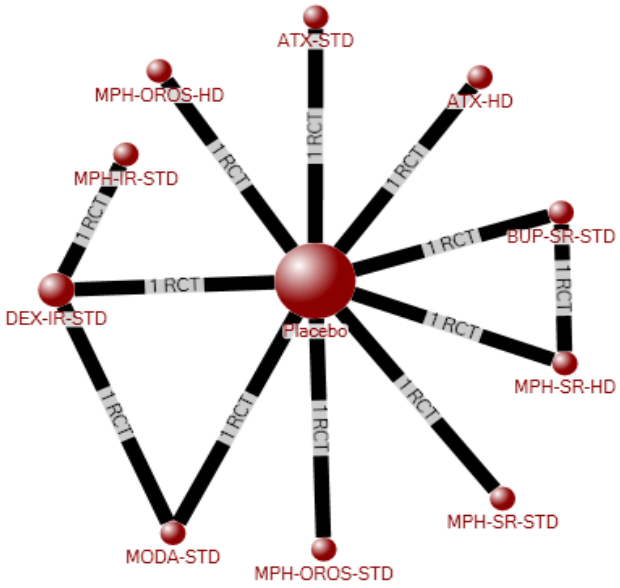
Reported as proportion who achieved clinical response (dichotomous)

Patient-reported response

Nine studies assessed the proportion of patients who responded to ADHD treatment using a patient-reported scale (9, 15, 27, 33, 36-38, 61, 62). One study was excluded because only the responder rate in the placebo arm was reported (36). Of the included studies, four used Conners' Adult ADHD Rating Scale (9, 33, 37, 38), two used Adult ADHD Rating Scale (15, 27), and two used the ADHD Rating Scale (61, 62).

The evidence network for the proportion of responders (based on patient-reported response) included eight studies involving 553 participants (Exhibit 13). Of these, two studies involved three arms and six studies involved two arms, providing 12 comparisons.

Exhibit 13: Evidence network, proportion of responders (patient-reported response)



Compared with placebo, atomoxetine (standard dose) and OROS methylphenidate (standard and high dose) were associated with a higher proportion of clinical responders based on patient-reported measures (Exhibit 14).

In the head-to-head comparison, atomoxetine (standard dose) was significantly better than most other pharmacotherapies. OROS methylphenidate (standard and high dose) was better than sustained-release methylphenidate (standard and high dose)

Exhibit 14: Proportion of responders based on patient-reported response — odds ratio (95% credible interval) for head-to-head comparisons of ADHD treatments

Treatment	Placebo	ATX-STD	ATX-HD	BUP-SR-STD	DEX-IR-STD	MPH-OROS-STD	MPH-OROS-HD	MPH-IR-STD	MPH-SR-STD	MPH-SR-HD	MODA-STD
ATX-STD	**20.20 (3.49, 164.90)**	—									
ATX-HD	2.12 (0.63, 7.13)	**0.06 (0.01, 0.48)**	—								
BUP-SR-STD	1.16 (0.33, 3.85)	**0.08 (0.01, 0.80)**	0.54 (0.09, 2.99)	—							
DEX-IR-STD	1.75 (0.43, 7.03)	0.32 (0.02, 4.06)	0.82 (0.13, 4.98)	1.51 (0.22, 9.55)	—						
MPH-OROS-STD	**6.45 (1.33, 38.53)**	0.23 (0.02, 2.31)	3.02 (0.40, 25.57)	5.68 (0.71, 46.60)	3.73 (0.45, 35.78)	—					
MPH-OROS-HD	**4.65 (1.18, 17.94)**	0.07 (0.00, 1.02)	2.22 (0.34, 12.90)	4.09 (0.64, 24.62)	2.66 (0.37, 18.50)	0.72 (0.08, 5.52)	—				
MPH-IR-STD	1.49 (0.18, 11.02)	**0.04 (0.00, 0.30)**	0.70 (0.06, 7.28)	1.29 (0.12, 13.29)	0.87 (0.19, 3.92)	0.23 (0.02, 3.00)	0.32 (0.03, 3.60)	—			
MPH-SR-STD	0.74 (0.26, 2.24)	**0.03 (0.00, 0.28)**	0.35 (0.07, 1.81)	0.65 (0.13, 3.41)	0.43 (0.07, 2.47)	**0.12 (0.01, 0.77)**	**0.16 (0.03, 0.94)**	0.50 (0.05, 5.23)	—		
MPH-SR-HD	0.64 (0.19, 2.25)	**0.09 (0.01, 0.92)**	0.30 (0.05, 1.68)	0.56 (0.16, 2.01)	0.37 (0.06, 2.42)	**0.10 (0.01, 0.83)**	**0.14 (0.02, 0.91)**	0.44 (0.04, 4.65)	0.86 (0.17, 4.42)	—	
MODA-STD	1.77 (0.41, 7.46)	**0.06 (0.01, 0.48)**	0.83 (0.12, 5.51)	1.56 (0.21, 10.63)	1.00 (0.23, 4.36)	0.27 (0.03, 2.37)	0.38 (0.05, 2.83)	1.21 (0.14, 9.40)	2.38 (0.37, 13.95)	2.77 (0.38, 18.89)	—

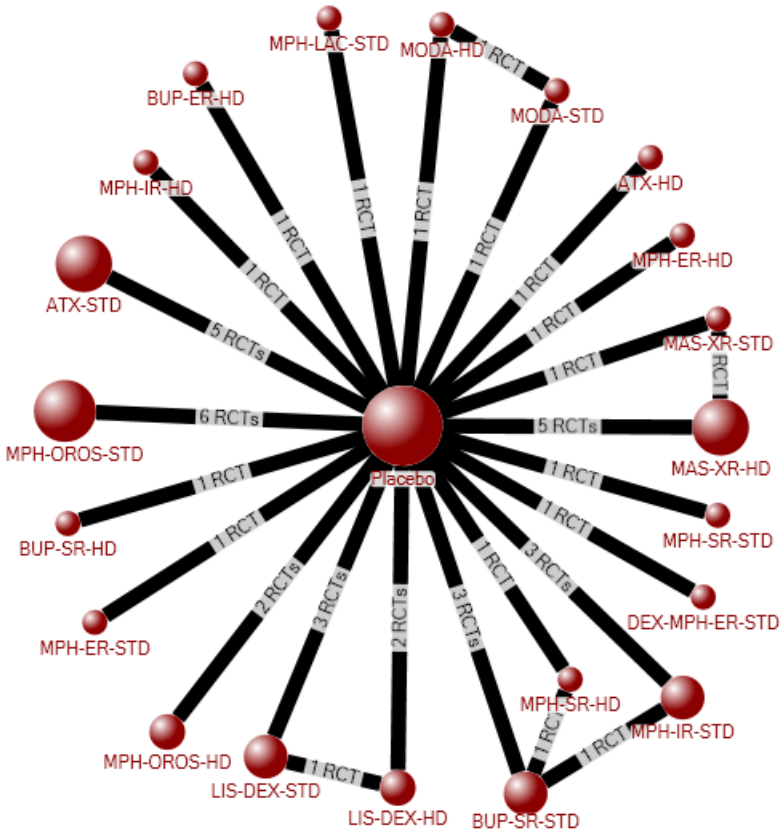
Observer-reported response

In total, 38 trials (37 publications) assessed the proportion of patients who responded to ADHD treatment using an observer-reported scale (5, 7, 8, 12, 13, 15, 18, 22-24, 26, 27, 30-34, 38, 39, 42, 43, 45-48, 50-59). One study was excluded from the analysis because only the responder rate in the placebo arm was reported (36).

