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RESEARCH REPORT

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Reduced drug use as an alternative valid outcome in individuals with stimulant use disorders: Findings from 13 multisite randomized clinical trials

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Abstract

Background and aims: Total abstinence has historically been the goal of treatment for substance use disorders; however, there is a growing recognition of the health benefits associated with reduced use as a harm reduction measure in stimulant use disorders treatment. We aimed to assess the validity of reduced stimulant use as an outcome measure in randomized controlled trials (RCTs) of pharmacological interventions for stimulant use disorder.

Design: We conducted a secondary analysis of a pooled dataset of 13 RCTs.

Setting and participants: Participants were individuals seeking treatment for cocaine or methamphetamine use disorders (N = 2062) in a wide range of treatment facilities in the United States.

Measurements: We validated reduced stimulant use against a set of clinical indicators drawn from harmonized measurements, including severity of problems caused by drug use, comorbid depression, global severity of substance use and improvement, severity of drug-seeking behavior, craving and high-risk behaviors, all assessed at the end of the trial, as well as follow-up urine toxicology. A series of mixed effect regression models was conducted to validate reduction in frequency of use against no reduction in use and abstinence.

Findings: More participants reduced frequency of primary drug use than achieved abstinence (18.0% vs. 14.2%, respectively). Reduced use was significantly associated with decreases in craving for the primary drug [60.1%, 95% confidence interval (CI) = 54.3%–64.7%], drug seeking behaviors (41.0%, 95% CI = 36.6%–45.7%), depression severity (39.9%, 95% CI = 30.9%–48.3%), as well as multiple measures of global improvement in psychosocial functioning and severity of drug-related problems, albeit less strongly so than abstinence. Moreover, reduced use was associated with sustained clinical benefit at follow-up, as confirmed by negative urine tests (adjusted odds ratio compared with those with no reduction in use: 0.50, 95% CI = 0.35–0.71).

Conclusion: Reduced frequency of stimulant use appears to be associated with meaningful improvement in various clinical indicators of recovery. Assessment of reduced use, in addition to abstinence, could broaden the scope of outcomes measured in randomized

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controlled trials of stimulant use disorders and facilitate the development of more diverse treatment approaches.

KEYWORDS
cocaine use disorder, harm reduction, methamphetamine use disorder, non-abstinence outcomes, secondary data analysis, Stimulants

INTRODUCTION

There are currently no evidence-based pharmacological treatments for stimulant use disorders [1–3]. Although abstinence is historically considered the most desirable clinical endpoint in substance use disorder treatment, relying exclusively on abstinence as an outcome in previous clinical trials may have masked possible beneficial effects of treatment modalities [2].

One possible explanation for the historical lack of interest in reduced use as an outcome measure might have been that this outcome is often a less acceptable treatment goal from the patients' and clinicians' point of view when the primary drug is an illicit drug such as cocaine or methamphetamine rather than alcohol and cannabis [4, 5]. This view is partly because of the stigma associated with using illicit drugs—particularly injection drugs. However, treatment goals and needs differ across individuals; therefore, finding more feasible and personalized goals for those who do not prefer or cannot achieve total abstinence is warranted [6].

Another impediment in establishing reduced use as an outcome measure for illicit drugs is likely the difficulty in quantifying the amount of the drugs used. Researchers in the alcohol field have had impressive success in establishing low-risk use as a viable outcome measure partly because of the relative ease in measuring the amount of alcohol consumed [7–10]. Unstandardized size measures in the illicit drug market, impurity of illicit drugs, multiple modes of consumption and alternate formulations of stimulant drugs, which may have different pharmacokinetic and pharmacodynamic properties make it difficult to define a standard measure of use for these drugs.

In the context of the ambiguities in measurement, attempts at quantifying stimulant use have focused on the frequency of use [11–14]. For example, following a meeting held by the Analgesic, Anesthetic and Addiction Clinical Trial Translations, Innovations, Opportunities and Networks (ACTTION) in collaboration with the Food and Drug Administration, a group of investigators provided evidence-based recommendations for quantifying frequency of stimulant use for future studies on the treatment of stimulant use disorders [14]. The group recommends that 'any measure of reduction should be based on the frequency of days of stimulant use (either per week or per month)' and further cautioned that measures based on the quantity of use per day are less reliable [14].

It is conceivable that any reduction in the frequency of stimulant use would also reduce the harms associated with these drugs, although more needs to be known about the potential clinical benefits of reduced use. There is an emerging body of evidence on the association of reduction-based outcomes with improvement in physical and psychosocial functioning [11, 13, 15].

Analyzing pooled data from six RCTs of behavioral interventions for cocaine use disorder, Roos and colleagues [11] provided initial evidence that reduced use may be a viable and clinically relevant outcome. Inspired by the World Health Organization's alcohol drinking risk levels [16–18], they defined three levels based on the frequency of past 30-day use, including, abstinence, use on 1 to 4 days and use on 5+ days. The study showed that any reduction in the frequency of stimulant use was associated with clinically meaningful improvement in psychosocial functioning based on the Addiction Severity Index (ASI), specifically in the psychological, legal, employment and other drug use problems domains.

