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Naltrexone and Combined Behavioral Intervention Effects on Trajectories of Drinking in the COMBINE study

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Abstract

Objective—COMBINE is the largest study of pharmacotherapy for alcoholism in the United States to date, designed to answer questions about the benefits of combining behavioral and pharmacological interventions. Trajectory-based analyses of daily drinking data allowed identification of distinct drinking trajectories in smaller studies and demonstrated significant naltrexone effects even when primary analyses on summary drinking measures were unsuccessful. The objective of this study was to replicate and refine trajectory estimation and to assess effects of naltrexone, acamprosate and therapy on the probabilities of following particular trajectories in COMBINE. It was hypothesized that different treatments may affect different trajectories of drinking.

Methods—We conducted exploratory analyses of daily indicators of any drinking and heavy drinking using a trajectory-based approach and assessed trajectory membership probabilities and odds ratios for treatment effects.

Results—We replicated the trajectories ("abstainer", "sporadic drinker", "consistent drinker") established previously in smaller studies. However, greater numbers of trajectories better described the heterogeneity of drinking over time. Naltrexone reduced the chance to follow a "nearly daily" trajectory and Combined Behavioral Intervention (CBI) reduced the chance to be in an "increasing to nearly daily" trajectory of any drinking. The combination of naltrexone and CBI increased the probability of membership in a trajectory in which the frequency of any drinking declined over time. Trajectory membership was associated with different patterns of treatment compliance.

Conclusion—The trajectory-analyses identified specific patterns of drinking that were differentially influenced by each treatment and provided support for hypotheses about the mechanisms by which these treatments work.

Keywords

alcohol research; naltrexone; acamprosate; combined behavioral intervention; clinical trial; trajectory-based analysis

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1. Introduction

Some of the heterogeneity of clinical findings in studies evaluating the efficacy of pharmacotherapies and behavioral therapies in the treatment of alcohol dependence can be attributed to the wide use of standard statistical analytical tools of summary drinking measures that poorly reflect the distributions, variability, and complexity of drinking data. Novel statistical analysis tools based on trajectories over time provide a more realistic and complete picture of treatment effects on drinking behavior. In secondary analyses of data from the VA naltrexone study (Krystal et al., 2001) and the Women's naltrexone study (O'Malley et al., 2007), we successfully used trajectory analyses to examine whether there were distinct trajectories of drinking during treatment and whether naltrexone modified the chance of following a specific trajectory (Gueorguieva et al., 2007). The results of these analyses were remarkably similar across the two studies and revealed three trajectories ("abstainers", "sporadic drinkers", and "consistent drinkers"). Despite negative findings on the primary summary measures based on more traditional analytic methods, in the trajectory-based reanalysis we demonstrated that naltrexone significantly decreased the chance of being in the "consistent drinker" trajectory. In a similar reanalysis using latent growth mixture models of the Project MATCH data, Witkiewitz et al. (2007) also identified three trajectories of drinking and were able to detect interactions between baseline self-efficacy and treatment (Cognitive Behavioral Therapy vs. Motivational Enhancement) for frequent drinkers that had not been detected in the original analyses. These three studies demonstrate the ability of trajectory-based approaches based on mixture models to capture heterogeneity in drinking data and to identify trajectories where treatment effects are more pronounced.

Trajectory analyses have been also applied to large-scale observational studies of developmental patterns of alcohol use (Muthén and Muthén, 2000ab;Hill et al., 2000; Chassin et al., 2000; Del Boca et al., 2003;Greenbaum et al. 2004). For example, Muthén and Muthén (2000ab) have explored the development of heavy drinking and alcohol-related problems from ages 18 to 37 in a nationally representative sample from the National Longitudinal Study of Youth. Hill et al. (2000) and Chassin et al. (2000) have assessed developmental trajectories of adolescent binge drinking. Chung et al. (2004,2005) have analyzed drinking patterns and the relationship of drinking patterns and symptom occurrence in treated adolescents.

In the current manuscript we perform exploratory trajectory analyses to investigate the effects of naltrexone, acamprosate and the Combined Behavioral Intervention (CBI) in the COMBINE Study. The COMBINE Study (Anton et al., 2006) represents the largest study of pharmacotherapy for alcoholism in the United States. It was designed to answer questions about the benefits of combining behavioral and pharmacological interventions. Naltrexone, an opiate antagonist, was studied based on evidence that it reduced the risk of heavy drinking and increased the percentage of days abstinent in most studies (Kranzler and Van Kirk, 2001; Pettinati et al., 2006; Srisurapanont and Jarusuraisin, 2005). Acamprosate, thought to reduce glutamatergic hyperactivity associated with protracted abstinence, was chosen because it had been demonstrated to maintain abstinence within varied behavioral treatment frameworks (Mann et al., 2004; Mason et al., 2001, 2005; Soyka et al., 2002). The behavioral interventions examined included Medical Management (MM) (Pettinati et al., 2004, 2005) and the Combined Behavioral Intervention (CBI) (Longabaugh et al., 2005; Miller et al., 2004). MM was designed as a means of enhancing medication compliance and reinforcing of sobriety that could be used in a primary care or managed care settings by nonspecialists (Fleming et al., 1997). CBI integrated components from cognitive behavioral, motivational enhancement, and 12-step facilitation therapies originally developed for and evaluated positively in Project MATCH (1997ab).

At the time COMBINE was designed, summary measures derived from timeline reports of daily drinking were the standard approach to assessing outcomes (Babor et al., 1994; Finney et al., 2003). In COMBINE, the two primary outcomes were time to the first day of heavy drinking and percent days abstinent in the 16-week treatment period. The primary findings were that either naltrexone (+ MM) or CBI (+ placebo naltrexone + MM) improved outcomes compared to MM + placebo and that there was no additional advantage of combining CBI with naltrexone over each monotherapy. The fact that there was no advantage of combined treatment with CBI and naltrexone was unanticipated. In addition, the failure to find an effect of acamprosate either alone or in combination with CBI or naltrexone was particularly unexpected given the positive studies of acamprosate (Mann et al., 2004; Mason et al., 2005) and of the combination of acamprosate and naltrexone (Kiefer et al., 2003; Feeney et al., 2006) conducted in Europe.