Of the included studies, 7 used Conners' Adult ADHD Rating Scale (8, 13, 22, 23, 30, 33, 38), 11 used the ADHD Rating Scale (ADHD-RS) (5, 12, 24, 34, 36, 46, 52, 54, 58, 59), 3 used Adult ADHD Investigator Symptom Rating Scale (AISRS) (41, 50, 53), 11 used the Clinical Global Impressions scale (CGI; Improvement or Severity) (15, 18, 26, 27, 39, 43, 45, 47, 51, 56, 57), 3 used the Wender–Reimherr Adult Attention Deficit Disorder Scale (31, 32, 55) and 3 used a combination of two scales (CGI plus ADHD-RS or AISRS) (7, 42, 48).

The evidence network for the proportion of responders (based on observer-reported response) included 37 trials involving 6829 participants (Exhibit 15). Of these, 5 trials involved three arms and 32 trials involved two arms, providing 47comparisons.

Exhibit 15: Evidence network, proportion of responders (observer-reported response)



Compare with placebo, mixed amphetamine salt (high dose), atomoxetine (standard dose), lisdexamfetamine (standard and high dose), OROS methylphenidate (standard dose), immediate-release methylphenidate (high dose) were associated with a higher proportion of responders based on observer-reported measures (Exhibit 16).

There were few significant differences between the pharmacotherapies. Of note, high-dose mixed amphetamine salt and standard-dose lisdexamfetamine were significantly better than sustained-release methylphenidate.

Exhibit 16: Proportion of responders based on observer-reported response — odds ratio (95% credible interval) for head-to-head comparisons of ADHD treatments

	Placebo	MAS-XR-STD	MAS-XR-HD	ATX-STD	ATX-HD	BUP-SR-STD	BUP-SR-HD	BUP-ER-HD	DEX-MPH-ER-STD	LIS-DEX-STD	LIS-DEX-HD	MPH-OROS-STD	MPH-OROS-HD	MPH-ER-STD	MPH-ER-HD	MPH-IR-STD	MPH-IR-HD	MPH-LAC-STD	MPH-SR-STD	MPH-SR-HD	MODA-STD	MODA-HD
MAS-XR-STD	2.33 (0.44, 11.88)	—																				
MAS-XR-HD	**4.77 (1.90, 12.21)**	2.05 (0.40, 11.10)	—																			
ATX-STD	**3.46 (1.47, 8.85)**	1.49 (0.24, 10.49)	0.73 (0.21, 2.70)	—																		
ATX-HD	1.72 (0.25, 11.48)	0.74 (0.06, 9.03)	0.36 (0.04, 3.00)	0.49 (0.06, 3.88)	—																	
BUP-SR-STD	1.73 (0.53, 5.81)	0.74 (0.10, 5.89)	0.36 (0.08, 1.68)	0.50 (0.11, 2.17)	1.01 (0.11, 9.40)	—																
BUP-SR-HD	4.81 (0.56, 39.74)	2.08 (0.14, 30.38)	1.01 (0.10, 10.26)	1.39 (0.13, 13.64)	2.81 (0.17, 47.74)	2.76 (0.24, 31.10)	—															
BUP-ER-HD	2.38 (0.38, 14.42)	1.03 (0.09, 11.87)	0.50 (0.06, 3.72)	0.69 (0.08, 5.05)	1.38 (0.10, 19.85)	1.37 (0.15, 11.98)	0.49 (0.03, 7.86)	—														
DEX-MPH-ER-STD	2.39 (0.38, 14.18)	1.04 (0.09, 12.01)	0.50 (0.06, 3.71)	0.69 (0.08, 4.87)	1.40 (0.10, 18.56)	1.39 (0.16, 11.68)	0.50 (0.03, 7.81)	1.01 (0.08, 12.84)	—													
LIS-DEX-STD	**5.79 (2.01, 16.41)**	2.49 (0.35, 17.87)	1.22 (0.30, 4.87)	1.67 (0.40, 6.33)	3.36 (0.38, 30.12)	3.35 (0.68, 15.83)	1.20 (0.11, 12.93)	2.45 (0.30, 20.03)	2.42 (0.30, 20.07)	—												
LIS-DEX-HD	**4.67 (1.28, 16.92)**	2.01 (0.25, 16.31)	0.98 (0.20, 4.66)	1.34 (0.27, 6.21)	2.73 (0.28, 26.91)	2.69 (0.45, 15.51)	0.97 (0.08, 11.87)	1.96 (0.21, 18.30)	1.95 (0.21, 18.04)	0.81 (0.19, 3.38)	—											
MPH-OROS-STD	**3.79 (1.74, 8.81)**	1.63 (0.27, 10.81)	0.80 (0.23, 2.78)	1.10 (0.33, 3.63)	2.22 (0.29, 18.08)	2.18 (0.52, 9.67)	0.79 (0.08, 8.07)	1.60 (0.23, 12.26)	1.59 (0.23, 12.12)	0.65 (0.18, 2.56)	0.81 (0.19, 3.86)	—										
MPH-OROS-HD	2.64 (0.71, 9.70)	1.14 (0.14, 9.70)	0.55 (0.11, 2.76)	0.77 (0.15, 3.55)	1.53 (0.15, 15.40)	1.53 (0.25, 8.79)	0.55 (0.05, 6.69)	1.10 (0.12, 10.55)	1.10 (0.12, 10.61)	0.46 (0.08, 2.47)	0.56 (0.09, 3.66)	0.70 (0.15, 3.14)	—									
MPH-ER-STD	2.03 (0.35, 11.65)	0.88 (0.08, 10.03)	0.43 (0.06, 3.04)	0.59 (0.08, 3.98)	1.19 (0.09, 15.81)	1.17 (0.13, 9.56)	0.42 (0.03, 6.63)	0.85 (0.07, 10.68)	0.85 (0.07, 10.44)	0.35 (0.04, 2.70)	0.43 (0.05, 3.82)	0.54 (0.07, 3.56)	0.76 (0.09, 6.89)	—								
MPH-ER-HD	4.03 (0.62, 24.90)	1.74 (0.14, 20.45)	0.84 (0.11, 6.37)	1.16 (0.14, 8.45)	2.34 (0.17, 33.09)	2.33 (0.25, 20.47)	0.83 (0.05, 14.03)	1.68 (0.12, 23.18)	1.69 (0.13, 21.87)	0.70 (0.08, 5.79)	0.86 (0.09, 8.25)	1.06 (0.13, 7.63)	1.53 (0.15, 14.23)	1.98 (0.15, 24.78)	—							

