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Assessing Craving and its Relationship to Subsequent Prescription Opioid Use Among Treatment-Seeking Prescription Opioid Dependent Patients

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Abstract

Background—Craving is viewed as a core feature of substance use disorders and has been shown to predict future drug use, particularly over the short term. Accordingly, craving is often assessed in treatment settings as a marker of risk for subsequent drug use. The identification of the briefest measure that maintains predictive validity is of particular value for both clinical and research settings to minimize assessment burden while maintaining utility for the prediction of use.

Methods—Data from a multi-site clinical trial of treatment for prescription opioid dependence were examined to evaluate whether a brief, 3-item craving scale administered each week predicted urine-confirmed self report of prescription opioid use in the subsequent week. Logistic regression models examining the association between craving and presence or absence of opioid use in the

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Author Disclosures

Conflict of Interest

All other authors declare they have no conflicts of interest.

Contributors

Drs. McHugh and Weiss designed this secondary analysis. Drs. McHugh and Fitzmaurice undertook the statistical analysis, and Dr. McHugh wrote the first draft of the manuscript. Drs. Fitzmaurice, Carroll, Griffin, Hill, Wasan, and Weiss contributed to the interpretation and presentation of study findings. All authors contributed to and have approved the final manuscript.

following week were conducted, controlling for opioid use in the previous week, treatment condition, and lifetime history of heroin use.

Results—Greater craving was associated with a higher odds of prescription opioid use in the following week. For each one-unit increase on this 10-point scale, the odds of using opioids in the subsequent week was 17% higher. In addition to an item assessing urges, items assessing cue-induced craving and perceived likelihood of relapse in an environment where drugs were previously used contributed uniquely to this association.

Conclusions—A brief measure of prescription opioid craving predicted prescription opioid use among individuals in treatment. This measure offers an efficient strategy to inform the assessment of risk for use in this population.

Keywords

prescription opioids; craving; cue-induced craving; buprenorphine

1. INTRODUCTION

Craving is a core feature of substance use disorders, as evidenced by its recent addition to the diagnostic criteria for these disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013). Much of the research on craving has focused on whether it may precipitate substance use and thus serve as a risk marker during treatment. A number of studies have examined whether craving at treatment entry predicts outcomes following treatment, with some studies supporting this association (Anton et al., 1996; Sinha et al., 2011), some finding no association (Ahmadi et al., 2009; Dreifuss et al., 2013), and others finding associations only for particular types of craving (e.g., stress-induced craving; Sinha et al., 2006).

Although self-reported craving may have inconsistent predictive validity for long-term substance use disorder treatment outcomes, several studies have demonstrated that drug craving is associated with proximal (e.g., within the next week) substance use (Hartz et al., 2001; Moore et al., 2013; Weiss et al., 2003). Because craving is influenced by contextual factors such as substance-related cues, stress, and withdrawal symptoms, it may serve as a marker for immediate use, and associations with substance use may weaken over longer periods of time (Shiffman et al., 1997).

The evidence supporting the predictive validity of craving for proximal substance use highlights the value of regular assessment of craving during treatment. Once heightened risk has been identified, providers may choose to implement specific strategies to attempt to mitigate the risk of use in the near future. However, demands on time and resources in clinical settings necessitate that assessments be as brief as possible while still yielding meaningful information. In research settings, efficient assessment strategies have the dual benefit of minimizing participant burden and providing additional time for the assessment of other pertinent constructs. Self-report craving measures vary dramatically in length, ranging from a single item (Connor et al., 2005; West and Ussher, 2010) to more than 40 items (Heishman et al., 2001; Tiffany et al., 1993). Although lengthy, multi-dimensional

assessments may be of particular value in certain research settings, the briefest possible measure that still indicates level of risk is preferable clinically and in research settings in which assessment burden is a concern, or in which repeated measures are collected. A previous multi-site study of treatment for cocaine dependence demonstrated that a brief, 3-item craving measure developed by our group predicted cocaine use in the following week, when controlling for current cocaine use (Weiss et al., 2003). It is unclear whether the predictive validity of this measure extends to other substances of abuse.

As the prevalence of prescription opioid dependence has rapidly escalated in the past 15 years (Johnston et al., 2012; Substance Abuse and Mental Health Services Administration, 2012), studies have begun to examine craving in this population. However, the association between opioid craving and proximal opioid use has yet to be examined. A study in chronic pain patients receiving opioids for pain found that self-reported craving for medication was associated with aberrant drug behaviors (e.g., positive urine toxicology) assessed 6 months later (Wasan et al., 2009). Although this study included participants both with and without prescription opioid use disorders, these results suggest that craving for prescription opioids is a risk marker for later opioid misuse, at least among those with chronic pain.

