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Social Network Moderators of Naltrexone and Behavioral Treatment Effects on Heavy Drinking in the COMBINE Study

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Abstract

Background—Oral naltrexone is an efficacious medication for treatment of alcohol dependence, but small effect sizes and variability in outcomes suggest the presence of person-level moderators of naltrexone response. Identification of contextual or psychosocial moderators may assist in guiding clinical recommendations. Given the established importance of social networks in drinking outcomes, as well as the potential effects of naltrexone in reducing cue reactivity which may be especially important among those with more heavy drinkers and more alcohol cues in their networks, we examined pretreatment social network variables as potential moderators of naltrexone treatment effects in the COMBINE study.

Methods—The sample included all COMBINE study participants in medication conditions with full data on the Important People Inventory (IPI) and covariates at intake ($N = 1,197$). The intake IPI assessed whether participants had any frequent drinkers in their network and the average frequency of contact with these drinkers. The effects of treatment condition, pretreatment network variables, and their interactions on percent heavy drinking days were tested in hierarchical linear models, controlling for demographics and baseline clinical covariates.

Results—In treatment conditions involving medical management and combined behavioral intervention (CBI), the effects of active naltrexone on heavy drinking were significantly greater for individuals with frequent drinkers in their network ($z = -2.66, p < 0.01$) and greater frequency of contact with those drinkers ($z = -3.19, p < 0.01$). These network variables did not moderate the effects of active naltrexone without CBI.

Conclusions—When delivered in conjunction with behavioral interventions, naltrexone can be more potent for alcohol-dependent adults who have greater contact with frequent drinkers prior to treatment, which may indicate patterns of environmental exposure to alcohol. Contextual, social risk factors are a potential avenue to guide personalized treatment of alcohol dependence.

Keywords

Alcohol Dependence; Naltrexone; Pharmacotherapy; Social Network; Moderators

Common approaches for the treatment of alcohol dependence include individual or group psychotherapy (Martin and Rehm, 2012; Orchowski and Johnson, 2012), 1 of 4 FDA-approved medications (Garbutt, 2009), Alcoholics Anonymous (AA) or other mutual help organizations (Kelly and Yeterian, 2012), or some combination of these approaches. Despite major advances in research methodology and the development of effective psychotherapies and medications, many individuals who receive empirically supported treatment for alcohol dependence do not experience sustained reductions in drinking and associated problems (Litten et al., 2012). Consequently, a burgeoning area of clinical research is the investigation of factors that mediate or moderate response to various treatments (Babor, 2008; Kranzler and Edenberg, 2010; Longabaugh, 2007). By explaining the processes through which change occurs (mediation) or why some individuals have better response to a treatment (moderation), these studies inform both future research investigations and clinical practice. As more knowledge is gained regarding differential response to various treatments, more personalized interventions can be delivered (Kranzler and McKay, 2012).

Oral naltrexone is 1 FDA-approved, efficacious medication for the treatment of alcohol dependence (Anton et al., 1999; Maisel et al., 2013), but despite its overall efficacy, many individuals continue drinking during and following naltrexone treatment. The effect sizes of naltrexone in meta-analyses are modest (Maisel et al., 2013), and rates of naltrexone compliance are typically poor (Swift et al., 2011). While it is a useful tool for cessation or reduction in alcohol use, particularly for heavy drinking, the wide variability in outcomes suggests individual difference factors may moderate response to naltrexone.

Previous investigations of naltrexone moderators have focused primarily on characteristics linked to biological vulnerability (Anton et al., 2008; Capone et al., 2011; Oroszi et al., 2009), including the μ -opioid receptor gene (OPRM1), with the Asp40 allele associated with greater naltrexone-induced blunting of alcohol reward (Ray and Hutchison, 2007; Setiawan et al., 2011) and stronger clinical response to naltrexone (Anton et al., 2008; Oslin et al., 2003). Fewer studies have examined psychosocial moderators of naltrexone effects. Male participants had greater naltrexone-induced blunting of stimulating alcohol effects (Ray et al., 2008), current smokers had stronger clinical response to naltrexone (Fucito et al., 2012), and longer duration of abstinence has predicted stronger effects of naltrexone on heavy drinking (Maisel et al., 2013). However, as noted in a recent review, the current evidence for naltrexone moderators is still insufficient for guiding treatment (Garbutt et al., 2014). Further empirical evidence of psychosocial moderators of naltrexone, especially those that are easily assessed in clinical settings, could assist in developing more targeted clinical strategies for the treatment of alcohol dependence.

