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Gabapentin Combined with Naltrexone for the Treatment of Alcohol Dependence

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Abstract

Objective—Naltrexone, an efficacious medication for alcohol dependence, does not work for everyone. Symptoms (e.g. insomnia, mood instability), most evident during early abstinence, might respond better to a different pharmacotherapy. Gabapentin may reduce these symptoms and early relapse. This clinical trial evaluated whether gabapentin, in conjunction with naltrexone, was better than naltrexone alone and/or placebo during the early drinking cessation phase (first six weeks) and whether this effect persisted.

Method—A total of 150 alcohol-dependent individuals randomly received sixteen weeks of naltrexone alone (50 mg/day [N= 50]), with gabapentin (up to 1200 mg/day [N=50] for the first six weeks), or double placebo (N= 50) while receiving medical management.

Results—During the first six weeks, the naltrexone/gabapentin group had 1) a longer delay to heavy drinking than the naltrexone-alone group (p =0.04) which was similar to the placebo group, 2) had less heavy drinking days than the naltrexone-alone group (p= 0.0002) which did worse than placebo, and 3) had less drinks/drinking day than the naltrexone-alone group (p=0.02) and the placebo group (p=0.01). These differences faded over the remaining study weeks. Poor sleep was associated with more drinking in the naltrexone-alone group, but not in the combined group, while an alcohol withdrawal history was associated with better response in the combined group.

Conclusion—The addition of gabapentin to naltrexone improved drinking outcomes over naltrexone alone during the first six weeks after cessation of drinking. This effect did not endure once gabapentin was discontinued. Future studies should evaluate gabapentin alone and over longer durations of treatment.

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Disclosures
The following individuals assisted in the collection of data: Allison Hardy, Sharon Kantala, Danielle Larson Moore, Steven LaRowe, Sarah Miles, Amanda Mountford, Sarah Jackson, Abraham Tiffany, and Glenna Worsham.
Dr. Anton reports for the last two years, being a consultant for Eli Lilly, Merck, Hythiam, Johnson & Johnson, and GlaxoSmithKline serving as a scientific advisory board member for Merck, Hythiam, Novartis, and Johnson & Johnson; and receiving grant support from Eli Lilly, Merck, Hythiam, Schering Plough, Lundbeck, Alkermes, GlaxoSmithKline, Johnson & Johnson, and Abbott Laboratories. Dr. Myrick reports serving on a speaker's bureau for Bristol-Myers Squibb and Alkermes. Dr. Wright, Dr. Latham, Dr. Baros, Dr. Waid, and Dr. Randall have no interest to disclose.

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Introduction

While there are several medications that are approved by the FDA, including disulfiram, naltrexone (both oral and long acting injectable), and acamprosate, as well as a few others (e.g. topiramate) that have been shown to be effective in the treatment of alcohol dependence, many individuals do not respond totally, if at all, to them. There is a need for new medications, especially those targeted to different aspects of the alcohol dependence, ranging from individual phenomenological to genetic differences. One such phenomenological difference may be defined by a set of signs and symptoms that might change over time as individuals attempt to stop drinking. For instance, it is well known that the period immediately after termination of alcohol consumption is a “high risk time” for relapse drinking. This “early abstinence period” might be defined by certain phenomena that are likely to ameliorate overtime with continued abstinence. These signs and symptoms could range from easily observed alcohol withdrawal symptoms, to a more subtle, but still meaningful constellation of problems including sleep difficulty, irritability, concentration problems, anxiety, and dysphoria. Some have labeled this constellation of lingering symptoms that occur after the initial cessation period as “protracted alcohol withdrawal” (1). While not well defined, it is highly likely that some of these symptoms might be experienced for those who do not show florid alcohol withdrawal symptoms on cessation of drinking. Nevertheless, this constellation of symptoms, and the associated craving that could manifest secondary to them, might not be particularly responsive to medications that reduce alcohol reinforcement or cue-induced craving such as naltrexone (2) (3) (4). Since clinician soften cannot predict, a priori, what sort of symptoms specific individuals will exhibit as well as what sort of craving (withdrawal based versus reward based) will be the most salient, it might be wise to attempt to reduce both in order to improve treatment efficacy. We and others have previously shown that anticonvulsants in general (5) (6) (7) and gabapentin in particular (1) (8) (9) were able to ameliorate acute alcohol withdrawal and could actually be useful in preventing relapse (10) especially in those with previous alcohol withdrawal symptoms (11). Gabapentin, which works by modulating both GABA and glutamate tone, is an especially appealing drug since it hypothetically can “normalize” the known GABA deficits and glutamate excess that is thought to underlie alcohol withdrawal (12) and perhaps parts of the early abstinence, or protracted withdrawal syndrome (13). It is also safe to use in alcoholics as it appears to have limited, to no, adverse interaction with alcohol (14) (9) and it is excreted by the kidney rather than the liver, which is known to be compromised in many alcoholics.

