Effects of the Serotonin Transporter Gene Promoter Polymorphism on Mirtazapine and Paroxetine Efficacy and Adverse Events in Geriatric Major Depression

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Background: The “long/short” polymorphism (5HTTLPR) in the promoter of the serotonin transporter gene (SLC6A4) has been proposed as a pharmacogenetic marker for antidepressant efficacy. Some but not all studies have found that the short form of 5HTTLPR (S allele) results in decreased efficacy of selective serotonin reuptake inhibitors.

Objective: To determine if the 5HTTLPR polymorphism influences the efficacy and tolerability of mirtazapine and paroxetine hydrochloride, 2 frequently prescribed antidepressants with differing pharmacologic profiles, in geriatric depression.

Design: Double-blind, randomized 8-week study.

Setting: Eighteen academic and private outpatient clinics.

Patients: We evaluated 246 cognitively intact patients 65 years or older with major depression.

Interventions: Antidepressant therapy with 15 to 45 mg/d of mirtazapine (n=124) or 20 to 40 mg/d of paroxetine (n=122).

Main Outcome Measures: The Hamilton Depression Rating Scale–17 and Geriatric Depression Scale, severity of adverse events and dosing compliance indexes, and discontinuations due to adverse events. Outcome measures were stratified according to 5HTTLPR genotypes.

Results: Geriatric Depression Scale scores indicated that S allele carriers treated with paroxetine showed a small impairment in antidepressant response. Among mirtazapine-treated patients, there was little indication that the 5HTTLPR genotype affected antidepressant efficacy. However, the 5HTTLPR polymorphism had a dramatic effect on adverse events. Among paroxetine-treated subjects, S allele carriers experienced more severe adverse events during the course of the study, achieved significantly lower final daily doses, and had more discontinuations at days 14, 21, 28, 42, and 49. Surprisingly, among mirtazapine-treated subjects, S allele carriers had fewer discontinuations due to adverse events, experienced less severe adverse events, and achieved higher final daily doses.

Conclusions: These results support the hypothesis that the S allele of 5HTTLPR at the SLC6A4 locus is associated with a poor outcome after treatment with selective serotonin reuptake inhibitors. However, the major effect was on the tolerability of these drugs rather than efficacy. Results from mirtazapine-treated patients indicate that the effect of this polymorphism on outcome may depend on the mechanism of antidepressant action.

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GENETIC DIFFERENCES among patients may contribute to differences in medication response and the severity of adverse effects. The 5HTTLPR (“long/short”) polymorphism in the serotonin transporter (5-HTT) gene (SLC6A4) promoter region has been studied as a marker for selective serotonin reuptake inhibitor treatment response. Smeraldi et al. showed that the short form of 5HTTLPR (S allele) impaired the efficacy of fluvoxamine maleate in a sample of 102 patients with major depression. This effect was also reported among patients with psychotic depression. The same effect of the 5HTTLPR polymorphism was reported in a study with 57 geriatric patients with major depression treated with paroxetine hydrochloride. Subsequently, this finding was confirmed in a group of 60 paroxetine-treated patients with depression. In a study of 37 patients with depression who
were receiving fluoxetine, those homozygous for the S allele of 5HTTLPR showed a higher frequency of agitation and insomnia after treatment. Selective serotonin reuptake inhibitors are thought to act through the inhibition of the 5-HTT, so a promoter variant that affects the expression of this protein could affect efficacy and adverse events even though the protein structure is unchanged. In some cell biology and imaging studies, the long (L allele) and short versions of the 5HTTLPR polymorphism have been found to differentially affect the abundance of the 5-HTT.