Potential psychosocial moderators could be identified by considering of naltrexone's hypothesized and empirically supported mechanisms of action. Naltrexone reduces alcohol cravings (Ray et al., 2010), possibly due to attenuation of reactivity in the presence of alcohol cues (Lukas et al., 2013; Myrick et al., 2008). Naltrexone has reduced cravings in

human alcohol-administration research (Kruse et al., 2012), attenuated cue-induced brain activation (Myrick et al., 2008), and led to reductions in drinking that were mediated by craving (Subbaraman et al., 2013). One psychosocial factor, that is, could be related to cue-induced craving is exposure to other drinkers. Individuals with prodrinking social networks typically have poorer treatment outcomes (Litt et al., 2007; Longabaugh et al., 2010), and pretreatment networks have moderated the effects of psychosocial interventions (Wu and Witkiewitz, 2008). The influence of social networks on drinking outcomes may act, in part, via greater craving due to more frequent exposure to alcohol cues and opportunities to drink (Hunter-Reel et al., 2009; Kelly et al., 2011). Alcohol cues within a social situation context are associated with greater appetitive and arousal responses, as compared to cues presented in the absence of a social context (Nees et al., 2012). Consequently, the effects of naltrexone may be stronger in individuals with more frequent drinkers in their network, who may frequently encounter alcohol cues and experience greater benefit from the attenuation of cue reactivity and craving provided by naltrexone.

This study examined whether baseline social network drinking variables moderated response to naltrexone in the context of a multisite clinical trial of medication and behavioral treatment for alcohol dependence. We hypothesized that the effects of active naltrexone on heavy drinking would be larger for participants who had frequent drinkers in their network and more frequent contact with these drinkers prior to entering treatment. We also explored the relationship between network variables and craving at baseline, expecting networks with frequent drinkers and frequent contact with these drinkers to be associated with greater craving. A secondary aim was to examine whether any interactions between network variables and naltrexone persisted during post treatment follow-up.

MATERIALS AND METHODS

Participants

This study involved secondary analyses of the COMBINE study, a multisite, randomized clinical trial that was designed to examine the unique and combined efficacy of naltrexone, acamprostate, and behavioral treatment for alcohol dependence. Full details of the original trial were provided in previous reports (Anton et al., 2006) and are described briefly here. Participants were recruited from outpatient and inpatient referral sources at 8 study sites and in the community. Inclusion criteria included a DSM-IV diagnosis of alcohol dependence, a period of 4 to 21 days of abstinence prior to the baseline assessment, frequent drinking (>14 drinks per week for women, >21 drinks per week for men), and occurrence of at least 2 heavy drinking days in a 30-day period during the previous 90 days. Key exclusion criteria were current (i.e., past 90 day) abuse or dependence on other drugs, unstable medical problems, or current psychiatric disorders requiring medication. This study excluded the combined behavioral intervention (CBI)-only condition ($n = 157$) and 29 participants from the remaining COMBINE sample who were missing responses from the baseline Important People Inventory ($n = 17$), craving assessment (IPI) ($n = 7$), or demographic covariates ($n = 5$). Participants in the current sample ($N = 1,197$) averaged 44 years of age, 69% were male, and 43% were married. Participants were primarily (77%) Caucasian, with 11% Hispanic, 8% African-American, and 4% "other" ethnicity.

