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

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ABSTRACT

Background: This meta-analysis (PROSPERO-ID: CRD42022362962), pooled effect estimates of outcomes, from placebo-controlled randomized clinical trials (RCTs) examining bupropion efficacy and safety for amphetamine-type stimulant use disorder (ATSUD) treatment.

Method: Electronic databases were searched for records published to October 31st, 2022, including MEDLINE, CINAHL, PsycINFO, EBM Reviews, EMBASE, PubMed, Web of Science, trial registries. Inclusion criteria were RCTs comparing bupropion to placebo in ATSUD. Cochrane RoB2 tool and GRADE evidence certainty assessment were employed. Outcomes included amphetamine-type stimulant (ATS) use by urinalysis, retention in treatment, treatment adherence, ATS craving, addiction severity, depressive symptom severity, drop-out following adverse events (AEs), and serious AEs. Random-effect meta-analysis was conducted presenting standardized mean difference (SMD), risk ratio (RR), and risk difference (RD).

Results: Eight RCTs (total N=1239 participants) were included. Bupropion compared to placebo was associated with reduced ATS use (RR: 0.90; 95% CI: 0.84, 0.96), end-of-treatment ATS craving (SMD: −0.38; 95%CI: −0.63, −0.13), and adherence (RR: 0.91; 95%CI: 0.84, 0.99). Subgroup analysis showed greater reduction in ATS use with longer trial duration (12 weeks) (RR: 0.85; 95%CI: 0.78, 0.93) and greater reduction in end-of-treatment ATS craving in studies with mixed ATS use frequency (SMD: −0.46; 95%CI: −0.70, −0.22) and male-only samples (SMD: −1.26; 95%CI: −1.87, −0.65).

Conclusion: Bupropion showed a significant modest reduction in ATS use and ATS craving (both rated as very low-quality evidence), larger in males (craving), and with longer treatment (ATS use). These results may inform future studies. More research is warranted on who might benefit from bupropion as ATSUD treatment.

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1. Introduction

Recent reports indicate that the use of amphetamine-type stimulants (ATS) (including amphetamine, methamphetamine, and dexamphetamine) is growing worldwide (GBD_2016_Collaborators, 2018; UNODC, 2021). In 2019, the total amount of ATS seized by law enforcement rose to an all-time high, with a six-fold increase compared to the year before (UNODC, 2021). Consequently, ATS use disorder (ATSUD) is a serious public health concern. In the year 2020 alone, 7 million people reported using prescription stimulants and/or methamphetamine without or not following physician recommendations in the United States (US). Further, in those aged 12 years and older in 2020 in the US, 0.6% (1.5 million persons) reported having a past-year methamphetamine use disorder (SAMHSA, 2021). Similar trends have been witnessed in Canada (Nickel et al., 2022). Amphetamine-type stimulant use disorder has a considerable medical, legal, and socioeconomic impact. It has been strongly associated with higher rates of death by both communicable and non-communicable diseases, suicide, overdose, aggression, and criminal activities (Carrillo Beck et al., 2022; Darke et al., 2017; Herbeck et al., 2015; Paulus and Stewart, 2020). Moreover, a higher prevalence of severe and chronic psychiatric complications, such as mood and psychotic disorders, has been long recognized in this population (Carrillo Beck et al., 2022; Paulus and Stewart, 2020).

There is currently no official medication approved by the U.S. Food and Drug Administration or Health Canada for the treatment of ATSUD although pharmacological approaches are included in the guidelines recently published by the American Society of Addiction Medicine and the American Academy of Addiction Psychiatry (ASAM, AAAP, 2023). As a result, psychosocial intervention remains the first line of treatment for ATSUD and practitioners rely mostly on non-pharmacological practices such as supportive care, cognitive behavioural therapy, and contingency management (CM) (SAMHSA, 2020). While there are significant evidence regarding the efficacy and usefulness of these therapeutic modalities, the implementation challenges of treatments such as CM and the need for diverse treatment options to improve outcomes call for the deployment of complementary or alternative approaches (AshaRani et al., 2020). Pharmacological interventions may hence be useful in helping engaging and retaining people with ATSUD, and potentially improving overall outcomes (AshaRani et al., 2020; Brecht and Herbeck, 2014; Lanyon et al., 2019).

A growing number of studies have tried to fill the knowledge gap and lay an evidence-based framework for the pharmacological treatment of ATSUD (Chan et al., 2019; Pérez-Mañá et al., 2013). However, the low quality of original studies, participant recruitment challenges, low retention rates, and the lack of clinical significance of various pharmacological interventions have prevented the development of strong recommendations (Lee et al., 2018; Pérez-Mañá et al., 2013). Nonetheless, many of these studies have pointed out bupropion as a potentially promising candidate warranting further investigations in the treatment of ATSUD (Lee et al., 2018; Siefried et al., 2020). Bupropion is approved for the treatment of depression and smoking cessation and has shown some benefits in the treatment of attention-deficit/hyperactive disorder (ADHD) due to its stimulant-like effect (Rau et al., 2005; Wilens et al., 2005). It has been shown that bupropion increases the level of dopamine and noradrenaline in the neuronal synapsis to exert its central effects by inhibiting the uptake of these monoamine neurotransmitters (Rau et al., 2005). It has been argued that its ability to regulate (i.e., elevate) dopamine neurotransmission in the reward-related circuits of the brain, and thereby reduce ATS cravings, makes this molecule potentially useful in the treatment of ATSUD (Newton et al., 2006; Simmler et al., 2013). There is accumulating evidence regarding the safety and efficacy of this molecule, alone or in combination with other treatments (e.g., bupropion combined with extended-release injectable naltrexone in the Trivedi et al. study), in improving various outcomes in people with ATSUD (Trivedi et al., 2021).

In this systematic review and meta-analysis, we investigate the latest evidence in the literature, focusing on placebo-controlled randomized trials examining the efficacy and safety of bupropion for the treatment of individuals with ATSUD. In the absence of any recommended pharmacological intervention, available evidence regarding the efficacy and safety of bupropion was pooled with respect to the selected main (i.e., proportion of ATS-positive urine analysis) and secondary outcomes (e.g., retention in treatment) included in this meta-analysis. Finally, subgroup analyses were conducted to verify the effect of other parameters potentially influencing the response to bupropion treatment in the ATSUD population.

2. Methods

2.1. Study conceptualization and registration

The meta-analysis was developed as a complementary study in parallel with another meta-analysis on the effect of prescription psychostimulants (i.e., methylphenidate and amphetamine salts) on different outcomes in persons with ATSUD. First, a limited search was conducted in PubMed, Web of Science, and Scopus to ascertain the presence of poolable studies on the subject. After verifying that there was no other recently registered meta-analysis on the same subject, the study protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) on October 7th, 2022 with the identification code CRD42022362962 (Appendix 1). This systematic review with meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 (checklists in Appendices 2 and 3) (Page et al., 2021).

2.2. Search methods

Search strategies were designed by a librarian (DZ). The reproducible searches for all databases are available in the Electronic Supplementary Material Appendix [#4]. The strategies were then peer-reviewed by another senior information specialist before execution using the PRESS Checklist (McGowan et al., 2016).

