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SEROTONIN TRANSPORTER TRIALLELIC GENOTYPE AND RESPONSE TO CITALOPRAM AND RISPERIDONE IN DEMENTIA WITH BEHAVIORAL SYMPTOMS

Alexandre Y. Dombrovski, M.D.¹, Benoit H. Mulsant, M.D.^{1,2,*}, Robert E. Ferrell, Ph.D.³, Francis E. Lotrich, M.D., Ph.D.¹, Jules I. Rosen, M.D.¹, Meredith Lotz^{1,4}, Patricia R. Houck, M.S.¹, Sati Mazumdar, Ph.D.^{1,4}, and Bruce G. Pollock, M.D., Ph.D.^{1,2,5}

¹Western Psychiatric Institute and Clinic, Department of Psychiatry, University of Pittsburgh School of Medicine, Advanced Center for Interventions and Services Research in Late-Life Mood Disorders

²Center for Addictions and Mental Health, University of Toronto, Canada

³Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh

⁴Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh

⁵Rotman Research Institute at Baycrest, University of Toronto

Abstract

Objective—The risk/benefit ratio of pharmacotherapy for behavioral symptoms of dementia is questionable: second-generation antipsychotics (SGAs) are poorly tolerated, and efficacy of alternative treatments, e.g. selective serotonin-reuptake inhibitors (SSRIs), is uncertain. Biomarkers of treatment response may improve this risk/benefit ratio. The length polymorphism of the serotonin transporter promoter gene (5-HTTLPR/SLC6A4) may moderate tolerability of SSRIs and expression of behavioral symptoms in dementia.

Methods—We assessed the effect of 5-HTTLPR on tolerability and efficacy of citalopram and risperidone in a 12-week randomized controlled trial which included non-depressed patients with dementia hospitalized for behavioral or psychotic symptoms. Genotypes including the A/G polymorphism of the L allele (rs25531) were determined for 92/103 participants. We used pattern-mixture models to account for dropout.

Results—Low-expression alleles (S and Lg) predicted greater early and overall side effects of citalopram and early treatment discontinuation. These results held after excluding African-American participants and in covariate analyses. Unexpectedly, low-expression alleles seemed to predict greater early side effects of risperidone (but not early discontinuation) and poorer early response of psychosis symptoms to risperidone.

Conclusion—5-HTTLPR may be a useful biomarker of SSRI intolerance in dementia. Our findings of intolerance of an SGA and persistence of psychosis in patients with low-expression alleles needs to be replicated.

Address correspondence and reprint requests: Benoit H. Mulsant, M.D., Geriatric Mental Health, CAMH, 1001 Queen Street West, Toronto, Ontario, Canada M6J 1H4. Phone: (416) 535 8501 x3655. Fax: (416) 583 1307. benoit_mulsant@camh.net.

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Trial Registration: <http://www.clinicaltrials.gov/>; Identifier: NCT00073658

Keywords

Dementia; Psychomotor Agitation; Psychotic Disorders; Antipsychotics; risperidone; Antidepressive Agents; Serotonin Reuptake Inhibitors; citalopram; 5-HTTLPR protein; human

Introduction

Behavioral and psychiatric symptoms affect the majority of patients with dementia at some point in the course of their disease (Holtzer et al., 2003, Ropacki and Jeste, 2005), causing great distress to families and caregivers (Black and Almeida, 2004), and often precipitating institutionalization. Regrettably, we lack a safe and effective pharmacological treatment for these symptoms. The commonly used second-generation (atypical) antipsychotics (SGA) help only a minority of patients, are poorly tolerated (Schneider et al., 2006) and increase mortality (Schneider et al., 2005). Evidence to support the use of alternative agents remains scarce. Our group has reported on the efficacy of the selective serotonin reuptake inhibitor (SSRI) citalopram in one open (Pollock et al., 1997) and two double-blind randomized trials: one placebo-controlled (Pollock et al., 2002) and one with risperidone as the active comparator (Pollock et al., 2007). However, the clinical utility of SSRIs has yet to be confirmed. Given this uncertainty, the now questionable risk/benefit ratio of medications would be improved if we could predict which patients are more likely to tolerate medications and favorably respond to them (Schneider et al., 2006).