In the present study, we investigate the correlates of reduced frequency of stimulant use, extending the work of Roos and colleagues [11] by leveraging a much larger and more diverse sample. We analyze harmonized data from 13 RCTs designed to evaluate the impact of pharmacological treatments among people with cocaine and methamphetamine use disorders. This study also builds on our prior work with harmonized RCT data in which we observed that a sizeable proportion of people with stimulant use disorders did not attain abstinence, but did reduce frequency of stimulant use [19]. The objective of this study was to investigate the effects of the transition to 'reduced use' or 'abstinence' on a broad range of clinical indicators of improvement. We used a similar frequency of use cut-off as in Roos *et al.* [11] and our previous study [19]. More specifically, we compared 'no reduced use', 'reduced use' and 'abstinence' in association with multiple outcomes, including severity of problems caused by drug use, comorbid depression, global severity of substance use and improvement, severity of drug-seeking behavior, craving for the primary and secondary drug and high-risk behaviors, all measured both at baseline and end of trial, as well as urine toxicology at the end of follow-up phase as evidence of sustained improvement.

METHODS

Overview

We conducted secondary data analysis using pooled harmonized datasets from RCTs of various pharmacological interventions for people with either cocaine or methamphetamine use disorder. The RCTs included in the current study were selected from the National Institute on Drug Abuse (NIDA)-funded RCTs available on the NIDA data share website (https://datashare.nida.nih.gov/). We selected

13 of 76 studies that were released up to October 2022 if they: (1) were RCTs addressing treatment for cocaine and/or methamphetamine use disorder; (2) had consistent eligibility criteria; and (3) consistently measured drug use and other clinical outcomes. We further limited our study to pharmacological interventions because there was considerable heterogeneity between behavioral and pharmacological interventions in terms of duration of active treatment, assessment points and eligibility criteria. Moreover, the majority of the behavioral treatment trials lacked the core set of instruments required for assessing the study outcomes. The study selection procedure is summarized in Figure S1.

As the focus of the study was on examining the validity of reduced use as a treatment outcome rather than the effect of specific treatments, we pooled data from the intervention and control groups of RCTs, while adjusting the analyses for the intervention and control arms. The original de-identified raw data were harmonized using methods previously described Susukida *et al*. [20] The 13 RCTs included in this study used similar eligibility criteria, recruitment processes and study protocols, as well as a common set of outcome measures. Studies were all double-blind RCTs and consistently underwent rigorous quality assurance procedures [12]. Most of the trials had an active phase of 12 weeks (range = 8–15 weeks, mean = 11 weeks). The characteristics of the 13 RCTs are presented in Table 1.

Participants

Participants of the RCTs were individuals seeking treatment in a wide range of treatment facilities [21–33]. They were all 18 years or older and met the criteria for cocaine dependence or methamphetamine dependence based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). All participants had at least one positive urine test for the primary drug of use at baseline. Participants with methamphetamine dependence were ineligible for RCTs of cocaine dependence and vice versa.

Measurements

We used a set of key measurements that have been harmonized across trials [20]. We first determined the frequency of use for the primary drug (i.e. cocaine or methamphetamine) at baseline and the end of each trial. Frequency of use was assessed with the drug use section of the Addiction Severity Index-Lite (ASI-Lite), in which days of use of specific drugs in the past month were measured. For this study, the frequency of use in the past 30 days was categorized into no use (i.e. 0 days), low-frequency use (i.e. 1–4 days of use) and high-frequency use (i.e. 5+ days of use). Next, we categorized changes in level of use of the primary drug from baseline to the end of trial in three mutually exclusive groups: (1) abstinence, that is, no use at the end of the trial; (2) reduced use, that is, a transition from high- to low-frequency use; and (3) no reduced use, including participants with no change in frequency of use and participants who transitioned from low- to high-frequency use. Participants with no self-reported stimulant use were considered abstinent only if they had negative urine toxicology results during the final month of treatment. Those with missing data on urine toxicology were excluded from analyses, regardless of self-reported stimulant use. A detailed description of this classification method, including urine drug toxicologic examination as a validator of abstinence, is provided in our previous article [19].

Problems caused by drug use were assessed using the composite scores of ASI for the severity of participants' problems on subscales that are sensitive to change over the short course of treatment, as described by McGahan *et al*. [34]. These included ASI subscales for drug use (drugs other than the primary drug of use), alcohol use, legal problems, family/social problems and psychiatric problems. We removed the employment and medical domains of the ASI from the analysis because the items included in these domains tend to stay stable over a short period of time. We also excluded the primary drug in the calculation of the ASI drug domain composite score to avoid overlap among outcomes.