	Placebo	MAS-XR-STD	MAS-XR-HD	ATX-STD	ATX-HD	BUP-SR-STD	BUP-SR-HD	BUP-ER-HD	DEX-MPH-ER-STD	LIS-DEX-STD	LIS-DEX-HD	MPH-OROS-STD	MPH-OROS-HD	MPH-ER-STD	MPH-ER-HD	MPH-IR-STD	MPH-IR-HD	MPH-LAC-STD	MPH-SR-STD	MPH-SR-HD	MODA-STD	MODA-HD
MPH-IR-STD	1.41 (0.43, 4.31)	0.61 (0.08, 4.55)	0.30 (0.06, 1.26)	0.41 (0.09, 1.66)	0.83 (0.09, 7.20)	0.81 (0.17, 3.67)	0.29 (0.03, 3.20)	0.59 (0.07, 4.96)	0.59 (0.07, 4.84)	0.24 (0.05, 1.12)	0.30 (0.05, 1.66)	0.37 (0.09, 1.44)	0.54 (0.09, 2.89)	0.69 (0.08, 5.48)	0.35 (0.04, 3.04)	—						
MPH-IR-HD	**7.78 (1.11, 52.11)**	3.39 (0.26, 42.68)	1.65 (0.18, 13.24)	2.26 (0.26, 17.90)	4.57 (0.30, 66.18)	4.50 (0.46, 41.99)	1.63 (0.09, 28.43)	3.29 (0.23, 45.47)	3.30 (0.24, 44.86)	1.35 (0.15, 11.64)	1.68 (0.17, 16.29)	2.06 (0.24, 15.98)	2.96 (0.28, 30.03)	3.87 (0.28, 49.75)	1.93 (0.13, 27.27)	5.56 (0.61, 53.11)	—					
MPH-LAC-STD	2.46 (0.42, 14.01)	1.06 (0.10, 11.96)	0.52 (0.07, 3.61)	0.72 (0.09, 4.78)	1.45 (0.11, 18.56)	1.42 (0.17, 11.56)	0.51 (0.03, 7.77)	1.04 (0.08, 13.20)	1.02 (0.08, 13.01)	0.42 (0.06, 3.18)	0.52 (0.06, 4.64)	0.65 (0.09, 4.33)	0.93 (0.10, 8.37)	1.23 (0.10, 14.60)	0.61 (0.05, 7.74)	1.75 (0.22, 14.33)	0.32 (0.02, 4.27)	—				
MPH-SR-STD	1.17 (0.19, 7.65)	0.51 (0.04, 6.33)	0.25 (0.03, 2.02)	0.34 (0.04, 2.65)	0.68 (0.05, 10.07)	0.68 (0.07, 6.32)	0.24 (0.02, 4.25)	0.49 (0.04, 7.07)	0.49 (0.04, 6.89)	0.20 (0.02, 1.77)	0.25 (0.03, 2.53)	0.31 (0.04, 2.30)	0.44 (0.05, 4.55)	0.58 (0.05, 7.76)	0.29 (0.02, 4.28)	0.83 (0.10, 7.69)	0.15 (0.01, 2.23)	0.48 (0.04, 6.22)	—			
MPH-SR-HD	0.57 (0.09, 3.66)	0.24 (0.02, 2.93)	**0.12 (0.01, 0.97)**	0.16 (0.02, 1.28)	0.34 (0.02, 4.76)	0.33 (0.05, 2.10)	0.12 (0.01, 2.03)	0.24 (0.02, 3.29)	0.24 (0.02, 3.26)	**0.10 (0.01, 0.85)**	0.12 (0.01, 1.22)	0.15 (0.02, 1.12)	0.21 (0.02, 2.14)	0.28 (0.02, 3.76)	0.14 (0.01, 1.96)	0.40 (0.05, 3.70)	0.07 (0.01, 1.10)	0.23 (0.02, 3.06)	0.49 (0.03, 6.65)	—		
MODA-STD	1.04 (0.17, 5.96)	0.44 (0.04, 5.05)	0.22 (0.03, 1.55)	0.30 (0.04, 2.05)	0.61 (0.05, 7.96)	0.60 (0.07, 4.96)	0.21 (0.01, 3.48)	0.43 (0.04, 5.52)	0.43 (0.03, 5.47)	0.18 (0.02, 1.40)	0.22 (0.02, 1.99)	0.27 (0.04, 1.84)	0.39 (0.04, 3.65)	0.51 (0.04, 6.17)	0.26 (0.02, 3.39)	0.73 (0.09, 6.11)	0.13 (0.01, 1.86)	0.42 (0.03, 5.26)	0.89 (0.06, 11.45)	1.83 (0.13, 23.27)	—	
MODA-HD	0.79 (0.13, 4.67)	0.34 (0.03, 3.91)	0.17 (0.02, 1.23)	0.23 (0.03, 1.59)	0.46 (0.03, 6.07)	0.45 (0.05, 3.89)	0.16 (0.01, 2.64)	0.33 (0.03, 4.15)	0.33 (0.03, 4.25)	0.14 (0.02, 1.05)	0.17 (0.02, 1.57)	0.21 (0.03, 1.42)	0.30 (0.03, 2.73)	0.39 (0.03, 4.75)	0.20 (0.02, 2.63)	0.56 (0.07, 4.78)	0.10 (0.01, 1.44)	0.32 (0.03, 3.91)	0.67 (0.05, 8.76)	1.39 (0.10, 17.91)	0.76 (0.12, 4.59)	—

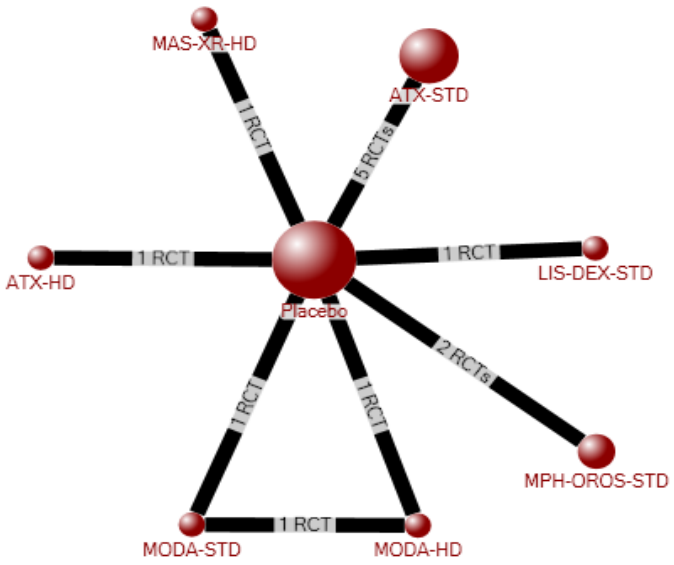
Quality of life

Thirteen studies assessed the effect of ADHD treatments on quality of life (8, 16-18, 22, 30, 33-35, 38, 39, 44, 51). Two were not included in the analysis because insufficient data were provided (22, 34). Of the included studies, six assessed quality of life using the Adult ADHD Quality of Life (AAQoL) scale (8, 16, 17, 38, 39, 44), four used the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) (18, 30, 33, 35), and one used the ADHD Impact Module Adult Version (AIM-A) (51). Because the AIM-A scale has several subscales and no summary score was reported, we choose the "Living with ADHD" subscale for analysis.

For each of the scales, a higher score indicates improved quality of life. All of the included studies involved a parallel design.

The evidence network for quality of life included a total of 11 studies involving 3394 participants (Exhibit 17). The network involved 10 two-armed studies and 1 three-arm studies, providing 13 comparisons.

Exhibit 17: Evidence network for quality of life



Compared with placebo, mixed amphetamine salt (high dose) and atomoxetine (standard dose) were both associated with significant increases in quality of life (Exhibit 18).

There were no significances differences in quality of life among the treatments.