Another reason to examine craving specifically in patients dependent on prescription opioids is the possibility that craving in this population differs in some ways from craving for illicit drugs. A recent report from our group found that craving in response to opioid cues was less robust in this population than in those dependent upon heroin (McHugh et al., in press). One potential explanation for this difference is that the associative conditioning of prescription drug cues may differ from illicit drug cues because the pairing of drug use and contextual cues is less unique for prescription drug cues, which are encountered in numerous settings (e.g., pharmacies, advertisements). Thus, research examining the role of cue-induced craving in this population is of particular interest.

The aim of the current analysis of data from a multi-site study of prescription opioid dependence treatment was to examine whether craving for prescription opioids predicted use of these drugs in the following week. A brief, 3-item craving measure was used to assess three different domains of craving: general craving, cue-induced craving, and likelihood of use if exposed to an environment in which drugs were previously used. In this study, we examined the concurrent and predictive validity of this measure. in a prescription opioid dependent population. We hypothesized that greater craving would be associated with a higher likelihood of opioid use in the following week, when controlling for current use. In an exploratory analysis, the associations between the individual craving scale items and subsequent use were examined to evaluate the relative importance of these three domains of craving. This study is novel in its examination of the relationship between craving and prescription opioid use over brief time intervals, its extension of a validated measure to a new population, and its consideration of the incremental importance of various domains of craving.

2. METHODS

2.1. Procedures

The Prescription Opioid Addiction Treatment Study (POATS) was a large, randomized controlled trial conducted in the National Drug Abuse Treatment Clinical Trials Network. For a full description of POATS, see Weiss and colleagues (2010). POATS was conducted at 10 treatment programs across the United States. The study design included two phases. In Phase 1, participants received a 4-week buprenorphine-naloxone taper and were randomly assigned to receive standard medical management (Fiellin et al., 1999) alone, or medical management and concurrent individual drug counseling (Mercer and Woody, 1999; Woody et al., 1977). Participants who relapsed during Phase 1 were eligible to participate in Phase 2, during which they received 12 weeks of buprenorphine-naloxone; they were again randomized to receive standard medical management alone or with concurrent individual drug counseling. The primary results of this study were that only a small number of participants (<7%) achieved successful outcomes (defined as abstinence or near abstinence) in Phase 1; almost half of participants in Phase 2 achieved successful outcomes. Counseling was not associated with treatment outcome in either phase (Weiss et al., 2011).

Individuals with a current Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (American Psychiatric Association, 1994) diagnosis of prescription opioid dependence were recruited for POATS. Inclusion criteria included a diagnosis of opioid dependence specifically for prescription opioids and use of prescription opioids on at least 20 days in the previous month. Participants with significant heroin use (defined as 5 or more days of heroin use in the previous 30 days, history of heroin injecting, or history of opioid dependence based on heroin use alone), a significant pain condition for which ongoing opioid therapy was indicated, or any medical or psychiatric condition contraindicated for study participation were excluded (Weiss et al., 2010).

For this secondary analysis of POATS data, we examined whether craving in a given study week was associated with opioid use (defined dichotomously as use versus no use) in the subsequent week. Data from Phase 2 (12 weeks of buprenorphine-naloxone stabilization) were utilized to maximize the available number of weeks to examine this study question, while minimizing the potential impact of other variables on both craving and use (i.e., all participants were receiving study medication during this time period). Phase 1 data were not analyzed because any participant who relapsed in Phase 1 was immediately offered Phase 2 treatment, thus. Thus, the number of available weeks for analysis was inconsistent across Phase 1 participants, potentially introducing bias to the analysis during this phase.

2.2. Measures

The Opioid Craving Scale, a modification of the Cocaine Craving Scale (Weiss et al., 1995, 1997, 2003), was used to measure opioid craving. This scale consisted of three items rated on a visual analogue scale from 0–10: (1) How much do you currently crave opiates? (rated from *not at all* to *extremely*), (2) In the past week, please rate how strong your desire to use opiates has been when something in the environment has reminded you of opiates (rated from *no desire* to *extremely strong*), and (3) Please imagine yourself in the environment in

which you previously used opiates. If you were in this environment today and if it were the time of day that you typically used opiates, what is the likelihood that you would use opiates today? (rated from *not at all* to *I'm sure I would use opiates*). The Cocaine Craving Scale has demonstrated strong internal consistency reliability (Weiss et al., 1997, 2003) and predictive validity relative to cocaine use (Weiss et al., 2003) in cocaine-dependent populations. The total score was calculated by averaging the scores on the three items. The current manuscript examined the predictive validity of the modified Cocaine Craving Scale for prescription opioids (Opioid Craving Scale).

