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Cue-Induced Craving in Dependence Upon Prescription Opioids and Heroin

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Abstract

Background and Objectives—Cues associated with heroin use (e.g., needles, powder) elicit robust craving responses in individuals dependent upon heroin. Elevated cue-induced craving may be a risk factor for relapse and can persist after periods of drug abstinence. Despite the growing prevalence of opioid dependence involving prescription opioids, published studies have yet to examine whether cue-induced craving is also present in prescription opioid dependence.

Methods—A sample of 50 adults diagnosed with opioid dependence (20 prescription opioid users, 25 heroin users, and 5 mixed opioid users) completed a cue reactivity assessment. Participants were administered a series of 90 pictures, including heroin-specific, prescription opioid-specific, and neutral images, and were asked to rate craving and cue salience after each image.

Results—Both the prescription opioid and heroin groups experienced significantly more craving to drug than to neutral stimuli. The prescription opioid group reported significantly less craving to prescription opioid stimuli than the heroin group to heroin stimuli; however, this effect was smaller and non-significant when controlling for group differences in cue salience.

Discussion and Conclusions—This study found evidence for cue-induced craving in individuals dependent upon prescription opioids. Further research is needed to better understand the role of cue reactivity in the course and treatment of opioid dependence involving prescription opioid use.

Scientific Significance—As elevated craving reactivity to drug cues may reflect a risk factor for relapse, understanding the nature of cue-induced craving in individuals with opioid dependence is important to improving treatments for this population.

Introduction

Elevated craving in the presence of drug-related cues is a common phenomenon in individuals who are dependent upon heroin.^{1–4} Greater cue-induced craving may be a

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

marker of relapse propensity following treatment⁵ and may continue—to a lesser extent—even following periods of extended abstinence.^{6,7} Although the presence of cue-induced craving has been well-established in heroin-dependent samples, published studies have yet to examine the degree to which this is also present in those dependent upon prescription opioids.

The prevalence of dependence on prescription opioids has increased dramatically over the past 15 years.^{8,9} As the representation of this group has rapidly increased in treatment settings¹⁰ there has been a significant need for research to determine how this population may be similar or different from heroin-dependent populations. Given important differences in the nature of the drug and its distribution (e.g., opioid analgesics can be legally obtained via a prescription), cue-induced craving may differ between heroin and prescription opioid users. Nonetheless, the powerful reinforcing effects of prescription opioids may still elicit conditioned craving responses similar to other drugs of abuse. Treatment studies have found evidence of similar craving outcomes in prescription opioid and heroin dependence following buprenorphine induction.¹¹ In chronic pain samples, there is evidence of craving for medication¹² and greater craving may be a marker of risk for misuse of prescribed opioids.¹³ However, the degree of craving elicited by drug cues and its strength relative to heroin cues remains unknown.

The overarching aim of the current study was to examine cue-induced drug craving in participants seeking treatment for dependence upon prescription opioids. We hypothesized that (1) prescription opioid dependent participants would report more craving in response to images of prescription opioid stimuli relative to neutral stimuli, and (2) prescription opioid dependent participants would report less ability to resist using opioids when viewing prescription opioid stimuli relative to neutral stimuli. In exploratory analyses, we tested whether cue reactivity differed between those dependent on prescription opioids relative to heroin and whether there were differences in cue reactivity to prescription opioid stimuli based on the type of prescription opioid cue (e.g., crushed pill vs. whole pill images).

Methods

Participants

A sample of 52 participants (11 women) was recruited from the inpatient alcohol and drug abuse treatment unit of a private psychiatric hospital. Adults ages 18 and older presenting for the treatment of opioid dependence and receiving detoxification were eligible to participate. Exclusion criteria included significant visual impairment, cognitive impairment, or the presence of uncontrolled bipolar disorder or a psychotic disorder that could interfere with the ability to complete study procedures. Participants with co-occurring other substance use and psychiatric disorders were eligible to participate. Participants could not be in withdrawal (see Procedures below) at the time of study procedures.

Procedures

All procedures were approved by the local Institutional Review Board. Participants completed a single laboratory session lasting between 1–1.5 hours. After participants

provided informed consent, a trained research staff member administered the Clinical Opiate Withdrawal Scale,¹⁴ a validated interviewer-administered measure of opioid withdrawal symptoms. To be eligible, participants had to achieve a score of less than 4, below the recommended cut-off for mild opioid withdrawal.¹⁵ Participants then completed a battery of self-report measures and an assessment of cue-induced craving. Finally, participants were debriefed and compensated with a \$15 gift card to a local vendor.

