H. Sharafi et al,
Prescription psychostimulants for the treatment of amphetamine-type stimulant use disorder: A systematic review and meta-analysis of randomized placebo-controlled trials,
Addiction (journal), 2023

Main points:

"Background and Aims:
There is currently no standard of care for pharmacological treatment of amphetamine-type stimulant (ATS) use disorder (ATSUD). This systematic review with meta-analysis (PROSPERO CRD42022354492) aimed to pool results from randomized placebo-controlled trials (RCTs) to evaluate efficacy and safety of **Prescription Psychostimulants** for **Amphetamine-Type-Stimulant Use Disorder**. . . .
"Ten RCTs (n = 561 participants) were included in the meta-analysis. . . .

"Conclusions: Among individuals with amphetamine-type stimulant use disorder, treatment with **Prescription Psychostimulants** may decrease **Amphetamine-Type-Stimulant** use and craving. While effect size is limited, it may increase with a higher dosage of medications."

"Ten RCTs [30–39] were included, enrolling 561 participants. The characteristics of the studies are summarized in Table 1. Overall, 143 participants were included from three studies testing maximum total daily doses of 60 mg [30, 37] and 110 mg [39] of dextroamphetamine for 2–12 weeks, and 418 participants were included from seven studies testing maximum total daily doses of 54 mg [33, 34, 36, 38], 60 mg [35], 72 mg [31] and 180 mg [32] of methylphenidate for 10–24 weeks. In the included studies, participants' mean age range was 31.9–41.5 years, and 52.9–81.8% were males (Table 1)."

TABLE 1 Characteristics of the included studies.

Study identification, ref.	Study dates	Study location(s)	No. of participants	Age (mean), years	Male sex, %	ADHD, %	Trial medication and maximum dose/day	Randomized treatment duration	Additional interventions[a]
Galloway 2011 [30]	Sep 2006–Aug 2011	USA	60	37.3	56.7	15	Dextroamphetamine, 60 mg	8 weeks	Motivational enhancement therapy
Konstenius 2010 [31]	Feb 2006-June 2007	Sweden	24	37.4	79.2	100	Methylphenidate, 72 mg	12 weeks	Individual skills training programme
Konstenius 2014 [32]	Apr 2007–Sep 2011	Sweden	54	41.5	NA	100	Methylphenidate, 180 mg	24 weeks	Cognitive-behavioural therapy
Ling 2014 [33]	Oct 2010–Jul 2014	USA	110	39.1	81.8	29.1	Methylphenidate, 54 mg	10 weeks	Motivational incentives and cognitive-behavioural therapy
Longo 2010 [39]	Jul 2004–Dec 2007[b]	Australia	49	31.9	61.2	NA	Dextroamphetamine, 110 mg	12[c] weeks	Standard psychotherapeutic care[d]
Miles 2013 [34]	Mar 2004–Dec 2009	Finland/New Zealand	79 (78)[e]	36.5	62.8	NA	Methylphenidate, 54 mg	22 weeks	Engagement with addiction service
Noroozi 2020 [35]	Sep 2013–Jun 2016	Iran	62	32.1	71.0	NA	Methylphenidate, 60 mg	12 weeks	Modified Matrix treatment[f]
Rezaei 2015 [36]	Jun 2013–Aug 2014	Iran	56	35.2	73.2	NA	Methylphenidate, 54 mg	10 weeks	NI
Thompson 2021 [37]	NA	USA	34 (29)[g]	37.2	52.9	NA	Dextroamphetamine, 60 mg	3 (2)[h] weeks	Residential substance use treatment
Tiihonen 2007 [38]	Mar 2004–NA	NA	34	37.6	70.6	NA	Methylphenidate, 54 mg	20 weeks	Unstructured psychosocial treatment[i]

Abbreviations: ATS = amphetamine-type stimulant; NA = not available; NI = not indicated; ref = reference.
[a]Both trial arms received psychological treatment, otherwise indicated.
[b]Only recruitment date available.
[c]There was an additional 4 weeks of follow-up with gradual dose reduction. The results from this follow-up phase were excluded from the meta-analysis.
[d]An introductory appointment followed by a four-session cognitive–behavioural model developed for amphetamine users.
[e]Seventy-nine were randomized, and after allocation and follow-up one was removed because of not being eligible for the study.
[f]Modified Matrix treatment for stimulant treatment is a structured treatment consisting of 24 sessions using motivational enhancement, psychoeducational and cognitive, behavioural treatment techniques.
[g]Thirty-four included in the trial started with 1 week of stabilization on dextroamphetamine (in all trial participants) and 29 were retained in the 2 weeks of randomized treatment.
[h]One week of stabilization on dextroamphetamine (in all trial participants) followed by 2 weeks of randomized treatment.
[i]Unstructured psychosocial treatment with elements of cognitive therapy and psychoeducation, counseling, and support.

All of the following text consists of quotations from the article.

DISCUSSION
In this meta-analysis, we studied the effect of **Prescription Psychostimulants** on **Amphetamine-Type-Stimulant Use Disorder** by combining the available data in placebo-controlled trials. To the best of our knowledge, this is the first study that exclusively focuses upon the treatment of this population using **Prescription Psychostimulants**.

This is important because, despite the growing prevalence of **Amphetamine-Type-Stimulant Use Disorder**, especially in North America, most of the treatment recommendations are based upon pharmacotherapy trials in cocaine use disorder [40, 41].

Moreover, previous meta-analyses on the treatment of **Amphetamine-Type-Stimulant Use Disorder** using **Prescription Psychostimulants** included bupropion and modafinil as psychostimulants [10, 42]. While these medications share some effects with typical **Prescription Psychostimulants**, their mechanism of action and neurochemical effects are different from those of typical **Prescription Psychostimulants**, resulting in an additional source of heterogeneity in the meta-analysis [43].

Notwithstanding some limitations and the relative scarcity of studies, our meta-analysis showed that **Prescription Psychostimulant** treatment,

specifically at higher doses, may have some benefits in decreasing the number of positive UAs during treatment and warrant further investigation.

The main analysis results also suggest that PP treatment may be effective in reducing **Amphetamine-Type-Stimulant** craving, but no statistically significant differences were found between PP treatment and placebo regarding other tested outcomes.

In the subsequent subgroup analyses, we observed significant effect modification by the type of medication, intervention dose, duration of treatment and ADHD status on various reported outcomes, which may guide future research efforts.

Our results showed a very high level of heterogeneity in the included study results, with pooled effects in favour of **Prescription Psychostimulant** treatment compared to placebo in terms of reduced **Amphetamine-Type-Stimulant** use as evaluated by UA, after excluding studies with a high risk of bias.

Our meta-analysis, therefore, showed a relatively small risk reduction, with an average of approximately 11% in the proportions of **Amphetamine-Type-Stimulant**-positive UA among those treated with **Prescription Psychostimulants** compared to placebo. However, the clinical significance of such reduction may need to be assessed while considering other factors such as the burden and consequences of **Amphetamine-Type-Stimulant** use and the absence of other approved medications for **Amphetamine-Type-Stimulant Use Disorder**.

Interestingly, the subgroup analysis showed that study participants had more benefits from high-dose PP, with a moderate risk reduction (approximately 29%) of **Amphetamine-Type-Stimulant** use as evaluated by UA. Such differences in the treatment effect were not present when using lower PP doses. While these findings should be interpreted with caution, as only one study [32] was available for high-dose PP (> 162 mg methylphenidate), they may support a dose–response relationship where higher stimulant doses may be associated with better treatment outcomes.

Methylphenidate and dextroamphetamine are used for the management of ADHD at maximum daily doses of 108 and 50 mg for adults, respectively [29]. Our results suggest that people with longterm high-dose exposure to **Amphetamine-Type-Stimulant** may require doses higher than the clinically recommended doses of **Prescription Psychostimulants** to generate an agonist effect that would potentially lead to a reduction in **Amphetamine-Type-Stimulant** use. This is in line with the conclusion of a previous meta-analysis by Tardelli et al. [40], which showed a beneficial effect of higher doses of **Prescription Psychostimulants** (including

modafinil) for the treatment of stimulant use disorder (i.e. **Amphetamine-Type-Stimulant Use Disorder** and cocaine use disorder).

While promising, the clinical significance of such effect and the optimal dose titration (i.e. rate and maximum dose) and dispensing regimens (i.e. supervised versus take-home dosing) still need to be ascertained in future studies [40]. In our subgroup analysis, treatment with methylphenidate (but not with dextroamphetamine) reduced **Amphetamine-Type-Stimulant** use. However, there was only one study [30] which had a high risk of bias that tested dextroamphetamine; therefore this difference in the results of the subgroup analysis should be considered with caution.

The PP treatment was not significantly different from placebo regarding the self-reported number of days of **Amphetamine-Type-Stimulant** use. This absence of association may be explained in part by the recall and social desirability biases and missing data that are commonly observed for patient-reported outcomes. While our meta-analysis results for self-reported **Amphetamine-Type-Stimulant** use are not in agreement with those by UA, a recent meta-analysis showed high agreement between self-report and biological testing for measurement of substance use [44].