Opioid use was measured using urinalysis-confirmed self-report. Self-reported opioid use was assessed using the Timeline Followback calendar method (Sobell and Sobell, 1992). A week was coded as positive for use if any of the following criteria were met: (1) the participant self-reported use for that week; (2) the participant denied use, but provided a positive urine toxicology screen for opioids; or (3) the urine toxicology screen was missing for that week.

2.3. Data Analysis

The Opioid Craving Scale total score and individual item scores were examined for skewness and univariate outliers to determine the appropriate analytic plan. Given evidence of non-normality in the baseline (i.e., pre-induction) craving data, differences in craving based on sociodemographic and clinical variables of interest were examined using non-parametric tests, including Mann-Whitney U tests for dichotomous variables and Kruskal-Wallis tests for categorical variables with more than two levels. The association between craving at baseline and continuous variables was examined using Spearman's rho.

We then examined whether craving in each week predicted opioid use in the subsequent week during treatment. This analysis focused on the post-induction active treatment weeks of Phase 2 of the trial (weeks 2–12), to maximize the number of available weeks for analysis. This was evaluated using a logistic regression model, utilizing the generalized estimating equations (GEE) approach to appropriately account for repeated measures on the same subjects. In addition to including craving as the key independent variable of interest, the logistic model also controlled for treatment condition (counseling vs. no counseling), history of heroin use (a predictor of poor treatment outcome in the trial), and opioid use in the previous week. Potential predictors of outcome, including those identified in previous analyses (Dreifuss et al., 2013; Weiss et al., 2011) as well as those that may reflect variability in disorder severity were also added as covariates; these variables included age, lifetime history of major depressive disorder, using opioids via a route of administration other than oral/sublingual, and history of prior treatment for opioid dependence. Data on craving and opioid use were lagged in this model, such that the dependent variable was opioid use on the weeks following each assessment of craving. This model was run both with the Opioid Craving Scale total score, and with the individual scale items to evaluate the relative contribution of the domains of craving assessment by each of these items. To facilitate the interpretation of the results, the total score and individual item scores were coded to utilize the same scale (0–10). All analyses were conducted in SPSS Version 20.

3. RESULTS

3.1. Preliminary Analyses

In Phase 2 of the POATS trial, 360 participants were randomized to a treatment condition. This sample was 42% female, mostly self-identified as White (91%), and many were employed full time on average in the past 3 years (60%). The mean age of the sample was 32.5 years (*SD* = 9.7) with a mean of 12.9 years (*SD* = 2.2) of education.

At the Phase 2 baseline visit, participants reported a moderate to high level of craving for opioids; the mean total Opioid Craving Scale score was 6.9 (*SD* = 2.8, median = 7.3, range = 0–10). Given evidence for a negative skew in the data, non-parametric tests were utilized for all baseline comparisons. At baseline, all individual scale items exhibited moderate and significant correlations with each other (Spearman's rho range from .66–.72, all *p*s <.001), and each individual item was highly correlated with the total score (Spearman's rho range from .85–.92, all *p*s <.001).

Craving was significantly higher among women (mean difference = 3.36, $p < .001$) and those with a lifetime history of heroin use (mean difference = 2.19, $p < .05$). Craving was not associated with race ($z = -0.07$, $p = .94$), or age (Spearman's rho = −0.06, $p = .26$). There were no significant differences in craving between those who did and did not first receive opioids from a legitimate source ($z = -0.02$, $p = .98$), or those who did and did not use opioids via a nonaccepted route of administration (e.g., intranasal, crushed; $z = -0.51$, $p = .54$).

3.2. Craving and Opioid Use Over Time

Almost all participants (*N*=354) had sufficient data available to be included in lagged logistic regression analysis. In the model examining the Opioid Craving Scale total score (see Table 1), craving was significantly associated with use in the following week (*OR* = 1.17, 95% CI = 1.11, 1.22, $p < .001$). This association was significant despite controlling for a range of variables associated with outcome, such as opioid use in the previous week and buprenorphinenaloxone dose. As there were no significant interaction effects of craving and time, craving by presence of chronic pain, or craving by presence of past heroin use these interaction terms were excluded from the final model. This suggests that the association between craving and opioid use was not moderated by heroin use or the presence of chronic pain, and was consistent over time.

