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Clinical validation of reduction in cocaine frequency level as an endpoint in clinical trials for cocaine use disorder

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Abstract

Background: Despite calls for non-abstinence endpoints in randomized clinical trials (RCTs) for cocaine use disorder, there is a lack of data validating non-abstinence endpoints. We conducted a clinical validation of reduction in cocaine frequency level as a non-abstinence endpoint in RCTs for cocaine use disorder (CUD).

Methods: We utilized a pooled dataset (n=716; 63.6% male, 51.4% non-Hispanic white) from seven RCTs for CUD. We specified three cocaine frequency levels at baseline and end of treatment (EOT): abstinence, low frequency (1–4 days/month), and high frequency (5+ days/month). Multiple regression analyses were conducted.

Results: Among the sample, 38.3% had at least a one-level reduction from baseline to EOT, whereas 61.7% did not change/increased frequency level. At least a one-level reduction in cocaine frequency level from baseline to EOT versus no change/increase was significantly associated with better functioning up to one year following treatment on measures of cocaine use, as well as psychological, employment, legal, and other drug use problem severity domains of the Addiction Severity Index (ASI). We also conducted analyses only among those at the high frequency level at

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Contributors

All authors contributed to the conceptualization of the paper. Authors Roos and Kiluk planned the specific analyses. Author Roos conducted the analyses and wrote the initial draft of the manuscript. Authors Witkiewitz, Nich, Mun, Mendonca, Babuscio, Yip, DeVito, Miguel, Kiluk, and Carroll assisted with the interpretation of analyses and manuscript writing and review. All authors contributed to and have approved the final manuscript.

Author Disclosures

Conflicts of Interest

No conflicts declared.

baseline and found those who reduced to low frequency use at EOT had similar outcomes at follow-up as those who reduced to abstinence.

Conclusions: At least a one-level reduction in cocaine frequency level from pretreatment to EOT can be a clinically meaningful endpoint given its relation to sustained clinical benefit up to one-year following treatment. These data parallel recent findings regarding reduction in drinking risk level among individuals with alcohol use disorder.

Keywords

Cocaine Use Disorder; Harm Reduction; Endpoints; Non-Abstinence Endpoints; Reduction In Cocaine Use

1. Introduction

In the treatment of cocaine use disorder (CUD), there is broad consensus that complete abstinence from cocaine use is the ideal outcome. Treatment programs for CUD commonly employ urine drug screening to monitor abstinence during treatment, and ongoing cocaine use or lapse to any cocaine use is typically viewed as a negative outcome. Yet, highlighting abstinence as the only acceptable outcome is inconsistent with the disease course and may deter individuals from seeking treatment. Specifically, CUD is a chronic relapsing condition (McLellan et al., 2000) and expecting extended periods of abstinence, particularly during early phases of recovery, may be too stringent (Kiluk et al., 2017). From a clinical perspective, overemphasis on abstinence may prevent clinicians from recognizing and reinforcing meaningful reductions to low frequency patterns of use (Roos et al., in press). It is also important to note that rather than striving for abstinence, some clients may prefer to work towards gradually reducing their cocaine use over time (McKeganey et al., 2004) and may be more interested in a treatment that was open to reduction goals. Furthermore, focusing on abstinence-based outcomes may also undermine the detection of clinically meaningful treatment effects (Kiluk et al., 2016).

Regulatory agencies in the United States and Europe support sustained abstinence from cocaine as a valid clinical trial efficacy endpoint for approving pharmacotherapies for CUD (FDA, 2013). However, recently, there has been a call for more research on the validity and utility of alternative non-abstinence endpoints in clinical trials for drug use disorders (FDA, 2018; Kiluk et al., 2016; Volkow et al., 2018). For instance, recent draft guidance from the FDA outlining endpoints for demonstrating effectiveness of drugs for medication treatment of opioid use disorder indicates drug use patterns other than abstinence could be used as a threshold for defining response to treatment (FDA, 2018). Importantly, the FDA guidance advocates for the identification of a *binary* "pass/fail" endpoint that captures reduction in use (i.e., did the individual achieve a significant level of reduction in their pattern of drug use?), which can be readily interpreted and utilized to compute the percentage of responders to a given treatment (FDA, 2018).

