JAMA Psychiatry | Original Investigation

Evaluating Reduced Use and Abstinence as Outcomes in Pharmacotherapy Trials for Stimulant Use Disorder
A Meta-Analysis of 12 Randomized Controlled Trials

Masoumeh Amin-Esmaeili, MD, MPH; Mehdi Farokhnia, MD, MPH; Ramin Mojtabai, MD, MPH, PhD; Lorenzo Leggio, MD, PhD; Renee M. Johnson, PhD, MPH; Ryoko Susukida, PhD

IMPORTANCE Cocaine and methamphetamine use disorders are major public health challenges with no approved pharmacological treatments. Reliance on complete abstinence as the sole end point in randomized controlled trials (RCTs) may hinder identification of effective therapies, as it is often overly stringent, whereas reduced stimulant use is a promising alternative given its association with improved health outcomes.

OBJECTIVES To evaluate the treatment effect of pharmacological interventions tested in RCTs for stimulant use disorder, comparing reduced use to total abstinence.

DESIGN, SETTING, AND PARTICIPANTS A meta-analysis was conducted of 12 US National Institute on Drug Abuse–sponsored multisite RCTs conducted between 2001 and 2011 evaluating pharmacological interventions among people seeking treatment for cocaine or methamphetamine dependence. One-stage individual participant meta-analysis was used, and analyses were performed between August 2024 and November 2025.

EXPOSURE Tested pharmacotherapies included topiramate, bupropion, modafinil, ondansetron, tiagabine, cabergoline, reserpine, selegiline, and baclofen, each compared to placebo in double-blind trials. All participants received cognitive behavioral therapy regardless of treatment assignment.

MAIN OUTCOMES AND MEASURES The primary outcome was reduced drug use based on self-report, defined as a transition from high frequency (≥5 days/month) to low frequency (1-4 days/month) of stimulant use or transition to abstinence. Abstinence, verified by urine toxicology, served as the secondary outcome. Mixed-effects logistic regression models with random study effects and inverse probability weighting were used to estimate pooled treatment effects.

RESULTS A total of 2000 participants were included (1134 in cocaine RCTs and 866 in methamphetamine RCTs), of whom 587 (29.4%) were women, with a mean (SD) age of 39.7 (8.6) years. Overall, 446 participants (31.2%, weighted) achieved reduced use, whereas 184 (13.3%, weighted) achieved abstinence at the trial end point. No significant differences were observed between the pooled active treatment and placebo groups for either outcome, overall or when stratified by stimulant type. In analyses of individual medications, cabergoline showed positive effect sizes (Cohen *h*, 0.352; 95% CI, 0.115-0.590), indicating significantly higher rates of reduced cocaine use with cabergoline than pooled placebo.

CONCLUSIONS AND RELEVANCE The present findings of this meta-analysis underscore the importance of evaluating a continuum of outcomes rather than focusing solely on abstinence in RCTs. The results suggest that reductions in stimulant use may serve as meaningful efficacy signals that could be underestimated when relying solely on stringent outcomes, such as abstinence.

JAMA Psychiatry. 2026;83(8):799-806. doi:10.1001/jamapsychiatry.2026.1092
Published online June 3, 2026.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Masoumeh Amin-Esmaeili, MD, MPH, Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, 550 Broadway, 2nd Floor, Rm 213H, Baltimore, MD 21205 (mamines1@jh.edu).

Cocaine and methamphetamine use disorders are pressing public health problems and are associated with substantial morbidity, mortality, and social burden.[1-6] Despite decades of research, no pharmacological treatment has yet received approval for stimulant use disorder.[7] One contributing factor may be the long-standing emphasis on complete abstinence as the only acceptable treatment end point. Given the chronic, relapsing nature of stimulant use disorder[8] and the high likelihood of lapses during early treatment, abstinence may represent an overly stringent and unattainable goal for many individuals, particularly within the limited duration of randomized controlled trials (RCTs).

For alcohol use disorder, reduced consumption has been qualified by key regulatory agencies, including the US Food and Drug Administration (FDA) and European Medicines Agency, as an acceptable outcome, consistent with a substantial body of evidence demonstrating dose-response associations between reductions in drinking levels and improvements in health, functioning, and alcohol-related harms, supported by epidemiologic data, clinical validation studies, and analyses of RCTs.[9,10] By contrast, comparable evidence linking reduced stimulant use to FDA-accepted clinical outcomes is limited, and reduced use has not yet been accepted as a regulatory end point for medications targeting stimulant use disorder.

Despite this regulatory gap, a growing body of evidence has highlighted the clinical relevance of alternative, more achievable end points, such as reductions in the frequency of stimulant use.[11-13] In our previous work, we empirically evaluated such nonabstinence outcomes in patients with cocaine or methamphetamine use disorder who participated in RCTs, regardless of whether participants received active treatment or placebo.[12,14] We compared *reduced use*, defined as a transition from high (≥5 days/month) to low (1-4 days/month) frequency of use, as well as transition to abstinence, with *no reduced use*, which included no change or increased frequency of use. Findings showed that while abstinence was associated with the greatest overall improvements in several clinical indicators compared to no reduced use, reduced use was also associated with significant and clinically meaningful improvements in craving, drug-seeking behaviors, depression, and drug-related problems measured by several functional domains of the Addiction Severity Index-Lite (ASI-Lite), including drug, alcohol, employment, and psychiatric domains, as well as improvement in global functioning from baseline to the end of the trial.[12] Importantly, reduced use was also significantly associated with sustained improvement, as indicated by no positive urine test results at the end of follow-up.[12] These findings suggest the potential value of examining reduced use in addition to abstinence as a treatment outcome for stimulant use disorder. Similarly, in another pooled sample of individuals with cocaine use disorder, Roos and colleagues[11] demonstrated that 1- or 2-level reductions in cocaine use frequency from baseline to the end of treatment were associated with improvements in cocaine-related problems, psychiatric symptoms, and other indicators of global functioning, with benefits sustained over 12 months of follow-up.