Although there was no statistically significant interaction between PP treatment and retention outcome, higher doses and longer duration of treatment were significantly associated with higher retention rates in our subgroup analyses. Trial participants benefited from higher PP doses (> 162 mg methylphenidate and > 75 mg dextroamphetamine) with a higher probability (about 131% increase) of retention in treatment.

Our subgroup analysis also showed a moderate effect size, with an 83% increase in the probability of retention in treatment only in those with a treatment duration of 20 weeks and more. This result is in line with a previous meta-analysis by Bhatt et al. [42], which showed better retention in treatment in those with a treatment duration of more than 12 weeks. This may be explained in part by the possible beneficial cumulative effect of a longer duration of pharmacological intervention using the maximum therapeutic tolerated dose.

Our results also showed a significant effect favouring treatment

with **Prescription Psychostimulants** for end-point craving. The corresponding significant beneficial effect presented a small to moderate effect size of reduction in craving of approximately 0.29 SMD. However, early-stage craving did not significantly differ between the PP treatment and placebo arms. These differential effects between early-stage and end-point craving scores may result from the inclusion of a study [37] with craving scores reported at a very early time-point (week 2), when it is possible that the full effect of treatment may not have been reached. Given the short delay of the action of psychostimulants, the interaction of time with craving measurements and the precise role of biological and psychosocial determinants of the individuals receiving active treatment in later stages of intervention warrants further investigations.

Our meta-analysis included dropout following AEs, reported by most included studies as an important proxy of treatment safety. The pooled results showed that PP treatment was not significantly associated with higher dropout following AEs, reflecting the relative safety of PP treatment. However, the methods for collecting AEs varied among studies, and it remains difficult to verify whether some AEs were under-reported. This underlies the importance of standardized reporting of AEs in future trials.

Our meta-analysis has been strengthened using the GRADE and RoB 2 tools for bias and evidence assessment, which may help to enhance the applicability of the results. However, the present met**a-a**nalysis has its limitations.

First, some of the included trials had relatively small sample sizes, some of which included specific samples (e.g. with ADHD), adding to the heterogeneity caused by various treatment doses and durations. This heterogeneity was also evident in the results observed in some subgroup analyses (e.g. by dose and duration of treatment).

Secondly, some of the studies excluded individuals with complicated and severe mental and physical disorders, as well as other concomitant substance use disorders, limiting the generalizability of our results to the wider populations.

Thirdly, many important outcomes, such as treatment compliance, addiction severity and anxiety symptom severity, were excluded due to a lack of sufficient data

Received: 29 May 2023 | Accepted: 10 August 2023

DOI: 10.1111/add.16347

REVIEW

ADDICTION SSA

Prescription psychostimulants for the treatment of amphetamine-type stimulant use disorder: A systematic review and meta-analysis of randomized placebo-controlled trials

Heidar Sharafi[1,2] | Hamzah Bakouni[1,2] | Christina McAnulty[1,2] | Sarah Drouin[1] | Stephanie Coronado-Montoya[1,2] | Arash Bahremand[1,2] | Paxton Bach[3,4] | Nadine Ezard[5,6,7] | Bernard Le Foll[8,9,10,11,12,13] | Christian G. Schütz[14] | Krista J. Siefried[5,6,7] | Vitor S. Tardelli[15] | Daniela Ziegler[16] | Didier Jutras-Aswad[1,2]

Correspondence
Didier Jutras-Aswad, CHUM Research Centre, 900 St-Denis, Viger Tower, Room R05.746, Montreal, Quebec H2X 1P1, Canada.
Email: didier.jutras-aswad@umontreal.ca

Funding information
Canadian Institutes of Health Research (CIHR), Grant/Award Number: REN-181675; Université de Montréal and Centre de recherche du Centre hospitalier de l'Université de Montréal (CRCHUM)

Abstract

Background and Aims: There is currently no standard of care for pharmacological treatment of amphetamine-type stimulant (ATS) use disorder (ATSUD). This systematic review with meta-analysis (PROSPERO CRD42022354492) aimed to pool results from randomized placebo-controlled trials (RCTs) to evaluate efficacy and safety of prescription psychostimulants (PPs) for ATSUD.

Methods: Major indexing sources and trial registries were searched to include records published before 29 August 2022. Eligible studies were RCTs evaluating efficacy and safety of PPs for ATSUD. Risk of bias (RoB) was assessed using the Cochrane RoB 2 tool. Risk ratio (RR) and risk difference were calculated for random-effect meta-analysis of dichotomous variables. Mean difference and standardized mean difference (SMD) were calculated for random-effect meta-analysis of continuous variables.

Results: Ten RCTs (n = 561 participants) were included in the meta-analysis. Trials studied methylphenidate (n = 7), with daily doses of 54–180 mg, and dextroamphetamine (n = 3), with daily doses of 60–110 mg, for 2–24 weeks. PPs significantly decreased endpoint craving [SMD −0.29; 95% confidence interval (CI) = −0.55, −0.03], while such a decrease did not reach statistical significance for ATS use, as evaluated by urine analysis (UA) (RR = 0.93; 95% CI = 0.85–1.01). No effect was observed for self-reported ATS use, retention in treatment, dropout following adverse events, early-stage craving, withdrawal and depressive symptoms. In a sensitivity analysis, treatment was associated with a significant reduction in UA positive for ATS (RR = 0.89; 95% CI = 0.79–0.99) after removing studies with a high risk of bias. In subgroup analyses, methylphenidate and high doses of PPs were negatively associated with ATS use by UA, while higher doses of

For affiliations refer to page 222

PPs and treatment duration (≥ 20 weeks) were positively associated with longer retention.

Conclusions: Among individuals with amphetamine-type stimulant use disorder, treatment with prescription psychostimulants may decrease ATS use and craving. While effect size is limited, it may increase with a higher dosage of medications.

KEYWORDS
Amphetamine, amphetamine-related disorders, dependence, methamphetamine, pharmacotherapy, psychostimulant, stimulant use disorder, treatment

INTRODUCTION

In the last decades, an ever-growing prevalence of people who use amphetamine-type stimulants (ATS) has been reported in various regions of the world [1–3]. According to the World Drug Report 2022, 34 million people used amphetamines in the year 2020 alone [2]. Amphetamine-type stimulant use disorder (ATSUD) has turned into a major health issue globally, with an estimated age-standardized prevalence of 64.7 cases per 100 000 people in 2016 [1].

Despite the alarming prevalence and severe socio-medical consequences, there is still no established pharmacotherapy recommendation for the treatment of ATSUD. Clinicians rely mainly upon psychosocial-based interventions, which are found to offer short-term efficacy and are accompanied by difficulties in implementation [4–6]. As current modalities have limited efficacy, recent studies indicate that more than 60% of the population receiving treatment for ATSUD relapse within the first 12 months with a small percentage in remission after 5 years [7].

Multiple groups have tried to establish a pharmacological treatment framework to improve the standard of care for ATSUD based on the available evidence [4, 5, 8]. In most cases, however, the varying quality of primary studies, the heterogeneity of reported results and insufficient sample size have prevented authors from conducting a meta-analysis or issuing any official recommendations [5, 9]. Nonetheless, in most of these studies, agonist therapy using prescription psychostimulants (PPs) possessed the strongest evidence of efficacy and has been discussed as the most likely class to have the potential for the treatment of ATSUD [5, 9, 10]. It has been argued that agonist therapy using PPs could potentially be a viable strategy in this population and reduce harms associated with ATSUD, with limited adverse events [10]. Of note, agonist therapy for opioid use disorder is a standard of care that has led to significant harm and mortality reduction. Such a widespread strategy for the treatment of ATSUD has not been established due to limited evidence [5, 9, 11, 12] and should be properly assessed; given many differences between stimulant and opioid use disorders, for example, there are often periods of stimulant high-dose binge use followed by cessation and withdrawal, while opioid users frequently try to maintain a desired level of opioid effect which is targeted by agonist therapy [13].

In this meta-analysis we conducted a rigorous review of the literature, focusing upon randomized placebo-controlled trials (RCT) comparing the therapeutic effect of PPs (i.e. methylphenidate, dextroamphetamine and lisdexamphetamine) with placebo in the treatment of ATSUD. Our objective was to pool the published and unpublished evidence available on the efficacy and safety of PPs in the treatment of ATSUD to quantify the probability of the benefits of such treatment. We aimed to address the knowledge gap regarding the efficacy of PPs in the outcomes of the treatment of ATSUD using meta-analysis followed by subgroup analyses focusing upon key potential effect-modifying factors.

METHODS

Study conceptualization and registration

This study concept was conceived in March 2022, followed by a preliminary search to define the target outcomes and to confirm the availability of studies for each candidate outcome. The study protocol was submitted to the international Prospective Register Of Systematic Reviews (PROSPERO) in August 2022 (Supporting information, Appendix S1). The original PROSPERO submission and updates are accessible on PROSPERO with identification CRD42022354492. This study was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 (Supporting information, Appendices S2 and S3) [14].

