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5-HTTLPR Genotype and Daily Negative Mood Moderate the Effects of Sertraline on Drinking Intensity

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Abstract

We previously reported moderating effects of age of onset of alcohol dependence (AD) and a functional polymorphism (5-HTTLPR) in the gene encoding the serotonin transporter protein in a sample of 134 individuals participating in a 12-week, placebo-controlled trial of sertraline (Kranzler et al. 2011). To understand more fully the effects seen in that study, we examined moderation by negative moods reported each evening, with nighttime drinking intensity (i.e., the number of standard drinks consumed at night) as the dependent variable. We found a daily anxiety $\times$ age of onset $\times$ 5-HTTLPR polymorphism $\times$ medication interaction, which reflected a daily anxiety $\times$ medication group effect for early-onset individuals homozygous for the high-expression (L') allele, but not others. Specifically, on days characterized by relatively high levels of anxiety, early-onset L' homozygotes receiving placebo reduced their drinking intensity significantly. In contrast, early-onset L' homozygotes treated with sertraline non-significantly increased their drinking intensity. These findings implicate anxiety as a key moderator of the observed effects pharmacogenetic effects. These findings have important implications because of the high prevalence of AD and the frequency with which SSRIs and other antidepressants are prescribed for a variety of psychiatric disorders.

Keywords

SSRI; Alcohol Dependence; 5-HTTLPR

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INTRODUCTION

In a 12-week, parallel-groups, placebo-controlled trial of the efficacy of sertraline, we found moderating effects of both age of onset of alcohol dependence (AD) and a functional polymorphism in the gene encoding the serotonin transporter protein (5-HTT) (Kranzler et al. 2011). Sertraline is a selective serotonin (5-HT) reuptake inhibitor (SSRI). SSRIs act at the 5-HTT, a key regulator of serotonergic tone in the central nervous system. A functional insertion/deletion polymorphism in the 5-HTT linked promoter region (5-HTTLPR) of *SLC6A4*, which encodes the 5-HTT, results in long (L) and short (S) alleles (Lesch et al. 1996). These alleles differentially modulate the transcriptional activity of the gene's promoter, resulting in differences in mRNA concentration, protein density, and 5-HT uptake activity in human lymphoblastoid cells, platelets, and brain (Heils et al. 1996, Greenberg et al. 1999, Murphy et al. 2004, Praschak-Rieder et al. 2007). A single nucleotide polymorphism (SNP; rs25531) is tightly linked with the L-specific insertion and encodes an A → G exchange 18 bp upstream from the L-specific repeat of the gene (Perroud et al. 2010). The SNP also appears to affect function, such that the L_G allele is similar to the lower activity S allele (Hu et al. 2006). Based on their activity levels, the S and L_G alleles are typically grouped together as S' alleles; the L_G allele is identified as the L'-allele.

Specifically, we found that the moderating effect of age of onset on the response to sertraline was conditional on genotype. Although there were no main or interaction effects among S' allele carriers, L' homozygotes showed opposite effects of medication treatment as a function of age of onset. At the end of treatment, late-onset alcoholics (LOAs: individuals meeting DSM-IV criteria for AD at age 25 or older) reported fewer drinking days (DDs) and heavy drinking days (HDDs) when treated with sertraline than placebo. In contrast, early-onset alcoholics (EOAs: individuals meeting DSM-IV criteria for AD prior to age 25) had fewer DDs and HDDs when treated with placebo than sertraline. These findings were consistent with prior studies of SSRIs in the treatment of AD, in which earlier-onset, higher vulnerability patients were found to have poorer drinking outcomes when treated with either fluoxetine (Kranzler et al. 1996) or fluvoxamine (Chick et al. 2004) than with placebo and later-onset, lower vulnerability patients showed better drinking outcomes with sertraline treatment than with placebo (Pettinati et al. 2000). The findings reported by Kranzler et al. (2011) differed from the earlier studies in that they found the effects of sertraline to be conditional on 5-HTTLPR genotype. Johnson et al. (2011) found that effects of the 5-HT₃ antagonist ondansetron were also conditional on 5-HTTLPR genotype. The basis for these pharmacogenetic findings involving the 5-HTTLPR polymorphism remains to be determined.

