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Using ecological momentary assessment to examine the relationship between craving and affect with opioid use in a clinical trial of clonidine as an adjunct medication to buprenorphine treatment

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Abstract

Background: In a recent clinical trial (NCT00295308), we demonstrated that clonidine decreased the association between opioid craving and moderate levels of stress and affect in patients receiving buprenorphine-based opioid agonist therapy.

Objectives: To examine the relationship between illicit opioid use and craving and affect during the evaluation of clonidine as an adjunct medication in buprenorphine treatment for opioid use disorder. Secondly, to examine whether those relationships are driven by within- or between-participant factors.

Methods: This was a secondary data analysis from our original trial. Participants (N = 108, female: n = 23, male n = 85) receiving buprenorphine were randomized to receive adjunct clonidine or placebo. Participants used portable electronic devices to rate stress, mood, and craving via ecological momentary assessment (EMA) four times randomly each day. To associate the EMA data with illicit opioid use, each EMA report was linked to participants' next urine drug screen (thrice weekly). We used generalized linear mixed models to examine the interaction between treatment group and illicit opioid use, as well as to decompose the analysis into within- and between-participant effects.

Results: Craving for opioids and cocaine was increased when participants were using illicit opioids; this effect was greater in the clonidine group. For affect, mood was poorer during periods preceding opioid-positive urines than opioid-negative urines for clonidine-treated participants, whereas there was no difference for placebo participants.

Conclusion.—This secondary analysis provides evidence that illicit opioid use was linked to stronger negative affect and craving in participants maintained on clonidine in opioid agonist therapy.

Introduction

Alpha-2 adrenoceptor agonists block stress-induced drug-seeking behavior in the rat reinstatement model (1–3) and reduce drug craving in human laboratory studies (4–6). Therefore, we undertook a clinical trial in which we showed that opioid-dependent participants randomized to receive the alpha-2 agonist clonidine as an adjuvant to buprenorphine had longer periods of continuous abstinence and maintained a longer time to initial lapse (7). Because this trial included assessment of daily experiences using ecological momentary assessment (EMA), we were able to show that moderate stress was unrelated to opioid craving for those in the clonidine condition (7). This finding supports the idea that the behavioral mechanism of alpha-2 agonists is similar in rats and humans. We also found similar effects of clonidine (i.e., reduced likelihood of opioid craving) across affective descriptors. In general, it was only at the highest point of negative affect, or the lowest point of positive affect, that clonidine participants experienced the same levels of craving as the placebo participants (7). In other words, during clonidine administration, moderate problems with affect were not accompanied by the increases in craving seen in placebo-treated controls.

Having shown a disassociation of affect from craving, the logical next question would be, “Is affect disassociated from opioid *use*?” There are several reasons to expect that use, or abstinence, would be associated with changes in affect, with several possible competing explanations for relationships between affect and use. For example, many studies show an improvement in general quality of life in opioid-using participants who undergo substance use treatment (8). More specific to the current work, depressive symptomatology has been shown to decrease sharply in those undergoing opioid agonist therapy (9, 10), and depression is a risk factor for relapse (11, 12). These findings suggest that there could be a between-participant relationship between general levels of affect and success in treatment. Despite extensive research examining depression and opioid use, depressive symptomatology only measures an extreme form of negative affect over a period of weeks; thus, it cannot be used to elucidate the relationships within a person between momentary mood states and drug use.

Examining mood at a within-person level, there is a plethora of research showing that affect, particularly negative affect, can play a key role in triggering lapses and use in people attempting to maintain abstinence from abused drugs in general (13–15), and opioids in particular (16). Complicating the causal inferences of negative affect and lapses is the abstinence-violation effect (17), which leads users to feel negative affect (amongst other things) when they lapse. The relationship between use and affect could be bidirectional, as there is evidence that opioids themselves can elicit positive mood (18, 19) while opioid withdrawal is associated with poor affect, and opioid use that alleviates withdrawal symptoms could thus improve affect. Some of the effects on affect are mitigated in the

context of opioid agonist maintenance because it presumably staves off withdrawal and could also enhance affect.