The primary goal of this study was to evaluate whether gabapentin, when added for the first six weeks of a 16-week treatment course of naltrexone, would be well-tolerated and improve the efficacy of naltrexone alone. Secondary goals were to evaluate the effects of this combination of medications on parameters such as sleep (15) and mood that have been thought to predict poor outcome to treatment. In addition, we explored whether a history of alcohol withdrawal symptoms would be predictive of a response to this combination of medications.

Methods

This was a randomized controlled clinical trial (clinical trials. Gov #NCT00183196) approved by our institution’s IRB. After initial screening and assessment, alcohol dependent individuals received either 1) naltrexone plus active gabapentin (n=50), 2) naltrexone plus placebo gabapentin (n=50), or 3) placebo naltrexone and placebo gabapentin (n=50), using a double dummy placebo controlled medication design. Naltrexone or its matching placebo was given as 25 mg for 2 days and then 50 mg/day for up to 16 weeks. Gabapentin (300 mg capsules) or its matching placebo was given as one capsule at night (300 mg/day) on day 1,

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one capsule in the morning and at night (600 mg) on day 2, one capsule morning, noon, and night (900 mg/day) day 3–4, then one capsule in the morning, one at noon, and two at night (1200 mg/day) on day 5 through day 42 (six weeks).

All subjects met DSM-IV criteria for alcohol dependence, consumed on average 5 or more standard drinks per day for men and 4 or more for women, were able to maintain sobriety for 4 days prior to randomization, and lived within 50 miles of our study site in a stable living situation. Exclusion criteria included: meeting DSM-IV criteria for other substance dependence (except nicotine), abused illicit drugs in the past 30 days or a positive urine drug screen, meeting DSM-IV criteria for an axis 1 disorder, having current suicidal or homicidal ideation, needing maintenance with psychotropic or anticonvulsant medication, unstable medical conditions, liver enzymes (ALT and AST) more than 3 times normal, use of either of the study medications, disulfiram, or acamprosate within the last 30 days, taking an opiate medication on a routine basis, having legal charges pending, and more than one previous inpatient medical detoxification treatment.

Subjects had to abstain from alcohol for at least four consecutive days before random assignment to study medication. During the assessment period, the following were administered: SCID-IV, Alcohol Dependence Scale (ADS) (16), Obsessive Compulsive Drinking Scale (OCDS) (17), Form-90 (modified time-line followback method for documenting alcohol consumption) (18), Profile of Mood States (POMS) (19), the Beck Depression Scale (20), Epworth Sleepiness Scale (21), and Insomnia Sleep Index (22), and the Clinical Institute Withdrawal Assessment for Alcohol-Revised (23). Lab tests included a health screen, liver function tests, pregnancy test (females) and alcohol use markers gamma-glutamyltransferase (GGT) and carbohydrate-deficient transferrin (24).

Medication was dispensed in identically packaged blister cards. Each naltrexone or gabapentin and their identical placebo capsules also contained 100 mg. of riboflavin. Subjects were provided up to 16 sessions of Combined Behavioral Intervention (CBI) therapy using the COMBINE Study CBI treatment manual (25) which combined cognitive behavioral therapy, motivation interviewing and twelve step facilitation techniques in a client “needs based” approach. A physician or nurse evaluated physical complaints and encouraged medication adherence.