Procedures

Following inclusion/exclusion screening, informed consent, and completion of a baseline assessment protocol, participants underwent random assignment to 1 of 9 treatment conditions, each involving 16 weeks of treatment. Four conditions ($n = 594$) involved a maximum of 9 brief medical management (MM) appointments and either active naltrexone and acamprosate, naltrexone and placebo, acamprosate and placebo, or double placebo. Four conditions ($n = 603$) involved MM and the same 4 combinations of pharmacotherapy with an adjunct CBI, which involved up to 20 sessions integrating cognitive-behavioral therapy, motivational enhancement, and support system involvement. There was also a CBI-alone condition without MM or medication ($n = 157$) excluded from these analyses due to our primary interest in examining active naltrexone effects. Participants were followed for 1 year post treatment; this study focuses only on the active treatment phase.

Measures

Measures of drinking outcomes were obtained at baseline and monthly during treatment, while predictor variables and covariates were obtained at baseline.

Drinking Outcomes—In this study, the primary drinking outcome was percent heavy drinking days (PHDD), assessed with the Form-90 (Tonigan et al., 1997) at baseline and the Timeline Follow-Back (Sobell and Sobell, 1992) during treatment. Within-treatment measures of PHDD assessed at monthly intervals captured drinking during the previous 4 weeks. Post treatment measures of PHDD were assessed at 3 time points during the year after treatment (weeks 26, 52, and 68 postrandomization). We selected PHDD as the primary outcome measure due to the relatively stronger empirical basis for naltrexone effects on heavy drinking as compared to total abstinence or frequency of any drinking (Maisel et al., 2013).

Social Network Drinking—Participants were administered the IPI (Longabaugh et al., 2010) at baseline prior to treatment assignment. The IPI involves listing up to 10 individuals who (i) are important to the participant and (ii) the participant has contacted in the last 4 months. Our goal was to test relatively basic indicators that separately reflected the (i) presence of frequent drinkers in one's social network and (ii) the frequency of contact with these drinkers. From the 9 IPI items reported for each network member, we utilized 2 items: drinking frequency, which ranged from 0 ("not in the past 4 months") to 7 ("daily"), and frequency of contact, which ranged from 1 ("once in past 4 months") to 7 ("daily"). From these responses, 2 network variables were computed. The first was a dichotomous variable that reflected whether participants had at least 1 weekly drinker in their network ("weekly drinker network"). The second variable reflected the average intensity of contact with these drinkers, computed as the mean contact score across all network members who drank at least once a week ("drinker contact frequency"). While the IPI was repeated at the end of treatment assessment, we were most interested in the baseline IPI because this study was designed to identify moderators of treatment efficacy, which could potentially be identified prior to treatment and ideally inform treatment decisions. End of treatment IPI would not be useful for informing clinicians at the start of treatment regarding which treatment may be most effective.

Baseline Craving—Baseline craving was assessed with the Obsessive Compulsive Drinking Scale (OCDS). This self-report scale includes 14 items rating the frequency and intensity of alcohol-related thoughts and urges, efforts to control these urges, and quantity and frequency of drinking in the last week (Anton et al., 1996). Similar to prior research (Witkiewitz et al., 2011), we removed the 2 drinking items because our interest was in utilizing the OCDS as a direct measure of craving intensity/frequency. The total score of the remaining 12 items was used as the craving score.

Treatment Condition—Our primary interest was to determine whether the effects of active naltrexone in the COMBINE study were moderated by weekly drinker networks and drinker contact frequency. We were also interested in examining whether providing behavioral skills training could further enhance the naltrexone effects. To maintain maximal statistical power and avoid excessive analysis of the 9-cell design and all potential interactions, treatment conditions were placed into 4 distinct groups: (i) MM, placebo naltrexone, and no CBI ($n = 297$), (ii) MM+ placebo naltrexone + CBI ($n = 301$), (iii) MM + naltrexone + no CBI ($n = 297$), and (iv) MM + naltrexone + CBI ($n = 302$). The CBI-only group was excluded from analyses. Using dummy-coded contrast variables in multilevel models (described further below), this strategy allowed us to examine the specific moderating effects of active naltrexone both with and without CBI, similar to previous studies of moderators in the COMBINE study (Greenfield et al., 2010). Moreover, we were interested in naltrexone with or without CBI because CBI focuses explicitly on skills for managing high-risk social networks (e.g., drink refusal skills), whereas naltrexone is a medication that does not include skills training. If the cue-reactivity aspects of naltrexone are sufficient for reducing the impact of a heavy drinking social network then we were interested in that possibility and wanted to separate the cue-reactivity aspects of naltrexone without CBI to the combination of cue-reactivity reduction and skills training for reducing the influence of heavy drinkers in one's network.

