Short communication

Naltrexone for the treatment of alcohol dependence among African Americans: Results from the COMBINE Study

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ABSTRACT

These analyses of the COMBINE Study were designed to examine the effects of naltrexone among African Americans during the course of the 16-week treatment. Participants (total $n = 100$; 70% male) who received naltrexone during the 16-week treatment trial ($n = 51$) were compared to those who received placebo ($n = 49$), controlling for acamprosate and behavioral intervention. Results did not support the efficacy of naltrexone on percent days abstinent, time to first heavy drinking day, and global clinical outcome in this subsample of African Americans. These results suggest that further work is needed to test naltrexone, as well as other medications, in this population and to identify treatment responders via genetics or other psychosocial predictor variables. Implications for pharmacogenetic studies of naltrexone are discussed.

1. Introduction

Naltrexone (NTX) is an opioid receptor antagonist with empirically supported efficacy for the treatment of alcoholism when used in combination with behavioral treatments (Srisurapanont and Jarusuraisin, 2005). Shortly after two initial trials suggested that naltrexone resulted in significantly fewer drinking days and lower rates of relapse after 3 months of treatment (O'Malley et al., 1992; Volpicelli et al., 1992), naltrexone was advanced as one of the more promising pharmacological interventions for alcohol dependence (Litten et al., 1996). More recent trials of naltrexone have generally demonstrated beneficial effects on heavy drinking rates, particularly among those who are compliant with the medication (Anton et al., 1999; Chick et al., 2000; Monti et al., 2001; Morris et al., 2001). Results from the COMBINE Study have also supported the efficacy of naltrexone in combination with medical management (MM), an intervention delivered by health care professionals and focusing on psychoeducation, medication adherence planning, and abstinence recommendation (Anton et al., 2006).

Treatment response to naltrexone, however, is not uniform and while some patients seem to benefit from this pharmacotherapy, others do not. Recently, genetic markers have been examined as predictors of clinical response to naltrexone for alcoholism. Studies have found that carriers of the Asp40 allele of the gene coding for the mu-opioid receptor (OPRM1), which represents the prin-

cipal target of naltrexone, show better treatment response to this medication, as compared to homozygotes for the major (Asn40) allele at this locus (Anton et al., 2008; Oroszi et al., 2009; Oslin et al., 2003). These results may be related to higher alcohol-induced reward among carriers of the Asp40 allele (Ray and Hutchison, 2004) and higher naltrexone-induced blunting of alcohol reward among these individuals (Ray and Hutchison, 2007). Nevertheless, there are important ethnic differences with regard to the estimated frequency of this possibly treatment-informative polymorphism. The estimated minor allele (Asp40) frequency is approximately 20% in individuals of European Ancestry, 58% in Asians, and <5% in individuals of African descent (www.ncbi.nlm.nih.gov/projects/SNP). To the extent that this polymorphism of the OPRM1 gene may predict clinical response to naltrexone, individuals of African descent would possibly be less likely to benefit from naltrexone, at least through the mechanisms conferred by this genetic variant. In light of the literature on the pharmacogenetics of naltrexone, the analyses of the COMBINE Study (COMBINE Study Research Group, 2003a,b) presented herein were designed to examine the effects of naltrexone among African Americans during the course of the 16-week treatment.

2. Methods

2.1. Participants and procedures

The rationale and methods of the COMBINE Study have been described in detail elsewhere (2003a,b). In brief, COMBINE was designed to test the outcome of different levels of pharmacotherapy and psychotherapy interventions for alcoholism. A total of 1383 participants were recruited at 11 U.S. sites, including 109 African Americans (AA) which represent the focus of this report. All participants were outpatients who

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met criteria for alcohol dependence and who had been drinking heavily for the 90-day period preceding study entry [heavy drinking was defined as >21 drinks (>14 for women) per week with at least 2 heavy drinking days (i.e., ≥5 drinks in a day for men; ≥4 drinks for women) during a consecutive 30-day period within the 90 days prior to the baseline evaluation] (Anton et al., 2006). Exclusion criteria were any serious mental illness or unstable medical conditions, current dependence on any drug other than alcohol, nicotine, or marijuana, and taking or requiring any medication that interfered with the study medications.

Participants were randomly assigned to one of nine treatment conditions and received 16 weeks of active treatment. Eight of these groups (AA, $n = 100$) received medical management plus either active/placebo naltrexone or active/placebo acamprosate. These four medication groups were then further divided by two levels of behavioral counseling (i.e., Combined Behavioral Intervention [CBI] vs. no CBI). A ninth group (AA, $n = 9$) received CBI alone, without MM or pills and will not be included in the analyses presented herein given the focus on naltrexone response. In this study AA individuals who received naltrexone during the 16-week treatment trial ($n = 51$) were compared to those who received placebo ($n = 49$) regardless of psychotherapy intervention or use of acamprosate. The sample size was adequately powered (i.e., power ≥0.80) to detect medium-to-large effect sizes (Cohen, 1992).