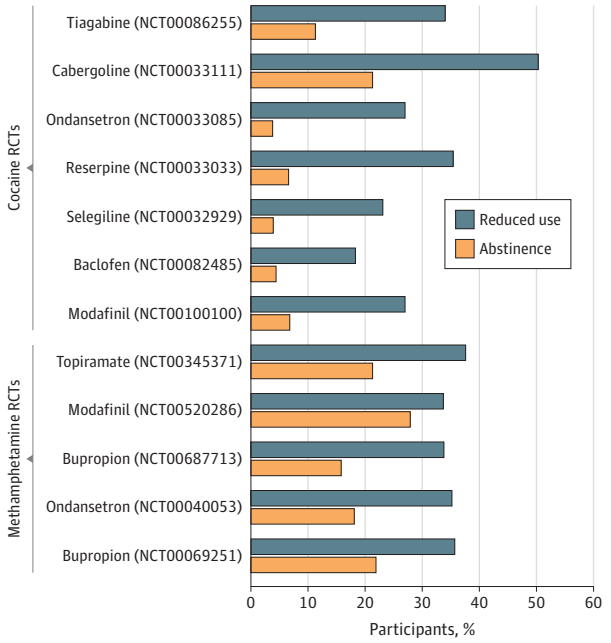
Key Points

Question Do pharmacotherapies for stimulant use disorder show evidence of benefit when reduced use is evaluated as an outcome?

Findings In this meta-analysis of 12 randomized controlled trials, no medication demonstrated a significant benefit over placebo for abstinence. When reduced use was evaluated, pooled treatment effects remained nonsignificant; however, effect size estimates were consistently larger in magnitude than those observed for abstinence, and a positive signal for reduced cocaine use was observed for cabergoline in medication-specific analyses.

Meaning Evaluating reduced stimulant use alongside abstinence may provide additional clinically relevant information for interpreting treatment effects in pharmacotherapy trials for stimulant use disorder.

Figure 1. Bar Graph Showing the Proportion of Participants Who Achieved Reduced Use and Abstinence in Randomized Controlled Trials (RCTs) of Cocaine and Methamphetamine Use Disorders



Our study was inspired by a comparable paradigm shift that occurred in the alcohol field, where total abstinence was historically regarded as the only indicator of treatment success.[15] Following consensus recommendations from the National Institute on Alcohol Abuse and Alcoholism, the FDA now qualifies "percent no heavy drinking days" as an acceptable outcome for alcohol use disorder RCTs.[15-17] Even more compelling is a recent body of work in the alcohol field showing that a minimum 2-level reduction in the World Health Organization Risk Drinking Levels leads to several physical and psychological benefits and is now an FDA-qualified outcome for alcohol use disorder RCTs.[9,17] Several studies show that reductions in drinking frequency and/or intensity, even without complete abstinence, can yield significant gains in health and psychosocial functioning,[9,10,18,19] an approach

Table. Effect of Pharmacological Interventions on Reduced Use and Abstinence at the End of Randomized Controlled Trials (RCTs) for Cocaine and Methamphetamine Use Disorders

Outcome	Predicted proportion, %[a]		Effect size, Cohen *h* (95% CI)[b]	*P* value
	Active treatment	Placebo		
Pooled sample (12 RCTs)				
Reduced use[c]	32.5	29.3	0.068 (−0.044 to 0.180)	.29
Abstinence	13.6	12.7	0.026 (−0.072 to 0.124)	.89
Cocaine (7 RCTs)				
Reduced use[c]	28.6	27.6	0.022 (−0.128 to 0.171)	.83
Abstinence	6.7	7.1	−0.013 (−0.143 to 0.117)	.61
Methamphetamine (5 RCTs)				
Reduced use[c]	37.9	32.1	0.122 (−0.047 to 0.291)	.18
Abstinence	22.5	20.2	0.057 (−0.105 to 0.219)	.75

[a] Marginal predicted proportions were estimated using mixed-effects logistic regression models with random intercept for site identifier and random slope for treatment arms to account for between-study heterogeneity. Models were weighted using inverse probability weighting and adjusted for sociodemographic factors (sex, age, race and ethnicity, marital status, and employment status), as well as length of the trial.

[b] Cohen *h* is a standardized effect size for differences in proportions. $|h|<0.20$ is considered negligible; 0.20, small; 0.50, medium; and 0.80, large. Positive *h* values indicate higher response rates in the active treatment group compared with placebo.

[c] Reduced use was defined as either abstinence or a reduction in frequency of use from baseline to the end of the trial as opposed to no reduction or increased use.

that parallels our and other current efforts to redefine meaningful outcomes for cocaine and methamphetamine use disorders RCTs.

Building on this evolving framework and our prior work, the present meta-analysis examines how treatment effect estimates differ when applying a traditional abstinence-based outcome vs a reduced use outcome. This study leverages our previous large-scale data harmonization effort,[12,14,20] which integrated individual-level data from 12 US National Institute on Drug Abuse–sponsored pharmacotherapy RCTs for cocaine and methamphetamine use disorders. The harmonization process involved aligning key variables across trials, including eligibility criteria, outcome measures, and sociodemographic covariates, to enable cross-study comparability and pooled analyses using consistent definitions. Using this dataset, we conducted a 1-stage individual participant data meta-analysis (IPD-MA)[21-23] to examine whether the estimated effects of pharmacological interventions differed by the type of outcome measure used. This approach enables us to demonstrate how interpretations of treatment efficacy may change when moving from a strict abstinence-based model to a more attainable reduced use outcome.

Methods

Overview

This study is a meta-analysis using harmonized datasets from RCTs that evaluated various pharmacological interventions for individuals diagnosed with stimulant use disorder, either cocaine or methamphetamine use disorder. We aimed to evaluate reduction in the frequency of stimulant use, as well as abstinence, and to assess the efficacy of pharmacological interventions both within each RCT and in the pooled sample compared with the pooled placebo group.