1.1. Non-Abstinence Drinking Reduction Outcomes in Alcohol Use Disorder Clinical Trials

In the alcohol treatment field there has been several recent studies examining non-abstinence outcomes among individuals receiving treatment for alcohol use disorder (Kline-Simon et al., 2013; Mann et al., 2017; Witkiewitz et al., 2017; Witkiewitz et al., 2018; Witkiewitz et al., 2016). Most recently, several studies have examined categorical reductions in World Health Organization (WHO, 2000) drinking risk levels from pretreatment to end of treatment as an endpoint for clinical trials. The risk levels are derived from reports of number of standard drinks over a period of time (14 grams of pure alcohol in one standard drink), which are then converted to grams of pure alcohol consumed per day on average. The four drinking risk levels [(low risk (1 to 40 grams per day for men /1 to 20 grams per day women), medium risk (41 – 60 /21 – 40), high risk (61 – 100 /41 – 60), and very high risk (101+ /61+)] and abstinence have been evaluated in AUD clinical trials and epidemiological data. Studies among individuals receiving outpatient treatment for AUD have found that achieving a one- or two-level reductions in WHO drinking risk level from pretreatment to end of treatment is associated with fewer alcohol-related consequences and improved mental health one-year following treatment (Witkiewitz et al., 2017), as well as improved markers of physical health and better quality of life one-year following treatment (Witkiewitz et al., 2018). The reductions in drinking risk level from pre-treatment to end of treatment also appear to be well-maintained one-year following treatment (Witkiewitz et al., 2019). Moreover, several large epidemiological studies in the U.S. have provided further support from reductions in WHO drinking risk level as a meaningful outcome. One- and two-level reductions of drinking risk level over a 3-year period have been found to predict lower odds of subsequent alcohol dependence (Hasin et al., 2017), drug use disorders (Knox et al., 2019b), liver disease (Knox et al., 2018), and anxiety and depressive disorders (Knox et al., 2019a). Altogether, evidence is accumulating that reductions in WHO drinking risk levels may be meaningful clinical trial endpoint and are predictive of how a person feels and functions following treatment. Here, we test whether a similar approach may be helpful in evaluating treatments for CUD.

1.2 Cocaine Use Endpoints in Cocaine Use Disorder Clinical Trials

Our research group has conducted a systematic program of research to better understand how various abstinent and non-abstinent cocaine use endpoints are associated with how clients feel and function during and following treatment. Some of our work has focused on *patterns of sustained abstinence*. Specifically, we have shown that achieving at least three or more consecutive weeks of abstinence is associated with improved functioning (Carroll et al., 2014a; Kiluk et al., 2014), and better mental health at follow-up (Miguel et al., 2019).

Some of our work has alternatively focused on *patterns of cocaine use frequency*. For example, we have found that individuals reporting one to four days of cocaine use in the final month of treatment, relative to those reporting five or more days of cocaine use, had greater likelihood of achieving ‘problem-free functioning’ (no days of problems on the Addiction Severity Index; McLellan et al., 1992) at follow-up assessments up to one-year following treatment (Kiluk et al., 2017). In another recent study (Roos et al., in press), we utilized repeated measures latent class analysis in a large pooled dataset (n = 720) to

empirically identify distinct patterns of cocaine use frequency over time during the first eight weeks of treatment. We found three distinct patterns of cocaine use over time: sustained abstinence (10.6% of the sample), low frequency use (about one day of cocaine use per week, on average; 66.3% of the sample), and persistent frequent use (about 4 days of cocaine use per week, on average; 23.1% of the sample).When these patterns were compared for post-treatment functioning outcomes, we found individuals who achieved the low frequency pattern (one cocaine use day per week, i.e., four days per month) reported similar levels of functioning following treatment as those completely abstinent. Furthermore, those who achieved the low frequency pattern reported less problem severity in several domains on the Addiction Severity Index (ASI; cocaine use, psychological, family, employment, and legal domains) than those showing persistent frequent cocaine use (Roos et al., in press). Importantly, our work thus far on patterns of cocaine use frequency has converged on the finding that *one to four days of cocaine use per month* is a common and identifiable pattern of use, and this pattern is associated with meaningful outcomes at follow-up.

1.3. Current Study

Given that reduction in WHO drinking risk level from pretreatment to the last month of treatment has been shown to be a meaningful and useful non-abstinence endpoint among individuals receiving treatment for AUD, a similar approach could be useful for establishing a non-abstinence reduction-based clinical trial endpoint among individuals receiving treatment for CUD. However, to date no studies have evaluated a *reduction* in categorical cocaine use levels from pretreatment to the last month of treatment as an endpoint among individuals receiving treatment for CUD. Our systematic program of research on cocaine use patterns provides the foundation for selecting categorical cocaine frequency levels and testing whether reducing at least one cocaine frequency level is a clinically meaningful endpoint. Using a pooled dataset (n=716) from seven randomized clinical trials for CUD, the current study provides an initial evaluation of the clinical validity of reduction in cocaine use frequency levels as a non-abstinence reduction-based endpoint. Given our prior findings, we chose abstinence, low frequency use (one to four days of cocaine use in a month), and high frequency use (five or more days of cocaine use in a month) as the three categorical cocaine use frequency levels. The current study builds upon prior work by evaluating “at least a one level reduction in cocaine frequency level” as a non-abstinent binary endpoint in clinical trials for cocaine use disorder.

