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Brief report

# Evaluating Nicotine Craving, Withdrawal, and Substance Use as Mediators of Smoking Cessation in Cocaine- and Methamphetamine-Dependent Patients

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## Abstract

**Introduction:** Smoking is highly prevalent in substance dependence, but smoking-cessation treatment (SCT) is more challenging in this population. To increase the success of smoking cessation services, it is important to understand potential therapeutic targets like nicotine craving that have meaningful but highly variable relationships with smoking outcomes. This study characterized the presence, magnitude, and specificity of nicotine craving as a mediator of the relationship between SCT and smoking abstinence in the context of stimulant-dependence treatment.

**Methods:** This study was a secondary analysis of a randomized, 10-week trial conducted at 12 outpatient SUD treatment programs. Adults with cocaine and/or methamphetamine dependence ( $N = 538$ ) were randomized to SUD treatment as usual (TAU) or TAU+SCT. Participants reported nicotine craving, nicotine withdrawal symptoms, and substance use in the week following a uniform quit attempt of the TAU+SCT group, and self-reported smoking 7-day point prevalence abstinence (verified by carbon monoxide) at end-of-treatment.

**Results:** Bootstrapped regression models indicated that, as expected, nicotine craving following a quit attempt mediated the relationship between SCT and end-of-treatment smoking point prevalence abstinence (mediation effect = 0.09, 95% CI = 0.04% to 0.14%,  $P < .05$ , 14% of total effect). Nicotine withdrawal symptoms and substance use were not significant mediators ( $P_s > .05$ , <1% of total effect). This pattern held for separate examinations of cocaine and methamphetamine dependence.

**Conclusions:** Nicotine craving accounts for a small but meaningful portion of the relationship between smoking-cessation treatment and smoking abstinence during SUD treatment. Nicotine craving following a quit attempt may be a useful therapeutic target for increasing the effectiveness of smoking-cessation treatment in substance dependence.

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## Introduction

Smoking is highly prevalent among patients with substance dependence, with 60%–90% estimated to smoke.<sup>1,2</sup> While introducing smoking cessation into concurrent substance use disorder (SUD)

treatment does not harm SUD treatment outcomes,<sup>3,4</sup> achieving successful smoking cessation is highly challenging.<sup>5,6</sup> New therapeutic targets for clinicians could improve the effectiveness of smoking-cessation interventions within SUD treatment and enhance long-term

substance use abstinence, which is associated with successful smoking cessation.<sup>7</sup> Further, given evidence that nicotine use heightens the craving for and use of other substances,<sup>8,9</sup> reducing nicotine use may lessen substance use and aid SUD treatment outcomes.<sup>4</sup>

One important potential treatment target is nicotine craving, which sometimes predicts or mediates successful smoking abstinence.<sup>10</sup> Nicotine craving has not been evaluated as a mediator of smoking abstinence during SUD treatment, despite evidence that nicotine craving may be heightened during co-occurring substance use.<sup>11</sup> Importantly, nicotine craving findings are inconsistent<sup>12</sup> and do not always account for successful smoking cessation.<sup>13</sup> This study follows recommendations to address this challenge by identifying moderators and treatment contexts that account for variation in the relationship between nicotine craving and outcomes.<sup>14</sup>

Several considerations about nicotine craving are informative in the context of SUD treatment. First, nicotine craving during SUD treatment occurs alongside craving for other substances. Craving shares characteristics across substances,<sup>15</sup> meaning that craving for different substances is somewhat undifferentiated and prone to being influenced by shared causes and/or by each other.<sup>16</sup> Consequently, an attempt to quit smoking while quitting illicit stimulant use could induce nicotine craving that is particularly potent and linked to smoking outcomes for some participants. Second, postquit nicotine craving tends to be a stronger predictor of smoking-cessation outcomes than prequit nicotine craving.<sup>14</sup> As a result, we chose to examine nicotine craving in the week following the introduction of smoking-cessation treatment and a uniform quit attempt by participants. We note that this study focuses on background craving (vs. more episodic, cue-specific craving<sup>17</sup>), although it is not specifically designed to tease apart these types.