Like other studies, the primary outcome measures used by COMBINE have a number of potential limitations. For example, time to the first heavy day of drinking does not take advantage of the daily reports of drinking that occur after the first event. The distribution of percentage of days abstinent is skewed and subject to ceiling effects. None of these summary measures allow description of temporal trends of the data and the standard statistical analyses that are typically applied to these measures poorly reflect the multimodal distribution of drinking data.

Advances in longitudinal statistical modeling enable the use of daily drinking data. Growth modeling (Lindsey, 1993; Longford, 1993; Diggle 1994; Raudenbush and Bryk, 2002) assumes that every individual follows the same type of trajectory over time, while mixture approaches (Muthén and Muthén, 2001ab; Nagin, 1999; Dolan et al., 2005) allow data-driven identification of distinct classes of developmental trajectories. Thus, it is possible to identify subgroups of subjects who show distinct patterns of clinical response within a clinical trial based on the structure of the data generated by that trial, i.e., subgroups that might not have been hypothesized a priori by the investigative team.

For heterogeneous populations, the trajectory-based approach appears to be more powerful than the analysis of traditional summary measures of drinking and time to event models. For example, trajectories capture information on frequency of drinking, duration of abstinence and rate of change over time. If we were to fit a model using summary measures of drinking we would have to analyze three highly correlated such measures to capture all these aspects of drinking. Although no direct comparison of trajectory models to multiple time-to-event methods (Wang et al., 2002) has been performed to date, the purposes of these analyses are different and these procedures should be regarded as complementary rather than competing. In trajectory models the goal is to identify subgroups of subjects who might be more or less responsive to interventions while in multiple time-to-event models the goal is to take into account drinking behavior for the population as a whole beyond the first episode of drinking.

The main objective of the trajectory re-analyses of the drinking data in COMBINE was to estimate distinct trajectories of any drinking and heavy drinking and to assess the effects of naltrexone, acamprosate and CBI on these trajectories. We hypothesized that different treatments may affect different trajectories of drinking. In particular, we predicted that there would be at least three trajectories of drinking over time, similar to those obtained in the VA naltrexone study and the women's naltrexone study ("abstainers", "sporadic drinkers" and "consistent drinkers") on any and heavy drinking. We anticipated that naltrexone would significantly decrease the chance to belong to a "consistent drinker" trajectory as compared to "sporadic drinker" and "abstainer" trajectories and we hypothesized that CBI would have a similar effect. Based on the original COMBINE analyses, we did not anticipate that the combination of CBI and naltrexone would be more beneficial than either CBI or naltrexone

alone. We also planned to explore acamprosate effects on the probability to follow particular trajectories although we did not anticipate observing significant results given that the tests of acamprosate effects were not significant in the original COMBINE analyses.

Given the larger sample size, we further hypothesized that we would be able to find a larger number of classes of drinking patterns over time in which the "sporadic drinker" and "consistent drinker" classes might split into subclasses that might show stronger treatment effects. In particular, we anticipated that naltrexone might be associated with a trajectory of decreasing drinking over time. Sinclair (1990) hypothesized that extinction of drinking behavior should occur over time with naltrexone due to attenuation of alcohol reinforcement, and preclinical studies have demonstrated that naltrexone progressively reduces the onset and duration of drinking over multiple sessions (Hyttia & Sinclair, 1993). Consistent with this perspective, naltrexone increased the number of days to a second episode of drinking following a lapse in abstinence among alcohol dependent patients (e.g., Anton et al., 1999). At the same time, CBI teaches new skills for coping with situations that otherwise lead to drinking. The benefit of CBI may not emerge until later during treatment, however, because CBI requires several sessions to impart this information (Longabaugh et al., 2005). This benefit could conceivably involve an improvement over time or maintenance of initial improvement. Clinical trials of cocaine abusers provide evidence that Cognitive Behavior Therapy, a component of CBI, has a delayed emergence of efficacy involving maintenance of improvements relative to comparison treatment conditions in which initial gains deteriorated over time (Carroll et al., 1994; Carroll et al., 2000).

2. Methods

The COMBINE study enrolled 1,383 abstinent alcohol dependent patients. Eight groups received medication management (MM) and either placebos, naltrexone, acamprosate, or naltrexone + acamprosate. Half of these groups also received the CBI. Participants on different treatments were found to be comparable on seventy-six pretreatment characteristics (Anton et al., 2006). Analyses of the two primary endpoints, time to the first day of heavy drinking and percent days abstinent, revealed that either naltrexone or CBI without naltrexone improved outcomes compared to MM + placebo. A ninth group received CBI alone with no pills in order to examine placebo effects in secondary analyses.

The "Timeline Follow Back" (TLFB) was used to collect daily drinking data. TLFB is the most comprehensive self-report measure and has good reliability and internal consistency on summary drinking measures (Sobell and Sobell, 1992,1995). In this trajectory-based reanalysis we focused on the daily binary indicator of drinking (1 if any drinks were consumed by the subject on that day, 0 otherwise) or heavy drinking (1 if 5 or more drinks were consumed by males and 4 or more drinks were consumed by females on that day, 0 otherwise).

We used the approach of Nagin (1999) and Nagin and Tremblay (2001) to identify distinct trajectories of drinking patterns during the first 16 weeks of the trial and to estimate how naltrexone, acamprosate and CBI (alone or in combination) affect the probability of following a particular trajectory. The models assumed fixed polynomial trends over time within each trajectory class and modeled the effect of treatment (naltrexone, acamprosate, CBI and their interactions) on trajectory membership via a generalized logistic regression model with the number of outcome categories equal to the number of trajectory classes. Thus, we estimated how the odds of being in a trajectory compared to a reference trajectory varied depending on treatment.

