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Meta-analysis of naltrexone and acamprosate for treating alcohol use disorders: When are these medications most helpful?

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Abstract

Aims—Although debates over the efficacy of oral naltrexone and acamprosate in treating alcohol use disorders tend to focus on their global efficacy relative to placebo or their efficacy relative to each other, the underlying reality may be more nuanced. This meta-analysis examined *when* naltrexone and acamprosate are most helpful by testing: (1) the relative efficacy of each medication given its presumed mechanism of action (reducing heavy drinking versus fostering abstinence) and (2) whether different ways of implementing each medication (required abstinence before treatment, detoxification before treatment, goal of treatment, length of treatment, dosage) moderate its effects.

Methods—A systematic literature search identified 64 randomized, placebo-controlled, English-language clinical trials completed between 1970 and 2009 focused on acamprosate or naltrexone.

Results—Acamprosate had a significantly larger effect size than naltrexone on the maintenance of abstinence, and naltrexone had a larger effect size than acamprosate on the reduction of heavy drinking and craving. For naltrexone, requiring abstinence before the trial was associated with larger effect sizes for abstinence maintenance and reduced heavy drinking compared to placebo. For acamprosate, detoxification before medication administration was associated with better abstinence outcomes compared to placebo.

Conclusions—In treatment for alcohol use disorders, acamprosate has been found to be slightly more efficacious in promoting abstinence and naltrexone slightly more efficacious in reducing heavy drinking and craving. Detoxification before treatment or a longer period of required abstinence before treatment is associated with larger medication effects for acamprosate and naltrexone, respectively.

Debates over the utility of oral naltrexone and acamprosate often focus on global efficacy (i.e., does each medication work better than placebo?) or relative efficacy (i.e., does one medication work better than the other?). However, in practice, knowledge of global or even relative efficacy may not be enough; clinicians may be most interested in *when* each medication is more efficacious. For example, if a patient is focused on maintaining abstinence, would naltrexone or acamprosate be more helpful? If acamprosate is chosen, should it be administered only after the patient has been detoxified? A more nuanced

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approach to understanding when each medication is most efficacious will help to move this debate forward and should facilitate the implementation of both medications.

Despite recommendations to consider oral naltrexone and acamprosate in various treatment guidelines (1-3), the proportion of people with alcohol use disorders receiving these medications has been very low (4-6). Several reviews and meta-analyses have reported small or mixed effects for each medication (7-14), and treatment providers cite concerns over efficacy as one barrier to greater medication use (5). Instead of further tests of the global or relative efficacy of each medication, clinicians and researchers need to know in what ways and under what circumstances each medication is more helpful.

Different Outcomes, Different Effects? Abstinence, Heavy Drinking, and Craving

Differences in the pharmacological properties of naltrexone and acamprosate have led to the hypothesis that each medication is more effective on certain drinking outcomes than on others (13). Naltrexone is a “highly selective” opioid antagonist thought to block endogenous opioids triggered by alcohol (15, p. 597). Although the mechanism is not completely understood, naltrexone may work by decreasing dopaminergic activity (16). Naltrexone is therefore hypothesized to reduce craving and help prevent relapse to heavy drinking by reducing the rewarding effects of alcohol if drinking does occur (8, 16, 17). Acamprosate is thought to modulate the glutamate system and promote abstinence by “resetting” the balance between the GABA and glutamate systems that is disrupted in alcohol use disorders (18, p. 364). Because of these properties, it is believed to be ineffective if the patient starts drinking again. Although it is sometimes called an anti-craving medication, its impact on craving tends to be mixed (19, 20). Acamprosate is therefore hypothesized to be more effective at promoting and maintaining abstinence and less effective at reducing craving or relapse to heavy drinking if any drinking occurs (13).

Although these hypotheses have been noted in previous reviews, only one early meta-analysis tested medication type (naltrexone versus acamprosate) as a moderator of effect size. In that analysis, Kranzler and van Kirk (9) found no significant difference between the medications on abstinence rate or on percentage of days abstinent. The current meta-analysis expands on their findings in two major ways: (1) by including other drinking outcomes, such as heavy drinking and craving, and (2) by capitalizing on over 40 additional naltrexone and acamprosate trials that have been conducted since their review. Other meta-analyses that have considered the differential effects hypothesis (13) did not formally test medication type as a statistical moderator of effect size. Accordingly, we test the following hypotheses at both end-of-treatment and follow-up: (1) acamprosate is superior to naltrexone in promoting abstinence, (2) naltrexone is superior to acamprosate in preventing relapse to heavy drinking, and (3) naltrexone is superior to acamprosate in reducing craving.

Study Characteristics as Moderators of the Effects of Naltrexone and Acamprosate

We also examine several study characteristics hypothesized to moderate the efficacy of each medication. Information on these moderators may help to promote clinical implementation of these medications (21). Clinicians need and want more tailored conclusions regarding the efficacy of these medications (5, 22), and a test of moderators of the main effect of each medication will help to shed light on when each medication is most efficacious. To our knowledge, no meta-analysis has examined all of the following five study characteristics as moderators of effect sizes for naltrexone and acamprosate.

Abstinence, detoxification, and goal of treatment

Controversy exists regarding whether patients starting naltrexone treatment need to be abstinent. Naltrexone is thought to be helpful in reducing the rewarding effect of a first drink and to "diminish the strength of triggers" (23, p. S74). For example, Sinclair (24) theorized that naltrexone is more effective when some drinking is occurring and with a psychotherapy treatment focused on coping with "slips." Researchers have suggested that it may even be beneficial to start a naltrexone trial without a period of abstinence or detoxification (25). However, more recent work has found that patients taking naltrexone benefit from beginning the medication while abstinent (26, 27). In contrast, there is substantial consensus that acamprosate is more effective when patients have been detoxified and are not currently drinking in the days leading up to medication initiation (13, 28, 29). The biological mechanisms of acamprosate are thought to reduce potential subsequent drinking in the "absence of alcohol" (23, p. S71). For example, Kampman and colleagues (30) found that acamprosate was not helpful in reducing drinking for those who began the medication at the start of detoxification. Similarly, researchers have posited that acamprosate may be most efficacious in studies where abstinence is the goal of treatment (18).

We examined three measures of the role of abstinence in medication treatment: (1) length of required abstinence period before medication treatment started, (2) whether or not detoxification was provided before the medication treatment began, and (3) whether or not the goal of treatment was abstinence. We examined these variables as moderators of the medication effects of both acamprosate and naltrexone. However, we expected that these study characteristics would be especially important moderators of the effect of acamprosate, such that acamprosate would be most effective when there was a period of abstinence and/or detoxification before treatment and when the goal of treatment was abstinence.

Medication administration features

In addition to our predictions regarding the role of abstinence in treatment, we also tested two factors relevant to administering naltrexone and acamprosate.

Length of medication administration—Naltrexone rarely has been administered for more than 3 months in clinical trials (31). However, a few studies have provided longer-term naltrexone treatment and several studies have provided longer-term acamprosate treatment. We conducted moderator analyses to examine whether longer prescribed treatment time is associated with larger medication (versus placebo) effect sizes.

Medication dosage—Finally, although both medications have commonly-recommended dosages, clinical trials also have investigated different dosages. However, the relative efficacy of these varying dosages is not established, so we examined whether the efficacy of naltrexone and acamprosate varied at different dosages.

Method

Inclusion Criteria

The meta-analysis included randomized, placebo-controlled trials testing the efficacy of naltrexone or acamprosate in populations 18 years of age or older. Other study eligibility criteria included a focus on treating alcohol misuse/alcohol use disorder (excluding studies focusing on alcohol withdrawal, alcohol detoxification, alcohol challenges, etc.), publication between 1970 and 2009, reporting in the English language, assignment of at least five participants to each condition, and assessment of at least one drinking outcome. Finally, participants could not be in an inpatient setting for the entire time of medication treatment and follow-up period.