Exhibit 18: Quality of life: standardized mean differences (95% credible interval) for head-to-head comparisons of ADHD treatments

Treatment	Placebo	MAS-XR-HD	ATX-STD	ATX-HD	LIS-DEX-STD	MPH-OROS-STD	MODA-STD	MODA-HD
MAS-XR-HD	**0.78 (0.18,1.38)**	—						
ATX-STD	**0.32 (0.10,0.65)**	-0.47 (-1.06,0.25)	—					
ATX-HD	0.52 (-0.16,1.22)	-0.26 (-1.16,0.65)	0.20 (-0.58,0.92)	—				
LIS-DEX-STD	0.53 (-0.09,1.14)	-0.26 (-1.12,0.60)	0.21 (-0.53,0.83)	0.01 (-0.91,0.92)	—			
MPH-OROS-STD	0.12 (-0.31,0.53)	-0.67 (-1.42,0.05)	-0.20 (-0.76,0.24)	-0.40 (-1.20,0.39)	-0.41 (-1.17,0.34)	—		
MODA-STD	-0.02 (-0.63,0.59)	-0.80 (-1.65,0.05)	-0.34 (-1.07,0.27)	-0.54 (-1.44,0.36)	-0.55 (-1.41,0.31)	-0.14 (-0.87,0.60)	—	
MODA-HD	-0.06 (-0.65,0.55)	-0.85 (-1.72,0.02)	-0.38 (-1.08,0.24)	-0.58 (-1.49,0.32)	-0.59 (-1.44,0.28)	-0.18 (-0.91,0.57)	-0.04 (-0.64,0.56)	—

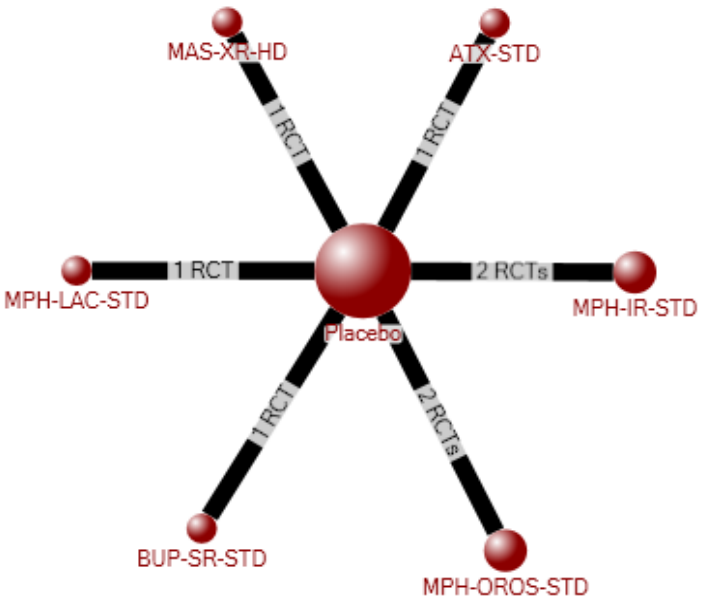
Executive function

Of the included studies, 11 assessed executive function (11, 14, 23, 24, 30, 34, 41, 45, 50, 51, 60). Of these, two were cross-over studies (11, 60). Two studies were not included in the analysis because insufficient data were reported (34, 50), and one was excluded because participants received concurrent problem-based ADHD therapy (14).

Of the studies included in the analysis, three studies assessed executive function using the Brown Attention-Deficit Disorder Scale (11, 41, 51), three used the Global Assessment of Functioning scale (23, 45, 60), and two used the Sheehan Disability Scale (24, 30). For the Sheehan Disability Scale and the Brown Attention-Deficit Disorder Scale, a lower score indicates improvement. For the Global Assessment of Function Scale, a higher score indicates improvement; the direction of data assessed using this scale was reversed before analysis, such that lower scores in Exhibit 20 indicate improvement.

The network for executive function included eight studies and a total of 2140 patients (Exhibit 19). All eight studies involved two arms, providing eight comparisons.

Exhibit 19: Evidence network for executive function



There were no significant differences in executive function between placebo and any of the included ADHD treatments (Exhibit 20).

There were no significant differences among the treatments for executive function.

Exhibit 20: Executive function: standardized mean differences (95% credible interval) for head-to-head comparisons of ADHD treatments

	Placebo	MAS-XR-HD	ATX-STD	BUP-SR-STD	MPH-OROS-STD	MPH-IR-STD	MPH-LAC-STD
MAS-XR-HD	-0.63 (-5.49, 4.26)	—					
ATX-STD	-0.41 (-5.35, 4.43)	0.23 (-6.74, 7.16)	—				
BUP-SR-STD	-0.58 (-5.46, 4.28)	0.05 (-6.82, 6.86)	-0.18 (-7.05, 6.84)	—			
MPH-OROS-STD	-1.32 (-4.86, 2.06)	-0.69 (-6.75, 5.20)	-0.91 (-6.81, 5.03)	-0.74 (-6.72, 5.07)	—		
MPH-IR-STD	0.42 (-3.03, 3.86)	1.05 (-4.96, 7.02)	0.82 (-5.18, 6.85)	1.00 (-5.00, 6.82)	1.74 (-3.06, 6.65)	—	
MPH-LAC-STD	-0.37 (-5.17, 4.53)	0.26 (-6.59, 7.17)	0.04 (-6.89, 7.00)	0.21 (-6.71, 7.08)	0.95 (-4.90, 6.92)	-0.79 (-6.67, 5.18)	—

Driving behaviour

Five studies evaluated driving behavior among participants with ADHD using an assessment scale (7, 8, 17, 20, 33) (Exhibit 21). Of these, three studies reported no significant difference in self-assessed driving behaviour following treatment with an ADHD pharmacotherapy (atomoxetine) (8, 17, 33). One study reported no self-assessed difference in driving anger following treatment with atomoxetine (20). Two studies reported improved self-reported driving following treatment (lisdexamfetamine, atomoxetine) (7, 20).

Two studies reported no change in observer-reported driving behaviour following treatment with atomoxetine (8, 20), while one study reported improved driving following treatment with atomoxetine (17). Of note, the study that reported an improvement had a much longer treatment duration (6 mo) compared to the studies that reported no difference (4 or 12 wk).

Exhibit 21: Driving behaviour among participants with ADHD following pharmacotherapy

Author, year	Scale; time of assessment	Treatment duration	Comparison	Finding
Durell 2013 (8)	Driving Behavior Survey Self-Report (DBS; self, observer)	12 wk	Placebo v. ATX (standard dose)	"After 12 weeks of treatment, there was no statistically significant difference between atomoxetine-treated and placebo-treated participants on the … DBS-Self, the DBS-Other, …"
Sobanski 2011 (33)	German Driver Coping Questionnaire (self)	12 wk	No treatment v. ATX (standard dose)	"In both groups coping strategies for driving-related stress did not change from baseline to endpoint"
Biederman 2012 (7)	Manchester Driving Behavior Questionnaire† (self)	6 wk	Placebo v. LDX (high dose)	"LDX treatment was associated with significant improvements in self-reported driving behaviors that were independent of improvement in symptoms of ADHD. These results suggest that

Author, year	Scale; time of assessment	Treatment duration	Comparison	Finding
				LDX may reduce behaviors associated with driving risks in young adults with ADHD."
Adler 2008 (17)	Driving Behavior Survey (self, observer)	6 mo	Placebo v. ATX (standard dose)	"At 6 months, both the atomoxetine and placebo groups reported better driving behaviors by self-report; however, there were no statistically significant differences between treatment groups using the self-reported total score. In the subsample where observer ratings were available, patients in the atomoxetine group (n = 156) were rated as significantly more improved in driving than those in the placebo group (n = 96)…"
Barkley 2007 (20)	Driving Anger Scale (self); Safe Driving Behaviour Rating Scale (self, observer)	4 wk cross-over	Placebo v. ATX (standard dose)	Significant beneficial effects [of atomoxetine] were evident on … self-ratings of safe driving behavior... No beneficial effects were evident, however, on ratings of others on these same parameters…" No significant differences were observed on the Driving Anger Scale (self).

Note: ATX = atomoxetine, DBQ = Driving Behavior Questionnaire, LDX = lisdexamfetamine.
*Name of scale not reported
†US version

One study assessed driving behaviour following a single dose of pharmacotherapy administered 1.5 hours before testing (63). Verster and colleagues (63) reported that "Relative to placebo, methylphenidate significantly improved subjective driving quality and mental effort when driving was significantly less. After methylphenidate, patients reported that their driving style was significantly less unpredictable, less dangerous, less foolish and less tensed." The authors also noted that participants were not less inconsiderate or irresponsible following a single dose of methylphenidate (63).