The bidirectional relationship between affect and use becomes even more complicated when including craving, which may itself also have bidirectional relationships with affect and use. There is evidence that negative affect can lead to opioid craving (20), or that negative affect co-occurs with opioid craving (21–23), making them potentially difficult to distinguish, at least in laboratory conditions where actual drug use is prevented (24). Craving *per se* may also be an aversive state or have aversive aspects(25). Traditionally, craving is thought of as promoting drug use, with use then relieving craving (e.g.,18, 26). However, increases in craving with increased drug intake have also been observed (27, 28). In these cases, the direct effects of drug use could “prime” craving, or increased use could lead to larger changes as the direct effects “wear off” or increased withdrawal effects, which could increase craving.

Questions about affect and substance use can be examined with EMA in ways that have advantages over traditional surveys and interviews. First and foremost is the momentary nature of the data, which removes many of the biases caused by memory. In addition to the usual cognitive biases, specifically relevant for the present study is that people’s present affective state can influence the recall of past affective states (29). A second advantage is temporal resolution. The degree to which it is possible to discuss the timing of the relationship between affect and use depends upon the temporal resolution of the measures of affect (and use). Past studies have often used broad time scale measures that assess affect over weeks or months. Because each EMA affect entry is made at a momentary level, the only limit to the resolution of the relationship between affect and use is the frequency of assessment of use. In our study, we asked participants to initiate an EMA entry for each instance of opioid use, but later comparison of these reports with thrice-weekly urine screens showed that they were incomplete (a problem we have addressed in our ongoing EMA studies by meeting with each participant every week to reinforce agreement between EMA reports and urine results). Therefore, the temporal resolution of this data set is limited by the thrice-weekly schedule of urine testing. However, within each 48-hour or 72-hour bin of urine-verified use or abstinence, we have real-time assessments of affect via EMA.

One additional advantage of EMA methods is that they can distinguish between within-participant effects and between-participant effects using a relatively simple procedure. By creating models that include participant means (which contain only between-participant variance), and mean-centered predictors (which contain only within-participant variance), it is possible to determine the relative importance of these components to the analysis. This determination allows researchers to determine whether an observed overall relationship merely reflects better affect in people who are abstinent, or whether it instead (or also) reflects temporal relationships between affect and abstinence within each person.

The present study is a secondary data analysis examining the relationship between affective states and craving during periods when participants were known to have used illicit opioids compared to periods when they were known to have not used. In addition, the study examines if the effects seen are modified by the inclusion of clonidine to buprenorphine

treatment. Secondly, the study clarifies whether these effects are driven by factors that are within-subject, between-subject, or both. This analysis will help shed light on the behavioral mechanisms through which clonidine increased the time to lapse and longest periods of abstinence in participants in our clinical trial.

Method

Participants

Participants were outpatient volunteers seeking treatment for dependence on heroin or prescription opioids. Inclusion criteria were physical dependence on opioids and age between 18 and 60 years. The main exclusion criteria were current psychotic disorder, history of bipolar disorder or schizophrenia, current major depression, current dependence on alcohol or sedatives, cognitive impairment that would preclude informed consent or valid self-report, pregnancy or breastfeeding, use of contraindicated medications such as beta-blockers, and medical illness that would compromise participation.

The Institutional Review Board (IRB) of the NIDA Intramural Research Program approved this study. Participants gave written informed consent.

Study Design

The study tested clonidine as an adjuvant medication to buprenorphine for opioid relapse prevention in a double-blind, placebo-controlled efficacy trial. Participants attended our outpatient treatment-research clinic in Baltimore seven days per week for sublingual buprenorphine (buprenorphine alone: 8–24 mg/day) and attended weekly counseling sessions for up to 28 weeks. These 28 weeks were broken up into 4 phases; weeks 1–6 buprenorphine stabilization and abstinence initiation phase, weeks 7–8 induction (onto placebo or clonidine) phase, weeks 9–20 clonidine/placebo intervention phase, and weeks 21–28 maintenance (buprenorphine only) phase. In all phases participants' urine samples were collected under observation three times a week and tested for opioids (morphine, oxycodone and methadone tests), cocaine, marijuana, amphetamines, benzodiazepines, phencyclidine, and barbiturates. Because we theorized that clonidine would help with relapse prevention, establishing opioid abstinence was a key component of the design. To facilitate opioid abstinence, participants earned a voucher for each opioid-negative urine sample during the abstinence initiation and induction phases of the study. The value of the vouchers started at \$4 and increased by \$4 for each consecutive opioid-negative urine sample. If a urine sample was opioid-positive or missed, no voucher was given, and the value of the next voucher was reset to \$4. Participants who demonstrated opioid abstinence in weeks five and six (six consecutive negative urine screens) were randomized by an investigator having no contact with the participants to receive oral clonidine or matching placebo in conjunction with their daily sublingual buprenorphine. As reported previously(7), 90 (43%) participants failed to be randomized after enrolling in the study. Of these 90, 45 (50%) were not randomized due to a loss of contact, 32 (35%) failed the initial abstinence portion of the study, and 13 were removed for other reasons. Those who were randomized were older (38.8 ± 8.1 vs 36.3 ± 8.7 , $p = 0.05$) and used heroin on fewer days per month