Search Criteria

Several citation databases were searched for relevant trials, including PubMed, Embase, and PsycInfo. For example, we conducted one PubMed search with the terms “naltrexone” and “acamprosate,” in addition to terms for alcohol use disorders and problem drinking (e.g., “alcohol*,” “problem drinkers,” “hazardous drinkers,” “heavy drinkers”) and terms for randomized controlled trials (e.g., “randomized controlled,” “randomized trial,” “clinical trial”). This particular search returned 442 citations, of which 235 potentially relevant articles were identified based on the titles and abstracts. Of the relevant articles, 111 were excluded because they did not meet our inclusion criteria (e.g., they were alcohol challenge studies), 60 were primary articles that met our inclusion criteria, and 64 were secondary articles for trials that met our inclusion criteria (e.g., follow-up report, analysis of a sub-sample).

To complete the sample of studies, the reference sections of included reports, as well as numerous relevant meta-analyses and reviews (e.g., 31, 32, 33), were manually searched for previously unidentified trials. The database searches plus the search of reviews produced a total of 64 randomized controlled trials (see Appendix A) that met our eligibility criteria. If information presented in the primary or secondary articles was not sufficient to calculate effect sizes, the authors were contacted.

Coding of Moderators

Study characteristics were rated by two trained coders, who reached adequate reliability using 25% of the sample of studies (Kappa's and Intraclass Correlations > 0.70). For the study features used in the moderator analyses, both coders rated all of the studies and reached consensus with the first author on any discrepancies.

For *abstinence before treatment*, coders recorded the minimum number of abstinent days required before the start of treatment (“0” days was entered for studies not requiring abstinence). For *detoxification before treatment*, coders recorded whether or not all participants received detoxification treatment directly prior to being assigned to receive medication or placebo. For this variable, we were attempting to capture medical detoxification for alcohol withdrawal, so a study report had to specifically state that detoxification had occurred – it was not enough that patients had been hospitalized or that they had stopped drinking prior to the start of treatment. It may be possible that researchers were more likely to report detoxification if it was provided on an inpatient basis rather than an outpatient basis, so we would have missed some instances of purely outpatient detoxification if researchers failed to report this part of the design. For *goal of treatment*, we coded studies as having a goal of abstinence if it was explicitly reported that either the medication or the concurrent psychosocial treatment (if provided) had an abstinence goal. If the study had a different goal, such as moderate (non-problem) drinking, or if no information was provided, the goal was coded as “other.”

For *length of treatment*, the number of days of intended medication administration was recorded for each study. For *dosage*, we divided the naltrexone studies into those that used the most-commonly recommended dose of 50 mg per day and those that used a higher dose of 100 mg or more. For acamprosate, we created three groups based on the daily dosages: (1) 1998 mg, (2) dosage was determined by weight, with people over 60 kg receiving 1998 mg and those under 60 kg receiving 1332 mg, and (3) other dosages.

Outcome Measures

Abstinence outcomes—We calculated effect sizes for several different, commonly-used abstinence outcomes, including: *abstinence rate* (i.e., the number of participants who were

continuously abstinent from any drinking for some specified period), *percent days abstinent* (i.e., the number of days of abstinence divided by the total number of days in the assessment "window"), and *time to the first drink* (i.e., number of days until relapse to a first drink). We present results for an aggregate measure of abstinence outcomes ("Abstinence aggregate"), which collapses across the effect sizes for the specific abstinence variables presented in each study. For example, if a study presented abstinence rate and percent days abstinent, we calculated the effect size for each of these variables and then created the aggregate effect size measure (more details on these calculations are described below). This aggregate allows us to use one effect size per study (so that study independence is preserved and studies with more outcomes are not given greater weight), but still take into account the different abstinence variables presented.

Heavy drinking—Several outcome variables assessed "heavy drinking," although the definition varied somewhat by study. Frequently, it was classified as 5 or more standard drinks per day for men and 4 or more standard drinks per day for women (8). Heavy drinking outcomes included: *heavy drinking rate* (i.e., proportion of participants who relapsed to heavy drinking), *percent days heavy drinking* (i.e., the number of days of heavy drinking divided by the total number of days in the assessment "window"), *time to the first heavy drinking day* (i.e., number of days until relapse to heavy drinking), and *drinking quantity*. Measures of drinking quantity varied, but the most common was the number of standard drinks per drinking day. Therefore, if more than one drinking quantity measure was provided, we gave priority to number of drinks per drinking day. We present results for an aggregate effect size of these variables ("Heavy drinking aggregate"). As with the abstinent aggregate effect size above, we calculated the effect size for the heavy drinking variables presented in the study and then collapsed across multiple effect sizes to create the aggregate effect size.

Craving—We examined craving as a secondary outcome, as craving is thought to be one mechanism through which these medications may reduce drinking. The questionnaires used to measure craving most often were the Obsessive Compulsive Drinking Scale (OCDS) (34) or the Visual Analog Scale (VAS) (35). If data for both were reported, we included the effect size for the OCDS, as this was the more common measure.

Heavy drinking and craving—We hypothesized that naltrexone would be superior to acamprosate on both heavy drinking and craving outcomes. Because acamprosate studies tend not to assess many heavy drinking outcomes (13), to maximize our sample size, we calculated an aggregate effect size for heavy drinking and/or craving outcomes ("Heavy drinking and craving aggregate").

Effect Size Calculations

Two coders calculated the effect sizes and double-checked them for accuracy. For continuous outcomes, we calculated the standardized mean difference using the formula for Cohen's *d* (36) in the computer program ES: A Computer Program for Effect Size Calculation (37). We then applied Hedges *g* correction for small sample bias (38, 39). For dichotomous outcomes, we calculated the Odds Ratio for 2 × 2 tables (40) and then converted them to *g*'s for comparison purposes (38). When proportions or means and standard deviations were not presented, a test statistic (e.g. *F*, *t*) or *p*-value was transformed into a standardized mean difference (38, 41). For test statistics from ANCOVA results, we followed the conversions in Borenstein (38, Table 12.3). We assumed a partial correlation of 0.50 (42) because the most common covariate was baseline drinking, and estimates of the stability of drinking over time are in the range of $r = 0.50$ for heavy drinkers followed for at least 3 months (43). In the absence of other data, if the results were presented as statistically

"significant," we calculated an effect size consistent with $p = .05$ (44). If the results were presented only as statistically "non-significant," then we assigned the effect size a value of zero (44). In all, 73.6% of the effect sizes were from means and standard deviations or from proportions, 16.8% were from test-statistics, and the remaining 9.7% were from descriptions of results in the text. Scores on "negative" outcomes (e.g., drinking problems) were reversed, so that a positive effect size always indicates that medication was superior to placebo. Effect size values of 0.2 were considered small, values of 0.5 were considered medium, and values of 0.8 were considered large per Cohen (36).

For studies with multiple subgroups, we used two strategies to deal with stochastically dependent effect sizes (45). These studies included nine trials which examined interactions of medication and psychosocial treatment, in which participants were randomized to medication/placebo and to different types of psychosocial treatments (e.g., cognitive-behavioral therapy versus medication management). However, because these psychosocial treatments were not consistent across studies, we did not have the statistical power to examine these effect sizes separately. Instead, we collapsed across these psychosocial subgroups to obtain the main effect of medication versus placebo. Where raw data (e.g., means/standard deviations or proportions) were provided, we were able to collapse across more than one psychosocial subgroup (46). If raw data were not provided, we calculated the effect size from other information for each subgroup (e.g., *F*-test) and then collapsed the effect sizes based on Borenstein's (46) recommendations and formulae for adjusting the variance (p. 227, formula 24.2). These formulae were used for 2.3% of the effect sizes. These procedures ensured that we had the correct sample size and variance estimates for all effect sizes, including studies in which multiple medication groups were compared with a common placebo group.