2. Method

2.1. Participants and Procedures

We conducted secondary data analyses from a pooled dataset (total N=720) of seven independent randomized clinical trials evaluating outpatient-based behavioral treatment and/or pharmacotherapy for CUD. Although all participants in the pooled dataset met criteria for cocaine dependence, four participants did not report any cocaine use in the 28-days prior to baseline. Given the focus of this paper is on reduction in cocaine frequency level from this baseline period to the end of treatment period, we excluded these participants from the available sample in the current analyses. Therefore, in the current study the available sample included 716 individuals. An overview of the seven trials is shown in Table

1. The seven trials in the pooled dataset had shared measures and methodological features, thereby facilitating data integration. Demographic and treatment-related descriptive information of the pooled sample is shown in Table 2.

2.2. Measures

2.2.1. Cocaine Use and Cocaine Use Frequency Levels—For each of the seven clinical trials, a calendar-based Timeline Follow-Back method (Sobell and Sobell, 1992) was used to assess self-reported cocaine use on each day of the study period. Urine drug screens were administered weekly during the respective treatment periods and at each of the follow-up assessments.

The three cocaine frequency levels were: abstinence (no cocaine use in past month), low frequency use (one to four days of cocaine use in the past month), and high frequency use (5 or more days of cocaine use in the past month). These frequency levels at baseline and end of treatment (EOT) were based on the self-reported days of cocaine use during the 28-day period prior to the assessment and our prior work examining cocaine use patterns that were associated with meaningful improvements in functioning at follow-up (Kiluk et al., 2017; Roos et al., in press).

We created a binary variable to indicate a reduction in frequency level from baseline to EOT, "at least one-level reduction in frequency level" endpoint. Participants were coded as "Yes" if the reduced from the high frequency level to low frequency use or abstinence at EOT, or if they reduced from the low frequency level at baseline to abstinence at EOT. Participants were coded as "No" for this indicator if they exhibited no change in frequency level (i.e., high frequency at baseline and high frequency at EOT or low frequency at baseline and low frequency at EOT) or an increase in frequency level (i.e., low frequency at baseline and high frequency at EOT).

2.2.2. Functioning—For each clinical trial, the Addiction Severity Index (ASI) (McLellan et al., 1992) was used to measure functioning. The ASI is a well-established semi-structured interview that assesses problem severity across multiple life domains: psychological, medical, employment, family/social, legal, cocaine use, other drug use, and alcohol use. Higher scores indicate greater problem severity.

2.3. Statistical Analyses

2.3.1. Overview—SPSS 24 was used for descriptive analyses and t-tests. Mplus Version 8 (REF) was used for all other analyses. T-tests and chi-squares were used to evaluate differences in baseline functioning by cocaine frequency level at baseline. Multiple regression models were used to evaluate functioning and cocaine-related outcomes at the 6- and 12-month post-treatment follow-ups by change in cocaine frequency level. The specific outcome variables examined at follow-up included the cocaine, other drug use, alcohol, medical, psychological, family, employment, and legal problem severity domains of the ASI, as well as number of cocaine use days and results of the urine drug screen. All seven trials included a 6-month follow-up. Only four out of the seven trials had 12-month follow-up, thus only those four trials were included in models with 12-month follow-up outcomes.

Because we pooled data from 7 independent clinical trials, our data represents a clustered data structure. Therefore, we used the sandwich estimator, which adjusts standard errors to account for non-independence of observations related to clustering.

2.3.2. Missing Data—At the end of treatment, 125 (17.4%) participants had missing data for the timeline follow-back cocaine use data. At the 6-month follow-up (included in all seven trials of the pooled sample, n = 716), 132 (18.4%) participants had missing data for the for the Addiction Severity Index (ASI), 202 (28.2%) had missing data for the urine drug screen, and 100 (13.9%) had missing data for the timeline follow-back cocaine use data. At the 12-month follow-up (included in four out of seven trials of the pooled sample, n = 454), 165 (28.4%) participants had missing data for the for the Addiction Severity Index (ASI), 165 (36.3%) had missing data for the urine drug screen, and 99 (21.8%) had missing data for the timeline follow-back cocaine use data. For estimating model parameters, we employed full information maximum likelihood estimation, which provides the variance-covariance matrix for all available data and is the preferred method when some data is missing at follow-up assessments in clinical trials for substance use disorders (Hallgren and Witkiewitz, 2013; Witkiewitz et al., 2014). Hence, for the analyses we were able to allow for missingness and include all available datapoints for each participant.

