Drug and Alcohol Dependence 198 (2019) 126–132

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Short and long-term improvements in psychiatric symptomatology to validate clinically meaningful treatment outcomes for cocaine use disorders

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ARTICLE INFO

Keywords:
Clinically significant outcomes
Randomized clinical trial
Cocaine use disorders
Psychiatric symptomatology
Brief Symptom Inventory

ABSTRACT

Background: Substantial efforts have been made to identify clinically meaningful non-abstinence cocaine use outcomes by establishing associations between targeted drug use outcomes and long-term functional improvements. Psychiatric symptomatology is prevalent among those seeking treatment for cocaine use disorder (CUD). Establishing an association between cocaine use outcomes and improvements in psychiatric symptomatology would support clinical validity to these outcome measures.

Method: With data pooled from 5 clinical trials evaluating treatment for CUD (n = 474) multiple linear mixed models were conducted to determine how five specific cocaine use outcome measures performed in terms of improvements in psychiatric symptomatology assessed with the Brief Symptom Inventory (BSI) at baseline, end-of-treatment and 6-month follow-up.

Results: Three outcome measures performed comparably well (maximum days of consecutive abstinence, 3 or more weeks of abstinence and end-of-treatment abstinence), in that they consistently predicted improvements in several BSI composite scores at the end-of-treatment and follow-up. The poorer-performing outcome measures were complete abstinence during treatment, percentage of negative urinalysis results and percentage of days abstinent. Improvements in the BSI's global index of distress, positive symptom total, as well as depression, interpersonal sensitivity, obsessive-compulsion, phobic-anxiety and psychoticism dimensions were consistently associated with outcome effects, while anxiety, hostility, paranoid ideation and somatization were not.

Conclusion: The consistent short and long-term association of three outcome measures evaluated here (maximum days of consecutive abstinence, 3 or more weeks of abstinence and end-of-treatment abstinence) with improvements psychiatric symptomatology adds support to their clinical relevance as well as their adoption in trials and treatments for CUD.

1. Introduction

Achievement of complete cocaine abstinence is broadly accepted among clinicians and researchers as a clinically meaningful treatment outcome (Donovan et al., 2012; Roll et al., 2006) and is currently the only outcome accepted by the US Food and Drug Administration (FDA) when evaluating pharmacological trials for cocaine use disorders (CUD) (FDA: Psychopharmacologic Drugs Advisory Committee, 2013). However, there is no consensus on the ideal length of continuous abstinence required to determine a meaningful indicator of treatment success (Winchell et al., 2012). Moreover, giving the chronic relapsing nature of CUD, limiting treatment success to the achievement of prolonged periods of cocaine abstinence may be an overly restrictive and relatively insensitive measure since only a limited number of individuals tend to meet this standard and all of those with significant functional improvements but one or two cocaine lapses would be considered as treatment failures (Carroll et al., 2014a; Ciraulo et al., 2003). Thus, there has been recent interest in identification of clinically meaningful outcome measures other than complete abstinence (Carroll et al., 2014a; Donovan et al., 2012; Kiluk et al., 2017, 2016).

A critical aspect for an outcome to be considered clinically meaningful is that it must establish associations with long-term improvements in medical and/or psychosocial problems related to CUD (Kiluk et al., 2016; McLellan et al., 2000; Winchell et al., 2012). However,

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https://doi.org/10.1016/j.drugalcdep.2019.01.046
Received 2 August 2018; Received in revised form 11 December 2018; Accepted 27 January 2019
Available online 20 March 2019
0376-8716/

measuring long-term functional improvements remains a challenge, due to the brief duration of most clinical trials and the lack of consensus on how to best determine improvements in functionality (Tiffany et al., 2012). Thus, only a limited number of studies have established associations between CUD treatment outcomes and indices of longer-term functional improvements (Carroll et al., 2014a; Kiluk et al., 2017, 2014).