To create the aggregate measures described earlier (i.e., for abstinence, heavy drinking, and heavy drinking plus craving), we combined multiple effect sizes within studies using the aggregation procedure in R (47) with the packages MAd (48) and RcmdrPlugin.MAd (49). These procedures are similar to calculating an average effect size per study, but they account for the within-study correlations among dependent variables (45). Correlations among outcome variables in studies on alcohol use vary a great deal (e.g., in Project MATCH, dependent variables were correlated between $r = .36$ and $r = .65$; 50). We therefore tested several correlations ($r = .30$, $r = .50$, $r = .70$) and examined whether they affected our analyses (46). In general, the overall estimates did not vary a great deal (i.e., no significant tests of main effects or moderators became non-significant and no non-significant tests became significant). We therefore used $r = .50$ (42) for the within-study correlation estimate among outcome variables for the aggregated effect sizes.

Sample Size Decisions

Dichotomous outcomes—In studies that had dichotomous outcomes (e.g., abstinence Y/N, relapse to heavy drinking Y/N), most authors considered drop-outs to have relapsed. We followed this principle and used a worst-case scenario for calculating the effect sizes for dichotomous variables. If the original trial did not assume a worst-case scenario (3.9% of effect sizes), we recalculated the proportions, counting drop-outs as relapsed.

Continuous outcomes—Whenever possible, we calculated effect sizes for continuous outcomes using the *n* of each group presented with the results. Often, studies were not able to follow-up all participants, so means and standard deviations for drinking outcomes were presented for the smaller sample of participants successfully followed. If it was unclear how many participants were included in the analyses (e.g., no *n*'s presented with the analysis and no description of how missing data were handled), we calculated the effect sizes using the

number of participants followed-up by the researchers (i.e., we assumed missing data were not imputed).

Meta-analyses

Our pre-specified analysis plan included comparing the effect sizes for naltrexone and acamprosate on the outcomes of abstinence, heavy drinking, and craving, and testing our a priori moderators of the main effects of each medication. We calculated overall effect sizes using a random-effects model, given our goal of generalizability and our assumption of heterogeneity of effects (51). Because we were interested in moderators that might explain variability in effect sizes across studies, we calculated the *Q*-statistic, a measure of the heterogeneity of effect sizes, with a significant *p*-value suggesting that effect sizes varied across studies (46). We also calculated the I^2 statistic, which measures the degree of variability in effect sizes across the studies (46). Conventions are that 0% represents no observed heterogeneity, 25% is low heterogeneity, 50% is moderate heterogeneity, and 75% is high heterogeneity (52). We considered an effect to be heterogeneous if the I^2 was at least low to moderate heterogeneity (~35%) and if the *Q*-statistic was significant (e.g., 53).

Analyses were conducted using Comprehensive Meta-Analysis (CMA, version 2.2.048), Stata (version 10), and R (version 2.13.1). For categorical moderators (medication, detoxification before treatment, goal of treatment, dosage), we conducted univariate mixed-effects tests of subgroups in CMA in order to present the aggregate effect size for each subgroup (53, 54). The mixed-effects method allows for calculation of random-effects model within subgroups and fixed-effect model across the subgroups (55). For continuous moderators (length of treatment and number of days of required abstinence) and for meta-regressions with the five moderators, we used the restricted maximum likelihood meta-regression in R's *metafor* program (56). We also utilized the *metan* macros in Stata to create forest plots. Finally, to test for outliers exerting undue influence, we removed one study at a time and examined the aggregate effect size without each study.

Publication bias—To assess the possibility that the published studies included in the meta-analysis were not representative of the total population of studies that have been conducted ("file-drawer problem"; 57), we used three methods: (1) inspecting the funnel plot for each main effect analysis, (2) using Duval and Tweedie's trim-and-fill procedure (58), and (3) conducting Egger's (59) test of the intercept. The funnel plot and the trim-and-fill procedure plot the relationship between effect sizes and a measure of the sample size (the standard error). There will be an asymmetrical plot when bias is present, such that smaller studies will be more likely to be published when they show large effects rather than smaller ones (i.e., smaller samples with smaller effects will be missing from the plot). Egger's test of the intercept similarly tests the association between effect size and precision of the study (inverse of the standard error).

Results

Descriptive information on the characteristics for each medication trial and for the moderators of interest across the 64 studies is presented in Table 1. For 45 trials of naltrexone versus placebo, the total number of participants was 5,434 (M = 120.76, SD = 91.59, range: 20 – 627). For 16 trials of acamprosate versus placebo, the total number of participants was 4,349 (M = 271.81, SD = 184.21, range: 56 – 601). Finally, three studies randomized participants to receive naltrexone, acamprosate, or placebo and had a total of 1,210 participants (M = 403.33, SD = 448.98). These studies included the COMBINE Study (60), which had the largest number of participants of any study (n = 921) included in our analyses.

Efficacy of Naltrexone versus Acamprosate

To test our main hypotheses, we used medication (naltrexone versus acamprosate) as a dummy-coded moderator variable. The last columns in Table 2 present the tests of significance for these subgroup comparisons. These analyses excluded the three studies that tested both naltrexone and acamprosate in the same trial because of the dependency created by the use of a common placebo group. However, we use these trials' findings as a comparison for our meta-analytic results. We present the results for end-of-treatment outcomes and for post-treatment follow-up outcomes separately.

End-of-Treatment Outcomes

Overall, 54 studies included at least one abstinence outcome, 47 studies included at least one heavy drinking outcome, and 36 studies included a craving outcome.

Abstinence—For abstinence outcomes, the overall effect size for acamprosate studies (g = .359, k *[number of studies]* = 15) was significantly larger than the overall effect size for naltrexone studies (g = .116, k = 36, $p < .001$). The forest plot for aggregated abstinence effect sizes is presented in Figure 1.

Heavy drinking—For the heavy drinking outcomes, the difference between naltrexone and acamprosate studies on the aggregate effect size was not significant (p = .159), probably due to low statistical power (only 5 acamprosate studies had any heavy drinking outcomes). However, the effect sizes were in the expected direction, with naltrexone having a larger effect on heavy drinking outcomes (g = .189, k = 39) compared to acamprosate (g = .072, k = 5). The forest plot for the heavy drinking aggregate is presented in Figure 2.

Craving—For craving, the overall effect size for naltrexone studies (g = .144, k = 26) was marginally significantly larger than the overall effect size for acamprosate studies (g = .034, k = 9, p = .075), as predicted.

Heavy drinking and craving—Finally, given that we hypothesized that naltrexone would be superior to acamprosate for the outcomes of both heavy drinking and craving (possibly due to the stronger effects for naltrexone on reducing craving and thus preventing relapse to heavy drinking) (19), we examined the heavy drinking and craving aggregate effect size. As predicted, naltrexone studies had significantly larger effect sizes for heavy drinking and craving (g = .180, k = 42) compared to acamprosate studies (g = .041, k = 9, p = .004).

Follow-up Outcomes

Only 7 naltrexone studies and 7 acamprosate studies included data from follow-ups after the end of medication administration. Naltrexone studies had follow-up points at 3, 6, 9 and/or 12-months, and acamprosate studies had follow-up points at 3, 6, and/or 12-months after the end of treatment. For abstinence outcomes, acamprosate had a marginally significantly larger overall effect size (g = .397, k = 6) than naltrexone (g = .152, k = 5, p = .057) at the last follow-up point after treatment ended. For the outcomes of heavy drinking and craving, only one acamprosate study provided data. However, naltrexone studies tended to have effect sizes for heavy drinking outcomes at the last follow-up point (g = .135, k = 6) that were slightly smaller compared to end-of-treatment (g = .189, k = 39). Although only two studies provided data, the naltrexone-placebo effect sizes for craving at the last follow-up point were close to zero (g = .053).

Moderators of the Main Effects of Naltrexone and Acamprosate

Next, we examined the five hypothesized moderators of the effects of naltrexone and acamprosate. Descriptive information on and intercorrelations among these moderators are presented in Table 3. Unsurprisingly, the highest correlations were between required abstinence before the study and detoxification (see the bottom half of Table 3). We considered creating a composite of these two variables, but we felt that they were distinct enough conceptually and empirically (52) to warrant treating them separately, particularly because the original study reports would often use separate inclusion criteria for detoxification and for the minimum required number of days of abstinence. The remaining moderators were correlated between $r = .03$ and $r = .36$.