Included Studies in the Pooled Dataset

The original deidentified datasets were obtained from the publicly accessible NIDA Data Share platform. The data were harmonized based on methodologies previously reported.[24] The study included data from 12 multisite RCTs (N = 2000), all of which had comparable eligibility criteria, recruitment strategies, and key measures. Among the included studies on methamphetamine use disorder, 5 separate RCTs evaluated 4 different medications, including (1) topiramate, an anticonvulsant[25]; (2) bupropion (evaluated in 2 RCTs),[26,27] a norepinephrine and dopamine reuptake inhibitor; (3) modafinil,[28] a central nervous system stimulant; and (4) ondansetron,[29] a 5-HT3 serotonin-receptor antagonist. In cocaine use disorder RCTs, ondansetron,[30] modafinil,[31] and 5 other medications were assessed: (1) tiagabine,[32] a selective γ-aminobutyric acid (GABA) reuptake inhibitor; (2) cabergoline,[33] a dopamine receptor agonist; (3) reserpine,[34] an adrenergic blocking agent; (4) selegiline,[35] a monoamine oxidase inhibitor; and (5) baclofen,[36] a GABA-B receptor agonist. All medications were compared with a placebo in a double-blind fashion, and all participants received cognitive behavioral therapy regardless of treatment assignment. eTable 1 in Supplement 1 summarizes the characteristics of the included RCTs. Each RCT received appropriate institutional review board approval, and each participant signed an informed consent form.

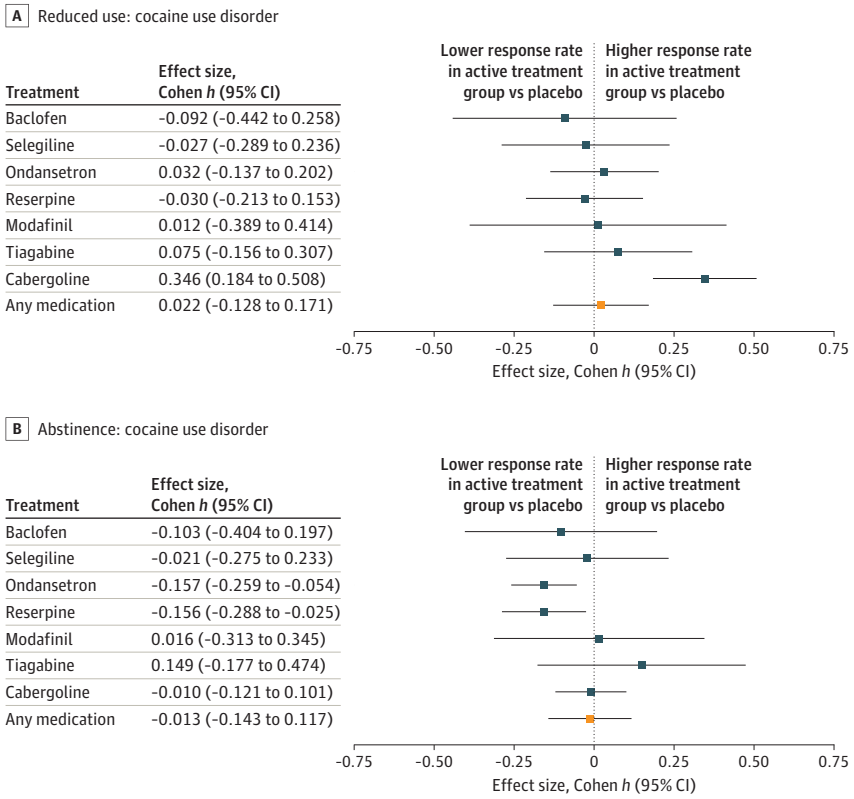
Participants

Participants in the original RCTs sought treatment across various treatment centers. All participants were aged 18 years or older and met the *DSM-IV* criteria for either cocaine dependence (n = 1134) or methamphetamine dependence (n = 866) (henceforth referred to as cocaine use disorder and methamphetamine use disorder, respectively, for consistency with the current *DSM-5* terminology). Each participant had at least 1 positive urine test result for their primary drug of use during the baseline assessment. Cocaine and methamphetamine use disorder trials were mutually exclusive; participants with one disorder were not enrolled in trials targeting the other.

Measurements

The outcome was constructed based on the self-reported frequency of cocaine or methamphetamine use from baseline to

Figure 2. Forest Plot Showing Treatment Effects on Reduced Use (A) and Abstinence (B) for Each Individual Medication vs a Pooled Placebo Group in Randomized Controlled Trials for Cocaine Use Disorder



the end of each trial. The frequency of use was derived from the drug use section of the ASI-Lite, which records the number of days of drug use in the past month. Following prior work from our group[12,14] and others,[11] frequency of use was categorized into the following 3 levels: no use (0 days), low-frequency use (1-4 days/month), and high-frequency use (≥5 days/month). Participants who self-reported no drug use were classified as abstinent only if their urine drug test results were negative during the final treatment month. Individuals with missing urine samples were labeled as missing, even if they reported no use. The primary outcome was defined based on 2 mutually exclusive categories: (1) reduced use, defined as at least 1-level reduction in frequency, either transition from high- to low-frequency use (≥5 to 1-4 days/month), or from high- or low-frequency use to abstinence (0 days/month); and (2) no reduced use, which included no change or increased frequency of use. Additionally, a binary variable was created for abstinence (yes/no) as the secondary outcome. Outcome definitions build on our previous work,[12] which demonstrated that reduced stimulant use was significantly associated with (1) meaningful improvements in mental health symptoms, (2) declines in functional and social problems associated with drug use, (3) lower intensity of craving, and (4) overall improvements in well-being and global functioning. To provide descriptive context for the frequency-based outcome definitions, we summarize the distribution of days of use at baseline and end of trial across transition categories among participants with reduced use (eTable 2 in Supplement 1).

