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TREATMENT OUTCOMES IN TYPE A AND B ALCOHOL DEPENDENCE 6 MONTHS AFTER SEROTONERGIC PHARMACOTHERAPY

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Abstract

Background: Evidence supporting the use of serotonergic medications for the treatment of alcohol dependence is available from studies where pharmacotherapy targeted specific alcoholic subtypes. We previously established with Babor's alcohol typology that Type A “lower-risk/severity” alcoholics (n=55) had better treatment response to 14 weeks of sertraline (200mg/day) than placebo, and this was not found for Type B “higher-risk/severity” alcoholics (n=45). The purpose of this study is to assess in this original study group whether treatment gains in the Type A alcoholics were maintained, or, if treatment outcomes changed for the Type B alcoholics, after discontinuing pharmacotherapy. **Methods:** After the end of a 3-month course of 200mg/day of sertraline, the subjects were interviewed at several time points about their alcohol drinking, if any, using the Timeline Followback method. For 90% of the original study group, mixed effects and GEE models were used to compare monthly drinking amounts over a 6-month post-treatment period to drinking amounts in the last month of treatment. **Results:** We found that Type A alcoholics who had been treated with sertraline, in contrast to placebo, maintained the good outcomes they had achieved during treatment for at least 6 months following pharmacotherapy. We found that Type B alcoholics who had been treated with sertraline, in contrast to placebo, continued to show no advantage for pharmacotherapy in the 6 months after completing treatment. In addition, heavy drinking in Type B alcoholics increased over the 6 months post-pharmacotherapy in those initially treated with sertraline, compared to placebo. **Conclusions:** These data support the importance of considering alcohol subtype when pharmacologically treating alcohol dependence.

Keywords

Alcohol Dependence; Alcohol Subtypes; Alcohol Treatment; Sertraline; Follow-up

Introduction

Effective pharmacological treatments of alcohol dependence have emerged worldwide over the past 20 years. For example, naltrexone (an opioid antagonist), acamprosate (glutamateNMDA and calcium channel activity, although precise mechanism unknown), and more recently, topiramate (GABA facilitator and glutamate function inhibitor) have been shown to be more effective than placebo in reducing excessive alcohol drinking (Garbutt et

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al., 1999; Johnson et al., 2003; Kranzler and Van Kirk, 2001; Litten and Allen, 1998; Streeton and Whelan, 2001; Swift, 1999). While the overall evidence for treating alcoholics with serotonergic medications has not been as compelling (Garbutt et al., 1999), more recent studies have demonstrated the efficacy of selective serotonin reuptake inhibitors (SSRIs) in specific alcoholic subtypes using Babor's criteria (Babor et al., 1992) for Type A and B alcoholism (Kranzler et al., 1996; Pettinati et al., 2000). Others have given a serotonin receptor antagonist ($5\text{-}HT_3$; ondansetron), and observed reductions in drinking in selected alcoholic subtypes distinguished by early vs. late onset of alcoholism (Johnson et al., 2000; Kranzler et al., 2003). As medications become widely used in clinical practices across the globe, it is important to determine not only which subjects respond to pharmacotherapy, but also whether treatment gains will be maintained after completing pharmacotherapy.

Differential Response in Type A and B Alcoholics to SSRIs

Two studies (Kranzler et al., 1996; Pettinati et al., 2000) that evaluated SSRIs for treating alcohol dependence classified subjects into Type A or B, using Babor's well-defined criteria for differentiating low from high risk alcoholics (Babor et al., 1992). Type A alcoholics are relatively uncomplicated in their history and presentation, despite excessive alcohol consumption, and diagnostically meeting alcohol dependence criteria. Type B alcoholics are more likely to have early-onset alcoholism, childhood risk factors, sociopathy, psychopathology, polysubstance use, and higher levels of alcohol-related severity (Babor et al., 1992; Pettinati et al., 2003). Pettinati and colleagues (2000) found that Type A alcoholics had more favorable outcomes when treated with sertraline (200mg/day for 14 weeks) than placebo. No advantage for sertraline was found in Type B alcoholics. In an earlier study, Kranzler and colleagues (1996) had reported that Type B alcoholics actually had worse drinking outcomes with fluoxetine (60mg/day for 12 weeks) than placebo. In their study, no advantage for fluoxetine was found in Type A alcoholics. These two studies had somewhat different results but, nonetheless, supported the idea that serotonergic pharmacotherapy may be differentially effective when the treatment is specific to alcoholic subtype.