The cue reactivity assessment was completed on a computer and consisted of the presentation of 90 pictures (40 heroin-specific, 40 prescription opioid-specific, and 10 neutral), which were used for the first time in this study. All images were matched for the same background and for the presence of drug paraphernalia (e.g., pill bottles, spoons), and the order of images was randomly selected for each participant. Prescription opioid stimuli included commonly used classes of opioid analgesics (e.g., oxycodone, hydrocodone). Following each image, participants answered three questions related to that image. Two items were adapted from a previously validated measure¹⁶ to assess opioid craving ("How much do you have an urge or craving for opioids right now?") and the ability to resist craving ("If you saw this image in your life how well could you resist the urge to use? "). The third item assessed cue salience ("How much did the picture remind you of times that you have used opioids? "). Participants responded to each item using a visual analogue scale ranging from 0 (Not at all) to 10 (Extremely/Very Much).

Two versions of the task were developed to test for habituation of craving to repeated stimulus presentations at shorter (6 second) and longer (10 second) cue exposures; the proportion of participants receiving each of these versions was equated between the heroin and prescription opioid groups. Individual data points were excluded for the following reasons: (1) missing values (1.6% of all responses), (2) invalid responses (i.e., out of range scores; 0.2%), or (3) answers provided in a response time less than 250ms (0.2%). Mean craving, resistance, and salience scores were calculated for each stimulus type and subtype (e.g., prescription opioid, heroin) for each participant.

Measures

Sociodemographic characteristics and a brief opioid use history were collected using a modified version of a questionnaire used in a previous study of prescription opioid dependence.¹⁷ The Obsessive Compulsive Drug Use Scale (OCDUS)¹⁸ is a 13-item questionnaire adapted from the Obsessive Compulsive Drinking Scale¹⁹ to measure heroin craving in the previous week ("heroin" was replaced with "opioid" for the current study). The OCDUS has demonstrated strong internal consistency reliability and concurrent validity¹⁸ and had adequate internal consistency reliability in the current sample ($\alpha = .81$).

Data Analysis

Descriptive statistics were used to evaluate data for normality and univariate outliers. As anticipated, craving responses to the neutral stimuli indicated very low craving reactivity to neutral cues. This resulted in a non-normal distribution, and thus non-parametric tests were used for analyses involving these stimuli. Due to extreme outlier responses to neutral stimuli ($>3 SD$ from the mean), three participants were not included in analyses involving these

stimuli. Participants reporting primary heroin use (heroin group) were compared to those reporting primary prescription opioid use (prescription opioid group) with respect to sociodemographic and opioid use variables. A small group of participants endorsed both opioid types as their primary drug of abuse (mixed group); only descriptive data are presented for this subsample.

With repeated presentation of stimuli, there is risk of either craving habituation (i.e., decreases over time) or potentiation (i.e., increases over time). To determine whether either of these effects was present, we used repeated-measures ANOVAs to examine mean craving ratings for both stimulus types (prescription opioid and heroin) from the first 1/3rd of trials and the last 1/3rd of trials and the main and interaction effects of task version (6 vs. 10 second). These ANOVAs were run for both prescription opioid stimuli (including the prescription opioid and mixed opioid groups) and heroin stimuli (heroin and mixed opioid groups). Results from these analyses were used to determine whether to control for the duration of stimulus presentation in analyses.

To evaluate whether participants exhibited craving reactivity to drug stimuli, paired sample Wilcoxon signed-rank tests were used to compare mean craving and mean resistance in response to drug versus neutral stimuli. Differences in craving between prescription opioid and heroin dependent participants were examined utilizing independent samples *t*-tests comparing mean ratings in response to the primary substance of abuse (i.e., prescription opioid stimuli for the prescription opioid group and heroin stimuli for the heroin group). Group differences in cue salience were also calculated. In the case of that a significant difference in cue salience was found between the groups, a subset of images was selected based on equivalent salience ratings. Group differences were then re-tested with this new stimulus set to provide an estimate of craving removed from the effect of differences in cue salience. We believed that matched cues would allow for a more direct means to remove the influence of salience than would statistically covarying this factor.

Finally, within the prescription opioid and mixed opioid groups, paired-sample *t*-tests were conducted examining differences in mean craving to different subtypes of stimuli. Sidak correction was used to adjust the alpha level for multiple comparisons.