When considering the three Opioid Craving Scale items separately, each item was significantly associated with subsequent week use when considered independently of the other items, including Item 1 (general craving; *OR* = 1.11, 95% CI = 1.06, 1.16, $p < .001$), Item 2 (cue-induced craving; *OR* = 1.14, 95% CI = 1.10, 1.19, $p < .001$), and Item 3 (likelihood of using in a previous drug use environment; *OR* = 1.14, 95% CI = 1.09, 1.19, $p < .001$). Thus, when considered separately (i.e., without controlling for the other items), for each 1-unit increase in an item, the increase in the odds of using opioids in the following week ranged from 11% (Item 1) to 14% (Items 2 and 3). However, entering all three items concurrently, Items 2 and 3 were associated with a higher likelihood of opioid use, but Item 1 was no longer significantly associated with opioid use (see Table 2). Similar to the

previous model, lifetime heroin use and use of opioids in the previous week were associated with opioid use the next week, and there were no significant effects of time or treatment condition. When considering all items together, for every 1-unit increase (on a 10-point scale) in cue-induced craving, participants had a 13% higher odds of using, and for every 1-unit increase in self-reported likelihood of use if in a former drug-using environment, participants had a 6% higher odds of using.

4. DISCUSSION

In this large clinical trial of treatment for prescription opioid dependence, we examined whether craving in any given week during the treatment trial was associated with urineconfirmed self report of opioid use in the subsequent week. The 3-item Opioid Craving Scale total score predicted opioid use in the following week, controlling for current opioid use and a history of heroin use. Each one-unit increase in the score on this scale was associated with a 17% higher odds of using opioids in the following week. Upon further examination of the individual items, although the general craving item ("How much do you currently crave opiates?") was significantly associated with subsequent use, this association was no longer significant when controlling for items measuring cue-induced craving and self-reported likelihood of use if in a former drug-using environment.

These results replicate previous findings in the treatment of cocaine dependence using the same measure (Weiss et al., 2003) as well as other studies suggesting an association between craving and use when measured proximally (Hartz et al., 2001; Moore et al., 2013; Weiss et al., 2003). Thus, this study provides further support for the stronger predictive validity of craving when considering near-term outcomes relative to long-term outcomes. Moreover, this finding extends the literature to the population with prescription opioid dependence and identifies the relative importance of individual domains of craving for the prediction of later use.

This study found that general craving (i.e., non-cued, non-contextual urges to use) was associated with opioid use in the subsequent week, but did not have an incremental benefit in the prediction of use relative to cue-induced craving and self-reported likelihood of use. This may suggest that craving in response to cues or environmental contexts is a more important risk marker, or possibly that participants more accurately report craving when they are asked to estimate its severity within a particular context. Thus, the commonly administered single-item assessment of craving ("Are you craving opioids now?" or a variant) may be enhanced by including a question about cue-induced craving.

Moreover, a number of treatment outcome studies have shown that self-reported confidence in one's ability to maintain abstinence (self-efficacy) is associated with better treatment outcome (Dolan et al., 2008; Ludwig et al., 2013; Vielva and Iraurgi, 2001); however, much like studies of craving and longer-term outcomes, this finding is not always consistent (Demmel et al., 2006). Similar to cue-induced craving, self-efficacy may also be a better predictor of the likelihood of proximal use (Barta et al., 2009; Gwaltney et al., 2005). This suggests that patients may be relatively skilled at estimating their own risk of using drugs. Although theories of craving have varied with respect to the inclusion of self-efficacy, this

variable appears to add valuable information to the prediction of future use, and thus may be important to include in regular clinical assessment.

The Opioid Craving Scale demonstrated internal consistency, reliability, and concurrent and predictive validity in this study and may be a valuable tool for use in both clinical and research settings. Together, these results suggest that both cue-induced craving and self-assessment of one's risk of using are strongly associated with of the odds of near-term use; thus, administering these questions in clinical settings may provide a marker of risk for use among those with prescription opioid dependence. In research settings, this measure may provide a brief and efficient means of assessing opioid craving, which may be of particular value for studies requiring the use of repeated measures. Additionally, the exploratory findings with respect to the relative predictive validity of the measure items raises an important question for future research about the domains of craving that may be most important in understanding risk for subsequent substance use.