Maintaining Treatment Gains after Completing Pharmacotherapy

Investigators studying successful response to pharmacotherapy have typically focused on the treatment period. There have been two published investigations of naltrexone where drinking data were provided during the post-treatment period. In both studies, naltrexone-treated subjects had fewer relapses to heavy drinking while in treatment. In a follow-up study of 80 alcohol dependent subjects randomized to 12 weeks of either naltrexone (50 mg) or placebo, O'Malley and colleagues (1996) found that the naltrexone-treated subjects approximately doubled their rates of drinking and heavy drinking over the 6 months after completing naltrexone treatment. They concluded that the initial benefit derived from naltrexone during treatment diminished once pharmacotherapy was completed.

In another naltrexone follow-up study of 124 alcohol dependent subjects randomized to 12 weeks of either naltrexone (50 mg) or placebo, Anton and colleagues (2001) reported that there was no longer a difference in the extent of drinking between naltrexone- and placebo-treated subjects after naltrexone had been discontinued for 8 weeks. Thus, in both of these naltrexone follow-up studies, the initial treatment effect diminished in less than 6 months after medication was stopped.

There are no good data with respect to discontinuing SSRIs, primarily because there has not been a clear-cut pharmacotherapy effect with serotonergic treatment in most studies. Kranzler and colleagues (1996) reported no effect of medication group by alcoholic subtype at 6-months post-treatment. However, this study had not originally found an SSRI advantage in either alcoholic subtype. (Their main finding was a medication disadvantage for Type B alcoholics.)

Because our original study had reported an advantage for sertraline in Type A alcoholics, it was relevant to study the post-treatment period in those same subjects.

Therefore, the current study is the first report that we are aware of that provides post-treatment data on discontinuing an SSRI (sertraline) after successful response (i.e., reduced drinking and increased abstinence) by subjects with Type A alcohol dependence.

Methods

Subjects

In the original sertraline trial, subjects were 100 treatment-seeking outpatients (52 men and 48 women) who met DSM-III-R criteria for alcohol dependence [based on administration of the Structured Clinical Interview for DSM-III-R, Patient Edition (SCID-P; Spitzer et al., 1990a)]. They had given informed consent to participate in a 14-week, double-blind, placebo-controlled treatment trial of sertraline for the treatment of alcohol dependence that would include weekly counseling during the trial and post-treatment evaluation visits. Treatment lasted for 14 weeks and consisted of 200mg/day of sertraline or four placebo capsules/day and weekly sessions of manual-guided Twelve-Step Facilitation (TSF) therapy (Nowinski et al., 1995). All subjects were encouraged to attend community-based support groups.

All subjects were 18 years or older, were actively drinking in the preceding 30 days prior to study entry, and were required to be abstinent from alcohol for at least 3 days prior to randomization. Subjects were excluded if they met criteria for another current substance dependence disorder, had a serious or unstable medical illness, or currently needed other psychotropic medications. It should be noted that the original prospective design for this study required recruiting alcohol dependent outpatients with and without lifetime depression. There were a comparable number of subjects with (n = 53) or without (n = 47) a lifetime DSM-III-R diagnosis of major depression. A brief description of the methods used in the clinical trial and in the subtyping procedure is provided below. (For a detailed description of the methods, see Pettinati et al., 2000 and Pettinati et al., 2001)

There were 90% who completed the research assessments at the end of the clinical trial, and these subjects comprise the sample for this follow-up study (total n = 90; n = 48 for Type A; n = 42 for Type B). At the end of the 14-week treatment trial, subjects were interviewed at 2, 4, 6, 12 and 24 weeks (6 months) post-treatment to assess drinking status, as well as other areas of functioning.

Assessments

The amount of daily drinking was recorded at each visit during treatment and follow-up using the Timeline Followback method (TLFB; Sobell and Sobell, 1992). If the subject discontinued treatment prior to the completion of 14 weeks or missed a scheduled follow-up session, the TLFB was administered at the next scheduled assessment point to obtain a continuous daily record of drinking during the trial and follow-up period.

After completion of the treatment phase, subjects were classified, using a *k*- means clustering procedure, with either Type A or Type B alcohol dependence. Subtype assignment was based on the four dimensions originally utilized by Babor and colleagues (1992): Vulnerability, Addiction Severity, Chronicity, and Psychopathology. In the current study, 13 measures obtained at entry to treatment, related to the four dimensions identified by Babor and colleagues, were used to make the classification. We have described these measures in detail elsewhere (Pettinati et al., 2000). While the measures were not identical to those used by Babor and colleagues (Babor et al., 1992), the dimensions were the same as those used by others (e.g., Kranzler et al., 1996), and an independent consultant, knowledgeable in the original Babor

classification, confirmed the acceptability of the measures we used in this study to represent the four dimensions of the typology. The underlying constructs for this typology are strengthened when different operational definitions of the construct are validated. All scores were standardized and then entered into a cluster analysis to avoid disproportionate contributions to the solution based on different metrics. Higher scores indicated greater risk/severity and the majority of the mean values were in the anticipated direction (i.e., Type B more severe than Type A). As reported in Pettinati et al., 2000, MANOVA revealed highly significant differences between subtypes on most of the measures selected for distinguishing the two types of alcoholics at the start of treatment.