Co-occurring psychiatric disorders are highly prevalent among individuals with CUD and represent a severe burden with direct impact on how individuals feel and function in their daily lives (Conner et al., 2008; Conway et al., 2006; Ford et al., 2009; Grant et al., 2004). Nonetheless, only a few treatment trials for CUD have found improvements in psychiatric symptoms (Miguel et al., 2017; Petry et al., 2013). This is possibly due to the fact that most treatment trials for CUD do not directly target psychiatric symptoms and thus treatment effects for this outcome tend to be less robust. As a consequence, most individual studies are likely underpowered to detect effects on psychiatric symptomatology. Nonetheless, due to the high prevalence and burden related to these disorders, improvements in psychiatric symptomatology is a desirable treatment outcome.

Moreover, if specific cocaine outcome measures are associated with improvements in longer-term psychiatric symptomatology, this would support the clinical relevance of these outcome measures. To address this question, we used a dataset pooled from 5 independent randomized controlled trials (RCTs) of treatments for CUD to determine if specific cocaine use outcome measures predict improvements in psychiatric symptomatology at end-of-treatment and 6-month follow-up assessments.

2. Material and methods

2.1. Participant and study design

Data used for these analyses was composed of a sample of 474 individuals pooled from five RCTs designed to evaluate pharmacological and/or behavioral treatments for CUD in different outpatient settings. Primary outcome results and CONSORT diagrams for each study have been published (Carroll et al., 2008, 2014b; Carroll et al., 2018, 2016; Carroll et al., 2012). All five trials shared common characteristics such as similar inclusion/exclusion criteria, identical assessment battery and similar treatment duration (8 or 12 weeks). Urine specimens were collected twice weekly in studies 1, 3 and 5 and thrice weekly in studies 2 and 4. All other assessments followed the same collection schedule (baseline, end-of-treatment and 6-month follow-up). All participants were 18 years or older, seeking outpatient treatment for cocaine use who met Diagnostic and Statistical Manual (DSM-IV) criteria for cocaine abuse or dependence (American Psychiatric Association, 1994). Study 1 was originally composed of a broader substance use disorder sample (n = 77), but only those who reported cocaine as their primary drug of choice were included in these analyses (n = 45). Additionally, 3 participants (two in Study 2; one in Study 3) did not complete the Brief Symptom Inventory assessment at baseline and thus were excluded from the analyses. Table 1 presents an overview of all 5 trials included in the dataset.

2.2. Measures

2.2.1. Cocaine outcome measures

Our group recently compared how 15 primary outcome measures commonly used in clinical trials for CUD treatment performed in regard to the sensitivity to treatment effects and association with cocaine use during follow-up (Carroll et al., 2014a). Of these 15 outcome measures, 3 continuous measures (maximum days of consecutive abstinence; percentage of days abstinent; percentage of urine specimens negative for cocaine) and 2 dichotomous measures (retained and abstinent at the last week of treatment; 3 or more weeks of continuous abstinence) performed comparatively well, being both sensitive to treatment effects and significantly associated with several follow-up outcomes. For the present study, only these 5 best-performing outcome measures were considered in our analyses. The *maximum days of consecutive abstinence*, *percentage of days abstinent* and *3 or more weeks of continuous abstinence* outcome measures were computed using self-reported cocaine use via the Timeline Follow-back method (Robinson et al., 2014; Sobell and Sobell, 1992). The *percentage of cocaine-negative urine specimens* outcome measure was based on the urine toxicology results collected during the active phase of each participant's treatment. Finally, the *retained and abstinent at the last week of treatment* outcome measure was computed using the Timeline Follow-back method and the completion of a study visit during the final scheduled week of treatment.

In addition, since complete abstinence during treatment is still widely considered to be the most desirable treatment outcome, we included this outcome measure for comparison reasons only. Participants met this criterion if they reported abstinence (zero days of cocaine use) during the entire treatment period on the Timeline Follow-back, and submitted one or more cocaine-negative urine specimens and zero cocaine-positive urine specimens during treatment.

2.2.2. Psychiatric symptomatology

The number and severity of psychiatric symptomatology were determined using the Brief Symptom Inventory (BSI) (Derogatis and Melisaratos, 1983) assessed at 3 different time-points (baseline, end-of-treatment and 6-month-follow-up). The BSI is a self-report instrument that measures a number of symptoms and level of distress experienced during the past week using a 5-point Likert scale (from 'not at all' to 'extremely'). It consists of 53 items covering nine symptom dimensions: Depression, Anxiety, Hostility, Interpersonal Sensitivity, Obsession-Compulsion, Phobic anxiety, Paranoid ideation, Psychoticism and Somatization; and two global indices of distress: Global Severity Index (GSI), and Positive Symptom Total (PST). The GSI and the 9 BSI symptom dimensions provide the level of distress (ranging from 0 to 4) while the PST provides the total number of symptoms (ranging from 0 to 53) (Derogatis, 1993).

