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Cravings as a mediator and moderator of drinking outcomes in the COMBINE Study

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Abstract

Aims—Investigators of the COMBINE (Combining Medications and Behavioral Interventions for Alcoholism) Study examined whether combining medications with a behavioral intervention would improve outcomes over monotherapies. Unexpectedly, the combination did not offer any advantage over either treatment alone. This study aimed to explain the lack of incremental benefit offered by the combination over either monotherapy by assessing the role of cravings as a treatment mediator and moderator.

Design—Secondary mediation and moderation analyses of COMBINE study data.

Setting—Eleven United States academic sites.

Participants—863 patients randomized to one of four treatment groups: naltrexone (100mg/d; n=209), the Combined Behavioral Intervention (CBI, n=236), naltrexone and CBI combined (n=213), and placebo naltrexone (n=205).

Measurements—Percent Days Abstinent (PDA) measured between 13 and 16 weeks post-baseline. Cravings, the potential mediator/moderator, was measured at baseline, week 4 and week 12 using the Obsessive-Compulsive Drinking Scale.

Findings—Compared to placebo, naltrexone, CBI, and the combination all increased PDA by an additional 6–10 percentage points for those with high cravings ($p < 0.05$ for all three treatment groups). None had significant effects on PDA for those with low cravings. The effects of all three treatments were at least partially mediated by cravings; craving reduction explained 48–53% of treatment effects ($p < 0.05$ for all three treatment groups). Furthermore, naltrexone appeared to reduce cravings at 4 weeks, while CBI did not reduce cravings until 12 weeks.

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Conclusions—Naltrexone and the behavioral intervention both improved abstinence by reducing cravings and were no longer effective once cravings were low. Furthermore, naltrexone reduced cravings by 4 weeks, while the behavioral intervention took longer to affect cravings. The COMBINE naltrexone + CBI combination may not have been more beneficial than either monotherapy because craving reduction was a common mechanism of both, and neither worked when cravings were low.

INTRODUCTION

In the treatment of alcoholism, a combination of pharmaceutical and behavioral treatments may improve outcomes over either monotherapy [1–3]. The primary goal of the COMBINE study was to examine whether a combination of treatments would improve drinking outcomes (percent days abstinent, time to first heavy drinking day) compared to either medication (naltrexone and/or acamprosate) or a combined behavioral intervention (CBI) alone. Contrary to expectation, there were no meaningful differences in abstinence across the naltrexone, CBI, and naltrexone + CBI arms (those who received acamprosate did not have better outcomes than placebo). COMBINE investigators concluded that naltrexone alone is sufficient for abstinence promotion based on the lack of added benefit from CBI [4].

Subsequently, a series of commentaries on the COMBINE study encouraged exploration of treatment mechanisms to explain the unexpected lack of incremental benefit shown in the combination therapy [5, 6]. Some questioned the recommendation for naltrexone monotherapy and suggested that future analyses focus on mediators of change for both behavioral and pharmacologic interventions [5].

Current Study

We examined cravings as a treatment mediator and moderator to improve understanding of the lack of incremental benefit offered by the combined naltrexone + CBI treatment compared to either monotherapy in the COMBINE Study. Specifically, we 1) determined the extent to which cravings mediated treatment effects on abstinence for the three treatment groups (naltrexone, CBI, and naltrexone + CBI), and 2) assessed whether cravings moderated effects on abstinence.

Although naltrexone and CBI have plausible distinct mechanisms of action, or “mediators” [7], craving is a plausible common mechanism of both. A number of clinical trials have shown cravings to mediate the effects of naltrexone [8, 9], while patients with the highest levels of baseline craving also appeared to benefit especially from naltrexone [9–12]. Others have found that patients treated with naltrexone reported fewer cravings before, during, and after a relapse [13]. These findings suggest that craving levels mediate naltrexone efficacy, and that moderation by cravings is also possible since the extent of the naltrexone effect could be influenced by craving levels [14].

Although the literature consistently highlights craving reduction as a primary mediator of naltrexone efficacy, the causal chain of CBI is less understood. CBI was developed for COMBINE, precluding past examination of potential mediators or moderators. However, CBI was intended to address symptoms that might lead to relapse, such as craving [15]. Furthermore, some consider craving to function according to cognitive and behavioral processes [16], which CBI addresses. Although not biologically obvious, CBI might alleviate craving via cognitive and behavioral coping skills, enhanced self-efficacy, or increased motivation for abstinence [16].