Covariates—Baseline covariates were selected to represent baseline demographic and clinical variables previously associated with drinking outcomes in the COMBINE study or other alcohol treatment research including gender, age, marital status (currently married vs. not), and alcohol dependence severity, as indicated by the number of alcohol dependence criteria endorsed on the Structured Clinical Interview for DSM-IV (First et al., 1997).

Statistical Analysis

Our hypotheses were examined using hierarchical linear models (HLMs), an appropriate method for the analysis of multiple time points nested within individuals. Models included random person-level intercepts to account for clustering of observations and random time slopes to account for individual variability in PHDD over time. Pretreatment levels of heavy drinking were incorporated into the model by including Week 0 in HLM. Separate models examined the treatment and follow-up phases. During treatment time was coded in 4-week increments, with each participant providing up to 5 observations of PHDD (baseline and Weeks 4, 8, 12, and 16), while 3 observations of PHDD were obtained during follow-up (Weeks 26, 52, and 68). All covariates, network variables, and treatment condition indicators were time-invariant. Although summary statistics of PHDD did indicate positive

skew, model residuals did not violate HLM assumptions. Consequently, PHDD was not transformed for statistical models. All available data were included, a preferred method for handling missing data assumed missing-at-random (Hallgren and Witkiewitz, 2013; Schafer and Graham, 2002). Similar to previous reports of the COMBINE study (Witkiewitz et al., 2011), restricted maximum-likelihood estimation was utilized to account for the multisite design. All statistical analyses were performed in STATA 10.1 (StataCorp, 2007).

Preliminary analyses examined summary statistics and correlations between baseline drinking, network variables, and craving. We then estimated a covariate model of within-treatment PHDD that examined the effects of time (linear and quadratic), gender, age, marital status, alcohol dependence severity, baseline craving, and treatment condition on PHDD. The main effects of weekly drinker network and drinker contact frequency (grand-mean centered) were then tested as time-invariant, fixed effects in separate HLM models. Moderation between these variables and active naltrexone was examined by testing the interaction of each network variable with the treatment condition indicators, with active naltrexone conditions compared to the matching placebo naltrexone condition (CBI or no CBI) as a referent in the multilevel model, controlling for the other treatment conditions and interactions. The resulting model controlled for the effects of the 4 treatment groups on PHDD while estimating whether the network drinking variables moderated the specific effects of active naltrexone.

RESULTS

Summary of Baseline Network Variables

Of the 1,197 participants in the current sample, 81% ($n = 970$) had a “weekly drinker network,” reporting at least 1 weekly drinker in their social network at baseline. The mean drinker contact frequency score was 4.43 ($SD = 2.39$), with the median slightly greater (5.17), indicating that over half of the sample contacted weekly drinkers in their network greater than “once or twice a week.” A small but notable percentage of the sample (14%) contacted frequent drinkers on a daily basis. As expected due to random assignment, analyses revealed no statistically significant treatment group differences on weekly drinker network, $X^2(3) = 1.86$, $p = 0.60$, or drinker contact frequency, $F(3, 1,193) = 0.68$, $p = 0.56$, indicating the treatment groups were similar on these variables at baseline.

Baseline Craving, Heavy Drinking, and Network Drinking

Table 1 displays Pearson and point-biserial correlations between baseline craving, heavy drinking, weekly drinker network, and drinker contact frequency. Greater baseline craving was significantly correlated with greater heavy drinking ($r = 0.10$, $p < 0.001$) and, contrary to our expectation, no weekly drinker network ($r = -0.07$, $p = 0.02$) and lower drinker contact frequency ($r = -0.09$, $p = 0.002$). We suspected that lower craving scores in patients with high-risk networks may have been partially due to suppressed responses on the 2 OCDS social interference items, as persons with networks supportive of drinking might experience less interpersonal distress related to their alcohol use. In post hoc analyses of OCDS scores after removing the 2 social interference items, the correlation was reduced and no longer significant for weekly drinker network ($r = -0.05$, $p = 0.07$), and reduced for

drinker contact frequency ($r = -0.08, p < 0.004$), partially supporting this assumption. Baseline heavy drinking was not associated with weekly drinker network ($r = 0.02, p = 0.52$) or drinker contact frequency ($r = 0.03, p = 0.25$). Because greater craving was significantly associated with greater heavy drinking, weekly drinker network, and drinker contact frequency at baseline, all subsequent models controlled for baseline craving.