The serotonin transporter promoter region functional (Smith et al., 2004, Hariri et al., 2002) length polymorphism (5-HTTLPR; SLC6A4) has been proposed as a biomarker of drug response and tolerability. A growing body of literature links its low-expression S allele to SSRI intolerance in depression (Smith et al., 2004, Murphy et al., 2004, Hu et al., 2007, Smits et al., 2007), although no studies exist in dementia. We also have two reasons to believe that 5-HTTLPR may have value in predicting treatment response in patients with the behavioral disturbance of dementia. First, agitation in Alzheimer's disease (AD) is associated with altered function of the 5HT system, as demonstrated by an altered response to the serotonergic agonist fenfluramine (Mintzer et al., 1998). Second, early studies suggest that neurodegeneration in AD may be more likely to trigger psychosis and aggression in people with the high-expression long (L) allele of the 5-HTTLPR (Sukonick et al., 2001, Sweet et al., 2001). However, this finding has not been universally replicated (Assal et al., 2004, Pritchard et al., 2007), and a subsequent study suggested that the variable number of tandem repeats sequence polymorphism of this gene may be associated with aggression (Ueki et al., 2007) in AD. While the 5HT transporter is the presumed therapeutic target of SSRIs, to our knowledge, the impact of its length polymorphism on treatment response in dementia has not been studied. However, in older (Pollock et al., 2000, Durham et al., 2004) and younger (Arias et al., 2003, Mrazek et al., 2008) Caucasian patients with depression, the low-expression S allele has been associated with poor SSRI response, although evidence in other ethnic groups is less consistent (Serretti et al., 2007). Thus, if SSRIs affect symptoms of psychosis and agitation in dementia through the same mechanism, one should expect a poorer treatment response in patients with the low-expression genotype. In summary, one may expect a better risk/benefit ratio of SSRI treatment in dementia patients with the L allele, determined by better tolerance and therapeutic response.

On the other hand, most studies of schizophrenia, with one exception (Dolzan et al., 2008), indicate that the 5-HTTLPR has no effect on the efficacy of antipsychotics (Arranz et al., 2000, Arranz et al., 1998, Kaiser et al., 2001) or their extrapyramidal side effects (Segman et al., 2003, Guzey et al., 2007). To our knowledge, whether 5-HTTLPR affects the tolerability and response to SGA has not been tested in patients with dementia.

We have reported on the results of a 12-week randomized, controlled trial comparing the serotonergic antidepressant citalopram to the second-generation antipsychotic risperidone for psychotic symptoms and agitation associated with dementia (Pollock et al., 2007). We found no differences in efficacy and a greater side effect burden with risperidone compared to citalopram. Before the study was initiated, the 5-HTTLPR was hypothesized to modify efficacy and tolerability of citalopram and risperidone. We predicted early treatment discontinuation and greater side effects of citalopram but not risperidone in patients with the S allele of the 5-HTTLPR. We also predicted that the therapeutic effects of citalopram but not of risperidone will be attenuated in patients with the S allele. Since a polymorphism within the L allele (Lg) may result in lower transcription efficiency, functionally comparable to the S allele (Hu et al., 2006, Zalsman et al., 2006), we also considered it in our analyses (below, we denote the low-expression S and Lg alleles as S*).

Methods

As required by the University of Pittsburgh Institutional Review Board, participants' authorized representatives provided written informed consent with participants' verbal assent.

