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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.

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

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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, 2000a,b; Hill et al., 2000; Chassin et al., 2002; Del Boca et al., 2003; Greenbaum et al., 2004). For example, Muthén and Muthén (2000a,b) 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. (2002) 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, 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, 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 (1997a,b).

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, 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, 2000a,b; 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 (Hyytia and 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