Comorbid depression was measured by the Hamilton Depression Rating Scale (HAM-D) [35] in almost all of the trials except for CSP1025 and CTN0052 in which the Montgomery-Asberg Depression Rating Scale (MADRS) [36] and Hospital Anxiety and Depression Scale (HADS) [37], respectively, were used. We computed HAM-D equivalent scores based on MADRS, using published calibration data [38]. We were not able to find a HAM-D equivalent score for HADS; therefore, depression data is considered missing for CTN0052.

The severity of primary drug use, global improvement and the severity of drug-seeking were assessed at the end of the trial using the Clinical Global Impression (CGI) scale [39]. Both observer- and patient-administered versions of the scale were administered across studies with some modifications in the number and content of the questions. We selected three questions common across trials: (1) current severity of symptoms related to the primary drug; (2) global improvement of drug-related problems since the beginning of the study; and (3) current severity of drug-seeking. The last question was only rated by observers. Each individual question is considered a separate indicator in the analysis and scores that range from 1 to 7, with higher scores indicating greater severity in symptoms, less improvement (worsening problems) and greater drug-seeking, respectively.

Craving was assessed using three items of the Brief Substance Craving Scale (BSCS) [40]—a self-administered tool that asks individuals to rate the frequency, intensity and length of their craving. Craving for the primary and secondary drug of use was measured separately. The BSCS score ranges from 0 to 12, with a higher score indicating more severe craving.

HIV risk behaviors, including injecting drug use and sexual risk behaviors, were measured with two different questionnaires: the HIV Risk-Taking Behavior Survey (HRBS) [41] and the Risk Behavior Survey (RBS) [42]. Although these tools have different sets of questions and total scores, they share a number of harmonizable questions. We generated a dichotomous variable using these five shared items: (1) injecting drugs; (2) history of needle-sharing; (3) history of engaging in transactional sex; (4) having multiple sexual partners (two or

TABLE 1 Characteristics of the 13 RCTs of stimulant use disorder pharmacological treatments included in this study.

Study ID	No. of study sites, states	Treatment	Length of study (weeks)		Target population	*n*	Female %	Mean age	White %	Missingness in outcome %
			Active	Total[a]						
CTO-0012 [21]	4 sites in OH, MA and TX	Tiagabine	12	19	Cocaine dependence and ≥1 UDS^+ during 2 weeks of screening	141	32.6	42.0	29.1	43.3
CTO-0007 [22]	2 sites in CA and SC	Cabergoline	12	17	Cocaine dependence and ≥1 UDS^+ during 2 weeks of screening	140	15.0	40.1	37.9	46.4
CTO-0005 [25]	1 site in TX	Ondansetron	8	12	Cocaine dependence and ≥1 UDS^+ during 2 weeks of screening	64	15.1	36.3	39.1	20.3
CTO-0001 [27]	3 sites in OH and MA	Reserpine	12	17	Cocaine dependence and ≥1 UDS^+ during 2 weeks of screening	119	29.4	41.0	19.5	30.3
CSP-1019 [28]	16 sites in MD, CA, SC, CO, WA, OH, TX, MI, LA, UT and AZ	Selegiline Transdermal	8	12	Cocaine dependence and ≥3 UDS^+ during 2 weeks of screening	300	22.0	40.7	26.5	15.0
CSP-1021 [29]	8 sites in CA, VA, CO, PA, MD, TX and UT	Baclofen	8	12	Cocaine dependence and ≥3 UDS^+ during 2 weeks of screening	160	20.6	42.7	25.8	19.4
MDS-0004 [23]	6 sites in NY, TX, OH and PA	Modafinil	12	16	Cocaine dependence and ≥1 UDS^+ during 3 weeks of screening	210	28.1	41.8	29.5	22.4
CTN-0052 [26]	6 sites in PA, SC, FL, OH and TX	Buspirone	15	16	Cocaine dependence and used crack cocaine ≥4 times in 28 days before admission	62	37.1	46.1	22.6	6.5
CSP-1025 [30]	8 sites in VA, CA, MO, HI, IA and UT	Topiramate	12	16	Methamphetamine dependence and ≥1 UDS^+ during 4 weeks of screening	140	36.4	38.0	75.0	37.1
CSP-1026 [24]	8 sites in PA, CA, MO, HI, IA, UT and CO	Modafinil	12	16	Methamphetamine dependence and ≥1 UDS^+ during 3 weeks of screening	210	41.0	39.0	67.6	34.8
MDS-0007 [31]	4 sites in OH, MA and TX	Bupropion	12	16	Methamphetamine dependence and ≥1 UDS^+ during 4 weeks of screening	205	35.1	39.3	53.9	41.5
CTO-0011 [32]	6 sites in TX, CA, MO, HI and IA	Ondansetron	8	12	Methamphetamine dependent and ≥1 UDS^+ during 2 weeks of screening	155	36.8	35.9	73.6	14.8
CTO-0008 [33]	5 sites in CA, MO, HI and IA	Bupropion	12	16	Methamphetamine dependence and ≥1 UDS^+ during 2 weeks of screening	156	33.3	36.2	75.6	33.3
Pooled sample		–	–	–	–	2062	29.6	39.9	45.1	27.9

Abbreviations: AZ, Arizona; CA, California; CO, Colorado; FL, Florida; HI, Hawaii; IA, Iowa; LA, Louisiana; MA, Massachusetts; MD, Maryland; MI, Michigan; MO, Missouri; OH, Ohio; PA, Pennsylvania; SC, South Carolina; TX, Texas; USD^+, Positive Urine Drug Screening; UT, Utah; VA, Virginia; WA, Washington.