General Study Procedures

Subjects were seen by a CBI therapist and a health care provider on weeks 1, 2, 3,4, 6, 8, 10, 12, and 16 of treatment. Similar to procedures used in the COMBINE study, a research assistant assessed alcohol intake (timeline follow back calendar method), craving (OCDS), symptom checklist, and the POMS in all groups. Liver function tests and %CDT were measured at week 3, 6, 10, and 16. Reasons for ”early termination” were recorded and full 16-week drinking data was collected where possible.

Statistical Analysis

Group differences in baseline variables, study retention, therapy adherence, and medication compliance, were analyzed with ANOVA or chi-square methods (SAS 8.2 analytic package). Subjects with at least one post-randomization outcome measurement were included in the efficacy analyses. Two people in the placebo group, two in the naltrexone-only group, and two in the naltrexone/gabapentin group did not return for at least one post-randomization evaluation.

Time to the first heavy drinking day, was analyzed using Cox regression with baseline percent heavy drinking days as a covariate with missing data due to drop-out censored. A pre-planned, 2-step analysis was conducted evaluating 1) the overall survival curve from

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study entry through week 16 and 2) only the first six weeks when both naltrexone and gabapentin were taken together. To evaluate any differential response between those who had, or did not have, a history of alcohol withdrawal symptoms/treatments (those who either experienced alcohol withdrawal symptoms at study entry or had past inpatient detoxification treatment) this variable was entered into the above cox regression analysis along with medication group to evaluate interactions.

Percent heavy drinking days per week, and drinks per drinking day, were analyzed first over the whole trial and secondarily in the two phases described above. If a significant overall effect was found, between-group comparisons were undertaken and reported. The OCDS and sleep quality was similarly analyzed. The analytic plan used was a linear mixed model evaluating main effects of group, time and group × time interactions (SAS 9.2, PROC MIXED).

Alcohol consumption markers (%CDT and GGT) were analyzed using the generalized estimating equation approach (SAS Proc Genmod) across measurements at baseline, 3, 6, 10, and 16 weeks as binary outcome variables (positive result indicating heavy drinking). An unstructured covariance matrix was employed.

After complete description of the study to the subjects, written informed consent was obtained.

Results

Subject Population

The flow chart of subject recruitment and randomization is given in figure 1. Characteristics of the subject population are given in table 1. The average age is in the mid-40's, mostly male and Caucasian. On average they drank about 12–13 drinks per drinking day on about three quarters of the days in the 90 days prior to randomization. Of note, 9–14% of subjects were medically detoxified prior to participation in the treatment study (almost exclusively as outpatients by study physicians). There were no between medication group differences on any demographic or drinking variable.

Retention and Adherence

On average subjects received 10–11 CBI therapy sessions and 82–88% of subjects provided all 16-week drinking data. Subjects took about the same number of medication capsules across all treatment groups (range 92–96% of prescribed medication). There were no between group statistical differences.

Drinking Outcomes

Time to first heavy drinking day is given in figure 2. There was an interaction of treatment phase by medication group (0.02). In phase one, the naltrexone/gabapentin group had a longer time to relapse than the naltrexone-alone group (p=0.04) that in turn was not different from the placebo treated group. However, over the remainder of the trial there were no treatment group differences.

For percent heavy drinking days (figure 3) there was a significant difference between medication groups over the 16-week study (F=6.59, DF 2,142 p=0.0018). During the first phase (through week 6), those treated with naltrexone-alone actually did worse than placebo (t= 2.35, DF 142, p=0.020) while the naltrexone/gabapentin group did similarly to placebo (t=1.42, DF 142, p =0.16) but significantly better than naltrexone-alone (t= 1.4, DF 142,

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p=0.0002). While the naltrexone/gabapentin group appeared to do better, even after gabapentin was stopped, this did not reach statistical significance.