Covariate Effects

As shown in Table 2, the preliminary covariate model indicated that linear time, quadratic time, marital status, and baseline craving were significant predictors of within-treatment PHDD, while age, gender, and alcohol dependence severity were not. Being currently married ($b = -2.75, SE = 1.07, \beta = 0.08, p = 0.01$) and having lower baseline craving ($b = 0.31, SE = 0.08, \beta = 0.07, p < 0.001$) predicted lower PHDD during treatment.

Treatment Condition Effects on Heavy Drinking

When examining the treatment group contrasts, we found that MM + naltrexone without CBI had significantly lower PHDD than MM + placebo naltrexone without CBI ($b = -2.98, z = -2.00, \beta = -0.09, p = 0.04$), while PHDD did not differ significantly between the active and placebo naltrexone conditions with CBI ($b = -0.18, z = 1.48, \beta = -0.005, p = 0.90$). Postmodel Wald tests also indicated no statistically significant differences in PHDD between the treatment groups involving active naltrexone with no CBI, active naltrexone with CBI, or placebo naltrexone with CBI, similar to prior reports of PHDD in the COMBINE study (Greenfield et al., 2010).

Main Effects of Weekly Drinker Network and Drinker Contact Frequency

Controlling for linear and quadratic time, age, gender, marital status, alcohol dependence severity, baseline craving, and treatment condition, weekly drinker network did not predict greater PHDD ($b = 1.91, SE = 1.35, \beta = 0.06, p = 0.16$), while greater drinker contact frequency had a threshold but nonsignificant association with greater PHDD ($b = 0.42, SE = 0.22, \beta = 0.03, p = 0.06$). These results indicated that controlling for baseline covariates and treatment condition, there were no statistically significant associations between having weekly drinkers in one's network or frequency of contact with drinkers and heavy drinking during treatment.

Moderation of Naltrexone Effects by Weekly Drinker Networks and Contact Frequency

The goal of these analyses was to separately test whether having a weekly drinker network and greater frequency of contact with network drinkers resulted in stronger naltrexone effects on heavy drinking during treatment. Interaction terms between the treatment group indicators and network drinking variables were tested in HLMs, with the active naltrexone condition compared to the matching placebo condition (with or without CBI) in all analyses. As shown in Table 3, weekly drinker network significantly moderated the effects of active naltrexone in the CBI conditions ($b = -10.20, z = -2.66, \beta = -0.30, p = 0.008$). As compared to the MM + placebo naltrexone + CBI group, the combination of MM + active naltrexone + CBI resulted in relatively lower PHDD for participants with at least 1 weekly drinker in their network at baseline (Fig. 1). Weekly drinker network did not moderate the effects of MM +

naltrexone without CBI ($b = -0.44$, $z = -0.12$, $\beta = 0.01$, $p = 0.91$), indicating that the relative effect of active naltrexone in the non-CBI conditions was not altered by the presence of weekly drinkers in one's social network.

Moderation analyses of drinker contact frequency revealed similar results, with evidence of significant moderation of naltrexone effects found in the CBI conditions only. As compared to MM + placebo naltrexone + CBI, the relative advantage of MM + active naltrexone + CBI was greater for participants with greater drinker contact frequency ($b = -2.00$, $z = -3.19$, $\beta = -0.14$, $p = 0.001$). As shown in Fig. 2, the effect of active naltrexone on PHDD in the CBI conditions was incrementally greater for participants with greater drinker contact frequency, with a 2 standard deviation increase in contact frequency score (equivalent to 4.77) associated with an additional 0.28 standard deviation reduction in heavy drinking due to active naltrexone, equivalent to 9.4 PHDD. In the non-CBI conditions, the effects of active naltrexone were relatively consistent and not significantly moderated by drinker contact frequency ($b = -0.11$, $z = -0.18$, $\beta = -0.01$, $p = 0.86$). Overall, the results indicated that more frequent pretreatment contact with other drinkers was associated with greater benefits of active naltrexone on PHDD, but only in the context of adjunctive CBI.