Witkiewitz and colleagues used the COMBINE data to examine how the cravings module specific to the CBI groups affected heavy drinking, and found that those who received the

module had fewer heavy drinking days, and that receiving the module moderated the effects of negative mood on heavy drinking; these moderated effects were mediated by craving reduction [17].

Thus, naltrexone and CBI may be working through the same mechanism. We hypothesized that both naltrexone and CBI were *mediated* by cravings, i.e., naltrexone and CBI were effective because they reduced craving, and craving reduction was crucial for achieving abstinence [18, 19]. Further, we examined the possibility that cravings *moderated* the treatment effects; specifically, once cravings were reduced to a minimal level by treatment, any additional therapy mediated by cravings could not provide incremental benefit (because cravings cannot be reduced further).

METHODS

Sample

For a detailed description of the COMBINE Study, please see [4, 7]. Briefly, COMBINE investigators randomized 1,383 newly abstinent participants to nine groups. Over a 16-week period, patients received either active/placebo naltrexone, or active/placebo acamprosate (total of 4 medication conditions: placebo, naltrexone, acamprosate, and naltrexone + acamprosate) either with or without the combined behavioral intervention (4 medication regimens x 2 CBI regimens = 8 groups). The ninth and final group received CBI only, without placebo or active medication [4].

Current analyses included seven of these nine groups; because groups receiving active acamprosate (3 mg/d) without naltrexone did not have significant main effects [4], we focused on active naltrexone (100 mg/d), CBI (up to 20 sessions), and active naltrexone + CBI groups. We thus excluded 1) those who received active acamprosate without either naltrexone or CBI and 2) those who received active acamprosate + CBI. To be consistent with the original COMBINE analyses, we collapsed groups across acamprosate categories and analyzed 4 groups of interest: 1) those who received naltrexone but no CBI (n=209); 2) those who received CBI but no naltrexone (n=236); and 3) those who received both CBI and naltrexone (n=213). The comparison group consisted of 4) those who received placebo and no CBI (n=205). Group sizes differ from those reported from the original COMBINE analyses [4] because the current analyses required complete cravings data.

Measures

The outcome, percent days abstinent (PDA), was the proportion of abstinent days between 13 and 16 weeks of treatment calculated from Form-90 data [4]. Cravings were measured at baseline, 4 weeks, 12 weeks, and 16 weeks using the Obsessive Compulsive Drinking Scale (OCDS) [4, 20]. The OCDS is a 14-item, self-report instrument developed to measure obsessive thoughts and compulsive behaviors regarding alcohol use [20]. Each item is rated on a 5-point (0–4) response scale, such that total OCDS scores ranged from 0–56. The cravings and PDA measurements do not overlap to ensure proper temporality, i.e., that the mediator occurs before the outcome. All analyses were performed for the sample of those not missing PDA at 16 weeks or mediator variables (cravings at four and twelve weeks) and controlled for baseline measures of PDA, cravings, and stress, as well as treatment site.

Statistical Analyses

First, we estimated total treatment effects to provide a reference point for the magnitudes of the mediation and moderation results. Next, we determined the extent to which 4- and 12-week cravings mediated treatment effects on abstinence for the three groups (i.e., the proportion of the total treatment effects we can attribute to cravings reduction). The

mediation analyses yielded estimates of the direct effect, or the treatment effects not attributable to cravings, as well as an indirect effect, or the treatment effect that was attributable to cravings. The indirect effect was used to calculate the proportion of the treatment effect attributed to craving reduction. Finally, we assessed whether 4- and 12-week craving levels moderated the naltrexone group, CBI group, and naltrexone + CBI group treatment effects on 16-week percent days abstinent (i.e., if treatment effects differed for high vs. low craving levels).

Targeted maximum likelihood estimation (TMLE) was used for estimation [21]. TMLE is a semi-parametric estimator that depends on estimation of both the outcome regression (i.e., the mean PDA at week 16 conditional on covariates, mediators, and treatment), and the treatment mechanism (i.e. the probability of treatment conditional on covariates and mediators). Unlike estimators based only on outcome regressions or treatment mechanisms, TMLE is doubly robust, meaning it is consistent if either the outcome regression or the treatment mechanism is estimated consistently. TMLE is also a substitution estimator, guaranteeing that the estimate falls within allowable bounds (i.e., 0–100 since we are estimating effects on percent days abstinent). Additionally, if both the outcome regression and treatment mechanism are estimated consistently, TMLE is efficient, achieving the minimum variance of all regular estimators [21]. Moderation effects were estimated using the ‘tmle’ package in the statistical computing platform R [22]. Mediation effects were estimated with the TMLE algorithm from Lendle and van der Laan [23].