It is also important to consider alternative mediators such as withdrawal symptoms and substance use that could account for the effects of smoking-cessation treatment. Nicotine withdrawal symptoms are conceptually separate from nicotine craving<sup>18</sup> and are a plausible mediator of smoking cessation,<sup>19</sup> despite having relatively small<sup>20</sup> and inconsistent<sup>21</sup> effects. In terms of substance use, clinical and laboratory research suggest a complex bidirectional connection between nicotine and other substance use including alcohol,<sup>8,22,23</sup> opioids,<sup>24–29</sup> and illicit stimulants,<sup>9,30–35</sup> such that the use of each may heighten the use of the other. Thus, we tested substance use as an alternative mediator, but considered this relationship unlikely based on the absence of past correlations between substance use and the success of attempts to quit smoking.<sup>36</sup>

Overall, this study examined nicotine craving as a mediator of the relationship between smoking-cessation treatment and successful smoking cessation in a large sample of cocaine and/or methamphetamine-dependent patients who were also nicotine dependent. This study was a secondary analysis of a multisite trial conducted by the National Institute on Drug Abuse (NIDA) National Drug Abuse Treatment Clinical Trials Network (CTN) to evaluate the impact of concurrent SUD and nicotine dependence treatment. We hypothesized that nicotine craving in the week following an attempt to quit smoking would mediate smoking abstinence at the end of treatment. We also tested whether potential alternative mediators, nicotine withdrawal symptoms and substance use, would account for the relationship between smoking treatment and smoking outcome. Finally, to examine the generalizability of the mediation effect and overall pattern of results, we examined these relationships separately for cocaine and methamphetamine dependence. Together, these tests provide information about the presence, magnitude, and specificity

of nicotine craving as a mediator of smoking cessation in the context of stimulant-dependence treatment.

## Methods

### Participants

Patients ( $N = 538$ ) completed a 10-week randomized controlled trial comparing outpatient substance use treatment as usual (TAU;  $n = 271$ ) with substance use treatment as usual plus smoking-cessation treatment (TAU+SCT;  $n = 267$ ; for more information see<sup>6,37</sup>). All patients were cocaine and/or methamphetamine dependent according to *DSM-IV-TR* criteria,<sup>38</sup> smoked at least 7 cigarettes per day, had a carbon monoxide level  $\geq 8$  ppm, had smoked cigarettes for at least 3 months, and were interested in quitting smoking. See [Table 1](#) for sample characteristics.

### Measures

#### Nicotine Craving

A single item measuring the “desire to smoke” over the past 24 hours (scale ranging from 0 = “None” to 4 = “Severe”) was used from the eight-item Minnesota Nicotine Withdrawal Scale.<sup>39</sup> Consistent with the typical separation of this item from the others,<sup>18</sup> a confirmatory factor analysis testing the Minnesota Nicotine Withdrawal Scale as one dimension found that the craving item demonstrated a low loading when included (standardized beta = 0.35), and the model fit was significantly better ( $\Delta\chi^2 = 37.28$ ,  $\Delta df = 6$ ,  $P < .001$ ) when comparing the model with no craving item [ $\chi^2(14, N = 496) = 36.71$ ,  $P = .001$ , comparative fit index = 0.98, root mean square error of approximation = 0.055,  $\chi^2/df = 2.62$ ] to the model including the item [ $\chi^2(20, N = 496) = 73.99$ ,  $P < .001$ , comparative fit index = 0.96, root mean square error of approximation = 0.071,  $\chi^2/df = 3.70$ ].

#### Withdrawal Symptoms

The sum total of the remaining seven items of the Minnesota Nicotine Withdrawal Scale was used to represent nicotine withdrawal symptoms as an alternative mediator. Items included “anger, irritability, frustration,” “anxiety, nervousness,” “difficulty concentrating,” “impatience, restlessness,” “hunger,” “awakening at night,” and “depression.” Cronbach’s alpha was .84 in the current sample.