Table 1
Overview of the Clinical Trials included in the dataset.

Study	Behavioral treatment conditions	Pharmacological treatment conditions	Treatment duration	Baseline n (%)	End of Treatment n (%)	6-month follow-up n (%)	Primary outcomes citation
1	CBT4CBT + TAU *vs* TAU	–	8 weeks	45 (100%)	27 (60%)	22 (48.9%)	Carroll et al. (2008)
2	TSF + TAU *vs* TAU	Disulfiram vs placebo	12 weeks	111 (100%)	90 (80.1%)	78 (70.3%)	Carroll et al. (2012)
3	CBT4CBT + TAU *vs* TAU	–	8 weeks	100 (100%)	73 (73%)	80 (80%)	Carroll et al. (2014a,b)
4	CM + CBT *vs* CBT	Disulfiram vs placebo	12 weeks	98 (100%)	65 (66.3%)	73 (74.5%)	Carroll et al. (2016)
5	CBT4CBT + TAU *vs* TAU	Galantamine vs placebo	12 weeks	120 (100%)	100 (83.3%)	104 (86.7%)	Carroll et al. (2018)
Total	–	–	–	474 (100%)	355 (74.9%)	357 (75.3%)	–

CBT4CBT = Computer based training for cognitive behavioral therapy; TAU = Treatment as usual; TSF = Twelve-step facilitation; CBT = Cognitive behavioral therapy; CM = Contingency Management.

2.3. Data analyses

Descriptive analyses were conducted for demographic and baseline characteristics and analyses of variance (ANOVA) with Bonferroni post-hoc tests conducted to compare the BSI composite scores by time (baseline, end-of-treatment and 6-month follow-up). Multiple linear mixed models were conducted to examine the association of each cocaine outcome measure with the BSI composite scores over time (baseline, end-of-treatment, 6-month follow-up). For each model, the two BSI global indices and the nine BSI symptom dimensions were assigned separately as the primary outcome (target) of the model. For every primary outcome, five different mixed models were conducted with each of the five cocaine outcome measures assigned separately as a fixed factor. For all mixed models, participants and study were included as random intercepts and gender, time, the specific cocaine outcome measure being compared and the interaction between the cocaine outcome measure and time were included as fixed factors. Finally, time 1 (BSI baseline assessment) was set as reference for the repeated measure. For the purpose of this study, only the cocaine outcome measure and time interaction results are presented.

Given the number of separate models being tested, corrections for multiple comparisons were conducted using the Bonferroni method. As a result, the level of significance was set at $p < .01$. Statistical analyses were performed with SPSS Statistics software package, version 24.0 (IBM Corporation, Armonk, NY).

3. Results

3.1. Sample description

Of the 474 participants included in the study, 355 (75%) and 357 (75%) completed the end-of-treatment and 6-month follow-up assessments, respectively. The pooled sample had a mean age of 39.5 (SD = 8.7) years, was predominantly male (n = 280; 59%), single (n = 337; 71%), unemployed (n = 304; 64%), with at least a high school degree (n = 368; 77%) and a previous history of arrest (n = 324; 68%). About half of the sample reported being White/Caucasian (n = 244; 51%), a third reported being Black/African-American (n = 152; 32%), 14% reported being Hispanic (n = 68) and 2% reported being from another race/ethnicity (n = 10). Mean age of cocaine onset was 20.9 (SD = 6.3), with an average of 9.8 (SD = 8.2) years of lifetime cocaine use. The majority of participants reported smoking as their primary route of cocaine administration (n = 339; 71%) with an average of 14.4 (SD = 8.8) days of cocaine use in the previous 28 days of the baseline assessment. Co-occurring DSM-IV lifetime alcohol dependence was high (n = 285; 60%), followed by lifetime major depressive disorder (n = 92; 19%), lifetime anxiety disorder, (n = 62; 13%) and antisocial personality disorder (n = 50; 10%).