Search methods

The search strategies were designed by an experienced librarian (D.Z.). The complete search strategy for this systematic review is reported in Supporting information, Appendix S4. The literature search was run on 29 August 2022. The strategies were reviewed by another senior information specialist before execution using the PRESS checklist [15]. The following electronic databases were searched: MEDLINE (Ovid), CINAHL (EBSCOhost), PsycINFO (Ovid), EBM Reviews (Ovid), EMBASE (Ovid), PubMed, Web of Science and Scopus, with keywords covering three domains of 'amphetamine-type stimulant use disorder', 'psychostimulant' and 'clinical trial'. We searched several clinical trial registries (ClinicalTrials.gov, International Clinical Trials Registry Platform and International Standard Randomized Controlled Trial Number Registry, Health Canada Clinical Trials

Database and UK Clinical Trials Gateway). In addition, we completed the search with Google Scholar. Reference lists of the included articles and relevant systematic reviews were manually screened to identify additional studies.

Study screening and selection

Any published/unpublished RCTs of PPs for the treatment of ATSUD were included. The inclusion criteria were (a) clinical trials with a randomized and placebo-controlled design; (b) interventional studies with PPs including methylphenidate, dextroamphetamine, lisdexamphetamine and other amphetamine salts; and (c) studies that included individuals with ATSUD diagnosed using the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) or DSM-5 criteria for stimulant use disorder [16, 17]. The exclusion criteria were (a) other clinical trial designs, such as open-label trials, human laboratory studies and animal studies; and (b) trials with fewer than 10 participants in each of the placebo/PP arms, which may also help to reduce any potential biases in estimates associated with very small studies [18].

The search results were imported to Covidence® after the removal of duplicates in EndNote by the librarian (D.Z.) using the method described by Bramer *et al.* [19]. Two reviewers (H.S. and H.B.) screened the titles/abstracts of search entries independently. Any conflicts in the title/abstract screening were resolved through mutual consensus. The same reviewers contributed independently to the eligibility assessment of studies after retrieval of the study full-text/report. Any conflicts in the study eligibility assessment were resolved through mutual discussions and, in the cases of disagreement, a consensus was achieved through consultation with the study supervisor (D.J.A.).

Outcomes

Following the initial search and selection of candidate studies a set of 11 target outcomes were considered for inclusion in the meta-analysis, including ATS abstinence, self-reported ATS use, retention in treatment, treatment compliance, ATS craving, withdrawal symptom severity, addiction severity, psychiatric symptom severity, overall functioning, executive functioning (cognition) and treatment safety. Some of these outcomes were adopted from a previous meta-analysis [10]. In-depth assessment of the studies after the final search resulted in the transformation of the included outcomes in the meta-analysis with the following definitions:

- Amphetamine-type stimulant use assessed by urine analysis (UA) was defined as qualitative or quantitative testing of urine for amphetamine and/or methamphetamine through the randomized treatment phase of the study. The collective results of UA were pooled as the total proportion of positive UA in intervention arms.
- Self-reported ATS use was defined as a declaration of ATS use by trial participants during part or all of the randomized treatment phase, and evaluated using tools such as time-line follow-back (TLFB) [20] and Addiction Severity Index (ASI, drug subscale) [21]. The mean ± standard deviation (SD) of self-reported days of use was collected and pooled in the meta-analysis.
- Retention in treatment was defined as the proportion of individuals retained in the trial who received treatment or placebo until the end of the randomized treatment phase.
- Dropout following adverse events (AEs) was defined as the proportion of individuals for whom treatment was discontinued following observation of AEs.
- Amphetamine-type stimulant craving was measured using scales such as the Visual Analog Scale (VAS). For ATS craving, two different time-point measurements were included for data pooling: (a) early-stage ATS craving was defined as the mean ± SD of measurement, taking the latest time-point available between weeks 2 to 4; (b) end-point ATS craving was defined as the mean ± SD of craving measured at the last treatment visit in the trials of longer than 4 weeks.
- Withdrawal symptom severity was evaluated using scales such as Amphetamine Withdrawal Questionnaire (AWQ) [22] and Methamphetamine Selective Severity Assessment (MSSA) [23] for the end-point (last treatment visit) measurement (mean ± SD).
- Depressive symptom severity was evaluated using scales such as the Beck Depression Inventory (BDI and BDI-II) [24] for the end-point (last treatment visit) measurement (mean ± SD).

Data extraction

Two reviewers (C.M. and S.C.M.) independently extracted the data from the included studies using a structured Excel sheet (Supporting information, Appendix S5) and conflicts were resolved through mutual discussion [the authors confirm that the data supporting the findings of this meta-analysis are available within Appendix S5 (structured data extraction Excel sheet)]. The remaining conflicts were resolved through discussion with the primary author of the study (H.S.). The on-line WebPlotDigitizer version 4.6 tool was used for the extraction of values from study graphs [25]. Authors of the included studies were contacted for the required results when measurement values were not available or retrievable (Supporting information, Appendix S6).

Risk of bias, publication bias and evidence certainty assessment

For the assessment of risk of bias, we used criteria from the Risk of Bias assessment tool (RoB 2) of the Cochrane Collaboration [26]. The RoB 2 Excel tool was used independently by two researchers (H.S. and S.D.). Conflicts were resolved through mutual discussion. Publication bias was assessed for outcomes found in eight or more

studies using visual evaluation of funnel plots for the asymmetrical distribution of study results. Two reviewers (H.S. and H.B.) independently assessed the certainty of the evidence by employing the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) [27]. Disagreements in the evidence certainty assessment were resolved through mutual discussion.

Data analysis

Outcomes with two or more poolable results were kept for meta-analysis. The risk ratio (RR) and the 95% confidence interval (CI) were calculated for the meta-analysis of outcomes with dichotomous variables. The risk difference (RD) and the 95% CI were calculated when the event was rare in dichotomous outcomes. The mean difference (MD) and the 95% CI were calculated for outcomes with continuous data measured by a single measurement tool and scale. The standardized mean difference (SMD) and 95% CI were calculated for outcomes with continuous data measured by different measurement tools and/or scales. For weighting and calculation of between-study variations, random-effect meta-analysis was employed using the inverse variance method. The main analysis included all available and poolable studies. All statistical analyses and corresponding graphs (forest and funnel plots) were executed using Review Manager version 5.4 [28]. A *P*-value ≤ 0.05 was considered statistically significant.

Subgroup analyses were selected based on potential effect-modifying factors and were applied to all study outcomes using the following variables: trial medication (methylphenidate versus dextroamphetamine), maximum daily dose of medication (low versus high dose), active treatment duration (< 20 versus ≥ 20 weeks) and attention-deficit/hyperactivity disorder (ADHD) in the study population (all-ADHD population versus mixed population/not described). For subgroup analysis by the maximum daily dose of medication, a low-level cut-off of 72 mg/day for methylphenidate and 40 mg/day for dextroamphetamine was used following the maximum total daily doses recommended for the management of ADHD according to medication monographs. As an additional exploratory subgroup analysis by PP dose, a high-level cut-off of 162 mg/day for methylphenidate and 75 mg/day for dextroamphetamine was included. This high-level cut-off covers substantially (> 50%) higher than the maximum total daily dose recommended by the Canadian ADHD Resource Alliance (CADDRA) [29]. For sensitivity analyses, studies with a high risk of bias were removed from the meta-analysis.

RESULTS

Search and study selection results

The PRISMA flow diagram is presented in Figure 1. Briefly, we identified 15 962 records via the indexed electronic search method. Among