Studies of naltrexone and acamprosate varied systematically in their general study design characteristics. Acamprosate studies had a longer planned medication administration period than naltrexone studies ($p < .001$), were more likely to have abstinence as a goal ($p = .025$), and were significantly more likely than naltrexone studies to have detoxification before the trial began ($p < .001$). To test when each medication is most beneficial, we examined whether any of the hypothesized moderators accounted for heterogeneity in the main effects for naltrexone versus placebo and for acamprosate versus placebo. We only conducted moderator tests if we first found significant heterogeneity (based on the I^2 and Q statistics) in the main effects. For all of the analyses presented below, we included the effect sizes for naltrexone versus placebo or acamprosate versus placebo from the three randomized controlled trials (RCTs) that included both medications, in order to utilize all available data and because we were no longer comparing naltrexone and acamprosate studies to each other.

Moderation of the main effects of naltrexone—The effects of naltrexone versus placebo on abstinence outcomes had significant heterogeneity ($Q = 58.7$, $p = .017$, $I^2 = 35.3\%$, $k = 39$). Of the moderators, only longer required abstinence was significantly associated ($b = .019$, $p = .015$) with larger effect sizes on abstinence. When the five moderators were entered into the meta-regression, length of required abstinence before treatment remained the only significant moderator of abstinence effects ($b = .022$, $p = .039$).

For heavy drinking outcomes, there also was significant heterogeneity in naltrexone studies ($Q = 66.7$, $p = .005$, $I^2 = 38.5\%$, $k = 42$). Longer required abstinence was significantly associated ($b = .023$, $p = .025$) with larger effect sizes on heavy drinking. In addition, the 37 studies without detoxification had a significantly smaller aggregated effect size ($g = .174$) than the 5 studies with detoxification ($g = .382$, $p = .032$). When the five moderators were entered into the meta-regression, abstinence before treatment remained a significant moderator ($b = .030$, $p = .017$) controlling for all other moderators. In addition, treatment goal emerged as a significant moderator ($b = .136$, $p = .040$) in that studies with “other” treatment goals (not explicitly abstinence) had a larger aggregate effect size ($g = .235$, $k = 23$) on reducing heavy drinking than studies with explicit abstinence goals ($g = .153$, $k = 19$). Finally, for craving, there was significant heterogeneity ($Q = 45.0$, $p = .016$, $I^2 = 40.02\%$, $k = 28$), but no significant moderators.

Moderation of the main effects of acamprosate—We found significant heterogeneity in the main effects of acamprosate versus placebo on abstinence outcomes ($Q = 71.6$, $p < .001$, $I^2 = 76.3\%$, $k = 18$). Tests of the moderators revealed three statistically significant relationships. Longer required abstinence before medication receipt was significantly associated with larger effect sizes ($b = .033$, $p < .001$). Similarly, studies with detoxification before the treatment had a significantly larger effect size ($g = .455$, $k = 12$) than those without detoxification ($g = .074$, $k = 6$, $p < .001$). Studies that administered acamprosate dosage by weight had a larger effect size ($g = .451$, $k = 8$) than studies that

administered 1998 mg/day to all participants (g = .239, k = 6, p = .045). For the meta-regression analysis with the five moderators entered, although the sample size of studies was small (k = 18), detoxification before treatment was significantly associated with larger effect sizes (b = .275, p = .004). There was no significant heterogeneity in the effect of acamprosate versus placebo on heavy drinking outcomes (Q = 10.2, p = .180, I^2 = 31.09%, k = 8) or on craving (Q = 5.9, p = .824, I^2 = 0.00%, k = 11).

Publication Bias

When we examined the funnel plot, studies with larger standard errors (i.e., smaller sample sizes), which were more likely to be published early, had a slight tendency to have larger effect sizes. For the random effects model using Duval and Tweedie's Trim and Fill method, no studies were trimmed (overall point estimate went unchanged). However, there was significant bias indicated by Egger's test of the intercept ($t_{(62)}$ = 1.81, 1-tailed p-value = .04), such that smaller studies tended to have larger effect sizes. Although some bias may be present, tests of our central hypotheses remained unchanged when we attempted to account for this bias. For example, when we restricted the studies to those with at least 100 participants, we found all of our results were unchanged (e.g., for the abstinence aggregate, acamprosate [g = .353, k = 13] was still superior to naltrexone [g = .120, k = 21, p = .001]).

Sensitivity Tests

To ensure that our results were not influenced by decisions made regarding the calculation of effect sizes, we examined the effects of these decisions by examining sensitivity analyses for all of our outcomes (abstinence, heavy drinking, and craving). Across the studies, the majority of effect sizes came from proportions or means and standard deviations, and the rest were from test-statistics or from the text. We tested source of effect size data as a moderator to examine if there were any differences between the effect sizes based on raw numbers versus effect sizes based on test statistics or the text, but these tests were not significant (p > .10 for all outcomes). Similarly, we tested whether there were any differences when we excluded studies for which we had re-calculated effect sizes to assume the worst-case outcome (i.e., that participants who had dropped out had relapsed). The results remained unchanged without these studies and the assumption of relapse was not a significant moderator of any outcome.

Some of the studies used “atypical” designs, including (a) three studies with targeted naltrexone (participants took naltrexone when they felt they would be in a high-risk situation) in addition to, or instead of, daily naltrexone (25, 61, 62), (b) two studies in which all participants received naltrexone in Phase 1 before moving on to Phase 2 which randomized to naltrexone versus placebo (63, 64), (c) one naltrexone study in which all participants also received sertraline (65), (d) two naltrexone studies which only provided effect size data for completers (66, 67), and (e) four naltrexone studies that administered the medication either in an inpatient setting or in mixed settings (inpatient and/or outpatient) (68-71). Our tests indicated that these studies were not outliers (i.e., did not unduly influence overall effect sizes). In addition, removing all the atypical studies did not change the statistical significance of the findings and the size of the aggregate effect sizes changed very little (more detailed information is available from the authors).

Given the larger number of naltrexone studies, there was greater variability in some aspects of study design. In particular, nine naltrexone studies included co-morbid samples (five with co-morbid cocaine dependence and four with co-morbid psychiatric disorders). We conducted sensitivity analyses without these nine studies. As with our other sensitivity analyses, our main results remained essentially unchanged. The effect size for naltrexone versus placebo on abstinence outcomes increased from g = .116 to g = .131, for heavy

drinking it increased from $g = .189$ to $g = .213$, and for the heavy drinking and craving aggregate, it increased from $g = .180$ to $g = .200$. All of the comparisons between naltrexone and acamprosate (Table 1) were confirmed.

Finally, as our last sensitivity analysis, we only included studies with concurrent psychosocial treatment (83% of the total studies). Again, we confirmed our main findings. For abstinence outcomes, the main effects changed very little for naltrexone (from $g = .116$ to $g = .113$) and for acamprosate (from $g = .359$ to $g = .331$), and the difference between the two medications was still significant ($p = .013$). Similarly, for the heavy drinking and craving aggregate, the main effects changed very little for naltrexone (from $g = .180$ to $g = .176$) and acamprosate (from $g = .041$ to $g = .036$), and the difference between the two medications was still significant ($p = .006$). In other words, although there was heterogeneity in the main effects of each medication, a number of sensitivity analyses conducted to probe this heterogeneity did not change the results.

Discussion

As predicted, acamprosate studies had larger effect sizes than naltrexone studies on abstinence outcomes. Although very few acamprosate studies provided data on heavy drinking outcomes and thus power to detect a significant difference was limited, naltrexone studies tended to have larger effect sizes on heavy drinking outcomes. In particular, as predicted, when outcomes of heavy drinking and craving were combined, naltrexone was statistically superior to acamprosate. Although the studies varied in design and methodology (particularly naltrexone studies), sensitivity analyses revealed that these findings were consistent even when sub-samples of more homogenous naltrexone studies were examined.