[a]Total study period which includes follow-up period.

more); and (5) consistent condom use with regular, casual or paid partners. If there were any positive responses to the first four items or a negative response to the fifth item, participants were classified as having HIV risk behaviors.

Additionally, we created a composite indicator of clinical improvement at the end of the trial using the number of days of having problems in the past 30 days in three domains of ASI (i.e. family/social, legal and psychiatric domains). This is a modified version of 'Problem Free Functioning (PFF)' that has been validated by Kiluk and colleagues [43] as a proxy indicator of clinical improvement. It is a dichotomous variable with clinical improvement defined by 0 days of problems in all included domains and no improvement by one or more days of problems in either of the domains.

Last, we also used urine toxicology results for the primary drug during the follow-up as an indicator of sustained improvement.

Statistical procedures

We described patterns in transitions from one frequency level of drug use to another from baseline to the end of the trial. We accounted for missingness by using inverse probability weighting (IPW) based on socio-demographic variables associated with the observed outcomes.

Consistent with recommendations for one-stage individual participant data meta-analyses [44], a series of weighted regression analyses were performed to examine the association of each individual clinical indicator with the three outcome categories. This approach is associated with the least amount of bias and suitable coverage for analyzing a pooled dataset of multiple trials [45, 46]. Continuous clinical indicators, including the ASI domains composite scores, depression score (HAM-D), global severity of use, global improvement, global severity of seeking the primary drug and craving for the primary and secondary drug, were analyzed using a series of mixed effect regression models. We used multilevel mixed effects generalized linear model, implemented in the Stata 'meglm' command with a 'gamma' distribution and 'log' link, which accommodates non-normally distributed data [47]. For dichotomous variables, including PFF, positive urine test for primary drug at follow-up and any HIV risk behavior, mixed logistic regression models were used. The β coefficients and the standard errors from linear regression models, as well as the odds ratio and 95% CI from logistic regression models, were computed. Additionally, following the work by Roos *et al*. [11], a binary outcome, where 1 indicates at least one-level reduction in the frequency level and 0 represents no reduction or increase in the frequency level, was calculated and the regression models were re-run with this new outcome as a sensitivity analysis. Furthermore, we illustrated the percent change in the scores of the continuous measures from baseline to the end of trial for the three outcome categories.

All the analyses were weighted using IPW and controlled for socio-demographic factors including sex, age, education, marital and employment status, as well as history of injection drug use, lifetime years of drug use and active treatment versus placebo group. For each individual clinical indicator, we also included the baseline measure of the indicator in the regression model. We accounted for the heterogeneity of the original studies by including study ID as a fixed effect. A robust variance–covariance matrix was used.

All analyses were conducted on the pooled sample as well as on cocaine and methamphetamine RCTs, separately. The analysis plan was not pre-registered, and the results should be considered exploratory. Analyses were performed with Stata version 16.0 (StataCorp) and statistical significance was set at $P < 0.05$ (two-tailed).

RESULTS

Of the 2062 participants enrolled in the 13 RCTs, 1196 were in RCTs for cocaine use disorder and 866 in RCTs for methamphetamine use disorder. A total of 1487 (72.1%) had data available at the end of the trial for the outcomes of interest and the baseline covariates included in the IPW. Most participants (67.9%, 95% CI = 65.4–70.2) had no change in level of use or transitioned from low- to high-frequency use. Nearly one-third (32.1%, 95% CI = 29.8–34.6) had at least a one-level reduction in the frequency of use, indicated by abstinence at the end of the trial (14.2%, 95% CI = 12.5–16.1) or by a transition from high- to low-frequency use of their primary drug (18.0%, 95% CI = 16.1–20.0). The pattern of change in use from baseline to end-of-trial was significantly different based on the primary drug ($P = 0.017$). Participants in methamphetamine RCTs were more likely to be in the abstinence versus reduced use category (21.3% vs 13.9%, respectively), whereas participants in the cocaine RCTs were less likely to be in the abstinence versus reduced use category (9.1% vs 20.9%). The proportion of participants reporting polydrug use at the end of the trial (i.e. those who reported using one or more drugs in addition to their primary drug) was low (16.6%).