Participant Flow and Interventions

Our 12-week randomized clinical trial included 103 non-depressed inpatients with dementia of the Alzheimer type (DAT; with late onset, n=86; with early onset, n=5), vascular dementia (n=1), or dementia not otherwise specified (NOS; n=9) with moderate or higher severity of behavioral disturbance as evidenced by a rating of 3 or higher (moderate to severe) on at least one of the agitation or psychosis items of the Neurobehavioral Rating Scale (NBRS) (Levin et al., 1987, Mulsant et al., 1997). Diagnosis of DAT was made using DSM-IV criteria and the criteria for probable or possible Alzheimer's disease established by the NINCDS/ADRDA Work Group (McKhann et al., 1984). Diagnosis of vascular dementia was made using the DSM-IV criteria and the criteria for definite, probable or possible established by the NINDS-AIREN (Roman et al., 1993). The results of computed tomography and structural magnetic resonance imaging, when available, were considered in making consensus diagnoses. We excluded patients with a major depressive episode within the past six months or clinically significant depressive symptoms defined by a rating of 12 or higher on the Cornell Scale for Depression in Dementia (CSDD) (Alexopoulos et al., 1988), a current or past diagnosis of schizophrenia, schizoaffective disorder, delusional disorder, psychotic disorders NOS, bipolar disorder, mental retardation, cognitive deficits following head trauma, or a current diagnosis of delirium, substance-induced persisting dementia, Parkinson's disease, drug/alcohol abuse or dependence. After randomization, two participants were judged to have a diagnosis that should have led to their exclusion (one with DAT, late onset, with delirium randomized to citalopram and one with substance-induced persisting delirium randomized to risperidone). We included these two participants in all analyses, following the intent-to-treat principle.

We tapered all psychotropics, except for cholinesterase inhibitors and lorazepam up to 2 mg. Participants were randomly assigned to citalopram (starting dose 10 mg, target dose 20–40 mg/d) or risperidone (starting dose 0.5 mg, target dose 1–2 mg/d) and treated for up to 12 weeks under double-blind conditions. Treatment was discontinued if patients' agitation or psychosis worsened significantly, if new medical symptoms put their safety or health in danger, or for administrative reasons such as moving away or withdrawal of consent. Inpatients experiencing clinical improvement were discharged to long-term care facilities, where they continued in the study.

Clinical Assessments

After a clinical and laboratory evaluation for reversible causes of dementia, agitation, or psychosis, we assessed participants at the time of enrolment, at randomization, after receiving study medication for 3 days, 7 days, then weekly for five weeks, then every two weeks, and at the time of discharge from the hospital or termination if the study was terminated early. Psychosis and agitation were rated using the NBRs, based on direct observation of the participants, interviews with participants and nursing staff, and chart review of all notes for the three days preceding the rating. The NBRs is a 28-item observer-rated instrument combining the psychopathology covered by the Brief Psychiatric Rating Scale with more comprehensive assessment of impairments seen in dementia. Scoring is on a 7 point scale (0 not present; 1 very mild; 2 mild; 3 moderate; 4 moderately severe; 5 severe; 6 extremely severe) (Levin et al., 1987, Mulsant et al., 1997). Adverse effects were assessed with the UKU side effect scale, with 48 items rated on a scale of 0–3 for degree of severity (Lingjaerde et al., 1987). Cognitive impairment was measured by the Mini-Mental Status Examination (MMSE) (Folstein et al., 1975). Comorbid physical conditions were assessed with the Cumulative Illness Rating Scale adapted for Geriatrics (CIRS-G) (Miller et al., 1992). Our raters received initial and yearly training for the NBRs, CIRS-G, MMSE, and UKU, and interrater reliability was good to excellent (Pollock et al., 2007).

Genetic Methods

We obtained samples from 92 of the 103 randomized participants. Samples from the remaining 11 participants could not be obtained because of their psychiatric or physical condition (n=5), problems with intravenous access (n=3), or unknown reasons (n=3). DNA was isolated from blood lymphocytes using the PureGene™ kit (Gentra Systems, Minneapolis, MN). The serotonin transporter gene (SLC6A4) promoter polymorphism was typed by DNA amplification (PCR) using flanking primers 5'-TCCTCCGCTTTGGCGCCTCTTCC-3' (forward) and 5'-TGGGGGTTGCAGGGGAGATCCTG-3' (reverse) (Wendland et al., 2006). The L allele was subtyped for rs25531. This A>G single nucleotide polymorphism was concurrently detected by digesting the amplified fragments with MspI (New England Biolabs, Beverly, Massachusetts), where the A>G substitution creates an additional MspI site. Amplification products were simultaneously resolved by electrophoresis on 3.5% agarose gels and visualized by ethidium bromide staining and UV transillumination (Edenberg and Reynolds, 1998). Sequence confirmed controls of each genotype were run with each plate.

Statistical Analysis

We conducted all analyses using SAS (SAS Institute, 2000). First, we compared participants' baseline group characteristics using t or χ^2 tests. In our efficacy and tolerability analyses, we included all randomized and genotyped participants who received at least one dose of study medication and who completed the baseline and at least one post baseline evaluation. We used two-tailed statistical tests.