Both the outcome regression and the conditional probability of treatment were estimated using the SuperLearner algorithm, a cross-validation based ensemble method [24]. The algorithm combines a library of data-adaptive machine learning methods and parametric models to build an estimator that performs as well or better than any algorithm in the library. The use of a library of methods helps circumvent potentially problematic assumptions like normality, while cross-validation helps avoid over-fitting. In our application for the outcome regression, the library included generalized linear models (GLM) [25], generalized additive models [26], gradient boosting [27], the elastic net algorithm [28], polynomial spline regression [29], the random forest algorithm [30], ridge regression [25], Bayesian linear models [31], support vector machines [32], and the deletion/substitution/addition (DSA) algorithm [33]. For the treatment mechanism, the library included GLMs, k-nearest neighbors [25], and the DSA algorithm [33]. Libraries for the treatment mechanism and outcome regression differed because treatments were categorical while outcomes are continuous. The SuperLearner data-adaptive approach to modeling does not impose any structure (e.g., linear regression) onto the data *a priori*. For example, linear regressions assume normality and linearity whereas SuperLearner makes no such assumptions. Therefore instead of forcing the data into a linear regression structure that may not fit, our approach allows the data to inform model specification without over-fitting.

RESULTS

Descriptives

Table 1 displays average PDA at each follow-up time for each treatment group. At baseline, average PDA was about 25% for all groups. Within the first four weeks of treatment, average PDA increased to 75–80% for all groups, including placebo. By the end of treatment at 16 weeks, average PDA was down to 66.4% for placebo, 73.9% for naltrexone, 72.8% for CBI and 74.6% for the combination. Table 2 displays average cravings for each treatment group at each follow-up time. The pattern for cravings over time was similar to that of PDA, with large initial improvements for all groups, but more stable improvements for the active treatments compared to the placebo group. At baseline, craving levels were similar across all groups, ranging from 26.4–27.1 on a scale of 0–56. Cravings dropped to

half their baseline levels for all groups, including placebo, within the first four weeks of treatment. By the end of treatment, average craving was highest for the placebo group and lowest for the combination.

As noted in the Methods, an advantage of the SuperLearner approach is the ability to test and combine multiple model forms. Here the highest weighted algorithms chosen by SuperLearner were Bayesian linear models, polynomial spline regression, random forests, and the deletion/substitution/addition (DSA) algorithm.

Total treatment effects

The average difference in PDA between 13–16 weeks compared to placebo was 6.3, 5.7, and 4.6, for naltrexone, CBI, and the combination, respectively (Table 3). Results when excluding those missing cravings (n=142) data were stronger for all treatments; we show these effects for comparison because the moderation/mediation analyses only included cases with cravings data.

Mediation by cravings

Table 4 displays direct and indirect effects, or mediation results, for effects of each treatment on PDA. The indirect effect is the treatment effect on PDA attributable to cravings, while the direct effect is the treatment effect that does not work through cravings [14, 34]. Naltrexone and the combination effects appeared mediated by 4-week cravings, indicated by significant indirect effects. For example, in the naltrexone group PDA was 3.9 percentage points higher due to cravings reduction (indirect effect), and a further 3.3 percentage points higher due to other unexamined mechanisms (direct effect), yielding a 7.2 percentage point higher level of PDA (total effect) compared to placebo. When examining 12-week cravings, the indirect effects for all three treatments were significant; thus each treatment appeared to be mediated by 12-week cravings, with 3.5 (combination), 3.9 (CBI), and 4.9 (naltrexone) percentage point higher levels of PDA due to cravings reduction. When analyzing both 4- and 12-week cravings as mediators simultaneously, results did not suggest any stronger mediation than found at each time individually; craving reduction at one time-point yielded about a 4 percentage point increase in PDA, above which there was no effect of accounting for craving reduction at other time-points.