In regard to the general level of treatment outcome, the mean number of maximum days of consecutive abstinence was 16.1 (SD = 19.4), the mean percentage of days abstinent from cocaine was 66.2 (SD = 27.2), and the mean percentage of cocaine-negative urine specimens submitted during treatment was 25 (SD = 33.6). Over a quarter of the sample achieved at least 3 consecutive weeks of abstinence (27%; n = 142), a fifth of the sample was retained and abstinent at the last week of treatment (n = 103), but only 27 participants achieved our definition of complete abstinence from cocaine during the entire treatment (6%). All BSI composite scores assessed at baseline were not significantly associated with the outcome measures (r's ranged from -.08 to .09).

Additionally, Table 2 presents the mean BSI composite scores collected at each time point. As can be seen, the mean scores for all BSI composites were significantly higher at baseline when compared to the end-of-treatment assessment. Also, the mean PST, GSI and the depression, anxiety, obsession-compulsion, paranoid ideation, psychoticism and somatization dimension scores were significantly higher at baseline in comparison to the 6-month follow-up assessment.

Table 2
Brief Symptom Inventory scores by time.

	Baseline mean (SD)	End-of-Treatment mean (SD)	6-month-follow-up mean (SD)	F	*p.*
PST	21.8 (13.6)[a]	14.1 (15.1)[b]	17.6 (15.7)[c]	28.9	.001
GSI	.68 (.56)[a]	.41 (.53)[b]	.54 (.60)[c]	22.6	.001
Depression	.83 (.75)[a]	.53 (.74)[b]	.65 (.76)[b]	20.4	.001
Anxiety	.61 (.65)[a]	.33 (.53)[b]	.47 (.65)[c]	16.9	.001
Hostility	.58 (.63)[a]	.33 (.59)[b]	.48 (.67)[a]	15.4	.001
Interpersonal Sensitivity	.69 (.78)[a]	.42 (.68)[b]	.57 (.75)[a]	13.2	.001
Obsession-compulsion	.90 (.80)[a]	.55 (.71)[b]	.71 (.82)[c]	21.4	.001
Paranoid Ideation	.77 (.73)[a]	.49 (.65)[b]	.60 (.73)[b]	16.8	.001
Phobic Anxiety	.37 (.61)[a]	.27 (.52)[b]	.33 (.58)[a,b]	3.1	.044
Psychoticism	.61 (.69)[a]	.40 (.62)[b]	.49 (.67)[b]	10.8	.001
Somatization	.54 (.54)[a]	.32 (.48)[b]	.43 (.56)[c]	16.1	.001

PST = Positive Symptom Total, GSI = Global Severity Index.
Each subscript letter denotes a subset of variables whose column proportions/means do not differ significantly from each other at the .05 level.

3.2. Cocaine outcome measures performance predicting improvements in psychiatric symptomatology

As can be seen in Table 3, the *maximum days of consecutive abstinence* outcome significantly predicted improvements in the PST at both time-points as well as improvements in the GSI distress score at end-of-treatment. This outcome was also significantly associated with improvements in 4 BSI dimensions at the end-of-treatment (depression, interpersonal sensitivity, obsession-compulsion, psychoticism) and 2 BSI dimensions at the 6-month follow-up (obsession-compulsion, psychoticism). Additionally, the *maximum days of consecutive abstinence* outcome were associated with improvements in the phobic anxiety dimension at the end-of-treatment and in the GSI and the depression and interpersonal sensitivity dimensions at the 6-month follow-up at a trending level (p. < .05).

The *percentage of days abstinent* outcome was significantly associated with improvements in the PST at the 6-month follow-up and trends towards predicting improvements in the PST at the end-of-treatment. This outcome was also associated to improvements in the PST at the end-of-treatment and with the GSI and the hostility, interpersonal sensitivity and obsession-compulsion dimensions at the 6-month follow-up at a trending level.

The *percentage of cocaine-negative urine specimens'* outcome significantly predicted improvements in the psychoticism dimension. Additionally, this outcome predicted improvements in the PST, GSI and the depression, interpersonal sensitivity and obsession-compulsion dimensions at end-of-treatment and in the psychoticism dimension at the 6-month follow at a trending level.