We then examined the effects of 5-HTTLPR on treatment discontinuation using survival analysis. Using a mixed model analysis of the main tolerability (UKU scores) and efficacy outcomes (NBRs psychosis and agitation), we compared genotype groups stratified by treatment assignment (citalopram or risperidone). Based on previous findings of the effect of 5-HTTLPR polymorphism on early SSRI response (Durham et al., 2004, Pollock et al., 2000), we examined data for the first four weeks of the trial and for the entire study period (twelve weeks). Mixed model analyses use all the data that are collected longitudinally and also account for the within-subject correlation between measures. Routine application of these models can lead to erroneous conclusions when data are not missing at random, particularly in a population with a high dropout rate such as patients with the behavioral disturbance of dementia. Thus, we investigated the reasons for dropping out and effects of different dropout

times on the parameter estimates using a pattern-mixture model (Mazumdar et al., 2006). We stratified the observed data according to the reason for missing values: dropouts due to inefficacy or intolerance (psychiatric, medical or neurological reasons) and all others (completers and dropouts for administrative reasons). Due to small cell sizes in the stratified model, genotypes were examined as two rather than three groups. Because the S allele of the 5-HTTLPR gene may be functionally dominant (Collier et al., 1996, Lesch et al., 1996), particularly for antidepressant response (Durham et al., 2004, Pollock et al., 2000, Smeraldi et al., 1998), we classified its genotypes into two groups: (1) those with the LaLa and (2) those with S*La (SLa or LgLa) and those with S*S* (SS or SLg or LgLg) alleles. We then modeled the change in adverse effects (measured by UKU scores) within each pattern, and combined the parameter estimates. Using SAS-PROC MIXED, our mixed models included genotype (group), week (time), and group by time interaction terms. The intercept and the week terms were assumed to be random effects. We used an unstructured covariance matrix. Final estimates for genotype, time, and their interaction were obtained by averaging over the missing data pattern estimates, taking into account the sample proportion of each pattern. We followed a similar procedure in our analysis of efficacy (using the psychosis and agitation subscales of the NBRs). To account for possible confounding factors, we first used univariate regression analyses to identify significant baseline covariates for each outcome (side effects, psychosis, agitation). These included age, gender, diagnosis subtype (Alzheimer vs. Lewy body dementia), cognitive impairment measured by the Mini-Mental Status Examination score (as a proxy of disease stage), years since onset of dementia, and burden of physical illness (measured by the Cumulative Illness Rating Scale adapted for Geriatrics). The variables that were associated with each of the outcomes were included as covariates in an additional set of mixed-effects analyses.

To ascertain the robustness of our findings to population stratification effects, we also conducted sensitivity analyses excluding African-American participants. In another set of sensitivity analyses, we examined the effects of the S/L polymorphism with the undifferentiated L allele, ignoring its A/G polymorphism (rs25531).

Results

Group characteristics

Genotype data were obtained for 92 of the 103 randomized participants. Their age, burden of physical illness, baseline level of agitation, and side effect ratings did not differ from those of the 11 participants whose samples could not be obtained. However, these 11 participants had a higher baseline level of psychosis (mean [SD] NBRs psychosis score 6.3 [4.0] vs. 3.2 [3.1], $t[95]=2.35$, $p=0.02$). Within each treatment arm, the genotype groups did not differ significantly in terms of age, gender, or race (see Table 1). Overall, S and L allele distribution in the randomized sample did not deviate significantly from the Hardy-Weinberg equilibrium (Chi-square=0.84, $p=0.36$). Among citalopram- and risperidone-treated participants, levels of psychosis and agitation were similar across the genotype groups at randomization. End doses of citalopram and risperidone were also similar across the genotype groups. Exposure to cholinesterase inhibitors, benzodiazepines, opioid analgesics, and drugs with anticholinergic activity was also similar across the genotype groups (see Table 1). No other psychotropic drugs were taken by study participants, except for one participant in the risperidone group who received low-dose quetiapine.