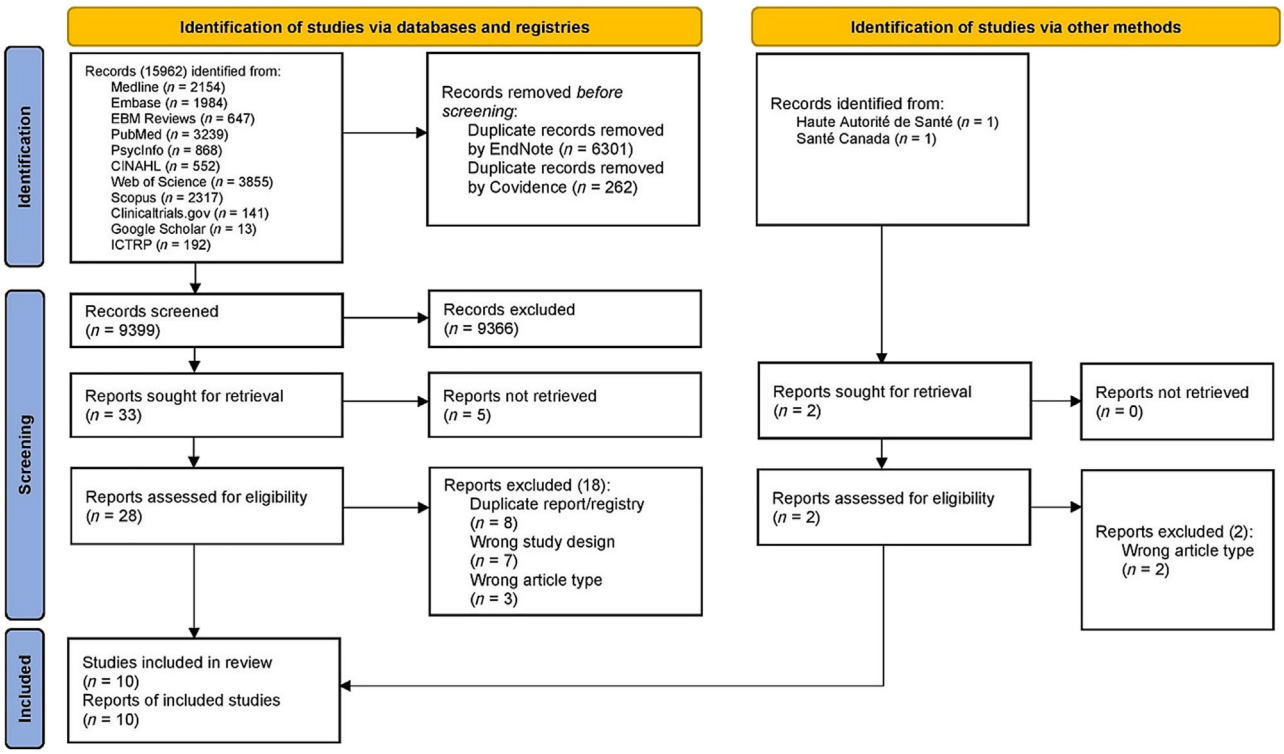

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram for results of search, screening and eligibility assessment of studies.

the 33 records selected for full-text screening, 28 full-text articles were available and retrieved for the full-text-based assessment of eligibility. Finally, 18 full-text articles and two additional records from other search methods (grey literature and governmental resources) were excluded in this stage, leaving 10 studies for inclusion in the systematic review and meta-analysis. The detailed reasons for the exclusion of these 20 records are described in Supporting information, Appendix S7.

Characteristics of included studies

Ten RCTs [30–39] were included, enrolling 561 participants. The characteristics of the studies are summarized in Table 1. Overall, 143 participants were included from three studies testing maximum total daily doses of 60 mg [30, 37] and 110 mg [39] of dextroamphetamine for 2–12 weeks, and 418 participants were included from seven studies testing maximum total daily doses of 54 mg [33, 34, 36, 38], 60 mg [35], 72 mg [31] and 180 mg [32] of methylphenidate for 10–24 weeks. In the included studies, participants' mean age range was 31.9–41.5 years, and 52.9–81.8% were males (Table 1).

Selected outcomes

The included outcomes and their analysis approaches are summarized in Table 2. The following outcomes had two or more available and poolable results: ATS use by UA, self-reported ATS use, retention in treatment, dropout following AEs, early-stage craving, end-point craving, withdrawal symptom severity and depressive symptom severity. Treatment compliance, addiction severity, anxiety symptom severity and executive function were removed from the meta-analysis, as fewer than two poolable results were available for these outcomes (Table 2).

Intervention effects

Amphetamine-type stimulant use by assessment of urine analysis

Eight studies reported the number of positive UA for a total of 12 208 reported UA. Prescription psychostimulants' association with ATS use by UA (RR = 0.93; 95% CI = 0.85–1.01) did not reach statistical significance (P = 0.07). The heterogeneity was very high (I^2 = 94%) in between-study results (Table 3 and Supporting information, Figure S1a). In the risk of bias assessment, four of the eight studies had a high risk of bias (Table 3 and Supporting information, Figure S1b). In the evaluation of publication bias using a funnel plot, there was no visible sign of publication bias (Supporting information, Figure S1c). The evidence obtained through the main analysis was rated as low quality in the GRADE assessment (Supporting information, Table S1). In the sensitivity analysis, after removing the studies with a high risk of bias, the ATS use by UA effect estimate became statistically significant (RR = 0.89; 95% CI = 0.79–0.99) (Supporting information, Table S2). In the subgroup analysis, the effect estimate was significantly different by the type of medication favouring methylphenidate (Table 4). Furthermore, ATS use by UA was significantly lower using high-dose PPs (methylphenidate > 162 mg) compared to low-dose (methylphenidate ≤ 162 mg and dextroamphetamine ≤ 75 mg) (Table 4).

Self-reported amphetamine-type stimulant use

The results of self-reported ATS use were available for five studies that included a total of 227 participants. The pooled effect estimate (SMD = −0.11; 95% CI: = −0.37, 0.15) was statistically non-significant with a low heterogeneity (I^2 = 0%) in inter-study results (Table 3 and Supporting information, Figure S2a). For this outcome, three of the five studies had a high risk of bias (Table 3 and Supporting information, Figure S2b). The evidence for this outcome was rated as low quality in the GRADE assessment (Supporting information, Table S1). After removing the three studies with a high risk of bias in the sensitivity analysis, the results did not change significantly (Supporting information, Table S2). Furthermore, the subgroup analyses did not show any statistically significant results (Table 4).

Retention in treatment

All included studies had available results for retention in treatment for 561 participants. The pooled effect estimate (RR = 1.11; 95% CI = 0.93, 1.33) was statistically non-significant, with a low heterogeneity (I^2 = 25%) in inter-study results (Table 3 and Supporting information, Figure S3a). For this outcome, no study was rated with a high risk of bias assessment (Table 3 and Supporting information, Figure S3b). The funnel plot showed a moderate asymmetry (interpreted as a sign of publication bias) in the distribution of studies' results (Supporting information, Figure S3c). The evidence of the main analysis was rated as medium quality in the GRADE assessment (Supporting information, Table S1). In the subgroup analysis, retention in treatment was significantly higher using high-dose PPs (methylphenidate > 162 mg and dextroamphetamine > 75 mg) compared to low-dose PPs (methylphenidate ≤ 162 mg and dextroamphetamine ≤ 75 mg) (Table 4). There was also a statistically significant difference in retention by the duration of treatment favouring ≥ 20 weeks (Table 4).

Dropout following adverse events

All studies reported the number of participants who dropped out following an AE during treatment, and included a total of 556 participants. The pooled effect estimate (RD = −0.01; 95% CI = −0.03, 0.01)

TABLE 1 Characteristics of the included studies.

Study identification, ref.	Study dates	Study location(s)	No. of participants	Age (mean), years	Male sex, %	ADHD, %	Trial medication and maximum dose/day	Randomized treatment duration	Additional interventions[a]
Galloway 2011 [30]	Sep 2006–Aug 2011	USA	60	37.3	56.7	15	Dextroamphetamine, 60 mg	8 weeks	Motivational enhancement therapy
Konstenius 2010 [31]	Feb 2006-June 2007	Sweden	24	37.4	79.2	100	Methylphenidate, 72 mg	12 weeks	Individual skills training programme
Konstenius 2014 [32]	Apr 2007–Sep 2011	Sweden	54	41.5	NA	100	Methylphenidate, 180 mg	24 weeks	Cognitive-behavioural therapy
Ling 2014 [33]	Oct 2010–Jul 2014	USA	110	39.1	81.8	29.1	Methylphenidate, 54 mg	10 weeks	Motivational incentives and cognitive-behavioural therapy
Longo 2010 [39]	Jul 2004–Dec 2007[b]	Australia	49	31.9	61.2	NA	Dextroamphetamine, 110 mg	12[c] weeks	Standard psychotherapeutic care[d]
Miles 2013 [34]	Mar 2004–Dec 2009	Finland/New Zealand	79 (78)[e]	36.5	62.8	NA	Methylphenidate, 54 mg	22 weeks	Engagement with addiction service
Noroozi 2020 [35]	Sep 2013–Jun 2016	Iran	62	32.1	71.0	NA	Methylphenidate, 60 mg	12 weeks	Modified Matrix treatment[f]
Rezaei 2015 [36]	Jun 2013–Aug 2014	Iran	56	35.2	73.2	NA	Methylphenidate, 54 mg	10 weeks	NI
Thompson 2021 [37]	NA	USA	34 (29)[g]	37.2	52.9	NA	Dextroamphetamine, 60 mg	3 (2)[h] weeks	Residential substance use treatment
Tiihonen 2007 [38]	Mar 2004–NA	NA	34	37.6	70.6	NA	Methylphenidate, 54 mg	20 weeks	Unstructured psychosocial treatment[i]

Abbreviations: ATS = amphetamine-type stimulant; NA = not available; NI = not indicated; ref = reference.

[a]Both trial arms received psychological treatment, otherwise indicated.

[b]Only recruitment date available.

[c]There was an additional 4 weeks of follow-up with gradual dose reduction. The results from this follow-up phase were excluded from the meta-analysis.

[d]An introductory appointment followed by a four-session cognitive–behavioural model developed for amphetamine users.

[e]Seventy-nine were randomized, and after allocation and follow-up one was removed because of not being eligible for the study.

[f]Modified Matrix treatment for stimulant treatment is a structured treatment consisting of 24 sessions using motivational enhancement, psychoeducational and cognitive, behavioural treatment techniques.

[g]Thirty-four included in the trial started with 1 week of stabilization on dextroamphetamine (in all trial participants) and 29 were retained in the 2 weeks of randomized treatment.