Adequate information with respect to pre-treatment profiles and relevant outcome measures permitted 100% of the sample to be classified with either Type A or B alcohol dependence. Further post-hoc analyses revealed that three of the 13 measures were the most significant in classifying subjects (Pettinati et al., 2000). At the start of treatment, higher scores were found in Type B vs. Type A subjects respectively on 1) depressive symptoms at time of randomization [14.6 vs. 5.3 using the 24-item Hamilton Rating Scale for Depression (HAM-D; Hamilton, 1960)]; 2) drinks per drinking day (12.2 vs. 7.1 using the TLFB method); and 3) childhood conduct disorder symptoms (1.32 vs. 0.37 using the Antisocial Personality Disorder module of the SCIDII; Spitzer et al., 1990b)).

Statistical Methods

All subjects who were randomized and completed the research portion of the clinical trial were included in analyses using the Statistical Package for the Social Sciences (SPSS, 2002) and the Statistical Analysis System (Littell et al., 1996). The last month of the clinical trial was used as the initial time point for the follow-up analyses. Differences among groups on pretreatment demographic and drinking variables were examined, using log-linear models for binary characteristics and analysis of variance models for continuous characteristics.

We compared the four groups, defined by Babor subtyping and medication group (TypeA-Sertraline, TypeA-Placebo, TypeB-Sertraline, TypeB-Placebo), on the basis of repeated measures of self-reported drinking behaviors over the final month of treatment and over 6 months post-treatment. In the Pettinati and colleagues (2000) study, the advantage of sertraline vs. placebo for Type A alcoholics was seen in lower percentage of days drinking and higher percentage of abstinent subjects during the trial. In the current follow-up analyses, number of days drinking, number of heavy days drinking, and percentage of subjects abstinent were examined over the 6 months of the post-treatment period. The number of heavy days drinking was added, because of increased reporting of this outcome measure in recent publications (e.g., Balldin et al., 2003; Johnson et al., 2003).

We used linear mixed effects models (Gibbons et al., 1993) to compare monthly levels of drinking days, and monthly levels of heavy drinking days, after both responses were initially log-transformed to reduce skewness to acceptable levels. We used generalized estimating equations (GEE) models (Diggle et al., 2002) to compare log-odds of abstinence across the same time points, as non-linear mixed effects models for binary responses (Hedeker and Mermelstein, 2000) failed to converge satisfactorily due to the relatively small group sizes.

Mixed effects models require the specification of a covariance structure among the repeated measurements across time and of the possible group trends over time (Gibbons et al., 1993). The models we used to compare time trends included the main effects of alcoholic subtype, medication group, and linear and quadratic effects for month, together with the one-way and two-way interactions among these variables. We used Bayesian Information Criterion (BIC; Littell et al., 2000) comparisons to remove terms that did not significantly contribute to model fit. We followed the recommendations of Littell and colleagues (2000) to choose a covariance

structure for the repeated measurements, by using BIC comparisons of model fit for a variety of covariance structures in a model containing the full set of variables described above. For the GEE models, estimates of time trends are not very sensitive to the choice of covariance structure (Diggle et al., 2002), and we used a compound symmetry structure for the working correlation matrix.

To assess the sensitivity of our analyses to missing data, we used a pattern-mixture approach (Hedeker and Gibbons, 1998; Little, 1993) to test for differences in relationships across observed patterns of missing data.

Results

Demographics and Pre-treatment Clinical Characteristics

Ninety of the original 100 subjects completed the research assessments at the end of the clinical trial and, therefore, comprise the sample for the current study. The numbers of subjects lost-to-follow-up during the clinical trial were not significantly different among the four groups [TypeA-Sertraline - n = 3; TypeA-Placebo - n = 4; TypeB-Sertraline - n = 1; TypeB-Placebo - n = 2; χ^2 (3) = 1.67, p = 0.644]. Therefore, the demographic and clinical characteristics of the post-treatment study group are almost identical to the profile of the original study of 100 subjects (Pettinati et al., 2000). In the post-treatment study group, 52.2% were male, 81.1% Caucasian, and the mean age was 45.0 ± 10.3 years. Most subjects were employed and were of middle to upper socioeconomic status with moderate to severe alcohol dependence. The average number of years of problem drinking was 15.8 ±10.2 years, and the number of previous alcohol treatments was 1.06 ± 3.25.