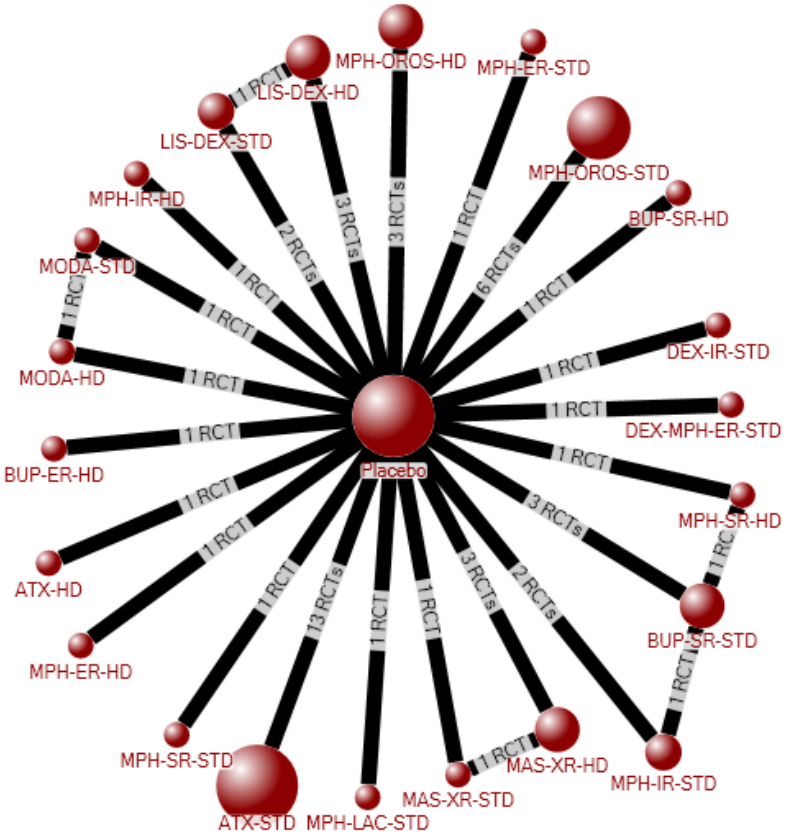
Safety

Withdrawals due to adverse events

Forty-four RCTs (42 publications) reported withdrawals due to adverse events (5-9, 12-18, 22-24, 26, 27, 29-40, 42-48, 50-52, 59, 64, 65). Two publications reported two RCTs (5, 6). Four RCTs involved a cross-over design (5, 59, 65). The duration of treatment was between three weeks and six months.

The network for withdrawals due to adverse events included 44 trials, involving 8091 participants (Exhibit 22). Of the studies, 6 involved 3 arms and 38 involved 2 arms, providing 56 comparisons.

Exhibit 22: Evidence network, withdrawals due to adverse events



Compared with placebo, mixed amphetamine salts (high and standard dose), lisdexamfetamine (high dose), OROS methylphenidate (standard and high dose), long-acting capsule methylphenidate (standard dose), and modafinil (standard and high dose) were associated with significantly higher odds of withdrawal due to adverse events (Exhibit 23).

In the head-to-head comparisons, sustained-release bupropion (standard dose) was associated with lower odds of withdrawal compared with mixed amphetamine salt (standard dose), OROS methylphenidate (standard dose). Compared with long-acting capsule methylphenidate (standard dose), both sustained-release bupropion (standard dose) and extended-release methylphenidate (standard dose) were associated with lower odds of withdrawal due to adverse events (Exhibit 23).

Owing to the large number of zero event counts in the network, reliable estimates for high-dose atomoxetine, sustained-release bupropion, extended-release bupropion, immediate-release methylphenidate, and sustained release methylphenidate could not be obtained.

Exhibit 23: Withdrawals due to adverse events* — odds ratio (95% credible interval) for head-to-head comparisons of ADHD treatments

	Placebo	MAS-XR-STD	MAS-XR-HD	ATX-STD	ATX-HD	BUP-SR-STD	BUP-SR-HD	BUP-ER-HD	DEX-MPH-ER-STD	DEX-IR-STD	LIS-DEX-STD	LIS-DEX-HD	MPH-OROS-STD	MPH-OROS-HD	MPH-ER-STD	MPH-ER-HD	MPH-IR-STD	MPH-IR-HD	MPH-LAC-STD	MPH-SR-STD	MPH-SR-HD	MODA-STD	MODA-HD
MAS-XR-STD	**4.83 (1.48, 17.10)**	—																					
MAS-XR-HD	**3.55 (1.59, 9.08)**	0.74 (0.27, 2.05)	—																				
ATX-STD	**3.09 (2.25, 4.35)**	0.64 (0.18, 2.20)	0.87 (0.33, 2.16)	—																			
ATX-HD	...	...	...	...	—																		
BUP-SR-STD	0.74 (0.19, 3.13)	**0.15 (0.02, 0.93)**	0.21 (0.04, 1.03)	0.24 (0.06, 1.06)	...	—																	
BUP-SR-HD	...	...	...	...	...	...	—																
BUP-ER-HD	...	...	...	...	...	...	...	—															
DEX-MPH-ER-STD	1.55 (0.48, 6.06)	0.32 (0.06, 1.89)	0.43 (0.10, 2.18)	0.50 (0.15, 2.05)	...	2.13 (0.32, 15.10)	...	...	—														
DEX-IR-STD	1.85 (0.26, 16.65)	0.39 (0.03, 4.46)	0.52 (0.06, 5.76)	0.60 (0.08, 5.55)	...	2.53 (0.22, 35.18)	...	...	1.15 (0.11, 14.32)	—													
LIS-DEX-STD	2.58 (0.85, 9.76)	0.54 (0.10, 3.02)	0.73 (0.16, 3.41)	0.83 (0.26, 3.30)	...	3.53 (0.55, 24.33)	...	...	1.66 (0.28, 9.87)	1.43 (0.11, 14.76)	—												
LIS-DEX-HD	**3.21 (1.01, 14.55)**	0.68 (0.12, 4.29)	0.93 (0.19, 4.90)	1.04 (0.31, 4.78)	...	4.41 (0.70, 34.78)	...	...	2.11 (0.35, 13.88)	1.86 (0.14, 20.32)	1.30 (0.47, 3.47)	—											
MPH-OROS-STD	**4.02 (2.32, 7.34)**	0.84 (0.21, 3.07)	1.15 (0.40, 3.13)	1.31 (0.69, 2.48)	...	**5.48 (1.18, 23.87)**	...	...	2.62 (0.59, 9.46)	2.16 (0.23, 17.46)	1.55 (0.37, 5.52)	1.25 (0.26, 4.46)	—										
MPH-OROS-HD	**2.76 (1.15, 6.72)**	0.56 (0.13, 2.42)	0.76 (0.23, 2.46)	0.89 (0.34, 2.25)	...	3.71 (0.71, 18.10)	...	...	1.74 (0.34, 7.82)	1.45 (0.15, 12.93)	1.04 (0.22, 4.27)	0.83 (0.16, 3.51)	0.68 (0.24, 1.90)	—									
MPH-ER-STD	1.59 (0.67, 4.13)	0.33 (0.07, 1.53)	0.44 (0.13, 1.58)	0.51 (0.20, 1.41)	...	2.16 (0.39, 11.36)	...	...	1.02 (0.20, 4.65)	0.86 (0.08, 8.01)	0.61 (0.13, 2.68)	0.48 (0.09, 2.21)	0.39 (0.14, 1.19)	0.58 (0.17, 2.10)	—								
MPH-ER-HD	3.33 (0.31, 74.26)	0.69 (0.05, 19.98)	0.95 (0.07, 24.49)	1.09 (0.10, 24.03)	...	4.77 (0.29, 120.30)	...	...	2.16 (0.13, 60.74)	1.81 (0.08, 67.20)	1.28 (0.08, 38.75)	1.00 (0.05, 31.20)	0.83 (0.07, 18.75)	1.24 (0.09, 28.64)	2.12 (0.15, 49.66)	—							
MPH-IR-STD	3.28 (0.56, 22.72)	0.67 (0.08, 6.51)	0.93 (0.13, 7.42)	1.07 (0.17, 7.39)	...	4.44 (0.57, 35.97)	...	...	2.03 (0.22, 21.39)	1.81 (0.10, 33.36)	1.28 (0.13, 12.74)	1.02 (0.08, 10.46)	0.82 (0.13, 6.04)	1.18 (0.17, 10.71)	2.03 (0.29, 17.06)	0.97 (0.03, 20.77)	—						
MPH-IR-HD	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	—					
MPH-LAC-STD	**7.40 (2.34, 34.16)**	1.56 (0.30, 9.23)	2.12 (0.50, 10.54)	2.39 (0.72, 11.31)	...	**10.15 (1.58, 76.14)**	...	...	4.83 (0.77, 32.26)	4.21 (0.32, 47.05)	2.94 (0.48, 17.90)	2.28 (0.33, 14.52)	1.85 (0.50, 8.90)	2.73 (0.65, 14.98)	**4.63 (1.07, 26.26)**	2.25 (0.09, 41.53)	2.36 (0.23, 20.91)	...	—				
MPH-SR-STD	0.86 (0.03, 37.90)	0.18 (0.01, 9.06)	0.25 (0.01, 11.29)	0.28 (0.01, 11.92)	...	1.20 (0.03, 72.44)	...	...	0.55 (0.02, 27.74)	0.48 (0.01, 29.36)	0.34 (0.01, 14.20)	0.27 (0.01, 11.29)	0.21 (0.01, 10.57)	0.31 (0.01, 15.37)	0.53 (0.02, 27.01)	0.25 (0.00, 20.53)	0.27 (0.01, 15.39)	...	0.11 (0.00, 4.78)	—			
MPH-SR-HD	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	—		