Table 2 presents the mean (SD) and median (interquartile range) scores, and/or proportions of each clinical indicator across the three outcome categories (i.e. abstinence, reduced use, no reduced use), along with statistical tests for group comparisons. Point estimates of the clinical indicators for 'reduced use' were generally in-between 'abstinence' and 'no reduced use'. For instance, mean depression scores among those who experienced 'abstinence', 'reduced use' and 'no reduced use' were 3.05, 3.47 and 4.61, respectively. Similar to the 'abstinence' category, 'reduced use' showed a significant association with nearly all clinical indicators of improvement, compared to 'no reduced use' ($P < 0.010$), except for the psychiatric problems ($P = 0.128$) and family/social relationship domains of ASI ($P = 0.592$), PFF ($P = 0.170$) and HIV risk behavior ($P = 0.967$). Compared to 'no reduced use', 'reduced use' was associated with a lower probability of positive urine toxicology for the primary drug at the end of follow-up.

As expected, those who experienced abstinence showed better clinical improvement, compared to those who reduced their use, on nearly all clinical indicators ($P < 0.009$), except for ASI-alcohol composite score, which was marginally significant ($P = 0.053$). Furthermore, there were no significant differences between 'abstinence' and

TABLE 2 Association of clinical indicators with change in frequency of stimulant (cocaine or methamphetamine) use at the end of the trial.

	Abstinence, *n* = 205		Reduced use, *n* = 271		No reduced use, *n* = 1002	
	Weighted mean (SD)	Median (IQR)	Weighted mean (SD)	Median (IQR)	Weighted mean (SD)	Median (IQR)
ASI composite score						
ASI-other drugs	0.05 (0.06)	0.02 (0.08)	0.12 (0.07)	0.11 (0.10)	0.16 (0.10)	0.17 (0.14)
ASI-alcohol	0.06 (0.09)	0.01 (0.08)	0.11 (0.13)	0.07 (0.18)	0.13 (0.16)	0.08 (0.21)
ASI-legal	0.03 (0.09)	0.0 (0.0)	0.04 (0.11)	0.0 (0.0)	0.08 (0.16)	0.0 (0.05)
ASI-family/social	0.11 (0.16)	0.0 (0.20)	0.12 (0.16)	0.05 (0.2)	0.15 (0.18)	0.07 (0.23)
ASI-psychiatry	0.09 (0.14)	0.0 (0.16)	0.10 (0.15)	0 (0.17)	0.14 (0.18)	0.0 (0.26)
Depression severity (HAM-D)[b]	3.05 (3.32)	2.0 (5.0)	3.47 (3.49)	2.0 (4.0)	4.61 (4.83)	3.0 (6.0)
Severity of use-self rated[b,c]	1.76 (0.99)	1.0 (1.0)	2.57 (1.35)	2.0 (1.5)	3.24 (1.45)	3.0 (2.0)
Global improvement-self rated[b,c]	1.20 (0.51)	1.0 (0.0)	1.70 (0.92)	1.0 (1.0)	2.36 (1.20)	2.0 (2.0)
Severity of use-observer rated[b,c]	1.94 (1.01)	2.0 (1.0)	2.79 (1.07)	3.0 (1.0)	3.67 (1.29)	4.0 (2.0)
Global improvement-observer rated[b,c]	1.45 (0.75)	1.0 (1.0)	1.96 (0.98)	2.0 (1.0)	2.75 (1.18)	3.0 (2.0)
Severity of seeking primary drug-observer rated[b,c]	1.58 (0.92)	1.0 (1.0)	2.33 (1.24)	2.0 (2.0)	3.29 (1.58)	3.0 (2.0)
Craving for primary drug (BSCS)[b]	0.98 (1.91)	0.0 (1.0)	2.14 (2.27)	3.0 (3.0)	3.90 (3.02)	3.0 (5.0)
Craving for secondary drug (BSCS)[b]	4.70 (2.14)	4.0 (3.0)	4.63 (2.18)	5.0 (3.0)	5.45 (2.48)	6.0 (4.0)

TABLE 2 (Continued)

	Comparison of different patterns[a]					
	Reduced use vs no reduced use		Abstinence vs no reduced use		Abstinence vs reduced use	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
ASI composite score						
ASI-other drugs	−0.28 (−0.37 to −0.20)	<0.001	−1.18 (−1.40 to −0.97)	<0.001	−0.90 (−1.09 to −0.71)	<0.001
ASI-alcohol	−0.18 (−0.34 to −0.02)	0.025	−0.35 (−0.70 to 0.01)	0.053	−0.16 (−0.52 to 0.19)	0.360
ASI-legal	−0.63 (−1.15 to −0.11)	0.018	−1.66 (−2.44 to −0.88)	<0.001	−1.03 (−1.97 to −0.10)	0.031
ASI-family/social	−0.05 (−0.21 to 0.11)	0.556	−0.43 (−0.71 to −0.16)	0.002	−0.39 (−0.66 to −0.11)	0.006
ASI-psychiatry	−0.18 (−0.42 to 0.05)	0.128	−0.67 (−1.12 to −0.22)	0.004	−0.48 (−1.00 to 0.03)	0.067
Depression severity (HAM-D)[b]	−0.16 (−0.30 to −0.02)	0.022	−0.52 (−0.67 to −0.38)	<0.001	−0.36 (−0.55 to −0.17)	<0.001
Severity of use-self rated[b,c]	−0.24 (−0.31 to −0.16)	<0.001	−0.55 (−0.64 to −0.45)	<0.001	−0.31 (−0.41 to −0.21)	<0.001
Global improvement-self rated[b,c]	−0.33 (−0.40 to −0.26)	<0.001	−0.66 (−0.74 to −0.59)	<0.001	−0.34 (−0.42 to −0.25)	<0.001
Severity of use-observer rated[b,c]	−0.24 (−0.28 to −0.19)	<0.001	−0.61 (−0.70 to −0.52)	<0.001	−0.37 (−0.46 to −0.29)	<0.001
Global improvement-observer rated[b,c]	−0.34 (−0.41 to −0.27)	<0.001	−0.63 (−0.72 to −0.55)	<0.001	−0.29 (−0.38 to −0.20)	<0.001
Severity of seeking primary drug-observer rated[b,c]	−0.30 (−0.36 to −0.23)	<0.001	−0.65 (−0.77 to −0.53)	<0.001	−0.35 (−0.48 to −0.23)	<0.001