[h]One week of stabilization on dextroamphetamine (in all trial participants) followed by 2 weeks of randomized treatment.

[i]Unstructured psychosocial treatment with elements of cognitive therapy and psychoeducation, counseling, and support.

TABLE 2 Overview of outcomes assessed in the meta-analysis by the included studies and their analysis approach.[a]

Study	Intervention	Outcomes											
		ATS use by UA	Self-reported ATS use	Retention in Tx	Dropout following AEs	Tx Compliance	Early-stage ATS craving	End-point ATS craving	Withdrawal symptom severity	Addiction Severity	Depressive symptom severity	Anxiety symptom severity	Executive function
Galloway 2011	d-AMP	ITT[b], WTP	ITT[b], WTP	ITT, WTP	ITT, WTP		ITT[b,c], W4	ITT[b,c], EOT	ITT[b,c], EOT				
Konstenius 2010	MPH	ITT[d], WTP	ITT[b], WTP	ITT, WTP	ITT, WTP		ITT[b,c], W4	ITT[b,c], EOT			ITT[d], C-LOCF		
Konstenius 2014	MPH	ITT[d], WTP		ITT, WTP	ITT, WTP								
Ling 2014	MPH	ITT[d], WTP	ACA, LMT	ITT, WTP	ITT, WTP		ACA, W4	ACA, EOT					
Longo 2010	d-AMP		ITT[d], WTP	ITT, WTP	ITT, WTP				ACA, EOT				
Miles 2013	MPH	ITT[d], WTP		ITT, WTP	ITT, WTP								
Noroozi 2020	MPH	ITT[b], WTP	ACA, LMT	ITT, WTP	ITT, WTP		ACA, W4	ACA, EOT	ACA, EOT		ACA, EOT		
Rezaei 2015	MPH	ITT[d], WTP		ITT, WTP	ITT, WTP			ITT[d], EOT			ITT[d], EOT		
Thompson 2021	d-AMP			ITT, WTP	ITT, WTP		ITT[d], W2		ITT[d], EOT				
Tiihonen 2007	MPH	ITT[d], WTP		ITT, WTP	ITT, WTP								

The outcomes included in the meta-analysis.
The outcomes and their results were removed from the meta-analysis following the lack of poolable results in the articles and technical limitations for pooling the results.
The available results of the included outcomes from the articles.
The available results of the included outcomes from the authors of the included studies or other meta-analyses.
The unavailable results of the included outcomes after correspondence with the authors.
The results technically couldn't be pooled with the results of the other studies.

Abbreviations: ACA = available case analysis; AEs = adverse events; ATS = amphetamine-type stimulant; C-LOCF = change from baseline to last observation carried forward; d-AMP = dextroamphetamine; EOT = end of treatment; ITT = intention-to-treat; LMT = last month of treatment; MPH = methylphenidate; Tx = treatment; UA = urine analysis; W = week; WTP = whole treatment phase.

[a]The information included for each study outcome is the analysis approach and duration or time-point of measurement.

[b]ITT analysis without clear evidence of imputation of missing data.

[c]The extracted results from a graph which were expected to be mean ± standard deviation (SD); however, the authors did not mention which central tendency (mean/median) and dispersion [SD/standard error of the mean (SEM)/interquartile range (IQR)] were used for the presentation of the results.

[d]ITT analysis with the imputation of missing data.

TABLE 3 Main results of the meta-analysis for included outcomes.[a]

Outcome	No. of studies	Total no. of participants/ samples	Heterogeneity (I^2), %	Effect estimate (95% CI)	*P*-value for overall effect	Risk of bias results (overall), *n*	Publication bias[b]	Evidence certainty (GRADE)
ATS use by urine analysis		Urine samples		Risk ratio				
	8	12 208	94	0.93 (0.85, 1.01)	0.07	Low risk, 2 some concerns, 2 high risk, 4	Undetected	⨁⨁◯◯ Low
Self-reported ATS use		Participants		Standardized mean difference				
	5	227	0	−0.11 (−0.37, 0.15)	0.41	Low risk, 2 some concerns, 0 high risk, 3	Not evaluated	⨁⨁◯◯ Low
Retention in treatment		Participants		Risk ratio				
	10	561	25	1.11 (0.93, 1.33)	0.24	Low risk, 5 some concerns, 5 high risk, 0	Moderate asymmetry	⨁⨁⨁◯ Medium
Dropout following AEs		Participants		Risk difference				
	10	556	0	−0.01 (−0.03, 0.01)	0.50	Low risk, 5 some concerns, 5 high risk, 0	Minor asymmetry	⨁⨁⨁◯ Medium
Early-stage ATS craving		Participants		Standardized mean difference				
	5	231	90	−0.78 (−1.70, 0.15)	0.10	Low risk, 1 some concerns, 1 high risk, 3	Not evaluated	⨁◯◯◯ Very low
End-point ATS craving		Participants		Standardized mean difference				
	5	234	0	**−0.29 (−0.55, −0.03)**	**0.03**	Low risk, 1 some concerns, 0 high risk, 4	Not evaluated	⨁⨁⨁◯ Medium
Withdrawal symptom severity		Participants		Standardized mean difference				
	4	138	76	−0.57 (−1.32, 0.18)	0.14	Low risk, 0 some concerns, 1 high risk, 3	Not evaluated	⨁◯◯◯ Very low
Depressive symptom severity		Participants		Mean difference				
	3	112	62	−1.31 (−3.40, 0.77)	0.22	Low risk, 0 some concerns, 0 high risk, 3	Not evaluated	⨁◯◯◯ Very low

Abbreviations: AEs = adverse events; ATS = amphetamine-type stimulant; *n* = number; CI = confidence interval; GRADE = Grading of Recommendations, Assessment, Development and Evaluation.

[a]The statistically significant ($P < 0.05$) results are shown in bold type.

[b]Visual evaluation of funnel plot for the asymmetrical distribution of studies interpreted as publication bias.

TABLE 4 Subgroup analysis of the effect estimates by medication, maximum dose, duration of treatment and attention-deficit/hyperactivity disorder.[a]

Number of studies/effect estimates		ATS use by UA		Self-reported ATS use		Retention in treatment		Dropout following AEs	
		n	RR (95% CI)	*n*	SMD (95% CI)	*n*	RR (95% CI)	*n*	RD (95% CI)
Medication	Methylphenidate	7	**0.91 (0.83, 1.00)***	3	−0.15 (−0.52, 0.21)	7	1.10 (0.85, 1.42)	7	−0.01 (−0.03, 0.02)
	Dextroamphetamine	1	**1.04 (0.96, 1.11)**	2	−0.06 (−0.44, 0.31)	3	1.20 (0.84, 1.69)	3	−0.01 (−0.06, 0.04)
Maximum daily dose with low-level cut-off[b]	Low dose	6	0.97 (0.93, 1.01)	3	−0.15 (−0.52, 0.21)	6	1.04 (0.83, 1.29)	6	−0.00 (−0.03, 0.02)
	High dose	2	0.86 (0.60, 1.24)	2	−0.06 (−0.44, 0.31)	4	1.34 (0.89, 2.02)	4	−0.02 (−0.07, 0.02)
Maximum daily dose with high-level cut-off[c]	Low dose	7	**0.98 (0.94, 1.02)**	4	−0.10 (−0.39, 0.20)	8	**1.04 (0.90, 1.20)**	8	−0.00 (−0.03, 0.02)
	High dose	1	**0.71 (0.68, 0.76)***	1	−0.17 (−0.73, 0.40)	2	**2.31 (1.24, 4.30)***	2	−0.08 (−0.16, 0.01)
Duration of treatment	< 20 weeks	5	0.97 (0.86, 1.08)	5	−0.11 (−0.37, 0.15)	7	**1.04 (0.89, 1.21)**	7	−0.00 (−0.03, 0.02)
	≥ 20 weeks	3	0.88 (0.78, 1.00)	0	–	3	**1.83 (1.11, 3.02)***	3	−0.03 (−0.08, 0.02)
ADHD in study population	All ADHD population	2	0.93 (0.55, 1.59)	1	0.07 (−0.73, 0.87)	2	1.31 (0.32, 5.38)	2	−0.05 (−0.14, 0.05)
	Mixed population/not described	6	0.97 (0.94, 1.00)	4	−0.13 (−0.41, 0.14)	8	1.10 (0.95, 1.27)	8	−0.01 (−0.03, 0.02)