We fit two sets of models for any and heavy drinking. In the first set of models we fixed the number of trajectories to three to be able to compare our results to the results from the analyses

of the VA naltrexone trial and the women's naltrexone study. The second set of models involved model selection (number of trajectory classes and degree of the polynomial trends over time such as linear, quadratic) based on the Schwartz Bayesian criterion (BIC) and on having at least 5% of subjects in each trajectory class. BIC is a criterion of how well the model fits the data while keeping model complexity low. Only the final models (i.e. the models that provided the best fit according to BIC) are presented in the Results section. Percent days abstinent and percent heavy drinking days in 90 days prior to study entry were included as covariates for any drinking and heavy drinking respectively.

Classification accuracy was assessed using the entropy measure (Muthén, 2004) with values close to 1 indicating excellent classification of individuals to trajectory classes. Overall tests of treatment effects were performed first, followed by adjusted (at 0.01 level) pairwise comparisons among trajectories. Because we have a priori hypotheses regarding naltrexone and CBI interaction based on the results of COMBINE (Anton et al., 2006), post-hoc comparisons were performed even if the overall naltrexone by CBI interaction was significant at 0.10 rather than at 0.05 level.

In an additional exploratory analysis each subject was assigned to the most likely drinking trajectory and compliance measures (full compliance with prescribed medication dose and number of MM sessions attended) was compared across trajectories of any drinking using nonparametric tests (Kruskal-Wallis for the comparison among all trajectories and Wilcoxon rank-sum test for pairwise comparisons).

Our modeling strategy allowed the data to guide the choice of the number of trajectories that best fit the data and to determine the shape of each trajectory over time. It also allowed the use of all available data on each subject and estimation of the proportion of the population whose treatment response corresponds most closely to each trajectory group. For the analysis we used a customized SAS procedure (PROC TRAJ) developed by Jones et al. (2001). Test statistics for overall treatment effects, odds ratios and associated confidence intervals were calculated in PROC IML. An adjusted confidence level of 99% was used for post-hoc testing in the models with more than three trajectories. Since 94% of the subjects (treatment group range, 92%-96%) provided complete within treatment drinking data (Anton et al., 2006), we do not believe that our results may be materially biased due to missing data.

3. Results

3.1. Replication of drinking trajectories

Figure 1 and Figure 2 plot the estimated trajectories for any and heavy drinking respectively when the number of trajectories was restricted to three. The models with third-degree polynomials fit better than the models with second-degree polynomials and are presented here. The three trajectory patterns over time are similar to the trajectories estimated for the VA naltrexone trial and the Women's study and are interpreted as "abstainers" (48.2% of the sample), "sporadic drinkers" (35.5%) and "consistent drinkers" (16.3%) for any drinking and "abstainers from heavy drinking" (59.9%), "sporadic heavy drinkers" (29.5%) and "consistent heavy drinkers" (10.5%) for heavy drinking. In understanding these labels, the "abstainers" trajectory label does not mean that total abstinence occurred across the entire study period, but rather that the chance for drinking to occur on a particular day was close to 0. Entropies of the two models are excellent (0.97 and 0.98 respectively) thus, most subjects were clearly assigned to a particular trajectory.

Tests for overall treatment effects (naltrexone, acamprosate, CBI and their interactions) did not reveal any significant effects for any drinking (all p-values > 0.15) while for heavy drinking the naltrexone by CBI interaction was significant at the 0.10 level (p=0.08). Post-hoc tests for

heavy drinking (Table 1) revealed that for subjects not receiving CBI, naltrexone compared to no naltrexone increased the chance for being in the "abstainers from heavy drinking" trajectory compared to the "consistent heavy drinkers" and "sporadic heavy drinkers" trajectories (OR=1.86, 95% CI: (1.10, 3.16) and OR=1.48, 95% CI: (1.02, 2.14) respectively). For subjects not receiving naltrexone, CBI compared to no CBI increased the chance for being in the "abstainers from heavy drinking" trajectory compared to the "consistent heavy drinkers" trajectory (OR=1.81, 95% CI: (1.07, 3.06)). Subjects on the combination of naltrexone and CBI compared to subjects receiving neither naltrexone nor CBI were significantly more likely to be "abstainers from heavy drinking" than "consistent heavy drinkers" (OR=2.04, 95% CI: (1.18, 3.53)). There were no acamprosate effects either alone or in combination.

Estimated membership probabilities in each trajectory by treatment (averaged over acamprosate) are shown in Figure 3 (for any drinking) and Figure 4 (for heavy drinking). The differences in trajectory membership probabilities were not statistically significant for any drinking (Figure 3). Figure 4 shows that each treatment alone (i.e., naltrexone, CBI) and the combination lowers the chance to be in the "consistent heavy drinkers" trajectory but the combination is not better than either treatment alone. Furthermore, the monotherapies appear to lower the chance for membership in the "sporadic heavy drinkers" trajectory slightly, while the combination does not have this effect.

3.2. Any drinking outcome – increasing the number of trajectories

In the first analyses, we restricted the number of trajectories to three to be able to replicate prior results. However, according to Schwartz-Bayesian information criterion we need more trajectories to describe the data adequately. According to our model selection algorithm described in the Methods section, we selected the model with six trajectory classes as the best fitting one for any drinking. Entropy of this model was excellent (0.95).

Figure 5 plots the estimated trajectories for any drinking with six trajectories. From least severe to most severe, we interpret these trajectories as "abstainers" (trajectory T1, 37% of the sample), "infrequent drinkers" (trajectory T2, 24.4%), "frequent to infrequent drinkers" (trajectory T3, 12.2%), "increasing to frequent drinkers" (trajectory T4, 10.9%), "increasing to nearly daily drinkers" (trajectory T5, 8%), and "nearly daily drinkers" (trajectory T6, 7.3%). The first three trajectories ("T1: abstainers", "T2: infrequent drinkers" and "T3: frequent to infrequent drinkers") can be interpreted as "good outcome" trajectories as there is little or decreasing drinking in them. The last three trajectories ("T4: increasing to frequent drinkers", "T5: increasing to nearly daily drinkers" and "T6: nearly daily drinkers") can be interpreted as "poor outcome" trajectories in which drinking is frequent and/or increasing. Estimated membership probabilities in each trajectory by treatment (averaged over acamprosate) are shown in Figure 6.