TABLE 2 (Continued)

			Comparison of different patterns[a]									
			Reduced use vs no reduced use				Abstinence vs no reduced use			Abstinence vs reduced use		
			β (95% CI)			P	β (95% CI)		P	β (95% CI)		P
Craving for primary drug (BSCS)[b]			−0.58 (−0.73 to −0.42)			<0.001	−1.38 (−1.74 to −1.02)		<0.001	−0.80 (−1.18 to −0.43)		<0.001
Craving for secondary drug (BSCS)[b]			−0.13 (−0.22 to −0.04)			0.006	−0.16 (−0.28 to −0.04)		0.009	−0.03 (−0.18 to 0.12)		0.686
	n	Weighted %[d]	n	Weighted %[d]	n	Weighted %[d]	Adjusted OR (95% CI)		Adjusted OR (95% CI)		Adjusted OR (95% CI)	
Problem-free functioning	101	57.8	128	46.2	351	39.3	1.25 (0.91–1.71)	0.170	3.14 (2.12–4.66)	<0.001	2.52 (1.62–3.93)	<0.001
Stimulants in urine at follow-up[b,e]	13	11.2	120	66.6	550	78.6	0.50 (0.35–0.71)	<0.001	0.03 (0.02–0.07)	<0.001	0.07 (0.03–0.15)	<0.001
HIV risk behavior	89	49.0	154	60.5	532	61.1	1.01 (0.76–1.33)	0.967	0.44 (0.27–0.71)	0.001	0.44 (0.25–0.75)	0.003

Abbreviations: ASI, Addiction Severity Index; β, regression coefficient; BSCS, Brief Substance Craving Scale; HAM-D, Hamilton Depression Scale; IQR, interquartile range; OR, odds ratio.
[a]The analyses are weighted using inverse probability weighting (IPW) and controlled for sex, age, race, marital status, unemployment, years of education, injecting drug use, lifetime years of cocaine or methamphetamine use, treatment arms, as well as the baseline score of each clinical indicator. *P* values <0.05 indicate statistical significance.
[b]Not measured in CTN0052 (*n* = 62).
[c]Based on the Clinical Global Impression-self/observer-rated.
[d]The percentages are weighted using IPW, but the numbers represent the original numbers.
[e]All the outcomes were assessed at the end of trial except urine toxicology tests for stimulants at follow-up, which were assessed at the end of the follow-up.

'reduced use' on a number of clinical indicators, including the ASI composite score for alcohol ($P = 0.360$) and psychiatric problems ($P = 0.067$) domains and craving for secondary drugs ($P = 0.686$).

Similar associations were found for most of the clinical indicators when cocaine and methamphetamine RCTs were analyzed separately. However, some of the associations lost statistical significance because of reduced power. For instance, compared to 'no reduced use', 'reduced use' was significantly associated with a lower score on the ASI legal and alcohol domains at the end of the trial in cocaine RCTs, whereas the statistical tests did not reach significance in methamphetamine RCTs (Tables S1 and S2).

Figure 1 shows the percent change in the scores of ASI domains from baseline to the end of the trial in the three outcome categories. Consistent with mixed regression analyses, participants with 'reduced use' experienced a significant decrease in almost all ASI domain scores, except for legal and family/social, compared to those with 'no reduced use'. We observed a similar pattern for comorbid depression, self- or observer-rated severity of use, drug-seeking behavior and craving for the primary drug (Figure 2). The percent change in clinical indicators scores was similar for cocaine and methamphetamine RCTs when they were analyzed separately (Figures S2–S5). Additional analysis using the alternative binary outcome of having at least one level reduction in the frequency of use showed qualitatively similar results (see Tables S3–S5).

