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Modeling longitudinal drinking data in clinical trials: An application to the COMBINE study☆

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ABSTRACT

Background: There is a lack of consensus in the literature as to how to define drinking outcomes in clinical trials. Typically, separate statistical models are fit to assess treatment effects on several summary drinking measures. These summary measures do not capture the complexity of drinking behavior. We used the COMBINE study to illustrate a statistical approach for examining treatment effects on high-resolution drinking data.

Methods: This is a secondary data analysis of COMBINE participants randomly assigned to naltrexone, acamprosate, with medical management and/or combined behavioral intervention (CBI). Using a Poisson hurdle model, abstinence and number of drinks were simultaneously modeled as a function of treatment and covariates. An emphasis was placed on the evaluation of "risky drinking" (3 drinks/day for women and 4 for men).

Results: During treatment, naltrexone increased the odds of abstinence vs placebo naltrexone (OR = 1.35 [1.06, 1.65]) but receiving CBI in addition to naltrexone (vs not) obscured this effect; thus, the naltrexone effect was largest in the group not receiving CBI (OR = 1.87 [1.29, 2.46]). Naltrexone vs placebo naltrexone also reduced the risk of drinking in those who resumed risky drinking (RR = 0.58 [0.24, 0.93]) and increased the odds of maintaining low risk drinking (OT = 1.99 [1.07, 2.90]). Both effects were strongest in the absence of CBI when only "medical management" was provided.

Conclusions: The hurdle model is an appropriate statistical tool for assessing the effect of treatment on the two part drinking process, abstinence and number of drinks. When applied to COMBINE, results bolster the use of naltrexone in promoting abstinence and reduction in risky drinking.

1. Introduction

The combined pharmacotherapies and behavioral interventions for alcohol dependence (COMBINE) study was the largest study ever performed of pharmacotherapy for alcoholism in the United States (COMBINE Study Group, 2003; Anton et al., 2006). It was designed to assess the benefits of combining behavioral and pharmacological interventions in the treatment of alcohol dependence, a leading preventable cause of morbidity and mortality and a major contributor to health care costs (Mokdad et al., 2000; Grant et al., 2004; McKenna et al., 2005). In the COMBINE study, naltrexone (Kranzler and Van Kirk, 2001), acamprosate (Mason, 2003; Mann et al., 2004), and combined behavioral intervention (CBI), were given in combination according to a placebo-controlled $2 \times 2 \times 2$ factorial design over 16 weeks (Table 1). It was hypothesized that acamprosate would be effective in promoting abstinence while naltrexone would be effective in reducing the amount of drinking once any drinking had occurred; CBI was proposed to reinforce behaviors toward abstinence and/or to reduce relapse once any drinking had occurred, and it was hypothesized to interact positively with naltrexone (O'Malley et al., 1992; Anton et al., 1999). A medical management (MM) procedure designed to reflect what might occur in primary care practice was provided for participants in all but one study group.

In the COMBINE study, the two a priori defined primary outcomes were 'time to the first day of heavy drinking' and 'percent days abstinent' in the 16-week treatment period as derived from calendar recall; these summary measures are the most common

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Table 1
Study design and randomization sample size. ACA = acamprosate, NTX = naltrexone, CBI = cognitive behavioral intervention.

		Placebo ACA	ACA
No CBI	Placebo NTX	153	152
	NTX	154	148
CBI	Placebo NTX	156	151
	NTX	155	157

primary outcomes specified in clinical trials of alcohol use disorders (Babor et al., 1994; Finney et al., 2003). Naltrexone (+MM alone) or CBI (+placebo acamprosate + naltrexone + MM) increased time to first heavy drinking day compared to MM alone + placebo acamprosate but, contrary to expectation, there was no additional advantage of combining CBI with naltrexone over each monotherapy. No effects of either medication on percent days abstinent were found. The failure to find main effects of acamprosate, (alone or in combination with CBI or naltrexone), was unexpected given the positive results from studies of acamprosate (Mason, 2003; Mann et al., 2004) and of the combination of acamprosate and naltrexone conducted in Europe (Kefer et al., 2003; Feeney et al., 2006).