The following electronic databases were searched: MEDLINE (Ovid), CINAHL (EBSCOhost), PsycINFO (Ovid), EBM Reviews (Ovid), EMBASE (Ovid), PubMed and Web of Science. We searched several clinical trial registries (clinicaltrials.gov, International Clinical Trials Registry Platform, International Standard Randomised Controlled Trial Number, Health Canada Clinical Trials Database, UK Clinical Trials Gateway, and Australian New Zealand Clinical Trials registry). To complete, other searches were run on Google Scholar, Food and Drug Administration (FDA), Health Canada, and Agence Européenne des médicaments (EMA). Reference lists of all included articles and relevant systematic reviews were also manually searched to verify the presence of any additional records.

2.3. Study screening and selection

The study inclusion criteria were: 1) any randomized placebo-controlled clinical trials; 2) trials including bupropion treatment arm of any dosage with or without any other medications (such as naltrexone) or psychosocial interventions; 3) studies on populations with a diagnosed ATSUD using Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) or DSM-5 criteria (APA, 1994, 2013). The reports' language was limited to English, Spanish, Portuguese, German, Arabic, Persian, and French. The exclusion criteria were: 1) other types of clinical trials such as open-label trials, human laboratory, and animal trials; and 2) trials with fewer than five participants per each of the placebo/bupropion arms, to limit potential biases associated with very small sample sizes (Turner et al., 2013).

The search results were transferred to Covidence® after duplicate elimination in EndNote by the librarian (DZ), following the methodology suggested by Bramer et al. (Bramer et al., 2017). Two researchers

(HB and HS) screened titles/abstracts of included records independently, and all conflicts during title/abstract screening were resolved by reaching a consensus. The same researchers independently evaluated the eligibility of full-text/report retrieved for the retained studies (Appendix 5: studies excluded in the eligibility assessment). Conflicts in study eligibility evaluation were settled through discussions and a consultation with the study supervisor (DJA) when needed.

2.4. Outcome measures

After the initial selection of identified records, the following outcomes were targeted in the meta-analysis: ATS use by urine analysis (UA), self-reported ATS use, retention in treatment, treatment adherence, ATS craving, withdrawal symptoms severity, addiction severity, anxiety symptoms severity, depressive symptoms severity, cognition, and treatment safety. After final identification and revision of all included records, four outcomes were removed due to a lack of sufficient data: self-reported ATS use, withdrawal symptoms severity, anxiety symptoms severity, and cognition. The following outcome measures were thus included in the meta-analysis:

Amphetamine-type stimulant use by UA was measured using qualitative or quantitative probing of urine for amphetamine and/or methamphetamine during the randomized treatment phase of the trial. The overall proportion of ATS-positive UA or ATS-positive weeks (e.g., with at least one ATS-positive UA per week) confirmed by UA per intervention arm was pooled together in the meta-analysis.

Retention in treatment was measured by the proportion of participants completing the trial and receiving either treatment or placebo at the end of the randomized period of the trial.

Adherence to treatment was measured by the total proportion of medication taken (pills/tablets counts), using any reported pill count methods. We preferably used clinician-based measures when available, such as clinician-reported pill counts and medication event monitoring systems (MEMS) caps.

Amphetamine-type stimulant craving was captured using reported validated scales in each trial such as Visual Analog Scale (VAS) (Mean ±SD) and Brief Substance Craving Scale (BSCS) (Mean±SD) (Somoza et al., 1995). Two different time-point measurements were chosen for final data pooling: ATS craving at week 4 and at the end of treatment (i.e., the last treatment visit in trials with more than 4 weeks).

Addiction severity was captured at the end of the trial, using Addiction Severity Index (ASI) (Mäkelä, 2004), including measurement (Mean ±SD) of seven sub-scores: medical status, employment status, alcohol use, drug use, legal status, family/social relationship, and psychiatric status.

Depressive symptom severity was measured using Hamilton Depression Rating Scale (HAM-D), Beck Depression Inventory (BDI), and Patient Health Questionnaire (PHQ-9) for the endpoint (last treatment visit in randomized stage) measurement (Mean±SD).

Drop-out following adverse events (AEs) was measured by the proportion of individuals with treatment discontinuation due to reported AEs.

Serious AEs were measured by the proportion of individuals with any reported serious AEs (e.g., necessitating hospitalization, life-threatening, or causing treatment drop-out).

2.5. Data extraction

Two researchers (HB and HS) independently extracted data from the included records (Appendix 6), and conflicts were settled through a consensus. The online WebPlotDigitizer V4.6 tool was employed for the extraction of values from published study graphs included in the articles when needed (Rohatgi, 2022). Some missed outcomes were extracted directly from the study datasets available online. If measurement values were not completely accessible via published and other online data sources, authors of the included studies were contacted by email (Appendix 7).

2.6. Risk of bias assessment and evidence grading

The criteria from the Risk of Bias Assessment tool (RoB2) of Cochrane Collaboration were employed to evaluate bias risks in the included studies (Higgins et al., 2011). The RoB2 Excel tool was used independently by two researchers (HB and SD), and conflicts were settled by a consensus. The risk of publication bias was estimated using funnel plots for outcomes with five or more studies.

The strength of evidence for each study outcome obtained through data pooling was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria: study design and risk of bias, imprecision, inconsistency, indirectness, and magnitude of effect (Guyatt et al., 2011). Two review researchers (HB and HS) independently assessed the evidence for different outcomes using the GRADE criteria. Conflicts were settled through a consensus (Appendix 8).

2.7. Data analysis

2.7.1. Strategy for data synthesis

For each outcome, the trials with fully available data were selected for pooling of overall effects. For outcomes with continuous measures, standardized mean difference (SMD) with 95% confidence intervals (95% CI) was used. For outcomes with dichotomous measures, proportions were used with the risk ratio (RR) and risk difference (RD) and their 95% CI. The data were pooled by conducting random-effect meta-analysis models in Review Manager (Version 5.4.1) calculated via inverse variance method of studies' size effects (Collaboration, 2020). A threshold of P-value $\leq$0.05 was used to determine statistical significance.

2.7.2. Subgroups and sensitivity analysis

Subgroup analyses were conducted using factors with possible effects modification of main pooled effects. The included outcomes were entered into subgroup analysis (i.e., with intergroup difference testing) by the additional pharmacological intervention (i.e., bupropion vs. bupropion/naltrexone), bupropion dosage (i.e., 300 versus 450 mg/day), study participant characteristics at baseline (i.e., ATS use frequency and sex), and treatment duration. Sensitivity analyses were further conducted by excluding: 1) some studies with a high risk of bias by RoB2 assessment; and 2) one study using ATS-positive weeks.

