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Detecting Change in Psychiatric Functioning in Clinical Trials for Cocaine Use Disorder: Sensitivity of the Addiction Severity Index and Brief Symptom Inventory

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Abstract

Background: Assessment instruments commonly used in clinical trials to measure functional outcomes in substance users may lack sensitivity to detect change during treatment, potentially limiting findings regarding benefits of reduced drug use. This study evaluated the sensitivity of the Addiction Severity Index (ASI) to detect change in psychiatric functioning among cocaine users.

Methods: Data were pooled across five clinical trials for cocaine use disorder (N = 492) that included a 12-week treatment period and 6-month follow-up. Within-person cohen's d′ was used to evaluate effect size of change on the Psychiatric Composite Score of the ASI (ASI-Psych) and Global Severity Index (GSI) of the Brief Symptom Inventory, as well as cocaine use.

Results: Effect sizes were larger for GSI than ASI-Psych from baseline to week 12 (GSI d′ = 0.59; ASI-Psych d′ = 0.16), and 6-month follow-up (GSI d′ = 0.48; ASI-Psych d′ = 0.10). For those with non-zero ASI-Psych at baseline (n = 252), medium effect sizes were found over the 12-week period (d′ = 0.53) and 6-month follow-up (d′ = 0.47). Effect sizes for change in days of cocaine use were most similar to GSI in either sample.

Conclusions: The ASI Psychiatric Composite Score may have limited sensitivity to detect change in psychiatric functioning among clinical trial participants who reduce cocaine use. It may be useful for detecting change amongst those reporting some psychiatric problems at the start of treatment. Future research should consider an instrument's sensitivity to change when assessing the potential functional benefits of reducing cocaine use.

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Contributors

Author BDK designed the study, planned the analyses and wrote the initial draft of the manuscript. Authors CRR, MA, RG, CN, and TAB contributed to the statistical analyses, interpretation of data, and the written manuscript. Author KMC designed the 5 trials that contributed data to this study and contributed to the planned analyses and interpretation of results. Author KMC reviewed an initial draft of the manuscript but passed away prior to this final manuscript submission. All other authors have approved the final manuscript.

Conflict of Interests

All authors declare no conflicts of interest.

1. Introduction

Most treatments (pharmacotherapy or behavioral) for cocaine use disorder (CUD) are designed to help individuals reduce or discontinue cocaine use, yet treatment endpoints based solely on measures of cocaine abstinence have limitations as indicators of treatment success. The lack of standard methods regarding the frequency and type of biological sample collection, the complexity of combining self-report and biological sources of data, and the impact of missing data create considerable challenges in defining meaningful change in quantity/frequency of illicit drug use (Donovan et al., 2012; Kiluk et al., 2016). Furthermore, outcome measures based solely on results of biological indicators of drug consumption are considered only markers of drug use disorders and deemed surrogate endpoints in clinical trials (Winchell, Rappaport, Roca, & Rosebraugh, 2012). According to guidelines from the US Food and Drug Administration's Center for Drug Evaluation and Research (CDER), a meaningful outcome measure to evaluate treatment benefit should demonstrate change in how an individual feels, functions, or survives (Center for Drug Evaluation and Research, 2014). In other words, a treatment endpoint based on measures of cocaine abstinence (or reduced consumption) should be associated with improvement in the key physical and psychosocial problems that characterize the disorder in order to be deemed clinically meaningful (Kiluk et al., 2016).

However, measurement of the association between cocaine use and functional outcomes presents its own challenges in clinical trials. It is generally assumed that abstinence from cocaine would be accompanied by improvements in an individual's functioning in various areas such as physical, psychological, and social domains. However, empirical evidence supporting this direct link has been mixed (Borders et al., 2009; Carroll et al., 2014; McLellan, Luborsky, Woody, O'Brien, & Kron, 1981; Simpson, Joe, & Broome, 2002). While this may be due in part to the measurement of functional status as a direct or indirect consequence of drug use (Kiluk, Fitzmaurice, Strain, & Weiss, 2019), it may also reflect differences in an instrument's sensitivity to detect change over time. Assessment measures commonly used in clinical trials to measure functional outcomes may not be particularly sensitive to change during a relatively brief treatment period, thereby limiting the potential to reveal clinical benefits associated with reduction/improvement in cocaine use patterns.