Table 1 provides the demographic and pre-treatment clinical variables for sertraline and placebo groups according to their alcoholic subtype. One person in the TypeA-Sertraline group reported 30 lifetime alcohol treatments, while all other members of the group reported less than 4. That subject was excluded from the comparisons for lifetime alcohol treatments; including that subject would increase the group mean from 0.46 to 1.56. Main effect and interaction models were fit for each of the nine variables. None of the alcoholic subtype by medication group interactions, or the medication group main effects, were significant at the $p < .05$ level. There were expected main effects for alcoholic subtype because of the criteria that comprised the different definitions of the two alcoholic subtypes. Type A and B differed in age [$F(1,87) = 14.55$, $p < 0.001$], years of education [$F(1,87) = 6.95$, $p = 0.010$], and years of problem drinking [$F(1, 87) = 5.06$, $p = 0.027$]. Actual drinking and abstinent rates at the end of the trial and during the 6 months post-treatment period are provided in Table 2.

Modeling Sertraline Efficacy at Treatment Completion and Post-Pharmacotherapy

A covariance structure model comprising a Toeplitz structure (i.e., gradual decreases in response variances across the time points, and decreasing correlations between points further apart in time; Littell et al., 2000) on the residual errors provided a good fit for the mixed effects models for both the drinking and heavy drinking responses. For the GEE models of abstinence, there was good agreement between the standard errors based on a compound symmetry model and the non-model-based empirical standard errors, suggesting that the compound symmetry model provides a good fit to the covariance structure. For all models, there was good agreement between the observed and predicted group means (for the mixed effects models) and group proportions (for the GEE models) across the end-of-treatment and post-treatment time points.

Establishing Sertraline Efficacy at Treatment Completion

It will be recalled that in the original study (Pettinati et al., 2000), the Type A group showed an advantage of sertraline vs. placebo on percent days drinking and percent of subjects

abstinent. The results found for the 90 subjects in the current follow-up study were generally consistent with those results, although the differences were slightly less significant for the days drinking. Over the last month of the clinical trial (the baseline for the follow-up analyses), the TypeA-Sertraline group had fewer days drinking than the TypeA-Placebo group [$t(88) = -1.89$, $p = .06$] and had a higher percentage of subjects abstinent than the TypeA-Placebo group [odds ratio of 4.15, χ^2 (1) = 6.07, p = 0.01]. On the other hand, the TypeB-Sertraline group did not demonstrate an advantage over the TypeB-Placebo group in the number of drinking days [t (88) = 1.14, p = 0.26], nor in the percentage of subjects abstinent [odds ratio of 0.89, χ^2 (1) = 0.05, p = 0.83].

Drinking Days Post-Treatment. The best model for the log of drinking days included a significant interaction of alcoholic subtype and medication group [F(1, 86) = 4.52, p = 0.036], with nonsignificant main effects for alcoholic subtype [F(1, 86) = 0.08, p = 0.78] and medication group [F(1, 86) = 0.21, p = 0.65; see Figure 1]. There was no significant change in drinking days per month over time [F(1, 442) = 3.24, p = 0.07]. The form of the interaction was that the TypeA-Sertraline and TypeB-Placebo groups had lower rates of drinking across time than the TypeA-Placebo and TypeB-Sertraline groups: the estimated log of drinking rates were 1.05 (SE = 0.24) for TypeA-Sertraline, 1.74 (0.27) for TypeA-Placebo, 1.54 (0.29) for TypeB-Sertraline, and 1.09 (0.26) for TypeB-Placebo. This similarity between TypeA-Sertraline and TypeB-Placebo and the parallel similarity between TypeA-Placebo and TypeB-Sertraline accounted for the absence of the main effects.

Heavy Drinking Days Post-Treatment. The best model for the log of heavy drinking days had a significant alcoholic subtype by medication group by time interaction [F(1, 439) = 6.70, p=0.01], and a significant main effect of time [F(1, 439) = 4.03, p=0.05], indicating that time trends in heavy drinking days were different across the four groups (see Figure 2). Neither the alcoholic subtype [F(1, 86) = 1.07, p=0.30] and medication group [F(1, 86) = 0.01, p=0.90] main effects, nor the alcoholic subtype by medication group [F(1, 86) = 1.35, p=0.25], alcoholic subtype by month [F(1, 439) = 0.30, p=0.58], and medication group by month [F(1, 439) = 0.77, p=0.38] interaction effects were significant. The estimated log of heavy drinking rates at the end of treatment were 0.45 (SE = 0.22) for TypeA-Sertraline, 0.70 (0.25) for TypeA-Placebo, 0.98 (0.26) for TypeB-Sertraline, and 0.67 (0.24) for TypeB-Placebo, so the ordering of groups was similar to that for any drinking at the end of treatment. The estimated monthly rates of change in log of heavy drinking over the 6 months of follow-up were −0.00 (SE = 0.04) for TypeA-Sertraline, 0.06 (0.04) for TypeA-Placebo, 0.12 (0.05) for TypeB-Sertraline, and −0.02 (0.04) for TypeB-Placebo. Only the rate of increase for the TypeB-Sertraline group was significantly different from 0 [t(439) = 2.67, p = 0.008], indicating that the rate of heavy drinking increased in the TypeB-Sertraline group over the follow-up, but remained close to end-of-treatment rates in the other three groups. The estimated log of heavy drinking rates at the end of follow-up were 0.42 (SE = 0.23) for TypeA-Sertraline, 1.08 (0.26) for TypeA-Placebo, 1.71 (0.29) for TypeB-Sertraline, and 0.56 (0.26) for TypeB-Placebo.