Thus, the aim of the current study was to elucidate the mechanism of the effects seen in Kranzler et al. (2011). To this end, we examined the efficacy of sertraline in attenuating the link between negative mood states (assessed daily in the early evening) and proximal alcohol use (occurring in the evening after the report of mood) and whether this interactive effect varied as a function of genotype and age of onset of alcohol dependence. Empirical typologies (e.g., Babor et al. 1992, Buydens-Branchey et al. 1989, Johnson et al. 2000) have shown that EOAs have more mood symptoms than LOAs. Further, Kranzler et al. (2011) showed the greatest effect of sertraline in EOAs with the L'L' genotype, where it was significantly associated with more frequent drinking and heavy drinking than placebo. Thus, we hypothesized that negative mood would be most predictive of later drinking, particularly in early-onset alcoholics with the high expression 5-HTTLPR genotype, and that sertraline would modify those relations. To understand the moderating effects of genotype on the response to sertraline, we used a micro-longitudinal design that allowed us to (a) measure daily mood and drinking behavior relatively free of recall error and bias and (b) focus on the

within-person associations between daily mood and alcohol consumption, thereby reducing error variance and enhancing statistical power.

METHODS AND MATERIALS

Kranzler et al. (2011) provided a detailed description of the methods employed in the clinical trial. Patients were recruited through advertisements and referrals by area clinicians. The institutional review board of the University of Connecticut Health Center approved the consent form and study protocol and the study was conducted in accordance with the Declaration of Helsinki. Study participants gave written informed consent and were paid to complete daily reports and for the completion of a research assessment at the end of treatment.

Patients were 18-65 years old, with a DSM-IV diagnosis of AD (American Psychiatric Association 1994) during the preceding month, were abstinent from alcohol for at least 3 days prior to baseline, were able to read English, showed no evidence of cognitive impairment, and expressed an intention to stop drinking. Women of childbearing potential were required to be practicing reliable birth control and to have a negative serum pregnancy test. A current DSM-IV diagnosis of dependence on any substance other than alcohol and nicotine; use of psychoactive drugs, disulfiram, acamprosate, or naltrexone; and a current diagnosis of DSM-IV major depressive disorder (MDD), psychotic disorder or untreated medical illness were exclusionary.

The final sample of 134 individuals was, on average, 47.5 years old ($SD = 9.8$) and mostly male (81%) and European American (92%). Overall, the study sample had completed a mean of 14.5 yrs of education ($SD = 2.3$).

Assessments

The Structured Clinical Interview for DSM-IV (SCID) (First et al. 2001) was used to assess psychiatric diagnoses and the age of onset of AD.

Interactive Voice Response Technology (IVR) uses the telephone to administer survey questions (Kranzler et al. 2004). Patients called daily late in the day to rate their mood and report their alcohol consumption for that day by pressing the keys on the keypad, with responses entered automatically in a database. They reported the number of standard drinks of beer, wine, and liquor that they consumed that day and (separately) the previous evening, after the daily survey. We chose this method as an alternative to having participants report on their drinking at the end of the night. We believe that the resultant loss of some daily data – due to the need to have consecutive daily reports (described below) – was necessary to avoid asking these heavy drinkers to report their drinking at a time when fatigue and the effects of heavy drinking were more likely to reduce the validity of reports.

We assessed discrete daily mood states with single-item descriptors selected from existing models (Larsen and Diener 1992) and our previous research. In the current study, we focused on three negative moods: sad, nervous and angry. Participants rated how they felt on a 5-point scale (0 = “not at all” to 4 = “extremely”). Use of single-item indicators in daily studies is common to reduce participant burden and has been shown to be valid in daily diary studies (van Hooff et al. 2007). The validity of single-item measures of depressed (Skooch et al., 2010), anxious (Davey et al., 2007) and angry (Mittleman et al., 1997) mood is well documented.