(24.7 ± 7.9 vs 26.8 ± 6.8 , $p = 0.05$) than participants who were not randomized. There were no differences in education, employment, years of heroin use, cocaine use, race or sex.

Participants randomized to clonidine were titrated up to a dose of 0.3 mg/day over two weeks, and then maintained on that dose throughout the intervention phase. During the induction and intervention phases, nurses interviewed participants for adverse events weekly; as indicated, clonidine/placebo dosages were adjusted in 0.1-mg increments at the discretion of a physician who was blind to assignment. At the end of the intervention phase, clonidine/placebo was tapered to zero over two weeks and buprenorphine treatment continued (maintenance phase). Participants then chose to either transfer to another opioid agonist treatment program or taper off buprenorphine.

Ecological Momentary Assessment

During the second week of the induction onto clonidine or placebo, participants were issued a portable electronic device (PalmOne Zire 21, Palm Tungsten E2, or HTC TyTN II smartphone) used to capture EMA data. Participants completed prompts throughout the 12-week intervention phase and the eight-week maintenance phase. The device issued alerts at four randomly selected times during participants' waking hours each day, prompting the participants to complete a series of questions about affect and craving (i.e., a random prompt entry). Participants were given the stem "Right now, I feel" and asked about their feelings in the following order: happy, stressed, tired, relaxed, bored, and irritated. They were then asked if "Right now," they were craving cocaine, heroin/opiates, or tobacco. The response options were "YES!!", "yes??", "no??", and "NO!!." These responses were coded with the values 4, 3, 2, and 1, respectively.

Data Analysis:

For the analyses reported here, we linked each EMA response to the next urine result. Responses made on Monday and Tuesday were linked to urine samples collected on Wednesday; responses made on Wednesday and Thursday were linked to urine samples collected on Friday; responses made on Friday, Saturday and Sunday were linked to urine samples collected on Monday. Responses that were linked to missing urine screen results were dropped from the analyses. The unit of analysis was an individual EMA response. Responses linked to the same urine sample were not averaged. We used only responses given during the intervention phase, when participants were receiving stable doses of clonidine (or placebo).

General linear mixed models were created (SAS Proc Mixed) to examine the impact of drug condition, opioid use, and their interaction on affect and craving. Although causation could be bidirectional between affect and opioid use, the models required that we designate predictors and dependent variables.

In all the mixed models, we used an autoregressive error structure. Denominator degrees of freedom were conservatively set to reflect the number of participants rather than the number of measurement occasions, as recommended by Bolger and Laurenceau (30). The predictors were treated as fixed, but each model used a random intercept. Alpha was set at .05, two-

tailed, for all analyses. Tukey's method was used to adjust p-values for multiple comparisons in pairwise testing.

We also created models to determine whether the relationships found between opioid use and affect were the result of between-person differences or within-person associations. Mixed models correct for situations in which participants differ in their ranges of responses on the outcome variable, but the models do not automatically account for such between-person differences in observed values of predictor variables (e.g., many more drug-use periods in some participants than in others) (31). Thus, when an effect is significant in a mixed model, it is not possible to tell if the effect is being driven by between-subject factors (i.e. the average level of the independent variable impacts the dependent variables), within-subject factors (i.e. the momentary change in the independent variable impacts the dependent variable), or both. Therefore, we examined the within and between components of the interaction using a modified model-based method (31) in which momentary values were centered on person-level means to remove all between-person variance. The centered value was entered in the model along with the person's mean (person-level means, across participants, contain only between-person variance). We treated opioid use (dichotomously coded as 0 or 1) as a numeric variable so that person-level "means" could be calculated. This mean is the percentage of reports that were made when the participant's next urine was positive for opiates. A secondary model was then constructed with the centered variable, the mean level of opioid use, and each variable's interaction with drug group. This allowed for the direct examination of the within and between components of the analysis.