Tests for overall treatment effects revealed significant main effect of CBI (p=0.006). Adjusted post-hoc tests revealed that subjects on CBI compared to those not receiving CBI were less likely to be in the "T5: increasing to nearly daily drinkers" trajectory than in all other trajectories. This effect was statistically significant for all trajectories (see first four rows of Table 2 for odds ratios and 99% confidence intervals) except for "T4: increasing to frequent drinkers".

There was also an interaction between CBI and naltrexone (p=0.06). For subjects who received naltrexone, CBI compared to no CBI increased the chance to be in the "T4: increasing to frequent", "T3: frequent to infrequent" and "T6: nearly daily drinkers" trajectories compared to the "T5: increasing to nearly daily" trajectory. For subjects who did not receive naltrexone, CBI compared to no CBI increased the chance for being in the "T2: infrequent drinkers" trajectory compared to the "T5: increasing to nearly daily" trajectory. (See Table 2 for odds

ratios and confidence intervals for these effects.) Subjects on naltrexone who did not receive CBI were significantly more likely than subjects on placebo and no CBI to be "T1: abstainers" compared to "T6: nearly daily drinkers" or "T4: increasing to frequent drinkers" (OR=2.82, 95% CI: (1.34, 5.93) and OR=2.17, 95% CI: (1.21, 3.89) respectively). Subjects who received both CBI and naltrexone compared to those who received neither were more likely to be in the "T1: abstainer" and "T3: frequent to infrequent drinkers" trajectories than in the "T5: increasing to nearly daily drinkers" trajectory (OR=2.81, 95% CI: (1.37, 5.74) and OR=3.52, 95% CI: (1.55, 8.00) respectively).

In summary, CBI appears to have a unique effect on reducing the likelihood of increasing to nearly daily drinking. Naltrexone has a unique effect on decreasing nearly daily drinking, and the combination of naltrexone and CBI increases the chance of decreasing drinking.

3.3. Treatment adherence by trajectory of any drinking

Compliance rates by trajectory are presented in Table 3. There were significant differences in compliance (full adherence with prescribed medication, number of CBI sessions attended for subjects who received CBI and number of MM sessions attended) among the trajectories ($p<.0001$). Compared to "T1: abstainers" all other trajectories were associated with significantly worse medication compliance (all $p<.0001$). Subjects in the "T5: increasing to nearly daily drinkers" trajectory had worse compliance than did subjects in the "T1: abstainers", "T2: infrequent drinkers" and "T3: frequent to infrequent drinkers" trajectories. Compared to abstainers, all other trajectories except "T2: infrequent drinkers" were associated with significantly fewer MM sessions attended (all $p<.01$). Among CBI participants, "T5: increasing to nearly daily drinkers" or "T6: nearly daily drinkers" attended significantly fewer CBI sessions than "T1: abstainers", "T2: infrequent drinkers" and "T3: frequent to infrequent drinkers" ($p<.05$). Additionally, "T4: increasing to frequent drinkers" had worse CBI compliance than did "T1: abstainers" ($p=.01$).

3.4. Heavy drinking outcome – increasing the number of trajectories

We selected the model with four trajectories as best fitting for heavy drinking. The results were similar to the results with three trajectories and are available upon request. The four-trajectory model also identified trajectories of "abstainers from heavy drinking" and "consistent heavy drinkers" but there were two rather than one trajectory in between. Subjects in the first of these two middle trajectories had about 15% chance of heavy drinking throughout the 16 weeks. Subjects in the second one increased their chance of drinking from 30% to about 40%.

3.5. Covariate Analyses

Both baseline percent days abstinent and percent heavy drinking days were significantly associated with post-randomization drinking trajectories. In the three-trajectory models, higher percent days abstinent was associated with significantly lower chance to be in the "consistent drinkers" trajectory (OR=0.97, 95% CI = (0.96, 0.98)) than in the "abstainers" trajectory. And higher percent heavy drinking days was associated with significantly higher chance to be in the "consistent heavy drinkers" trajectory (OR= 1.02, 95% CI = (1.01, 1.03)) than in the "abstainers from heavy drinking" trajectory. Similarly in the six-trajectory model for any drinking, higher percent days abstinent was associated with significantly lower chance to be in the "T5: increasing to nearly daily" and "T6: nearly daily drinkers" trajectories.

4. Discussion

In these re-analyses of COMBINE data, we identified six clinically useful trajectories of any drinking, replicated a three trajectory solution for heavy drinking, showed that naltrexone and CBI increase the probability of lower risk trajectories and established an association between

compliance and drinking trajectories. Although the overall conclusions about the efficacy of naltrexone, CBI and acamprosate are consistent with the conclusions drawn based on traditional summary measures, we believe that the application of trajectory analyses to the COMBINE study data helped provide a more complete and nuanced representation of drinking during treatment and the aspects of drinking that the various treatments affected. For example, in the original COMBINE analyses, the overall percentage of days abstinent was high and the differences between treatments, while significant, small. However, the trajectory analyses reveal several patterns of response that vary in the frequency of initial drinking and changes in the frequency over time. The treatments also influenced membership in some but not every trajectory of response, providing insights into how these treatments operate and suggesting that there are subgroups of individuals who derive greater benefit from specific treatments than observed on summary measures averaged over the entire sample. Although we replicated the finding of three trajectories of drinking seen in the VA naltrexone study and the women's study, for any drinking six trajectories better reflected the data in the COMBINE Study. This could be due to the larger sample size and the fact that there were two levels of behavioral intervention in COMBINE, a low intensity medication management approach (MM) and a more intensive approach combining CBI with MM, whereas the other studies all provided only a more intensive weekly CBI. Consistent with the primary outcome paper, trajectory analysis did not reveal significant effects of acamprosate alone or in combination with other treatments.