For those who reported abstinence from cocaine at EOT, urine drug screen results were considered to validate self-reported recent abstinence. For participants who self-reported abstinence at EOT and did not submit any urine drugs screens during the final month of treatment (n= 66), they were coded as “missing” for the reduction in frequency level from baseline to EOT variable. For participants who self-reported abstinence at EOT and submitted at least one urine drug screen positive for cocaine during the final month of treatment (n=10), they were coded as “No” for the reduction in frequency level from baseline to EOT variable. Of note, the pattern of results shown below were highly similar to the patterns of results from analyses with cocaine frequency level variables alternatively computed with: 1) self-reported cocaine use only, or 2) when coding self-reported abstinence and missing urine as “No” (instead of missing) for the reduction in frequency level from baseline to EOT variable.

2.3.3. Regression Models—We first evaluated the relation between frequency level reduction and follow-up functioning outcomes among only those who started out at the high frequency level at baseline. Hence, the three possible levels among those in the high frequency level at baseline were: remaining in the high frequency at EOT (high-to-high), reducing one level to the low frequency level at EOT (high-to-low), and reducing two levels to the abstinence level at EOT (high-to-abstinent). For these regression models, we controlled for age, gender, race, and education status, and for models with ASI composites as the outcome, we also controlled for the baseline value of the ASI outcome. We also evaluated at least one-level reduction in frequency level (versus no change or increase in frequency level) as a predictor of follow-up outcomes among the full sample. For these regression models, we controlled for age, gender, race, education status, and baseline cocaine frequency level, and for models with ASI composites as the outcome, we also controlled for the baseline value of the ASI outcome. Effect sizes for mean differences at

EOT were computed as Cohen's d for mean differences in continuous outcomes and as odds ratios (ORs) for binary outcomes. Given the large number of analyses conducted in the current study, we adopted a more stringent alpha ($p \leq .01$) to indicate statistical significance across all analyses.

3. Results

3.1. Cocaine Frequency Levels

Table 3 provides an overview of the percentages of cocaine frequency levels in the sample at baseline and end of treatment (EOT), as well as the patterns of frequency level reductions over time. At baseline, the majority of participants (n = 597, 83.3%) were in the high frequency level and there were no abstainers. Most participants (n=318; 61.7%) either did not change frequency level or increased frequency level from baseline to EOT. The remaining participants (n=197, 38.3%) had at least a one-level reduction from baseline to EOT. Most of those who reduced had a one-level reduction from high frequency to the low frequency level at EOT (n=134, 26.0%) and a minority reduced two levels (n=63, 12.3%).

3.2. High Frequency versus Low Frequency Use at Baseline

Table 4 presents the baseline ASI scores among participants in the high frequency level versus the low frequency level at baseline. Compared to participants in the low frequency level, participants in the high frequency level at baseline had significantly greater problem severity in the cocaine and other drug use domains of the ASI.

3.3. Reductions in Cocaine Use Levels and Outcomes among those in the High Frequency Level at Baseline

Tables 5 and 6 provide a summary of differences in 6- and 12-month outcomes by level reductions among participants who started in the high frequency level at baseline. Compared to participants who remained in the high frequency level from baseline to EOT (high-to-high), participants who reduced from the high frequency level at baseline to the low frequency level at EOT (high-to-low) had significantly less problem severity in the cocaine domain at month 6, psychological domain at months 6 and 12, employment domain at month 12, and legal domain at month 6, as well as significantly fewer cocaine use days at months 6 and 12. Compared to the high-to-high subgroup, participants who reduced two levels from the high frequency level at baseline to abstinence at EOT (high-to-abstinent) had significantly less problem severity in the cocaine domain at month 6, psychological domain at month 6, and employment domain at month 6, as well as significantly less cocaine use days at months 6 and 12.

When comparing the high-to-low subgroup to the high-to-abstinent subgroup, some significant differences emerged. Compared to the high-to-low subgroup, the high-to-abstinent subgroup had significantly lower problem severity on the cocaine domain at month 6 but not at month 12, fewer days of cocaine use at month 6 but not at month 12, and significantly greater odds of negative urine at month 6 and 12. However, compared to the high-to-low subgroup, the high-to-abstinent subgroup had significantly *greater* problem severity in the psychological domain and legal domains at month 12. There were no other

significant differences between the high-to-low subgroup and the high-to-abstinent subgroup on the domains of the ASI at month 6 and 12.

3.4 At Least a One-Level Reduction in Frequency Level as Predictor of Follow-up Outcomes

Table 7 provides a summary of the results from the regression models testing at least a one-level reduction versus no change or increase in frequency level from baseline to EOT as a predictor of 6- and 12-month functioning and cocaine-related outcomes among the full sample. At the 6-month follow-up, at least a one-level reduction in cocaine use frequency from baseline to EOT was associated with less problem severity in the cocaine, psychological, and legal domains, as well as fewer cocaine use days and greater odds of a cocaine negative urine. At the 12-month follow up, at least a one-level reduction in cocaine use frequency from baseline to EOT was associated with less problem severity in the psychological, employment, and other drug use domains, as well as fewer cocaine use days.

