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Post-Treatment Outcomes in a Double-Blind, Randomized Trial of Sertraline for Alcohol Dependence

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Abstract

Background—Pharmacotherapy studies in alcohol dependence (AD) are generally of short duration and do not include post-treatment follow-up. We examined the durability of treatment effects in a placebo-controlled trial of sertraline for AD.

Methods—As previously reported, patients received 12 weeks of treatment with sertraline ($n = 63$) or placebo ($n = 71$), followed by assessments at 3 and 6 months post-treatment (Kranzler et al., 2011, *J Clin Psychopharmacol* 31:22–30). We examined the main and interaction effects with time of 3 between-subject factors (medication group, age of onset of AD [late-onset alcoholics, LOAs, vs. early-onset alcoholics, EOAs], and the tri-allelic 5-HTTLPR genotype) on drinking days (DDs) and heavy drinking days (HDDs).

Results—The medication group effect, which was significant during treatment, remained significant during the 3-month follow-up period for L'/L' LOAs, with the sertraline group having fewer DDs than the placebo group ($p = 0.027$). However, the medication group effect seen in L'/L' EOAs during treatment was no longer significant ($p = 0.48$). There were no significant effects in S' carriers at the 3-month follow-up visit, or in either genotype group at the 6-month follow-up.

Conclusions—The beneficial effects of sertraline observed in LOAs during treatment persisted during the 3-month post-treatment period. Additional studies are needed to validate these pharmacogenetic findings, which together with the effects seen during active treatment support the use of sertraline only in LOAs.

Keywords

Post-Treatment Outcomes; Selective Serotonin Reuptake Inhibitor; Age of Onset; Alcohol Dependence; 5-HTTLPR

Alcohol dependence (AD) is a chronic, relapsing disorder. However, pharmacotherapy trials have generally been of limited duration, with most being 3 months and only a minority being as long as 4 to 12 months in duration (Kranzler et al., 2009). Further, comparatively few AD pharmacotherapy trials have included post-treatment followup visits, which provide information on the durability of treatment effects. Thus, there is inadequate information on the optimal duration of pharmacotherapy for AD.

Serotonergic agonists, including selective serotonin reuptake inhibitors (SSRIs), have shown inconsistent effects on drinking behavior in humans. One approach to resolving the variable clinical findings has been to subtype alcoholics by age of onset of alcoholism, premorbid characteristics, and severity of alcohol-related problems. For example, during 12 weeks of active treatment, the SSRI fluoxetine resulted in poorer alcohol-related treatment outcomes than placebo in Type B (earlier onset/higher severity; Babor et al., 1992) alcoholics (Kranzler et al., 1996). These effects did not persist during a 6-month post-treatment follow-up.

A study of the SSRI sertraline also showed medication effects that were moderated by alcoholism subtype (Pettinati et al., 2000). In that study, Type A (later-onset/lower vulnerability) alcoholics treated with sertraline were more likely to be abstinent from alcohol and had fewer drinking days (DDs) than those receiving placebo (Pettinati et al., 2000). In a 6-month post-treatment follow-up of this sample, Dundon and colleagues (2004) found that Type A alcoholics maintained the positive outcomes that they achieved during the last month of treatment with sertraline. In contrast, Type B alcoholics treated initially with sertraline reported more heavy drinking days (HDDs) over the 6-month post-treatment period than those who had received placebo. In a multicenter, placebo-controlled trial, early-onset/higher vulnerability (Type II; Cloninger, 1987) alcoholics were more likely to relapse to drinking when treated with the SSRI fluvoxamine than placebo (Chick et al., 2004). However, that study did not include a post-treatment follow-up assessment.

We (Kranzler et al., 2011) conducted a 12-week, parallel-groups, placebo-controlled trial of the efficacy of sertraline in a sample of 134 patients with DSM-IV AD (American Psychiatric Association, 1994). Treatment effects in early-onset alcoholics (EOAs; onset of AD at ≤25 years of age) were compared with those of late-onset alcoholics (LOAs; onset >25 years of age) in the context of the moderating effects of a functional polymorphism (5-HTTLPR) in the serotonin transporter gene. Variation at this locus includes higher-activity long (L) and lower-activity short (S) alleles (Lesch et al., 1996). The presence of an A → G single nucleotide polymorphism (SNP) in the L-specific repeat of the gene reduces its activity (Hu et al., 2005), such that the L_G allele is similar to the lower-activity S allele (both are referred to here as S' alleles and are differentiated from the high-activity L' allele).