Experts disagree on what are the most relevant summary measures of drinking outcomes in clinical treatment trials (Cisler and Zweben, 1999; Meyer, 2001; Wang et al., 2002; Johnson et al., 2004; Mckay et al., 2006; Shirley et al., 2010; Prisciandaro et al., 2012) and Cochrane reviews have demonstrated a lack of consensus in primary outcome definitions across alcohol trials (Srisurapanont and Jarusuraisin, 2008; Rosner et al., 2009). Further, when drinking outcomes are analyzed as summary measures, for example, when consumption over a 16-week period is summarized into a single endpoint (e.g., percent days abstinent), high resolution information about the complexity of drinking behavior is lost. As a result, the power to detect significant differences in drinking outcomes may be reduced. The limitations of two of the most commonly used summary statistics are illustrated in Fig. 1. Fig. 1 displays 16 weeks of daily drinking data for 4 patients from the COMBINE study for whom summary measures may be uninformative. Patients 1 and 2 had one early onset heavy drinking day in the entire 16-week treatment period but did not drink any other day in that period. Patients 3 and 4 never officially met a predefined heavy drinking day in those 16 weeks, even though they drank several drinks on many days since the start of the study. Therefore, in the "time to first heavy drinking day" analysis of the original trial report, patients 1 and 2 are considered early treatment 'failures', while patients 3 and 4 are considered a treatment 'success'. Patients 3 and 4 have similar percent days abstinent even though patient 4 drinks more on non-abstinent days, a behavior that is undetectable when analyzing the summary statistic "percent days abstinent". These illustrations underscore the limitations of summary endpoints in assessing drinking behavior.

Instead, abstinence and the number of drinks consumed throughout the study period may be conceptualized as separate but correlated processes. These outcomes are usually analyzed using generalized linear models (GML) but zero-inflated Poisson or binomial (ZIP, ZIB) regression may be used to model consumption if data violate the assumptions of GLMs. There have been several applications of such zero inflated models in the substance use literature (Le and Galea, 2010; Hu et al., 2011; Meszaros et al., 2011; DeSantis et al., 2011; Fielder et al., 2012; Peeters et al., 2012; Walley et al., 2012). However, the statistical assumption of zero inflated models is that zero drinking arises from a set of patients who have zero risk of drinking. Given that all patients in the COMBINE study are substance-dependent at baseline, this assumption is unreasonable. An alternative 2-part Poisson hurdle model that assumes subjects remain at risk for drinking for the duration of the study is more appropriate (e.g., Mullahy, 1986; McLachlan and Peel, 2000; Bandyopadhyay et al., 2011). Thus, the objective of this paper is to re-analyze the COMBINE data using a two-part hurdle model, to extend this model to accommodate low and high risk drinking definitions, and formally to compare results to those obtained from the original trial report.

2. Methods

2.1. Participants and procedures

Participants in the COMBINE study included 1383 eligible alcohol dependent individuals who were randomly assigned to 1 of 9 groups for 16 weeks of treatment. In a $2 \times 2 \times 2$ factorial design (consisting of $n = 1226$ patients), all eight groups received MM, 4 groups received more intensive counseling (CBI), and patients in all 8 groups received either active/placebo naltrexone or active/placebo acamprosate yielding 4 medication groups, within each level of counseling (CBI/no CBI). This is illustrated in Table 1. Naltrexone, an opioid receptor antagonist, was studied based on evidence that it reduced the risk of heavy drinking in most studies (Kranzler and Van Kirk, 2001; Srisurapanont and Jarusuraisin, 2008) while acamprosate, thought to reduce glutamatergic hyperactivity associated with protracted abstinence, was thought to maintain abstinence within varied behavioral treatment frameworks (Mason, 2003; Mann et al., 2004). Medical management was designed as a means of enhancing medication compliance and reinforcing sobriety that could be used in a primary care or managed care setting by nonspecialists (Pettinati et al., 2004, 2005; Miller, 2004; Longabaugh et al., 2005). A ninth group received CBI alone and no pills – as in previous COMBINE reports, this group was not analyzed here since it is outside the $2 \times 2 \times 2$ factorial design. This results in a total sample size of 1226 of which data are available on 1195 for the current analysis.

2.2. Measures

Individuals were assessed 9 times during the 16 weeks of treatment and 3 additional times (i.e., 26, 52, and 68 weeks post-randomization) during the 52 weeks following treatment. Drinking was assessed via time line follow-back (TLFB), a calendar recall method that has been extensively validated to provide accurate measures of daily drinking. Secondary outcomes including mood and quality of life were also obtained. Primary and secondary analyses of the clinical trial have been reported (Anton et al., 2006; LoCastro et al., 2009; Witkiewitz et al., 2010; Gueorguieva et al., 2010; Prisciandaro et al., 2012) and data are publicly available for download following registration on the National Institute on Alcohol Abuse and Addiction website. The reader is referred to the primary report for further information on study design and measures (Anton et al., 2006).

2.3. Statistical analyses

Abstinence and reduction in drinking are conceptualized as separate but correlated processes; abstinence was the target of acamprosate and reduction in drinking the target of naltrexone (Littleton and Zieglgansberger, 2003). Since it was initially hypothesized that the two medications might affect different facets of the alcohol consumption process (i.e., abstinence violation and subsequent alcohol consumption), the Poisson hurdle model, which promotes a 2-stage decision making process that parallels this conceptualization, is a useful tool to assess treatment effects (Fielder et al., 2012). The first stage involves moving through a zero realization state (i.e., abstinence days). Once this "zero hurdle" is crossed,