The *retained and abstinent at the last week of treatment* outcome significantly predicted improvements in the PST, GSI and the psychoticism dimension at both time-points along with improvement in the obsession-compulsion dimension at the 6-month follow-up only. Additionally, this outcome also showed trends towards predicting improvements in interpersonal sensitivity and paranoid ideation at both time-points, depression and obsession-compulsion at the end-of-treatment, and phobic anxiety and somatization at the 6-month follow-up.

The *3 or more weeks of consecutive abstinence* outcome significantly predicted improvements in the PST, GSI and in the depression and psychoticism dimensions at the end of treatment and in the interpersonal sensitivity dimension at both time-points. This outcome measure was also associated with improvements in the obsession-compulsion and paranoid ideation dimensions at the end of treatment

Table 3
Cocaine outcome measures, the global indexes of distress and the 9 BSI symptom dimension distress scores.

Changes from baseline to the end-of-treatment	PST Estimate (SE)	GSI Estimate (SE)	Depression Estimate (SE)	Anxiety Estimate (SE)	Hostility Estimate (SE)	Interpersonal Sensitivity Estimate (SE)	Obsession-compulsion Estimate (SE)	Paranoid Ideation Estimate (SE)	Phobic Anxiety Estimate (SE)	Psychoticism Estimate (SE)	Somatization Estimate (SE)
Maximum days of cocaine abstinence	−.132*** (.034)	−.004*** (.001)	−.006*** (.002)	−.002 (.001)	−.002 (.001)	−.005** (.002)	−.006*** (.002)	−.004* (.002)	−.002 (.002)	−.006*** (.002)	−.001 (.001)
% of days abstinent	−.064* (.026)	−.001 (.001)	−.001 (.001)	−.001 (.001)	−.001 (.001)	−.002 (.001)	−.002 (.001)	−.001 (.001)	.000 (.001)	−.002 (.001)	.000 (.001)
% of negative cocaine urine exams	−.053* (.021)	−.002* (.001)	−.002* (.001)	−.001 (.001)	.000 (.001)	−.002* (.001)	−.002* (.001)	−.001 (.001)	−.001 (.001)	−.003*** (.001)	.000 (.001)
Completed treatment and abstinent in last week	−5.51*** (1.52)	−.152** (.057)	−.212* (.083)	−.086 (.064)	−.075 (.065)	−.178* (.079)	−.182* (.080)	−.195* (.081)	−.067 (.066)	−.233** (.075)	−.068 (.058)
At least 3 weeks of continuous cocaine abstinence	−5.14*** (1.41)	−.144** (.053)	−.267*** (.076)	−.101 (.060)	−.028 (.061)	−.217** (.072)	−.185* (.074)	−.181* (.074)	−.071 (.060)	−194** (.069)	−.005 (.054)
Sustained Abstinent during active treatment	−.748 (2.52)	.044 (.093)	.018 (.135)	.104 (.105)	.109 (.107)	−.022 (.126)	−.052 (.131)	−.026 (.129)	.096 (.105)	−.074 (.119)	.203 (.093)
Changes from baseline to the 6-month follow-up	**PST Estimate (SE)**	**GSI Estimate (SE)**	**Depression Estimate (SE)**	**Anxiety Estimate (SE)**	**Hostility Estimate (SE)**	**Interpersonal Sensitivity Estimate (SE)**	**Obsession-compulsion Estimate (SE)**	**Paranoid Ideation Estimate (SE)**	**Phobic Anxiety Estimate (SE)**	**Psychoticism Estimate (SE)**	**Somatization Estimate (SE)**
Maximum days of cocaine abstinence	−.108*** (.036)	−.003* (.001)	−.004* (.002)	−.002 (.001)	−.003 (.001)	−.005* (.002)	−.006** (.002)	−.004 (.002)	−.002 (.001)	−.005** (.002)	−.002 (.001)
% of days abstinent	−.069** (.025)	−.002 (.001)	−.001 (.001)	−.001 (001)	−.003* (.001)	−.003* (.001)	−.004* (.001)	−.002 (.001)	−.001 (.001)	−.002 (.001)	−.001 (.001)
% of negative cocaine urine exams	−.038 (.022)	−.001 (.001)	−.001 (.001)	.000 (001)	−.001 (.001)	−.001 (.001)	−.002 (.001)	−.001 (.001)	−.001 (.001)	−.002* (.001)	.000 (.001)
Completed treatment and abstinent in last week	−5.01** (1.62)	−.181** (.066)	−.153 (.088)	−.117 (.078)	−.141 (.079)	−.207* (.079)	−.275** (.093)	−.216* (.091)	−.149* (.072)	−.242** (.080)	−.163* (.069)
At least 3 weeks of continuous cocaine abstinence	−3.80* (1.49)	−.109 (.060)	−.173* (.080)	−.058 (.071)	−.034 (.061)	−.224** (.083)	−.174* (.085)	−.163* (.083)	−.055 (.066)	−.110 (.073)	−.015 (.061)
Sustained Abstinent during active treatment	−1.20 (2.69)	−.023 (.107)	−.062 (.143)	.086 (.125)	−.036 (.129)	−.079 (.150)	.190 (.152)	−.067 (.148)	.022 (.118)	−.089 (.128)	.091 (.110)