We found that the moderating effect of age of onset on the response to sertraline during treatment was conditional on genotype (Kranzler et al., 2011). Although S'-allele carriers showed no main or interaction effects, in L' homozygotes, the effects of medication group varied by age of onset and study week. At the end of the 12-week treatment period, LOAs reported fewer DDs and marginally fewer HDDs when treated with sertraline than placebo. In contrast, EOAs had significantly fewer DDs and HDDs when treated with placebo than with sertraline. The theoretical and empirical bases by which variation at 5-HTTLPR could moderate the response to treatment with an SSRI such as sertraline are discussed in detail in that report (Kranzler et al., 2011). We present here the post-treatment outcomes from that study using a moderator analysis similar to the within-treatment analysis, to test the hypothesis that the within-treatment effects would persist beyond the period of active treatment.

MATERIALS AND METHODS

The institutional review board of the University of Connecticut Health Center approved the treatment and follow-up procedures. Study participants gave written informed consent to participate after procedures and possible side effects were explained to them. They were paid \$50 to complete research assessments at the end of treatment and at 3 and 6 months post-treatment.

Study Treatments

Patients were randomly assigned to treatment with sertraline or placebo using a computerized urn randomization (i.e., balancing) procedure. Patients received study medication in capsules under double-blind conditions, at a maximum dosage of 200 mg/d of sertraline (or 4 placebo capsules). After 12 weeks of treatment, the study medication was tapered over 2 weeks and discontinued. During treatment, patients also received up to 9 coping skills training sessions (i.e., sessions were held weekly for 6 weeks and then biweekly for 6 weeks).

Patients

Following screening and baseline assessments, 134 treatment-seeking patients from the community were randomly assigned to treatment, including 63 patients in the sertraline group (21 EOAs and 42 LOAs) and 71 patients in the placebo group (25 EOAs and 46 LOAs). The mean age of the sample was 47.5 years ($SD = 9.8$); 81% were men and 92% were European American. Patients had completed a mean of 14.5 years of school ($SD = 2.3$). They met a mean of 5.8 ($SD = 1.1$) DSM-IV criteria for current AD and nearly two-thirds (64.9%) had had prior alcohol treatment. During the pretreatment period, patients drank on 67.9% of days ($SD = 26.3\%$), drinking heavily (defined as 4 standard drinks in a day for women and 5 in a day for men) on 56.5% of days ($SD = 29.5\%$). They consumed a mean of 6.4 ($SD = 4.4$) standard drinks per day and 9.8 ($SD = 5.9$) standard drinks per drinking day. There were no significant main effects of medication group or interaction effects of medication group by age of onset on any of the demographic or clinical indicators examined. Patient characteristics, broken down by medication group by age of onset group, are presented elsewhere (see Table 1 in the study by Kranzler et al., 2011).

Assessments

The Structured Clinical Interview for DSM-IV (SCID; First et al., 2001) was used to assess the presence of psychiatric diagnoses, including lifetime major depressive disorder (MDD) and AD (as well as its age of onset). We (Kranzler et al., in press) have shown previously that this approach to subtyping individuals with AD is more useful as a moderator of medication effects than the Type A/B distinction by Babor and colleagues (1992). Thus, we limited the examination of post-treatment effects to those seen with age of onset as determined using the SCID.

The Timeline Follow-Back (TLFB) method (Sobell and Sobell, 1992) was used at each treatment visit to estimate alcohol consumption during the preceding 1 to 2 weeks and during the 90-day period covered by the 3- and 6-month post-treatment follow-up assessments.

Interactive voice response (IVR) technology (Kranzler et al., 2004), which uses the telephone to administer survey questions, was used during the 12-week treatment period to measure drinking behavior through daily reports of standard drinks of different beverages consumed.

Consistent with the within-treatment analyses (Kranzler et al., 2011), we used the score from the Short Index of Problems (SIP; Miller et al., 1995) as a covariate in the analyses.