The percent of treatment effects attributable to cravings was calculated as the ratio of the indirect effect to the total effect, or $(\text{indirect effect})/(\text{indirect effect} + \text{direct effect}) \times 100$. Thus 48–53% of each treatment effect could be attributed to craving reduction. Interestingly, the indirect, or mediated, effect was significant for naltrexone for both 4- and 12-week cravings ($p=0.001$, $p=0.004$, respectively), but not significant for CBI until examining 12-week cravings (Table 4); this supports the patterns shown in Tables 1 and 2, and suggests that naltrexone affected cravings sooner than CBI. Consistent with these results, *post hoc* analyses of treatment effects on cravings (not shown) found that naltrexone significantly affected earlier cravings (4 weeks) while CBI worked later, significantly affecting 12-week cravings. The combination marginally affected 12-week cravings.

Moderation by cravings

Table 5 displays the effects of each treatment arm (naltrexone, CBI, combination) on PDA stratified by cravings at 4- and 12-weeks to assess moderation. When cravings were low at 4 weeks, none of the active treatments were more effective than the placebo. However, when cravings were high at 4 weeks, all of the treatments were similarly effective in increasing PDA. For example, if cravings were high for everyone at 4 weeks and everyone were to get CBI only, average 16-week PDA would be 12.9 percentage points higher than if cravings were high for everyone at 4 weeks and everyone got the placebo. Results were similar for

naltrexone groups and even stronger for the combination. The pattern of results was similar but weaker across 12-week craving levels.

DISCUSSION

To improve understanding of the lack of incremental benefit in abstinence offered by the combined naltrexone + CBI treatment compared to either monotherapy in the COMBINE Study, we assessed cravings as a potential treatment moderator and mediator. The results indicated that craving reduction was a common mechanism to both therapies and may explain why the combination was not more effective than either monotherapy. Mediation analyses showed that craving reduction explained about half of all treatment effects. Moderation analyses showed that naltrexone, CBI, and the combination all effectively increased abstinence when cravings were high, while none worked when cravings were low.

Here, average cravings levels at baseline were similar to those previously reported in comparable populations [1]; non-treatment-seeking alcohol-dependent individuals usually score 7–15 on the OCDS, treatment-seeking clinic patients score 15–20, and alcoholic inpatients score 20–25 [1]. The descriptive results showed large initial improvements in cravings and PDA for all treatment groups, including placebo, but with more stable improvements for the active treatment groups. Cravings and PDA also correlated across follow-ups: average PDA was higher when average cravings were lower, which highlights the value of cravings, as measured by the OCDS, as a predictor of drinking. Notably, average cravings within the CBI only group remained about the same level as that of the placebo group at 4 weeks into treatment, whereas cravings were already lower among groups receiving naltrexone, indicating that naltrexone reduced cravings earlier than CBI.

The mediated, or indirect, effect of cravings for the naltrexone group was significant by the first follow-up. On the other hand, the indirect effect for the CBI group was not significant until the second follow-up. This pattern was similar to the descriptive results, and implied that naltrexone reduced cravings more quickly than CBI, which makes sense when considering differences between taking daily medication vs. attending weekly CBI sessions. *Post hoc* analyses of treatment effects on cravings found that naltrexone significantly reduced earlier cravings (4 weeks) while CBI worked later, significantly reducing 12-week cravings. Thus, hypothetically, a patient taking both naltrexone and CBI might have experienced craving reduction early on (since naltrexone worked on 4-week cravings) but then received no benefit from CBI (because no treatments worked when cravings are low). This may explain why the combination was not more effective than either monotherapy.

Furthermore, the mediation analyses showed that indirect effect point estimates did not change meaningfully when accounting for cravings at one vs. two time points; the unchanging magnitudes of the indirect effects implied that accounting for cravings at both time-points did not explain any additional treatment effect, either because 1) cravings could be reduced only to a certain point (e.g., “none”), and/or 2) once cravings reached a particular threshold, or low point, reducing cravings any lower did not enhance abstinence outcomes. We know from the *post hoc* analyses that none of the treatments reduced cravings to “none,” suggesting a possible threshold of craving reduction.