For drinks per drinking day (figure 4) there was a significant difference between medication groups over the 16-week study (F=4.77, DF 2,95 p=0.01). During the first phase (through week 6), those treated with naltrexone-alone were not significantly better than placebo, while the naltrexone/gabapentin group did significantly better than placebo (t=2.65, DF 81, p =0.01) and also significantly better than naltrexone alone (t= 2.57, DF 81, p=0.02). After gabapentin was stopped, there were no significant differences between groups.

Craving

There were no significant differences between the groups on the OCDS total score in either phase of the study. However, on the resistance control factor (RCI), a subscale we had found previously to be most responsive to naltrexone (17), the medication groups differed at a trend level (F=2.33, DF 2,139 p=0.10) with significant differences being evident only during phase 1. There was no significant difference between placebo and naltrexone-alone groups but the naltrexone/gabapentin group showed a significantly lower score, i.e. more control over drinking urges, than the naltrexone alone group (t= 2.16, DF 139, p=0.04) and somewhat better than the placebo group (t= 1.69, DF 139, p=0.09).

Biomarkers of Drinking

The probability of having a positive GGT showed a significant group by time interaction ($X^2(8)=16.8$, p=0.032) with the naltrexone/gabapentin group having significantly less positive GGT values than the other two medication groups during phase 1 ($X^2(2)=7,82$, p =0.02) and at a trend level in phase 2 ($X^2(2)=5.55$, p=0.06).

The probability of having a positive %CDT showed an almost significant group by time interaction ($X^2(8) =14.7$, p =0.06) with the naltrexone/gabapentin group having significantly less positive %CDT values than the other two groups during the gabapentin phase ($X^2(1)$ =6.37, p =0.012 compared to the naltrexone-alone group and $X^2(1) =5.23$, p =0.022 compared to the placebo group). There were no significant differences after gabapentin was stopped.

Overall, the blood tests of heavy alcohol consumption were consistent with the verbally reported drinking showing similar between-group effects.

Sleep Quality, Mood State, and Treatment Response

Overall, there was a marginally significant difference between the groups over the course of the study (F=2.66, DF 2,140 p=0.07) but during the first phase of the study, while there was no significant difference in reported sleep between the placebo and naltrexone-alone group, the naltrexone/gabapentin group reported significantly better sleep than either the placebo alone group (t=2.49, DF 140, p=0.02) or the naltrexone-alone group (t=2.49, DF 140, p=0.03).

Poor sleep quality (high ISI) was significantly related to heavy drinking, but only in the naltrexone-alone group (B=0.261 (0.12), t (139) =2.13, p=0.035). That is, in the naltrexone-alone group, but not in the other two groups, individual subjects were more likely to drink heavily during periods in which they reported poor sleep.

There were no statistical or trend levels for POMS scores or factors to be significantly different between medication groups or differentially predict treatment outcomes.

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History of Alcohol Withdrawal and Treatment Response

Figure 4 shows an overall alcohol withdrawal history by medication group interaction (p=0.03). Those with an alcohol withdrawal history who received the naltrexone/gabapentin had significantly less relapse to heavy drinking than those treated with placebo (p=0.03) while in those with no alcohol withdrawal history there was no difference between these medication groups. An analysis of heavy drinking days during phase 1 essentially found the same relationship. Alcohol withdrawal history had no effect on the naltrexone alone versus placebo comparison.

Side Effects

Both active medication groups reported more dizziness than placebo (p = 0.006). The naltrexone/gabapentin group reported more daytime somnolence than the other two groups (p= 0.02), more blurred vision (p= 0.02) and more premature ejaculation (p=0.02) than the placebo group. All were of a mild to moderate nature.