Kirouac and Witkiewitz (2019) recently evaluated the sensitivity to change of non-consumption measures of alcohol use disorder treatment, such as temptation/craving, self-efficacy, and alcohol-related consequences using data from two large multi-site RCTs (Project MATCH and COMBINE). Pre- to post-treatment effect sizes were found to be at least in the medium range for all non-consumption measures, with some showing very large effect sizes similar to primary alcohol consumption outcomes. Also, measures of alcohol temptation/craving and alcohol abstinence self-efficacy were predictive of longer-term consumption outcomes, highlighting their potential value as meaningful outcomes of alcohol treatment. Sensitivity to change has yet to be examined for non-consumption measures in drug use disorder trials, including those of broader functional outcome measures.

One of the most commonly used assessment instruments in clinical trials with drug-using populations designed to measure the severity of problems across multiple domains of

functioning is the Addiction Severity Index (ASI; McLellan, Luborsky, Woody, & O'Brien, 1980). Although originally designed as a diagnostic evaluation to support treatment decision-making, the instrument is also often used to monitor change in a patient's status in various areas (medical, legal, employment, drugs, alcohol, family/social, and psychiatric status). There is a robust literature establishing the psychometric properties of the ASI over the past 40 years (e.g., Alterman, Bovasso, Cacciola, & McDermott, 2001; Alterman, Cacciola, Habing, & Lynch, 2007; Cacciola, Alterman, Habing, & McLellan, 2011; McLellan, Cacciola, Alterman, Rikoon, & Carise, 2006); however one area with little devoted attention is the sensitivity to detect change over time. While the value of the ASI as a screening and predictive tool is clear, its value in detecting change over time in functional outcomes in clinical trials remains uncertain.

For instance, the Psychiatric Status section on the ASI was developed to measure the severity of psychological or emotional problems, and there is solid evidence that the summary score (Composite Score) is a valid indicator of psychiatric functioning. It has demonstrated correlations with other indicators of psychiatric functioning such as the Symptom Checklist (SCL) and Short-Form Health Survey (SF-12; 36) (Cacciola et al., 2011; Calsyn et al., 2004). It has performed reasonably well at detecting mental health disorders in individuals seeking treatment for substance use in usual care settings (Cacciola, Pecoraro, & Alterman, 2008; Rush, Castel, Brands, Toneatto, & Veldhuizen, 2013), as well as among individuals with substance use disorders participating in RCTs (Susukida, Mojtabai, & Amin-Esmaeili, 2020). There is also support for its predictive validity in terms of future psychiatric care (Drymalski & Nunley, 2016; Thylstrup, Bloomfield, & Hesse, 2018). However, there is limited evidence of its sensitivity to change over time. Some studies of individuals entering drug treatment have not reported significant change on ASI Psychiatric Composite Scores over periods up to 18-months (Guydish, Sorensen, Chan, & Bostrom, 1999), whereas others have shown statistically significant improvement in shorter periods (Coviello et al., 2001; Deane, Kelly, Crowe, Coulson, & Lyons, 2013). A systematic review of studies within opioid substitution programs in low- and middle-income countries that included longitudinal measurement with ASI (5 studies; combined n = 504) reported a statistically significant pooled standardized mean difference in ASI Psychiatric Status from baseline to a 6- or 12-month follow-up, suggesting reduction in psychiatric severity over time (Feelemyer, Des Jarlais, Arasteh, Phillips, & Hagan, 2014). Yet, it is unclear whether the Psychiatric Composite Score can detect change/improvement over time during the course of clinical trials evaluating treatment for CUD.

Our research group has produced a line of research evaluating various cocaine use outcome measures within clinical trials with an emphasis on their association with long-term outcomes including measures of functioning. This work has generally found greater rates of cocaine abstinence (e.g., higher percentage of days abstinent) or greater reductions in cocaine use frequency during treatment were associated with less problem severity in several areas of functioning following treatment, including psychiatric functioning (Kiluk, Babuscio, Nich, & Carroll, 2017; Kiluk, Nich, Witkiewitz, Babuscio, & Carroll, 2014; Miguel et al., 2019; Roos et al., 2019). However, while statistically significant, the magnitude of these associations has been relatively modest. Whether this is impacted by the assessment instrument's sensitivity to detect change has yet to be determined. This

study aimed to evaluate the sensitivity of the ASI Psychiatric Composite Score (ASI-Psych) at detecting change in psychiatric symptomatology using a pooled dataset of individuals seeking treatment for CUD participating in a clinical trial. The magnitude of change in ASI-Psych was evaluated in the context of the change reported on another measure of psychiatric symptomatology (Brief Symptom Inventory), as well as the magnitude of change in cocaine use during the trial.