Gamma-glutamyl-transpeptidase (GGTP), a liver enzyme the concentration of which reflects recent drinking, was measured at the end of treatment and at the 3- and 6-month post-treatment follow-up visits. We correlated changes in GGTP concentration with changes in self-reported alcohol consumption to validate the latter.

Genotyping Procedure

We used a 2-stage TaqMan 5' nuclease allelic discrimination assay (Nakamura et al., 2000; Hu et al., 2005) that was modified from the procedure employed by Hu and colleagues (2006) to differentiate S and L alleles. L_A versus L_G allele-specific probes were used to characterize the A $\rightarrow$ G SNP in the L allele. The L_G and S alleles were grouped together as S' (lower expression) alleles, and the L_A allele was designated as the L' (higher expression) allele.

Data Preparation

We calculated the percentage of DDs and HDDs from the treatment period data, which were based on IVR reports augmented by TLFB data. Specifically, drinking data from the TLFB were inserted on days when the patient did not complete an IVR report, resulting in self-reported data on drinking being available on 80% of days (mean = 67.2 days [SD = 26.3]; median = 84 days). During treatment, days for which self-report data were missing were re-coded as HDDs, which is a conservative approach to the imputation of missing data. We also calculated the percentage of DDs and HDDs from available 3- and 6-month post-treatment TLFB assessments.

Data Analysis

We used 2-level hierarchical linear models (HLMs) to examine medication group (coded sertraline = 0, placebo = 1) differences in the percentage of DDs and HDDs as a function of age of onset (coded 0 = LOA, 1 = EOA), 5-HTTLPR genotype (coded L'/L' = 0, S'-allele carriers = 1), and time (initially coded with the following linear contrast: 0 = treatment, 1 = 3-month follow up, and 2 = 6-month follow up). Additional models coding each subsequent wave as zero were estimated to test different conditional effects of medication group for each time point. In follow-up models testing conditional effects for S'-allele carriers or EOAs, the coding was reversed so that those groups were coded 0. Consistent with the analysis of within-treatment data (Kranzler et al., 2011), all DD and HDD models included sex (0 = male, 1 = female), age (grand-mean centered), a lifetime diagnosis of MDD (0 = no, 1 = yes), and SIP total score (grand-mean centered) as covariates. Intercepts and slopes were treated as random effects. We report the fixed effects with robust standard errors.

We used an analytic model similar to that employed in the analysis of within-treatment effects to avoid methodological confounding. However, in contrast to our report on treatment effects (Kranzler et al., 2011), which examined within-treatment time (i.e., study week) as a factor, the present analysis examined only changes in overall drinking levels across three 12-week periods, that is, treatment and the 3- and 6-month follow-up periods. This enabled us to evaluate the persistence of changes observed during the active treatment period.

All subjects were included in the models, regardless of the number of waves. This is consistent with recent recommendations for methods to maximize the accuracy of parameter estimates in data with missing values (Mallinckrodt et al., 2008; Singer and Willett, 2003). This approach is also preferred to other missing data techniques such as last-observation-carried forward (LOCF) (Prakash et al., 2008), which we used to re-estimate the models as a check. For example, with LOCF, if a patient had treatment and 3-month follow-up data, but not 6-month follow-up data, we carried forward the 3-month value. For patients with neither 3- nor 6-month follow-up data, we carried forward the treatment values for both periods. Results using the LOCF method were substantively the same as those from the 2-level HLMs.