PST = Positive Symptom Total, GSI = Global Severity Index, * $p < .05$, ** $p < .01$, *** $p < .001$.

and in the depression, obsession-compulsion and paranoid ideation dimensions at the 6-month follow-up at a trend level. Finally, the *complete abstinence during treatment* outcome was not significantly associated with improvements in any BSI composites at either time-point.

4. Discussion

The aim of this study was to evaluate how well different cocaine outcome measures predicted short and long-term improvements in psychiatric symptomatology in a pooled dataset from 5 randomized clinical trials of treatment for CUD. We found, first, that mean BSI composite scores were significantly lower at the end-of-treatment and 6-month follow-up compared to baseline, suggesting some efficacy of these interventions in reducing psychiatric symptomatology. Second, in terms of the association of treatment outcome measures with changes in psychiatric symptomatology, these data suggest that all five cocaine outcome measures evaluated consistently predicted improvements in the number and severity of psychiatric symptoms; however, only a portion of these associations achieved statistical significance after correcting for multiple comparisons. The association with improvements in psychiatric symptomatology varied among outcome measures but were similar across the 2 time-point assessments with a slightly higher consistency seen for the end-of-treatment assessment as compared to the 6-month follow-up. Third, with respect to the sensitivity of the BSI composites to the effects of each outcome measure, both indexes of global distress and the depression, interpersonal sensitivity, obsessive-compulsion, phobic anxiety and psychoticism symptom dimensions suggested higher sensitivity while anxiety, hostility, paranoid ideation, and somatization dimensions were less sensitive to outcome effects.

4.1. Poorer-performing outcome measures

In contrast to our expectations, these data suggest that the *percentage of days abstinent* and the *percentage of cocaine-negative urine specimens* had limited associations with short and long-term improvements in psychiatric symptomatology. These findings differ from our previous findings that showed a significant association between both of these outcomes with lower scores on the Addiction Severity Index and with lower percentage of days of cocaine use at follow-up (Carroll et al., 2014a). As expected, the *complete abstinence during treatment* outcome measure was not significantly associated with improvements in psychiatric symptomatology at the end-of-treatment or follow-up. This finding is consistent with previous findings and offers additional evidence to the limitations of exclusively using this outcome to determine treatment success (Carroll et al., 2014a; Donovan et al., 2012; Kiluk et al., 2014; McLellan et al., 2000).