4. Discussion

We conducted the first clinical validation of categorical reductions in cocaine frequency level as a non-abstinence endpoint in a pooled dataset of 716 individuals receiving treatment for CUD. We specified three frequency levels at baseline and EOT: abstinence, low frequency use (one to four days of cocaine use in the past month), and high frequency use (5 or more days of cocaine use in the past month). Our findings provide the first evidence that reductions in cocaine frequency level is a clinically meaningful binary endpoint. That is, individuals who achieved either a one-level or two-level reduction in cocaine frequency category from baseline to EOT had more favorable outcomes during the 12-month post-treatment follow-up period, as compared to those who showed no change or an increase in cocaine frequency category level. This was evident across several indicators of functioning, including the cocaine, psychological, employment, legal, and other drug use problem severity domains of the ASI, as well as cocaine use measures such as the self-reported days of cocaine use and urine drug screen. Effect sizes were in the small-to-medium sized range.

Importantly, when evaluating reduction in frequency level only among those who started at the high frequency level at baseline, we found a similar pattern of results. Specifically, among individuals at the high frequency level at baseline, those who reduced to the low frequency level at EOT had similar outcomes at follow-up as those who reduced to abstinence, and significantly better outcomes as those who remained at the high frequency level at EOT. Hence, reducing to low frequency cocaine use can be a clinically meaningful outcome specifically among those initiating treatment with high levels of cocaine use.

Altogether, our findings suggest that in addition to abstinence, categorical reductions in cocaine frequency by the end of treatment can be meaningful and are linked with sustained clinical benefit up to one-year following treatment. Findings from this study parallel findings from an expanding body of literature showing that categorical reductions in levels of alcohol use among individuals with alcohol use disorder is linked with substantial clinical benefit following treatment (Witkiewitz et al., 2019; Witkiewitz et al., 2017; Witkiewitz et al., 2018). Our findings provide evidence that adopting a similar approach to targeting

reductions in cocaine use frequency is viable and practical for CUD, and may be useful as an endpoint for clinical trials.

The current findings have implications for how the efficacy of treatments in clinical trials for CUD might be evaluated. For a proximal endpoint (measured at the termination of treatment), to be considered valid and meaningful, it should be associated with clinical benefit following treatment, such as how a person feels and functions in the long-term (Kiluk et al., 2016). To our knowledge, this study is the first to identify a clinically meaningful *binary* endpoint that captures reductions in cocaine use from baseline to EOT. Importantly, the advantage of a binary indicator, relative to a continuous indicator, is that differences between treatment groups can be more easily interpreted. Moreover, a binary indicator allows for an evaluation of the percentage of responders (i.e., those who achieved a given criterion), which is the FDA recommended approach when evaluating the efficacy of a medication on a change in drug use patterns (FDA, 2018).

It is important to note that our findings still support abstinence as an ideal outcome. Participants who reduced to abstinence in the current sample had the fewest cocaine use days and the greatest odds of a urine drug screen negative for cocaine at follow-up. Hence, these results reaffirm that the ability to achieve a sustained period of abstinence during treatment predicts favorable outcomes in the long-term. Interestingly, among individuals who started out at the high frequency level at baseline, those who reduced to abstinence at EOT actually had greater problem severity in the psychological and legal domains of the ASI at the 12-month follow-up, as compared to those who reduced to the low frequency at follow-up. The reason for this finding it not clear, but could possibly be related to the “sick-quitter” effect in which some abstainers are those who are at the highest end of the dependence severity spectrum (Shaper et al., 1988). The greater legal problems among those who changed from the high level at baseline to the abstinence level at EOT could also be related to the finding that criminal justice involvement has been linked to abstinence outcomes (Kelly et al., 2013; Kiluk et al., 2015). Alternatively, it may be the case that some life problems not necessarily the direct result of cocaine use and these problems may not change in response to a reduction in cocaine use (Kiluk et al., 2019; McLellan et al., 1981).

The current study has several limitations. Although the sample was demographically diverse, all the clinical trials were conducted in the New Haven County area of Connecticut. Thus, the findings might not generalize to other geographic or cultural contexts. Also, while the sample included individuals meeting DSM-IV criteria for current cocaine dependence who identified cocaine as their principal drug of abuse, the findings may not be specific to cocaine, as participants may have used other drugs in addition to cocaine. Only four of seven studies had a 12-month follow-up, thus sample sizes were smaller and potentially more unreliable for analyses with 12-month outcomes. It was not possible to biologically confirm different levels of cocaine use each day, given this is not possible with urinalysis. Additionally, the current study did not consider when the days of cocaine use occurred during the final month of treatment (i.e., four days of cocaine use in a row during the final week versus one day of cocaine use each of the 4 final weeks). Future work on endpoints could consider the particular timing of cocaine use days during treatment. However, the

disadvantage of this option in that computing the endpoint may become more complicated and time-intensive for clinicians and researchers.