Other studies of the effects of the 5HTTLPR on antidepressant treatment outcomes have yielded contradictory results. Minov et al found no effect of the 5HTTLPR polymorphism on response in 104 patients receiving a variety of antidepressant treatment regimens. Treatment heterogeneity could have masked genetic effects in that study. However, Kim et al studied 102 Korean patients treated with fluoxetine and found that the S allele was associated with a better treatment response. A similar result was obtained in a study with Japanese patients. Another study with Japanese patients found no association between the 5HTTLPR polymorphism and fluvoxamine-induced nausea. One explanation for these divergent results may be that the effect of the 5HTTLPR polymorphism is dependent on ethnic background, so studies conducted with Asian patients might yield different results from those conducted with patients of other races. However, a study with Chinese patients reported a better response to fluoxetine in patients with the L/L genotype, as has been reported in European subjects.

The selective serotonin reuptake inhibitor paroxetine inhibits the 5-HTT, thus decreasing the reuptake of serotonin. Mirtazapine increases serotonin release through noradrenergic stimulation of excitatory α1-adrenergic receptors located on serotoninergic neurons and by blockade of the inhibitory α2-adrenergic heteroreceptor located on the serotonergic cell body. Mirtazapine also blocks serotonin types 2A (5-HT2A), 2C, and 3 receptors and augments adrenergic neurotransmission. Because of the differing interactions of paroxetine and mirtazapine with the 5-HTT, we sought to determine if the 5HTTLPR polymorphism predicts antidepressant efficacy in geriatric patients with major depression treated with these agents. We also tested the effects of the 5HTTLPR on adverse events during treatment with paroxetine and mirtazapine.

METHODS

PATIENT SAMPLE AND TREATMENT

The study group included 255 outpatients 65 years or older with major depressive disorder who were randomized to mirtazapine or paroxetine in a double-blind design at 18 US centers. All patients provided written informed consent. Details of the study design and overall clinical outcomes have been described previously. Of the 255 randomized patients, 254 received the study medication; 246 (mirtazapine, n=124; paroxetine, n=122; all subjects–treated group) provided a DNA sample and had at least 1 postbaseline measure of efficacy, adverse events, or compliance. At baseline, all patients scored higher than the age-adjusted 25th percentile on the Mini-Mental State Examination, and all had Hamilton Depression Rating Scale (HDRS)–17 scores of 18 or higher. Starting doses were 15 mg/d for mirtazapine and 20 mg/d for paroxetine hydrochloride. Dosages for both medications were increased to 30 mg/d after 14 days, with the option to increase to 45 mg/d of mirtazapine or 40 mg/d of paroxetine hydrochloride at subsequent visits. Exclusion criteria were clinically significant unstable medical illness, history of treatment resistance, principal psychiatric diagnoses other than major depression, use of other psychotropic medications, and electroconvulsive therapy within the previous 6 months. According to self-report, 20 patients were from minority backgrounds. For mirtazapine, these included 1 Asian, 4 African Americans, and 2 patients from other minority backgrounds. For paroxetine, there were 2 Asians, 6 African Americans, and 5 from other minority backgrounds. All other subjects were of self-reported white European ancestry.

LABORATORY METHODS AND CLINICAL EVALUATION

Genomic DNA was extracted from frozen whole blood as described previously. We determined 5HTTLPR genotypes by polymerase chain reaction and gel electrophoresis. Plasma drug levels were obtained after 4 weeks of treatment as described elsewhere. Efficacy outcome measures (determined at baseline and at days 7, 14, 21, 28, 42, and 36) included the HDRS-17 and the Geriatric Depression Scale (GDS). Measures related to adverse events included the severity of adverse events, medication compliance, and time to discontinuation due to an adverse event. At each visit, clinicians specifically assessed patients for adverse events and rated their severity as mild (1), moderate (2), or severe (3). Adverse event ratings for each patient were summed across the entire trial and were adjusted to take into account treatment duration and mean daily dose. The amount of medication taken was determined by counting the number of prescribed tablets remaining at each clinic visit. Dosage compliance was determined by the total number of medication doses taken divided by the total number of capsules given.