Study Treatments—Patients were randomly assigned 1:1 to parallel treatment with sertraline or placebo using a computerized urn randomization procedure (Wei 1978) to

balance the treatment groups on six variables: age of onset of AD, current age, sex, educational level, past diagnosis of MDD, and the duration of abstinence prior to screening. Randomization was performed by a research pharmacist who provided the medications to a research nurse for dispensing to participants under double-blind conditions. The initial dosage was 50 mg/day, with a gradual increase to a maximum dosage of 200 mg/day for a total of 12 weeks of treatment, after which the study medication was tapered over 2 weeks and discontinued. In addition to study medication, all patients received a structured, manual-guided individual intervention, consisting of 9 coping skills training sessions.

Genotyping Procedure—Genotyping was conducted via a two-stage TaqMan™ 5′ nuclease allelic discrimination assay modified from the procedure used by Hu et al. (2005, 2006) to differentiate S and L alleles (Nakamura et al. 2000, Covault et al. 2007). L_A and L_G allele-specific probes (6FAM-CCCCCTGCACCCCCAGCATCCC-MGB and VIC-CCCCCTGCACCCCCGGCATCCCC-MGB, respectively) served to characterize the rs25531 A → G SNP associated with the L-insertion allele. L_G and S alleles were coded as S′ and the L_A allele as L′. As reported in Kranzler et al. (2011), the genotype distribution did not differ significantly from Hardy-Weinberg expectations ($\chi^2_{(1)} = 2.36, p = 0.12$).

Data Configuration and Analysis—We used Generalized Estimating Equations (GEE) to test whether the association between early evening negative affect levels and subsequent nighttime drinking varied as a function of *5-HTTLPR* genotype [L′/L′ (coded 0) vs. S′-carriers (coded 1)], medication condition [placebo (coded 0) vs. sertraline (coded 1)], and age of onset [early onset (coded 0) vs. late onset (coded 1)]. We also controlled for sex (coded 0 = male, 1 = female), drinking up to reporting time and day of the week (using six dummy codes with Saturday as the reference day). Because nighttime drinking was obtained one day subsequent (reported on day $t+1$) to early evening affect and earlier day alcohol consumption (reported on day t), two consecutive days of daily reporting were required for one complete daily record. Thus, one missing daily report resulted in two missing data points for analysis.

We used the number of standard drinks consumed each evening (i.e., drinking intensity) as the primary dependent measure in the analyses. Drinking intensity is a useful outcome measure because it is closely associated with the adverse effects of drinking (e.g., through accidents, problematic interpersonal behaviors). To examine the question of how individuals' nighttime drinking levels (i.e., drinking intensity) changed on days characterized by relatively higher or lower levels of negative affect, we person-mean-centered these predictors by subtracting each person's overall mean from their daily reports. Person-mean centering yields an unbiased estimate of the within-person association (see Stone and Shiffman, 1994). Each person's overall mean for the affect variables was included in their respective models as a control variable. Given the count nature of the outcome (and the large number of zeros and positive skew at the daily level of analysis), we estimated a negative binomial regression with log link (Coxe et al., 2009). To reduce the influence of extremely high reports of nighttime or daytime drinking (which occurred on 0.3% of nighttime values and 0.2% of the daytime values), we recoded any value greater than 20 to 20.

We entered the predictors of interest in several steps. First, we included all of the control variables and medication group (coded 0 = placebo, 1 = sertraline), *5-HTTLPR* genotype (coded 0 = L′/L′, 1 = S′-carriers), age of onset (coded 0 = early onset, 1 = late onset), and one of the negative affect variables (both the person-mean centered value and the overall mean levels). We then entered the three 2-way product terms for the interactions among medication group, *5-HTTLPR* genotype, age of onset, and the daily negative affect variable, followed by the 3-way product terms, and finally the 4-way effect.