Of the six trajectories of any drinking, three reflected trajectories of poor or worsening outcomes. Naltrexone and CBI influenced the probability of being in these less desirable trajectories as is most clearly seen from Figure 6. Specifically naltrexone alone reduced the probability of being in the "T6: nearly daily" trajectory and in the "T4: increasing to frequent trajectory". This finding is consistent with a potential mechanism of this treatment, in which decreased reinforcement from alcohol could lead to reductions in drinking (Sinclair, 1990). Naltrexone has been shown to alter responses to alcohol even after a single dose in the laboratory (Swift et al., 1994;King et al., 1997; McCaul et al., 2001) and in clinical trials (O'Malley et al., 1996;Volpicelli et al., 1995). It also reduces the probability of continued drinking following an initial episode of alcohol consumption in clinical trials (Anton et al., 1999) and in laboratory paradigms (O'Malley et al., 2003;Anton et al., 2004;Krishnan-Sarin et al., 2007).

In contrast, CBI with or without naltrexone reduced the probability of being in the "T5: increasing to nearly daily" trajectory while it did not decrease the probability of being in the "T6: nearly daily drinking trajectory" (Figure 6). This finding is consistent with the potential mechanism of a behavioral treatment in which learning new skills can prevent relapse in the face of high-risk situations. Unlike naltrexone, which occupies brain opiate receptors after a single dose and therefore may have immediate therapeutic effects, a single session of CBI may be insufficient to prevent early relapse to nearly daily drinking. In CBI, training in new coping skills does not begin until after the first four – five sessions, which focus on building motivation for change and development of a treatment plan (Longabaugh et al. 2005). As a result, participants who resume nearly daily drinking and potentially discontinue therapy early will not experience the potential benefit of learning new coping skills. In contrast, individuals who receive adequate exposure to CBI will have new tools that they can use to cope with situations that might otherwise lead to escalation of their drinking.

This reasoning may explain why CBI does not significantly change the probability to be in the worst trajectory when compared to placebo. However, it does not explain why the combination of CBI and naltrexone compared to naltrexone alone appears to increase the probability of being in the "T6: nearly daily" trajectory. One can interpret these findings in two ways. If one chooses to focus on the "T6: nearly daily drinking" trajectory by itself, then it seems that CBI may worsen outcome when added to naltrexone. On the other hand, one might choose to focus

on the combination of the two worst trajectories ("T5: increasing to nearly daily" and "T6: nearly daily" drinking) since both groups end up with the same undesirable outcome: nearly daily drinking. In this case, looking at the combination of the two topmost bars in Figure 6 by treatment, one can see that CBI decreases the probability of being in the two least desirable trajectories considered together and hence is associated with good outcome overall.

The remaining three trajectories of any drinking reflect outcomes that are more positive. Both naltrexone (alone or in combination with CBI) and CBI alone increased the probability of being in the "T1: abstainer" trajectory and CBI increased the chance of being in the "T2: infrequent drinkers" trajectory. The most novel trajectory identified was the "T3: frequent to infrequent" trajectory in which the frequency of drinking declined over time. Interestingly, naltrexone plus CBI increased the chance to be in this trajectory. One can imagine that naltrexone may have decreased the reinforcing value of alcohol while the new cognitive and behavioral tools taught in CBI capitalized on this effect (or vice versa). Both processes would require some time to have their effect based on an extinction model for naltrexone and a skill acquisition model for CBI. This finding is of note in relationship to the findings of the primary outcome analyses of the COMBINE study (Anton et al., 2006), in which the combination of naltrexone plus CBI did not improve outcomes across a number of drinking outcome measures over that of either naltrexone or CBI alone. The difference between the present results and those from the primary COMBINE outcome paper highlights the potential benefit of more refined trajectory methods in identifying the efficacy of interventions for drinking subtypes.

As would be expected, baseline drinking was a strong predictor of trajectory membership and was an important covariate in the analyses. For example, individuals with higher days of abstinence pretreatment were less likely to be in the "T6: nearly daily" and "T5: increasing to nearly daily" trajectories, levels of drinking that they did not engage in before treatment.

With regard to trajectories of heavy drinking, the analysis of the COMBINE Study replicated the three trajectory patterns (i.e., "abstainers from heavy drinking", "sporadic heavy drinkers" and "consistent heavy drinkers") found in the VA naltrexone trial. Consistent with the results of that study, naltrexone (with or without CBI) reduced the probability of being in the consistent heavy drinking trajectory and increased the probability of being in the abstainer trajectory. CBI without naltrexone also reduced the probability of being in the consistent heavy drinking trajectory and increased the probability of being in the abstainer from heavy drinking trajectory. In contrast to the VA study, naltrexone also reduced the probability to be in the sporadic heavy drinking trajectory, but only in the absence of CBI. It may be that this effect of naltrexone is only evident in combination with less intensive therapy. In the VA Study, all participants received therapy that was more intensive (i.e., weekly Twelve Step Facilitation Therapy and medication adherence counseling).

In contrast to the analyses of any drinking, increasing the number of trajectories was less informative for heavy drinking. For simplicity of presentation, we chose to focus on the three-trajectory solution. Given that heavy drinking is a less frequent event than any drinking, it is perhaps not surprising that we observed fewer trajectories. It is conceivable that additional unique trajectories might be identified in other studies depending on participant characteristics, the treatments studied, and other methodological issues. For example, topiramate studies have enrolled consistent heavy drinkers who were actively drinking at the time of randomization (Johnson et al., 2003,2007). The application of trajectory analyses to these data might identify a trajectory of heavy drinking in which individuals move from frequent heavy drinking to infrequent heavy drinking or abstaining from heavy drinking.