4.2. Better performing outcome measures

The *maximum days of consecutive abstinence* and the *3 or more weeks of continuous abstinence* outcomes were consistently associated with short and long-term improvements in psychiatric symptomatology. These findings replicate the literature showing that durations of cocaine abstinence are associated with improvements in psychiatric symptomatology, lower frequency of cocaine use and other functional improvements at follow up assessments (Carroll et al., 2014a; Higgins et al., 2000; Kiluk et al., 2017, 2014; Petry et al., 2013). However, different from our previous findings, (Carroll et al., 2014a; Kiluk et al., 2014) the more consistent predictive performance observed for these outcomes in comparison to the *percentage of days abstinent and* the *percentage of cocaine-negative urine specimens* suggest that outcomes reflecting achievement of continuous abstinence might show a stronger association with improvements in psychiatric symptomatology in comparison to outcomes that reflect frequency of use overall. Given that individuals commonly use cocaine in binge-like patterns (i.e., short, intense bursts of repeated cocaine use followed by brief periods of abstinence), it makes sense that an indicator of longer periods of consecutive abstinence was associated with improvement in psychiatric symptoms. The fact that a more consistent association with improvements in psychiatric symptoms were observed for the *3 or more weeks of continuous abstinence* outcome, even when dichotomous variables tend to show lower power over continuous variables, offer additional support for this assumption.

As observed for the *maximum days of consecutive abstinence* and the *3 or more weeks of continuous abstinence,* the *retained and abstinent at the last week of treatment* outcome consistently predicted short and long-term improvements in the number and severity of psychiatric symptoms. As an added advantage, this dichotomous outcome is readily interpretable and fairly easy to compute, making it more attractive for clinicians, policymakers, and researchers. Furthermore, this outcome is consistent with point-prevalence abstinence rates accepted as a meaningful outcome in the tobacco field (Hughes et al., 2003). Additionally, this outcome measure is relatively invulnerable to missing data since being retained in the last week of treatment is a necessary requirement of this outcome.

Finally, the *retained and abstinent at the last week of treatment* outcome may be especially promising outcome measure for psychosocial interventions that focus on acquisition of specific skills such as Cognitive Behavior Therapy (CBT). Although a generally effective intervention for CUD (Dutra et al., 2008), improvements in CBT tend to be delayed since the effects of this intervention increase as participants acquire specific skills through the completion of pre-determined treatment modules/sessions (Carroll and Kiluk, 2017; Carroll et al., 1994). As a consequence, outcome measures related to continuous abstinence, especially those dependent on the initiation of abstinence at the beginning of treatment, may be less sensitive to CBT and related treatments that may take time to achieve their effects.

4.3. Strengths and limitations

Some strengths of this study include the relatively large sample size, the high rates of end-of-treatment and 6-month follow-up assessments, and the methodological rigor of the randomized clinical trials which provided data for these analyses. Another strength is the diversity of our sample which includes substantial representation of women (41%) and ethnic minorities (49%). Finally, the use of a conservative correction approach such as the Bonferroni method adds statistical validity of our findings.

Nevertheless, the study has some important limitations that should be noted. First, data used in this study originated from clinical trials with different lengths of treatment (8 or 12-weeks). It is important to consider that the *maximum days of consecutive abstinence* outcome measure ranged from 0 to 56 days for the 8-week trials and 0–84 days for 12-week trials. Similarly, 50% of abstinence in the *percentage of days abstinent* outcome express 28 days of abstinence for the 8-week trials but 42 days of abstinence for the 12-week trials. Finally, from a mathematical perspective, the chances of achieving *3 or more weeks of continuous abstinence* are higher in a 12-week trial, while the chances of achieving complete abstinence during the entire treatment period are higher in an 8-week trial. The difference in the duration of treatment in our dataset has a direct impact in the range and expression of our outcome measures as well as on the chances of meeting the standards for these outcomes, and as so, need to be pondered when interpreting our findings. Given that the studies included in this pooled dataset were conducted in different settings (e.g., general outpatient, methadone maintenance clinic) and with different interventions (e.g., CBT, CM, disulfiram), in addition to differing lengths of treatment, the inclusion of 'study' in the regression models accounted for these differences. Secondly, our study had a substantial number of missing data during the end-of-treatment and 6-month-follow-up assessments (around 25% in either time-point). In that regard, it is possible that cocaine use and the severity of psychiatric symptomatology may have influenced

patients' attrition from the studies. As such, it is important to consider that different results might have been seen if data from these participants were included in these analyses.