RESULTS

Treatment and Adherence to Daily Reporting by IVR

The mean number of therapy sessions for the sample was 6.1 ($SD = 2.9$). The number of sessions did not differ by medication group, age of onset, or their interaction (p 's > 0.05). We had complete reports (i.e., both day t and $t+1$ values) for 7,190 person-days. This represents 64.6% of the possible 11,122 person-days [i.e., 134 patients $\times$ 83 days (day 84 was omitted because there was no report of nighttime drinking on the following day)]. Descriptive statistics broken down by study condition are shown in Table 1. Reporting days differed as a function of gene $\times$ medication group $\times$ age of onset ($p = 0.022$). Probing of this effect indicated that the gene $\times$ medication group interaction was significant for LOAs ($p = 0.04$), but not EOAs ($p = 0.17$). The form of the gene $\times$ medication group interaction among LOAs indicated that, in the L'/L' group, sertraline-treated subjects had significantly more daily reports than placebo participants. In contrast, in the S' carrier group, placebo-treated subjects had more daily reports than those treated with sertraline.

Drinking Behavior During Treatment

Subjects reported drinking on 27.8% of days, consuming 6.2 drinks ($SD = 5.5$) per drinking day. Daytime drinking (i.e., prior to the daily survey) was reported on 18.4% of the days and subjects reported a mean of 4.1 drinks ($SD = 3.4$) per daytime drinking period. Nighttime drinking was reported on 20.3% of the days and subjects reported a mean of 4.7 drinks ($SD = 3.8$) per nighttime drinking period.

Table 1 shows mean daytime and nighttime drinking measures by study condition. Nighttime drinking differed as a function of gene $\times$ medication group $\times$ age of onset ($p = 0.029$). The pattern of effects on drinking behavior is consistent with the effect for overall drinking levels reported in Kranzler et al. (2011). There was no age of onset $\times$ genotype $\times$ medication group effect on the mean daytime drinking level ($p = 0.19$).

Predicting Nighttime Drinking

The results of the GEE models are shown in Table 2. Block 1 contains all of the predictors with no interaction terms. Consistent with findings from published daily studies of drinking (Armeli et al. 2000, Todd et al. 2003), there were day-of-the-week effects on drinking, with subjects drinking significantly more on Saturday nights than Sunday, Monday or Tuesday nights. Earlier day drinking and mean levels of sadness were positively associated with nighttime drinking.

Of central interest, daily changes in anger (i.e., deviations from mean levels) were significantly related to nighttime drinking. Specifically, on days when individuals reported a level of anger greater than their mean level, they drank more later that night. Exponentiation of this slope reveals the rate of increase in drinking for a unit change in the predictor; for example, for every one unit increase in anger, drinking increased by a factor of 1.12 ($\exp[.111]$) or 12%.

We next entered the 2-way product terms in block 2. We found two significant interactions indicating that (a) the association between daily changes in anxiety and nighttime drinking was stronger in the positive direction for S'-carriers than L'/L' individuals and (b) the association between daily changes in sadness and nighttime drinking was stronger in the positive direction for early-onset individuals than late-onset individuals. In block 3, we entered the 3-way product terms. For all three models, as discussed above in relation to the data in Table 1, the onset $\times$ medication group $\times$ genotype product term was significant or marginally significant.

Finally, the 4-way term was entered into the models. It was significant in the model for anxiety. The form of this effect is shown in Figure 1 and indicates little effect of medication on the daily anxiety-drinking association except among early onset, L'/L' individuals. Probing of the 3-way daily anxiety $\times$ genotype $\times$ medication group interaction across age of onset indicated that the effect was significant for early-onset individuals ($p = 0.006$), but not late-onset individuals ($p = 0.25$). Moreover, among early-onset individuals, the daily anxiety $\times$ medication group interaction was significant for L'/L' individuals ($p = 0.001$), but not for S'-carriers ($p = 0.22$). Finally, tests of the simple slopes for early-onset, L'/L' individuals indicated a significant negative association between daily anxiety and nighttime drinking for placebo individuals ($p < 0.001$) and a non-significant positive association for participants taking sertraline ($p = 0.51$).

Repeating the analyses with only European Americans ($N=123$) yielded similar, but more robust findings for the study variables. Noteworthy was the fact that the 4-way interaction was now also significant ($p = .001$) in the sad mood model. The form of this effect was similar to the effect for anxiety shown in Figure 1. The effects involving anger did not change when limiting the sample to European Americans.