2. Methods

2.1 Overview

This is a secondary analysis of data pooled across five independent clinical trials conducted at Yale evaluating behavioral (e.g., cognitive behavioral therapy [CBT], twelve-step facilitation [TSF], interpersonal therapy [IPT], contingency management [CM], computer-based training for cognitive behavioral therapy [CBT4CBT]) and pharmacologic (e.g., disulfiram, galantamine) treatments for CUD in different populations (e.g., outpatient, methadone maintenance). The five trials shared common characteristics in terms of participant inclusion criteria, treatment duration (12 weeks), and schedule of assessments. Details of the five trials are as follows:

2.1.1 Study #1 (Carroll et al., 2004): 12-week trial evaluating four treatment arms (CBT plus disulfiram; CBT plus placebo; IPT plus disulfiram; IPT plus placebo) in a general outpatient sample of 121 individuals.

2.1.2 Study #2 (Carroll, Nich, Shi, Eagan, & Ball, 2012): 12-week trial evaluating four treatment arms (TSF plus disulfiram; TSF plus placebo; disulfiram plus standard counseling; placebo plus standard counseling) in sample of 112 individuals also receiving methadone maintenance therapy for opiate dependence.

2.1.3 Study #3 (Carroll et al., 2016): 12-week trial evaluating four treatment arms (disulfiram plus CM; disulfiram alone; placebo plus CM; placebo alone) in a general outpatient sample of 99 individuals. Participants in each of the four treatment arms also received weekly individual cognitive behavioral therapy.

2.1.4 Study #4 (Carroll, Nich, DeVito, Shi, & Sofuoglu, 2018): 12-week trial evaluating four treatment arms (CBT4CBT plus galantamine; CBT4CBT plus placebo; galantamine alone; placebo alone) in a sample of 120 individuals also receiving methadone maintenance therapy for opiate dependence;

2.1.5 Study #5 (Kiluk et al., 2018): 12-week trial evaluating three treatment arms (CBT; CBT4CBT plus clinical management; treatment as usual) in a general outpatient sample of 137 individuals. Of note, only those reporting cocaine as their primary drug were included in these analyses (n = 40).

2.2 Participants

Participants in all trials met the following criteria: (1) at least 18 years of age; (2) Diagnostic and Statistical Manual (DSM-IV; American Psychiatric Association, 1994) criteria for

current (past 28 days) cocaine abuse or dependence (DSM-5 and the accompanying structured clinical interview were not available at the start of these trials); (3) eligible for outpatient treatment (i.e., not experiencing current Psychotic or Bipolar episode); and (4) not physically dependent on another drug that would require detoxification.

2.3 Assessments

2.3.1 Addiction Severity Index (ASI; McLellan et al., 1992)—The ASI is an interview-based, multidimensional assessment designed to detect and measure the severity of problems in seven areas commonly affected by alcohol and drug use. Each section includes a range of items that tap potential problem symptoms for that area using a mixture of binary (yes/no), ordinal (rating scale from 0 -"not at all" to 4 –"extremely"), and discrete (e.g., days of problems) responses. A select combination of items within each area (ranging from 3 – 13 items) are summed and arithmetically weighted to create a Composite Score, a standardized summary score to indicate problem severity ranging from 0 to 1, with higher scores indicating greater problem severity. For the purpose of this study, only the ASI-Psych section was analyzed. The Composite Score for ASI-Psych is composed of 11 items, eight of which are binary questions (any significant period of psychiatric problem in past month; e.g., "experienced serious depression?" – yes/no), one discrete question ("how many days in past month have you experienced these psychological/emotional problems?"), and two ordinal questions (patient rating scale; "how troubled or bothered have you been by these psychological/emotional problems in past month?", and "how important to you now is treatment for these problems?"). The ASI was administered at baseline (week 0), monthly during the treatment period (week 4, week 8), at treatment endpoint (week 12), and at follow-up interviews up to 6-months after treatment endpoint (week 36).

2.3.2 Brief Symptom Inventory (BSI; Derogatis & Melisaratos, 1983)—The BSI is a 53-item self-report instrument for measuring the level of distress experienced during the past week regarding a number of psychiatric symptoms using a 5-point Likert scale (from 0 "not at all" to 4 "extremely"). The items cover symptom dimensions that form nine subscales (Depression, Anxiety, Hostility, Interpersonal Sensitivity, Obsession-Compulsion, Phobic anxiety, Paranoid Ideation, Psychoticism, and Somatization), and three global indices of distress: Global Severity Index (GSI), Positive Symptom Total (PST), and Positive Symptom Distress Index (PSDI). The GSI combines information about the number of symptoms and the intensity of distress and is a widely used measure of psychological distress in psychotherapy outcome research (Hill & Lambert, 2004). It is calculated using the sums from the nine symptom dimensions plus four additional items not included in any of the dimension scores, and dividing by the total number of items to which the individual responded (i.e., the mean of all 53 items if none were skipped). For the purposes of this study, only the GSI was included in analyses reported here, although results for the PST and PSDI were consistent with findings presented below (and available upon request). The BSI was administered at baseline, weekly during the treatment period up to week 12, and at each follow-up interview up to 6-months after treatment end (week 36).