We used F values to calculate effect-size r values (r_{effect} values) as specified by Rosnow et al. (32), with associated 95% confidence intervals to examine the within/between person effects. The Rosnow et al. (32) procedure for calculating r_{effect} values has not been formally tested in the context of intensive longitudinal data and is dependent on the method used to specify denominator degrees of freedom. Therefore, our reported r_{effect} values should be interpreted with caution in terms of cross-study comparisons (e.g., eventual inclusion in meta-analyses), but they are useful for comparisons of effects within our results.

Results

Participants.

Participants completed a total of 7,705 days of EMA and answered 24,306 random prompts in the intervention phase. This yielded on average 3.15 prompts completed out of the four intended each day, for a compliance percentage of 79%. Of the 118 participants randomized, ten did not provide data for this analysis (seven in the placebo group and three in the clonidine group) because they dropped out of the study either during or shortly after clonidine/placebo induction and never received a device for EMA. As reported previously (7) the two randomized groups did not differ on any relevant factors assessed before randomization. This is also true for the slightly smaller sample ($n = 108$, female: $n = 23$, male: $n = 85$) that provided data for this analysis.

Participants in the clonidine group provided 1,769 time points for urinalysis. Of these, 1,367 (77.2%) were negative, 308 (17.4%) were positive, and 94 (5.3%) were missing due to

not attending the clinic. Participants in the placebo group provided 1,619 time points for urine analysis. Of these, 1,197 (73.9%) were negative, 300 (18.5%) were positive, and 122 (7.5%) were missing due to not attending the clinic. Prior analysis revealed no overall differences in the percent positive urines between the two groups (7). Participants in the clonidine group provided 12,581 random entries in the intervention phase. Of these entries, 9,962 (79.2%) were followed by a negative urine; 1,971 (15.7%) were followed by a positive urine, and 648 (5.2%) were dropped because they were followed by a missing urine. Participants in the placebo group provided 11,725 random entries during the intervention phase. Of these entries, 8,776 (74.8%) were followed by a negative urine; 2,101 (17.9%) were followed by a positive urine, and 848 (7.3%) were dropped because they were followed by a missing urine.

The relationship between illicit opioid use and craving was increased by clonidine.

The associations of study-drug group and opioid use with craving for opioids, cocaine, and tobacco can be seen in Figure 1. Model results for craving can be seen in Table 1. In the sample as a whole, opioid, cocaine, and tobacco craving were higher when participants were opioid positive (at their next urine screen) than when opioid negative (opioid: $F_{(1,104)} = 161.21$, $p < 0.0001$ cocaine: $F_{(1,104)} = 46.79$, $p < 0.0001$, tobacco: $F_{(1,104)} = 8.06$, $p < 0.01$). As can be seen in the results of model two in Table 1, the increase in craving was driven solely by within-person variance for cocaine ($r_{\text{effect}} = 0.55$) and tobacco ($r_{\text{effect}} = 0.26$) craving and was driven by both within- ($r_{\text{effect}} = 0.78$) and between-person ($r_{\text{effect}} = 0.25$) effects for opioid craving.

For opioid and cocaine craving, there was also an interaction between study-drug group and opioid use. In both cases, these interactions reflected a greater association between opioid use and craving in the clonidine group than in the placebo group (opioid: $F_{(1,104)} = 11.75$, $p < 0.001$, cocaine: $F_{(1,104)} = 10.59$, $p < 0.01$). The increase in intensity of craving for both opioids and cocaine during use periods was greater in the clonidine group than the placebo group. As can be seen in Table 1, these interactions were driven by within-person relationships (opioid: $r_{\text{effect}} = 0.32$, cocaine: $r_{\text{effect}} = 0.24$), not between-person differences.

The relationship between negative affect and opioid use was only found in the clonidine group.