3. Results

3.1. Search results

The process by which relevant studies were identified is described in Fig. 1. A total of 2623 citations were retrieved. After duplicate record exclusion, we localized 2142 records which were included in screening using the inclusion and exclusion criteria. A total of 2107 records did not meet our criteria and were excluded from the meta-analysis. The remaining 35 records were selected for full-text reading; we excluded one record with non-retrievable full-text, leaving 34 records for full-text-based eligibility evaluation. We excluded 17 records that were duplicates of other records, leaving 17 records for full-text reading. Finally, our meta-analysis included eight records in the pooling and evidence assessment, after having excluded nine records not meeting eligibility criteria. A summary of the rationale for study exclusion is found in Appendix 5.

3.2. Characteristics of included studies

Our meta-analysis included eight placebo-controlled randomized trials (Anderson et al., 2015; Das et al., 2010; Elkashef et al., 2008; Ghoreishi et al., 2017; Heinzerling et al., 2013, 2014; Shoptaw et al., 2008; Trivedi et al., 2021) enrolling 1239 participants (see Table 1. Characteristics of studies). One of the included studies, by Trivedi et al.,

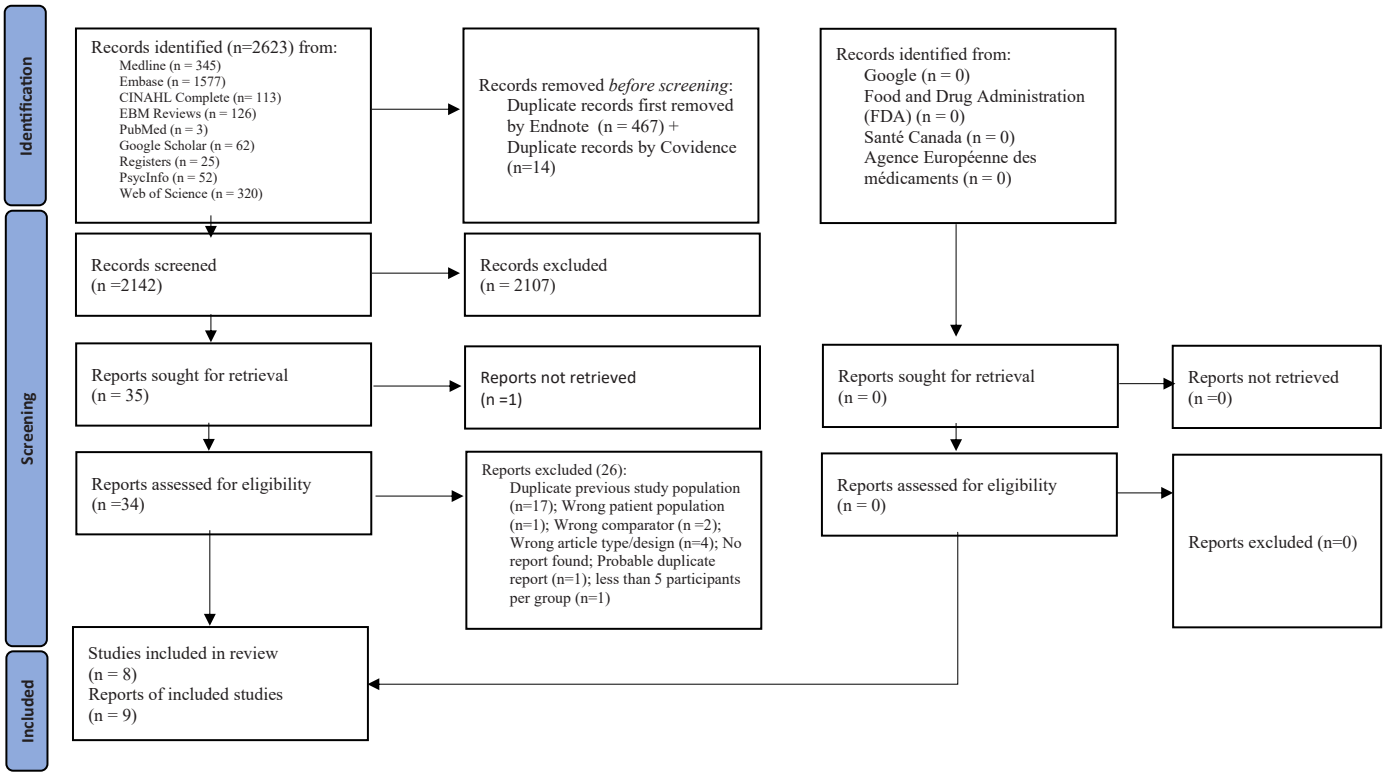

Fig. 1. PRISMA 2020 flow diagram for results of search, screening, and eligibility assessment of systematic review studies.

used re-randomization techniques of placebo non-responders at the end of the first stage of the study and was included as two separate reports (stage 1 and stage 2) (Trivedi et al., 2021). Overall, 611 participants were included from seven studies comparing bupropion (using 300 mg/day) to placebo (Anderson et al., 2015; Das et al., 2010; Elkashef et al., 2008; Ghoreishi et al., 2017; Heinzerling et al., 2013, 2014; Shoptaw et al., 2008), and a total of 628 participants were included from the two stages of Trivedi et al.'s study testing the efficacy and safety of bupropion (using 450 mg/day with naltrexone) compared to placebo (Trivedi et al., 2021).

3.3. Selected outcomes

The main outcome (ATS use by proportion of positive UA) was extracted from six studies (using intention-to-treat [ITT] analysis). One additional study reported a proportion of ATS-free weeks by UA (ITT) and was used to calculate the (Elkashef et al., 2008) proportion of ATS-positive weeks by UA (Elkashef et al., 2008). The urine sample was collected weekly in one study, twice weekly in two studies, and thrice weekly in three studies, and the overall ATS-positive UA proportion was calculated in each study and was considered comparable among studies. Only one study reported the ATS-positive weeks (based on weekly collected UA) instead, and the overall ATS-positive week proportion was calculated (Elkashef et al., 2008).

Other included outcomes used ITT approaches, with a few studies using or reporting available case analyses (see Table 2). Few outcome measures were missing from published reports and were retrieved by contacting authors (Shoptaw et al., 2008) or from online datasets (Anderson et al., 2015; Elkashef et al., 2008). End-of-treatment ATS craving and depressive symptoms severity outcomes had one study with results that could not be pooled with other studies (i.e., one study reported score differences between baseline and end-of-treatment) (Trivedi et al., 2021). Therefore, the end-of-treatment outcome average scores were calculated in the last study by adding baseline scores with the reported score difference and using SD from baseline.

3.4. Effects of intervention

Estimates of the main effects of bupropion compared to placebo for selected outcomes are summarized in Table 3.

3.4.1. Amphetamine-type stimulant use by UA

Seven reports included the number of ATS-positive UA (i.e., including one ATS-positive weeks), with a total of 15,664 collected and valid UA, with a heterogeneity approximating I^2=89% between studies. The pooled effect significantly favored bupropion compared to placebo (RR: 0.90; 95%CI: 0.84, 0.96). One out of seven studies had a high overall risk of bias with three of the studies with some concerns of bias. Additional sensitivity analysis showed a significant ATS use reduction in bupropion compared to placebo in studies without high risk of bias (RR: 0.87; 95%CI: 0.83, 0.92). Sensitivity analysis excluding Elkashef et al. (2008) study, which reported ATS-positive weeks, showed a similar significant ATS use reduction in bupropion compared to placebo (RR: 0.91; 95%CI: 0.85, 0.97). In the evaluation of publication bias using a funnel plot, there was a minor asymmetry in the distribution of study estimates (Figures S1a,b,c – Appendix 8). The evidence quality was rated very low in the GRADE assessment (Table S1 – Appendix 10).