Examining effect sizes by outcome helps to clarify when each medication might be most effective. Researchers conducting meta-analyses often aggregate across all types of (drinking-related) dependent variables in order to create an overall effect size. In our analysis, this type of calculation would be heavily weighted towards abstinence outcomes because acamprosate studies tended to have proportionately more “targeted” abstinence outcomes, whereas naltrexone studies more often included both abstinence and heavy drinking outcomes. Therefore, an analysis based on all included drinking-related outcomes would be likely to favor acamprosate, as it did in our sample (acamprosate overall $g = .325$, $p < .001$ compared to naltrexone overall $g = .160$, $p < .001$; difference between outcomes: $p = .010$). However, when we separated medication effects by type of outcome, acamprosate was only superior to naltrexone on abstinence-related outcomes, not on heavy drinking or craving outcomes.

Our findings on this issue are in line with previous meta-analyses on naltrexone and acamprosate (e.g., 9, 14), even though our analyses included at least 29 additional studies and excluded non-English language studies (which were included in some previous meta-analyses). For example, although Rosner and colleagues (13) had access to substantial unpublished data from pharmaceutical companies, our differential main effect findings were comparable. Those authors found larger effects for acamprosate when examining abstinence outcomes and larger effects for naltrexone when examining heavy drinking outcomes, although they did not formally test these differences.

RCTs with the Two Medications

Three trials have compared naltrexone versus acamprosate directly. Kiefer and colleagues (72) found few differences between naltrexone and acamprosate, with naltrexone showing a slight edge in time to first drink and time to relapse. Morley and colleagues (73) found no difference between the medications on a range of drinking outcomes. Anton and colleagues

(60) did not focus on the differences between the medications, but they found significant effects for the efficacy of naltrexone in combination with certain psychotherapies, but no significant efficacy for acamprosate.

At first glance, these findings contrast somewhat with our meta-analytic findings, but there are possible explanations for this discrepancy. One has to do with the moderators we examined. Our analyses indicated that both medications are more efficacious when detoxification before the trial and a few days of required abstinence were in place. Although the Kiefer et al. study found few differences between the medications, it found that both were superior to placebo. This study may have highlighted both medications under "optimal conditions" – detoxification was required, as was a long period of abstinence (12 days). Given these requirements, this study may have recruited particularly committed participants, allowing fewer differences to emerge under such optimal conditions.

The Anton et al. study found some efficacy for naltrexone, but none for acamprosate. The lack of any significant findings for acamprosate may have been related to the fact that detoxification was not required before the study; our moderator analyses have indicated that acamprosate is least effective when patients are not detoxified. Finally, Morley et al. found no differences between the medications and no significant effects of either medication compared to placebo. Again, this study did not require detoxification, had a relatively short minimum period of required abstinence (3 days), and did not explicitly report abstinence as a goal.

In sum, study characteristics may have been one reason why we found different meta-analytic effects compared to these three RCTs. Another explanation is that when we compared naltrexone and acamprosate studies to each other, we had the benefit of greater power than any one individual study (even with COMBINE having a very large sample). Finally, another reason may be that the studies were not always testing equal numbers of abstinence outcomes and heavy drinking outcomes. For example, in the Kiefer study (which showed trends of superiority for naltrexone), approximately two-thirds of the outcomes were heavy drinking or craving outcomes, which, as shown here, are more responsive to naltrexone effects.

Moderation of Main Effects of Each Medication

Abstinence, detoxification, and goal of treatment—For naltrexone, required abstinence before the trial was associated with greater abstinence and greater reductions in heavy drinking. This finding provides some evidence that patients receiving naltrexone may benefit from abstinence before the start of the medication, which is consistent with clinical guidelines for the use of naltrexone (for example, Veterans Health Administration guidelines recommend 3-5 days of abstinence before treatment; 1). Contrary to earlier theories on the administration of naltrexone (24), these findings for abstinence are consistent with more recent research that has demonstrated the benefits of starting naltrexone after participants have been abstinent for at least 4 days (27, 74).

Goal of treatment was also a significant predictor of reduced heavy drinking with naltrexone. In this case, studies with an "other" goal had larger effect sizes on reduced heavy drinking than those studies which explicitly stated an abstinence goal. In our coding, the "other" category included studies with a goal of moderate or non-problem drinking, but also studies for which a specific goal was unclear. Although this category is broad, compared to studies with an explicit abstinence-only goal, studies with "other" goals may have been more likely to include aspects of psychosocial treatment focused on dealing with "slips," which may have been helpful in reducing relapse to heavy drinking when drinking did occur.

For acamprosate, variables related to abstinence and detoxification before the trial also were significant moderators of abstinence outcomes. These findings support previous hypotheses and replicate findings in clinical trials (e.g., 30) that acamprosate is more effective when administered to patients who are not currently drinking. However, this review is the first to test these study characteristics as moderators of effect size at the meta-analytic level. Other explanations for these findings can be pointed to, in addition to the proposal that the pharmacological properties of acamprosate are most effective when individuals have already stopped drinking. For example, the studies that required abstinence and/or detoxification before the trial may have enrolled a more committed and motivated sample. Although the level of motivation of the sample would be randomly distributed across groups, a more motivated sample may have also been more likely to comply with their medications and the treatment regimen. In other words, these medications may work best when compliance is high and a more motivated sample is more likely to be more compliant. This possibility might be a useful focus of future research.

To reliably code the moderators, we had to rely on the information presented in the trial reports. For example, although we were not explicitly coding for inpatient detoxification, researchers may have been more likely to report detoxification if it occurred on an inpatient basis rather than an outpatient basis. In general, some participants were detoxified or abstinent before treatment began even in studies that did not require it. Importantly, however, this fact works against our hypotheses – for example, if some people in the "no detoxification" group were indeed detoxified (i.e., more noise in this category), we would expect it to be harder to find statistical differences between the trials that required detoxification versus those that did not. In the future, if more studies presented data separately by these moderators of interest (e.g., those individuals who were detoxified versus those who were not), a meta-analysis of these subgroups might be possible.

Length of treatment and length of follow-up—Our meta-analysis highlights that many studies testing pharmacotherapies for alcohol use disorders have been administered in relatively short trials (usually 90 days after initiation) and few have follow-up data. In general, although limited by statistical power, we did not find many differences between shorter and longer prescribed medication administrations. Similarly, there was a general lack of post-medication/placebo follow-up points. Our limited findings for follow-up effect sizes indicated that the effects tended to stay consistent or decline somewhat after medication treatment ended. Very few (22%) of the studies in this meta-analysis presented follow-up data, demonstrating a paucity of information in the literature regarding how long the benefits of these medications last after treatment (33). Future research could also examine medication adherence over the trial as a potential moderator, as previous work has demonstrated that greater adherence monitoring is associated with larger naltrexone-placebo effects (75). We focused on oral naltrexone in this review instead of injectable naltrexone because the administration of the oral form is comparable to the oral administration of acamprosate, but injectable naltrexone is one way that adherence may be increased (74).

Dosage—We generally found little difference between studies that administered 50 mg of naltrexone versus 100 mg or more of naltrexone. In fact, the effect sizes for the recommended dose of 50 mg were a bit higher than the effect sizes for larger doses. For example, for relapse to heavy drinking, the 35 studies with 50 mg dosage had an effect size of $g = .202$, whereas in the 6 studies with 100 mg or higher, the effect size was $g = .131$, although this difference was not significant. Similarly, we only found one significant dosage effect for acamprosate on abstinence outcomes, with acamprosate "dose by weight" studies having larger effect sizes than studies in which all participants received 1998 mg doses. Current SAMHSA guidance recommends two 333 mg tablets three times per day (1998 mg) rather than dosage based on weight (76).

Limitations and Strengths

Although the current review included 64 randomized controlled trials of naltrexone and acamprosate, the number of studies that could be included in any particular analysis (e.g., when we divided the analyses by outcome type) sometimes was limited. Consequently, some non-significant results may reflect a lack of statistical power. In addition, we tended to make conservative decisions in our effect size calculations (e.g., assigning an effect size of zero if the report stated that there was no treatment effect), so it is possible the effects of these medications were underestimated. However, when we removed studies that had effect sizes assigning zero for non-significant findings or effect sizes assigning a poor outcome when data were missing, our results changed very little.

