New Insights into the Efficacy of Naltrexone Based on Trajectory-Based Reanalyses of Two Negative Clinical Trials

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Background: The heterogeneity of clinical findings in studies evaluating the efficacy of naltrexone in the treatment of alcohol dependence has led to growing efforts to explore novel approaches to data analysis. The objective of this study was to identify distinct trajectories of daily drinking over time in two negative clinical trials and to determine whether naltrexone affected the probability to follow a particular trajectory.

Methods: The Veterans Affairs (VA) Cooperative Study #425 and the Women's Naltrexone Study failed to demonstrate efficacy on primary outcome variables. Separately for each study, we analyzed daily indicators of any drinking and heavy drinking using a semiparametric group-based approach.

Results: We estimated three distinct trajectories of daily drinking (both any and heavy drinking) which we described as "abstainer," "sporadic drinker," and "consistent drinker." Naltrexone doubled the odds of following the abstainer trajectory instead of the consistent drinker trajectory but did not significantly change the odds of following the abstainer trajectory as contrasted with the sporadic drinker trajectory.

Conclusions: Naltrexone may have a clinically meaningful effect for alcohol-dependent patients with a high chance of consistent drinking, even in studies where it failed to show efficacy in planned analyses.

Key Words: Alcohol research, clinical trial, latent class model, naltrexone, population heterogeneity, trajectory-based analysis

The heterogeneity of clinical findings in studies evaluating the efficacy of naltrexone in the treatment of alcohol dependence has led to growing efforts to explore novel approaches to study design and data analysis. Naltrexone is approved by the Food and Drug Administration (FDA) for the treatment of alcoholism, but evidence for its efficacy is not unequivocal. A number of small to medium size studies (Anton *et al.* 1999; Balldin *et al.* 2003; Guardia *et al.* 2002; Heinala *et al.* 2001; Kiefer *et al.* 2003, 2004; Kranzler *et al.* 1998; Latt *et al.* 2002; Morris *et al.* 2001; O'Malley *et al.* 1992, 1996; Volpicelli *et al.* 1992, 1997) and two large clinical trials (Anton *et al.* 2006; Garbutt *et al.* 2005) reported that naltrexone was effective in delaying relapse heavy drinking, reducing the intensity of drinking, or increasing percent days abstinence. Several systematic reviews indicated that naltrexone efficacy was associated with a small to moderate effect size (Berglund 2005; Bouza *et al.* 2004; Garbutt *et al.* 1999; Kranzler and Van Kirk 2001; Srisurapanont and Jarusuraisin 2005; Streeton and Whalen 2001). In contrast, a large randomized Veterans Affairs (VA) clinical trial (Krystal *et al.* 2001) and other clinical trials (Chick *et al.* 2000; Davidson *et al.* 2004; Gastpar *et al.* 2002; Killeen *et al.* 2004; Kranzler *et al.* 2000) found no significant benefit associated with naltrexone treatment. Some meta-analyses also found no effect of naltrexone on abstinence (Bouza *et al.* 2004; Garbutt *et al.* 1999).

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The sources of heterogeneity in these clinical trials are not clear. Since naltrexone is not an aversive treatment, it is not expected to stop people from drinking but may decrease frequency and volume of drinking. Hence, it may affect some measures of drinking but not others, which may explain the findings in some studies of a protective effect of naltrexone on heavy drinking but not on any drinking. Naltrexone is thought to act by reducing craving, thereby promoting self-management of drinking behavior. The efficacy of naltrexone might also be directly related to changes in compliance. Furthermore, multisite study effect sizes are generally smaller than single-site study effect sizes due to their larger population heterogeneity (Feinn and Kranzler 2005). The possibility that subgroups of alcohol-dependent patients might differ predictably in their response to naltrexone also has been suggested on the basis of molecular genetic data (Oslin *et al.* 2003).

The impact of heterogeneous patient responses to naltrexone on clinical trial results may be exacerbated by the reliance of all published studies on summary drinking measures. The use of analytic approaches that evaluate patterns of drinking rather than single events or summary measures may be better suited to evaluate naltrexone efficacy (O'Malley and Froehlich 2003; Wang *et al.* 2002). We hypothesize that by using daily drinking data and by accounting for compliance, we will not only be able to elicit meaningful patterns of alcohol use over time but may also see an increase in power for detecting treatment effects.

Recent advances in longitudinal statistical modeling (Rose and Chassin 2000) provide methods that enable the use of daily drinking data. Traditional growth modeling (Diggle 1994; Goldstein 2003; Lindsey 1993; Longford 1993; Raudenbush and Bryk 2002) assumes that every individual follows the same type of trajectory over time, while latent-class based approaches (Dolan *et al.* 2005; Muthén and Muthén 2000a, 2000b; Nagin 1999) 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.,

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subgroups that might not have been hypothesized a priori by the investigative team.

In the field of alcoholism research, trajectory-based analyses have been selectively applied to large-scale observational studies of developmental patterns of alcohol use (Chassin *et al.* 2002; Del Boca *et al.* 2004; Greenbaum *et al.* 2004; Hill *et al.* 2000; Khoo and Muthén 2000; Muthén 2000; Muthén and Muthén 2000a, 2000b). To our knowledge, however, trajectory-based approaches have not yet been applied to treatment research studies. The objective of this work was to determine whether trajectory-based methods would provide insights into two adequately powered trials that failed to demonstrate significant naltrexone efficacy.