RESULTS

Descriptive Statistics

As shown in Table 1, completion rates varied substantially across the study groups and follow-up periods. As reported in the study by Kranzler and colleagues (2011), overall, 61.9% of patients completed the 12-week treatment. Comparison of the completion rate among the 8 groups (which resulted from crossing medication group, age of onset, and genotype) was significant, $\chi^2(7) = 15.43$, $p = 0.031$. As shown in Table 1, it was lowest in the L'L' EOAs who were treated with sertraline and highest in the placebo-treated L'L' EOAs and the sertraline-treated L'L' LOAs. A total of 104 patients (77.6%) completed the 3-month assessment and 97 patients (72.3%) completed the 6-month assessment. Omnibus χ^2 tests indicated no significant differences in retention rates at the 3-month follow-up, $\chi^2(7) = 6.67$, $p = 0.46$, or the 6-month follow-up, $\chi^2(7) = 9.55$, $p = 0.22$. However, results from a logistic regression predicting the occurrence of at least 1 missed follow-up assessment from the study condition variables, genotype, and the control variables indicated significant effects for age [odds ratio (OR) = 0.91, $p < 0.001$], pretreatment DDs (OR = 1.157, $p = 0.0015$), SIP scores (OR = 0.93, $p = 0.016$), and age of onset of AD (OR = 0.21, $p = 0.006$). Specifically, younger patients, individuals with a greater proportion of DDs during pretreatment and lower SIP scores, and those with late-onset AD (i.e., LOAs) were more likely to miss a follow-up assessment. Medication group (OR = 0.50, $p = 0.12$), genotype (OR = 0.78, $p = 0.63$), dependence diagnosis (OR = 1.95, $p = 0.21$), and gender (OR = 1.52, $p = 0.47$) were not related to missing a follow-up assessment.

GGTP concentration was correlated with the 3-month assessment drinking frequency ($r = 0.26$, $p = 0.031$) and heavy drinking frequency ($r = 0.30$, $p = 0.004$) and 6-month assessment drinking frequency ($r = 0.23$, $p = 0.042$) and heavy drinking frequency ($r = 0.29$, $p = 0.009$).

Multilevel Regression Results

Drinking Days—Table 1 shows the percentage of DDs by time, medication group, age of onset, and 5-HTTLPR genotype across the treatment and follow-up periods. Based on the pattern of change, we first tested a model with a quadratic time $\times$ age of onset $\times$ medication group $\times$ 5-HTTLPR genotype interaction. Because none of the higher-order or lower-order effects involving the quadratic time predictor were significant, they were removed from the models. There was a significant 4-way interaction of time (linear) with the between-person factors ($b = -0.442$, $SE = 0.165$, $p = 0.009$) in predicting the percentage of DDs.

When we probed the lower-order (conditional) 3-way interactions, we found that the time $\times$ age of onset $\times$ medication group interaction was significant for L'/L' individuals ($b = 0.448$, $SE = 0.137$, $p = 0.002$), but not S'-carriers ($b = -0.006$, $SE = 0.090$, $p = 0.95$). Thus, for L'/L' individuals, the interaction of age of onset and medication group varied across time. Focusing on the simple effects of medication group, during treatment, L'L' LOAs who had received sertraline had fewer DDs than those who had received placebo ($b = 0.341$, $SE = 0.122$, $p = 0.007$). In contrast, during treatment, L'/L' EOAs who had received sertraline had more DDs than participants who had received placebo ($b = -0.429$, $SE = 0.132$, $p = 0.002$). These findings are similar to those reported in the study by Kranzler and colleagues (2011). At the 3-month post-treatment follow-up, the medication group effect remained significant for L'/L' LOAs, with the sertraline group having fewer DDs than the placebo group ($b = 0.226$, $SE = 0.101$, $p = 0.027$). This difference was significant despite a narrowing of the sertraline-placebo difference in L'L' LOAs compared with that seen during active treatment (Table 1). At the 3-month post-treatment assessment, there was no medication group effect on DDs in L'/L' EOAs ($b = -0.097$, $SE = 0.137$, $p = 0.48$). At the 6-month follow-up visit,

there were no significant medication group effects on DDs for either LOAs ($b = 0.114$, $SE = 0.123$, $p = 0.37$) or EOAs ($b = 0.236$, $SE = 0.219$, $p = 0.28$).

Heavy Drinking Days—Table 1 shows the percentage of HDDs by time, medication group, age of onset, and 5-HTTLPR genotype across the treatment and follow-up periods. Again, an initial model incorporating quadratic time effects was estimated, but none of the effects for quadratic time were significant. There was, however, a significant 4-way interaction of time (linear) with the between-person factors ($b = -0.381$, $SE = 0.169$, $p = 0.025$). Probing of the lower-order (conditional) 3-way interactions revealed that the time $\times$ age of onset $\times$ medication group interaction was significant for L'/L' individuals ($b = 0.387$, $SE = 0.145$, $p = 0.009$) but not S'-allele carriers ($b = -0.005$, $SE = 0.084$, $p = 0.95$). Thus, for L'/L' individuals, but not S'-allele carriers, the interaction of age of onset and medication group varied across time.