2.3.3 Cocaine use—Frequency of cocaine use was measured by self-report using a calendar-based Timeline FollowBack method (Robinson, Sobell, Sobell, & Leo, 2014;

Sobell & Sobell, 1992), and included biological verification with urine toxicology screens at each assessment visit.

2.4 Data Analysis

Analyses were conducted using SAS 9.4 (SAS, Cary, NC). The analytic plan focused on evaluating the magnitude of change on ASI-Psych from baseline to each monthly interval during treatment, and up to the final follow-up assessment (i.e., from week 0 to week 4; week 0 to week 8; week 0 to week 12; week 0 to week 36). The magnitude of change was also examined for GSI on the same schedule as a validation of the level of change in psychiatric symptomatology. Analyses were conducted for all randomized participants with data on ASI or BSI, as well as for the subgroup of participants with complete data on both ASI and BSI at all timepoints in order to evaluate change in scores within the same participants across instruments. We also conducted separate analyses for the subset of participants with ASI-Psych composite scores greater than zero at baseline to explore change in mean scores for those who reported psychiatric problem severity at baseline. Descriptive statistics for the ASI-Psych and GSI were computed for the full sample and each subgroup (those with complete data, and those with non-zero ASI-Psych at baseline) at each timepoint. Paired t-tests were used to evaluate the statistical significance of change from baseline in ASI-Psych and GSI scores at each timepoint. Correlations between ASI-Psych and GSI scores were also computed at each timepoint to evaluate the relationship between instruments. Within-persons Cohen's d' was used as a measure of effect size of change in ASI-Psych and GSI from baseline to each of the monthly intervals within treatment and at final follow-up. Lastly, we examined the effect size of change in the number of cocaine use days over time (across same intervals as ASI and BSI) using within-persons Cohen's d'. This allowed us to observe the magnitude of change in psychiatric functioning in the context of change in cocaine use. The reported effect sizes reflect within-person change on a given measure (ASI-Psych, GSI, days of cocaine use) rather than the effect of treatment versus a control condition in a standard effectiveness study.

3. Results

3.1 Participants

There were 492 randomized participants with data across the five trials. Table 1 provides a description of this sample overall and within each trial. As can be seen, the sample consisted of 31.5% female and 54.1% White, with a mean age of 38.1 (sd=8.6). On average, participants reported 13.0 (sd=8.5) days of cocaine use at baseline and 11.6% met DSM-IV criteria for a current mood or anxiety disorder. Within the pooled sample, 224 participants had complete data on both the ASI and BSI at each timepoint, and 252 participants reported ASI-Psych > 0 at baseline. Demographic and clinical characteristics at baseline are also provided for these subsamples in Table 1. The subsample with complete data on ASI and BSI (n=224) were slightly older (Mean age = 39.0 vs. 37.4) and less likely to have a current mood or anxiety disorder (8.5% vs. 14.2%) compared to those without complete data on ASI and BSI (n=268). The subsample with ASI-Psych > 0 at baseline (n=252) had a greater percentage of White participants (61% vs. 46%), a greater percentage with current mood or

anxiety disorder (18.3% vs. 4.2%), and were younger (Mean age = 37.2 vs. 39.1) compared to those with ASI-Psych = 0 at baseline (n=239).

3.2 ASI-Psych and GSI scores across timepoints

Mean scores on the ASI-Psych and GSI at each timepoint are provided in Table 2. Results of paired t-tests examining the difference in means at each timepoint from baseline indicated significant reductions in mean scores for the ASI-Psych during the treatment period in the full sample: [week 4: $t(450) = -2.31$, $p=.02$; week 8: $t(437) = -3.99$, $p<.001$; week 12: $t(443) = -3.35$, $p<.001$], but not at 6-month follow-up [week 36: $t(434) = -1.65$, p=.10]. Results of paired t-tests revealed significant reductions in GSI from baseline to week 4, 8, 12, and 36: [week 4: $t(370) = -10.42$, $p<.001$; week 8: $t(304) = -11.81$, $p<.001$; week 12: $t(379) = -11.79$, $p<.001$; and week 36: $t(354) = -7.28$, $p<.001$]. Results of Spearman correlations between ASI-Psych and GSI scores revealed significant correlations at each concurrent timepoint, with r's ranging from .45 to .54 (all $p<.001$).