Subgroup analysis of outcome measures as a function of treatment duration during the randomized trial stage showed significant differences between groups: participants undergoing a 12-week trial phase showed significant ATS use reduction in bupropion compared to placebo (RR: 0.85; 95%CI: 0.78, 0.93), and those having completed less than 12 weeks of treatment showed no significant effect (RR: 0.98; 95%CI: 0.89, 1.08). All other subgroup analyses showed no significant differences between groups (Figures S1-5 – Appendix 9).

3.4.2. Retention in treatment

Seven reports included retention in treatment, totaling 786 participants, with heterogeneity between studies approximating I^2=6%. The pooled effect estimate was non-significant comparing bupropion with placebo (RR: 0.97; 95%CI: 0.89, 1.05). Three out of the seven studies

Table 1
Characteristics of the included studies.

Study identification, ref	Study dates	Study location (s)	N of participants	Age (mean/ median), years	Male sex, %	Specification of ATS (methamphetamine, MA) use at baseline	ADHD, %	Trial medication and maximum dose/day	Randomized treatment duration	Psychological co-interventions
Shoptaw, 2008	October 2005 – May 2007	USA	73	34.6	61.1% (bupropion), 67.6% (placebo)	Subgroups of light and heavy ATS (MA) use*	NA	Bupropion SR, 300 mg daily	12 weeks	Contingency management and cognitive behavioral therapy
Elkashef, 2008	July 2003 - June 2005	USA	151	36	67%	Subgroups of light ATS (MA) use (≤18 days/month) vs. heavy ATS (MA) use (>18 days/month)	8% (bupropion), 19% (placebo)	Bupropion SR, 300 mg daily[a]	12 weeks	Standardized, cognitive-behavioral therapy of the Matrix Model
Das, 2010	September 2006 - November 2007	USA	30	38.1 (bupropion), 33.3 (placebo)	100%	No specification on use	NA	Bupropion SR, 300 mg daily[b]	12 weeks	Substance use counseling with cognitive behavioral therapy, motivational interviewing techniques, and incorporating Stages of Change Model
Heinzerling 2013	October 2009 - December 2011	USA	19	17.5 (bupropion), 17.7 (placebo)	42% (bupropion), 57% (placebo)	All <18/30 days	33% (bupropion), 0% (placebo)	Bupropion SR, 300 mg daily	8 weeks	Outpatient substance utilization counseling
Heinzerling, 2014	January 2009 - December 2012	USA	84	38.6 (bupropion), 38.1 (placebo)	83% (bupropion), 79% (placebo)	All ≤29/30 days	17% (bupropion), 12% (placebo)	Bupropion SR 300 mg daily	12 weeks	Cognitive Behavioral Therapy with counseling
Anderson, 2015	May 2008 - May 2011	USA	204	39.3	65%	All ≤29/30 days	NA	Bupropion SR 300 mg daily	12 weeks	Group psychotherapy
Ghoreishi et al., (2017)	NA	Iran	50	36.2 (bupropion), 34.8 (placebo)	100%	No specification on use	NA	Bupropion SR 300 mg daily	12 weeks	NA
Trivedi, 2021 (stage 1)	May 2017 - July 2019	USA	403	41: 41 (bupropion), 41 (placebo)	71.6% (bupropion), 67.7% (placebo)	All ≥18/30 days	NA	Bupropion SR 450 mg daily + naltrexone[c]	6 weeks[d]	NA
Trivedi, 2021 (stage 2)	May 2017 - July 2019	USA	225	41: 41 (bupropion), 42 (placebo)	68.4% (bupropion), 71.2% (placebo)	All ≥18/30 days	NA	Bupropion SR 450 mg daily + naltrexone[c]	6 weeks[e]	NA

Abbreviations: ref, reference; N, number; ATS, amphetamine-type stimulant; NA, not available; SR, sustained-release.
* Light-ATS (MA) use, defined as 0–2 of 6 urine drug screens during 2-week baseline period positive for ATS -metabolites, and baseline heavy-ATS (MA) use, defined as 3–6 of 6 urine drug screens during 2-week baseline period.
[a] Bupropion 150 mg SR once daily for 3 days, then 150 mg twice daily for 11 weeks of treatment; [b] Bupropion SR 150 mg SR once daily for one week, then 150 mg twice daily for 11 weeks of treatment.
[c] Bupropion SR 450 mg a day +injectable naltrexone (once every 3 weeks); [d] stage 1 before re-randomization; [e] stage 2 after re-randomization of placebo group non responders in stage 1.

Table 2
Overview of outcomes assessed in the meta-analysis by the included studies and their analysis approach and measurement method.

Study	Outcomes												
	ATS use	Self-reported use	Retention	Adherence	Craving W4	Craving EOT	Withdrawal symptoms severity	Addiction severity	Depressive symptoms severity	Anxiety symptoms severity	Cognition	Dropout following AEs	Serious AEs
Shoptaw, 2008	ITT¥, *		ITT	ITT¥	ITT¥, W4 VAS	ITT¥, W12 VAS			ITT¥, BDI			ITT	ITT¥
Elkashef, 2008	ITT¥, *		ITT	ITT¥	ACA, W4 BSCS	ACA, W12 BSCS		ACA	ACA, HAM-D				ITT¥
Das, 2010	ITT¥, *		ITT	ITT¥								ITT	ITT¥
Heinzerling, 2013	ITT¥, TES		ITT	ITT¥									ITT¥
Heinzerling, 2014	ITT¥, TES		ITT									ITT	ITT¥
Anderson, 2015			ITT		ACA, W4 BSCS	ACA, W12 BSCS			ACA, HAM-D			ITT	ITT¥
Ghoreishi, 2017					ITT¥, W4 VAS	ITT¥, W12 VAS		ITT¥					
Trivedi, 2021 (stage 1)	ITT¥, *		ITT	ITT¥		ITT¥, VAS**			ITT¥, PHQ-9**				ITT¥
Trivedi, 2021 (stage 2)	ITT¥, *		ITT	ITT¥		ITT¥, VAS**			ITT¥, PHQ-9**				ITT¥

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 the available datasets.
The unavailable results of the included outcomes after correspondence with the authors.