Again, we then focused on the simple effects of medication group for LOAs and EOAs in the L'/L' genotype group. The medication group effect on HDDs for the L'/L' LOAs did not reach significance ($b = 0.192$, $SE = 0.122$, $p = 0.12$). However, the medication group effect during treatment was significant for L'/L' EOAs ($b = -0.418$, $SE = 0.139$, $p = 0.004$), with the sertraline group having more HDDs than the placebo group. The medication group effect on HDDs in L'/L' LOAs was not significant at the 3-month ($b = 0.075$, $SE = 0.076$, $p = 0.33$) or 6-month ($b = -0.042$, $SE = 0.061$, $p = 0.49$) follow-up periods. Similarly, the medication group effect on HDDs for L'/L' EOAs was not significant at the 3-month ($b = -0.149$, $SE = 0.138$, $p = 0.95$) or 6-month ($b = -0.121$, $SE = 0.231$, $p = 0.60$) follow-up assessments.

For S'-allele carriers, in addition to there being no time $\times$ age of onset $\times$ medication group interaction, there was no overall (averaged across time) interaction of age of onset $\times$ medication group in predicting the percentage of DDs ($b = -0.106$, $SE = 0.129$, $p = 0.42$) or HDDs ($b = 0.116$, $SE = 0.114$, $p = 0.31$). Moreover, there were no overall (averaged across time) medication group effects in EOA S'-allele carriers for the percentage of DDs ($b = 0.038$, $SE = 0.103$, $p = 0.71$) or the percentage of HDDs ($b = -0.006$, $SE = 0.092$, $p = 0.95$) or for LOA S'-allele carriers for the percentage of DDs ($b = -0.067$, $SE = 0.078$, $p = 0.39$). There was, however, a marginally significant medication group effect for LOA S'-allele carriers, with the sertraline group showing a higher percentage of HDDs than the placebo group ($b = -0.122$, $SE = 0.066$, $p = 0.065$).

DISCUSSION

Although AD is a chronic, relapsing disorder, trials of medications to treat the disorder have been of comparatively short duration (Kranzler et al., 2009). Further, few AD treatment trials have included post-treatment follow-up evaluations, which provide information on the durability of treatment effects. Thus, there is inadequate information on the optimal duration of pharmacotherapy for AD.

The present study examined the duration of effects seen during a placebo-controlled trial of sertraline for AD (Kranzler et al., 2011). In that study, effects were seen only in L'-allele homozygotes, where age of onset of AD and 5-HTTLPR genotype moderated the effects of the medication on both DDs and HDDs. Specifically, sertraline-treated LOAs and placebo-treated EOAs had fewer DDs and HDDs than placebo-treated LOAs and sertraline-treated EOAs, respectively. Using a similar analytic approach to examine effects over the 6 months post-treatment, we found significant medication group $\times$ age of onset effects only in L'-allele homozygotes. Specifically, in individuals with this genotype, during the first 3 months of post-treatment follow-up, compared with placebo treatment, sertraline-treated LOAs had

fewer DDs and sertraline-treated EOAs had more HDDs. However, these effects did not persist during the second 3 months of follow-up.

The study sample was comparatively small, particularly the subgroups with the L'L' genotype. This limited the study's statistical power. Thus, replication in larger samples is needed. There was also a low rate of treatment completion, particularly in the L'L' EOA subgroup. This could have biased the within-treatment findings. However, we (Kranzler et al., 2011) previously found that multilevel modeling (which weights the contribution of each participant in the between-group comparisons according to the number of assessments of drinking data available) yielded results similar to those obtained with conservative imputation of missing data, which argues against a bias in our findings attributable to missing data. Further, during the post-treatment period, which is the focus of this report, the follow-up rates were comparable among the groups, supporting the validity of the observed findings. We identified a number of variables associated with missing a follow-up assessment (i.e., age of onset of AD, age, pretreatment drinking frequency, and SIP score). However, the impact of these variables on treatment outcome is impossible to gauge. Thus, we cannot rule out the possibility that these factors may have confounded the results.