Among the subsample with complete data on ASI and BSI (n=224), results of paired t-tests indicated no significant change from baseline in ASI-Psych mean scores. There were significant reductions in this subsample for GSI from baseline to week 4, 8, 12, and 36: [week 4: $t(223) = -8.19$, $p<.001$; week 8: $t(223) = -9.53$, $p<.001$; week 12: $t(223) = -9.60$, $p<.001$; and week 36: $t(223) = -7.43$, $p<.001$]. Spearman correlations between ASI-Psych and GSI scores in this subsample revealed significant correlations at each concurrent timepoint, with r's ranging from .44 to .51 (all $p<.001$).

Frequency distribution of mean scores on ASI-Psych at baseline revealed a large proportion of participants with a Composite Score of zero (n = 239), which reduced baseline mean scores in the full sample. Among those with ASI-Psych = 0 at baseline, only 6.3% also had GSI = 0 at baseline. See Table 2 for mean ASI and GSI scores at each time point for those with ASI-Psych > 0 at baseline. Results of paired t-tests examining the difference in means at each timepoint from baseline (for only this subsample >0 at baseline) revealed significant reductions in ASI-Psych at all timepoints: [week 4: $t(223) = -17.74$, $p<.001$; week 8: $t(217) = -17.91$, $p<.001$; week 12: $t(223) = -18.24$, $p<.001$; and week 36: $t(212) = -17.36$, $p<.001$]. This subsample also had significant reductions in GSI from baseline: [week 4: $t(185) = -7.76$, $p<.001$; week 8: $t(142) = -9.37$, $p<.001$; week 12: $t(185) = -9.94$, $p<.001$; and week 36: $t(158) = -5.26$, $p<.001$]. Results of Spearman correlations between ASI-Psych and GSI scores in this subsample also revealed significant correlations at each concurrent timepoint, with r's ranging from .32 to .55 (all $p<.001$).

3.3 Magnitude of change

Within-person cohen's d′ effect sizes for ASI-Psych and GSI scores, as well as self-reported days of cocaine use during the past 28, from baseline to each monthly time point during treatment and to 6-month follow-up are reported in Table 3. In the full sample (n = 492), the ASI-Psych demonstrated a small effect size of change during the 12-week treatment period (week 0 to week 12: d′ = 0.16), whereas the GSI scores were in the medium effect size range during the same time period (d′ = 0.59). In the longer-term (week 0 to week 36), the effect size of change for ASI-Psych was even smaller (d′ = 0.10) indicating very little

change over a 36-week period. Effect size of change for GSI scores from week 0 to week 36 remained in the medium range ($d' = 0.48$), similar to the magnitude of change during the 12-week treatment period. Effect sizes were large for change in self-reported days of cocaine use from baseline through end-of-treatment (week 0 to week 12: $d' = 0.79$) and through 6-month follow-up (week 0 to week 36: $d' = 0.76$).

For the subgroup of participants with complete data on both instruments at all time points (n = 224), effect sizes for ASI-Psych from week 0 to week 12, and from week 0 to week 36 were negligible ($d' = 0.04$ and $d' = 0.01$, respectively). Effect sizes for change in GSI and days of cocaine use in this subgroup during the treatment period were nearly identical to those found in the full sample (week 0 to week 12: GSI $d' = 0.64$; cocaine use $d' = 0.80$), indicating a medium and large effect size, respectively. This was also true of effect sizes for GSI and cocaine use through 6-month follow-up (week 0 to week 36: GSI $d' = 0.50$; cocaine use $d' = 0.79$).

For the subgroup of participants with ASI-Psych scores > 0 at baseline (n = 253), within person cohen's d' effect size was in the medium range for ASI-Psych from week 0 to week 12 ($d' = 0.53$) and from week 0 to week 36 (d' 0.47). Effect sizes for GSI scores within this subsample were in the medium-large range from week 0 to week 12 ($d' = 0.72$), and in the medium size range from week 0 to week 36 ($d' = 0.49$). Effect sizes for change in days of self-reported cocaine use in this subsample remained in the large range (week 0 to week 12: $d' = 0.82$; week 0 to week 36: $d' = 0.72$).