Number of studies/effect estimates		Early-stage craving		End-point craving		Withdrawal symptom severity		Depressive symptom severity	
		n	SMD (95% CI)	*n*	SMD (95% CI)	*n*	SMD (95% CI)	*n*	MD (95% CI)
Medication	Methylphenidate	3	−0.24 (−0.88, 0.40)	4	−0.26 (−0.56, 0.04)	1	−0.11 (−0.81, 0.60)	3	−1.31 (−3.40, 0.77)
	Dextroamphetamine	2	−1.51 (−3.04, 0.02)	1	−0.38 (−0.89, 0.14)	3	−0.72 (−1.64, 0.19)	0	-
Maximum daily dose with low-level cut-off[b]	Low dose	3	−0.24 (−0.88, 0.40)	4	−0.26 (−0.56, 0.04)	1	−0.11 (−0.81, 0.60)	3	−1.31 (−3.40, 0.77)
	High dose	2	−1.51 (−3.04, 0.02)	1	−0.38 (−0.89, 0.14)	3	−0.72 (−1.64, 0.19)	0	–
Maximum daily dose with high-level cut-off[c]	Low dose	5	−0.78 (−1.70, 0.15)	5	−0.29 (−0.55, −0.03)*	3	−0.62 (−1.60, 0.36)	3	−1.31 (−3.40, 0.77)
	High dose	0	–	0	–	1	−0.36 (−1.23, 0.50)	0	–
Duration of treatment	< 20 weeks	–	NA	5	−0.29 (−0.55, −0.03)*	4	−0.57 (−1.32, 0.18)	3	−1.31 (−3.40, 0.77)
	≥ 20 weeks	–	NA	0	–	0	–	0	–
ADHD in study population	All ADHD population	1	−1.12 (−1.99, −0.25)*	1	−0.23 (−1.03, 0.57)	0	–	1	**−7.30 (−13.80, −0.80)***
	Mixed population/not described	4	−0.70 (−1.80, 0.40)	4	−0.30 (−0.57, −0.02)*	4	−0.57 (−1.32, 0.18)	2	**−0.71 (−1.99, 0.56)**

Abbreviations: AEs = adverse events; ATS = amphetamine-type stimulant; CI = confidence interval; MD = mean difference; NA = not applicable; PT = psychological treatment; RD = risk difference; RR = relative risk; SMD = standardized mean difference; UA = urine analysis.

*The individual effect estimate is statistically significant ($P < 0.05$).

[a]The statistically significant subgroup differences are shown in bold type.

[b]For methylphenidate, low dose is ≤ 72 mg and high dose is > 72 mg. For dextroamphetamine, low dose is ≤ 40 mg and high dose is > 40 mg.

[c]For methylphenidate, low dose is ≤ 162 mg and high dose is > 162 mg. For dextroamphetamine, low dose is ≤ 75 mg and high dose is > 75 mg.

was statistically non-significant, with a low heterogeneity (I^2 = 0%) in inter-study results (Table 3 and Supporting information, Figure S4a). For this outcome, no study had a high risk of bias (Table 3 and Supporting information, Figure S4b). In the evaluation of publication bias, the funnel plot showed a minor asymmetry (interpreted as a sign of publication bias) in the distribution of studies' results (Supporting information, Figure S4c). The evidence from the main analysis was rated as medium quality in the GRADE assessment (Supporting information, Table S1). In the subgroup analysis, there was no significant difference between subgroups for all evaluated parameters (Table 4).

Investigating serious AEs (SAEs), eight studies [30–33, 35–38] contained the information necessary to extract the number of SAEs episodes. In these studies, no episode of SAEs was observed in the PP arm while one case of suicidal ideation was observed in the placebo arm. Due to the rare numbers of events, the SAEs were not subjected to data pooling in a meta-analysis.

Amphetamine-type stimulant craving

Five studies, which included 231 participants, had available results for early-stage craving. The pooled effect estimate (SMD = −0.78; 95% CI = −1.70, 0.15) was statistically non-significant with a very high heterogeneity (I^2 = 90%) in between-study results (Table 3 and Supporting information, Figure S5a). Three of the five included studies had a high risk of bias (Table 3 and Supporting information, Figure S5c). The evidence from the main analysis was rated as very low quality in the GRADE assessment (Supporting information, Table S1). The sensitivity analysis showed no significant change in the meta-analysis results (Supporting information, Table S2). In the subgroup analysis, no parameter significantly changed the results of early-stage craving (Table 4).

Five studies, including 234 participants, had available results for end-point craving. The pooled effect estimate (SMD = −0.29; 95% CI = −0.55, −0.03) favoured the PP arm, showing lower end-point craving scores than the placebo arm, with a low heterogeneity (I^2 = 0%) in inter-study results (Table 3 and Supporting information, Figure S5b). Four of five studies had a high risk of bias (Table 3 and Supporting information, Figure S5c). In the GRADE assessment, the evidence from the main analysis was rated as medium quality (Supporting information, Table S1). The subgroup analysis showed no significant difference between the subgroups in terms of end-point craving (Table 4).

Withdrawal symptom severity

Four studies, including 138 participants, had results for withdrawal symptom severity. The pooled effect estimate (SMD = −0.57; 95% CI = −1.32, 0.18) was statistically non-significant, with a high heterogeneity (I^2 = 76%) in between-study results (Table 3 and Supporting information, Figure S6a). For this outcome, three of four included studies had a high risk of bias (Table 3 and Supporting information, Figure S6b). The evidence obtained from the main analysis was rated as very low quality in the GRADE assessment (Supporting information, Table S1). In the subgroup analysis, none of the evaluated parameters was associated with a statistically significant change in the results of withdrawal symptom severity (Table 4).

Depressive symptom severity

Results for depressive symptom severity were available from three studies in this meta-analysis, including 112 participants. The pooled effect estimate (MD = −1.31; 95% CI = −3.40, 0.77) was statistically non-significant, with a high heterogeneity (I^2 = 62%) across the results of the included studies (Table 3 and Supporting information, Figure S7a). For this outcome, all three studies had a high risk of bias (Table 3 and Supporting information, Figure S7b). The evidence from the main analysis of depressive symptom severity was rated as very low quality in the GRADE assessment (Supporting information, Table S1). In the subgroup analysis, the effect estimate for depressive symptom severity was significantly different by ADHD status in the study population. While using PP was associated with reduced depressive symptom severity in a study with an all-ADHD sample, the same was not observed for studies without an all-ADHD sample (Table 4).

DISCUSSION

In this meta-analysis, we studied the effect of PPs on ATSUD by combining the available data in placebo-controlled trials. To the best of our knowledge, this is the first study that exclusively focuses upon the treatment of this population using PPs. This is important because, despite the growing prevalence of ATSUD, especially in North America, most of the treatment recommendations are based upon pharmacotherapy trials in cocaine use disorder [40, 41]. Moreover, previous meta-analyses on the treatment of ATSUD using PPs included bupropion and modafinil as psychostimulants [10, 42]. While these medications share some effects with typical PPs, their mechanism of action and neurochemical effects are different from those of typical PPs, resulting in an additional source of heterogeneity in the meta-analysis [43]. Notwithstanding some limitations and the relative scarcity of studies, our meta-analysis showed that PP treatment, specifically at higher doses, may have some benefits in decreasing the number of positive UAs during treatment and warrant further investigation. The main analysis results also suggest that PP treatment may be effective in reducing ATS craving, but no statistically significant differences were found between PP treatment and placebo regarding other tested outcomes. In the subsequent subgroup analyses, we observed significant effect modification by the type of medication, intervention dose, duration of treatment and ADHD status on various reported outcomes, which may guide future research efforts.

Our results showed a very high level of heterogeneity in the included study results, with pooled effects in favour of PP treatment compared to placebo in terms of reduced ATS use as evaluated by UA, after excluding studies with a high risk of bias. Our meta-analysis,

therefore, showed a relatively small risk reduction, with an average of approximately 11% in the proportions of ATS-positive UA among those treated with PPs compared to placebo. However, the clinical significance of such reduction may need to be assessed while considering other factors such as the burden and consequences of ATS use and the absence of other approved medications for ATSUD. Interestingly, the subgroup analysis showed that study participants had more benefits from high-dose PP, with a moderate risk reduction (approximately 29%) of ATS use as evaluated by UA. Such differences in the treatment effect were not present when using lower PP doses. While these findings should be interpreted with caution, as only one study [32] was available for high-dose PP (> 162 mg methylphenidate), they may support a dose–response relationship where higher stimulant doses may be associated with better treatment outcomes.

Methylphenidate and dextroamphetamine are used for the management of ADHD at maximum daily doses of 108 and 50 mg for adults, respectively [29]. Our results suggest that people with long-term high-dose exposure to ATS may require doses higher than the clinically recommended doses of PPs to generate an agonist effect that would potentially lead to a reduction in ATS use. This is in line with the conclusion of a previous meta-analysis by Tardelli *et al.* [40], which showed a beneficial effect of higher doses of PPs (including modafinil) for the treatment of stimulant use disorder (i.e. ATSUD and cocaine use disorder). While promising, the clinical significance of such effect and the optimal dose titration (i.e. rate and maximum dose) and dispensing regimens (i.e. supervised versus take-home dosing) still need to be ascertained in future studies [40]. In our subgroup analysis, treatment with methylphenidate (but not with dextroamphetamine) reduced ATS use. However, there was only one study [30] which had a high risk of bias that tested dextroamphetamine; therefore this difference in the results of the subgroup analysis should be considered with caution. The PP treatment was not significantly different from placebo regarding the self-reported number of days of ATS use. This absence of association may be explained in part by the recall and social desirability biases and missing data that are commonly observed for patient-reported outcomes. While our meta-analysis results for self-reported ATS use are not in agreement with those by UA, a recent meta-analysis showed high agreement between self-report and biological testing for measurement of substance use [44].