Post treatment Follow-Up

A secondary goal was to examine whether network risk factors moderated the effects of naltrexone in the post-treatment follow-up period. In HLMs examining all post-treatment measures of PHDD (Weeks 26, 52, and 68), weekly drinker network ($b = 4.12$, $SE = 2.31$, $\beta = 0.12$, $p = 0.07$) and drinker contact frequency ($b = 0.01$, $SE = 0.01$, $\beta = 0.04$, $p = 0.11$) did not predict PHDD during the follow-up phase. Furthermore, weekly drinker network did not moderate the effects of naltrexone on post treatment PHDD, with CBI ($b = -2.37$, $SE = 5.43$, $p = 0.66$) or without CBI ($b = -4.29$, $SE = 5.22$, $p = 0.41$). Results for drinker contact frequency were similar, as it did not moderate naltrexone effects on post treatment PHDD, with CBI ($b = -0.55$, $SE = 0.89$, $p = 0.54$) or without CBI ($b = -0.50$, $SE = 0.85$, $p = 0.56$). The interaction between these social network factors and naltrexone in the CBI conditions thus appeared to be limited to the active medication phase of treatment.

DISCUSSION

In this secondary analysis of the COMBINE study, we examined whether 2 pretreatment social network characteristics moderated the effects of naltrexone, with or without behavioral intervention, for alcohol dependence. In the context of adjunctive CBI, active versus placebo naltrexone reduced heavy drinking to a greater extent for participants who had weekly drinkers in their network and contacted these drinkers frequently prior to treatment. Without adjunctive CBI, active naltrexone was consistently more effective than placebo and not moderated by these network factors. Because these moderating effects did not persist into post treatment follow-up, they appear to be limited to the treatment phase when participants were receiving active medication. Overall, these findings provide support for the overall efficacy of naltrexone on heavy drinking during treatment, and preliminary support for stronger naltrexone effects in combination with behavioral treatment for patients with greater social network risk.

Patients with greater pretreatment social risk typically have poorer outcomes during alcohol treatment (Litt et al., 2007; Longabaugh et al., 2010). One plausible explanation for the association between baseline network drinking and poorer treatment outcomes is that individuals with more heavy drinkers in their networks may be especially prone to experiencing alcohol cues. As such, we expected that these negative social influences would contribute to poorer outcomes, unless these effects were countered by the presence of efficacious medication that attenuated reactivity to cues, particularly social context cues that tend to increase appetitive and arousing responses among individuals with alcohol dependence (Nees et al., 2012).

The results of this study partially supported our hypotheses, as we found significant moderation of naltrexone effects but only in the presence of adjunctive CBI. For the outcome of PHDD, the efficacy of MM, CBI, and active naltrexone was highly dependent on social network risk, as it was the best treatment for participants who contacted drinkers daily, but the worst for participants who had no drinker contact. We did not expect to find such poor outcomes for participants with low network risk in this condition, but other studies have found similar matching effects in which relatively intensive treatments are less effective for individuals that may not warrant highly structured support (Klein et al., 2002; Thornton et al., 1998; Tiet et al., 2007). It may also be the case that patients with lower social network risk may be engaging in excessive heavy drinking prior to treatment for other reasons (e.g., intrapersonal risk factors, including negative affect drinking) and may not benefit as much from the attenuation of cue reactivity and craving provided by naltrexone. The significant moderation of active naltrexone effects in CBI was also influenced by the pattern of outcomes in the MM, CBI, and placebo naltrexone group, where heavy drinking outcomes were relatively good for patients without frequent drinker contact (9.9 PHDD), but worse for those in daily contact with frequent drinkers (19.1 PHDD). The idea that certain medications may be more or less effective for certain types of drinkers has been proposed (Johnson, 2010). In prior reports of this sample, active naltrexone did not significantly improve drinking outcomes when patients also received MM and CBI (Anton et al., 2006; Greenfield et al., 2010), but the current study suggests that naltrexone in combination with a behavioral intervention may be less effective for individuals with lower social network risk, and incrementally more effective for those with greater network risk.