Methods and Materials

Veterans Affairs Cooperative Studies Program Study #425 Naltrexone in the Treatment of Alcohol Dependence

In this double-blind randomized trial (Krystal *et al.* 2001), 627 veterans with chronic, severe alcohol dependence were assigned to 3 months of naltrexone, 12 months of naltrexone, or placebo. Of the 627 subjects, 567 (10 female subjects) provided drinking data and were included in the analyses. Patients receiving naltrexone started with 25 mg once daily for 2 days, followed by 50 mg once daily for 3 or 12 months. Time to first day of heavy drinking (six or more drinks for men and four or more drinks for women) was defined as the primary outcome measure in the first 13 weeks of the trial.

Women's Naltrexone Trial

The second double-blind randomized clinical trial was conducted at the Substance Abuse Treatment Unit of the Connecticut Mental Health Center and enrolled 103 women with current alcohol dependence (O'Malley *et al.* in press). Eligible subjects were randomized to either naltrexone or matching placebo for 12 weeks. Of the 103 subjects, 98 had drinking data and were included in analyses. Patients receiving naltrexone started with 25 mg once daily for 2 days, followed by 50 mg once daily. The primary outcomes included time to first day of drinking and time to first day of heavy drinking defined as consuming four or more drinks on an occasion.

In both trials, no significant naltrexone effects were observed on the primary outcome measures (Krystal *et al.* 2001; O'Malley et al in press).

In both studies, the Timeline Follow-Back (TLFB) was used to retrospectively collect daily drinking data. Timeline Follow-Back is the most comprehensive self-report measure and has good reliability and internal consistency on summary drinking measures (Sobell and Sobell 1992, 1995). In the 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 six or more drinks were consumed by male subjects and four or more drinks were consumed by female subjects on that day, 0 otherwise). Although there is large individual variability in accuracy of reporting daily drinking (Searles *et al.* 2000), the trajectory-based approach smoothes the day-to-day data, thus creating stable data-driven patterns with much smaller variability than daily measures. At the same time, this approach captures drinking over time more precisely than traditional summary measures.

We used the approach of Nagin (1999) and Nagin and Tremblay (2001) to identify distinct trajectories of drinking patterns during the first 3 months of the trials (considered separately) and to estimate how naltrexone affects 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 and covariates on trajectory membership via a generalized logistic regression model. Model selection (number of trajectory classes and degree of the polynomial trends over time) was based on the Schwartz Bayesian criterion. Baseline covariates (age, percent drinking days and drinks per drinking day in the 90 days prior to study entry, posttraumatic stress disorder and major depression diagnosis in last month prior to study entry) were entered as main effects one at a time and jointly, and their effects on trajectory membership and on the relationship between naltrexone and trajectory membership were assessed. Lifetime cocaine dependence was also tested as a covariate in the VA trial. Medication compliance was measured using a microelectronic monitoring system (MEMS) (Cramer *et al.* 1989) of the medication bottle to remove the single daily pill (APREX Corporation, Fremont, California), recorded as a binary variable (1 if bottle was opened on a particular day, 0 otherwise), and treated as a time-dependent covariate in the analyses.

This 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 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, SAS Institute, Cary, North Carolina) developed by Jones *et al.* (2001).

We performed parallel analyses of the two clinical trials and then calculated a weighted average of the naltrexone effect estimates to obtain a meta-analytic estimate of the overall naltrexone effect. For model selection, we considered two and three class models and quadratic and cubic polynomials.

Results

Any Drinking Outcome

Figures 1 and 2 plot the estimated trajectories in the VA and women's clinical trials, respectively. The three trajectory patterns over time were similar for the two studies and were interpreted

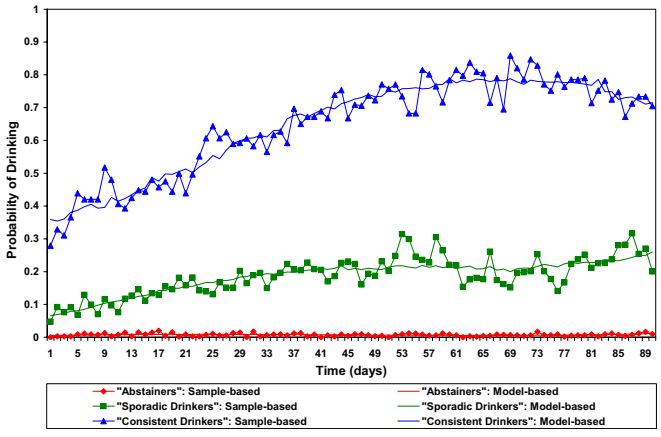

Figure 1. Trajectory analysis of any drinking in VA clinical trial. Medication compliance is considered as a time-dependent covariate. Solid lines without symbols represent model-based probabilities of any drinking over time for each trajectory group corresponding to average daily compliance rates. Solid lines with symbols represent sample-based probabilities of any drinking based on all subjects weighted by the posterior probability of trajectory membership. VA, Veterans Affairs.