	Placebo	MAS-XR-STD	MAS-XR-HD	ATX-STD	ATX-HD	BUP-SR-STD	BUP-SR-HD	BUP-ER-HD	DEX-MPH-ER-STD	DEX-IR-STD	LIS-DEX-STD	LIS-DEX-HD	MPH-OROS-STD	MPH-OROS-HD	MPH-ER-STD	MPH-ER-HD	MPH-IR-STD	MPH-IR-HD	MPH-LAC-STD	MPH-SR-STD	MPH-SR-HD	MODA-STD	MODA-HD
MODA-STD	3.97 (1.43, 12.38)	0.82 (0.17, 4.20)	1.11 (0.29, 4.45)	1.29 (0.43, 4.16)	…	5.43 (0.92, 31.21)	…	…	2.52 (0.44, 13.71)	2.14 (0.18, 21.29)	1.54 (0.29, 7.82)	1.19 (0.20, 6.28)	0.99 (0.29, 3.52)	1.45 (0.38, 6.03)	2.51 (0.62, 10.27)	1.19 (0.04, 18.18)	1.23 (0.14, 10.06)	…	0.54 (0.08, 2.65)	4.77 (0.09, 155.00)	…	—	
MODA-HD	4.18 (1.49, 13.09)	0.86 (0.17, 4.35)	1.16 (0.29, 4.57)	1.36 (0.45, 4.38)	…	5.73 (0.98, 33.32)	…	…	2.67 (0.47, 14.17)	2.24 (0.20, 22.80)	1.61 (0.30, 8.12)	1.25 (0.21, 6.63)	1.03 (0.31, 3.75)	1.52 (0.39, 6.55)	2.62 (0.63, 10.67)	1.24 (0.05, 19.14)	1.28 (0.14, 10.39)	…	0.57 (0.08, 2.80)	5.11 (0.09, 160.80)	…	1.05 (0.48, 2.26)	—

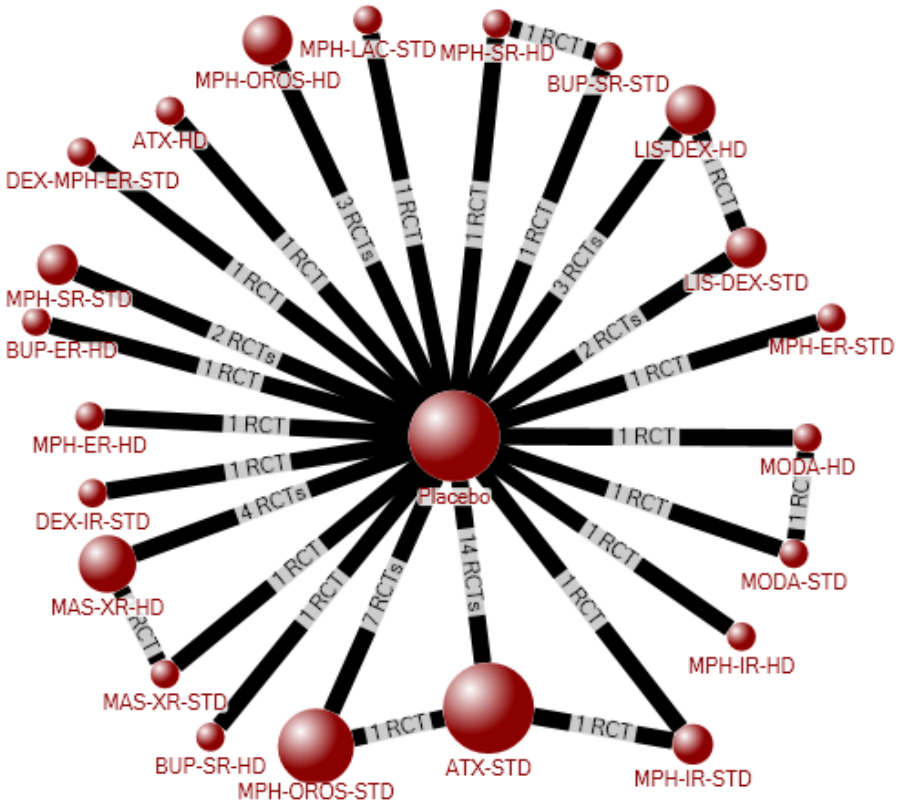
Note: HD = high dose, STD = standard dose. *"…" indicates that the estimates were not robust for a given treatment comparison.

All-cause treatment discontinuation

Forty-six RCTs (44 publications) were included for the outcome all-cause treatment discontinuation (5-9, 12, 13, 15-18, 22-24, 27, 29-44, 46-52, 58, 59, 64-66). Five trials involved a cross-over design (5, 58, 59, 65). The duration of treatment was between three weeks and six months.

The network for treatment discontinuation included 46 trials, involving 8968 participants (Exhibit 24). Of the included studies, 41 involved two arms and 5 involved three arms, providing 56 comparisons.

Exhibit 24: Evidence network, all-cause treatment discontinuation



Compared with placebo, atomoxetine (standard and high dose), OROS methylphenidate (standard dose), and extended-release methylphenidate (standard dose) were associated with significantly increased odds of treatment discontinuation. Compared with placebo, mixed amphetamine salt (high dose) was associated with significantly lower odds of treatment discontinuation (Exhibit 25).