The contribution of treatment adherence to treatment response has been emphasized for medications (Pettinati et al., 2006) and for behavioral interventions (Dearing et al., 2005). To

begin to explore this issue, we compared measures of compliance with medication, MM sessions and CBI sessions (for those who received CBI) for the various trajectories of any drinking. With the exception of the number of MM sessions attended for the infrequent drinker trajectory, adherence to each component of treatment was significantly higher in the abstainer trajectory compared to the remaining trajectories. In most studies, those who adhere to treatment experience better outcomes (Zweben et al., 2008; Fuller et al., 1986; Cramer et al., 2003). Adherence to an effective treatment, however, can improve outcomes relative to alternative treatment (e.g., placebo) (Baros et al., 2007; Volpicelli et al., 1997). In our analyses, the two trajectories in which drinking worsened over time (i.e., infrequent to frequent and frequent to nearly daily) were associated with the lowest treatment adherence raising the question of whether efforts to promote adherence (e.g., long acting formulations of medications or other behavioral interventions) might be useful in intercepting escalating use if identified early. Based on our analyses we cannot ascertain a causal relationship between compliance and outcome as better outcomes can lead to better compliance just as easily as better compliance can lead to better outcomes. In future analyses, we plan to examine trajectories of adherence to each of the COMBINE treatments and their statistical and temporal association with drinking trajectories and thus attempt to understand the relationship between treatment adherence and treatment outcomes.

Although trajectory analyses provided new information about treatment response, not all questions are answered by this approach. While we can say that a treatment alters the chance to be in a particular trajectory, the results do not tell us what happens for an individual participant. For example, naltrexone reduced the chance to be in the nearly daily trajectory and increased the chance to be in the abstainer trajectory. However, we cannot interpret this to mean that a particular individual will move directly from the daily trajectory to the abstainer trajectory or that a subject might be shifted to a better intermediate trajectory (e.g., frequent to infrequent) while another subject shifts from frequent to infrequent into the abstainer trajectory.

Furthermore, our analysis is predicated on the assumption that different classes of trajectories exist. When no categorically different trajectories exist, a substantial percent of subjects will not be reliably classified into any one trajectory. Our good classification accuracy gives some reassurance that in this study categorically different classes do exist.

Sample size and percent abstainers limit the number and shape of considered trajectories. However, since COMBINE is the largest to date study of pharmacotherapies and behavioral therapies for alcoholism, power to detect distinct trajectories in this study is greater than in most other studies.

Strict inclusion/exclusion criteria in COMBINE resulted in a relatively homogeneous sample of potentially more capable and compliant patients, who were able to achieve four days of abstinence prior to treatment. Thus, the trajectories that we identified and the probabilities of membership in each trajectory may not generalize to a more severe population.

In conclusion, the trajectory analyses provided new insights beyond the original findings from the COMBINE Study, which used more traditional summary outcomes and data analytic approaches. Distinct trajectories of response were identified that were differentially influenced by the various interventions. As such, our analysis of the COMBINE study data highlights the potential value of trajectory analysis as applied to clinical trials.

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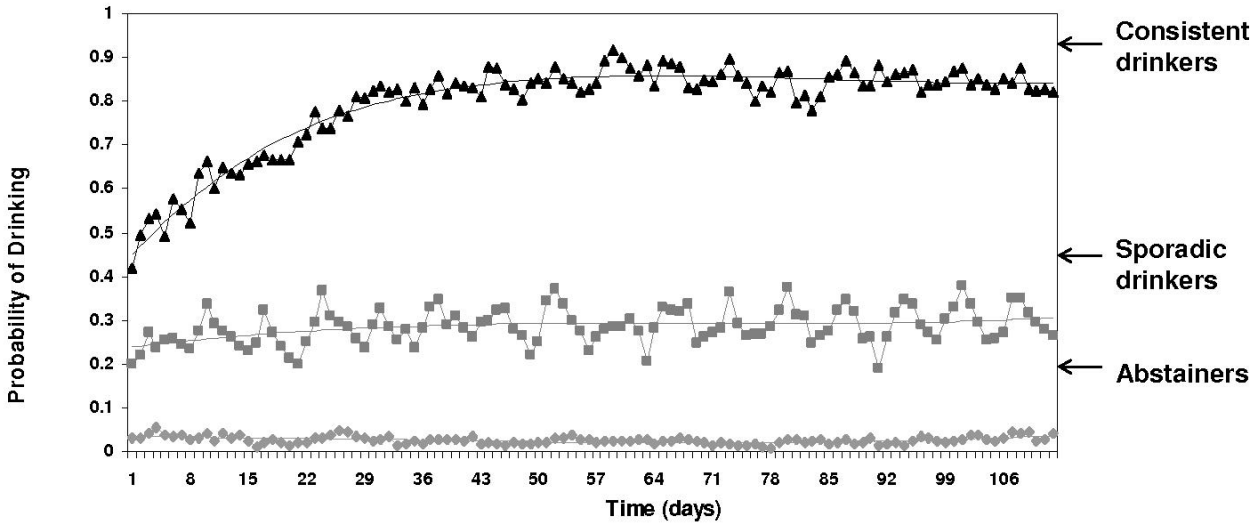

Figure 1.

Three trajectories of any drinking. Solid lines with symbols represent sample-based probabilities of drinking based on all subjects weighted by the posterior probability of trajectory membership. Solid lines without symbols represent model-based probabilities of drinking over time for each trajectory group.