Although mediation and moderation are sometimes framed as mutually exclusive [14], recent work has highlighted the importance of considering the possibility that mediators may also moderate treatment effects [34]. The present analysis is a perfect example of how a mediator also moderates, and how understanding this combination of phenomena illuminates our understanding of causal processes. Specifically, our findings suggested that 1) the COMBINE treatments reduced cravings, and that this cravings reduction increased PDA

(mediation), but also that 2) cravings reduction, once achieved, reduced the ability of the treatments to influence the outcome (moderation), thus explaining how two treatments operating on a common pathway might not achieve greater improvement than either treatment alone. If both treatments operated on the same pathway, but there were no moderation, we would have expected the combination to have improved PDA more than either treatment alone.

The current results are theoretically sound, as naltrexone may have reduced craving by blocking the conditioned activation of endogenous opioids [35] while CBI might have alleviated craving via cognitive and behavioral coping skills, enhanced self-efficacy, or increased motivation for abstinence [16]. Results from numerous clinical trials have demonstrated that naltrexone reduces craving levels [8, 13, 36–38]. Furthermore, cognitive/emotional states, positive and negative cues, mental processes, mood, and self-efficacy all influence craving levels, and CBI address these aspects of recovery [16].

Some investigators have suggested that the common mechanism of craving reduction makes naltrexone and CBI ideal for use in combination [39]. However, if naltrexone and CBI worked through the same pathway, i.e., craving reduction, and if a threshold effect of cravings existed, then combining the two would not have improved outcomes. Perhaps patients could choose between a pharmaceutical and behavioral therapy, because some may have better outcomes when allowed to choose their own treatments [40]. However, there have been no preference trials for pharmaceutical compared to behavioral treatments to date, and this remains a rich area for research.

The COMBINE Study Research Group reported significant differences (compared to placebo) in average 16-week PDA of 5.5, 4.1, and 2.0, for naltrexone, CBI only, and the combination, respectively; these estimates differ slightly from those reported in Table 3. Because the COMBINE authors used mixed models, their results should be interpreted as a participant's average added benefit in PDA over time when given treatment vs. placebo, conditional on treatment site and baseline PDA [41]. Targeted Maximum Likelihood Estimation makes fewer assumptions about the underlying data structure than mixed models (e.g., mixed models assume normality whereas TMLE does not). Furthermore, the results using TMLE are interpreted as the average treatment effect if *all* participants received active treatment vs. placebo; e.g., the average PDA was 6.3 percentage points higher if all participants received naltrexone compared to if all participants received placebo. Importantly, TMLE results corroborated the original COMBINE results — both in terms of significance and pattern of treatment effects — despite the differences in modeling procedures.

In this study, craving reduction explained about half of treatment effects, which suggests that reducing cravings should greatly improve drinking outcomes. Some have argued that craving reduction is key to abstinence, and that understanding “situational craving,” or alcoholics' responses to cues in their favorite drinking environments would enhance current treatment [18]. Health care providers might consider working with patients to learn how to best control cravings, whether through naltrexone or CBI-type methods.

Limitations

First, COMBINE investigators measured craving with the Obsessive Compulsive Drinking Scale (OCDS), which asks about thoughts and impulses to drink. The OCDS does not include items specifically tapping the desire to drink, which some would argue is the core of the cravings construct. However, the OCDS did correlate with the desire for alcohol as measured by an analog scale [43]. Next, analyses excluded 142 participants due to missing cravings data. Though average PDA was lower among those missing cravings data,

missingness did not differ by treatment group, which implies that bias is likely non-differential. Finally, half of each of the four treatment groups received active acamprosate while the other halves received placebo acamprosate. This indicates potential heterogeneity within groups, although any bias is likely minimal since acamprosate did not significantly affect outcomes in the main effects trial [4].

Directions for future research

Future analyses should also assess other potential moderators and mediators, such as social network composition (e.g., the number of drinkers in participants' social networks) or dependence severity measures (e.g., as measured by the Alcohol Use Disorders Identification Test (AUDIT) [42]). Moderation of naltrexone effects by genetic factors also may be possible. For example, Monterosso et al. have reported that patients with high familial loadings for alcohol problems also may especially benefit from naltrexone [12]. Investigators studying treatment might consider combining naltrexone or CBI with treatments that work on mechanisms other than cravings, since targeting multiple mediators could yield better outcomes. Finally, the dependent variable examined here was percent days abstinent (PDA). Analyses also could include examination of how craving mediates other outcomes, such as time to next drinking day or continuous abstinence, as well as more distal outcomes, such as PDA one-year post-treatment.