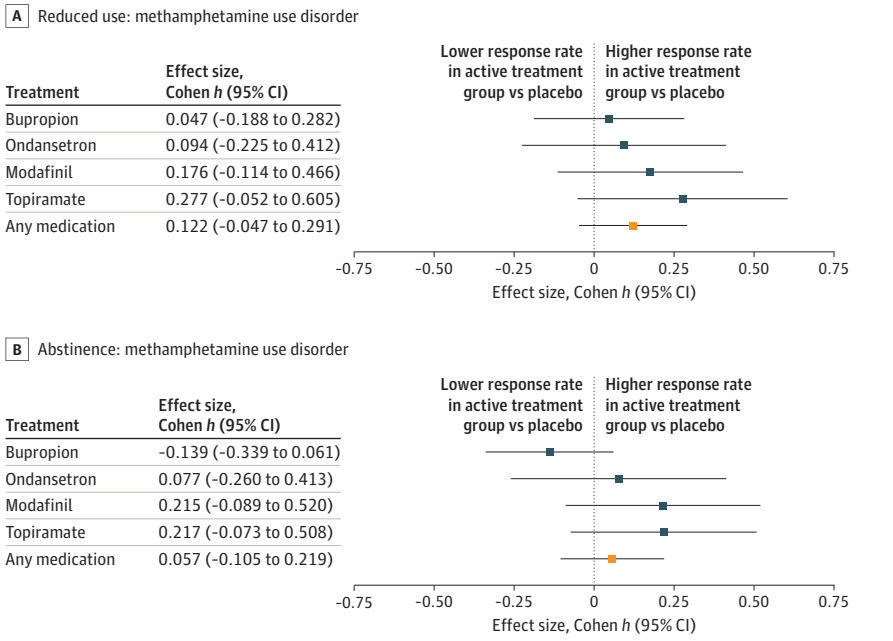
Statistical Analysis

The weighted proportion for both the primary outcome (reduced use) and secondary outcome (abstinence) was estimated for each individual RCT and the pooled sample, addressing missingness in outcomes using inverse probability weighting (IPW). To estimate the pooled treatment effect of any pharmacological intervention for achieving the study outcomes across the full sample as well as within cocaine and methamphetamine RCTs, a 1-stage IPD-MA[37,38] approach was applied using multilevel mixed-effect logistic regression. Next, a multicategory treatment variable was constructed, which combined all placebo arms into a pooled reference group and retained individual treatment arms separately. The analyses were repeated using the multicategory treatment variable to compare each active treatment against the pooled placebo group.

The random intercept (site identifier) and slope (treatment) were incorporated as random effects to account for heterogeneity across studies. In addition to IPW to account for missing outcome, all analyses were adjusted for sociodemographic factors, including sex, age, race and ethnicity, marital or relationship status, and employment status, as well as trial duration (in weeks).

Results were visualized in forest plots using standardized effect sizes. To generate standardized effect sizes (Cohen *h*) and

Figure 3. Forest Plot Showing Treatment Effects on Reduced Use (A) and Abstinence (B) for Each Individual Medication vs a Pooled Placebo Group in Randomized Controlled Trials for Methamphetamine Use Disorder



corresponding 95% confidence intervals, marginal predicted probabilities derived from the mixed-effects logistic regression models were used. Cohen *h* was computed as $h = \phi_{\text{Medication}} - \phi_{\text{Placebo}}$, where $\phi_x = 2 \times \arcsin(\sqrt{\text{proportion of x}})$. Standard errors and confidence intervals were obtained analytically using the delta method. Cohen *h* values of 0.20, 0.50, and 0.80 represent small, medium, and large effect sizes, respectively. All analyses were conducted using Stata version 18.5 (StataCorp). All statistical tests were 2-tailed, and results were considered statistically significant at $P < .05$.

Results

A total of 2000 individuals were included in the analyses, including 1134 participants in cocaine RCTs and 866 in methamphetamine RCTs, of whom 587 (29.4%) were women, with a mean (SD) age of 39.7 (8.6) years. Overall, 446 participants (31.2%, weighted) achieved reduced stimulant use, including 241 (28.2%, weighted) in cocaine RCTs and 201 (35.0%, weighted) in methamphetamine RCTs. Abstinence was achieved by 184 participants (13.3%, weighted) of the total sample, with a lower proportion in cocaine RCTs (7.1%, weighted; n = 60) compared with methamphetamine RCTs (21.1%, weighted; n = 124). **Figure 1** illustrates the proportions of participants with reduced use and abstinence across individual RCTs.

Across all trials, 228 participants (32.5%) receiving active medication achieved reduced use compared with 218 (29.3%) receiving placebo (*h* = 0.068; 95% CI, -0.044 to 0.180). Abstinence rates were 13.6% for active treatment and 12.7% for placebo (*h* = 0.026; 95% CI, -0.072 to 0.124). No statistically significant differences were observed between active treatment and placebo for either outcome in the pooled sample or in analyses stratified by cocaine and methamphetamine trials. The effect size estimates for reduced use were somewhat larger in magnitude than those for abstinence, although these differences did not reach statistical significance (**Table**).

When comparing individual medications with the pooled placebo group, none of the medications demonstrated a statistically significant positive effect on abstinence (eTables 3 and 4 in Supplement 1). By contrast, cabergoline was associated with a significantly higher predicted proportion of self-reported reduced cocaine use compared with placebo (44.2% vs 27.6%), with a small to medium effect size (Cohen *h* = 0.346; 95% CI, 0.184-0.508) (eTable 3 in Supplement 1). Forest plots depicting these effects for both outcomes are shown in **Figures 2** and **3**.

Discussion

In this pooled meta-analysis of 12 RCTs of pharmacological interventions for cocaine or methamphetamine use disorder, no medication demonstrated a statistically significant effect on achieving abstinence compared with placebo. When evaluating reduced use as the outcome, overall treatment effects were modest and not statistically significant in the full sample and when stratified by the target drug (cocaine or methamphetamine). Each individual trial was also assessed; although none of the medications demonstrated significant effects on abstinence, cabergoline showed a small to medium effect on reduced cocaine use. These results highlight the value of examining nonabstinence outcomes to further characterize and interpret treatment effects in people with stimulant use disorder.