Proportion of Abstinent Subjects Post-Treatment. For the GEE models for abstinence, the model-based and empirical standard errors were very similar, suggesting that the choice of compound symmetry for covariance structure was adequate. Here, we report the empirical standard errors. The best model for abstinence was similar to that for any drinking (see Figure 3). There was a significant interaction of alcoholic subtype and medication group (Z = −1.93, p = 0.05), with nonsignificant main effects for alcoholic subtype (Z = 1.57, p = 0.12) and medication group (Z = 0.21, p= 0.83), and no significant change in the odds of abstinent subjects over time (Z = −0.05, p= 0.96). The estimated probabilities of abstinent subjects for the four groups were 0.62 (SE = 0.09) for TypeA-Sertraline, 0.28 (0.09) for TypeA-Placebo, 0.39 (0.10) for TypeB-Sertraline, and 0.42 (0.08) for TypeB-Placebo. Thus, the ordering of the groups is

the same as that for the any drinking response, although the interaction is now largely due to the TypeA-Sertraline group showing better outcomes than the other three groups.

Sensitivity of Analyses to Missing Data Of the 90 subjects considered in these analyses, 63 (70.0%) provided data through to the end of follow-up. The dropout rates from the four groups were 5/27 (18.5%) for TypeA-Sertraline, 5/21 (23.8%) for TypeA-Placebo, 8/19 (42.1%) for TypeB-Sertraline, and 9/23 (39.1%) for TypeB-Placebo. A log-linear model fit to the three-way classification defined by alcoholic subtype, medication group, and drop-out status showed a significant association between subtype and drop out, with Type B subjects more likely to drop out than Type A subjects [odds ratio of 2.58, χ^2 (1) = 4.11, p = 0.04], with no significant effects for medication group [χ^2 (1) = 0.02, p = 0.88] or for the alcoholic subtype by medication group interaction [χ^2 (1) = 0.22, p = 0.64]. The mixed effects and GEE models described above allow the use of all data, complete or incomplete, provided by subjects, and will yield valid estimates and confidence intervals if missing data are ignorable (Laird, 1988). To assess the sensitivity of the analyses described above to this drop out, we used a pattern-mixture model approach (Little, 1993, Hedeker and Gibbons, 1998) to test for differences in regression relationships across observed patterns of missing data. As the sample size is small, we used the number of months of follow-up data provided by each subject as a (continuous) indicator of missing-data pattern, rather than as a discrete indicator. We reran each of the three analyses described above, including a main effect term for number of follow-up months, and interaction terms comprising number of follow-up months and the variables in the original models (Hedeker and Gibbons, 1998). These extra terms did not attain significance for any of the analyses, even at the $p < .20$ level. This suggests that the missing data are ignorable, for the purposes of these analyses.

In summary, the subject groups showed little change in outcomes in the 6 months after treatment, compared to their final treatment outcome status. However, there was an exception. Upon completion of sertraline treatment, heavy drinking days increased over the 6-month post-treatment period in the TypeB-Sertraline group, and this was not seen in the TypeB-Placebo group. As can be seen in Figure 2, the difference in drinking rates between TypeB-Sertraline and TypeB-Placebo groups increased substantially during the follow-up period, with the TypeB-Sertraline group demonstrating the poorest drinking outcomes during the follow-up period.

Discussion

Pettinati and colleagues (2000) had previously reported that Babor Type A (lower-risk/severity) alcoholics (Babor et al., 1992) had a favorable response to 200mg per day of sertraline, whereas Type B (higher-risk/severity) alcoholics did not. These findings were not due to subtype differences in medication noncompliance, treatment participation, support group attendance, or treatment attrition. Furthermore, as reported in Pettinati et al., 2001, with the same sample, sertraline was no better than placebo in reducing depressive symptoms measured by the Ham-D or Beck Depression Inventory for patients with or without a life-time history of depression. The present study extended these findings by determining whether or not response to sertraline in Type A alcoholics was sustained after completing treatment. Also, we investigated how Type B alcoholics, who did not respond to sertraline, managed in the post-treatment period.