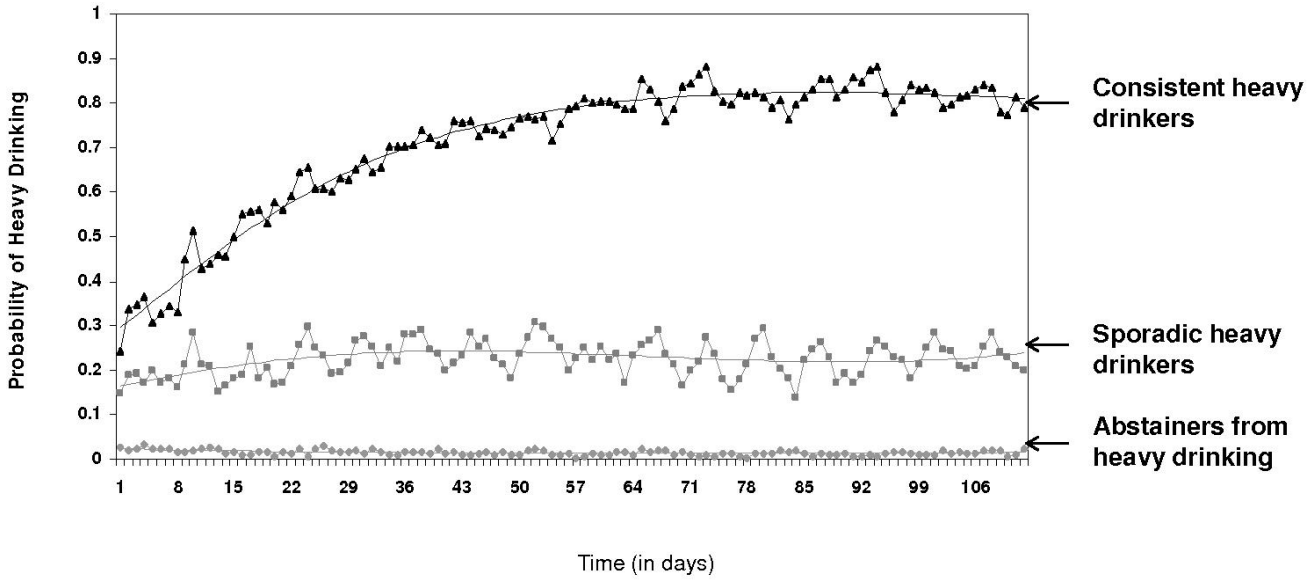

Figure 2.
Three trajectories of heavy drinking. Solid lines with symbols represent sample-based probabilities of drinking based on all subjects weighted by the posterior probability of trajectory membership. Solid lines without symbols represent model-based probabilities of drinking over time for each trajectory group.

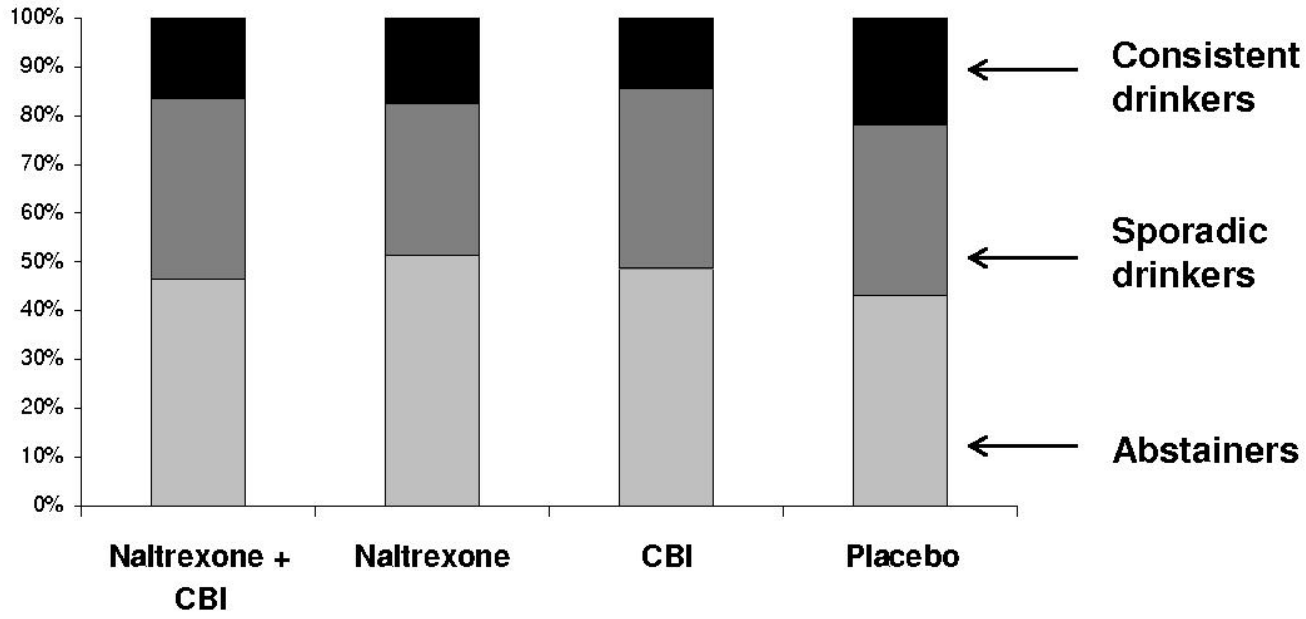

Figure 3.
Probabilities of trajectory membership in any drinking model with three trajectories.

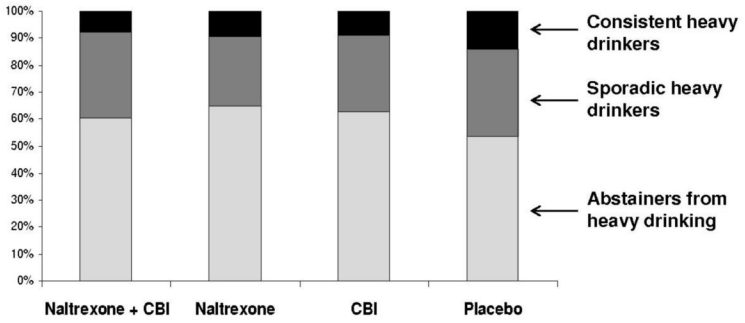

Figure 4.
Probabilities of trajectory membership in heavy drinking model with three trajectories.