5-HTTLPR and treatment discontinuation

More than half of the participants discontinued treatment before completing the study: of the citalopram-treated participants who were genotyped, 52% completed the 12-week trial, 25% discontinued treatment for psychiatric reasons, 17%, for medical reasons, and 6%, for

administrative reasons, compared to 43%, 25%, 25%, and 7%, respectively, in the risperidone group. Over 12 weeks of treatment with citalopram, time to treatment discontinuation differed across the 5-HTTLPR genotypes (log rank test $\chi^2[92]=7.1$, $p=0.029$), with the shortest time to treatment discontinuation in the S*S* (S*=S or Lg) group (see Figure 1a). The patterns of drop-out by group were qualitatively similar, but differences became statistically non-significant after excluding African-American participants ($\chi^2[92]=2.6$, $p=0.27$) and with the undifferentiated L allele ($\chi^2[92]=3.8$, $p=0.15$). 5-HTTLPR genotypes had no effect on time to treatment discontinuation in the risperidone arm (see Figure 1b).

Covariate analyses

Lewy body dementia (LBD) diagnosis ($\beta=3.99$, $p=0.0002$) and greater cognitive impairment (measured by MMSE score; $\beta=-0.20$, $p=0.0024$) were associated with higher baseline UKU scores. Less advanced dementia ($\beta=0.12$, $p=0.035$) and higher burden of physical illness (measured by the CIRS-G; $\beta=0.24$, $p=0.043$) were associated with higher baseline psychosis scores. More advanced dementia was associated with higher agitation scores ($\beta=-0.25$, $p=0.0003$). Age, gender, and years since onset were not associated with any of these variables (data not shown). Thus, diagnosis subtype and MMSE scores were included as covariates in our adverse effects analyses; MMSE and CIRS-G scores were included as covariates in our psychosis analyses; MMSE scores were included as a covariate in our agitation analyses.

Adverse effects of citalopram

The low-expression S*S*/S*La genotypes predicted greater adverse effects of citalopram, after accounting for different patterns in UKU scores among dropouts and completers over 12 weeks of treatment (see Table 2). This effect was apparent in the first four weeks of treatment (Table 2) and persisted after covarying for diagnosis subtype and cognitive impairment (Table 2). The results were the same after excluding African-American participants (pattern-mixture model estimate = $-0.50(0.15)$, $df=234$, $p=0.0014$). The results were qualitatively unchanged with the undifferentiated L allele (4 weeks: estimate = $-0.66(0.33)$, $df=132$, $t=-2.71$, $p=0.050$; 12 weeks: estimate = $-0.20(0.15)$, $df=288$, $p=0.16$).

Adverse effects of risperidone

The 5-HTTLPR genotype had no impact on adverse effects, after accounting for different patterns in UKU scores among dropouts and completers over 12 weeks of treatment (Table 2). However, we found an association between S*S*/S*La genotypes and greater early adverse effects of risperidone (in the first four weeks; Table 2). This association remained after excluding African-American participants (estimate = $-1.31(0.51)$, $df=90$, $p=0.012$), but was no longer present with the undifferentiated L allele (estimate = $-0.68(0.51)$, $df=115$, $p=0.18$).

Efficacy of citalopram

The 5-HTTLPR genotype had no impact on change in psychosis scores, after accounting for different patterns among dropouts and completers (Table 2). The results remained negative after covarying for MMSE scores (Table 2), after excluding African-American participants, and with the undifferentiated L allele (data not shown).

Efficacy of risperidone

Over 12 weeks of treatment with risperidone, we observed no significant effects of the 5-HTTLPR genotype on response of psychosis symptoms to risperidone. However, the S*S*/S*La genotypes predicted poorer early response (over the first four weeks) of psychosis symptoms to risperidone treatment (Table 2). The impact of the S*S*/S*La genotypes on early response of psychosis of risperidone remained after covarying for cognitive impairment and burden of physical illness (Table 2) and after excluding African-American participants

(estimate=-1.80 (0.48), df=82, p=0.0003), but was not statistically significant with the undifferentiated L allele (estimate=-0.79 (0.33), df=107, p=0.089). We also saw an apparently better response of agitation symptoms associated with the S*S*/S*La genotypes over 12 weeks of treatment (Table 2). However, this effect was no longer present after controlling for cognitive impairment (Table 2). A closer examination of the data revealed that this effect was caused by high agitation scores in one participant, who discontinued treatment at week 6. After excluding this participant, there was no impact of 5-HTTLPR on response of agitation symptoms to risperidone, while the statistically significant impact of 5-HTTLPR on early response of psychosis symptoms and early adverse effects of risperidone remained (data not shown).