#### Substance Use

The Timeline Follow-Back<sup>40–42</sup> measured two types of substance use, stimulant use and drug use, during week 4. Participants reported for each of the past 7 days whether they had used stimulants (cocaine, methamphetamine, and/or amphetamine) and/or any drugs (marijuana, alcohol, cocaine, methamphetamine, amphetamine, sedatives, opiates, and other), with self-report confirmed by urine drug screens. Scores represent the number of stimulant-free days and drug-free days.

#### Smoking Point Prevalence Abstinence

At the end of treatment (week 10), participants reported whether they had smoked in the previous 7 days, with this report verified by a carbon monoxide level of less than 8 ppm.<sup>43</sup>

#### Procedure

Participants were scheduled to attend two research visits per week for efficacy and safety assessments over the 10-week treatment. All TAU+SCT participants began a uniform quit attempt during week 3. They received extended-release bupropion 300 mg/d, nicotine

**Table 1.** Sample Characteristics and Nicotine and Substance Use Variables

	TAU ( <i>n</i> = 271)		TAU+SCT ( <i>n</i> = 267)		Total ( <i>n</i> = 538)	
	<i>M</i> or <i>n</i>	<i>SD</i> or %	<i>M</i> or <i>n</i>	<i>SD</i> or %	<i>M</i> or <i>n</i>	<i>SD</i> or %
Demographic and baseline variables						
Age	36.0	10.1	36.9	10.0	36.4	10.0
Sex (male)	135	49.8	145	54.3	280	52.0
Race						
Black	88	32.5	83	31.2	171	31.8
Caucasian	158	58.3	162	60.9	320	59.6
Other	25	9.2	22	7.9	47	8.6
Hispanic ethnicity	33	12.3	34	12.9	67	12.6
Education (years)	12.0	1.9	11.7	1.9	11.9	1.9
Average Cig/d	16.0	7.4	16.7	8.4	16.3	7.9
Type of stimulant dependence						
Cocaine only	154	57.0	147	55.1	301	56.1
Methamphetamine only	107	39.6	102	38.2	209	38.9
Both substances	9	3.3	18	6.7	27	5.0
Nicotine and substance use variables						
Nicotine craving	2.67 <sup>a</sup>	1.01	1.92 <sup>b</sup>	1.11	2.30	1.13
Nicotine withdrawal	7.50	5.60	7.08	5.56	7.29	5.58
Stimulant-free days	0.96	0.13	0.96	0.13	0.96	0.13
Drug-free days	0.87	0.25	0.88	0.25	0.88	0.25
Week 4 PPA	4 <sup>a</sup>	1.5	37 <sup>b</sup>	13.9	41	7.6
Week 10 PPA	6 <sup>a</sup>	2.2	78 <sup>b</sup>	29.2	84	15.6

Cig = cigarettes; PPA = point prevalence abstinence; SCT = smoking-cessation treatment; TAU = treatment as usual. Stimulant-free days and drug-free days are presented as proportions out of the last 7 days. Some totals may not sum to 100% due to rounding. No demographic or baseline variables differed significantly between the treatment groups. Treatment group differences are noted by unique letter superscripts (ie, "a" vs. "b") and are all significant at  $P < .05$ .

inhaler, individual 10-minute smoking-cessation counseling weekly for 10 weeks, and prize-based contingency management for smoking abstinence (carbon monoxide < 4 ppm) during the postquit phase. Participants in the TAU condition quit as desired during treatment and did not receive smoking-cessation support. Nicotine craving, nicotine withdrawal symptoms, stimulant-free days, and drug-free days were recorded each week, including the week (4) following the TAU+SCT group's uniform quit attempt.

### Analytic Plan

Mediation effects were tested using standard mediation analysis techniques<sup>44-46</sup> with bootstrapping in SAS 9.3 to calculate parameter estimates and 95% confidence intervals (CIs). Regressions in the mediation analyses used three approaches matched to the type of dependent variable: a logistic approach for end-of-treatment smoking point prevalence abstinence (PPA; binary variable), a proportional odds logistic approach for week 4 nicotine craving (multinomial variable), and an ordinary least squares approach for week 4 nicotine withdrawal symptoms, stimulant-free days, or drug-free days (continuous variables). Baseline average cigarettes smoked per day was entered as a covariate in all analyses, although the pattern of results was the same without this covariate. The relative importance of mediation effects was determined by comparing the estimated mediation effect to the estimated total effect. This approach follows recent recommendations to advance the conceptualization of proposed theoretical processes by emphasizing both the significance and magnitude of mediation effects.<sup>47</sup>

### Results

Participants completed treatment at similar rates [ $\chi^2(1, N = 538) = 0.23, P < .64$ ] in the TAU (90%) and TAU+SCT groups

(88%). See Table 1 for descriptive statistics for all nicotine and substance use variables.