Subjects with Type A alcohol dependence in this sample showed a consistent benefit from sertraline that lasted for at least 6 months after completing pharmacotherapy on the two drinking measures that demonstrated efficacy during treatment (days drinking and percentage of subjects with continuous abstinence). The same pattern seemed to be evident for days heavy drinking (see Figure 2). That is, those alcoholics without a current or underlying depression,

or any other concomitant problems, had a decided advantage with a 14-week course of sertraline (200mg/day) that resulted in significant reductions in drinking, and these outcomes lasted for at least 6 months after completing treatment. Ironically, these alcohol dependent subjects are the ones who are least likely to have medications prescribed for them in contemporary clinical practices, due to their uncomplicated profile at treatment entry.

In contrast, sertraline provided no significant advantage for subjects with Type B alcohol dependence during treatment, and this continued to be the case after they completed pharmacotherapy. In fact, a number of Type B alcoholics who had been treated with sertraline actually increased their heavy drinking in the 6 months after they stopped sertraline, compared to Type B alcoholics who had been treated with placebo. This finding that Type B alcoholics increase their heavy drinking after completing an unsuccessful 14-week course of an SSRI is counterintuitive and may have important clinical implications, given the widespread use of SSRIs in primary care and psychiatric settings where alcohol dependence may not be systematically evaluated. Thus, our finding of a lack of a beneficial effect of sertraline for Type B alcoholics, together with the finding reported by Kranzler and colleagues (1996) of a poorer treatment response to fluoxetine in Type B alcoholics, suggest that treatment with an SSRI alone is not indicated for most higher risk/severity alcoholics. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) is currently sponsoring two independent trials on the effectiveness of SSRIs in combination with naltrexone for treating comorbidly depressed (Type B) alcoholics.

While it is premature to put forth definitive explanations for our findings, some speculations are in order. The Type A alcoholics may be similar to heavy social drinkers (who have been shown to respond to SSRIs) in their underlying dysfunction (Naranjo and Knoke, 2001). Presumably, heavy alcohol exposure has caused serotonergic dysfunction that responds to SSRIs, and is wholly unrelated to depression. The Type A alcoholics were not depressed; the mean Ham-D score for this group was 5.3 when they started treatment vs. 14.6 for the Type B alcoholics.

With respect to the findings for the Type B alcoholics, it is possible that some subjects poorly synthesize serotonin, which could result in a neuroadaptive up-regulation of serotonergic receptors. This would make the serotonergic system overly sensitive to stimulation (Lee and Meltzer, 1991), and SSRIs would aggravate, not correct, the dysfunction (Johnson et al., 2000), which could eventually lead to increased drinking. Johnson and colleagues (2000) have also argued that there is an alcoholic subtype, which overlaps with early-onset alcoholism, which is genetically predisposed to a serotonergic transporter abnormality. The finding that the TypeB– Placebo group did not deteriorate over time in drinking days and heavy drinking days suggests that they maintained their gains as a result of the TSF therapy, a finding consistent with alcoholics in Project Match (Project Match Research Group, 1997). The better outcome of the TypeB-Placebo group vs. the TypeA-Placebo group (especially on drinking days) may be a function of baseline differences. Although Type B alcoholics were more severe at baseline in drinks per drinking day (an intensity measure), the Type A alcoholics had more drinking days (a frequency measure; Pettinati et al., 2000).

The research in this present study has several limitations discussed in more detail elsewhere (Pettinati et al., 2000) including generalizing from a research setting, basing alcohol drinking measures on self-report, and the clinical utility of subtyping based on cluster analyses. In addition, because the results were obtained for subjects participating in a clinical trial and not in a typical treatment setting, the findings may not readily generalize to some clinical settings, e.g., those that predominantly treat subjects with polysubstance use. The present follow-up study has further limitations. Subgroup sizes became somewhat smaller over the 6 months of follow-up due to attrition. This problem was more pronounced for Type B subjects. However,

missing data analyses suggested that the impact of dropout was largely ignorable, i.e., it did not bias the results reported here.

Finally, the limitations of the Babor typology should be mentioned. To date, the classification has been primarily based on a complex statistical method (cluster analysis) that is conducted post hoc. Thus, there are no data to support its feasibility in prospectively identifying Type A and Type B alcoholics. However, Pettinati et al. (2000) reported that three variables (number of depressive symptoms, drinks per drinking day, and number of conduct disorder symptoms) correctly classified 94% of the Type A and Type B subjects. Thus, it is conceivable that with further research, discriminative function equations could be developed that would identify distinct clinical markers to prospectively classify subjects as Type A or B alcoholics. Another criticism is that there is little consensus on the measures that could be used to define the purported factors that distinguish Type A and B alcoholics. However, the underlying four dimensions of the Babor typology have been defined by different sets of measurements (e.g., Babor et al., 1992 and Pettinati et al., 2000) which support the validity of the constructs. The classification has been criticized as a measure of disease severity, rather than being biologically determined (McBride et al., 2004), although this dimension is primarily relevant to understanding the differential treatment responses, and would not explain their actual occurrence. Finally, all current attempts at classifying subtypes alcohol dependence are limited (see review by Pettinati et al., 2003) and the field suffers most from a lack of empirical data.