Statistical methods included analysis of covariance (adjusted for baseline scores), the Cochran-Mantel-Haenszel statistic, and Cox proportional hazards analysis for survival data. Because discontinuations during the last 7 days of the study were difficult to define, survival analyses were terminated at day 49. To test for interactions between the 5HTTLPR polymorphism and the 5-HT3A, 102 T-to-C variant (dbSNP database identification number rs6313) that we previously found to affect paroxetine discontinuations, we used Cox proportional hazards analysis with an interaction term. All analyses were performed for the entire group and again with 20 patients from minority backgrounds omitted.

RESULTS

The baseline characteristics and clinical course for patients treated with paroxetine and mirtazapine stratified by 5HTTLPR genotype are presented in Table 1. Overall allele frequencies for the entire sample were 0.53 for the L allele and 0.45 for the S allele. Overall genotype frequencies for the entire sample were 32.0% for the L/L, 45.5% for the S/L, and 22.5% for the S/S genotypes. There were no significant differences between the paroxetine and mirtazapine groups in allele or genotype frequencies. For the full sample and treatment subsamples, there
were no deviations from the Hardy-Weinberg equilibrium. There were no differences among the genotype groups in mean age, numbers of men and women, numbers of people from minority backgrounds, or baseline Mini-Mental State Examination score for either treatment group. For the paroxetine group, baseline body weight was significantly greater for the L/L genotype group than for the S/L (P = .02) and S/S groups (P = .002). Because plasma drug concentrations and pharmacokinetics can potentially be affected by body weight, we included baseline body weight as a covariate in all subsequent analyses. There were no significant differences in baseline body weight among genotype groups for the mirtazapine-treated subjects. Two subjects lacked baseline body weight measurements and were excluded from the subsequent analyses, resulting in a final sample size of 244 subjects.

**Efficacy**

For both paroxetine and mirtazapine, when patients were stratified by 5HTTLPR genotype (S/S, S/L, and L/L), there were no significant differences among the 3 genotype groups at any time point for either the HDRS-17 or the GDS. Prior studies combined the S/S and S/L genotypes into an “S carrier” group for analysis.1,3 No differences were seen among paroxetine-treated patients on the HDRS-17 in this 2-level analysis (Figure 1A). For paroxetine-treated patients, carriers of the S allele showed significantly higher scores on the GDS (more depressed) at days 7 (P = .02; F1,212 = 5.28) and 28 (P = .04; F1,173 = 4.11) after adjusting for baseline body weight (Figure 1B). These differences between genotype groups were smaller than those reported previously in a sample of 51 geriatric patients treated with paroxetine.3 In that study, at week 2 there was a 29.6% decrease in HDRS-17 scores from baseline in S carriers but a 49.3% decrease from baseline for the L/L genotype. In our sample, with a 2-sided analysis and P = .01, the power to detect a difference of this magnitude would be 0.96.

The S allele carriers treated with mirtazapine showed lower HDRS-17 scores at day 14 (less depressed; P = .03; F1,285 = 4.96) (Figure 1C). The GDS scores for mirtazapine-treated patients with the S/S and S/L genotypes were significantly lower at baseline than those for patients with the L/L genotype (P = .03; F1,222 = 4.97) (Figure 1D). After adjusting for this difference, GDS scores for mirtazapine-treated S carriers were not significantly different from those of other subjects at any subsequent time point.