The associations of study-drug group and opioid use with affect can be seen in Figure 2. Model results for affect can be seen in Table 2. For the sample as a whole, the same pattern was present for five of the six affect variables assessed: affect was worse when the next urine screen was opioid-positive (stressed: $F_{(1,104)} = 19.80$, $p < 0.0001$, irritated: $F_{(1,104)} = 12.43$, $p < 0.001$, bored: $F_{(1,104)} = 8.55$, $p < 0.01$, relaxed: $F_{(1,104)} = 4.92$, $p < 0.05$, happy: $F_{(1,104)} = 6.19$, $p < 0.05$). As can be seen in table 2, breaking these models into within- and between-person components revealed that all the effects were driven by within-person relationships (stressed: $r_{\text{effect}} = 0.40$, irritated: $r_{\text{effect}} = 0.33$, bored: $r_{\text{effect}} = 0.28$, relaxed: $r_{\text{effect}} = 0.22$, happy: $r_{\text{effect}} = 0.23$). The only affect variable not significantly associated with the next opioid urine result was feeling tired.

The interaction between study-drug group and opioid use was significant for five of the six affect variables (all except relaxed), reflecting that the use/affect association was significant only in the clonidine group: when positive for illicit opioids, participants receiving clonidine reported that they were more stressed, tired, bored and irritated, as well as less happy, whereas there were no significant differences for participants in the placebo group (stressed: $F_{(1,104)} = 17.11$, $p < 0.0001$, irritated: $F_{(1,104)} = 10.59$, $p < 0.01$, bored: $F_{(1,104)} = 13.05$, $p < 0.01$, tired: $F_{(1,104)} = 11.20$, $p < 0.05$, happy: $F_{(1,104)} = 6.17$, $p < 0.05$). As can be seen in table 2, the interactions between treatment group and opioid use were driven solely by within-person relationships (Stressed: $r_{\text{effect}} = 0.38$, Tired: $r_{\text{effect}} = 0.26$; Bored: $r_{\text{effect}} = 0.34$, Irritated $r_{\text{effect}} = 0.31$, Happy: $r_{\text{effect}} = 0.22$), not between-person differences.

Discussion

For our sample as a whole, drug craving was higher during the 48-to-72-hour periods prior to opioid-positive urine screens, intervals during which opioid use very likely occurred. Craving for opioids, cocaine, and tobacco was driven by largely within-participant changes. This means that it was not simply that participants who were more often opioid-positive also craved at higher levels, but that when participants tested positive, they were more likely to have been craving. This association was greater for the clonidine group than the placebo group. The lack of an association between use and affect in the placebo-treated participants was surprising, but not without precedence. For example, a study from our group using EMA methods similarly found no increase in stress in the hours leading up to a drug use event (33).

In participants treated with clonidine, the association between use and affect was even more apparent than with craving. Increases in negative affect and decreases in positive affect associated with opioid use were seen only in the clonidine group. We interpret these results to suggest patients treated with clonidine (who achieved longer overall durations of opioid abstinence than those treated with placebo) used most frequently when craving and affect reached high levels. In the absence of the alpha-2 agonist effect, increased craving and negative affect were equally present in EMA entries relative to positive and negative urine opioid screens.

The mechanism behind these findings requires some conjecture. One possibility is changes in autonomic nervous system activity. Clonidine is known to reduce activation of the sympathetic nervous system (34), an effect that could reduce bodily reactions to emotion (35). This is the mechanism by which clonidine can be used to treat hyperarousal in Post-Traumatic Stress Disorder (36, 37). When used as an aid in opioid withdrawal, clonidine has a larger effect on the autonomic signs of withdrawal than on the self-reported symptoms of withdrawal (38). For our results, it is possible that clonidine attenuated the bodily cues that help drive the relationship between moderate levels of affect and use. At times of extreme affect, this effect was overridden, and the participant more likely to use. Framed another way, when a person in recovery is moderately irritated, noticeable peripheral indicators such as increased heart rate or sweat may bolster the otherwise moderate subjective experience to produce an affective experience leading to use. In the clonidine condition, these peripheral cues are attenuated, conferring some protection against use. However, if the subjective

irritation is sufficiently strong, the physical cues may occur despite clonidine's effect, or they may not be necessary to drive an association between affect and use.