Discussion

In the first study of the effect of the serotonin transporter polymorphism on treatment outcomes in dementia with behavioral disturbance, we examined the impact of this polymorphism on tolerability and efficacy of citalopram and risperidone. As we had hypothesized, the low-expression alleles (S and Lg) predicted early treatment discontinuation and greater adverse effects of citalopram. However, we observed no effects of the 5-HTTLPR genotype on the efficacy of citalopram. Unexpectedly, the low-expression alleles also seemed to predict greater early side effects and poorer early response of psychosis symptoms to risperidone. However, the effects on response to risperidone were not robust: they were not seen all sensitivity analyses and no effect was observed on early treatment discontinuation.

Strengths and limitations

A randomized controlled design, broad inclusion criteria, use of pattern-mixture models to handle missing data, and *a priori* stated hypotheses add to the validity of our findings. It is also reassuring that our results remained unchanged after minimizing potential population stratification by excluding African-American subjects, after controlling for relevant clinical characteristics, and with the undifferentiated L allele. On the other hand, a modest sample size constitutes the main limitation of our study. In addition, the lack of a placebo group in our trial precluded us from conducting a moderation analysis. When this trial was designed, both federal sponsors and our institutional review board felt that assigning patients with dementia hospitalized for the treatment of agitation or psychosis to placebo would be unethical. This opinion was based in part on the findings of superiority of risperidone over placebo in two previous efficacy trials conducted in long-term care patients (De Deyn et al., 1999, Katz et al., 1999). Given the modest effectiveness of risperidone in outpatients in the CATIE-AD trial (Schneider et al., 2006), the risk/benefit ratio of risperidone should be reconsidered. Further, we did not examine blood levels of citalopram and risperidone in this analysis. Missing genotype data on 11 randomized participants constitutes another limitation. It should be noted, however, that we did not rely on randomization to control the nuisance variables since all of our analyses were stratified by treatment arm. Finally, our findings of variation in a single gene offer only limited insight into the response of the serotonin system to medications in dementia with behavioral disturbance, and future studies examining a set of serotonergic genes should provide a fuller understanding of the effect of this system and enable analyses of epistatic effects.

5-HTTLPR and outcomes of SSRI treatment

Our observation of increased adverse effects of citalopram and earlier treatment discontinuation in patients with the low-expression S and Lg alleles of the serotonin promoter confirms previous findings in non-demented depressed older patients treated with paroxetine (Murphy et al., 2004) and in younger depressed patients treated with SSRIs (Perlis et al., 2003, Smits et al., 2007, Hu et al., 2007). Taken together, these data suggest that the risk/benefit ratio of SSRI treatment is more favorable in patients with the high-expression La allele.

Further, if our findings are replicated in other studies of dementia, this will make a case for considering the 5-HTTLPR genotype in the choice of SSRI vs. alternative treatments in real-life practice.

Our findings regarding the effect of 5-HTTLPR on response to citalopram parallel those of Murphy and colleagues (Murphy et al., 2004), who observed a prominent effect of the 5-HTTLPR S allele on adverse events and early discontinuation of paroxetine treatment for geriatric depression, but only a small effect on depressive symptoms. These results are in contrast with our previous finding of delayed response to paroxetine in depressed elderly with the S allele (Pollock et al., 2000), similar observations in younger European patients with depression (Smeraldi et al., 1998; Arias et al., 2003) and the observations of the opposite effects of the s allele in Japanese patients (Yoshida et al., 2002) and in Korean patients (Kim et al., 2006). Besides the ethnic background effects, one explanation of these discrepancies may be that differential SSRI efficacy in patients with variant 5-HTTLPR is mediated by adverse effects and medication adherence. In our study medications were administered by inpatient and long-term care staff, and adherence was likely more uniform. Another possible explanation may lie in the fact that earlier studies did not use pattern-mixture models to account for dropouts. Conceivably, the apparent differential response of depression associated with 5-HTTLPR in some studies could mainly be due to differential dropouts between the low- and high-expression allele groups (Hedeker and Gibbons, 1997).