**Adverse Events**

The 5HTTLPR polymorphism had a significant effect on discontinuations caused by adverse events for both medications. As previously reported, discontinuations due to adverse events were more frequent among paroxetine-treated patients than mirtazapine-treated patients.36 For paroxetine-treated patients, survival analyses showed a significant association between the number of T alleles and the probability of discontinuation due to adverse events at days 14, 21, 28, 42, and 49 (Figure 2A) (Cox regression analyses; χ2 tests; P < .05 for all). All statistical tests were adjusted for differences in baseline body weight. At the same time points, patients with the S/L genotype showed a significantly greater risk of discontinuation due to adverse events than those with the L/L genotype. Patients with the S/S genotype also showed a greater severity of adverse events than those with the L/L genotype (F1,221 = 5.52; P = .02) (Table 1). Paroxetine-treated patients with the S/S genotype had a lower final daily dose (S/S vs L/L: F1,221 = 8.63; P = .004; S/S vs S/L: F1,221 = 7.09; P = .008), decreased dosing compliance (S/S vs L/L: F1,221 = 19.12; P < .001; S/S vs S/L: F1,221 = 23.06; P < .001), and lower plasma levels at day 28 (S/S vs S/L: F1,160 = 4.30; P = .04; S/S vs S/L: F1,100 = 7.25; P = .008) (Table 1). Adverse events associated with discontinuations among paroxetine-treated patients with the S/S genotype included gastrointestinal complaints, fatigue, agitation, sweating, and dizziness.

Surprisingly, among mirtazapine-treated patients, the L allele was strongly associated with discontinuations due to adverse events. Survival analyses showed a signifi-

### Table 1. Patient Demographics, Baseline Characteristics, and Outcomes Stratified by Genotype

<table>
<thead>
<tr>
<th></th>
<th>Paroxetine Hydrochloride</th>
<th>Mirtazapine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S/S Genotype (n = 24)</td>
<td>S/L Genotype (n = 57)</td>
</tr>
<tr>
<td>Age, y</td>
<td>72.08 (4.99)</td>
<td>72.05 (4.88)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>F</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>Baseline body weight, kg</td>
<td>71.58 (9.25)</td>
<td>76.30 (17.22)</td>
</tr>
<tr>
<td>MMSE score</td>
<td>28.71 (1.30)</td>
<td>28.63 (1.11)</td>
</tr>
<tr>
<td>HDRS-17 score</td>
<td>22.58 (3.24)</td>
<td>22.56 (3.67)</td>
</tr>
<tr>
<td>GDS score</td>
<td>19.38 (5.06)</td>
<td>19.93 (5.50)</td>
</tr>
<tr>
<td>No. of discontinuations due to adverse events</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Adverse event index</td>
<td>67.51 (26.53)</td>
<td>54.88 (28.78)</td>
</tr>
<tr>
<td>Final daily dose, mg/d</td>
<td>23.19 (11.26)</td>
<td>30.74 (8.37)</td>
</tr>
<tr>
<td>Day 28 plasma drug concentration, ng/mL</td>
<td>51.03 (34.24)</td>
<td>84.47 (57.47)</td>
</tr>
</tbody>
</table>

Abbreviations: GDS, Geriatric Depression Scale; HDRS, Hamilton Depression Rating Scale; MMSE, Mini-Mental State Examination.

*Data are presented as mean (SD) unless otherwise indicated. The sample size was 244.*
cant association between the number of L alleles and the probability of discontinuation due to adverse events at days 14, 21, 28, 42, and 49 (Figure 2B) (Cox regression analyses; $\chi^2$ tests; $P<.05$ for all). The L/L genotype was also associated with a greater severity of adverse events (L/L vs S/S: $F_{1,201}=5.18; P=.02$) and a lower final daily dose (L/L vs S/S: $F_{1,221}=7.17; P=.008$; S/L vs S/S: $F_{1,221}=4.19; P=.04$) (Table 1). Among mirtazapine-treated patients, there were no significant differences in dosing compliance among the genotype groups and no significant differences in plasma levels at day 28 (Table 1). Adverse events associated with discontinuations among mirtazapine-treated patients with the L/L genotype included drowsiness, dizziness, and anxiety.