In conclusion, if this study is replicated, our data suggest that for those alcoholics who initially respond to sertraline pharmacotherapy with reductions in drinking, there is an extension of benefit from sertraline after stopping pharmacotherapy that appears to last at least for 6 more months. The results from the present study also suggested that sertraline, given alone, would not be useful and potentially detrimental to alcohol recovery in subjects with Type B alcoholism. This study adds to the growing body of literature that supports the importance of identifying and treating homogeneous subgroups of alcohol dependent subjects. It will be important to improve methods to identify those subjects who are most likely to benefit or not from serotonergic medications, and to replicate that pharmacotherapy benefits extend into the post-treatment period.

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Figure 1.
Mean Log of Drinking Days during the Last Month of Treatment and Six Months Post-treatment for Type A and Type B Alcoholics Treated with either Sertraline or Placebo

Figure 2.
Mean Log of Heavy Drinking Days during the Last Month of Treatment and Six Months Post-treatment for Type A and Type B Alcoholics Treated with either Sertraline or Placebo

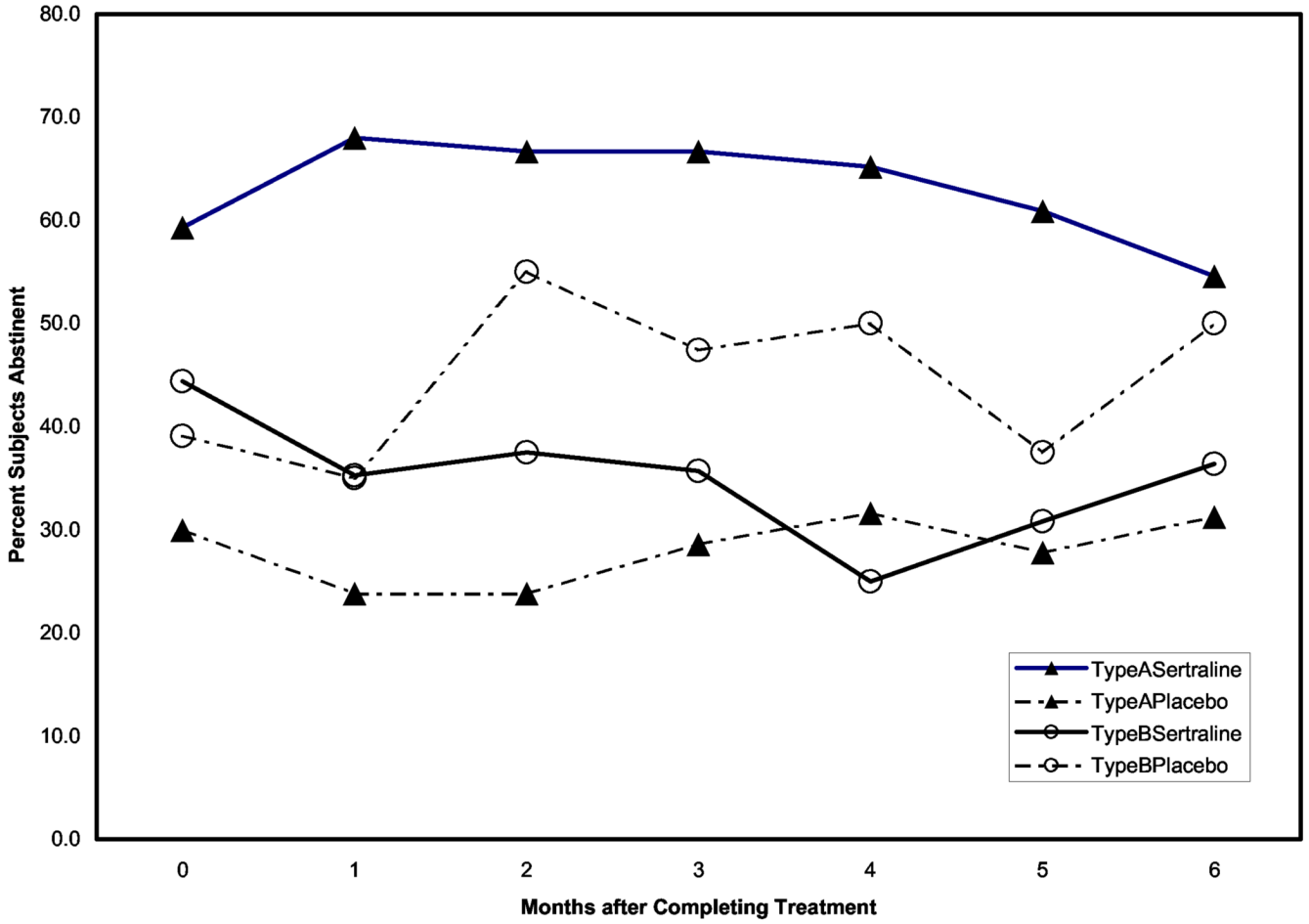

Figure 3.
Percent of Subjects Abstinent during the Last Month of Treatment and Six Months Post-treatment for Type A and Type B Alcoholics Treated with either Sertraline or Placebo