Another limitation stems from the fact that moderation tests in meta-analyses raise the possibility of the ecological fallacy (77). That is, finding that sample characteristics moderate medication effect sizes at the study level does not necessarily imply that individuals with and without those characteristics will experience similar effects. However, we purposely restricted our moderator tests to study characteristics and not sample characteristics; moderation tests seem to be especially problematic when dealing with the mean level of participant characteristics (e.g., average score on a scale for the sample) (78). We focused on characteristics of the study design and methodology that were relevant to all participants in a particular trial. RCTs to examine the impact of these characteristics at the participant level would be even more helpful, but researchers often do not have the statistical power, financial resources, participant pool, etc. to randomize participants to receive different design characteristics in addition to examining treatment-placebo effects.

In addition, we did not control or examine other variables as moderators due to power considerations, our desire to focus on characteristics relevant to the way treatment is delivered, and the fact that some characteristics are not reported or cannot be coded reliably. For example, one additional difference between naltrexone and acamprosate trials is the role of pharmaceutical companies. Researchers have noted that most acamprosate trials (75%) are either conducted by a pharmaceutical company or receive support from pharmaceutical companies (11), compared to industry sponsorship of approximately 16% of naltrexone studies (12). Although it is difficult to know how serious the bias might be because of this difference, pharmaceutical companies may have influenced what results were published, and this bias would have been more pronounced for acamprosate studies (13). Another difference is that most acamprosate studies were conducted in European countries, whereas most naltrexone studies were conducted in the USA. Instead of focusing directly on geographic location of the trial, we examined why differences in location might be associated with the efficacy of the medications. Researchers have hypothesized that European clinical trials are more likely to be abstinence-focused (13, 29), but we were able to address this difference with our abstinence-related moderators. In sum, we attempted to investigate some of the underlying characteristics that may influence when a medication will be most efficacious, but we could not capture all potential moderators. These limitations should be kept in mind when considering the results of this meta-analysis.

Lastly, most of the trials included in this meta-analysis (83%) included some sort of psychosocial intervention given to both the medication and placebo groups. Thus, medications were not compared to a “pure” no-treatment placebo condition – the placebo group was almost always getting some sort of psychotherapy for an alcohol use disorder, as well. This design feature may have dulled the medication effect, or, by increasing medication compliance, it may have had the opposite effect. Our sensitivity analyses indicated that focusing only on studies with concurrent psychosocial treatment did not change our results. Future analyses that include detailed coding of the types of psychotherapy might provide more understanding of when medication effect sizes vary. For

example, naltrexone has been shown to have particularly positive effects when combined with cognitive-behavioral therapy (79).

Despite these limitations, this meta-analysis had many strengths. It tested medication type (acamprosate versus naltrexone) as a statistical moderator of effects on different types of drinking outcomes (abstinence, heavy drinking, and craving). It further explored the main effects for each medication by examining a set of a priori moderators to determine circumstances under which each medication might be more efficacious.

Concluding Comments

Across medications and outcomes, the aggregated Hedges' *g* for naltrexone and acamprosate compared to placebo was 0.209 (CI: 0.157 – 0.262) – indicating a small but significant effect (36). In comparison to other medications prescribed for mental health (e.g., for depression), the effects of naltrexone and acamprosate are somewhat smaller (e.g., 9). Yet the effects of naltrexone and acamprosate still have clinical relevance as one line of treatment. For example, based on our effect sizes, 8 people would need to be treated with acamprosate to achieve an additional case of abstinence (NNT = 7.5), and 9 people would need to be treated with naltrexone to prevent an additional case of return to heavy drinking (NNT = 8.6).

More importantly, this meta-analysis highlights the need to better understand the outcomes for which, and the conditions under which, pharmacotherapy for alcohol use disorders is most efficacious. Given the prevalence of alcohol use disorders (80) and attempts to further integrate alcohol use disorder treatment into primary care and specialty mental health treatment (81), there has been an increased emphasis on including pharmacotherapy in all treatment settings (6, 82). When clinicians consider pharmacotherapy options, it will be critical that they know the contexts in which each medication is most helpful (e.g., with other psychosocial treatments, with a requirement for pre-treatment abstinence).

The findings presented here suggest that naltrexone should be considered for patients who have a goal of reducing heavy drinking days, whereas acamprosate is a better option for those who seek abstinence. Both medications seem to be more effective when participants are detoxified and abstinent when treatment begins. However, research is needed to investigate how these two medications might be usefully integrated with other treatments. Such expanded knowledge will be helpful in addressing concerns about medication efficacy, which has been a barrier to widespread implementation (5, 22).

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Appendix A. Full list of studies included in the meta-analysis

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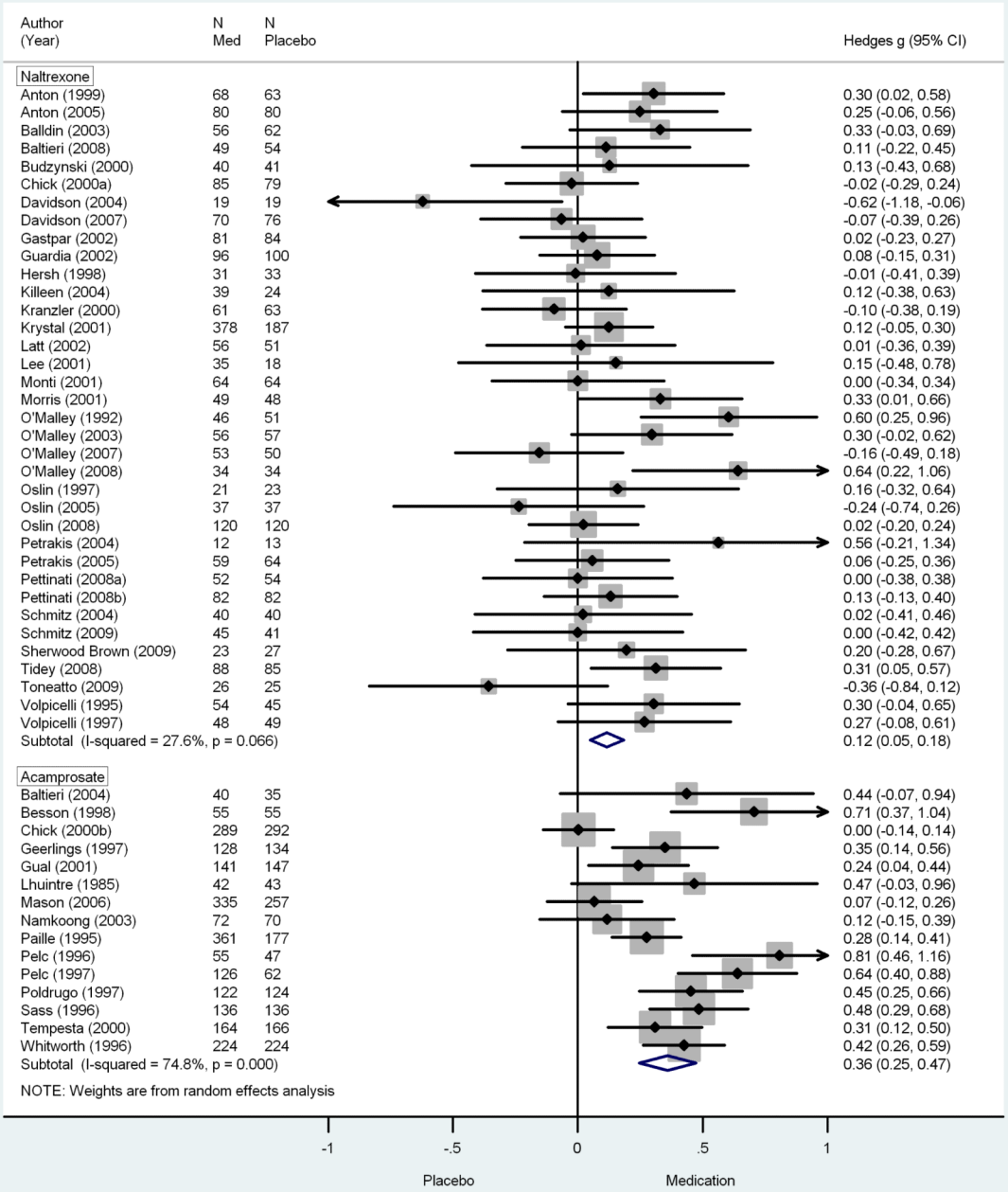

Figure 1.