We previously showed that the 5-HT$_{2A}$ 102 T-to-C polymorphism predicted discontinuations due to adverse events for paroxetine-treated patients in our study cohort.15 The $\chi^2$ analyses (5-HT$_{2A}$ 102 T-to-C genotype $\times$ 5HTTLPR genotype contingency tables) showed no significant associations between the frequencies of individual 5-HT$_{2A}$ 102 T-to-C genotype groups and 5HTTLPR genotype groups for either drug (mirtazapine: $\chi^2=1.0$; paroxetine: $\chi^2=7.1$). This indicates that the relative numbers of individuals in each of the 5-HT$_{2A}$ genotype groups were not dependent on the 5HTTLPR genotype. Cox proportional hazards regression analysis for paroxetine-treated patients showed significant effects for 5HTTLPR ($\chi^2=6.69; P=.01$; hazard ratio=2.62; S/S vs other genotypes) and 5-HT$_{2A}$ 102 T-to-C ($\chi^2=9.14; P=.003$; hazard ratio=3.03; C/C vs other genotypes) on discontinuations due to adverse events, but the interaction term in the analysis was not significant ($\chi^2=0.31$). This indicates that 5HTTLPR and 5-HT$_{2A}$ 102 T-to-C variants have additive but not interactive effects on paroxetine discontinuation.

Analyses performed with the 20 patients of minority backgrounds removed from the sample gave results similar to those for the full sample. For white patients treated with paroxetine, survival analyses showed a significant association between the number of S alleles and discontinuations due to adverse events at days 14, 21, 28, 42, and 49 (Cox regression analysis; $\chi^2$ tests; $P<.05$ for all). Similarly, for white patients treated with mirtazapine, there was a significant association between the number of L alleles and discontinuations due to adverse events at days 14, 21,

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**Figure 1.** Effects of the 5HTTLPR polymorphism on the efficacy of paroxetine hydrochloride (A and B) and mirtazapine (C and D). Patients are stratified according to 5HTTLPR genotype (S/S and S/L vs L/L). Data points represent mean values for the Hamilton Depression Rating Scale (HDRS)–17 and Geriatric Depression Scale (GDS).
28, 42, and 49 (Cox regression analysis; $\chi^2$ tests; $P<.05$ for all).

**COMMENT**

These results indicate that the 5HTTLPR polymorphism is a marker for medication discontinuation due to adverse events in geriatric patients treated with paroxetine and mirtazapine. For patients treated with paroxetine, discontinuations due to adverse events were most frequent among those with the S/S genotype. The S/L genotype was associated with an intermediate frequency of discontinuations, whereas L/L carriers had the fewest discontinuations, indicating a gene-dosage effect. Patients with the S/S genotype also had a greater severity of adverse events. These effects were significant even after adjustment for differences in baseline body weight. Paroxetine-treated patients with the S/S genotype showed lower medication compliance, resulting in lower plasma drug concentrations at day 28. In contrast, for patients treated with mirtazapine, discontinuations were most frequent among those with the L/L genotype.

Most prior studies of the 5HTTLPR and antidepressant treatment outcome have focused on measures of efficacy rather than adverse effects. For paroxetine-treated patients, we did find that the GDS showed impaired antidepressant efficacy for patients with the S/S genotype at 2 time points, thus confirming the results of some prior studies. However, the magnitude of this effect in our study was small in comparison with that for discontinuations due to adverse events. A recent report showed that in 37 patients with depression who were treated with fluoxetine, the S/S genotype was associated with an increased frequency of agitation and insomnia. In our study, among paroxetine-treated patients, 1 patient discontinued the medication because of agitation, 3 discontinued owing to fatigue, and none discontinued as a result of insomnia. It is unclear why our results differ from those of the fluoxetine study. Pharmacologic differences between fluoxetine and paroxetine could account for vari-ation in adverse effect profiles associated with the S/S genotype, as could the differing age distributions of the 2 samples. In any case, both studies show that disturbances in circadian rhythms and level of alertness are associated with the 5HTTLPR S/S genotype during treatment with selective serotonin reuptake inhibitors. Future studies of the 5HTTLPR and antidepressant therapy should include not only efficacy outcome measures but also measures of adverse events and discontinuation. In retrospective studies of the 5HTTLPR and treatment outcome, if the primary outcome measure is efficacy only, genetic effects on adverse events may be missed, particularly if the completion of a fixed duration of treatment is an inclusion criterion. Adverse events, if severe, could contribute to reports of a lack of efficacy in pharmacogenetic studies because physical or psychological discomfort may increase scores on certain items in depression rating scales.