Discussion

As hypothesized, gabapentin, when combined with naltrexone, appeared to be well–tolerated and to improve overall efficacy above that noted for naltrexone-alone and for placebo. Surprisingly, perhaps, naltrexone-alone was not superior to placebo in this study, and in fact, on some measures, worse. This is consistent with the results from the COMBINE Study (4), where naltrexone added nothing to the efficacy of the combined behavioral intervention (CBI). In the current study CBI was employed as the standard psychosocial intervention and was delivered, primarily, by the same therapists who delivered it for the COMBINE Study at our site, which was finished after this study had begun. In the COMBINE Study, only those who received naltrexone with a less intensive medical management approach showed efficacy over placebo. In that sense, the results of the current study are exactly what would have been predicted by the COMBINE Study, i.e. that CBI might mask the efficacy of naltrexone's pharmacological effects. Despite this, it appeared that adding gabapentin to naltrexone was better than naltrexone-alone or placebo on several drinking, craving, and blood-marker outcome variables especially during the first six weeks when subjects were receiving gabapentin. While some of the positive effects seen of combining gabapentin and naltrexone during this time could still be observed over the next 10 weeks, for the most part these were no longer significant, implying that gabapentin effects occurred only while study subjects were actually taking it. We had hypothesized a priori that gabapentin might work best during the initial phases of abstinence when acute, and protracted, alcohol withdrawal effects might be the most pronounced. The hope was that by using gabapentin to ameliorate symptoms like insomnia, irritability, and withdrawal craving during this period, naltrexone might have a greater chance of working, and would continue to work once gabapentin was stopped. This hypothesis could not be validly confirmed.

While we did find an additive response of gabapentin to naltrexone in those with a history of current, or past, alcohol withdrawal, and also found some favorable effects on sleep while individuals were taking gabapentin, the importance of these findings is not clear. Others reported that gabapentin worked better than placebo in preventing relapse in patients who had undergone benzodiazepine detoxification, but did not compare them to non-detoxified individuals (10). Our group recently reported that gabapentin worked significantly better than placebo only in those with clinically significant alcohol withdrawal at the time of study entry (11). In that study gabapentin was adjunctive to an initial intravenous flumazenil, so the direct effect of gabapentin, by itself could not be validly affirmed. Group specificity (working only in those with alcohol withdrawal symptoms) and gabapentin's longer-term period of dosing (over about 6–7 weeks, similar to the current trial) compared to flumazenil

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(2 days) does imply that gabapentin might have been the primary component of the effective treatment. Of note, in that study, those without current alcohol withdrawal actually did significantly worse on gabapentin compared to placebo, a finding consistent with reports in animals (26). In the current study, this effect was not observed. However, the group size of the current post hoc exploratory analysis was small, and the definition of alcohol withdrawal history was defined post hoc, limiting the validity of this finding and requiring replication. Nevertheless, the confluence of results suggests that more evaluation of gabapentin by itself is necessary especially in alcoholics who do, and do not have current, or possibly past, alcohol withdrawal symptoms.

Interestingly, when gabapentin was stopped, there appeared to be some increase in drinking, with worsening in sleep (data not shown) - also noticeable, to some degree in the placebo group. It is hard to determine if this was a physiological response to discontinuing gabapentin or just an effect of taking fewer pills, especially those at bedtime. In a controlled sleep study, gabapentin improved alcohol-disrupted sleep (27) and normalized sleep in non-treatment seeking alcoholics (28). Our group reported that gabapentin normalized sleep during alcohol withdrawal better than lorazepam but only in those with histories of multiple detoxifications (29). Karam-Hage and Brower (30) had originally proposed that gabapentin might work to reduce relapse drinking by “normalizing” sleep, particularly in those who might drink to assist with sleep. However, in a more recent study in alcoholic insomniacs, they found that, while gabapentin delayed onset to heavy drinking after initial abstinence, its efficacy was not attributable to improved sleep (15).

There was initial concern about the safety of gabapentin especially when it was ingested with alcohol. Several controlled studies done by us (31) and others (14) have assuaged that concern to a large degree. In this clinical trial, while there were some low-grade symptoms e.g. dizziness reported more frequently in the naltrexone plus gabapentin group, in general the medication was well tolerated, consistent with data from other relapse prevention trials with gabapentin alone (10) (11). Of note, since gabapentin is excreted in the urine, there would not be any expected interaction with naltrexone on liver metabolism and/or toxicity and none were noted in this trial.