In the head-to-head comparisons, mixed amphetamine salt (high dose) and extended-release methylphenidate (standard dose) were associated with significantly lower odds of treatment discontinuations relative to most other treatments (Exhibit 25).

Exhibit 25: All-cause treatment discontinuation* — odds ratio (95% credible interval) for head-to-head comparisons of ADHD treatments

	Placebo	MAS-XR-STD	MAS-XR-HD	ATX-STD	ATX-HD	BUP-SR-STD	BUP-SR-HD	BUP-ER-HD	DEX-IR-STD	DEX-MPH-ER-STD	LIS-DEX-STD	LIS-DEX-HD	MPH-OROS-STD	MPH-OROS-HD	MPH-ER-STD	MPH-ER-HD	MPH-IR-STD	MPH-IR-HD	MPH-LAC-STD	MPH-SR-STD	MPH-SR-HD	MODA-STD	MODA-HD
MAS-XR-STD	0.70 (0.33, 1.41)	—																					
MAS-XR-HD	**0.55 (0.35, 0.85)**	0.78 (0.38, 1.57)	—																				
ATX-STD	**1.37 (1.14, 1.61)**	1.95 (0.94, 4.18)	**2.50 (1.55, 4.05)**	—																			
ATX-HD	**3.83 (1.11, 13.05)**	**5.45 (1.35, 22.94)**	**7.04 (1.86, 25.54)**	2.80 (0.80, 9.76)	—																		
BUP-SR-STD	1.29 (0.40, 4.10)	1.85 (0.48, 7.60)	2.38 (0.69, 8.34)	0.94 (0.29, 3.02)	0.33 (0.07, 1.93)	—																	
BUP-SR-HD	...	...	...	...	...	...	—																
BUP-ER-HD	1.30 (0.53, 3.09)	1.85 (0.57, 5.90)	2.37 (0.86, 6.41)	0.95 (0.38, 2.29)	0.34 (0.08, 1.73)	1.00 (0.25, 4.23)	...	—															
DEX-IR-STD	2.16 (0.65, 8.20)	3.04 (0.78, 14.64)	**3.89 (1.13, 16.71)**	1.58 (0.47, 6.08)	0.58 (0.10, 3.49)	1.73 (0.29, 9.25)	...	1.68 (0.38, 8.32)	—														
DEX-MPH-ER-STD	0.83 (0.36, 2.02)	1.18 (0.40, 3.72)	1.53 (0.58, 4.01)	0.61 (0.26, 1.51)	**0.22 (0.05, 0.96)**	0.65 (0.15, 2.75)	...	0.64 (0.19, 2.33)	0.39 (0.08, 1.68)	—													
LIS-DEX-STD	0.75 (0.44, 1.30)	1.07 (0.44, 2.68)	1.36 (0.70, 2.75)	**0.55 (0.31, 0.99)**	**0.20 (0.05, 0.73)**	0.58 (0.16, 2.16)	...	0.57 (0.20, 1.68)	0.34 (0.08, 1.33)	0.90 (0.32, 2.56)	—												
LIS-DEX-HD	1.13 (0.60, 2.18)	1.60 (0.64, 4.32)	2.07 (0.97, 4.54)	0.83 (0.43, 1.64)	0.29 (0.08, 1.19)	0.88 (0.23, 3.49)	...	0.88 (0.29, 2.66)	0.52 (0.12, 2.02)	1.36 (0.46, 4.10)	1.51 (0.85, 2.79)	—											
MPH-OROS-STD	**1.44 (1.05, 1.96)**	2.06 (0.96, 4.51)	**2.64 (1.53, 4.52)**	1.06 (0.74, 1.50)	0.37 (0.11, 1.38)	1.12 (0.33, 3.69)	...	1.11 (0.43, 2.88)	0.67 (0.17, 2.33)	1.74 (0.68, 4.20)	**1.94 (1.01, 3.61)**	1.27 (0.61, 2.60)	—										
MPH-OROS-HD	1.39 (0.83, 2.27)	1.97 (0.82, 4.86)	**2.53 (1.28, 5.02)**	1.01 (0.59, 1.72)	0.36 (0.10, 1.40)	1.08 (0.31, 3.81)	...	1.06 (0.39, 3.03)	0.64 (0.15, 2.37)	1.67 (0.59, 4.50)	1.86 (0.87, 3.96)	1.23 (0.53, 2.69)	0.96 (0.52, 1.72)	—									
MPH-ER-STD	**0.40 (0.22, 0.72)**	0.57 (0.23, 1.48)	0.73 (0.36, 1.55)	**0.29 (0.16, 0.55)**	**0.10 (0.03, 0.40)**	0.31 (0.09, 1.16)	...	**0.31 (0.11, 0.89)**	**0.19 (0.04, 0.71)**	0.48 (0.17, 1.33)	0.54 (0.24, 1.20)	**0.36 (0.15, 0.83)**	**0.28 (0.14, 0.54)**	**0.29 (0.14, 0.64)**	—								
MPH-ER-HD	1.27 (0.24, 8.00)	1.81 (0.30, 12.79)	2.35 (0.41, 14.79)	0.93 (0.18, 5.87)	0.34 (0.04, 3.38)	0.99 (0.14, 9.16)	...	1.00 (0.16, 7.61)	0.60 (0.08, 5.11)	1.55 (0.24, 10.90)	1.72 (0.30, 10.91)	1.13 (0.19, 7.60)	0.89 (0.17, 5.54)	0.91 (0.16, 6.52)	3.16 (0.57, 20.48)	—							
MPH-IR-STD	2.37 (0.79, 7.32)	3.38 (0.89, 13.65)	**4.35 (1.31, 14.54)**	1.73 (0.58, 5.35)	0.61 (0.12, 3.07)	1.82 (0.39, 9.48)	...	1.82 (0.46, 6.94)	1.08 (0.18, 5.96)	2.83 (0.69, 11.03)	3.18 (0.92, 10.40)	2.12 (0.58, 7.00)	1.65 (0.53, 5.06)	1.67 (0.53, 5.91)	**5.83 (1.69, 20.70)**	1.81 (0.20, 14.09)	—					
MPH-IR-HD	1.07 (0.45, 2.73)	1.53 (0.49, 4.97)	1.96 (0.72, 5.53)	0.78 (0.32, 2.03)	0.28 (0.07, 1.24)	0.85 (0.19, 3.59)	...	0.83 (0.24, 2.92)	0.50 (0.10, 2.37)	1.30 (0.37, 4.45)	1.44 (0.51, 4.14)	0.95 (0.31, 2.81)	0.74 (0.29, 2.03)	0.77 (0.28, 2.29)	2.66 (0.92, 8.10)	0.86 (0.11, 5.20)	0.46 (0.11, 1.89)	—				
MPH-LAC-STD	1.44 (0.81, 2.62)	2.04 (0.83, 5.41)	**2.63 (1.30, 5.60)**	1.05 (0.58, 1.98)	0.38 (0.10, 1.48)	1.12 (0.32, 4.10)	...	1.10 (0.39, 3.30)	0.66 (0.16, 2.55)	1.74 (0.60, 4.82)	1.93 (0.88, 4.21)	1.28 (0.54, 2.97)	1.00 (0.52, 1.98)	1.04 (0.49, 2.29)	**3.60 (1.60, 8.26)**	1.14 (0.17, 6.44)	0.61 (0.17, 2.13)	1.34 (0.43, 3.95)	—			
MPH-SR-STD	0.94 (0.41, 2.06)	1.34 (0.44, 3.89)	1.71 (0.69, 4.21)	0.68 (0.30, 1.53)	0.24 (0.06, 1.15)	0.71 (0.18, 2.91)	...	0.72 (0.22, 2.38)	0.43 (0.09, 1.84)	1.12 (0.33, 3.62)	1.26 (0.45, 3.34)	0.84 (0.28, 2.17)	0.65 (0.27, 1.50)	0.68 (0.27, 1.71)	2.33 (0.84, 6.12)	0.73 (0.10, 4.27)	0.40 (0.09, 1.54)	0.87 (0.25, 2.88)	0.65 (0.23, 1.70)	—		
MPH-SR-HD	1.60 (0.48,	2.30 (0.58,	2.93 (0.84,	1.18 (0.35,	0.41 (0.09,	1.24 (0.42,	...	1.24 (0.27,	0.73 (0.13,	1.91 (0.43,	2.17 (0.56,	1.42 (0.36,	1.11 (0.33,	1.16 (0.33,	**4.01 (1.07,**	1.26 (0.14,	0.69 (0.13,	1.51 (0.33,	1.12 (0.30,	1.73 (0.41,	—		