Although there was no statistically significant interaction between PP treatment and retention outcome, higher doses and longer duration of treatment were significantly associated with higher retention rates in our subgroup analyses. Trial participants benefited from higher PP doses (> 162 mg methylphenidate and > 75 mg dextroamphetamine) with a higher probability (about 131% increase) of retention in treatment. Our subgroup analysis also showed a moderate effect size, with an 83% increase in the probability of retention in treatment only in those with a treatment duration of 20 weeks and more. This result is in line with a previous meta-analysis by Bhatt *et al.* [42], which showed better retention in treatment in those with a treatment duration of more than 12 weeks. This may be explained in part by the possible beneficial cumulative effect of a longer duration of pharmacological intervention using the maximum therapeutic tolerated dose.

Our results also showed a significant effect favouring treatment with PPs for end-point craving. The corresponding significant beneficial effect presented a small to moderate effect size of reduction in craving of approximately 0.29 SMD. However, early-stage craving did not significantly differ between the PP treatment and placebo arms. These differential effects between early-stage and end-point craving scores may result from the inclusion of a study [37] with craving scores reported at a very early time-point (week 2), when it is possible that the full effect of treatment may not have been reached. Given the short delay of the action of psychostimulants, the interaction of time with craving measurements and the precise role of biological and psychosocial determinants of the individuals receiving active treatment in later stages of intervention warrants further investigations.

Our meta-analysis included dropout following AEs, reported by most included studies as an important proxy of treatment safety. The pooled results showed that PP treatment was not significantly associated with higher dropout following AEs, reflecting the relative safety of PP treatment. However, the methods for collecting AEs varied among studies, and it remains difficult to verify whether some AEs were under-reported. This underlies the importance of standardized reporting of AEs in future trials.

Our meta-analysis has been strengthened using the GRADE and RoB 2 tools for bias and evidence assessment, which may help to enhance the applicability of the results. However, the present meta-analysis has its limitations. First, some of the included trials had relatively small sample sizes, some of which included specific samples (e.g. with ADHD), adding to the heterogeneity caused by various treatment doses and durations. This heterogeneity was also evident in the results observed in some subgroup analyses (e.g. by dose and duration of treatment). Secondly, some of the studies excluded individuals with complicated and severe mental and physical disorders, as well as other concomitant substance use disorders, limiting the generalizability of our results to the wider populations. Thirdly, many important outcomes, such as treatment compliance, addiction severity and anxiety symptom severity, were excluded due to a lack of sufficient data.

CONCLUSION

While not proven efficacious for a number of outcomes, our results suggest that relatively potent PP agonists, especially when used in high doses, may be more effective than placebo in diminishing ATS use, increasing retention in treatment and decreasing craving among individuals with ATSUD. Such use of PPs would be coherent with an agonist therapy approach, where doses that compensate for the use of ATS are required to have an impact upon outcomes. Given the presence of varying levels of bias in the included studies and the varying quality of evidence reported for different outcomes, our meta-analysis supports the need for further robust studies of psychostimulant/agonist therapy for ATSUD, looking into higher-dose slow-release formulations than have been used to treat ADHD,

exploring other forms of PPs and testing combinations with psychotherapeutic interventions for more sustained effects. Our results may support future well-powered RCTs that test potent psychostimulant agonists for the treatment of ATSUD while using both ATS use and patient-centred outcomes.

AUTHOR CONTRIBUTIONS

Heidar Sharafi: Conceptualization (equal); formal analysis (lead); investigation (lead); methodology (lead); project administration (equal); writing—original draft (lead); writing—review and editing (equal). **Hamzah Bakouni:** Investigation (supporting); methodology (supporting); writing—original draft (supporting); writing—review and editing (equal). **Christina McAnulty:** Investigation (supporting); methodology (supporting); writing—review and editing (equal). **Sarah Drouin:** Investigation (supporting); writing—original draft (supporting); writing—review and editing (equal). **Stephanie Coronado-Montoya:** Investigation (supporting); methodology (supporting); writing—review and editing (equal). **Arash Bahremand:** Writing—original draft (supporting); writing—review and editing (equal). **Paxton Bach:** Methodology (supporting); writing—review and editing (equal). **Nadine Ezard:** Methodology (supporting); writing—review and editing (equal). **Bernard Le Foll:** Methodology (supporting); writing—review and editing (equal). **Christian G. Schütz:** Methodology (supporting); writing—review and editing (equal). **Krista J. Siefried:** Methodology (supporting); writing—review and editing (equal). **Vitor S. Tardelli:** Methodology (supporting); writing—review and editing (equal). **Daniela Ziegler:** Investigation (supporting); methodology (supporting); writing—review and editing (equal). **Didier Jutras-Aswad:** Conceptualization (equal); funding acquisition (lead); methodology (supporting); project administration (equal); supervision (lead); writing—original draft (supporting); writing—review and editing (equal).

AFFILIATIONS

[1]Research Centre, Centre Hospitalier de l'Université de Montréal (CRCHUM), Montreal, Canada
[2]Department of Psychiatry and Addictology, Faculty of Medicine, Université de Montréal, Montreal, Canada
[3]Department of Medicine, University of British Columbia, Vancouver, Canada
[4]British Columbia Centre on Substance Use, St Paul's Hospital, Vancouver, Canada
[5]National Centre for Clinical Research on Emerging Drugs (NCCRED), University of New South Wales, Sydney, Australia
[6]St Vincent's Hospital Sydney Alcohol and Drug Service, Darlinghurst, Australia
[7]National Drug and Alcohol Research Centre (NDARC), University of New South Wales, Randwick, Australia
[8]Department of Pharmacology and Toxicology, Faculty of Medicine, University of Toronto, Toronto, Canada
[9]Department of Family and Community Medicine, Faculty of Medicine, University of Toronto, Toronto, Canada
[10]Department of Psychiatry, University of Toronto, Toronto, Canada
[11]Dalla Lana School of Public Health, University of Toronto, Toronto, Canada
[12]Translational Addiction Research Laboratory, Campbell Family Mental Health Research Institute, Center for Addiction and Mental Health, Toronto, Canada
[13]Waypoint Research Institute, Waypoint Centre for Mental Health Care, Penetanguishene, Canada
[14]Department of Psychiatry, University of British Columbia, Vancouver, Canada
[15]Departamento de Psiquiatria, Universidade Federal de São Paulo, São Paulo, Brazil
[16]Centre Hospitalier de l'Université de Montréal (CHUM), Montreal, Canada

ACKNOWLEDGEMENTS

This meta-analysis was supported by the Canadian Institutes of Health Research (CIHR) (grant number REN-181675), Université de Montréal and Centre de recherche du Centre hospitalier de l'Université de Montréal (CRCHUM). The study sponsor had no role in study conceptualization, data acquisition and analysis, interpretation of results and manuscript drafting and editing. We would like to express our kindest gratitude to Alfonso Ang, Marie Longo, Wyne Miles, Alireza Noroozi, Shahin Akhondzadeh and Ronald G. Thompson for providing us with the information and results of their studies.

DECLARATION OF INTERESTS

C.M. has received scholarships from the Institut universitaire sur les dépendances, the Gaulin Foundation, the Centre Hospitalier de l'Université de Montréal Research Centre and the Université de Montréal. S.C.M. received financial training support from the Vanier Canada Graduate Scholarship. P.B. is supported by a Health Professional-Investigator Award from Michael Smith Health Research BC, the St Paul's Foundation and the BC Centre on Substance Use. P.B. has no conflicts of interest to declare. B.L.F. has obtained funding from Pfizer Inc. (GRAND Awards, including salary support) for investigator-initiated projects. B.L.F. has obtained funding from Indivior for a clinical trial sponsored by Indivior. B.L.F. has in-kind donations of cannabis products from Aurora Cannabis Enterprises Inc. and study medication donations from Pfizer Inc. (varenicline for smoking cessation) and Bioprojet Pharma. B.L.F. was also provided a coil for a Transcranial Magnetic Stimulation (TMS) study from Brainsway. B.L.F. has obtained industry funding from Canopy Growth Corporation (through research grants handled by the Centre for Addiction and Mental Health and the University of Toronto), Bioprojet Pharma, Alcohol Countermeasure Systems (ACS), Alkermes, and Universal Ibogaine. B.L.F. has participated in a session of a National Advisory Board Meeting (Emerging Trends BUP-XR) for Indivior Canada and has been a consultant for Shinogi. B.L.F. is supported by CAMH, Waypoint Centre for Mental Health Care, a clinician–scientist award from the Department of Family and Community Medicine of the University of Toronto, and a Chair in Addiction Psychiatry from the Department of Psychiatry of the University of Toronto. D.J.A. receives study material from Cardiol Therapeutics for a clinical trial funded by the Quebec

Ministry of Health and Social Services, and holds a clinical scientist career award from Fonds de Recherche du Québec (FRQS).

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this meta-analysis are available within Appendix 5 (structured data extraction Excel sheet).