This study nonetheless provides the first evidence that at least a one-level reduction in cocaine frequency level may have validity and utility as an endpoint in clinical trials for CUD. Future work is needed to further validate this endpoint in other settings and samples, and to compare it with other endpoints. Future studies could also examine how this endpoint performs in detecting treatment effects in completed clinical trials.

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Highlights

- Sought to validate non-abstinence endpoint for cocaine dependence clinical trials
- Specified three categorical frequency levels similar to WHO drinking risk levels
- Levels were: 1) abstinence, 2) low: 1 – 4 days/month, 3) high: 5+ days/month
- At least one-level reduction associated with clinical benefit following treatment
- Reducing from high to low frequency also associated with clinical benefit

Table 1

Overview of Studies in Pooled Dataset

Citation	Behavioral Treatment Conditions	Medication Treatment Conditions	Length of Treatment (Weeks)	Length of Follow-up (Months)	*N* and sample
(Carroll et al., 1998)	CBT *v* TSF *v* Clinical Management	Disulfiram *v* no med	12	12	122 cocaine and alcohol dependent outpatients
(Carroll et al., 2004)	CBT *v* IPT	Disulfiram *v* placebo	12	12	121 cocaine dependent outpatients
(Carroll et al., 2012)	TSF *v* TAU	Disulfiram *v* placebo	12	12	111 cocaine dependent methadone-maintained
(Carroll et al., 2016)	CM+CBT *v* CBT	Disulfiram *v* placebo	12	12	99 cocaine-dependent outpatients
(Carroll et al., 2008)	CBT4CBT+TAU *v* TAU	--	8	6	42 cocaine-dependent outpatients
(Carroll et al., 2014b)	CBT4CBT+TAU *v* TAU	--	8	6	101 cocaine dependent methadone-maintained
(Carroll et al., 2018)	CBT4CBT+TAU *v* TAU	Galantamine *v* placebo	12	6	120 cocaine dependent methadone-maintained

Note: CBT = Cognitive-behavioral therapy; TSF = Twelve-step Facilitation; IPT = Interpersonal Therapy; CM = Contingency Management; TAU = Treatment-as-Usual; CBT4CBT = Computer-Based Training for Cognitive-Behavioral Therapy.

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Table 2.

Descriptive statistics at baseline for full pooled sample (n=716)

	N (%) or Mean (SD)
Female gender	260 (36.4%)
Race/Ethnicity	
White	368 (51.4%)
Latin-x	78 (10.9%)
Black	258 (36.0%)
Other	12 (1.7%)
Age	37.22 (8.68)
Completed high school	546 (76.4%)
Unemployed	444 (62.1%)
Referred by criminal justice system	97 (13.6%)
Route of Administration for Cocaine	
Smoke	523 (73.1%)
Nasal	139 (19.4%)
IV	50 (7.0%)
Speedball	1 (0.1%)
Oral	2 (0.3%)
Days of cocaine use in month prior to treatment	14.18 (8.61)

Note: SD = standard deviation.

Table 3

Cocaine Frequency Levels at Baseline and End of Treatment (EOT) and Level Reductions Over Time

Cocaine Frequency Level	Baseline n (%)	EOT n (%)
Abstinence (0 cocaine use days in past month)	0 (0%)	83 (16.1%)
Low Frequency (1–4 cocaine use days in past month)	119 (16.6%)	147 (28.5%)
High Frequency (5+ cocaine use days in past month)	597 (83.3%)	285 (55.3%)
Change in Cocaine Frequency Level from Baseline to EOT n (%)		
Increase 1 Level	34 (6.6%)	
No change	284 (55.1%)	
Decrease 1 Level	134 (26.0%)	
Decrease 2 Levels	63 (12.2%)	
All Categories of Level Reduction from Baseline to EOT n (%)		
High Freq Baseline → High Freq EOT	251 (48.7%)	
High Freq Baseline → Low Freq EOT	114 (22.1%)	
High Freq Baseline → Abstinence EOT	63 (12.2%)	
Low Freq Baseline → High Freq EOT	34 (6.6%)	
Low Freq Baseline → Low Freq EOT	33 (6.4%)	
Low Freq Baseline → Abstinence	20 (3.9%)	

Note. EOT = End of Treatment.