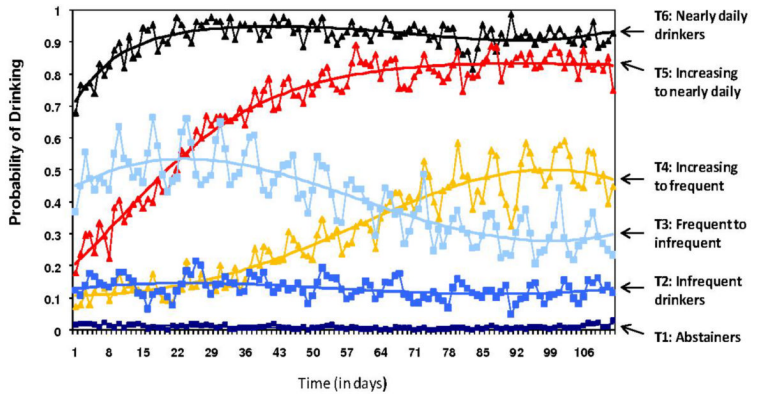

Figure 5.

Six trajectories of any drinking. Note: Solid lines with symbols represent sample-based probabilities of drinking based on all subjects weighted by the posterior probability of trajectory membership. Solid lines without symbols represent model-based probabilities of drinking over time for each trajectory group.

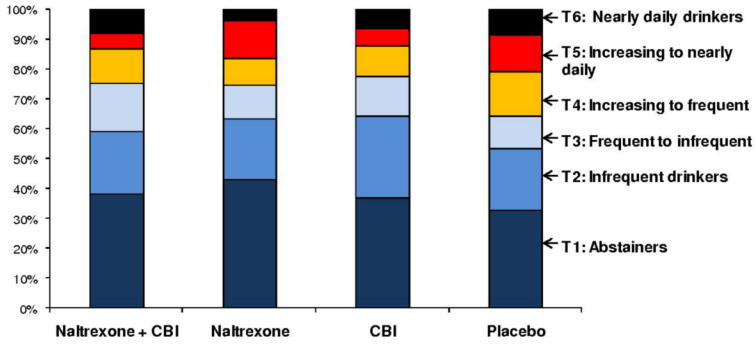

Figure 6.
Probabilities of trajectory membership in any drinking model with six trajectories.

Table 1

Odds ratios and 95% confidence intervals for the interaction between naltrexone and CBI on heavy drinking based on the model with three trajectories.

Comparison (averaged over acamprosate)	Odds ratio (Abstainers from Heavy Drinking vs. Sporadic Heavy Drinkers)	Odds ratio (Abstainers from Heavy Drinking vs. Consistent Heavy Drinkers)	Odds ratio (Sporadic Heavy Drinkers vs. Consistent Heavy Drinkers)
Naltrexone vs. no Naltrexone (No CBI)	1.48* (1.02, 2.14)	1.86* (1.10, 3.16)	1.26 (0.71,2.24)
CBI vs. no CBI (No Naltrexone)	1.33 (0.92,1.91)	1.81* (1.07, 3.06)	1.37 (0.77, 2.41)
CBI + Naltrexone vs. Neither	1.14 (0.80,1.63)	2.04* (1.18,3.53)	1.79 (1.00,3.20)

* Indicates odds ratios with $p < 0.05$.

Table 2

Significant odds ratios and 99% confidence intervals for the interaction between naltrexone and CBI, and for the main effect of CBI on any drinking based on the model with six trajectories.

Treatment Comparison (averaged over acamprosate)	Level of the Other Factor	Trajectory	Reference Trajectory	Odds Ratio (95% CI)
CBI vs. no CBI	Averaged over active and placebo naltrexone	Abstainers	Increasing to nearly daily	2.26 (1.38, 3.70)*
CBI vs. no CBI	Averaged over active and placebo naltrexone	Infrequent drinkers	Increasing to nearly daily	2.60 (1.55, 4.37)*
CBI vs. no CBI	Averaged over active and placebo naltrexone	Frequent to infrequent	Increasing to nearly daily	2.96 (1.67, 5.27)*
CBI vs. no CBI	Averaged over active and placebo naltrexone	Nearly daily drinkers	Increasing to nearly daily	2.69 (1.16, 6.24)*
CBI vs. no CBI	No naltrexone	Infrequent drinkers	Increasing to nearly daily	2.79 (1.38, 5.65)*
CBI vs. no CBI	Naltrexone	Increasing to frequent	Increasing to nearly daily	3.12 (1.32, 7.38)*
CBI vs. no CBI	Naltrexone	Frequent to infrequent	Increasing to frequent	3.49 (1.52, 7.99)*
CBI vs. no CBI	Naltrexone	Nearly daily drinkers	Increasing to nearly daily	4.73 (1.34, 16.75)*
Naltrexone vs. no naltrexone	No CBI	Abstainers	Nearly daily drinkers	2.82 (1.34, 5.93)*
Naltrexone vs. no naltrexone	No CBI	Abstainers	Increasing to frequent	2.17 (1.21, 3.89)*
Naltrexone and CBI vs. neither	--	Abstainers	Increasing to nearly daily	2.81 (1.37, 5.74)*
Naltrexone and CBI vs. neither	--	Frequent to infrequent	Increasing to nearly daily	3.52 (1.55,8.00)*

* Indicates odds ratios with $p < 0.01$.

Table 3

Compliance with medication and CBI by trajectory group.

Trajectory	Number of Subjects	Percent of Subjects	Full Compliance with Prescribed Medication: Median (IQR)	Number of MM Sessions Attended: Median (IQR)	Number of CBI Sessions Attended (only for CBI arms): Median (IQR)
Abstainers	450	37.0	98.4 (93.3,99.8)	9 (8-9)	12 (8-14)
Infrequent Drinkers	296	24.4	95.5 (86.5,98.7)	9 (8-9)	11 (8-13)
Frequent to Infrequent	151	12.2	94.9 (81.2,98.9)	9 (6-9)	11 (7-13)
Increasing to Frequent	131	10.9	92.7(80.0,97.8)	8 (6-9)	9 (6-12)
Increasing to Nearly Daily	95	8.0	93.0 (65.2,98.0)	7 (4-9)	7.5 (5-10.5)
Daily Drinkers	87	7.3	94.1 (81.7,99.2)	8 (3-9)	8 (3-12)