Results

One participant did not complete the cue reactivity task and one reported confusion with the task instructions; thus, data from these participants were not included in analyses. The remaining 50 participants (10 women) reported a mean age of 26.8 years ($SD = 8.3$). Participants self-reported race and ethnicity as primarily Caucasian (86%) and non-Hispanic (82%); however several participants did not report race ($n = 2$) or ethnicity ($n = 7$). The highest level of education attained was self-reported as: 10% less than high school, 24% high school/or equivalent, 52% some college, 10% college degree, and 4% graduate degree. Twenty participants (40%) self-reported prescription opioids as their primary drug of abuse, 25 (50%) reported heroin, and 5 (10%) used both prescription opioids and heroin equally.

Sociodemographic and opioid use characteristics for each subgroup are presented in Table 1. The prescription opioid and heroin groups did not differ on sociodemographic variables. The heroin group reported significantly more heroin use in the 30 days prior to admission, and the prescription opioid group reported significantly more prescription opioid use in that time period, providing support for the validity of participant self-classification into these groups. The primary opioid analgesic of abuse was immediate-release or extended-release oxycodone in the large majority of the prescription opioid group ($n = 18$, 95%) and the majority of the mixed opioid group ($n = 3$, 60%). Although more participants in the heroin group reported use of prescription opioids than participants in the prescription opioid group reported use of heroin, when combining the number of days of use of heroin and prescription opioids, there were no differences between groups in total days of use ($t[43] = -0.24$, $p = .81$). The heroin group reported significantly more opioid craving in the past week on the OCDUS.

There was no significant change in craving rating from the first to the last 1/3rd of trials for prescription opioids ($F[1, 21] = 2.54$, $p = .13$) or heroin ($F[1, 28] = 0.40$, $p = .54$). There was also no main or interaction effect of stimulus duration presentation ($ps > .34$), and thus all stimuli were included in subsequent analyses.

Reactivity to Drug vs. Neutral Stimuli

See Table 2 for group means for the cue reactivity task. Groups rated drug stimuli as significantly more salient than neutral stimuli: ($p < .001$ in the prescription opioid group, $p < .001$ in the heroin group), providing support for the relevance of these cues to opioid use.

As shown in Figure 1, comparisons of responses to drug-related vs. neutral stimuli indicated greater craving in response to prescription opioid relative to neutral stimuli in the prescription opioid group ($p = .001$) and greater craving in response to heroin stimuli in the heroin group ($p < .001$). The mixed group also exhibited substantially higher craving to both prescription opioid and heroin stimuli relative to neutral stimuli; however, inference tests were not run due to the small sample size of this subgroup.

Similarly, resistance to craving was significantly lower in response to drug stimuli relative to neutral stimuli for both the prescription opioid ($p < .001$) and heroin groups ($p < .001$). The mixed group also reported lower resistance in response to prescription opioid (mean difference = -3.44) and heroin stimuli (mean difference = -4.83).

Comparison between Prescription Opioid and Heroin Users

Results of comparisons between the prescription opioid and heroin groups are presented in Figure 2. The prescription opioid group reported significantly lower craving ($t[42] = -4.82$, $p < .001$, $d = -1.49$) and higher resistance ($t[42] = 5.34$, $p < .001$, $d = 1.65$) than the heroin group. Although on average, both groups reported a mean cue salience rating of moderate to high, the prescription opioid group reported significantly lower average cue salience relative to the heroin group (mean difference = -2.80 , $t[42] = -3.73$, $p < .01$, $d = -0.86$).

To examine whether differences in cue salience accounted for the observed differences between groups in craving, a subset of stimuli with matched salience were selected. Based

on mean craving ratings of heroin stimuli in the heroin group and prescription opioid stimuli in the prescription opioid group, 15 prescription opioid and 15 heroin stimuli were matched within a mean salience difference of ± 0.20 . The resultant subset of images had a mean salience rating of 5.80, reflecting a moderate level of salience. Mean craving ratings were recalculated for this subset of stimuli. When groups were compared based on craving for the primary opioid of abuse with this matched subset of stimuli, the craving difference was mitigated. There was evidence of a subtle trend for lower craving ($t[42] = -1.64, p = .11, d = -0.51$) and higher resistance in the magnitude of a medium effect size ($t[42] = 1.73, p = .09, d = 0.53$) in the prescription opioid group. See Figure 2.