Table 4

Comparison of High Frequency vs. Low Frequency Users at Baseline on Functioning Scores at Baseline

	Means (SD)		p-value	Effect Size (Cohen's d)
	High Frequency Use at Baseline (5 + days of cocaine use in past month) n =597	**Low Frequency Use at Baseline (1–4 days of cocaine use in past month) n =119**		
Baseline ASI Cocaine	.69 (.21)	.47 (.17)	<.001**	1.15
Baseline ASI Other Drug Use	.06 (.07)	.04 (.06)	.01*	.30
Baseline ASI Alcohol	.15 (.20)	.21 (.31)	.04	.23
Baseline ASI Medical	.15 (.28)	.21 (.31)	.07	.20
Baseline ASI Psychological	.16 (.19)	.16 (.19)	.76	.00
Baseline ASI Family	.16 (.18)	.15 (.16)	.71	.05
Baseline ASI Employment	.63 (.28)	.66 (.29)	.22	.10
Baseline ASI Legal	.09 (.17)	.05 (.11)	.03	.27

Note. ASI = Addiction Severity Index. SD = standard deviation. T-tests were used to evaluate mean differences at baseline.

* $p<0.05$

* $p\leq0.01$

** $p\leq0.001$

Table 5

Comparison of 6-Month Follow-up Outcomes by Cocaine Frequency Level Reductions among High Frequency Users at Baseline

	Means (SD)			Group Comparisons B (SE)		
	High Frequency Baseline to High Frequency EOT (High-to-high) n = 261	**High Frequency Baseline to Low Frequency EOT (High-to-low) n = 114**	**High Frequency Baseline to Abstinent EOT (High-to-abstinent) n = 63**	**High-to-low vs. High-to-high**	**High-to-abstinent vs. High-to-high**	**High-to-abstinent vs. High-to-low**
ASI Cocaine	.43 (.30)	.30 (.27)	.17 (.22)	−.10 (.03) * d=.45	−.20 (.04) ** d=.98	−.15 (.04) ** d=.52
ASI Other Drug Use	.05 (.09)	.04 (.08)	.03 (.05)	−.005 (.009) d=.11	−.01 (.008) d=.27	−.01 (.009) d=.14
ASI Alcohol	.05 (.13)	.07 (.14)	.07 (.13)	.004 (.01) d=.14	−.02 (.02) d=.15	−.03 (.02) d=0
ASI Medical	.08 (.21)	.07 (.19)	.10 (.25)	.001 (.02) d=.04	.04 (.02) d=.08	.04 (.03) d=.13
ASI Psychological	.16 (.21)	.12 (.16)	.11 (.18)	−.03 (.01) ** d=.21	−.04 (.01) * d=.25	−.01 (.01) d=.05
ASI Family	.10 (.17)	.08 (.12)	.09 (.15)	−.01 (.01) d=.13	−.01 (.01) d=.06	.01 (.01) d=.07
ASI Employment	.67 (.27)	.57 (.27)	.59 (.28)	−.06 (.03) d=.37	−.09 (.02) ** d=.29	.03 (.02) d=.07
ASI Legal	.08 (.16)	.03 (.10)	.04 (.12)	−.05 (.007) ** d=.37	−.03 (.02) d=.28	.02 (.01) d=.09
Cocaine Use Days	8.25 (9.20)	4.39 (6.8)	1.16 (2.89)	−.3.5 (.755) ** d=.47	−.6.07 (.27) ** d=1.03	−.5.8 (1.29) ** d=.61
Cocaine Negative Urine	63 (28.3%)	43 (46.7%)	41 (83.7%)	.47 (.18) OR = 1.59	1.16 (.08) ** OR = 3.18	.76 (.10) * OR = 2.1

Note.

* $p \leq 0.01$.

** $p \leq 0.001$.

B = Unstandardized regression coefficient. SD = standard deviation. SE = standard error. d= Cohen's d. OR = Odds Ratio. EOT = End of Treatment. ASI = Addiction Severity Index. In all models, we controlled for age, gender, race, and education status. For all models with ASI composites as the outcome, we also controlled for the baseline value of the ASI outcome.

Table 6

Comparison of 12-Month Follow-up Outcomes by Cocaine Frequency Level Reductions among High Frequency Users at Baseline