There is little evidence that low doses of alpha-2 agonists directly alter affect. There have been studies linking alpha-2 adrenoreceptors to depression (39, 40), but to our knowledge there have been no studies showing direct changes in affect due to alpha-2 agonists. In the present study, likewise, there was no main effect of treatment group on affect. However, it is possible that there is an interaction (i.e., a pharmacological interaction) between illicit opiates and clonidine that causes more negative affect when both are used. Our data cannot address this directly because we could only identify periods of use in terms of 48-to-72-hour bins, which include participants' preparations to use, use itself, direct effects of use, and (potentially) compensatory aftereffects of use. Nonetheless, we consider an enhancement of negative affect unlikely. To our knowledge, there has been no systematic examination of clonidine's ability to change the subjective effects or self-administration of opioids in humans; however, it is common for persons who use opioids to regard clonidine as a drug that can potentiate their using experience (41), and cases of clonidine dependence often involve co-administration with opioids (42, 43). Clonidine can also potentiate opioid analgesia (44–46). Because users report taking clonidine to enhance the effects of opioids, it seems unlikely that the combination would generally produce aversive affective experiences.

A final theory that cannot be ruled out is that stress is the driving force behind all of our measures of affect. As we have shown in previous work using EMA, stress has a strong relationship with other measures of affect in our population (33). Therefore, the effects we are seeing here could be simply a product of a relationship between stress and use, with increases in other measures of affect only secondary to stress.

The statistical main effects and interaction effects were driven mostly by within-person associations rather than between-person differences. This creates an important distinction for discussion. Most studies examine how means or proportions are associated with one another. In studying substance use disorders, we may look at percent positive urine and relate that to some other treatment outcome. These traditional analyses can miss associations in data when within-participant associations are aggregated up to between-participant levels (47). In our study, it is not simply that people who were more likely to use opioids were also more likely to have poorer mood. Rather, the association reflected the dynamics of use and affect within people. This result provides some hope that even though depressive symptomatology is a risk factor for poor outcomes in treatment (11, 12), the risk may exist more at state level than trait level and can thereby be reduced.

The main limitation of our data, as we have noted, is the comparatively low temporal resolution resulting from using thrice-weekly urine data to classify periods of use or nonuse of opioids. With these data, we cannot directly test more rapid dynamics, such as whether negative affect leads to lapses (16), which in turn (e.g., through the abstinence-violation effect) lead to more negative affect (17). Similarly, we cannot disaggregate the craving we detected into anticipatory craving, priming-induced craving, and craving as drug effects wore off; all of these may well have been present. We may be able to undertake higher-

resolution analyses in data we have been collecting in subsequent studies, as we now more closely monitor and incentivize reporting of drug use by EMA.

This study is part of a growing trend; the use of ambulatory data in clinical trials (48). Traditionally pharmaceutical clinical trials were built upon animal models to answer the question “Will this drug work?” The addition of ambulatory techniques can allow one with much greater confidence to address more complex questions of how a drug worked (or didn’t) within a clinical trial. Specifically related to substance use ambulatory technique has been used to explore standard treatments in smoking showing that decreased craving was the key variable in why combined therapies work better than singular ones (49). Several labs have used ambulatory techniques to explore the mechanism by which Topiramate reduces drinking behavior, showing that Topiramate does not exert its effect on drinking through expectancies and desire to drink (50) but rather through self-efficacy (51) and post-drink craving (52).

The present study demonstrated that participants treated with clonidine had greater craving, less positive affect, and greater negative affect in 48-to-72-hour periods when they were using illicit opioids than when they were not. Combined with the finding that those participants achieved longer durations of opioid abstinence overall, this secondary analysis provides refined understanding of how clonidine worked in the clinical trial: clonidine most likely minimized the behavioral impact of moderate levels of negative affect and craving, reducing the likelihood of use.

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Figure 1.

The effect of the treatment condition and illicit opioid use on the intensity of reported craving. The y-axis represents the model-predicted mean of craving (range 0–3). Error bars represent standard error of the mean. The * represents a difference between positive and negative use periods with a $p < .05$ adjusted for multiple comparisons using Tukey's method.

Figure 2.

The effect of the treatment condition and illicit opioid use on the intensity of reported mood. The y-axis represents the model-predicted mean of mood (range 0–3). Error bars represent standard error of the mean. The * represents a difference between positive and negative use periods with a $p < .05$ adjusted for multiple comparisons using Tukey's method.

Table 1.