DISCUSSION

This study examined the validity of reduced frequency of stimulant use as a treatment outcome for stimulant use disorders by exploring the association between reduced use and key clinical indicators, using a large, harmonized dataset from 13 RCTs. Compared to no change or increased frequency of use, the transition from high (5+ days a month) to low (1–4 days a month) frequency of use was generally associated with clinical benefits, as demonstrated by reductions in comorbid depression scores, drug-related problems in various domains of ASI, severity of drug-related symptoms and craving for the primary drug, as well as a significant global improvement. More importantly, a significant percentage of those who reduced their drug use had sustained improvement as indicated by no positive urine test for the primary drug during the month after termination of treatment. We found that although 'reduced use' might not be associated with the same level of improvement compared to 'abstinence', it is significantly superior to 'no reduced use', suggesting that reduction in use can be considered a viable outcome of treatment for individuals with stimulant use disorders. Furthermore, the association between reduced use and the clinical indicators of interest was generally consistent and in the same direction in individuals with cocaine and methamphetamine use disorders, albeit with some minor statistical differences.

Findings of the current study are consistent with similar studies in the alcohol field that have shown that transitioning from high- to low-risk drinking is associated with meaningful clinical benefits [7, 17, 18].

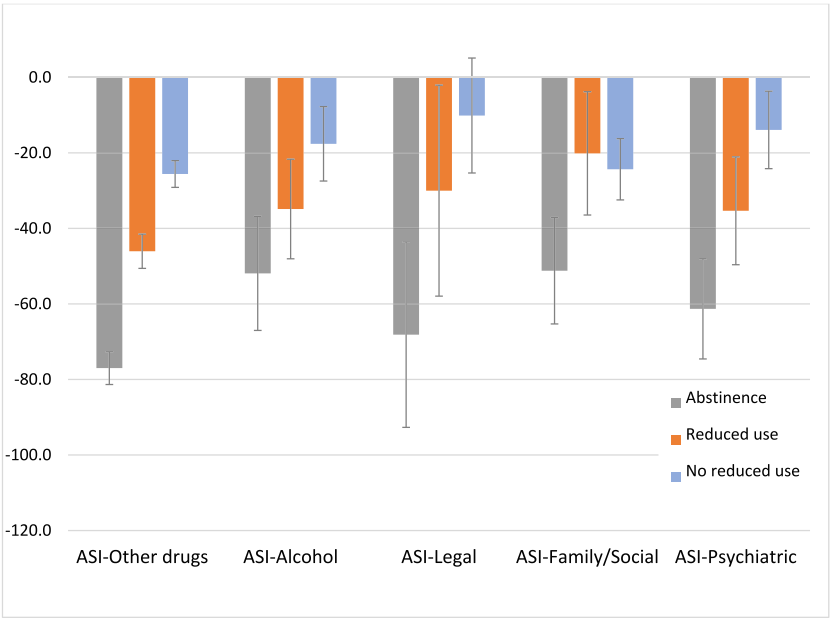

FIGURE 1 Percent change in the composite score of Addiction Severity Index (ASI) subscales across three categories of change in the frequency of stimulant use (cocaine or methamphetamine) from baseline to the end of the trial.

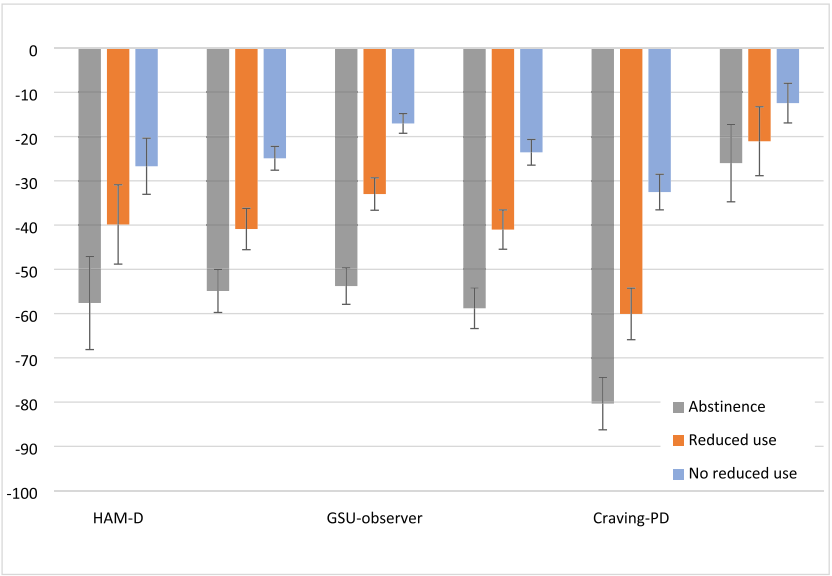

FIGURE 2 Percent change in the other clinical measures across three categories of change in the frequency of stimulant use (cocaine or methamphetamine) from baseline to the end of the trial. GSU-self, Global Severity of Use-self rated, based on Global Clinical Impression Scale (GCIS); GSU-observer, Global Severity of Use-observer rated, based on GCIS; Seek drugs-observer, Global severity of seeking the primary drug-observer rated based on GCIS; HAM-D, Hamilton Depression Scale.