ORCID

Paxton Bach https://orcid.org/0000-0002-2413-9133
Vitor S. Tardelli https://orcid.org/0000-0001-6040-7708
Didier Jutras-Aswad https://orcid.org/0000-0002-8474-508X

REFERENCES

1. Degenhardt L, Charlson F, Ferrari A, Santomauro D, Erskine H, Mantilla-Herrara A, et al. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Psychiatry. 2018;5:987–1012.
2. United Nations Office on Drugs and Crime (UNODC). World Drug Report 2022. Vienna, Austria: UNODC; 2022.
3. Crispo JAG, Liu L, Bach P, Ansell DR, Sivapathasundaram B, Nguyen F, et al. Amphetamine-related emergency department visits in Ontario, Canada, 2003–2020. Can J Psychiatry. 2023. https://doi.org/10.1177/07067437231158933
4. Cretzmeyer M, Sarrazin MV, Huber DL, Block RI, Hall JA. Treatment of methamphetamine abuse: research findings and clinical directions. J Subst Abuse Treat. 2003;24:267–77.
5. Lee NK, Jenner L, Harney A, Cameron J. Pharmacotherapy for amphetamine dependence: a systematic review. Drug Alcohol Depend. 2018;191:309–37.
6. Rawson RA, Marinelli-Casey P, Anglin MD, Dickow A, Frazier Y, Gallagher C, et al. Methamphetamine Treatment Project Corporate A. A multi-site comparison of psychosocial approaches for the treatment of methamphetamine dependence. Addiction. 2004;99:708–17.
7. Lanyon C, Nambiar D, Higgs P, Dietze P, Quinn B. Five-year changes in methamphetamine use, dependence, and remission in a community-recruited cohort. J Addict Med. 2019;13:159–65.
8. Paulus MP, Stewart JL. Neurobiology, clinical presentation, and treatment of methamphetamine use disorder: a review. JAMA Psychiatry. 2020;77:959–66.
9. Siefried KJ, Acheson LS, Lintzeris N, Ezard N. Pharmacological treatment of methamphetamine/amphetamine dependence: a systematic review. CNS Drugs. 2020;34:337–65.
10. Pérez-Mañá C, Castells X, Torrens M, Capellà D, Farre M. Efficacy of psychostimulant drugs for amphetamine abuse or dependence. Cochrane Database Syst Rev. 2013;9:CD009695.
11. Lim J, Farhat I, Douros A, Panagiotoglou D. Relative effectiveness of medications for opioid-related disorders: a systematic review and network meta-analysis of randomized controlled trials. PLOS ONE. 2022;17:e0266142.
12. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2014;2:CD002207.
13. Center for Substance Abuse Treatment. SAMHSA/CSAT Treatment Improvement Protocols. Treatment for Stimulant Use Disorders. Rockville, MD: Substance Abuse and Mental Health Services Administration; 1999.
14. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
15. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol. 2016;75:40–6.
16. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV Washington, DC: American Psychiatric Association; 1994.
17. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5 Washington, DC: American Psychiatric Association; 2013.
18. Turner RM, Bird SM, Higgins JP. The impact of study size on meta-analyses: examination of underpowered studies in Cochrane reviews. PLOS ONE. 2013;8:e59202.
19. Bramer WM, Giustini D, de Jonge GB, Holland L, Bekhuis T. De-duplication of database search results for systematic reviews in EndNote. J Med Libr Assoc. 2016;104:240–3.
20. Sobell L, Sobell M, Buchan G, Cleland P, Fedoroff I, Leo G et al. Timeline followback method (drugs, cigarettes, and marijuana). Presented at the 30th Annual Meeting of the Association for Advancement of Behavior Therapy, November 1996. New York, NY, 1996.
21. McLellan AT, Luborsky L, Woody GE, O'Brien CP. An improved diagnostic evaluation instrument for substance abuse patients. The Addiction Severity Index. J Nerv Ment Dis. 1980;168:26–33.
22. Srisurapanont M, Jarusuraisin N, Jittiwutikan J. Amphetamine withdrawal: I. Reliability, validity and factor structure of a measure. Aust NZ. J Psychiatry. 1999;33:89–93.
23. McGregor C, Srisurapanont M, Jittiwutikarn J, Laobhripatr S, Wongtan T, White JM. The nature, time course and severity of methamphetamine withdrawal. Addiction. 2005;100:1320–9.
24. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961;4:561–71.
25. Rohatgi A. Webplotdigitizer: version 4.6 2022 [cited 4 2]. Available at: https://automeris.io/WebPlotDigitizer. Accessed 28 Sep 2022.
26. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
27. Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, et al. GRADE guidelines: 5. Rating the quality of evidence—publication bias. J Clin Epidemiol. 2011;64:1277–82.
28. The Cochrane Collaboration. Review Manager (RevMan) version 5.4 ed. Copenhagen, Denmark: The Cochrane Collaboration; 2020.
29. Canadian ADHD Resource Alliance. Canadian ADHD Practice Guidelines 4.1 ed. Toronto, Canada: Canadian ADHD Resource Alliance; 2018.
30. Galloway GP, Buscemi R, Coyle JR, Flower K, Siegrist JD, Fiske LA, et al. A randomized, placebo-controlled trial of sustained-release dextroamphetamine for treatment of methamphetamine addiction. Clin Pharmacol Ther. 2011;89:276–82.
31. Konstenius M, Jayaram-Lindstrom N, Beck O, Franck J. Sustained release methylphenidate for the treatment of ADHD in amphetamine abusers: a pilot study. Drug Alcohol Depend. 2010;108:130–3.
32. Konstenius M, Jayaram-Lindstrom N, Guterstam J, Beck O, Philips B, Franck J. Methylphenidate for attention deficit hyperactivity disorder and drug relapse in criminal offenders with substance dependence: a 24-week randomized placebo-controlled trial. Addiction. 2014;109:440–9.
33. Ling W, Chang L, Hillhouse M, Ang A, Striebel J, Jenkins J, et al. Sustained-release methylphenidate in a randomized trial of treatment of methamphetamine use disorder. Addiction. 2014;109:1489–500.
34. Miles SW, Sheridan J, Russell B, Kydd R, Wheeler A, Walters C, et al. Extended-release methylphenidate for treatment of amphetamine/methamphetamine dependence: a randomized, double-blind, placebo-controlled trial. Addiction. 2013;108:1279–86.
35. Noroozi A, Motevalian SA, Zarrindast MR, Alaghband-Rad J, Akhondzadeh S. Adding extended-release methylphenidate to psychological intervention for treatment of methamphetamine

dependence: a double-blind randomized controlled trial. Med J Islam Repub Iran. 2020;34:137.
36. Rezaei F, Emami M, Zahed S, Morabbi MJ, Farahzadi M, Akhondzadeh S. Sustained-release methylphenidate in methamphetamine dependence treatment: a double-blind and placebo-controlled trial. Daru. 2015;23:2.
37. Thompson RG Jr, Oliveto A, Thostenson JD, Wilson MP, McGaugh J, Mancino MJ. Utility of a controlled amphetamine withdrawal paradigm among adults who use methamphetamine: a pilot clinical trial. J Psychopharmacol. 2021;35:1420–30.
38. Tiihonen J, Kuoppasalmi K, Fohr J, Tuomola P, Kuikanmaki O, Vorma H, et al. A comparison of aripiprazole, methylphenidate, and placebo for amphetamine dependence. Am J Psychiatry. 2007;164:160–2.
39. Longo M, Wickes W, Smout M, Harrison S, Cahill S, White JM. Randomized controlled trial of dexamphetamine maintenance for the treatment of methamphetamine dependence. Addiction. 2010;105:146–54.
40. Tardelli VS, Bisaga A, Arcadepani FB, Gerra G, Levin FR, Fidalgo TM. Prescription psychostimulants for the treatment of stimulant use disorder: a systematic review and meta-analysis. Psychopharmacology. 2020;237:2233–55.
41. British Columbia Centre on Substance Abuse (BCCSU). Stimulant use disorder—practice update 2022. Available at: https://www.bccsu.ca/wp-content/uploads/2022/06/Stimulant-Use-Disorder-Practice-Update_June2022.pdf. Accessed 2 May 2023.
42. Bhatt M, Zielinski L, Baker-Beal L, Bhatnagar N, Mouravska N, Laplante P, et al. Efficacy and safety of psychostimulants for amphetamine and methamphetamine use disorders: a systematic review and meta-analysis. Syst Rev. 2016;5:189.
43. Mereu M, Bonci A, Newman AH, Tanda G. The neurobiology of modafinil as an enhancer of cognitive performance and a potential treatment for substance use disorders. Psychopharmacology. 2013;229:415–34.
44. Bharat C, Webb P, Wilkinson Z, McKetin R, Grebely J, Farrell M, et al. Agreement between self-reported illicit drug use and biological samples: a systematic review and meta-analysis. Addiction. 2023;118:1624–48.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Sharafi H, Bakouni H, McAnulty C, Drouin S, Coronado-Montoya S, Bahremand A, et al. Prescription psychostimulants for the treatment of amphetamine-type stimulant use disorder: A systematic review and meta-analysis of randomized placebo-controlled trials. Addiction. 2024;119(2):211–24. https://doi.org/10.1111/add.16347