### Nicotine Craving as a Mediator of the Relationship Between Smoking-Cessation Treatment and Smoking PPA

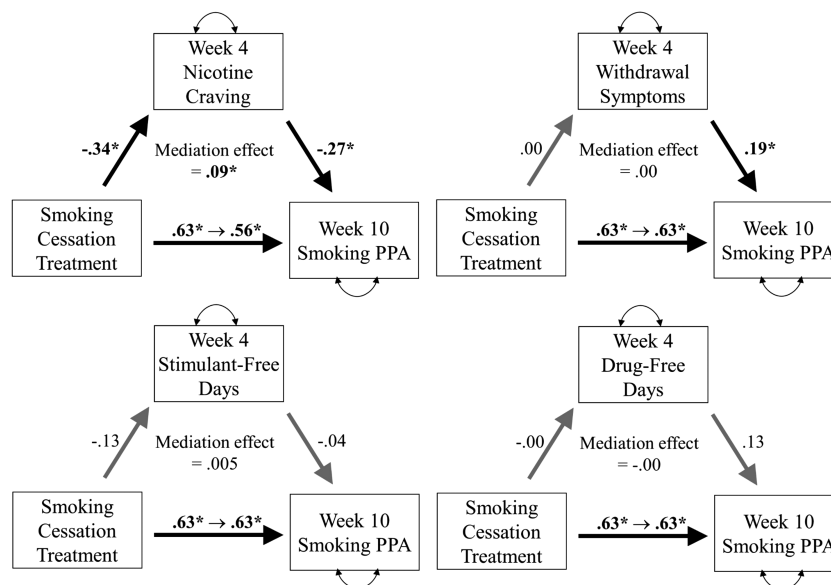
First, we tested the central hypothesis that week 4 nicotine craving would mediate the relationship between smoking-cessation treatment (TAU = 0, TAU+SCT = 1) and end-of-treatment smoking PPA (Smoking = 0, Abstinence = 1). As seen in Figure 1, as expected, nicotine craving was a significant mediator of the relationship between smoking-cessation treatment and end-of-treatment smoking PPA (mediation effect = 0.09, 95% CI = 0.04% to 0.14%,  $P < .05$ , model  $N = 496$ ), accounting for 14% of the total relationship.

### Nicotine Withdrawal Symptoms and Substance Use as Alternative Mediators

Next, we examined a series of models testing alternative mediators. Neither nicotine withdrawal symptoms (mediation effect = 0.000, 95% CI = -0.002% to 0.004%,  $P > .05, N = 496$ ), stimulant-free days (mediation effect = 0.005, 95% CI = -0.01% to 0.05%,  $P > .05, N = 521$ ), nor drug-free days (mediation effect = -0.000, 95% CI = -0.001% to 0.001%,  $P > .05, N = 521$ ) was a significant mediator. These variables each accounted for less than 1% of the total relationship between smoking-cessation treatment and smoking PPA.