Since gabapentin works on different neurophysiologic systems than naltrexone this combination of medication has some appeal. Naltrexone, as an opioid receptor antagonist, appears to reduce the reinforcing aspects of alcohol cues and consumption (3) (32), while reducing craving and slip drinking (33). Gabapentin, working to normalize GABA and glutamate balance, might work best at restoring normal overall brain activity and tone and be most useful in those that have imbalances in these systems-like those experiencing acute or protracted alcohol withdrawal symptoms. As such, this combination of medication makes pharmacological sense and is consistent with what is known about the neuroscience of addiction in general, and specifically, the effects of alcohol on the brain. However, it is possible, since GABA and glutamate systems also play a role in reinforcement, extinction, and cue-induced learning (34), that gabapentin might play a primary role in preventing alcohol relapse and reducing drinking similar to other anticonvulsants, like topiramate (35), that have similar basic pharmacological and brain effects. It should be noted, however, in some pilot work done by our group in a laboratory paradigm designed to test the alcohol anti-reinforcement effects of medication, that gabapentin did not appear to block craving and drinking behavior (36) in the same way that naltrexone had done previously (32, 37). However, others have found some effects of gabapentin on alcohol cue-induced craving (28).

Limitations of this study include being a single site study with a limited number of individuals with alcohol dependence who did not have other significant psychiatric

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conditions, who were not on psychiatric medications, who were medically stable, and who, for the most part, were motivated towards abstinence. Individuals received an efficacious psychosocial intervention along with medication and were encouraged to comply with medications and the study protocol. In addition, since this study was started prior to knowledge of the potential prediction of naltrexone response by a mu opioid receptor genetic polymorphism (38) we could not account for this potential confound. Finally, the independent effect of gabapentin alone could not be evaluated in this study design.

In sum, the addition of gabapentin to naltrexone for the treatment of alcohol dependence seems efficacious and well tolerated. While there are hints that this combination might work best in those who have previously experienced alcohol withdrawal symptoms, further study is needed to confirm this speculation. In addition, these data combined with that of others, suggest that future studies should explore the use of gabapentin-alone while taking into account current, or past, acute and protracted alcohol withdrawal signs and symptoms including sleep difficulties and craving. A better understanding of the role of gabapentin, and other anticonvulsants, on reinforcement and extinction issues is needed.

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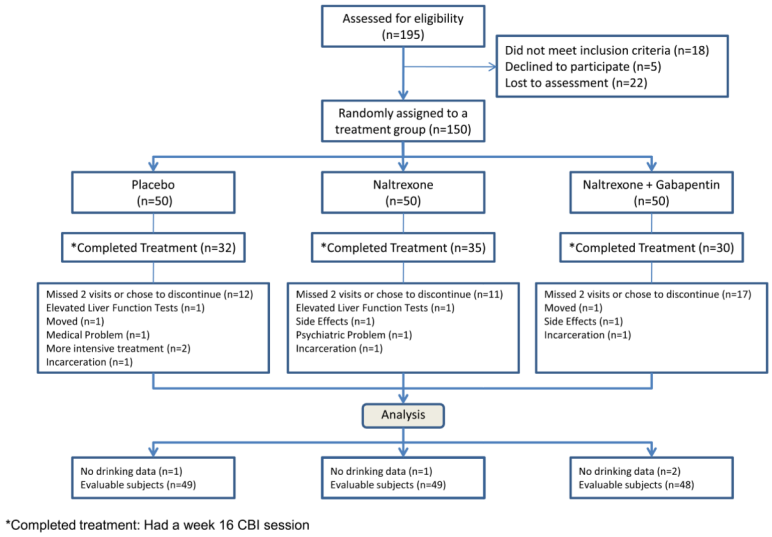

Figure 1.

Participant flow into a randomized, double-blind placebo-controlled trial combining naltrexone and gabapentin (for the first 6 weeks) with naltrexone-alone for treatment of alcohol dependence.