4. Discussion

This is the first study to evaluate the pre- to post-treatment sensitivity to change of assessments of psychiatric functioning within the context of clinical trials for CUD. The main findings revealed the ASI Psychiatric Composite Score, a widely-used indicator of psychiatric problem severity, demonstrated a statistically significant reduction yet small effect size over the course of a 12-week treatment period in a pooled sample of 492 cocaine treatment-seeking individuals. A separate indicator of psychiatric distress, the Global Severity Index calculated from the Brief Symptom Inventory, showed a greater magnitude reduction in scores during the same period with a larger effect size. The effect size of change on each measure was smaller when scores were examined from baseline to a 6-month follow-up time point (as compared to week 12), but still indicated the GSI had a substantially larger effect size than the ASI-Psych. This pattern of results was similar among different subgroups based on gender and race (data not presented, but available upon request). The findings were magnified when the sample was restricted to participants with complete data on both instruments over the course of the trial, suggesting the same participants showed much greater reductions in psychiatric symptoms as measured by the GSI compared to the ASI-Psych, which showed negligible change from baseline. While the ASI-Psych was not particularly sensitive to detecting change in psychiatric symptomatology overall, it did reveal greater change over time for those with some reported psychiatric problem severity at baseline. This may suggest a need to consider more individualized vs. general outcomes when evaluating treatment benefit beyond drug use.

Evidence of improved patient outcomes is needed to validate reduced drug use as a meaningful clinical trial endpoint in medications development (Volkow et al., 2018; Winchell et al., 2012). For measures of psychiatric functioning to be explored as endpoints to establish benefits of reduction in drug use, it is vital that such measures demonstrate sensitivity to change during treatment and beyond. Despite the benefits and ubiquitous presence of the ASI as a study assessment in drug use disorder randomized clinical trials, the findings presented here indicate the Psychiatric Composite Score may not provide sufficient sensitivity to detect improvement in psychiatric functioning among cocaine users. The statistically significant change over time and medium effect size found on the GSI suggests there was clear improvement in psychiatric symptomatology at the end of treatment and up to six months following treatment in this pooled sample. Yet this level of improvement was unobserved on ASI-Psych, particularly within the subset of participants who completed the BSI and ASI simultaneously. There was a statistically significant reduction in mean scores on ASI-Psych between baseline and end-of-treatment, which is consistent with prior randomized clinical trials of psychosocial treatments for cocaine dependence (Coviello et al., 2001; Crits-Christoph et al., 2001), as well as in trials of medication treatment for opioid use disorder (e.g., Streck, Ochalek, Badger, & Sigmon, 2018). However, the small within-person effect size evidenced here restricts the clinical meaningfulness of the statistical change in scores.

The limited change in ASI-Psych scores is particularly striking within the context of the large effect sizes found for change in cocaine use. Regardless of whether the full randomized sample or subsamples were examined, there appeared to be meaningful change in the frequency of cocaine use from baseline to end-of-treatment and up to 6-months following treatment. The finding that GSI scores also showed meaningful change (i.e., medium effect size) during the same period suggests potential for an association between reduction in cocaine use and improvement in psychiatric functioning. This has been reported in our prior work using different methods and a similar, although not identical, pooled sample (Miguel et al., 2019). However, this association could be missed (or have limited clinical significance) if relying on ASI-Psych scores as a sole indicator of psychiatric functioning, thereby further blurring the clinical benefits of reduced cocaine use.

A plausible explanation for the small magnitude of change in ASI-Psych is the lower limit (i.e., floor effect) of scores at baseline in this sample. With nearly half of the sample having an ASI-Psych score of zero at baseline, mean scores were suppressed resulting in little opportunity for change. This is supported through analyses that explored change over time in ASI-Psych scores for only those with non-zero scores at baseline, which showed statistically significant change through 6-month follow-up and medium effect sizes more comparable to GSI. In this case, the ASI-Psych may have utility as an outcome measure for those with at least some reported psychiatric problem severity at baseline. However, the high occurrence of zeros on ASI-Psych at baseline is concerning as only 6.3% also had GSI score of zero, suggesting participants in these clinical trials were not void of any psychiatric distress. Rather, it may be the measurement characteristics of the items contributing to the Composite Score on ASI-Psych that are problematic for detecting change in clinical trials. Eight of the eleven items are binary (yes/no) questions, with several indicating severe psychiatric problems (e.g., hallucinations, trouble controlling violent behavior, suicide,

taking prescribed medications). To produce a high Composite Score (i.e., > 0.7 out of maximum score of 1.0), nearly all binary symptoms would need to be present every day. Additionally, those reporting active psychotic symptoms or current suicidality are typically excluded from drug use disorder clinical trials, including those in this study, which restricts the potential range in ASI-Psych scores. While the ASI-Psych is a valid and useful screening tool for severe psychiatric problems, it's value as an outcome measure in clinical trials with less severe populations is limited. In comparison, the BSI includes far more items, uses a consistent 5-point response scale, and measures a wider range of symptoms (e.g., feelings of guilt, loneliness) that may capture milder levels of psychiatric distress among cocaine users seeking outpatient care. These measurement characteristics, including the difference in time frame assessed by each instrument (i.e., past 30 days for ASI; past 7 days for BSI) may have contributed to differences in effect sizes, as longer time frames are generally less sensitive to change than shorter time frames (Haynes, Smith, & Hunsley, 2018).