Abbreviations: ATS, amphetamine-type stimulant; AEs, adverse events; ITT, intention-to-treat; W, week; EOT, end of treatment; ACA, available case analysis.
¥ITT analysis without clear evidence of imputation of missing data.
*Calculated based on the proportion of participants with MA-free (or positive) weeks or visits.
**End-of-treatment outcome average scores were calculated by adding baseline with change scores and using SD from baseline.
TES calculation is based on the Treatment Effectiveness Score (mean number of negative UA or weeks of negative UA in each treatment arm); VAS, visual analog scale; PHQ-9, Patient Health Questionnaire; HAM-D, Hamilton Depression Rating Scale; BDI, Beck Depression Inventory.
Empty cells reflect that there was nothing on the inclusion of the outcome in the article and/or protocol of the study.

had some concerns of bias. In the evaluation of publication bias using a funnel plot, there was a minor asymmetry in the distribution of study estimates (Figures S2a-c – Appendix 8). The evidence quality was rated high in the GRADE assessment (Table S1 – Appendix 10). In subgroup analyses, no differences were observed between groups, with overall no significant effects of bupropion compared to placebo on retention (Figures S6-9 – Appendix 9).

3.4.3. Treatment adherence

Six reports included treatment adherence with pill-taking, including 119,680 provided pills, with heterogeneity between studies approximating I^2=99%. The pooled effect was significant favoring placebo over the treatment group (RR: 0.91; 95%CI: 0.84, 0.99). Two out of the six studies had a high risk of bias, and one study had some concerns about bias. Sensitivity analysis of outcome measures showed that studies without a high risk of bias had a significant effect favoring placebo compared to bupropion in terms of treatment adherence (RR: 0.89; 95% CI: 0.81, 0.98). In the evaluation of publication bias using a funnel plot, there was a major asymmetry in the distribution of study estimates potentially reflecting some publication bias for this outcome (Figures S3a-c – Appendix 8). The evidence quality was rated very low in the GRADE assessment (Table S1 – Appendix 10). Subgroup analyses showed no significant differences between groups (Figures S10-13 – Appendix 9).

3.4.4. Amphetamine-type stimulant craving

Craving at 4 weeks: Four reports included ATS craving at week 4, including 373 participants, with heterogeneity between studies approximating I^2=0%. The pooled effect estimate was non-significant when comparing bupropion with placebo (SMD: 0.04; 95%CI: −0.16, 0.24). All four included studies had a high overall risk of bias (Figures S4a-b –Appendix 8). The evidence quality was rated moderate quality in the GRADE assessment (Table S1 – Appendix 8). Subgroup analyses showed no significant differences between groups (Figures S14-15 – Appendix 9).

End-of-treatment craving: Six reports included end-of-treatment ATS craving, including 939 participants, with heterogeneity between studies approximating I^2=64%. The pooled effect was significant, favoring bupropion, i.e., lower end-of-treatment ATS craving scores compared to placebo (SMD: −0.38; 95%CI: −0.63, −0.13). All six included studies had a high risk of bias. In the evaluation of publication bias using a funnel plot, there was a minor asymmetry in the distribution of study estimates (Figures S5a-c, Appendix 8). The evidence quality was rated very low in the GRADE assessment (Table S1 – Appendix 10).

Subgroup analysis considering ATS use characteristics at baseline showed significant differences between groups for end-of-treatment ATS craving when comparing bupropion to placebo. Participants with mixed ATS use frequency showed significant craving reduction (SMD: −0.46; 95%CI: −0.70, −0.22), while those with less than daily ATS use frequency showed no significant change (SMD: 0.03; 95%CI: −0.31, 0.38). Subgroup analysis as a function of sex showed significant differences between groups, with the male-only population showing more significant craving reduction (SMD: −1.26; 95%CI: −1.87, −0.65). The mixed group of male and female participants also indicated a significant reduction (SMD: −0.29; 95%CI: −0.45, −0.13) in end-of-treatment craving for bupropion compared to placebo. Other subgroup analyses showed no significant differences between groups (Figures S16-19 – Appendix 9).

3.4.5. Addiction severity

Two reports included seven sub-scores of ASI, including 148 participants, with varied heterogeneity for ASI sub-scores between studies (I^2=0–96%). The two included studies had a high overall risk of bias (Figure S6a, Appendix 8).

The pooled effect suggested significantly lower sub-scores of ASI legal status for the bupropion compared to placebo (SMD: −0.47; 95% CI: −0.83, −0.11). The other sub-scores of ASI analyses showed varied average pooled effects which were all non-significant when comparing bupropion group with placebo: medical status score (SMD: −0.51; 95% CI: −1.54, 0.53), employment status score (SMD: −0.33; 95%CI: −1.17, 0.50), alcohol use score (SMD: −0.08; 95%CI: −0.40, 0.24), drug use score (SMD: −0.23; 95%CI: −0.90, 0.45), family/social relationship score (SMD: −0.53; 95%CI: −1.54, 0.47), and psychiatric status score (SMD: −0.90; 95%CI: −2.90, 1.09) (Figures S6b-h, Appendix 8). No

Table 3
The main results of the meta-analysis for the included outcomes[a].

Outcome	N of studies	Total N of participants/ samples/ pills number	Heterogeneity (I^2), %	Effect estimate (95%CI)	P-value for overall effect	Risk of bias results (overall), N	Publication bias[b]	GRADE rating
ATS use by urinalysis		*Urine samples (or weeks)*		*Risk ratio*				
	7	15664	89%	**0.90 (0.84, 0.96)**	<0.001	low risk, 3 some concerns, 3 high risk, 1	Minor asymmetry	⊕◯◯◯ Very low
Retention in treatment		*Participants*		*Risk ratio*				
	7	786	6%	0.97 (0.89, 1.05)	0.45	low risk, 4 some concerns, 3 high risk, 0	Minor asymmetry	⊕⊕⊕⊕ High
Treatment adherence		*Pills number*		*Risk ratio*				
	6	119680	99%	**0.91 (0.84, 0.99)**	0.03	low risk, 3 some concerns, 1 high risk, 2	Major asymmetry	⊕◯◯◯ Very low
ATS craving at week 4		*Participants*		*Std. mean difference*				
	4	373	0%	0.04 (−0.16, 0.24)	0.70	low risk, 0 some concerns, 0 high risk, 4	Not evaluated	⊕⊕⊕◯ Moderate
End-of-treatment ATS craving		*Participants*		*Std. mean difference*				
	6	939	64%	**-0.38 (−0.63, −0.13)**	0.003	low risk, 0 some concerns, 0 high risk, 6	Minor asymmetry	⊕◯◯◯ Very low
Addiction severity		*Participants*		*Std. mean difference*				
Medical status	2	148	88%	-0.51 (−1.54, 0.53)	0.34	low risk, 0 some concerns, 0 high risk, 2	Not evaluated	⊕◯◯◯ Very low
Employment status	2	148	82%	-0.33 (−1.17, 0.50)	0.43	low risk, 0 some concerns, 0 high risk, 2	Not evaluated	⊕◯◯◯ Very low
Alcohol use	2	148	0%	-0.08 (−0.40, 0.24)	0.63	low risk, 0 some concerns, 0 high risk, 2	Not evaluated	⊕⊕◯◯ low
Drug use	2	148	74%	-0.23 (−0.90, 0.45)	0.51	low risk, 0 some concerns, 0 high risk, 2	Not evaluated	⊕◯◯◯ Very low
Legal status	2	148	13%	**-0.47 (−0.83, −0.11)**	0.01	low risk, 0 some concerns, 0 high risk, 2	Not evaluated	⊕⊕◯◯ low
Family/social relationship	2	148	87%	-0.53 (−1.54, 0.47)	0.30	low risk, 0 some concerns, 0 high risk, 2	Not evaluated	⊕◯◯◯ Very low
Psychiatric status	2	148	96%	-0.90 (−2.90, 1.09)	0.37	low risk, 0 some concerns, 0 high risk, 2	Not evaluated	⊕◯◯◯ Very low
Depressive symptom severity		*Participants*		*Std. mean difference*				
	5	874	44%	-0.06 (−0.26, 0.14)	0.55	low risk, 0 some concerns, 0 high risk, 5	Moderate asymmetry	⊕◯◯◯ Very low
Drop-out following AEs		*Participants*		*Risk difference*				
	4	391	7%	0.03 (−0.01, 0.07)	0.09	low risk, 3 some concerns, 1 high risk, 0	Not evaluated	⊕⊕⊕◯ Medium
Serious AEs		*Participants*		*Risk difference*				
	8	1189	0%	-0.01 (−0.02, 0.01)	0.39	low risk, 6 some concerns, 2 high risk, 0	Moderate asymmetry	⊕⊕◯◯ low