Medication type (naltrexone versus acamprosate) as a moderator of abstinence outcomes aggregate (abstinence rate, percent days abstinent, and time to first drink). Top half of forest plot presents the effect sizes for naltrexone studies, and the bottom half presents the effect sizes for acamprosate studies.

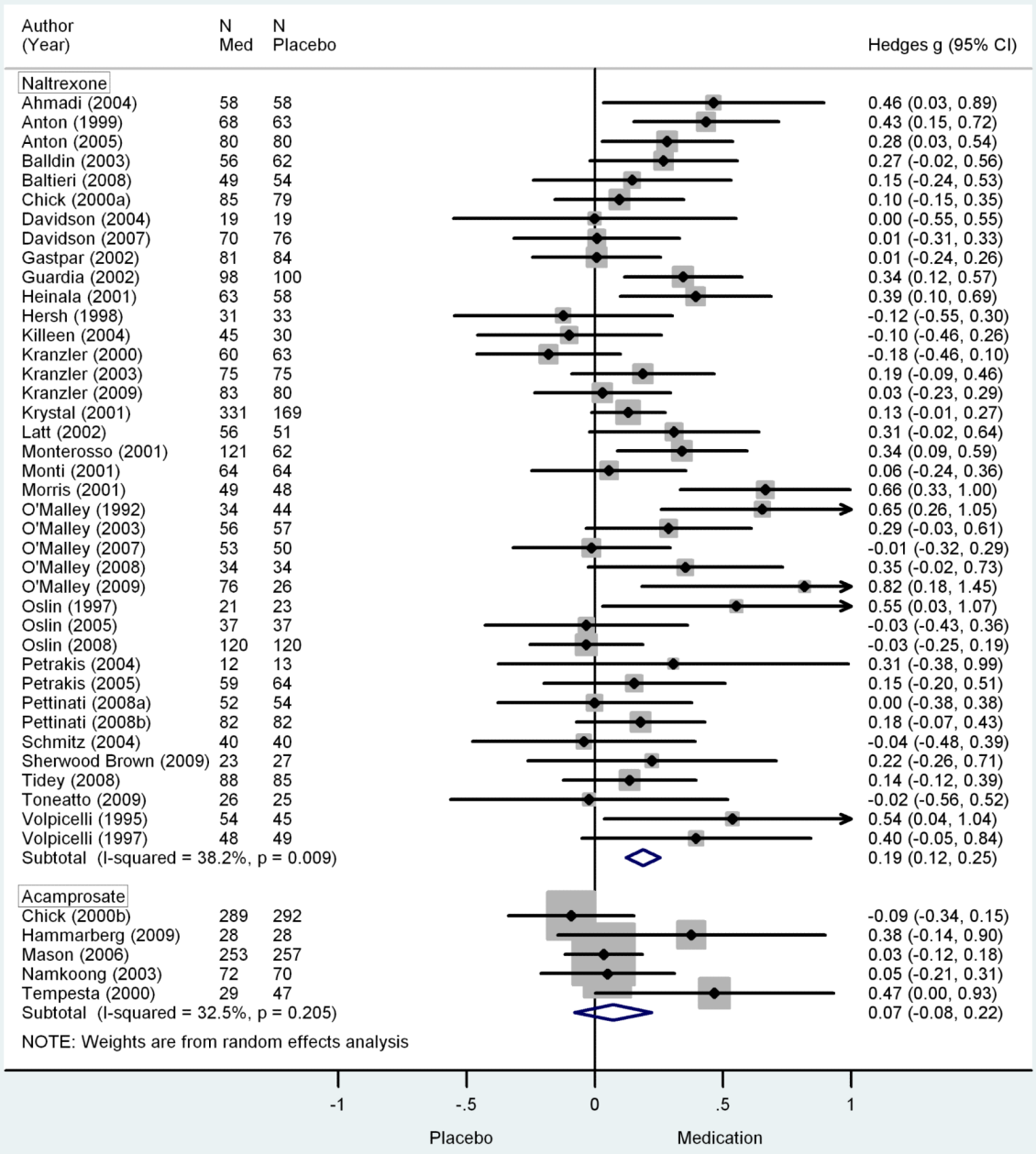

Figure 2.

Medication type (naltrexone versus acamprosate) as a moderator of heavy drinking outcomes aggregate (heavy drinking rate, percent days heavy drinking, time to first heavy drink, drinking quantity). Top half of forest plot presents the effect sizes for naltrexone studies, and the bottom half presents the effect sizes for acamprosate studies.

Table 1

Characteristics of the 64 randomized controlled trials testing naltrexone versus placebo (k = 45), acamprosate versus placebo (k = 16), or naltrexone, acamprosate, and placebo (k = 3). See Appendix A for the full reference list.

First Author	Year	Country	N total participants	Length of trial (days)	Dosage	Length of abstinence (days)	Detox before trial?	Goal of treatment
Naltrexone Studies								
Ahmadi	2004[a]	Iran	116	252	50 mg/d	3	No	Abstinence
Anton	1999	USA	132	84	50 mg/d	5	No	Other
Anton	2005	USA	161	84	50 mg/d	5	No	Other
Balldin	2003	Sweden	118	168	50 mg/d	14	No	Abstinence
Baltieri	2008	Brazil	103	84	50 mg/d	7	Yes	Other
Budzynski	2000	Poland	81	112	50 mg/d	28	Yes	Abstinence
Chick	2000a	UK	175	84	50 mg/d	5	No	Abstinence
Davidson	2004	USA	41	70	50 mg/d	0	No	Other
Davidson	2007	USA	146	84	50 mg/d	3	No	Abstinence
Galarza	1997	Puerto Rico	20	28	unspecified	0	No	Other
Gastpar	2002	Germany	171	84	50 mg/d	5	No	Abstinence
Guardia	2002	Spain	202	84	50 mg/d	5	No	Abstinence
Heinala	2001	Finland	121	224	50 mg[b]	0	No	Other
Hersh	1998	USA	64	49	50 mg/d	0	No	Other
Huang	2005	China	40	98	50 mg/d	14	Yes	Abstinence
Killeen	2004	USA	97	84	50 mg/d	0	No	Abstinence
Knox	1999	USA	68	20	50 mg/d	0	No	Abstinence
Kranzler	2000	USA	124	77	50 mg/d	3	No	Abstinence
Kranzler	2003	USA	153	56	50 mg[b]	0	No	Other
Kranzler	2009	USA	163	84	50 mg[b]	0	No	Other
Krystal	2001	USA	627	365[c]	50 mg/d	5	No	Abstinence
Latt	2002	Australia	107	84	50 mg/d	7[d]	Yes	Abstinence
Lee	2001	Singapore	53	84	50 mg/d	7	Yes	Abstinence