Across trials, the primary outcomes in the original studies were abstinence-based measures, most commonly urine toxicology–verified continuous abstinence during treatment.[25-36] None of the trials included in this pooled analysis prespecified categorical reductions in frequency of target stimulant drug as an outcome. Although several trials reported continuous measures of use or percentage change over time, reductions in frequency of use were not explicitly evaluated as an end point in the original RCTs. Reductions in stimulant use may not be fully reflected in urine toxicology, which primarily detects recent use and may miss partial or intermittent reductions, especially over short trials. This may explain why cabergoline showed an interpretable effect of the self-reported measure of drug use despite null findings on urine toxicology.

Cabergoline, an ergoline-derived dopamine D2 receptor agonist,[39] showed promise as a treatment for cocaine use disorder. We detected a small to moderate efficacy signal for cabergoline on reduced cocaine use. Cabergoline has the ability to modulate neuronal activity at the level of the mesolimbic dopaminergic system, which is a key aspect of the putative mechanisms related to cocaine use, reinforcement, and relapse.[40] The biological plausibility is 2-fold: (1) slow-onset, long-acting dopamine agonists are expected to have lower addictive potential, and (2) dopamine receptor agonists may attenuate cocaine's priming effects by counteracting the mesolimbic dopaminergic downregulation that results from chronic cocaine use.[41] These considerations positioned cabergoline as a promising candidate in the Cocaine Rapid Efficacy Screening Trial (CREST), which evaluated 19 pharmacological agents for cocaine use disorder.[42] In a pilot RCT, 3 of these candidate medications (hydergine, levodopa/carbidopa, and cabergoline) were each tested in 15 participants. Only participants randomized to cabergoline provided a significantly higher proportion of cocaine-negative urine samples compared with placebo (42.4% vs 25.0%; $P = .05$).[43] In the present study, we used data from a larger phase 2 trial (NIDA CTO-0007 [NCT00033111]; n = 140),[33] the findings of which (to the best of our knowledge) have not been published to date. While our analysis did not demonstrate superiority of cabergoline over placebo for achieving abstinence, it did show significant superiority for achieving reduction in cocaine use. Notably, nearly 50% of participants receiving cabergoline met the reduced use end point, suggesting a clinically interpretable treatment signal that was not captured when using abstinence as an outcome. Consistent with this signal, an open-label study also showed potential benefits of cabergoline in maintaining abstinence among detoxified cocaine users.[44] A more recent 12-week RCT of cabergoline in 60 male patients with methamphetamine use disorder found a significantly greater proportion of participants testing negative for methamphetamine in the cabergoline group than placebo group after week 7 of the trial, although the between-group differences observed in later weeks should be interpreted cautiously in light of the modest sample size and limited generalizability.[45]

Taken together, findings from prior studies (albeit pilot and limited in sample size) align with the modest treatment signal observed in the present analysis and underscore that cabergoline may warrant renewed investigation as a potential pharmacotherapy for cocaine use disorder, especially using novel and clinically meaningful outcomes like reduction in use.

Among other individual medications, topiramate in methamphetamine RCTs showed a positive (but not statistically significant) effect over placebo, aligning with growing interest in this agent as a potential candidate for stimulant use disorder. A 2025 systematic review focused on cocaine use disorder[46] reported that topiramate may facilitate early abstinence and reduce cocaine use, with general favorable treatment retention and tolerability. In the present analysis, evidence for topiramate was derived from methamphetamine RCTs. Although the evidence remains preliminary, these findings suggest that topiramate may warrant further investigation for stimulant use disorders, particularly in studies designed and powered to detect clinically meaningful reductions in use.

Notably, reductions in stimulant use were often observed in both active medication and placebo groups. These patterns have been observed in previous analyses of these data using trajectory analysis[47,48] and likely reflect nonspecific trial effects, such as participants' expectations and motivations, behavioral support, and engagement with a health care setting, rather than medication-specific mechanisms alone. These findings are consistent with other research supporting the contribution of nonspecific factors and placebo effect in recovery from different substance use disorders.[49-51]

Although the reduced use outcome in this study was based on prior work demonstrating associations with psychosocial and functional improvements,[11,12] the cutoffs for reduced use represented a pragmatic choice that admittedly required a degree of investigator judgment, underscoring the need for future research to establish empirically validated optimal thresholds linked to clinical, functional, and patient-centered outcomes.

Limitations

Several limitations of this study should be noted. First, pooling placebo participants across trials resulted in a substantially larger placebo sample compared with individual medication arms, which could affect the comparability of effect estimates. This approach was used to increase statistical power and precision and was supported by the high degree of methodological consistency across NIDA-sponsored trials, including randomized double-blind designs, common outcome measures, and standardized quality assurance and data monitoring procedures.[52] However, placebo groups were drawn from different studies that varied in setting, potentially introducing unmeasured heterogeneity even after accounting for the random effect of study sites in the 1-stage IPD-MA. Second, missing outcome data were addressed using IPW, a widely used approach in clinical trials and substance use research, as it models the probability of missingness based on observed covariates.[53] However, residual bias from nonrandom missingness cannot be ruled out. Third, although reduced use was statistically associated with improvements in clinical indicators in prior studies,[11,12] its broader clinical meaningfulness, such as impact on functioning, quality of life, or relapse risk, requires further validation, especially in the context of longer-term trials. Fourth, although most trials monitored adherence via pill counts, suboptimal medication exposure cannot be ruled out, and varia-

tion across studies should be considered when interpreting null findings. Notably, in the cabergoline trial, study medication was administered directly at clinic visits by the research team, so adherence was not a concern.[33] Finally, we conducted multiple comparisons without formal adjustment for the familywise error rate. Although the findings related to cabergoline remained statistically significant after Bonferroni correction for the 30 tests performed, these analyses were exploratory and hypothesis generating in nature. Therefore, the findings should be interpreted cautiously and not as confirmatory evidence. Replication in independent samples is warranted.

We also acknowledge that these results do not constitute definitive evidence for regulatory decision-making, but rather provide initial, yet robust, evidence that reduced use could be considered as a viable end point in stimulant use disorder clinical trials, pending validation studies in other datasets, prospective medication development studies, and other empirical evidence, which could ultimately lead to the qualification of such harm reduction end points by regulatory agencies.