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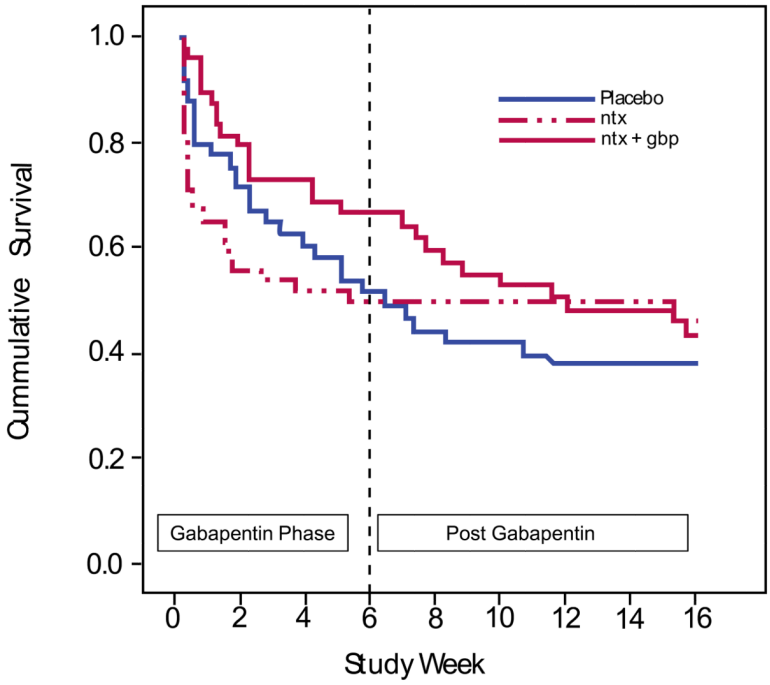

Figure 2.

Time to First Heavy Drinking Day

Cumulative survival of participants not having a heavy drinking day over the course of the study. During the first six weeks, the naltrexone/gabapentin group had more time to a first heavy drinking day than the naltrexone-alone group (p= 0.04), which in turn was not significantly different than the placebo group. There were no significant differences in the post-gabapentin phase.

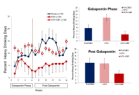

Figure 3.

Percent Heavy Drinking Days

Percent heavy drinking days per week during the trial (left panel) and the total over each period (right panel). During the first six weeks, those receiving naltrexone/gabapentin had less heavy drinking days than those receiving naltrexone-alone (p=0.0002) but similar to placebo (p=0.16). These effects faded after gabapentin was stopped (post-gabapentin) phase.

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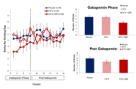

Figure 4.

Drinks Per Drinking Day

Average drinks per drinking day each week during the trial (left panel) and total over each period (right panel). During the first six weeks, those receiving naltrexone/gabapentin had less drinks/drinking day than those receiving naltrexone-alone (p=0.02) and placebo (p=0.01). There were no significant differences after gabapentin was stopped (post-gabapentin) phase.