In a previous report from the POATS study on baseline predictors of successful treatment outcome, craving at baseline was not one of the significant predictors of final treatment outcome (Dreifuss et al., 2013). This adds to the extant literature suggesting that craving is a better predictor of proximal relative to distal drug use.

There are several limitations to the current study. The participants in this study were currently enrolled in treatment and were receiving buprenorphine-naloxone, which reduces overall opioid craving (Ling et al., 1998). Thus, these results cannot necessarily be generalized to individuals who are not currently receiving opioid agonist therapy. Moreover, as this was a secondary data analysis, we were limited to the measures included in the initial trial. This study did not assess stress-induced craving, which may also have strong predictive validity for substance use disorder treatment outcomes (Sinha et al., 2011, 2006). Future studies including measures of stress-induced craving in this population will help to advance understanding of how different types of craving confer risk for later use. Because this is the first study to report on the psychometric properties of this measure in a prescription opioid dependent sample, replication of these findings are needed. Finally, the sample was relatively homogeneous with respect to race and many were employed full-time. Although this sample is representative of the overall population of those who misuse prescription opioids (Wu et al., 2011), the generalization of these findings to other groups is unknown.

A complex array of factors appears to contribute to the likelihood of lapse to use during substance use disorder treatment (Poling et al., 2007; Witkiewitz, 2011). In a large clinical trial of treatment for prescription opioid dependence, a brief, 3-item craving scale was associated with the odds of opioid use in the following week. Although a commonly used single-item assessment of craving was associated with use in the subsequent week, this item did not have an incremental benefit over the assessment of self-reported cue-induced craving and self-assessment of likelihood of opioid use in a former drug-using environment in this sample. Importantly, these variables were assessed using a self-report measure that can be administered in less than 1 minute within clinical settings. Assessing craving in the context of treatment using this measure may provide a valuable marker of risk for lapse. Such a

marker can serve to guide the implementation of treatment strategies to manage risk for lapse.

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Highlights

- Drug craving predicts future drug use, especially in the short term.
- A 3-item measure predicted prescription opioid use in the next week.
- For each 1 unit increase on the scale, the odds of using opioid was 17% higher.
- Brief assessment of prescription opioid craving may provide a marker of risk.

Table 1

Logistic Model Examining the Association between the Opioid Craving Scale Total Score and Opioid Use in the Subsequent Week

Variable	Estimate	SE	OR	95% CI	*p*
Heroin use	0.20	0.13	1.22	0.94, 1.58	.128
Treatment	0.15	0.11	1.16	0.94, 1.45	.170
Age	−0.01	0.01	0.99	0.97, 1.00	.040
Lifetime MDD	0.27	0.12	1.31	1.04, 1.65	.023
Prior opioid treatment	0.03	0.03	1.03	0.96, 1.10	.404
Route of opioid administration	0.58	0.20	1.79	1.22, 2.62	.003
Buprenorphine-naloxone dose	0.02	0.01	1.02	1.00, 1.03	.018
Time	0.01	0.01	1.01	0.98, 1.03	.487
Opioid use in previous week	1.97	0.12	7.15	5.65, 9.05	<.001
Opioid Craving Scale total	0.15	0.02	1.17	1.11, 1.22	<.001

Note. N = 354. SE = standard error, OR = odds ratio, CI = confidence interval, MDD = major depressive disorder.

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Table 2

Logistic Model Examining the Association between the Opioid Craving Scale Items and Opioid Use in the Subsequent Week

Variable	Estimate	SE	OR	95% CI	*p*
Heroin use	0.19	0.13	1.21	0.94, 1.56	.142
Treatment	0.17	0.11	1.19	0.96, 1.47	.139
Age	−0.01	0.01	0.99	0.97, 1.01	.051
Lifetime MDD	0.27	0.12	1.31	1.04, 1.66	.021
Prior opioid treatment	0.03	0.03	1.03	0.97, 1.09	.407
Route of opioid administration	0.56	0.20	1.75	1.18, 2.59	.005
Buprenorphine-naloxone dose	0.02	0.01	1.02	1.00, 1.04	.017
Time	0.01	0.01	1.01	0.99, 1.03	.602
Opioid use in previous week	1.96	0.12	7.10	5.61, 8.98	<.001
Opioid Craving Scale items					
Urges	−0.04	0.03	0.96	0.91, 1.02	.203
Cue-induced craving	0.12	0.03	1.13	1.06, 1.20	<.001
Likelihood of use	0.06	0.03	1.06	1.00, 1.13	.040

Note. N = 354. SE = standard error, OR = odds ratio, CI = confidence interval, MDD = major depressive disorder.

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