The finding that sertraline treatment affects drinking outcomes beyond the period of active treatment supports the use of the medication in LOAs, for whom active treatment was associated with fewer DDs. The effects of medication did not persist during the second 3 months of follow-up, consistent with the chronic, relapsing nature of AD. These findings partially replicate those reported by Dundon and colleagues (2004). They found that Type A alcoholics, who are similar in many ways to LOAs, had persistent beneficial effects of sertraline, that is, a lower frequency of drinking during the post-treatment follow-up. They also found that Type B alcoholics, who are similar in many ways to EOAs, when treated initially with sertraline, had more HDDs over the 6-month post-treatment period than those previously treated with placebo. In that study, the post-treatment effects persisted throughout the follow-up period. However, Dundon and colleagues (2004) analyzed drinking outcomes monthly over the 6 months of post-treatment follow-up compared with our use of 3-month blocks. Further, they focused on the subtypes identified by Babor rather than age of onset. These methodological differences could have contributed to the differences in our findings compared to those in the study by Dundon and colleagues (2004).

Sertraline is widely prescribed and AD is highly prevalent, thus these findings have important implications for the treatment of the disorder. Because in our study the impact of sertraline was limited to individuals with the L'L' genotype, additional pharmacogenetic studies are needed to validate these findings. The lack of beneficial effects in individuals with the S' allele, combined with the potentially harmful effects of sertraline in EOAs, raise the question of whether sertraline (or, for that matter, any SSRI) should be prescribed for the treatment of AD except in LOAs or individuals with co-occurring AD and MDD.

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Table 1
Cell Sizes, Completion Rates, and Drinking Outcomes by Treatment Period and Genotype Group

	L' homozygotes				S' carriers			
	Late onset		Early onset		Late onset		Early onset	
	Sertraline	Placebo	Sertraline	Placebo	Sertraline	Placebo	Sertraline	Placebo
Treatment								
N randomized	12	10	7	6	30	36	14	19
% completing treatment	83.3 (10)	40.0 (4)	14.3 (1)	83.3 (5)	56.7 (17)	72.2 (26)	50.0 (7)	68.4 (13)
% drinking days (DDs)	26.7 (34.1)	59.5 (30.1)	72.3 (20.6)	27.4 (37.9)	48.8 (35.6)	40.7 (35.1)	43.9 (42.4)	42.6 (30.9)
% heavy drinking days (HDDs)	19.8 (33.6)	40.1 (32.7)	64.8 (27.4)	21.4 (38.5)	38.1 (33.3)	26.5 (30.1)	36.7 (39.7)	34.8 (30.2)
3-month								
% completing follow-up	75.0 (9)	70.0 (7)	71.4 (5)	83.3 (5)	63.3 (19)	86.1 (31)	85.7 (12)	84.2 (16)
% DDs	14.8 (16.1)	27.1 (22.6)	36 (35.8)	31.3 (28.8)	31.5 (36.4)	34.8 (34.5)	24.6 (27.0)	45.3 (36.1)
% HDDs	4.7 (7.6)	4.6 (4.0)	33.6 (35.6)	16.7 (17.8)	17.8 (30.8)	17.6 (24.0)	16.5 (22.4)	30.1 (30.4)
6-month								
% completing follow-up	66.7 (8)	70.0 (7)	71.4 (5)	66.7 (4)	53.3 (16)	80.6 (29)	85.7 (12)	84.2 (16)
% DDs	15.7 (20.2)	25.1 (18.6)	24.7 (32.5)	40.8 (33.7)	42.3 (41.1)	39.5 (34.8)	36.3 (36.7)	47.8 (34.0)
% HDDs	1.9 (4.2)	1.6 (2.0)	20.4 (34.4)	28.7 (33.2)	30.4 (37.9)	21.5 (27.6)	27.2 (33.4)	33.8 (33.5)

Numbers of subjects completing treatment and each follow-up visit are in parentheses. Values for percentage of DDs and HDDs are from imputed data; standard deviations are in parentheses.