Conclusions

Given the growing prevalence of stimulant use disorder and stimulant-related overdose, identifying medication for stimulant use disorder is a priority. Our findings in this meta-analysis underscore the importance of evaluating pharmacotherapies across a continuum of treatment outcomes. The observed patterns suggest that moving beyond an abstinence-only framework toward one that recognizes reductions in use as an additional treatment outcome could help identify clinically relevant pharmacologic signals worthy of further investigation. Especially in short-term clinical trials, framing complete abstinence as the primary or sole treatment goal risks equating lapses with treatment failure and ignoring clinically meaningful reductions in drug use. In the real world, recognizing reduction in drug use as meaningful progress provides a more realistic and patient-centered approach for evaluating the outcome of addiction treatment.

ARTICLE INFORMATION

Accepted for Publication: March 12, 2026.

Published Online: June 3, 2026. doi:10.1001/jamapsychiatry.2026.1092

Author Affiliations: Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland (Amin-Esmaeili, Johnson, Susukida); Clinical Psychoneuroendocrinology and Neuropsychopharmacology Section, Translational Addiction Medicine Branch, National Institute on Drug Abuse Intramural Research Program and National Institute on Alcohol Abuse and Alcoholism Division of Intramural Clinical and Biological Research, National Institutes of Health, Baltimore, Maryland (Farokhnia, Leggio); Department of Psychiatry and Behavioral Sciences, Tulane Medical School, New Orleans, Louisiana (Mojtabai); Center for Alcohol and Addiction Studies, Department of Behavioral and Social Sciences, Brown University, Providence, Rhode Island (Leggio); Division of Addiction Medicine, Department of Medicine, School of Medicine, Johns Hopkins University, Baltimore, Maryland (Leggio).

Author Contributions: Dr Amin-Esmaeili had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: Amin-Esmaeili, Farokhnia, Mojtabai, Leggio, Susukida.
Drafting of the manuscript: Amin-Esmaeili, Mojtabai.
Critical review of the manuscript for important intellectual content: All authors.
Statistical analysis: Amin-Esmaeili, Mojtabai.
Obtained funding: Leggio, Susukida.
Administrative, technical, or material support: Farokhnia, Leggio, Susukida.
Supervision: Farokhnia, Johnson, Susukida.

Conflict of Interest Disclosures: Dr Mojtabai reported consulting fees from MindMed and royalties from UpToDate outside the submitted work. Dr Susukida reported grants from the US National Institutes of Health (contract 75N95024P00505) during the conduct of the study. No other disclosures were reported.

Funding/Support: This work was supported in part by the Intramural Research Program of the National Institutes of Health (NIH, contract 75N95024P00505). Drs Farokhnia and Leggio were supported by the NIH Intramural Research Program (National Institute on Drug Abuse/National Institute on Alcohol Abuse and Alcoholism; ZIA-DA000635). Dr Mojtabai's work was supported in part by the Louisiana Board of Regents Endowed Chairs for Eminent Scholars program.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The contributions of the US National Institutes of Health (NIH) authors were made as part of their official duties as NIH federal employees, are in compliance with agency policy requirements, and are considered works of the United States Government. However, the findings and conclusions presented in this paper are those of the authors and do not necessarily reflect the views of the NIH or the US Department of Health and Human Services.

Data Sharing Statement: See Supplement 2.

REFERENCES

1. Han B, Compton WM, Jones CM, Einstein EB, Volkow ND. Methamphetamine use, methamphetamine use disorder, and associated overdose deaths among US adults. *JAMA Psychiatry*. 2021;78(12):1329-1342. doi:10.1001/jamapsychiatry.2021.2588
2. Kariisa M, Seth P, Scholl L, Wilson N, Davis NL. Drug overdose deaths involving cocaine and psychostimulants with abuse potential among racial and ethnic groups - United States, 2004-2019. *Drug Alcohol Depend*. 2021;227:109001. doi:10.1016/j.drugalcdep.2021.109001
3. Ciccarone D, Shoptaw S. Understanding stimulant use and use disorders in a new era. *Med Clin North Am*. 2022;106(1):81-97. doi:10.1016/j.mcna.2021.08.010
4. Butler AJ, Rehm J, Fischer B. Health outcomes associated with crack-cocaine use: systematic review and meta-analyses. *Drug Alcohol Depend*. 2017;180:401-416. doi:10.1016/j.drugalcdep.2017.08.036
5. Diekhans K, Yu J, Pearring S, Almeida R, Rodda LN. The fourth wave of the opioid epidemic: increasing combination of fentanyl with stimulants. *Am J Public Health*. 2025;115(4):555-565. doi:10.2105/AJPH.2024.307948
6. Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: results from the 2023 National Survey on Drug Use and Health (HHS publication No. PEP24-07-021, NSDUH series H-59). Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. July 2024. https://www.samhsa.gov/data/sites/default/files/reports/rpt47095/National%20Report/National%20Report/2023-nsduh-annual-national.pdf
7. Chan B, Kondo K, Ayers C, et al. Pharmacotherapy for stimulant use disorders: a systematic review. US Department of Veterans Affairs; August 2018. https://pubmed.ncbi.nlm.nih.gov/30715830/
8. Heilig M, MacKillop J, Martinez D, Rehm J, Leggio L, Vanderschuren LJMJ. Addiction as a brain disease revised: why it still matters, and the need for consilience. *Neuropsychopharmacology*. 2021;46(10):1715-1723. doi:10.1038/s41386-020-00950-y
9. Witkiewitz K, Anton RF, O'Malley SS, et al; Alcohol Clinical Trials Initiative (ACTIVE) Workgroup. Reductions in World Health Organization risk drinking levels as a primary efficacy end point for alcohol clinical trials: a review. *JAMA Psychiatry*. 2025;82(12):1246-1254. doi:10.1001/jamapsychiatry.2025.2508
10. Witkiewitz K, Kranzler HR, Hallgren KA, et al. Drinking risk level reductions associated with improvements in physical health and quality of life among individuals with alcohol use disorder. *Alcohol Clin Exp Res*. 2018;42(12):2453-2465. doi:10.1111/acer.13897
11. Roos CR, Nich C, Mun CJ, et al. Clinical validation of reduction in cocaine frequency level as an

endpoint in clinical trials for cocaine use disorder. *Drug Alcohol Depend*. 2019;205:107648. doi:10.1016/j.drugalcdep.2019.107648