5-HTTLPR and outcomes of SGA treatment

As risperidone does not bind directly to the serotonin transporter, we did not expect its effects to vary between the low- and high-expression alleles. Yet, patients with low-expression alleles seemed to experience greater early adverse effects of risperidone in our study. These adverse effects were not severe enough to cause differential early treatment discontinuation, and it would be premature to conclude that patients with dementia who carry low-expression alleles are intolerant of SGAs until this finding is replicated. This finding should also be viewed with caution, since it was not replicated with the undifferentiated L allele. Nevertheless, such an effect is plausible in patients whose serotonin system is disrupted by neurodegeneration, given risperidone's affinity for the serotonin 2A receptor and its propensity to cause the possibly serotonergic-mediated side effects of headaches, vomiting, and dyspepsia (Aman et al., 2002, Marder and Meibach, 1994).

Our other unexpected finding of poor early response of psychosis to risperidone in participants with the low-expression S and Lg alleles is in contrast with most schizophrenia studies (Arranz et al., 2000, Arranz et al., 1998, Kaiser et al., 2001). This finding certainly requires replication, since it was not statistically significant with the undifferentiated L allele, and overall response over 12 weeks of risperidone treatment was not different between genotype groups. On the other hand, this effect is paralleled by seemingly increased early side effects of risperidone in patients with low-expression alleles. Thus, we may speculate that a functional serotonin system is necessary for the antipsychotic effect of the SGAs in dementia, at least in the first weeks of treatment – an explanation consistent with the antipsychotic effect of SSRIs in dementia (Pollock et al., 1997, Pollock et al., 2002, Pollock et al., 2007). These findings also need to be interpreted in light of our knowledge of serotonin-dopamine interactions, both direct (through serotonin receptors on the bodies of dopamine neurons) and indirect (mediated by GABA-ergic and glutamatergic input) (Di Giovanni et al., 2008, Wood and Wren, 2008). It is thus possible that serotonergic pathways modulate the dopaminergic antipsychotic effects of risperidone.

In summary, the presence of 5-HTTLPR low-expression S or Lg alleles may be a clinically useful biomarker of SSRI intolerance in dementia. Our findings of early intolerance and impaired early response of psychosis symptoms to SGA treatment in patients with the low-expression alleles require replication.

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1a. Citalopram

1b. Risperidone

Figure 1. Serotonin transporter genotype and treatment discontinuation for medical or psychiatric reasons

Over 12 weeks of treatment with citalopram, time to dropout for medical or psychiatric reasons differed across the 5-HTTLPR genotypes. No effects of 5-HTTLPR genotype on time to dropout were observed in the risperidone group.

Table 1

Baseline group characteristics (N=92)