Within the prescription opioid group, there was no difference in prescription opioid craving between those who reported a history of heroin use ($n = 7$) and those who denied heroin use ($n = 13$) (mean difference = 0.03, $t[18] = 0.03, p = .98, d = 0.01$). However, there was a trend toward more craving for heroin stimuli in the group who had previously used heroin (mean difference = 2.16, $t[18] = 2.07, p = .054, d = 0.98$) and significantly poorer resistance to heroin stimuli in this group (mean difference = $-2.72, t[18] = -3.14, p < .01, d = -1.48$).

Craving for Prescription Opioids by Stimulus Type

Prescription opioid stimuli were categorized as: non-opioid pills (e.g., over-the-counter pain relievers), oxycodone, hydrocodone, combinations of pills, and crushed pills. Table 2 presents the mean craving for each of these subtypes for the prescription opioid and mixed groups, combined ($n = 24$). Each pill type was compared to the non-opioid type and crushed pills were compared to each type of whole pill stimuli. Correcting for multiple comparisons ($\alpha = .05$), all stimuli were associated with significantly greater craving than the non-opioid stimuli, and crushed pill stimuli elicited greater craving than all types of whole pill stimuli. Due to insufficient heterogeneity in the sample with respect to the primary opioid analgesic of abuse and route of administration, differences in craving based on these factors could not be examined.

Discussion

Results from the current study suggest that amplified craving in response to drug-related cues that has been observed across a wide range of substances of abuse^{20,21} also occurs in prescription opioid dependent samples. Those with prescription opioid dependence rated opioid stimuli as more salient than neutral stimuli and reported higher craving and less ability to resist using in response to drugs cues.

Cue reactivity was less robust in the prescription opioid group than the heroin group, which was attributable—at least in part—to a greater salience of heroin cues. Although differences between groups in craving reduced to non-significance when controlling for salience, the heroin group continued to exhibit a pattern of higher craving in the magnitude of a medium effect size. This is consistent with the finding of greater self-reported craving over the previous week in the heroin group. Although it is possible that this greater craving in general is attributable to greater cue reactivity (i.e., the heroin group experienced more craving overall because of greater reactivity when cues were present), additional research is needed to clarify whether these types of craving are related and the direction of this association.

There are several potential explanations for the observed difference in cue salience between groups. First, prescription opioid-related images, such as pills and pill bottles, are more commonly observed in daily life than are heroin stimuli (e.g., needles, powder) and are likely to be encountered outside of the context of drug misuse. The degree of specificity of heroin stimuli to drug use may be more unique relative to prescription opioid cues, yielding greater salience and stronger associative learning for heroin cues, consistent with basic behavioral models of conditioning.²² Second, the strength of cue salience may vary based on route of drug administration. A larger portion of the heroin group reported intravenous drug use (84%) than the prescription opioid group (10%). These differences in route of administration may help to account for differences in cue salience and drug craving due to differences in the rapidity of drug effect. Of note, in the prescription opioid group, craving was highest for crushed pill stimuli, which is consistent with both the context specificity (i.e., more likely to only be encountered in drug-buying or misusing contexts) and the route of administration hypotheses (via crushed relative to whole pills). Finally, we cannot rule out the possibility that the difference in salience is related to the stimuli chosen for the current study (e.g., different or more varied stimuli may have yielded different salience ratings). Stimuli were selected to represent the commonly used opioid analgesics; however, given the high variability in pill color and shape based on manufacturer and dosage, there were certainly some that were missed. Moreover, it is possible that idiosyncratic cues were not captured by our images, such as paraphernalia used to crush pills and snorting or smoking equipment. Such cues may be more salient to some types of prescription opioid misuse than stimuli such as pill bottles. Nonetheless, even when matching heroin and prescription opioid stimuli based on equivalent salience ratings, the heroin group continued to exhibit greater cue induced craving in the magnitude of a medium effect size (albeit this was non-significant in this sample). Moreover, it is of note that the heroin stimuli also varied (e.g., powder of different colors and consistencies), and thus also were not ideographic. Future studies examining alternative cues for prescription opioid misuse will help to clarify the nature of these differences. For example, studies examining the process of obtaining a prescription (e.g., doctor's office, pharmacy) and the manipulation the drug (e.g., equipment used to grate or crush pills) may be of particular interest for this population.

There are several clinical implications of this finding. First, the specificity of craving to certain types of cues (e.g., crushed pills) in the prescription opioid group may be important to highlight in psychoeducation on relapse prevention and high risk situations. Second, treatments that attempt to extinguish conditioned craving responses to drug cues have often yielded weak outcomes for substance dependence, including opioid dependence.²³ However, attempts to improve such approaches by drawing from the basic science literature continue, and have promise to successfully target this risk factor in treatment.^{24–26} Extending these newer approaches to prescription opioid use may be a promising direction for future research.