Strengths of this study include a large and demographically heterogeneous sample, repeated assessment during treatment and through follow-up, and high rates of follow-up data collection on ASI (89% of randomized sample at 6-month follow-up). However, several limitations should also be noted. The clinical trials were conducted with participants eligible for outpatient treatment, potentially limiting the severity of psychiatric symptoms in this sample. Less than half of the pooled sample had complete data on both ASI and BSI, which limited the direct comparison of change in scores on both instruments within the same participants. Although those with complete data were largely similar to those without complete data in terms of demographic and baseline characteristics, those completing both assessments at all timepoints were less likely to have a current mood or anxiety disorder at baseline, which suggests they may have been more psychiatrically stable over the course of the trial. Also, we did not evaluate effect sizes for other ASI sections because the assessment battery did not include other objective measures to validate and determine sensitivity to detect change in other domains (e.g., medical or legal problems). All trials were conducted in Connecticut by a similar group of investigators potentially limiting the generalizability of findings. Lastly, because the clinical trials included combinations of different behavioral and pharmacologic treatments, with active control conditions, we were not able to evaluate the effect of treatment on change in psychiatric functioning in these pooled data.

Nevertheless, this study highlights the importance of demonstrating an instrument's sensitivity to change when evaluating potential clinical benefits of reductions in drug use. Despite the multiple strengths of the ASI as a comprehensive, multi-dimensional assessment of problems commonly affected by drug use, the composite scores may lack sensitivity to detect improvement in clinical trials. Subsequent research exploring the benefits of treatment should consider measures with sufficient sensitivity to detect change in the heterogeneous problems and consequences associated with substance use disorders.

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Her tremendous academic and scientific accomplishments are dwarfed by her kind, generous, and playful spirit. She will be forever missed.

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Highlights

- This study evaluated the effect size of change in psychiatric functioning.
- Cocaine users had limited change on ASI psychiatric domain during clinical trial.
- The Global Severity Index (GSI) from BSI showed medium effect size of change.
- Effect sizes for change in days of cocaine use were most similar to GSI.
- Assessing benefits of reduced cocaine use should consider sensitivity to change.

Table 1.

Demographic and baseline characteristics

Full sample						
Participant Characteristics	**Study #1 N = 121**	**Study #2 N = 112**	**Study #3 N = 99**	**Study #4 N = 120**	**Study #5 N = 40**	**Total N = 492**
Female (%)	32(26.4)	46(41.1)	27(27.3)	40(33.3)	10(25)	155(31.5)
White (%)	76(62.8)	72(64.3)	39(39.4)	62.5(51.7)	17(42.5)	266(54.1)
Unemployed (%)	70(57.9)	51(45.5)	66(66.7)	87(72.5)	12(30)	286(58.1)
Completed high school (%)	96(79.3)	93(83.0)	85(85.9)	86(71.7)	35(87.5)	395(80.3)
Criminal justice referred (%)	26(21.7)	2(1.8)	5(5.1)	1(.8)	7(17.5)	41(8.4)
Current mood or anxiety disorder (%)	19(15.8)	12(10.7)	9(9.1)	11(9.2)	6(15)	57(11.6)
Age – Mean (sd)	34.6(7.0)	38.3(7.5)	39.3(7.5)	38.4(9.4)	44.5(10.8)	38.1(8.6)
Days of cocaine use during past 28 - Mean (sd)	12.2(8.6)	15.4(8.9)	12.7(7.7)	13.8(8.4)	7.7(7.2)	13.0(8.5)
Sample with complete ASI and BSI data						
Participant Characteristics	**Study #1 N = 33**	**Study #2 N = 61**	**Study #3 N = 28**	**Study #4 N = 83**	**Study #5 N = 19**	**Total N = 224**
Female (%)	8(24.2)	23(37.7)	12(42.9)	30(36.1)	3(15.8)	76(33.9)
White (%)	22(66.7)	39(63.9)	14(50)	46(55.4)	7(36.8)	128(57.1)
Unemployed (%)	22(66.7)	26(42.6)	15(53.6)	60(72.3)	5(26.3)	128(57.1)
Completed high school (%)	28(84.8)	51(83.6)	24(85.7)	62(74.7)	17(89.5)	182(81.3)
Criminal justice referred (%)	8(24.2)	1(1.6)	4(14.3)	1(1.2)	2(10.5)	16(7.1)
Current mood or anxiety disorder (%)	2(6.1)	5(8.2)	2(7.1)	8(9.6)	2(10.5)	19(8.5) *
Age – Mean (sd)	35.9(6.1)	37.9(7.4)	39.2(6.4)	38.8(9.8)	48.4(10)	39(8.8) *
Days of cocaine use during past 28 - Mean (sd)	12.2(8.8)	15.3(8.6)	12.5(7.8)	12.9(8.3)	8.5(8.1)	13(8.5)
Sample with ASI-Psych > 0 at baseline						
Participant Characteristics	**Study #1 N = 82**	**Study #2 N = 56**	**Study #3 N = 54**	**Study #4 N = 41**	**Study #5 N = 19**	**Total N = 252**
Female (%)	23(28)	25(44.6)	13(24.1)	13(31.7)	5(26.3)	79(31.3)
White (%)	51(62.2)	42(75)	25(46.3)	24(58.5)	12(63.2)	154(61.1) **
Unemployed (%)	45(54.9)	26(46.4)	36(66.7)	32(78)	5(26.3)	144(57.1)
Completed high school (%)	63(76.8)	46(82.1)	45(83.3)	31(75.6)	18(94.7)	203(80.6)
Criminal justice referred (%)	20(24.4)	0(0)	1(1.9)	1(2.4)	1(5.3)	23(9.1)
Current mood or anxiety disorder (%)	16(19.5)	10(17.9)	7(17.6)	7(17.1)	6(31.6)	46(18.3) **
Age – Mean (sd)	34.6(6.5)	38.6(7)	39.2(7.4)	36.8(9.9)	39.2(10.7)	37.2(8) **
Days of cocaine use during past 28 - Mean (sd)	12.2(8.6)	15.3(9.2)	11.9(7.7)	13.8(8.6)	7.3(7.2)	12.7(8.6)