DISCUSSION

In this study, we applied a micro-longitudinal approach, using daily reports of negative mood and drinking behavior to examine moderation of the response to sertraline in a placebo-controlled trial of 134 patients seeking treatment for AD. We found that when EOAs homozygous for the high-expression (L') allele of the 5-HTTLPR polymorphism experienced levels of anxiety that were higher than their average level, placebo treatment was associated with a lower intensity of nighttime drinking. In contrast, although not statistically significant, drinking in the EOA L' homozygote group receiving sertraline was not reduced. This effect is clinically relevant in that L' homozygotes who were EOAs had generally high levels of drinking. Although other groups also failed to show reductions in drinking in response to higher anxiety, they were not drinking as heavily as the L'L' EOAs.

In EOAs with the L'L' genotype, on high-anxiety days, sertraline treatment was associated with non-significantly greater nighttime drinking than placebo treatment (see Figure 1). The lack of statistical significance of the anxiety-drinking association in the sertraline-treated subgroup is likely due both to the small number of early-onset subjects overall and the comparatively low frequency of daily reports in the sertraline-treated subgroup specifically, which together limited statistical power (see Table 1). Nonetheless, these findings may help to explain the medication effects seen in the published results of the clinical trial (Kranzler et al. 2011), which is the basis for the current analyses. Although SSRIs are widely used chronically as anxiolytics, acute SSRI administration can be anxiogenic in animals and humans (Kurt et al. 2000, Browning et al. 2007). The findings reported here implicate anxiety as a key moderator of the observed effects, though the specific mechanism by which sertraline seems to augment the drinking response remains to be determined. Alternate approaches (e.g., a human laboratory paradigm) may clarify the basis for our finding that high levels of anxiety reduced nighttime drinking in early-onset L' homozygotes treated with placebo, but not those in the group treated with sertraline. Research is also needed to identify other genetic and environmental factors that moderate the response to SSRIs in alcoholics. The lack of moderating effects of anxiety in the LOAs in our study suggests that reduced drinking that we observed in this group (Kranzler et al. 2011) may reflect a direct effect of sertraline on drinking behavior, rather than one mediated by the effects of negative mood. The effects of SSRIs on drinking behavior remain important because of the high prevalence of AD and the growing frequency with which SSRIs and other antidepressants are prescribed (Olfson and Marcus 2009).

The importance of identifying moderators of the response to sertraline is underscored by the inconsistent findings in the literature on the use of SSRIs to treat AD and evidence that SSRIs can have iatrogenic effects on drinking. In addition to studies showing reduced drinking, some studies of SSRIs have shown that they have no effect or can worsen drinking in a subgroup of alcoholics. The findings reported here are consistent with the interpretation that, although SSRIs can be used to reduce anxiety in some patients (e.g., those with social anxiety or panic disorder), in EOAs with the L'L' genotype) they can increase the effect of anxiety, leading to increased drinking. As discussed below, however, the modest statistical power available in the present study requires that these findings be examined in a larger study sample.

Our study had a number of strengths, the most important of which was the novel micro-longitudinal approach that enabled us to gain insight into the mechanism underlying the interactive effects seen in the original clinical trial (Kranzler et al. 2011). In a study of naltrexone treatment of problem drinkers, we found the use of evening reports paired with nighttime drinking to be useful in examining the moderating effect of variation in the mu-opioid receptor gene and desire to drink on the intensity of drinking and its modification by naltrexone treatment (Kranzler et al. 2012). The present study extends those initial findings by showing that the model is applicable to another medication (sertraline), which has a very different pharmacological profile than naltrexone. The current study also shows that functional variation in the gene encoding the 5-HTT [compared with the gene encoding the mu-opioid receptor in Kranzler et al. (2012)], and different subjective states [anxiety, rather than desire to drink in Kranzler et al. (2012)] significantly moderated the response to sertraline.