### Cocaine-Dependence Versus Methamphetamine-Dependence

Finally, we reran the models separately for cocaine and methamphetamine dependence to test whether the results would vary according to illicit-stimulant type. For cocaine dependence, nicotine craving



**Figure 1.** Path diagrams of nicotine craving, withdrawal symptoms, stimulant-free days, and drug-free days as mediators of the relationship between smoking-cessation treatment and smoking point prevalence abstinence (PPA). Bold values with an asterisk indicate significance at  $P < .05$ . Samples sizes were  $N = 496$  for the models examining nicotine craving and nicotine withdrawal symptoms and  $N = 521$  for the models examining stimulant-free days and drug-free days.

mediated the relationship between smoking-cessation treatment and smoking PPA (mediation effect = 0.08, 95% CI = 0.02% to 0.16%,  $P < .05$ , 15% of total effect,  $N = 283$ ), whereas nicotine withdrawal symptoms ( $N = 283$ ), stimulant-free days ( $N = 293$ ), and drug-free days ( $N = 293$ ) did not (all  $P$ s  $> .05$ ,  $< 0.1\%$  of total effect). For methamphetamine dependence, the same pattern held: nicotine craving was a significant mediator (mediation effect = 0.12, 95% CI = 0.02 to 0.22,  $P < .05$ , 12% of total effect,  $N = 188$ ), but nicotine withdrawal symptoms ( $N = 188$ ), stimulant-free days ( $N = 201$ ), and drug-free days ( $N = 201$ ) were not (all  $P$ s  $> .05$ , nicotine withdrawal symptoms and drug-free days  $< 0.1\%$  of total effect, stimulant-free days = 1% of total effect).

## Discussion

This study examined postquit nicotine craving, nicotine withdrawal symptoms, and substance use as mediators of smoking abstinence during SUD treatment. Nicotine craving in the week following a quit attempt was a significant mediator of the relationship between smoking-cessation treatment and smoking abstinence at the end of SUD treatment, accounting for 14% of the total effect. Nicotine withdrawal symptoms and substance use did not account for any meaningful portion of the relationship. These findings were consistent across cocaine and methamphetamine dependence, demonstrating that the pattern may generalize across substances in stimulant-dependence treatment.

These results suggest that nicotine craving has clinical significance, but only to the degree that moderators and contexts predicting the magnitude of the relationship are understood.<sup>48</sup> In this study, the mediation effect was relatively small in magnitude, but its presence suggests that nicotine craving in the week after a quit attempt has relevance for nicotine outcomes.<sup>14</sup> This timing is useful for clinicians and researchers attempting to predict outcomes within SUD treatment, as the increased variability and intensity of craving after a quit attempt may produce a clearer relationship between craving

and nicotine outcomes.<sup>14</sup> For instance, patients reporting higher levels of nicotine craving in the week after a quit attempt may require more intensive support for smoking cessation. In contrast, patients reporting lower levels of nicotine craving may find that learning about their greater likelihood of successful abstinence reinforces their motivation to quit smoking while undergoing SUD treatment. Similarly, the lack of meaningful mediation by postquit nicotine withdrawal symptoms and substance use diminishes the likelihood that assessing these factors at this time will be informative about nicotine outcomes.

While mediation findings do not establish causation, they identify a pathway through which the mediator and/or associated factors may lead to the outcome. In addition to teasing apart possible causes of nicotine craving, other constructs should be tested as moderators or mediators of the relationship between nicotine craving and smoking abstinence. For instance, nicotine craving may be particularly related to smoking outcomes among people with low to moderate anxiety, and relate to nicotine outcomes via downstream associations with self-efficacy.<sup>49,50</sup> Constructs such as anxiety and self-efficacy could be incorporated alongside nicotine craving to enrich conceptualizations.

## Limitations and Conclusion

These results highlight nicotine craving as critical for understanding smoking cessation among stimulant users, but could be extended in several ways. First, single item craving measures are less reliable, poorer predictors of abstinence than multiple item measures.<sup>51</sup> Second, mediation analyses do not establish causation. To advance research on nicotine craving, it is necessary to integrate experimental tests of causal mechanisms with longitudinal, process-oriented analyses. Third, cotinine verification of abstinence at the end of treatment may have detected higher levels of smoking than carbon monoxide verification, which is used for 7-day PPA. Finally, it is unclear how well findings about these illicit stimulants may translate to alcohol dependence or other substances.

Overall, nicotine craving accounts for a small but meaningful portion of the relationship between smoking-cessation treatment and smoking abstinence during SUD treatment. This evidence is encouraging for attempts to integrate effective smoking-cessation treatment into SUD treatment settings with high smoking rates.

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## Declaration of Interests

None declared.

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