Our study also extends the findings of Roos *et al.* [11] and provides additional evidence in favor of reduced stimulant use as a valid and clinically relevant treatment outcome. Compared to the Roos *et al.* study that focused on cocaine use disorder, we used a more diverse sample from multisite trials of both cocaine and methamphetamine use disorders conducted by different research groups, which enhances the generalizability of the findings. We also increased the power of the analyses by including a much larger sample size. As such, our study was well-powered to detect the association between changes in the frequency of use and most of the clinical outcome measures. Additionally, we used several indicators of improvement covering diverse aspects of clinical and psychosocial well-being, and not just measures limited to drug use. There has been growing interest in alternative definitions of recovery from substance use disorders that incorporate quality of life [48, 49], craving for drugs [50], drug-related harms [51] and psychosocial functioning [43, 52, 53] as treatment endpoints. Similarly, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) has recently developed a new definition of recovery from alcohol use disorder (AUD), which includes cessation of heavy drinking that is a non-abstinent recovery outcome and incorporates the importance of biopsychosocial functioning and quality of life [54]. Our findings suggest that reduced frequency of stimulant use is also associated with improved psychosocial functioning. These findings suggest the need to re-evaluate the traditional approach of exclusively relying on total abstinence as the only indicator of successful treatment, a goal that may not be achievable for all patients, especially after one treatment episode. Although sustainable functional improvement is an ideal endpoint for any

patient who seeks treatment, reduced use could be an intermediate milestone that is achievable by a wider group of patients. Reduction in use can be measured as an alternative outcome in short-term RCTs and possibly naturalistic treatment settings. However, the findings of current study can only statistically demonstrate significance of reduced use as a favorable endpoint in short-term clinical trials; evaluation of its clinical meaningfulness requires further clinical investigations examining patient-centered outcomes.

Nevertheless, reduced stimulant use bears some limitations as an optimal outcome measure. For example, we found that 'reduced use' has no significant superiority over 'no reduced use' in terms of reduction of HIV risk behaviors, whereas 'abstinence' is associated with lower odds of HIV risk behavior. This observation could be partly because of the fact that some of the drug-related risk behaviors such as injecting drug use or shared injections would simply not occur if individuals were abstinent. We also found no difference in the ASI family/social relationship and legal domain between participants with 'reduced use' and 'no reduced use'. Improvement of family/social relationships or legal problems may take a longer time than 8 to 12 weeks of a short trial and improving these outcomes may require additional psychosocial interventions. Differences in treatment goals and expectations among participants and their significant others or families may also impact their relationships.

Our study had several limitations that should be considered. The length of follow-up in most RCTs was short and there was little variation in the length of active treatment phase across trials. The only follow-up measure we used was based on urine drug tests and the other clinical indicators were not measured at follow-up. We also had a substantial number of missing assessment points and not all measures were completely consistent across the trials. Although we applied IPW to address missingness, this method can only adjust for data missing at random or missing completely at random [55, 56]. Results were not adjusted for missingness not at random. Although the study had a large and diverse sample, all data were pulled from RCTs conducted under well-controlled settings in the United States. Further studies are needed to understand whether and to what extent our findings may be generalizable to more naturalistic and community-based treatment settings in the United States and in other countries. We excluded behavioral treatment RCTs because of considerable heterogeneity in their eligibility criteria and duration of treatment and the lack of consistent outcome measures across behavioral and pharmacological treatment trials. However, existing literature shows similar findings among participants of behavioral treatment RCTs [15, 43]. Last, we opted not to adjust the analysis for multiple comparisons as recommended by some past literature [57–59]; findings need to be corroborated in future studies.

In conclusion, our study found strong evidence in support of 'reduced use' as a meaningful and desirable treatment outcome in individuals with stimulant use disorders. Further studies are needed to examine this measure along with other harm-reduction indicators of clinical improvement in studies with longer follow-up periods and to examine the use of these measures in assessments of treatment efficacy, in both research and clinical settings.

AUTHOR CONTRIBUTIONS

Masoumeh Aminesmaeili: Conceptualization (supporting); formal analysis (lead); investigation (supporting); methodology (supporting); software (lead); validation (lead); writing—original draft (lead); writing—review and editing (equal). **Mehdi Farokhnia:** Conceptualization (supporting); investigation (supporting); methodology (supporting); writing—review and editing (equal). **Ryoko Susukida:** Conceptualization (supporting); data curation (supporting); formal analysis (supporting); methodology (supporting); writing—review and editing (equal). **Lorenzo Leggio:** Conceptualization (supporting); writing—review and editing (supporting). **Renee M. Johnson:** Conceptualization (supporting); investigation (supporting); writing—review and editing (equal). **Rosa M. Crum:** Investigation (supporting); writing—review and editing (equal). **Ramin Mojtabai:** Conceptualization (equal); formal analysis (supporting); funding acquisition (lead); investigation (lead); project administration (lead); resources (lead); supervision (lead); writing—review and editing (equal).

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DECLARATIONS OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The primary data from completed RCTs are currently downloadable from the NIDA Data Share website: https://datashare.nida.nih.gov/.

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SUPPORTING INFORMATION

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