12. Amin-Esmaeili M, Farokhnia M, Susukida R, et al. Reduced drug use as an alternative valid outcome in individuals with stimulant use disorders: findings from 13 multisite randomized clinical trials. *Addiction*. 2024;119(5):833-843. doi:10.1111/add.16409

13. Roos CR, Nich C, Mun CJ, et al. Patterns of cocaine use during treatment: associations with baseline characteristics and follow-up functioning. *J Stud Alcohol Drugs*. 2019;80(4):431-440. doi:10.15288/jsad.2019.80.431

14. Amin-Esmaeili M, Susukida R, Johnson RM, et al. Patterns of reduced use and abstinence in multi-site randomized controlled trials of pharmacotherapies for cocaine and methamphetamine use disorders. *Drug Alcohol Depend*. 2021;226:108904. doi:10.1016/j.drugalcdep.2021.108904

15. Food and Drug Administration. *Alcoholism: Developing Drugs for Treatment Guidance for Industry*. US Department of Health and Human Services; 2015.

16. Anton RF, Litten RZ, Falk DE, et al. The Alcohol Clinical Trials Initiative (ACTIVE): purpose and goals for assessing important and salient issues for medications development in alcohol use disorders. *Neuropsychopharmacology*. 2012;37(2):402-411. doi:10.1038/npp.2011.182

17. US Food and Drug Administration. FDA qualifies drug development tool to facilitate clinical trial research on alcohol use disorder. Accessed December 5, 2025. https://www.fda.gov/drugs/drug-safety-and-availability/fda-qualifies-drug-development-tool-facilitate-clinical-trial-research-alcohol-use-disorder

18. Falk DE, O'Malley SS, Witkiewitz K, et al; Alcohol Clinical Trials Initiative (ACTIVE) Workgroup. Evaluation of drinking risk levels as outcomes in alcohol pharmacotherapy trials: a secondary analysis of 3 randomized clinical trials. *JAMA Psychiatry*. 2019;76(4):374-381. doi:10.1001/jamapsychiatry.2018.3079

19. Witkiewitz K, Hallgren KA, Kranzler HR, et al. Clinical validation of reduced alcohol consumption after treatment for alcohol dependence using the World Health Organization risk drinking levels. *Alcohol Clin Exp Res*. 2017;41(1):179-186. doi:10.1111/acer.13272

20. Susukida R, Amin-Esmaeili M, Mayo-Wilson E, Mojtabai R. Data management in substance use disorder treatment research: implications from data harmonization of National Institute on Drug Abuse-funded randomized controlled trials. *Clin Trials*. 2021;18(2):215-225. doi:10.1177/1740774520972687

21. Burke DL, Ensor J, Riley RD. Meta-analysis using individual participant data: one-stage and two-stage approaches, and why they may differ. *Stat Med*. 2017;36(5):855-875. doi:10.1002/sim.7141

22. Riley RD, Debray TPA, Fisher D, et al. Individual participant data meta-analysis to examine interactions between treatment effect and participant-level covariates: statistical recommendations for conduct and planning. *Stat Med*. 2020;39(15):2115-2137. doi:10.1002/sim.8516

23. Riley RD, Legha A, Jackson D, et al. One-stage individual participant data meta-analysis models for continuous and binary outcomes: comparison of treatment coding options and estimation methods. *Stat Med*. 2020;39(19):2536-2555. doi:10.1002/sim.8555

24. Snaith RP. The Hospital Anxiety and Depression Scale. *Health Qual Life Outcomes*. 2003;1(1):29. doi:10.1186/1477-7525-1-29

25. Elkashef A, Kahn R, Yu E, et al. Topiramate for the treatment of methamphetamine addiction: a multi-center placebo-controlled trial. *Addiction*. 2012;107(7):1297-1306. doi:10.1111/j.1360-0443.2011.03771.x

26. Elkashef AM, Rawson RA, Anderson AL, et al. Bupropion for the treatment of methamphetamine dependence. *Neuropsychopharmacology*. 2008;33(5):1162-1170. doi:10.1038/sj.npp.1301481

27. Anderson AL, Li SH, Markova D, et al. Bupropion for the treatment of methamphetamine dependence in non-daily users: a randomized, double-blind, placebo-controlled trial. *Drug Alcohol Depend*. 2015;150:170-174. doi:10.1016/j.drugalcdep.2015.01.036

28. Anderson AL, Li SH, Biswas K, et al. Modafinil for the treatment of methamphetamine dependence. *Drug Alcohol Depend*. 2012;120(1-3):135-141. doi:10.1016/j.drugalcdep.2011.07.007

29. Johnson BA, Ait-Daoud N, Elkashef AM, et al; Methamphetamine Study Group. A preliminary randomized, double-blind, placebo-controlled study of the safety and efficacy of ondansetron in the treatment of methamphetamine dependence. *Int J Neuropsychopharmacol*. 2008;11(1):1-14. doi:10.1017/S1461145707007778

30. Johnson BA, Roache JD, Ait-Daoud N, et al. A preliminary randomized, double-blind, placebo-controlled study of the safety and efficacy of ondansetron in the treatment of cocaine dependence. *Drug Alcohol Depend*. 2006;84(3):256-263. doi:10.1016/j.drugalcdep.2006.02.011

31. Anderson AL, Reid MS, Li SH, et al. Modafinil for the treatment of cocaine dependence. *Drug Alcohol Depend*. 2009;104(1-2):133-139. doi:10.1016/j.drugalcdep.2009.04.015