One rationale for predicting greater naltrexone response in patients with greater social risk was that these patients would experience greater craving, in response to more frequent exposure to alcohol-related cues. Instead, baseline craving was significantly and negatively correlated with drinker networks and drinker contact, although these correlations were weak in size ($r = -0.07$ and -0.09), perhaps driven by the large sample size of this study, and further reduced after removing the social interference items. These negative associations with craving were counterintuitive; given our hypotheses, however, it is plausible individuals who have not stopped drinking heavily will likely respond very differently to a questionnaire of craving than those who have stopped drinking or are trying to reduce their drinking in treatment. Prior research in actively drinking treatment-seeking alcohol-dependent subjects has also found similar counterintuitive findings, where greater subjective social support was associated with greater alcohol craving (Chakravorty et al., 2010).

Furthermore, a single baseline measure of craving may not accurately capture the frequency or intensity of craving tied to event-level contact with alcohol or other drinkers. For example, ecological momentary assessment studies in adolescents have found that the presence of peers corresponded with increased craving (Ramirez and Miranda, 2014) and that naltrexone blunted alcohol cue-related craving (Miranda et al., 2014). Using this methodology during treatment of adults might elucidate the direct relationship between drinker contact and event-level cue reactivity and craving that could not be examined directly with this study design.

It is important to note that in this study, pretreatment social network factors were treated as static variables, when in reality these characteristics often shift and some participants could have made significant changes in social networks during treatment. In the COMBINE study, social network measures were obtained at end-of-treatment and follow-up. Consideration of network changes over time could demonstrate whether naltrexone is more effective for participants who struggle to reduce their contact with other drinkers; however, such a test would not be useful for informing clinicians on the optimal treatment combination for drinkers with high-risk social networks at the start of treatment. The goal of the current study was to assess network variables as a potential moderator of treatment efficacy to help inform treatment selection, thus assessing social network changes after treatment was not consistent with this goal. That being said, it would be useful for future studies to incorporate changing social network variables as a moderator of naltrexone treatment response within the context of an intensive longitudinal design (e.g., ecological momentary assessment), such that it could be further examined whether naltrexone blunted craving responses in the moment of exposure to a heavy drinking social network member.

Because these effects were relatively small in relation to the overall changes in heavy drinking, and the persistence of these effects into post treatment follow-up are unknown, these findings should be considered preliminary and are in need of replication. In particular, while this study provides some rationale to provide naltrexone to patients with frequent-drinking networks, it is unclear whether the benefit associated with active naltrexone in these patients is cost-effective and merits incorporation into clinical decision making. This study does provide some evidence that patients without any frequent drinkers in their network may have similar heavy drinking outcomes from active naltrexone or behavioral intervention alone and thus may be ideal candidates for a single-modality treatment approach.

The study has several limitations, including restricted generalizability due to the limited demographic range of the sample and the rigorous conditions of the original clinical trial. In particular, the MM and CBI interventions were relatively resource-intensive and may not be feasible in nonresearch settings. Future studies are needed to test these patient–treatment interactions in a structure that more closely approximates clinical practice, which may involve less intensive behavioral and medical support. Importantly, the IPI does not distinguish between in person versus remote contacts with network drinkers. Studies that assess event-level exposure to alcohol and/or other drinkers might capture contextual contact with others' drinking or other alcohol cues more accurately. Due to missing IPI and demographic data, 29 participants (2% of the total COMBINE study sample) were excluded

from the analyses, which is an additional limitation. It is unlikely that including this 2% would have greatly influenced the results, but we note that the findings are applicable only to those with complete demographic, IPI, and OCDS data at baseline. Our conclusions are limited to heavy drinking outcomes only, as we did not examine other outcomes assessed in the COMBINE study. Finally, while this study found preliminary evidence for interaction effects that could potentially guide personalized treatment, these effect sizes of these interactions were relatively small, and replication of these findings is advised before guiding clinical practice.