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Table 1

Average percent days abstinent by treatment group and follow-up time

	Baseline Mean (SD)	0–4 weeks Mean (SD)	5–12 weeks Mean (SD)	13–16 weeks Mean (SD)
Placebo only	24.6 (23.9)	75.7 (28.7)	69.9 (33.7)	66.4 (35.4)
Naltrexone, no CBI	26.5 (24.7)	80.1 (25.9)	76.8 (31.7)	73.9 (32.6)
CBI, no naltrexone	24.8 (25.9)	78.0 (27.9)	76.2 (30.3)	72.8 (32.6)
CBI and naltrexone	25.2 (25.5)	74.9 (31.0)	75.7 (30.7)	74.6 (32.0)

Table 2

Average cravings by treatment group and follow-up time

	Baseline Mean (SD)	0–4 weeks Mean (SD)	5–12 weeks Mean (SD)	13–16 weeks Mean (SD)
Placebo only	26.8 (8.4)	13.5 (9.4)	12.7 (9.3)	11.9 (9.1)
Naltrexone, no CBI	26.4 (8.3)	11.8 (9.0)	10.3 (8.5)	10.8 (9.6)
CBI, no naltrexone	27.1 (7.8)	13.5 (8.9)	11.2 (8.5)	10.9 (8.6)
CBI and naltrexone	26.8 (8.3)	12.3 (8.6)	10.8 (9.2)	10.4 (8.9)

Table 3

Average increases in percent days abstinent (13–16 weeks post-baseline) relative to placebo group

Sample	Naltrexone RD ^a (SD)	P-value	CBI RD (SD)	P-value	Combination RD (SD)	P-value
Total effects, entire sample	6.3 (2.2) (N=302)	0.005**	5.8 (2.2) (N=305)	0.009**	4.6 (2.3) (N=309)	0.043*
Total effects, excluding those missing Cravings	7.9 (2.8) (N=209)	0.005***	5.9 (2.8) (N=236)	0.033*	9.0 (2.8) (N=213)	0.002***

^aRisk Difference = Difference in mean PDA for treatment vs. placebo

* P<0.05

** P<0.01

Table 4
Extent to which treatment effects on 13–16 week percent days abstinent is explained by 4- and 12-week cravings

Craving Levels		Naltrexone N = 205 RD ^a (SD)	P-value	CBI N = 236 RD (SD)	P-value	Combination N = 213 RD (SD)	P-value
4-week Cravings	Direct Effect	3.3 (2.4)	0.170	5.7 (2.3)	0.012 *	6.7 (2.3)	0.003 **
	Indirect Effect	3.9 (1.2)	0.001 **	−0.001 (1.2)	0.927	1.4 (1.1)	0.184 *
12-week Cravings	Direct Effect	4.1 (2.2)	0.059 †	2.3 (2.0)	0.250	5.4 (2.0)	0.008 *
	Indirect Effect	4.9 (1.7)	0.004 *	3.9 (1.7)	0.021 *	3.5 (1.5)	0.019 *
4- & 12-week Cravings	Direct Effect	3.7 (2.1)	0.078 †	3.0 (1.9)	0.115	4.7 (1.9)	0.015 *
	Indirect Effect	4.2 (1.7)	0.015 *	2.8 (1.8)	0.111	4.3 (1.8)	0.016 *
% effect explained by 4- & 12-week Cravings		53.2%		51.7%		47.8%	

^a Risk Difference = Difference in mean PDA for treatment vs. placebo

† P<0.10

* P<0.05

** P<0.01

Table 5

Differences in 13–16 week percent days abstinent for high versus low craving levels

Craving Levels	Naltrexone N = 209 RD ^a (SD)	P-value	CBI N = 236 RD (SD)	P-value	Combination N = 213 RD (SD)	P-value
4-weeks						
Low Cravings	0.73 (3.5)	0.835	0.15 (3.2)	0.963	1.0 (3.3)	0.764
High Cravings	10.3 (4.0)	0.011**	12.9 (3.8)	0.0007***	14.6 (4.0)	0.0003**
12-weeks						
Low Cravings	0.75 (2.8)	0.792	0.41 (2.2)	0.851	2.4 (2.1)	0.267
High Cravings	10.7 (4.1)	0.009**	6.1 (4.0)	0.128	9.6 (4.3)	0.0256*

^a Risk Difference = Difference in mean PDA for treatment vs. placebo

† P<0.10

* P<0.05

** P<0.01