Abbreviations: ATS, amphetamine-type stimulant; AEs, adverse events; CI, confidence interval; N, number.
[a] The statistically significant (P<0.05) results are marked in bold.
[b] Visual evaluation of funnel plot for asymmetrical distribution of studies interpreted as publication bias.

subgroup analyses were conducted for this outcome. The evidence quality was rated low for alcohol use and legal status sub-scores and was rated very low for the other sub-scores of ASI in the GRADE assessment (Table S1 – Appendix 10).

3.4.6. Depressive symptoms severity

Five reports included depressive symptom severity, including 874 participants, with heterogeneity between studies approximating I^2=44%. The pooled effect was non-significant comparing bupropion with placebo (SMD: −0.06; 95%CI: −0.26, 0.14). All five studies had a

high risk of bias. In the evaluation of publication bias using a funnel plot, there was moderate asymmetry in the distribution of study estimates, suggesting potential publication bias for this outcome (Figures S7a-c, Appendix 8). The evidence quality was rated very low in the GRADE assessment (Table S1 – Appendix 10). All subgroup analyses showed no significant differences between groups (Figures S20-22 – Appendix 9).

3.4.7. Drop-out following adverse events

Four reports included the number of participants who left the study following an AE during treatment, including 391 participants, with heterogeneity between studies approximating I^2=7%. The pooled effect was statistically non-significant comparing bupropion with placebo (RD: 0.03; 95%CI: −0.01, 0.07). One out of the four studies had some concerns of bias (Figures S8a-b, Appendix 8). The evidence quality was rated medium in the GRADE assessment (Table S1 – Appendix 10). All subgroup analyses showed no differences between groups (Figures S23-24 – Appendix 9).

3.4.8. Serious adverse events

Eight reports included the number of participants with serious AEs during treatment, including 1189 participants, with heterogeneity between studies approximating I^2=0%. The pooled effect was statistically non-significant when comparing bupropion with placebo (RD: −0.01; 95%CI: −0.02, 0.01). Two out of eight studies had some concerns of bias. In the evaluation of publication bias using a funnel plot, there was a moderate asymmetry in the distribution of study estimates (Figures S9a-c, Appendix 8). The evidence quality was rated low in the GRADE assessment (Table S1 – Appendix 10). All subgroup analyses showed no differences between groups (Figures S25-28 – Appendix 9).

4. Discussion

This meta-analysis pooled results from available studies comparing bupropion to placebo for the treatment of ATSUD. While the available studies had numerous limitations and the quality of evidence was overall relatively low, our meta-analysis suggests relatively modest benefits in terms of reduced ATS use and end-of-treatment craving in individuals receiving bupropion compared to placebo. However, our results favored placebo over bupropion regarding adherence by pill count. There were overall no significant differences between bupropion and placebo when testing all other selected outcomes.Table 4

Our meta-analysis showed a reduction of approximately 10% in the risk of ATS use, as measured by UA (13% after removing one study with high bias risk), with subgroup analysis demonstrating that participants who completed 12 weeks of bupropion treatment had a greater reduction of positive UA (i.e., approximately 15% risk reduction). This result may suggest that any beneficial effect may only be seen after a sustained use of bupropion (e.g., 12 weeks or more). A previous systematic review by Siefried et al. showed potential benefits of bupropion on ATS use reduction but without achieving statistical significance in the included studies (Elkashef et al., 2008; Shoptaw et al., 2008; Siefried et al., 2020), possibly because it did not include a more recent larger, positive trial (Trivedi et al., 2021). In addition to bupropion-induced enhancement of dopamine and noradrenaline at the synaptic level in the reward circuit (Newton et al., 2006; Rau et al., 2005; Simmler et al., 2013), possible clinical benefits could also be explained by other mechanisms, such as a reduction of methamphetamine-induced catecholamine release in brain or modulatory effects on central nicotinic receptors (Heinzerling et al., 2014). The overall modest benefit of bupropion on ATS use may reflect that ATSUD is difficult to treat, and that the observed overall low retention rates in bupropion treatment in addition to low medication adherence may contribute to the small effect size. Future efforts should focus on identifying specific populations that might benefit most from this intervention while testing treatment duration of longer than 12 weeks, as well as exploring complementary strategies to improve medication adherence and retain participants in treatment.

Our findings contrast with the results from a previous subgroup meta-analysis on the effect of psychostimulant treatment. Bhatt et al. reported no significant effect of bupropion on sustained abstinence from substances as determined by UA (Bhatt et al., 2016); It is worth mentioning that this meta-analysis did not include most of the other outcomes included in our meta-analysis, reported bupropion effect separately only in subgroup analyses, and did not include the more recent studies like Trivedi et al. (Trivedi et al., 2021). Another recent meta-analysis only included participants receiving cognitive behavioural therapy (CBT) in addition to bupropion and compared these participants with those on CBT alone; this study examining only 5 studies, however, reported no overall efficacy in terms of ATS use recurrence reduction in the combined treatment group (Apuy et al., 2023).

Our subgroup analysis comparing higher and lower doses of bupropion did not show a significant difference in average reduction in ATS use. However, it should be considered that only one study (using a large sample size) reported the effect of bupropion at 450 mg (in combination with naltrexone), in contrast to the rest of the studies using the lower 300 mg dose. It has been discussed that bupropion has some stimulant-like effects that may be dose-dependent and may help reduce potential dysphoria associated with withdrawal symptoms as well as possibly enhancing psychostimulant abstinence (Trivedi et al., 2021). In this regard, further trials testing higher doses of bupropion (and other psychostimulants) in the treatment of ATSUD seems necessary to establish the dose-response and optimization of the treatment (Trivedi et al., 2021). Finally, sufficient data on self-reported ATS use were not available for pooling in our meta-analysis. Future studies verifying the validity of patient-reported outcomes in comparison to other measures of ATS use are recommended, to better guide the research and enhance the follow-up on ATSUD treatment in the clinic (Yi et al., 2022).