Regarding the method used to determine our outcome measures, the *percentage of cocaine-negative urine specimens* outcome was computed relying solely on urine toxicology results. As a consequence, the lack of association of this outcome and improvements of psychiatric symptomatology may be due to its relative vulnerability to missing data (Carroll et al., 2014a; Donovan et al., 2012). On the other hand, participants may have falsely denied cocaine use in the self-report undermining the reliability of outcomes based solely on self-report (Winhusen et al., 2003). However, the fact that similar results were observed for the *percentage of cocaine negative urine specimens and the percentage of days abstinent* outcomes argues that the small association of these outcomes with improvements of psychiatric symptomatology are not related to vulnerability to missing data or the reliability of self-report cocaine use, but instead reflect that outcomes related to frequency of cocaine use are not strongly associated with improvements of psychiatric symptomatology. Furthermore, the fact that the *maximum days of consecutive abstinence* the *3 or more weeks of continuous abstinence* and the *retained and abstinent at the last week of treatment* outcome measures, who are based on self-report, consistently predicted improvements in psychiatric symptomatology offer additional support for this assumption.

Another important limitation lies in the fact that the analytical approach used in this study (linear mixed models for repeated measures) do not provide effect size estimates, limiting our ability to determine the impact of outcome measures on psychiatric symptomatology. However, findings from correlation analyses (data not shown) revealed that all 5 outcome measures were consistently negatively correlated with the BSI composite scores assessed at the end-of-treatment and follow-up (with r. coefficient varying from -.1 to -.2 for the correlations that achieved statistical significance). Based on the strength of these unadjusted correlations it is plausible to consider that the effects size of the outcome measures on improvements in psychiatric symptomatology tends to be modest.

Finally, this study looked exclusively at these outcomes' association with improvements in psychiatric symptomatology but did not address how these outcomes affect other problematic areas related to CUD. Furthermore, the psychiatric symptomatology evaluated in this study was measured using only the BSI and, while demonstrated to be valid in a number of studies for substance use disorders (Johnson et al., 2007; Petry et al., 2013; Polcin et al., 2010; Wang et al., 2010), this instrument does not cover all variants of psychiatric symptomology, for instance those related to mania and impulsivity.

4.4. Summary

To our knowledge, this is the first study to look at short and long-term improvements in psychiatric symptomatology as an approach to attribute clinical validity to treatment outcome measures other than complete abstinence. Based on their performance, *maximum days of consecutive abstinence*, *3 or more weeks of continuous abstinence* and *retained and abstinent at the last week of treatment* appear as the most promising candidates for clinically meaningful treatment outcomes. Furthermore, despite its clinical relevance, this study offers additional evidence for the limitations of exclusively using complete abstinence to determine a positive treatment outcome response.

Role of funding source

This study was supported by National Institute on Drug Abuse (NIDA) grants: R01 DA015969-09S1, P50-DA09241 and U10 DA015831 (Carroll, PI), R01DA030369-04S1 (Carroll/Paris, mPI), and R21DA041661 (Kiluk/Carroll, PI). Dr. Miguel and Dr. Mari were also supported by the Fundação de Amparo a Pesquisa de São Paulo (FAPESP) international postdoctoral fellowship grant (2017-05371-8, 2017-22004-9) as part of the Research and Innovation grant for Prevention of Mental Disorders and abusive use of Alcohol and other Drugs, "Pesquisas e Inovações em Prevenção de Transtornos Mentais e Uso Abusivo de Álcool e Outras Drogas", funded by the Division of Mental Health of the Brazilian Ministry of Health. NIDA and FAPESP had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Contributors

Author Miguel designed the study, planned the analyses and wrote the initial draft of the manuscript. Authors Kiluk, Babuscio, Nich and Mari contributed to the statistical analyses, interpretation of data, and the written manuscript. Author Carroll designed the 5 trials that contributed data to this study, contributed to the interpretation of analyses, and the written manuscript. All authors read and approved the final manuscript.

Conflict of interest

This study included data from 2 CBT4CBT trials. Author Carroll is a member of CBT4CBT LLC, which makes CBT4CBT available to qualified clinical providers and organizations on a commercial basis. Dr. Carroll works with Yale University to manage any potential conflicts of interest. All other authors declare that they have no conflicts of interest.

Acknowledgments

We would like to acknowledge Tami Frankforter and Karen Hunkele for their invaluable help in assembling the dataset as well as participants, research staff and colleagues who participated in the original clinical trials.

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