Within/Between models for craving effects

Model 1					Model 2			
	Model Term	df	F	p	Model Term	df	F	p
Opioid Craving	Group	1,104	0.1	0.76	Group	1,104	0.0	0.91
	OPI Positive	1,104	161.2	<.0001*	OPI Pos (within)	1,104	157.3	<.0001*
	Group × Pos	1,104	11.8	0.0009*	Group × Pos (within)	1,104	11.9	0.0008*
					OPI Pos (between)	1,104	7.1	0.009*
					Group × Pos (between)	1,104	0.4	0.55
Cocaine Craving	Group	1,104	0.3	0.76	Group	1,104	0.0	0.98
	OPI Positive	1,104	46.8	<.0001*	OPI Pos (within)	1,104	45.6	<.0001*
	Group × Pos	1,104	6.7	0.01*	Group × Pos (within)	1,104	6.5	0.01*
					OPI Pos (between)	1,104	1.7	0.20
					Group × Pos (between)	1,104	0.2	0.70
Tobacco Craving	Group	1,104	0.7	0.39	Group	1,104	1.7	0.19
	OPI Positive	1,104	8.1	0.01*	OPI Pos (within)	1,104	7.8	0.01*
	Group × Pos	1,104	2.4	0.12	Group × Pos (within)	1,104	2.6	0.11
					OPI Pos (between)	1,104	1.3	0.26
					Group × Pos (between)	1,104	1.5	0.23

Models for each of the craving variables. Model one is a traditional mixed model. Model two disaggregates within and between variance for each effect. Within participant variance is examined by centering the value for opioid positive around the percent likelihood of a positive report. Between participant variance is examined using the participants' percent likelihood of reporting an opioid positive urine.

Table 2.

Within/Between models for mood effects

Model 1					Model 2			
	Model Term	df	F	p	Model Term	df	F	p
Stressed	Group	1,104	1.7	0.20	Group	1,104	0.4	0.54
	OPI Positive	1,104	19.8	<.0001*	OPI Pos (within)	1,104	19.6	<.0001*
	Group × Pos	1,104	17.1	<.0001*	Group × Pos (within)	1,104	17.2	<.0001*
					OPI Pos (between)	1,104	0.3	0.61
					Group × Pos (between)	1,104	0.0	0.94
Irritated	Group	1,104	0.6	0.42	Group	1,104	0.2	0.69
	OPI Positive	1,104	12.4	0.0006*	OPI Pos (within)	1,104	12.4	0.0007*
	Group × Pos	1,104	10.6	0.002*	Group × Pos (within)	1,104	10.7	0.001*
					OPI Pos (between)	1,104	0.2	0.69
					Group × Pos (between)	1,104	0.0	0.93
Bored	Group	1,104	1.4	0.24	Group	1,104	0.9	0.35
	OPI Positive	1,104	8.6	0.004*	OPI Pos (within)	1,104	8.6	0.004*
	Group × Pos	1,104	13.0	0.0005*	Group × Pos (within)	1,104	13.3	0.0004*
					OPI Pos (between)	1,104	0.1	0.78
					Group × Pos (between)	1,104	0.2	0.665
Tired	Group	1,104	0.4	0.52	Group	1,104	0.0	0.95
	OPI Positive	1,104	2.1	0.16	OPI Pos (within)	1,104	2.0	0.16
	Group × Pos	1,104	11.2	0.001*	Group × Pos (within)	1,104	11.1	0.001*
					OPI Pos (between)	1,104	0.0	0.85
					Group × Pos (between)	1,104	0.0	0.79
Relaxed	Group	1,104	0.2	0.66	Group	1,104	2.7	0.10
	OPI Positive	1,104	4.9	0.03*	OPI Pos (within)	1,104	5.1	0.03*
	Group × Pos	1,104	0.1	0.71	Group × Pos (within)	1,104	0.1	0.82
					OPI Pos (between)	1,104	0.9	0.35
					Group × Pos (between)	1,104	4.2	0.04*
Happy	Group	1,104	0.2	0.62	Group	1,104	0.7	0.41
	OPI Positive	1,104	6.2	0.01*	OPI Pos (within)	1,104	5.9	0.02*
	Group × Pos	1,104	6.2	0.01*	Group × Pos (within)	1,104	5.5	0.02*
					OPI Pos (between)	1,104	0.0	0.80
					Group × Pos (between)	1,104	2.67	0.11

Models for each of the craving variables. Model one is a traditional mixed model. Model two disaggregates within and between variance for each effect. Within participant variance is examined by centering the value for opioid positive around the percent likelihood of a positive report. Between participant variance is examined using the participants' percent likelihood of reporting an opioid positive urine.