* Difference compared to sample without complete data (n=268); $p < 0.05$

** Difference compared to sample with ASI-Psych=0 at baseline (n=239); $p<.05$

Table 2.

ASI and BSI mean scores by timepoint

Full sample						
		Week 0	**Week 4**	**Week 8**	**Week 12**	**Week 36**
ASI-Psych						
	mean	0.15	0.13*	0.11***	0.12***	0.13
	sd	0.18	0.18	0.17	0.18	0.19
	N	491	452	439	445	436
Global Severity Index						
	mean	0.72	0.43***	0.32***	0.37***	0.45***
	sd	0.62	0.56	0.48	0.53	0.54
	N	486	374	307	383	358
Complete ASI & BSI data						
		Week 0	**Week 4**	**Week 8**	**Week 12**	**Week 36**
ASI-Psych						
	mean	0.11	0.10	0.11	0.11	0.11
	sd	0.17	0.16	0.17	0.17	0.17
	N	224	224	224	224	224
Global Severity Index						
	mean	0.65	0.37***	0.31***	0.31***	0.39***
	sd	0.57	0.47	0.44	0.48	0.47
	N	224	224	224	224	224
Baseline ASI-Psych > 0 only						
		Week 0	**Week 4**	**Week 8**	**Week 12**	**Week 36**
ASI-Psych						
	mean	0.29	0.19***	0.18***	0.18***	0.19***
	sd	0.16	0.19	0.2	0.2	0.21
	N	252	228	222	228	216
Global Severity Index						
	mean	0.95	0.58***	0.44***	0.47***	0.63***
	sd	0.64	0.65	0.56	0.58	0.59
	N	248	188	144	188	161

Paired t-tests of mean difference from week 0 at the following significance levels

* $p < .05$;

** $p < .01$;

*** $p < .001$

Table 3.

Within-person cohen's d' effect sizes across time points

	Week 0 – 4	Week 0 – 8	Week 0 – 12	Week 0 – 36
Full sample (n = 492)				
ASI-Psych	0.11	0.19	0.16	0.10
Global Severity Index	0.50	0.68	0.59	0.48
Cocaine use (days in past 28)	0.68	0.75	0.79	0.76
Complete ASI & BSI data (n = 224)				
ASI-Psych	0.06	0.04	0.04	0.01
Global Severity Index	0.55	0.64	0.64	0.50
Cocaine use (days in past 28)	0.59	0.71	0.80	0.79
Baseline ASI-Psych > 0 (n = 253)				
ASI-Psych	0.50	0.57	0.53	0.47
Global Severity Index	0.53	0.75	0.72	0.49
Cocaine use (days in past 28)	0.79	0.80	0.82	0.72