There are several limitations to the current study. First, many participants had at some point used both heroin and prescription opioids. Although participants appeared to accurately identify their primary current opioid of abuse based on days of opioid use prior to treatment, few participants were exclusive users of one type of opioid. Thus, it is unclear whether these results would differ in samples that had exclusively used one type of opioid. Future research

investigating differences among more refined subgroups (e.g., prescription opioid use only, initiation of use with prescription opioids and progression to heroin, etc.) will help to clarify the impact of use of multiple opioid types on cue reactivity. Second, we cannot rule out the possibility that differences observed between the prescription opioid and heroin groups was attributable to the selection of insufficiently salient prescription opioid cues. Given the greater potential heterogeneity of cues related to prescription opioids, future studies using ideographic stimuli may be needed to clarify differences between these opioid types. Finally, we do not have data on the course of opioid use over time, and thus it cannot be ruled out that the stronger craving in the heroin group is attributable to being further in the progression of opioid dependence (e.g., initiated via prescription opioids and progressed to heroin). Future research that examines the longitudinal course of opioid use and how it related to cue reactivity is needed to better understand the impact of duration of use and the use of multiple opioid types on cue-induced craving.

In summary, treatment-seeking opioid-dependent participants exhibited significant cue-induced craving in response to drug images. Although the magnitude of craving was lower in the prescription opioid-dependent than heroin-dependent group, this appeared to be in part attributable to a lower reported salience of prescription opioid images. These results raise the important possibility that prescription opioid cues are more ideographic, and the heterogeneity of these cues may be an important consideration in treatment settings for the identification of triggers for use. Although additional research is needed to clarify the nature of differences in cue reactivity between those dependent upon heroin and prescription opioids, this study provides support for the presence of robust cue-induced craving in response to drug uses among those with prescription opioid dependence.

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Figure 1.
Mean Craving by Stimulus Type (** $p < .001$)

Figure 2.
Craving Differences between Heroin and Prescription Opioid Dependent Participants

Table 1

Sample Characteristics

	Primary Opioid of Abuse			<i>t</i>	<i>p</i>
	Prescription Opioid (<i>n</i> = 20)	Heroin (<i>n</i> = 25)	Both (<i>n</i> = 5)		
Demographic					
age (years)	29.0 (10.4)	26.7 (6.4)	21.2 (1.3)	1.30	0.20
gender (% female)	10.0%	32.0%	0.0%		0.15
race (% Caucasian)	84.3%	91.7%	100.0%		0.68
education (% completed high school)	95.0%	88.0%	80.0%		0.62
Opioid Variables					
ever used heroin (%)	35.0%	100.0%	100.0%		<.001**
ever used prescription opioids (%)	100.0%	92.0%	100.0%		0.50
number of days of heroin use in the previous 30 days	0.9 (2.0)	26.3 (7.3)	22.0 (9.2)	-15.14	<.001**
number of days of prescription opioid use in previous 30 days	29.3 (9.7)	4.7 (8.8)	16.2 (11.2)	8.89	<.001**
first source of prescription opioids (% legitimate prescription)	30.0%	24.0%	0.0%		0.74
craving in past week	32.5 (6.9)	36.8 (5.3)	31.4 (6.4)	-2.35	0.02*

Note.

* significant at alpha = .05,

** significant at alpha = .01. *p*-values for categorical outcomes reflect Fisher's Exact Test (2-sided).

Table 2

Mean Cue Reactivity Results by Group and Stimulus Type

	Group	
	Prescription Opioid	Heroin
Craving		
Primary Drug of Abuse	2.89 (2.34)	6.51 (2.57)
Neutral	0.52 (0.76)	1.34 (2.18)
Resistance		
Primary Drug of Abuse	6.93 (2.32)	3.23 (2.17)
Neutral	9.42 (0.85)	8.79 (2.09)
Salience		
Primary Drug of Abuse	4.55 (2.45)	7.30 (2.46)
Neutral	1.03 (1.49)	0.70 (0.88)
Craving by Prescription Opioid Cue Type*		
Crushed Pills	5.10 (3.35)	n/a
Combined Pill Types	3.28 (2.80)	n/a
Oxycodone	3.94 (2.92)	n/a
Hydrocodone	2.55 (2.53)	n/a
Non-opioid Pills	0.71 (1.15)	n/a

Note.

* means are reported for the prescription opioid and mixed groups combined ($n = 25$)