While prior COMBINE reports did not reveal incremental advantages of combining active naltrexone and CBI on a number of drinking outcomes (Anton et al., 2006; Donovan et al., 2008), our findings suggest that supplementing behavioral interventions with naltrexone may be warranted specifically for individuals with elevated pretreatment contextual/interpersonal risk for heavy drinking. Moreover, this is the first known evidence that combined pharmacotherapy and psychotherapy effects on alcohol treatment outcomes may be moderated by contextual interpersonal factors. Future research should continue to explore potential moderators of alternative treatments, which will assist in bringing alcohol dependence treatment closer to a personalized medicine approach (Kranzler and McKay, 2012).

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Fig. 1. Interaction between weekly drinker network and treatment condition effects on percent heavy drinking days during treatment.

Fig. 2. Interaction between drinker contact frequency and treatment condition effects on percent heavy drinking days during treatment.

Table 1Correlations Between Heavy Drinking, Craving, and Social Network Variables at Baseline ($N = 1,197$)

	Percent heavy drinking days	OCDS	Weekly drinker network
Obsessive Compulsive Drinking Scale (OCDS) score	0.10***		
Weekly drinker network	0.02	-0.07*	
Drinker contact frequency	0.03	-0.09**	0.89***

*
 $p < 0.05$.**
 $p < 0.01$.***
 $p < 0.001$.

Table 2

Main Effects of Covariates on Percent Heavy Drinking Days During Active Treatment in the COMBINE Study ($N = 1,197$)

Covariate	<i>b</i> (SE)
Week (linear)	−9.93 (0.17)***
Week (quadratic)	0.47 (0.01)***
Marital status (married vs. not)	−2.75 (1.07)*
Age	0.09 (0.05)
Male gender	−0.46 (1.14)
Alcohol dependence severity	0.33 (0.46)
Baseline craving	0.31 (0.08)***

*
 $p < 0.05$;

 $p < 0.001$.

Table 3

Results of Full Model Examining Covariates, Treatment Condition, Baseline Network Variables, and Interactions on Percent Heavy Drinking Days During Active Treatment in the COMBINE Study ($N = 1,197$)

	Model with weekly drinker network b (SE)	Model with drinker contact frequency b (SE)
Week linear effect	-9.93 (0.17) ***	-9.93 (0.17) ***
Week quadratic effect	0.47 (0.01) ***	0.47 (0.01) ***
Marital status (married vs. not)	-2.62 (1.10) *	-2.67 (1.10) *
Age	0.09 (0.05)	0.09 (0.05)
Male gender	-0.28 (1.14)	-0.26 (1.14)
Alcohol dependence severity	0.35 (0.46)	0.35 (0.46)
Baseline craving	0.32 (0.08) ***	0.32 (0.08) ***
Treatment group ^a		
MM + Naltrexone + CBI	8.16 (3.47) *	8.71 (3.17) **
MM + Naltrexone no CBI	1.92 (3.30)	3.91 (3.03)
MM + placebo naltrexone no CBI	4.46 (3.42)	6.33 (3.14) *
Network main effect	5.78 (2.63) *	1.38 (0.43) ***
Network interaction with treatment group		
MM + Naltrexone + CBI	-10.20 (3.83) **	-2.00 (0.63) ***
MM + Naltrexone no CBI	-3.18 (3.69)	-1.04 (0.61)
MM + placebo naltrexone no CBI	-2.73 (3.79)	-0.93 (0.62)

CBI, combined behavioral intervention; MM, medical management.

^aReference group is MM + placebo naltrexone + CBI ($n = 301$), in comparison to MM + placebo naltrexone + no CBI ($n = 297$), MM + naltrexone + no CBI ($n = 297$), and MM + naltrexone + CBI ($n = 302$).

* $p < 0.05$,

** $p < 0.01$,

*** $p < 0.001$.