32. Winhusen T, Somoza E, Ciraulo DA, et al. A double-blind, placebo-controlled trial of tiagabine for the treatment of cocaine dependence. *Drug Alcohol Depend*. 2007;91(2-3):141-148. doi:10.1016/j.drugalcdep.2007.05.028

33. NIDA-CTO-0007: phase 2, double-blind, placebo-controlled trial of cabergoline for the treatment of cocaine dependence. US National Institute of Drug Abuse. Accessed December 5, 2025. https://datashare.nida.nih.gov/study/nida-cto-0007

34. Winhusen T, Somoza E, Sarid-Segal O, et al. A double-blind, placebo-controlled trial of reserpine for the treatment of cocaine dependence. *Drug Alcohol Depend*. 2007;91(2-3):205-212. doi:10.1016/j.drugalcdep.2007.05.021

35. Elkashef A, Fudala PJ, Gorgon L, et al. Double-blind, placebo-controlled trial of selegiline transdermal system (STS) for the treatment of cocaine dependence. *Drug Alcohol Depend*. 2006;85(3):191-197. doi:10.1016/j.drugalcdep.2006.04.010

36. Kahn R, Biswas K, Childress AR, et al. Multi-center trial of baclofen for abstinence initiation in severe cocaine-dependent individuals. *Drug Alcohol Depend*. 2009;103(1-2):59-64. doi:10.1016/j.drugalcdep.2009.03.011

37. Abo-Zaid G, Guo B, Deeks JJ, et al. Individual participant data meta-analyses should not ignore clustering. *J Clin Epidemiol*. 2013;66(8):865-873.e4. doi:10.1016/j.jclinepi.2012.12.017

38. Debray TP, Moons KG, van Valkenhoef G, et al; GetReal Methods Review Group. Get real in individual participant data (IPD) meta-analysis: a review of the methodology. *Res Synth Methods*. 2015;6(4):293-309. doi:10.1002/jrsm.1160

39. Colao A, Lombardi G, Annunziato L. Cabergoline. *Expert Opin Pharmacother*. 2000;1(3):555-574. doi:10.1517/14656566.1.3.555

40. Thomas MJ, Kalivas PW, Shaham Y. Neuroplasticity in the mesolimbic dopamine system and cocaine addiction. *Br J Pharmacol*. 2008;154(2):327-342. doi:10.1038/bjp.2008.77

41. Minozzi S, Amato L, Pani PP, et al. Dopamine agonists for the treatment of cocaine dependence. *Cochrane Database Syst Rev*. 2015;2015(5):CD003352. doi:10.1002/14651858.CD003352.pub4

42. Leiderman DB, Shoptaw S, Montgomery A, et al. Cocaine Rapid Efficacy Screening Trial (CREST): a paradigm for the controlled evaluation of candidate medications for cocaine dependence. *Addiction*. 2005;100(suppl 1):1-11. doi:10.1111/j.1360-0443.2005.00988.x

43. Shoptaw S, Watson DW, Reiber C, et al. Randomized controlled pilot trial of cabergoline, hydergine and levodopa/carbidopa: Los Angeles Cocaine Rapid Efficacy Screening Trial (CREST). *Addiction*. 2005;100(suppl 1):78-90. doi:10.1111/j.1360-0443.2005.00991.x

44. Maremmani I, Rugani F, Rovai L, et al. Long-term usefulness of cabergoline to patients in refraining from cocaine use after detoxification. *Addict Disord Their Treat*. 2012;11(1):1-5. doi:10.1097/ADT.0b013e31821e527d

45. Alipour M, Jafarian M, Rastgoo R, et al. Cabergoline in treatment of methamphetamine-dependent patients and its effect on serum level of glial cell-derived neurotrophic factor: a randomized, double-blind, placebo-controlled clinical trial. *Eur Addict Res*. 2021;27(6):457-468. doi:10.1159/000515398

46. Shanmugam S, Arunkumar S, Agrawal V, Kumar P. Topiramate Therapy in Cocaine Use Disorder: A Systematic Review and meta-analysis of Randomized Controlled Trials. *Trends Psychiatry Psychother*. 2025. doi:10.47626/2237-6089-2025-1117

47. Mojtabai R, Susukida R, Farokhnia M, Nguyen TQ, Dunn KE, Amin-Esmaeili M. Trajectories of craving in the course of pharmacotherapy trials for methamphetamine use disorder. *Addiction*. 2024;119(10):1803-1812. doi:10.1111/add.16610

48. Mojtabai R, Susukida R, Farokhnia M, et al. Cocaine craving and use during pharmacotherapy trials for cocaine use disorder: a multi-trajectory analysis. *Drug Alcohol Depend*. 2025;275:112841. doi:10.1016/j.drugalcdep.2025.112841

49. Del Re AC, Maisel N, Blodgett JC, Wilbourne P, Finney JW. Placebo group improvement in trials of pharmacotherapies for alcohol use disorders: a multivariate meta-analysis examining change over time. *J Clin Psychopharmacol*. 2013;33(5):649-657. doi:10.1097/JCP.0b013e3182983e73

50. Moore RA, Aubin HJ. Do placebo response rates from cessation trials inform on strength of addictions? *Int J Environ Res Public Health*. 2012;9(1):192-211. doi:10.3390/ijerph9010192

51. Litten RZ, Castle IJ, Falk D, et al. The placebo effect in clinical trials for alcohol dependence: an exploratory analysis of 51 naltrexone and acamprosate studies. *Alcohol Clin Exp Res*. 2013;37(12):2128-2137. doi:10.1111/acer.12197

52. Rosa C, Campbell A, Kleppinger C, Sampson R, Tyson C, Mamay-Gentilin S. Quality assurance of research protocols conducted in the community: the National Institute on Drug Abuse Clinical Trials Network experience. *Clin Trials*. 2009;6(2):151-161. doi:10.1177/1740774509102560

53. Dziura JD, Post LA, Zhao Q, Fu Z, Peduzzi P. Strategies for dealing with missing data in clinical trials: from design to analysis. *Yale J Biol Med*. 2013;86(3):343-358.