	Means (SD)			Group Comparisons B (SE)		
	High Frequency Baseline to High Frequency EOT (High-to-high) n = 126	**High Frequency Baseline to Low Frequency EOT (High-to-low) n = 85**	**High Frequency Baseline to Abstinent EOT (High-to-abstinent) n = 46**	**High-to-low vs. High-to-high**	**High-to-abstinent vs. High-to-high**	**High-to-abstinent vs. High-to-low**
ASI Cocaine	.32 (.27)	.25 (.23)	.17 (.22)	−.04 (.04) d=.27	−.10 (.04) d=.60	−.08 (.05) d=.35
ASI Other Drug Use	.05 (.08)	.02 (.06)	.03 (.10)	−.01 (.01) d=.42	.003 (.01) d=.22	.003 (.02) d=.12
ASI Alcohol	.06 (.14)	.08 (.12)	.09 (.18)	.02 (.02) d=.15	−.003 (.03) d=.18	−.01 (.02) d=.06
ASI Medical	.08 (.21)	.08 (.23)	.06 (.21)	−.001 (.02) d=0	.002 (.03) d=.09	−.004 (.03) d=.09
ASI Psychological	.13 (.19)	.08 (.14)	.10 (.16)	−.04 (.01) * d=.30	−.008 (.01) d=.17	.02 (.004) ** d=.13
ASI Family	.11 (.17)	.11 (.15)	.16 (.19)	.008 (.02) d=0	.05 (.03) d=.27	.04 (.03) d=.29
ASI Employment	.64 (.27)	.56 (.24)	.51 (.26)	−.06 (.01) ** d=.31	−.08 (.03) d=.49	−.07 (.05) d=.19
ASI Legal	.04 (.11)	.03 (.11)	.08 (.16)	−.009 (.02) d=.09	.01 (.03) d=.29	.03 (.007) ** d=.36
Cocaine Use Days	6.02 (8.15)	3.91 (5.98)	3.26 (7.88)	−.1.80 (.59) ** d=.29	−.1.95 (.67) ** d=.34	−.52 (.92) d=.09
Cocaine Negative Urine	47 (45.2%)	28 (45.9%)	22 (71%)	−.02 (.20) OR = .98	.53 (.23) OR = 1.69	.57 (.17) * OR = 1.76

Note. Note.

* $p \leq 0.01$.

** $p \leq 0.001$.

B = Unstandardized regression coefficient. SD = standard deviation. SE = standard error. d= Cohen's d. OR = Odds Ratio. EOT = End of Treatment. ASI = Addiction Severity Index. In all models, we controlled for age, gender, race, and education status. For all models with ASI composites as the outcome, we also controlled for the baseline value of the ASI outcome.

Table 7

At Least One-Level Reduction in Frequency Level as a Predictor of 6- and 12- Month Outcomes

6-Month Outcomes				
		At Least One-Level Reduction in Frequency Level?		
		NO (i.e., no change/increase in frequency level) n = 329	YES (i.e., reduced 1 or 2 frequency levels) n = 197	
	B (SE)	Means (SD) or N (%)		Effect Size
ASI Cocaine	−.12 (.03)**	.39 (.30)	.25 (.26)	d=.49
ASI Other Drug Use	−.009 (.008)	.05 (.08)	.03 (.07)	d=.26
ASI Alcohol	−.004 (.01)	.05 (.12)	.07 (.13)	d=.15
ASI Medical	.01 (.01)	.09 (.22)	.09 (.21)	d=0
ASI Psychological	−.04 (.01)*	.17 (.21)	.12 (.17)	d=.26
ASI Family	−.01 (.01)	.10 (.16)	.09 (.13)	d=.06
ASI Employment	−.07 (.02)	.67 (.27)	.57 (.27)	d=.37
ASI Legal	−.04 (.008)**	.08 (.16)	.03 (.11)	d=.36
Cocaine Use Days	−.4.32 (.57)**	7.02 (8.77)	3.05 (5.7)	d=.53
Cocaine Negative Urine	.68 (.06)**	97 (34%)	95 (59.7%)	OR = 1.95
12-Month Outcomes				
		At Least One-Level Reduction in Frequency Level?		
		NO n = 156	YES n = 145	
ASI Cocaine	−.09 (.04)	.31 (.27)	.21 (.23)	d=.39
ASI Other Drug Use	−.01 (.003)*	.04 (.08)	.02 (.07)	d=.26
ASI Alcohol	.003 (.01)	.07 (.15)	.08 (.14)	d=.06
ASI Medical	.01 (.01)	.08 (.21)	.09 (.25)	d=.04
ASI Psychological	−.04 (.01)*	.14 (.20)	.09 (.15)	d=.28
ASI Family	.00 (.02)	.12 (.17)	.12 (.16)	d=0
ASI Employment	−.08 (.01)**	.63 (.26)	.55 (.24)	d=.31
ASI Legal	.003 (.02)	.04 (.11)	.05 (.13)	d=.08
Cocaine Use Days	−.2.02 (.32)**	5.4 (7.6)	3.4 (6.38)	d=.28
Cocaine Negative Urine	.26 (.10)	56 (43%)	59 (56.7%)	OR = 1.29

Note.

*$p \leq 0.01$.

**$p \leq 0.001$.

B = Unstandardized regression coefficient. SD = standard deviation. SE = standard error. d= Cohen's d. OR = Odds Ratio. EOT = End of Treatment. ASI = Addiction Severity Index. In all models, we controlled for age, gender, race, education status, and baseline cocaine frequency level. For all models with ASI composites as the outcome, we also controlled for the baseline value of the ASI outcome.