First Author	Year	Country	N total participants	Length of trial (days)	Dosage	Length of abstinence (days)	Detox before trial?	Goal of treatment
Monterosso	2001	USA	183	84[e]	100+ mg/d	3	No	Other
Monti	2001	USA	128	84	50 mg/d	0	No	Other
Morris	2001	Australia	111	84	50 mg/d	3	No	Other
O'Malley	1992	USA	104	84	50 mg/d	7	No	Abstinence
O'Malley	2003	USA	113	168	50 mg/d	5	No	Other
O'Malley	2007	USA	107	84	50 mg/d	3	No	Abstinence
O'Malley	2008	USA	68	112	50 mg/d	4	No	Abstinence
O'Malley	2009	USA	102	42	100 mg/d 50 mg/d 25 mg/d	0	No	Other
Oslin	1997	USA	44	84	50 mg/d[f]	0	No	Abstinence
Oslin	2005	USA	74	84	50 mg/d	3	No	Abstinence
Oslin	2008	USA	248	168	100+ mg/d	3	No	Other
Petrakis	2004	USA	31	84	50 mg/d	0	No	Other
Petrakis	2005	USA	123	84	50 mg/d	3	No	Abstinence
Pettinati	2008a	USA	106	77	100+ mg/d	3	No	Abstinence
Pettinati	2008b	USA	164	84	100+ mg/d	3	No	Abstinence
Schmitz	2004	USA	80	84	50 mg/d	0	No	Other
Schmitz	2009	USA	86	84	100+ mg/d	0	No	Abstinence
Sherwood Brown	2009	USA	50	84	50 mg/d	0	No	Other
Tidey	2008	USA	180	21	50 mg/d	0	No	Other
Toneatto	2009	Canada	52	77	100+ mg/d	0	No	Other
Volpicelli	1995[g]	USA	99	84	50 mg/d	7	Yes	Other
Volpicelli	1997	USA	98	84	50 mg/d	unspecified	Yes	Other
Acamprosate Studies								
Baltieri	2004	Brazil	75	84	1998 mg/d	7	Yes	Abstinence
Besson	1998	Switzerland	118	360	DBW	5	Yes	Abstinence
Chick	2000b	UK	581	182	1998 mg/d	5	No[h]	Abstinence

First Author	Year	Country	N total participants	Length of trial (days)	Dosage	Length of abstinence (days)	Detox before trial?	Goal of treatment
Geerlings	1997	Netherlands, Belgium, Luxembourg	262	182	DBW	5	Yes	Other
Gual	2001	Spain	296	180	1998 mg/d	0	No	Abstinence
Hammarberg	2009	Sweden	56	21	1998 mg/d	0	No	Other
Lhuintre	1985	France	85	91	DBW	5	Yes	Abstinence
Mason	2006	USA	601	168	1998 mg/d 3000 mg/d	0	No	Abstinence
Namkoong	2003	Korea	142	56	DBW	1	No	Other
Paille	1995	France	538	360	1332 mg/d 1998 mg/d	7	Yes	Abstinence
Pelc	1996[i]	Belgium	104	180	DBW	21	Yes	Abstinence
Pelc	1997	Belgium, France	188	90	1332 mg/d 1998 mg/d	14	Yes	Abstinence
Poldrugo	1997	Italy	246	182	DBW	5	Yes	Abstinence
Sass	1996	Germany	272	336	DBW	14	Yes	Abstinence
Tempesta	2000	Italy	330	182	1998 mg/d	5	Yes	Abstinence
Whitworth	1996	Austria	455	360	DBW	5	Yes	Abstinence
Naltrexone and Acamprosate Studies								
Kiefer	2003	Germany	120	84	NTX: 50 mg/d; Acamp: 1998 mg/d	12	Yes	Abstinence
Anton	2006	USA	921	112	NTX: 100 mg/d Acamp: 3000 mg/d	4	No	Abstinence
Morley	2006	Australia	169	84	NTX: 50 mg/d Acamp: 1998 mg/d	3	No	Other

Notes. DBW = Dosage by weight.

[a] Ahmadi & Ahmadi (2002) is sometimes cited as the primary study in previous reviews.

[b] Daily or targeted naltrexone.

[c] This study had one condition with 3 months of naltrexone and one condition with 12 months of naltrexone.

[d] Study did not give minimum, but 7 days = bottom of the range of required abstinence.

[e] Some participants received naltrexone for 9 months, but we have outcomes at 3 months.

[f] Each week, dosage of 100 mg administered 2x and dosage of 150 mg administered 1x for an average of 50 mg/day.

[g] Volpicelli, Alterman, Hayashida, & O'Brien (1992) is often cited as the primary study in previous reviews. We used both Volpicelli (1992) and Volipicelli (1995) to calculate effect sizes. The 1995 article counts as the "primary" article because it presents results for the largest sample.

[h] As was sometimes the case, this study provided detoxification, but it occurred up to 5 weeks before screening (our criteria indicated that detoxification needed to directly precede the start of treatment).

[i] Pelc, Verbanck, Le Bon, Gavrilovix, Lion, & Lehert (1992) is sometimes cited as the primary study in previous reviews.

Table 2

Main effects and comparisons of naltrexone and acamprosate for the 61 studies with either naltrexone or acamprosate compared to placebo (excluding the 3 studies which included both medications).

		Main effect of each medication compared to placebo				Subgroup test of heterogeneity: Naltrexone versus Acamprosate	
Outcome	**Medication**	***g***	***CI***	***p***	***# studies***	***Q***	***p***
Abstinence aggregate	Naltrexone	.116	.049 - .183	.001	36	13.22	< .001
	Acamprosate	.359	.246 - .472	< .001	15		
Heavy drinking aggregate	Naltrexone	.189	.123 - .255	< .001	39	1.98	.159
	Acamprosate	.072	−.078 - .221	.346	5		
Craving	Naltrexone	.144	.045 - .244	.005	26	3.17	.075
	Acamprosate	.034	−.036 - .104	.347	9		
Heavy drinking and craving aggregate	Naltrexone	.180	.118 - .243	< .001	42	8.40	.004
	Acamprosate	.041	−.029 - .112	.246	9		

Table 3

Descriptive information (top half of table) and correlations (bottom half of table) for the moderators of interest.

Descriptive information

	Abstinence before trial			Detoxification before trial		Goal of treatment		Length of treatment	Dosage		
	Required (*k*)	**Not Required (*k*)**	**Length (days)[a]**	**Required (*k*)**	**Not Required (*k*)**	**Abstinence (*k*)**	**Other (*k*)**	**Average length (days)**	**50 mg (*k*)**	**100+ mg (*k*)**	**Other (*k*)**
Naltrexone	30	18	*M* = 3.87 (*SD* = 5.05)	8	40	24	26	*M* = 96.83 (*SD* = 57.96)	39	8	2
									1998 mg (*k*)	By weight (*k*)	Other (*k*)
Acamprosate	16	3	*M* = 6.21 (*SD* = 5.49)	13	6	13	6	*M* = 173.37 (*SD* = 107.96)	7	8	4

Correlations among moderators

	Length of required abstinence	Detoxification before trial	Goal of treatment	Length of treatment
Length of required abstinence	--	--	--	--
Detoxification before trial	Naltrex:[b] $r = 0.60^{**}$, 0.52^{**} Acamp:[c] $r = 0.59^{**}$	--	--	--
Goal of treatment	Naltrex: $r = 0.28^{+}$, 0.36^{*} Acamp: $r = 0.30$	Naltrex: $r = -0.04, 0.03$ Acamp: $r = 0.32$	--	--
Length of treatment	Naltrex: $r = 0.22, 0.22$ Acamp: $r = 0.09$	Naltrex: $r = -0.08, -0.10$ Acamp: $r = 0.36$	Naltrex: $r = 0.18, 0.21$ Acamp: $r = 0.33$	--
Dosage	Naltrex: $r = -0.09, -0.18$ Acamp: $r = 0.18$	Naltrex: $r = -0.20, -0.15$ Acamp: $r = 0.28$	Naltrex: $r = 0.11, 0.03$ Acamp: $r = 0.04$	Naltrex: $r = 0.03, -0.11$ Acamp: $r = 0.36$

Notes.

k = number of studies.

$^{+}p < .10$

$^{*}p < .05$

$^{**}p < .01$.

[a] Minimum length of required abstinence. If abstinence not required, length = 0 days.

[b] To accurately assess collinearity in specific analyses, correlations are for the naltrexone studies in abstinence moderator analyses (*k* = 39) and heavy drinking moderator analyses (*k* = 42), respectively.

[c] Correlations are for acamprosate studies in abstinence moderator analyses (*k* = 18).