2.2. Assessments and data analytic strategy

Outcome variables and covariates were culled from the COMBINED database. The Form 90 (Miller and Del Boca, 1994; Tonigan et al., 1997) was the primary measure of drinking outcomes. The outcome variables and related analyses were identical to those in the main report (Anton et al., 2006): (a) percent days abstinent (PDA); (b) time to first heavy drinking day (TTHD), operationalized as 5 or more drinks in a day for men and 4 or more drinks for women. In addition, we examined the effects of naltrexone on global clinical outcome (GCO), a composite measure of alcohol treatment outcome that takes into account alcohol consumption and alcohol-related problems (Cisler and Zweben, 1999). CGO classifies participants into one of four categories: 1 = abstinent, 2 = moderate drinking without problems, 3 = heavy drinking or problems, and 4 = heavy drinking and problems, which are further combined into either good clinical outcome (1 and 2) or not (3 and 4). The following analyses were conducted: (a) PDA was tested using a mixed effects general linear model; (b) TTHD was tested using a proportional hazards model; and (c) GCO was tested using a logistic regression. All models controlled for drinking at baseline (PDA), acamprosate, and CBI. Analyses were performed using SAS Statistical Software, version 9.1 (SAS Institute Inc., 2003), and using identical syntax to that of the main COMBINE Study analyses (Anton et al., 2006). Interactions terms were removed from the original models due to reduced sample size and related statistical power to detect interactive effects.

3. Results

3.1. Demographics

Participants in this subsample of African Americas were 70% male, the average age was 44 (SD = 10.12) years old, participants had an average of 13.07 (SD = 2.25) years of education, 41.7% were single, 35.2% were married or living together, and 22.2% were divorced or separated. The majority (57.9%) of the sample reported being employed, 27.9% were unemployed at study entry, 8.3% were retired, 3% were disabled, and 2.9% endorsed "other" to employment status. At baseline the mean percent days abstinent was 25.29 (SD = 26.62) and the mean percent heavy drinking days was 66.28 (SD = 29.98).

3.2. Percent days abstinent

Mixed model analyses of the effects of naltrexone on percent days abstinent during treatment revealed no significant main effect of naltrexone [$t(94) = 0.64$, $p = 0.52$, $B = 2.99$, SE = 4.64] after controlling for PDA at baseline [$t(94) = 0.74$, $p = 0.46$, $B = 0.06$, SE = 0.09], acamprosate [$t(94) = 1.95$, $p = 0.06$, $B = 8.93$, SE = 4.59], and therapy [$t(94) = 0.13$, $p = 0.89$, $B = 0.62$, SE = 4.67]. The average PDA for the naltrexone group was 90.1 (SE = 3.32) as compared to the 87.1 (SE = 3.19) for those receiving placebo.

3.3. Time to first heavy drinking day

Results of a proportional hazards model revealed no significant main effect of naltrexone for time to the first heavy drinking day

in this sample (HR, 1.16; 97.5% CI, 0.63–2.14; $p = 0.59$), after controlling for PDA at baseline (HR, 1.00; 97.5% CI, 0.99–1.01; $p = 0.37$), acamprosate (HR, 1.28; 97.5% CI, 0.70–2.35; $p = 0.59$), and therapy (HR, 1.01; 97.5% CI, 0.55–1.88; $p = 0.96$).

3.4. Global clinical outcome

Logistic regression analysis of the composite outcome measure (GCO) at the end of treatment revealed no main effect of naltrexone [Odds ratio (OR) = 1.19; 95% CI = 0.44–3.24; $p = 0.51$], after controlling for baseline PDA [OR = 0.99; 95% CI = 0.98–1.02; $p = 0.85$], acamprosate [OR = 0.53; 95% CI = 0.19–1.47; $p = 0.11$], and therapy [OR = 1.01; 95% CI = 0.37–2.75; $p = 0.99$]. Despite the lack of significant naltrexone, acamprosate, or therapy main effects, 75.6% of this sample was classified as having a good clinical outcome at the end of treatment (week 16), suggesting that three quarters of patients benefitted from the treatments provided in the COMBINE Study.

4. Discussion

These analyses of the COMBINE Study sought to examine the effects of naltrexone for the treatment of alcoholism among African Americans. Contrary to the reported outcomes for the larger study (Anton et al., 2006), composed primarily of individuals of European Ancestry, the present results did not support the efficacy of naltrexone on percent days abstinent, time to first heavy drinking day, and global clinical outcome in this subsample of African Americans. Although this sample seemed to benefit from treatment provided during the COMBINE Study, as evidence by marked improvements in drinking pre-post treatment (e.g., 75.6% of patients were classified as having a good clinical outcome at the end of treatment), this study found no support for the benefit of naltrexone in this sample. Of note, the current sample size was powered to detect medium-to-large effect sizes.

Addressing alcoholism treatment in minority populations represents an important goal, particularly in light of the recent pharmacogenetic literature suggesting that the single nucleotide polymorphism (Asn40Asp) of the OPRM1 gene that predicts a more positive clinical response to naltrexone (Anton et al., 2008; Oroszi et al., 2009; Oslin et al., 2003) is very infrequent (<5%) among individuals of African descent (Arias et al., 2006). These related pharmacogenetic findings suggest that African American individuals may be less likely to benefit from naltrexone, at least through the mechanisms conferred by this specific genetic variant. In the era of personalized medicine, allele frequency imbalance due to ethnicity should be carefully considered (Tate and Goldstein, 2004). Most importantly, these findings should not be interpreted as evidence that all individuals of African descent do not benefit from naltrexone treatment. Instead, these results suggest that further work is needed to test naltrexone in this population and to identify treatment responders via genetics (e.g., polymorphisms in opioid receptor genes, including mu, kappa, and delta receptors) or other psychosocial predictor variables, such as gender, family history, and comorbid psychopathology.

Contributors

The first author (LR) conceptualized the manuscript, undertook the statistical analysis, and wrote the first draft of the manuscript. The second author (DO) contributed to manuscript preparation, particularly the discussion of the findings. Both authors contributed to and have approved the final manuscript

Conflict of interest

Both authors declare that they have no conflict of interest.

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