	Placebo	MAS-XR-STD	MAS-XR-HD	ATX-STD	ATX-HD	BUP-SR-STD	BUP-SR-HD	BUP-ER-HD	DEX-IR-STD	DEX-MPH-ER-STD	LIS-DEX-STD	LIS-DEX-HD	MPH-OROS-STD	MPH-OROS-HD	MPH-ER-STD	MPH-ER-HD	MPH-IR-STD	MPH-IR-HD	MPH-LAC-STD	MPH-SR-STD	MPH-SR-HD	MODA-STD	MODA-HD
	5.26)	9.81)	10.57)	3.89)	2.38)	3.96)		5.35)	4.40)	8.51)	8.26)	5.66)	3.90)	4.22)	**14.63)**	10.30)	3.37)	6.60)	4.20)	7.32)			
MODA-STD	1.84 (0.94, 3.75)	**2.63 (1.00, 7.33)**	**3.36 (1.52, 7.83)**	1.34 (0.68, 2.83)	0.48 (0.13, 1.88)	1.43 (0.37, 5.59)	…	1.41 (0.46, 4.55)	0.85 (0.19, 3.59)	2.19 (0.73, 6.67)	**2.46 (1.03, 6.02)**	1.62 (0.64, 4.16)	1.29 (0.60, 2.76)	1.34 (0.57, 3.13)	**4.61 (1.88, 11.49)**	1.42 (0.21, 8.98)	0.79 (0.21, 2.88)	1.73 (0.54, 5.37)	1.29 (0.50, 3.13)	1.98 (0.69, 6.17)	1.14 (0.29, 4.66)	—	
MODA-HD	1.99 (0.99, 4.02)	**2.86 (1.05, 7.75)**	**3.64 (1.60, 8.39)**	1.45 (0.71, 3.05)	0.52 (0.14, 2.01)	1.55 (0.41, 6.03)	…	1.54 (0.47, 4.78)	0.93 (0.20, 3.78)	2.39 (0.77, 7.39)	**2.67 (1.11, 6.57)**	1.77 (0.68, 4.54)	1.39 (0.63, 3.00)	1.44 (0.62, 3.44)	**4.94 (2.01, 12.46)**	1.54 (0.21, 9.52)	0.86 (0.22, 3.09)	1.87 (0.56, 5.84)	1.39 (0.53, 3.41)	2.12 (0.75, 6.56)	1.23 (0.30, 4.91)	1.08 (0.60, 1.97)	—

*"…" indicates that the estimates were not robust for a given treatment comparison.

Serious adverse events

Twenty-eight RCTs (27 publications) were included for the outcome serious adverse events. Five trials involved a cross-over design (5, 53, 56, 58). The duration of treatment was between 1 and 24 weeks.

In total, 28 trials were included in the analysis of serious adverse events, involving 5493 participants. Of these, 15 trials reported that zero serious adverse events occurred during the treatment period. Owing to the large number of zero event counts, network meta-analysis resulted in effect estimates and credible intervals that were not robust.

We thus analyzed each treatment versus placebo in a pair-wise meta-analysis (Exhibit 26). Compared with placebo, none of the treatments were associated with increased odds of serious adverse events. Overall, there was no significant difference in serious adverse events between any ADHD treatment and placebo (OR 1.41, 95% CI 0.75-2.65).

Exhibit 26: Serious adverse events — Meta-analysis of ADHD pharmacotherapies versus placebo

Treatment	No. of studies (no. contributing date to MA)	Odds ratio (95% confidence interval)
MAS-XR-STD	1 (0)	Not estimable
MAS-XR-HD	4 (1)	2.98 (0.12, 73.75)
ATX-STD	5 (2)	1.56 (0.40, 6.02)
ATX-HD	1 (1)	0.32 (0.01, 8.00)
BUP-SR-HD	1 (0)	Not estimable
BUP-ER-HD	1 (0)	Not estimable
DEX-MPH-ER-STD	1 (1)	1.64 (0.08, 34.62)
LIS-DEX-STD	3 (1)	0.80 (0.03, 17.78)
LIS-DEX-HD	3 (1)	1.54 (0.06, 38.44)
MPH-OROS-STD	7 (5)	2.41 (0.78, 7.41)
MPH-OROS-HD	2 (0)	Not estimable
MPH-ER-HD	1 (1)	0.93 (0.06, 15.09)
MPH-LAC-STD	1 (1)	0.77 (0.20, 3.02)
Overall	31*	1.41 (0.75, 2.65)

Note: MA = meta-analysis.
*31 comparisons v. placebo from 28 studies (25 two-arm studies, 3 three-arm studies)

Cardiovascular events

Myocardial infarction
No studies reported myocardial infarction during the study period.

Stroke
One study reported stroke during the study period (51). One patient in the mixed amphetamine salt group was admitted to hospital with a possible transient ischemic attack. The final diagnosis was Tourette syndrome with vocal tic; however, the investigator felt that transient ischemic attack could not be ruled out. No events were reported in the placebo group.

Cardiovascular death
Thirty-one publications were included for the outcome cardiovascular death (5, 7, 12, 13, 18, 22-24, 30, 31, 35, 36, 38-44, 46-48, 50-53, 56, 58, 59, 64). One publication (5) reported data for two cross-over trials. Six trials involved a cross-over design (5, 53, 56, 58, 59). We inferred that zero cardiovascular deaths had occurred during the first period of the 6 cross-over studies in the intervention or control groups based on statements such as “No deaths or serious adverse events were reported in this study” (56). Among the studies that involved a parallel design, we inferred that zero cardiovascular deaths had occurred in 13 studies based on the reporting of zero serious adverse events (7, 12, 13, 23, 30, 31, 34, 38, 40, 46, 47, 50-52). The remaining studies reported that no deaths had occurred.

In total, zero cardiovascular deaths were reported during the treatment period in all studies.

Hospitalization
Two studies reported hospitalizations during the study period (34, 51).

Spencer and colleagues (34) reported serious adverse events requiring hospitalization. Two patients in the extended-release methylphenidate group experienced a serious adverse event that required hospitalization (ulcerative colitis/hypovolemic shock, fever/loss of consciousness); neither patient was withdrawn from the study.

Spencer and colleagues (51) reported that one patient in the mixed amphetamine salt group was admitted to hospital with a possible transient ischemic attack. The patient was discharged the following day, with a diagnosis of Tourette syndrome with vocal tic. The investigator disagreed with this diagnosis and felt that transient ischemic attack could not be ruled out.

Emergency room visits
None of the included studies reported emergency room visits during the study period.

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