Differences in the mechanisms of action of mirtazapine and paroxetine may account for the divergent effects of the 5HTTLPR on treatment efficacy and adverse events with these agents. Paroxetine directly interacts with the 5-HTT to increase the availability of serotonin in the synaptic cleft. Mirtazapine induces the release of norepinephrine as well as serotonin in the brain through antagonism of $\alpha_2$-adrenergic receptors on noradrenergic and serotonergic neurons. Norepinephrine release at synapses with serotonergic neurons also augments serotonin release. Thus, whereas paroxetine has a primarily serotonergic mode of action, mirtazapine has both serotonergic and noradrenergic actions. Although mirtazapine does not directly interact with the 5-HTT, individual differences in the abundance of this protein could affect the response to mirtazapine-induced changes in serotonergic neuronal activity. It is possible that efficient serotonin reuptake among mirtazapine-treated patients carrying the L/L genotype alters mirtazapine-induced changes in serotonergic activity (which occur through a
fundamentally different mechanism than changes induced by paroxetine) and therefore increases the likelihood of adverse events.

We previously demonstrated that the C/C genotype at the 5-HT<sub>1A</sub> 102 T-to-C polymorphism is a strong risk factor for discontinuation due to adverse events among paroxetine-treated patients. Subjects with both the 5HTTLPR S/S genotype and the 5-HT<sub>1A</sub> 102 T-to-C C/C genotype appear to be at exceptionally high risk for discontinuation. Whereas 7 of 10 paroxetine-treated subjects with the 5HTTLPR S/S and 5-HT<sub>1A</sub> T-to-C C/C genotypes discontinued the medication owing to adverse events, none of the 5 subjects with the L/L or T/T genotype who were receiving paroxetine discontinued. However, Cox proportional hazards analysis showed that the increase in risk for discontinuation due to the S/S or C/C genotype was additive, not interactive; thus, the 2 effects are independent in our sample. Notably, as the number of predictors in the model increases, cell size decreases, which can limit the power to detect an interaction.

Two prior studies found that among Asian patients, the effect of the 5HTTLPR depends on ethnic background. Our sample contained only 3 Asian patients (2 treated with paroxetine, and 1 treated with mirtazapine). However, re-analysis of our data with all 20 subjects of minority backgrounds removed provided results similar to those for the full sample.

Aging affects 5-HTT function. This could be one reason why our results differ from those performed with samples that included younger subjects. Another factor that could have affected outcomes in our study was the exclusion of patients with a history of treatment resistance and those hospitalized as inpatients. We do not know the plasma drug concentrations in patients who discontinued the medication before day 28 owing to adverse events, which could have affected the outcomes. Personality disorders and concurrent medical disorders could also affect outcomes, but these factors are difficult to quantify and were not included in the analysis. Because multiple outcomes were tested, some positive results could be due to type 1 statistical error.

In summary, these results show that the S allele at the 5HTTLPR polymorphism is associated with adverse events in geriatric patients with major depression treated with paroxetine. This effect was independent of the previously described association between the 5-HT<sub>1A</sub> 102 T- to-C polymorphism and adverse events with paroxetine. In addition, there was a modest effect of the 5HTTLPR on paroxetine efficacy in this patient population. The 5HTTLPR polymorphism may also be important in determining discontinuation due to adverse events during mirtazapine therapy, but surprisingly, the L allele confers greater risk with mirtazapine than the S variant associated with discontinuations among paroxetine-treated patients. Differences in the mechanisms of action of mirtazapine and paroxetine may account for the divergent effects of the 5HTTLPR polymorphism on treatment outcome with these agents. Replication of our findings could provide the basis for clinical use of this genetic variant in making rational medication choices before treatment is initiated.

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Previous Presentation: This study was presented at the Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, December 11, 2002.

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REFERENCES