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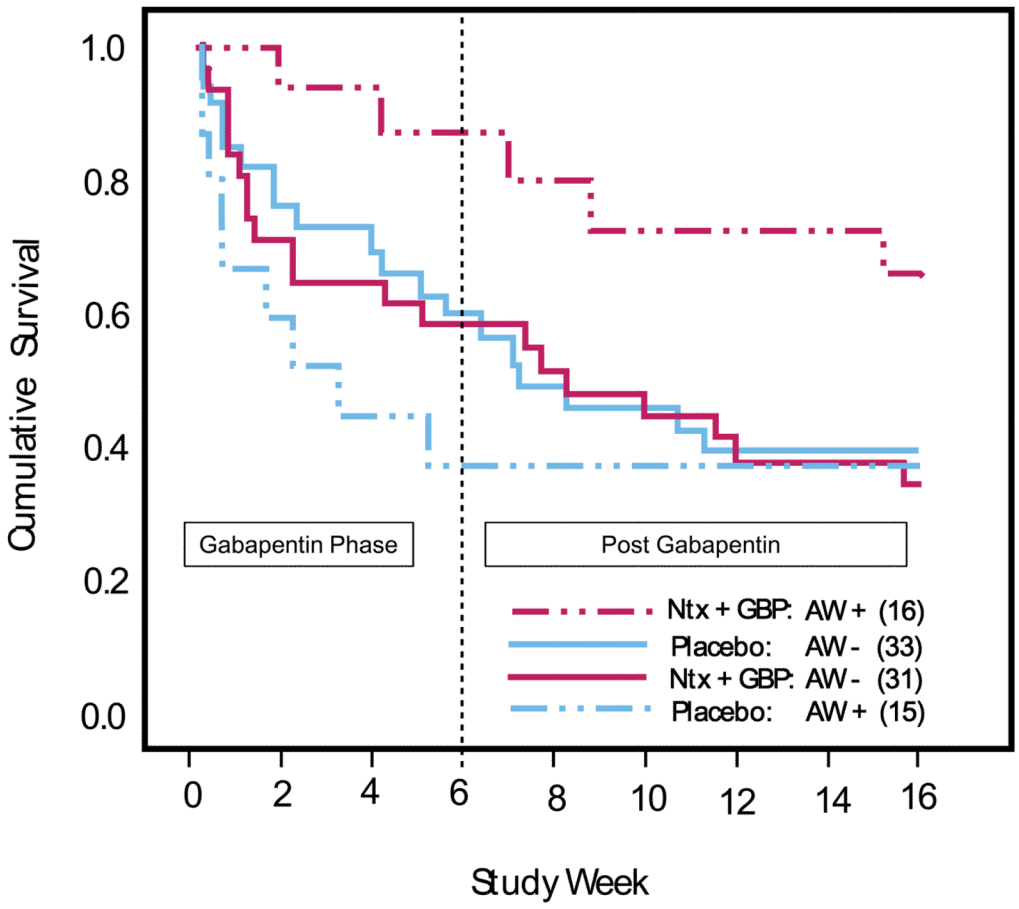

Figure 5.

Alcohol Withdrawal History and Treatment Response

Cumulative survival of participants not having a heavy drinking day over the course of the study for those with or without a history of alcohol withdrawal (AW). Those with a history of AW treated with naltrexone/gabapentin had more time to a first heavy drinking day compared to those receiving placebo (p= 0.03). For those without a history of AW there was no difference between medication groups.

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Table 1

Demographics and drinking characteristics of the study population by medication group.

Characteristic	Placebo (N= 49)	NTX (N=49)	NTX + GB (N=48)	Significance
Age (± SD)	46.6 (9.0)	44.4 (10.1)	43.0 (9.8)	0.19
Gender: Male N (%)	40 (82%)	39 (80%)	40 (83%)	0.89
Detoxed prior to study N (%)	6 (12%)	7 (14 %)	4 (8%)	0.67
Race N (%)				
Caucasian	43 (88)%	42 (86%)	42 (88%)	0.79
AA	5 (10%)	5 (10%)	6 (12%)	
Other	1 (2%)	2 (4%)	0 (0%)	
Drinks per Drinking Day (±SD)	12.0 (5.9)	12.1 (7.2)	12.8 (6.3)	0.68
Drinks per Day (± SD)	9.7 (5.3)	11.2 (6.7)	11.1 (6.4)	0.39
Percent Heavy Drinking Days (±SD)	73.1 (23.8)	77.1 (23.6)	77.6 (22.8)	0.6
Obsessive Compulsive Drinking Scale (±SD)	24.8 (8.4)	25.1 (8.4)	24.7 (10.2)	0.97
Beck Depression Scale (±SD)	12.3 (9.5)	12.8 (8.3)	15.3 (9.7)	0.23
Insomnia Sleep Index (±SD)	9.7 (6.6)	8.3 (6.2)	10.1 (6.0)	0.31
% Smoking (in last 30 days) N (%)	27 (55%)	29 (58%)	26 (55%)	0.93