The relatively modest effect size noted in this meta-analysis on ATS use may be due to other reasons, including low medication adherence and non-serious AEs associated with bupropion. Indeed, our meta-analysis showed a 10% risk reduction of medication adherence in the bupropion treatment group compared to placebo. This might also be related to the presence of non-serious AEs associated with bupropion and may be specific to the ATSUD population (Patel et al., 2016). Additional incentive including contingency management and medication adherence monitoring have been suggested to enhance bupropion treatment adherence and may be tested in future studies (Anderson et al., 2015; Heinzerling et al., 2014). The standardization of measurement of medication adherence such as employing other confirmatory methods e.g., urine or plasma testing and electronic medication package data capture should also be considered.

Further, there was a modest effect of −0.47 SMD in terms of improvement in the legal status sub-score of ASI in the bupropion group, with no overall improvement in other sub-scores. It might be hypothesized that legal status improvement of subjects may precede improvement in other psychosocial spheres later following bupropion treatment. Moreover, the absence of improvement in other spheres might be, in part, due to the high level of heterogeneity in the two studies that reported such outcomes (Elkashef et al., 2008; Ghoreishi et al., 2017). More studies with larger sample sizes and longer follow-up periods are warranted to ascertain any beneficial effect of bupropion treatment on the global functionality of the ATSUD population.

Our meta-analyses showed a small to moderate reduction of 0.38 SMD in end-of-treatment craving scores for bupropion compared to placebo. This is in line with a previous small clinical study showing reduced methamphetamine-induced subjective effects and cue-induced craving in participants treated with bupropion (Newton et al., 2006). The observed reduction in end-of-treatment ATS craving also corroborates and may explain in part the observed reduction in ATS use in participants using bupropion compared to placebo in our meta-analysis. This beneficial effect may be related to bupropion-induced inhibition of reuptake of dopamine and norepinephrine in the brain. In fact, it has

Table 4
Subgroup analyses of outcome measures by medication, maximum dose, duration of treatment, and sensitivity analysis by high risk of bias [a].

		ATS use by UA		Retention in treatment		Adherence		ATS craving at week 4		End-of-treatment ATS craving		Depression severity		Drop-out following AEs		Serious AEs	
Number of studies/Effect estimate		**N**	**RR (95%CI)**	**N**	**RR (95%CI)**	**N**	**RR (95%CI)**	**N**	**SMD (95%CI)**	**N**	**SMD (95%CI)**	**N**	**SMD (95%CI)**	**N**	**RD (95%CI)**	**N**	**RD (95%CI)**
Maximum dose /day and Addition of naltrexone	300 mg (without naltrexone)	5[1]	0.90 (0.81, 1.00)*	6	1.02 (0.88, 1.19)	4	0.95 (0.91, 1.00)*		-	4	-0.44 (−0.94, 0.07)	3	0.10 (−0.15, 0.35)		-	6	-0.01 (−0.04, 0.02)
	450 mg (with naltrexone)	2[2]	0.92 (0. 89, 0.94)*	1	0.95 (0.88, 1.02)	2	0.84 (0.72, 0.99)*		-	2	-0.37 (−0.54, −0.20)*	2	-0.18 (−0.48, 0.12)		-	2	-0.01 (−0.03, 0.01)
Methamphetamine (ATS) use characteristics	Mixed use frequency[+]	5[3]	0.90 (0.85, 0.94)*	4	0.95 (0.89, 1.02)	5	0.91 (0.83, 1.00)	3	0.0 (−0.27, 0.27)	5	**-0.46 (−0.70, −0.22)***	4	-0.11 (−0.33, 0.12)	2	0.0 (−0.07, 0.07)	5	-0.01 (−0.02, 0.01)
	Less than daily use frequency	2[4]	1.09 (0.56, 2.11)	3	1.01 (0.65, 1.56)	1	0.94 (0.92, 0.96)*	1	0.09 (−0.22, 0.40)	1	**0.03 (−0.31, 0.38)**	1	0.12 (−0.23, 0.48)	2	0.05 (−0.02, 0.11)	3	-0.01 (−0.05, 0.02)
Duration of treatment	12 weeks	4[7]	**0.85 (0.78, 0.93)***	5	1.04 (0.90, 1.20)	3	0.96 (0.90, 1.02)		-	4	-0.44 (−0.94, 0.07)	3	0.10 (−0.15, 0.35)		-	5	-0.01 (−0.04, 0.02)
	<12 weeks	3[8]	**0.98 (0.89, 1.08)**	2	0.78 (0.42, 1.45)	3	0.87 (0.77, 0.99)*		-	2	-0.37 (−0.54, −0.20)*	2	-0.18 (−0.48, 0.12)		-	3	0.0 (−0.02, 0.02)
Sex of participants	Only-male population	1[9]	0.80 (0.71, 0.90)*	1	1.00 (0.78, 1.29)	1	0.95 (0.91, 1.00)*	1	-0.07 (−0.62, 0.49)	1	**-1.26 (−1.87, −0.65)***		-	1	0.0 (−0.14, 0.14)	1	0.0 (−0.14, 0.14)
	Mixed-sex population	6[10]	0.91 (0.85, 0.97)*	6	0.98 (0.87, 1.11)	5	0.91 (0.83, 0.99)*	3	0.06 (−0.16, 0.27)	5	**-0.29 (−0.45, −0.13)***		-	3	0.03 (−0.02, 0.08)	7	-0.01 (−0.02, 0.01)

[+]Including daily and less than daily ATS use frequency or unspecified ATS use frequency.

Abbreviations: ATS, amphetamine-type stimulant; UA, urinalysis; AEs, adverse events; RR, relative risk; SMD, standardized mean difference; RD, risk difference; CI, confidence interval.

1. Das (2010), Elkashef (2008), Heinzerling (2013), Heinzeling (2014), Shoptaw (2008); 2. Trivedi (2021); 3. Das (2010), Elkashef (2008), Shoptaw (2008); 4. Heinzerling (2013), Heinzeling (2014); 5. Elkashef (2008), Shoptaw (2008); 6. Elkashef (2008), Heinzerling (2013), Shoptaw (2008); 7. Das (2010), Elkashef (2008), Heinzerling (2014), Shoptaw (2008); 8. Trivedi (2021), Heinzerling (2013); 9. Das (2010); 10. Elkashef (2008), Heinzerling (2013), Heinzeling (2014), Shoptaw (2008), Trivedi (2021).

[a] The statistically significant subgroup differences are marked bold.

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

been shown that as a result of a synaptic change in the reward system, cue-induced craving reactivity may potentially mediate the observed reduction in ATS craving and inhibit any methamphetamine use-related release of dopamine (Newton et al., 2006). In their trial using a combination of 450 mg bupropion with naloxone, Trivedi et al. demonstrated a marginally greater reduction in ATS craving in our subgroup analysis (Trivedi et al., 2021), and warrants further research.