These findings must be viewed in the context of the study's limitations. Although there was a significant gene $\times$ medication group $\times$ age of onset interaction, the gene $\times$ medication group interaction effect on adherence was only significant for LOAs. Despite the fact that the difference in IVR adherence did not reach statistical significance for EOAs, the cell size for EOAL' homozygotes was small, yielding modest statistical power. This was most evident among sertraline-treated participants, which due to a high rate of early discontinuation from treatment (see Kranzler et al. 2011) had a lower number of daily reports than any of the other groups (Table 1). Although it limited the statistical power, the differential rate of reporting appears to be independent of the observed effects on drinking behavior.

Based on the findings reported here, the use of a micro-longitudinal approach to examine pharmacogenetic effects on drinking behavior promises to contribute to our understanding of an important moderator of the effects of sertraline on drinking behavior in a subgroup of alcohol-dependent individuals. Further research applying this and other methods can be expected to clarify the mechanism(s) underlying effects observed in clinical trials and to use information from such studies to test interesting theoretical questions regarding medication effects in subgroups of patients. Pharmacogenetic clinical trials require large study samples, which are expensive and time-intensive to recruit and treat. An approach such as the one described here has the potential to reduce costs by enhancing statistical power in proof of concept studies by including many repeated measures across days of the study. Thus, micro-longitudinal pharmacogenetic studies can contribute to the effort to personalize the treatment of a variety of psychiatric and medical disorders.

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Figure 1.

Interaction between daily changes in nervous affect, 5HTTLPR genotype, medication condition and age of onset in predicting nighttime drinking. Low/high values for anxiety represent ± 1.5 points from mean levels (approximately the middle 95% of the person-mean-centered observed range)

Table 1

Descriptive statistics by study condition

	Early Onset				Late Onset			
	L'/L'		S' Carriers		L'/L'		S' Carriers	
	Sertraline	Placebo	Sertraline	Placebo	Sertraline	Placebo	Sertraline	Placebo
Person N	7	6	14	19	12	10	30	36
Mean complete person-days	30.43	60.00	51.79	58.05	56.67	38.30	52.17	60.03
Mean nighttime drinks per day	2.91	0.35	1.52	1.61	0.61	0.89	1.18	0.83
Mean daytime drinks per day	1.36	0.02	1.28	0.97	0.50	0.84	0.75	0.61

Note. Mean drinking values are based on un-weighted person means

Table 2
Results from negative binomial regressions predicting nighttime drinking

<i>Block</i>		<i>Anxiety</i>	<i>Sadness</i>	<i>Anger</i>
1	Sunday	-.416 **	-.413 **	-.412 **
	Monday	-.402 **	-.405 **	-.403 **
	Tuesday	-.308 **	-.315 **	-.312 **
	Wednesday	-.095	-.095	-.087
	Thursday	-.118	-.140	-.143
	Friday	.042	.019	.032
	Day drinks	.266 **	.267 **	.266 **
	Mean affect	.434 [†]	.514 *	.400
	Sex (male = 0, female = 1)	.393	.375	.369
	PC daily affect	.081 [†]	.070	.111 *
	5-HTTLPR (L'/L' = 0, S'-carriers = 1)	.138	.196	.200
	Drug (placebo = 0, sertraline = 1)	-.057	.029	.055
	Onset (early onset = 0, late onset = 1)	-.294	-.281	-.303
2	PC daily affect × 5-HTTLPR	.277 *	-.064	.072
	PC daily affect × Drug	.048	-.103	-.067
	5-HTTLPR × Drug	-.992	-.920	-.958
	PC daily affect × Onset	-.139 [†]	-.219 *	-.164
	Onset × Drug	.254	.254	.245
	Onset × 5-HTTLPR	.654	.784	.824
3	PC daily affect × Drug × 5-HTTLPR	-.331	-.210	.228
	Onset × Drug × 5-HTTLPR	2.520 *	2.355 [†]	2.482 *
	PC daily affect × Onset × 5-HTTLPR	-.292	.210	.045
	PC daily affect × Onset × Drug	-.422 [†]	-.034	.200
4	PC daily affect × Onset × Drug × 5-HTTLPR	1.643 **	.770 [†]	-.633

Note. PC = person-mean centered. Values are unstandardized partial slopes from block of entry.

[†]
p .10

*
p .05

**
p .01