Table 1

Demographics and Pre-treatment Clinical Characteristics of Follow-up Study Groups[1]

	Type A Alcoholism		Type B Alcoholism	
	Sertraline	**Placebo**	**Sertraline**	**Placebo**
n	27	21	19	23
% Males	55.6%	38.1%	47.4%	65.2%
Age	47.0	50.4	40.1	41.7
% Caucasian	74.1%	90.5%	73.7%	87.0%
% Married	25.9%	38.1%	42.1%	60.9%
% Middle/Upper SES	48.1%	52.4%	57.9%	65.2%
% Employed	92.6%	85.7%	84.2%	73.9%
Yrs Education	14.7	15.5	13.4	14.2
Yrs Problem Drinking	18.2	17.6	11.5	14.6
Alcohol Txs Lifetime	0.46	0.90	0.58	1.00

[1] Although some expected differences between alcoholic subtypes were found, there were no significant medication main effect or alcohol subtype by medication interactions.

Table 2

Means and Standard Errors of Non-transformed Outcome Variables of Follow-up Study Groups

	Final Month Treatment	1st Month Follow-up	2nd Month Follow-up	3rd Month Follow-up	4th Month Follow-up	5th Month Follow-up	6th Month Follow-up
Drinking Days[1]							
TypeA-Sertraline	5.70 (1.87)	5.72 (2.13)	7.17 (2.35)	6.96 (2.31)	7.91 (2.52)	7.48 (2.41)	7.36 (2.42)
TypeA-Placebo	9.00 (1.98)	10.24 (2.38)	10.81 (2.24)	9.95 (2.27)	11.37 (2.50)	10.06 (2.36)	10.06 (2.70)
TypeB-Sertraline	5.94 (1.97)	7.47 (2.45)	11.31 (2.86)	11.14 (2.98)	13.83 (3.21)	13.54 (3.40)	12.82 (3.55)
TypeB-Placebo	4.17 (1.41)	4.90 (1.69)	4.60 (1.72)	4.63 (1.78)	5.31 (2.10)	5.31 (2.05)	4.36 (2.17)
Heavy Drinking Days[2]							
TypeA-Sertraline	2.85 (1.48)	1.80 (1.32)	1.75 (1.19)	1.00 (0.63)	2.00 (1.34)	1.96 (1.30)	2.14 (1.31)
TypeA-Placebo	2.20 (0.89)	4.90 (2.08)	5.76 (2.22)	5.48 (2.19)	6.74 (2.61)	5.72 (2.40)	6.56 (2.66)
TypeB-Sertraline	4.94 (2.02)	5.53 (2.49)	9.63 (2.98)	8.86 (3.12)	11.08 (3.33)	11.54 (3.45)	10.55 (3.53)
TypeB-Placebo	2.48 (0.85)	2.00 (0.86)	1.65 (0.87)	2.05 (1.10)	2.06 (1.31)	1.94 (1.21)	0.64 (0.57)
Proportion Abstinent[3]							
TypeA-Sertraline	59.26 (9.64)	68.00 (9.52)	66.67 (9.83)	66.67 (9.83)	65.22 (10.15)	60.87 (10.41)	54.22 (10.87)
TypeA-Placebo	30.00 (10.51)	23.81 (9.52)	23.81 (8.52)	28.57 (10.10)	31.58 (10.96)	27.78 (10.86)	31.25 (11.97)
TypeB-Sertraline	44.44 (12.05)	35.29 (11.95)	37.50 (12.50)	35.71 (13.29)	25.00 (13.06)	30.77 (13.32)	36.36 (15.21)
TypeB-Placebo	39.13 (10.41)	35.00 (10.94)	55.00 (11.41)	47.37 (11.77)	50.00 (12.91)	37.50 (12.50)	50.00 (13.87)

[1] Analyses performed on log-transformed values. Alcoholic Subtype by Medication Group interaction: $F = 4.52$; $p = 0.036$.

[2] Analyses performed on log-transformed values. Alcoholic Subtype by Medication Group by Time interaction: $F = 6.70$; $p = 0.01$.

[3] Alcoholic Subtype by Medication Group interaction: $Z = -1.93$, $p = 0.05$.