Our meta-analysis did not show significant effects of bupropion compared to placebo on depressive symptom severity overall and in subgroup analyses. It is noteworthy that the depressive symptom scores of participants potentially varied at baseline. In addition, participants with severe depression were excluded from the analyzed studies, and this might have masked the proven beneficial effects of bupropion on depression. Other authors suggested that the absence of bupropion's effect on depressive symptom severity measures may be due to the psychological interventions offered to participants in both bupropion and placebo groups in such samples with no depression or with mild depressive symptoms. In fact, it was discussed that the access to other treatments by participants may be diluting the potential beneficial effects of bupropion on depressive symptoms (Heinzerling et al., 2014).

This study included subgroup analyses to examine the potential effect of bupropion on specific subpopulations of people with ATSUD. We found that biological sex may moderate bupropion's effect on ATS craving. Indeed, one study that included only male participants showed a larger reduction in end-of-treatment craving for bupropion; however, this study had a high risk of bias and these results should be interpreted cautiously (Ghoreishi et al., 2017). More research is required to investigate the potential effect of sex differences on ATSUD treatment and outcomes. Further, our subgroup analyses showed that participants receiving bupropion with mixed ATS use frequency (daily and less than daily ATS use frequency or unspecified ATS use frequency) at baseline had similar serious AEs and reported a greater reduction in end-of-treatment ATS craving when compared to participants with less than daily ATS use. However, one study in our meta-analysis, by Elkashef et al., showed that bupropion treatment compared to placebo was associated with less methamphetamine use in participants with low to moderate baseline methamphetamine use (Elkashef et al., 2008). The authors suggested that the neurotoxic effects of chronic use of high-dose methamphetamine might be responsible for such results (Elkashef et al., 2008; Shoptaw et al., 2008). Our meta-analysis did not have enough data to test such hypothesis. The potential differential effect of bupropion as a function of ATS use frequency may be verified in future trials.

Finally, the variations in populations in the included studies may have contributed to the moderate to high heterogeneity observed in our study. This might partly explain the non-significant overall pooled effects as well as our subgroup analyses for many of the outcomes. Also, one should interpret the reported significant results on ATS use, adherence, and craving with caution due to the presence of high heterogeneity levels. Indeed, the subgroup analyses only explained some of the heterogeneity observed for these outcomes (i.e., explanatory factors included treatment duration for ATS use; sex, and ATS use frequency for craving; and there were no heterogeneity explanatory factors for adherence). Further, the inclusion of Trivedi (2021) study with its large sample size may have skewed results to some extent more favourably towards bupropion efficacy compared with previous meta-analyses, and our results should be considered accordingly. However, there was no statistically significant difference between Trivedi's results and other studies in subgroup analyses. More research on the efficacy and safety of using other treatment modalities, and their combination among individuals with higher frequency and duration of ATS is warranted (Siefried et al., 2020). The latter may be critical to fine-tune recommendations and guide clinical treatment algorithms for various populations with ATSUD.

4.1. Strengths and limitations

The systematic search for all records and the use of GRADE and ROB2 Tools for a standard bias and evidence evaluation and reporting are among the strengths of this meta-analysis. The present meta-analysis also has limitations. Some of the included studies had a small sample size and high heterogeneity of the final pooled effects. Also, some studies excluded individuals with physical and mental comorbidities, limiting the extrapolation of pooled results to general ATSUD populations. Further, our meta-analysis mainly included adult populations with one small study conducted in adolescents. Given the particularities of this population, the generalization of our results to this population might not be judicious as additional research in this population is needed. Also, almost half of the included samples come from a combination study on bupropion with naltrexone. Despite conducting subgroup analyses by such a combination, it was difficult to distinguish the effect of such a drug combination from the effect of bupropion alone. Medication adherence was assessed by reported pill counts conducted mainly by clinicians in most of the studies. However, the validity of this method must be tested by other methods such as plasmatic- and urine-based medication-level testing (Heinzerling et al., 2014). Other potential heterogeneity sources, such as the use of amphetamine versus methamphetamine by participants, were not verified and may underlie different participant characteristics (Siefried et al., 2020). Moreover, the meta-analysis included lower proportions of women, with two studies conducted only in men; therefore, our results should be interpreted with caution. Many reported outcomes were classified as having high bias risk, mainly because of a lack of accessible information on missing data imputation. Many of the included studies had missing data mainly related to drop-out, which may be not missing at random. However, many of these studies had a low risk of bias on most of the other evaluated bias domains. Also, the quality and manufacture of unregulated amphetamine have changed over time, and our reported associations may be verified in future research focusing on ATSUD populations who might report using high-potency stimulants. We also pooled the proportion of ATS-positive UAs (in most studies) with the proportion of ATS-positive weeks (based on UA) in the Elkashef et al. study, and result interpretation should take this into consideration (Elkashef et al., 2008). However, sensitivity analysis by removing the last study showed similar results. Finally, most studies in our meta-analysis did not include or indicate other comorbid substance use disorders, such as opioid or alcohol use disorders, and our results may not be generalizable in polydrug use populations, warranting more research on the subject in additional population groups (Chan et al., 2020).

5. Conclusion

Notwithstanding many limitations and overall low quality of evidence, the results from our meta-analysis suggest that bupropion (300–450 mg/day) may have modest benefits for ATSUD treatment and the clinical relevance of such a relatively small effect should be verified. An analysis that focuses on who might benefit more from such a therapeutic intervention might yield more significant results while testing higher bupropion doses and longer treatment periods. It also suggests that one may develop and test additional therapeutic options while studying potentially clinically relevant effect modifiers to improve outcomes in ATSUD. Finally, putting more effort into improving psychosocial interventions is warranted.

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CRediT authorship contribution statement

Conceptualization: HB, DJA, HS; Methodology: HB, HS, AB, SD, PB, BLF, CGS, KS, VST, DZ, NE, DJA; Formal analysis: HB; Investigation: HB, HS, SD, DZ; Writing - Original Draft: HB, HS, AB, SD, DJA; Writing - Review & Editing: HB, HS, AB, SD, PB, BLF, CGS, KS, VST, DZ, NE, DJA; Supervision: DJA; Project administration: HB, DJA; Funding acquisition: DJA.

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Declaration of Competing Interest

PB is the site PI for upcoming trial on psychostimulants for the treatment of methamphetamine use disorder. CGS is a consultant at Clearmind Medicine. NE has received funding from the Australian National Health and Medical Research Council (NHMRC) to conduct a study examining lisdexamfetamine for the treatment of MAUD (APP1109466). KS has received funding from the National Centre for Clinical Research on Emerging Drugs (NCCRED) to conduct a pilot study of lisdexamfetamine for methamphetamine withdrawal (NCCRED is funded by the Australian Government Department of Health [4-EH8ULD4]). BLF has obtained funding from Pfizer Inc. (GRAND Awards, including salary support) for investigator-initiated projects. BLF has obtained funding from Indivior for a clinical trial sponsored by Indivior. BLF 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. BLF was also provided a coil for a Transcranial magnetic stimulation (TMS) study from Brainsway. BLF 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. BLF 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. DJA receives study material from Cardiol Therapeutics and Exka for clinical trials funded by the Quebec Ministry of Health and Social Services.

All other authors declare no conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2023.111018.

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