Characteristics	Citalopram 5-HTTLPR Genotype			Risperidone 5-HTTLPR Genotype		
	S*/S*	S*/S or Lg/La	La/La	S*/S*	S*/S or Lg/La	La/La
N	10	24	14	12	22	10
Age, mean (SD)	80.6 (10.28)	83.71 (5.16)	81.86 (6.04)	77.83 (12.23)	81.55 (9.08)	83.20 (5.05)
Female, % (N)	20.00 (2)	62.50 (15)	42.86 (6)	75.00 (9)	77.27 (17)	80.00 (8)
White, % (N)	70.00 (7)	79.17 (19)	85.71 (12)	75.00 (9)	86.36 (19)	70.00 (7)
Mint Mental State Examination: mean (SD)	4.88 (6.36)	12.68 (8.63)	10.40 (8.96)	7.00 (5.06)	13.22 (8.93)	13.85 (7.40)
Cornell Scale for Depression in Dementia, mean (SD)	13.20 (17.00)	8.17 (6.43)	11.43 (12.79)	12.75 (11.43)	12.00 (16.17)	15.5 (17.25)
Delusions or Hallucinations, % (N)	40.00 (4)	33.33 (8)	50.00 (7)	33.33 (4)	50.00 (11)	50.00 (5)
Neurobehavioral Rating Scale (NBR) Agitation Score, mean (SD)	9.20 (3.68)	9.79 (4.90)	10.29 (5.68)	9.83 (5.47)	8.36 (4.36)	8.50 (4.28)
NBR Psychosis Score, mean (SD)	5.44 (3.36)	6.38 (3.36)	5.62 (4.27)	5.82 (4.00)	6.19 (4.50)	8.33 (4.61)
UKU Total Score, mean (SD)	14.5 (6.54)	13.42 (5.30)	12.86 (4.72)	13.00 (3.67)	11.68 (4.59)	13.50 (3.03)
End dose (mg/day) (SD)	25 (10.80)	31.67 (9.63)	30.00 (10.38)	1.42 (5.6)	1.11 (4.6)	1.40 (3.2)
Cumulative Illness Rating Scale – Geriatrics (CIRSG), mean (SD)	8.33 (2.74)	9.67 (2.93)	10.43 (3.52)	7.25 (3.98)	9.32 (4.45)	10.20 (4.02)
Prevalence of medical conditions, indicated by corresponding CIRSG item scores ≥ 1						
Heart, % (N)	40 (4)	41.67 (10)	50 (7)	41.67 (5)	68.18 (15)	50 (5)
Vascular, % (N)	60 (6)	70.83 (17)	71.43 (10)	58.33 (7)	81.82 (18)	60 (6)
Hematopoietic, % (N)	60 (6)	45.83 (11)	50 (7)	25 (3)	36.36 (8)	60 (6)
Respiratory, % (N)	40 (4)	25 (6)	35.71 (5)	25 (3)	31.82 (7)	10 (1)
Eyes, ears, nose, throat, and larynx, % (N)	60 (6)	62.5 (15)	71.43 (10)	41.67 (5)	50 (11)	60 (6)
Upper gastrointestinal, % (N)	30 (3)	25 (6)	42.86 (6)	16.67 (2)	40.91 (9)	40 (4)
Lower gastrointestinal, % (N)	40 (4)	37.5 (9)	21.43 (3)	41.67 (5)	45.45 (10)	70 (7)
Liver, % (N)	11.11 (1)	8.3 (2)	0 (0)	8.33 (1)	4.55 (1)	1 (1)
Renal, % (N), Total N=9	10 (1)	42 (1)	21.43 (3)	0 (0)	18.18 (4)	1 (1)
Genitourinary, % (N)	80 (8)	79.17 (19)	85.71 (12)	50 (6)	54.55 (12)	60 (6)
Musculoskeletal/integumental, % (N)	70 (7)	58.33 (14)	64.29 (9)	41.67 (5)	63.64 (14)	80 (8)
Neurological, % (N)	0 (0)	29.17 (7)	21.43 (3)	8.33 (1)	13.64 (3)	20 (2)

Characteristics	Citalopram 5-HTTLPR Genotype			Risperidone 5-HTTLPR Genotype		
	S*/S*	S*/S or Lg/La	La/La	S*/S*	S*/S or Lg/La	La/La
Endocrine, metabolic, and breast, % (N)	10 (1)	41.67 (10)	42.86 (6)	16.67 (2)	36.36 (8)	40 (4)
Concomitant psychotropic medications						
Cholinesterase Inhibitor, % (N)	20 (2)	20.83 (5)	21.43 (3)	16.67 (2)	27.27 (6)	10 (1)
Benzodiazepine, % (N)	70 (7)	79.17 (19)	71.43 (10)	75 (12)	68.18 (15)	80 (8)
Opioid, % (N)	20 (2)	8.33 (2)	0	0	0	0
Anticholinergic, % (N)	10 (1)	12.5 (3)	28.57 (4)	16.67 (2)	13.64 (3)	40 (4)

* S* denotes the low-expression S or Lg alleles.

Table 2

Serotonin transporter genotype* (S*S*/S*La vs. LaLa) and treatment outcomes (two-pattern mixture model; N=92)

	Citalopram				Risperidone			
	Early response: 4 wk		Overall response: 12 wk		Early response: 4 wk		Overall response: 12 wk	
	Group difference [†] (SE)	p (df)	Group difference (SE)	p (df)	Group difference (SE)	p (df)	Group difference (SE)	p (df)
NBRS[‡] Psychosis score								
	-0.06 (0.43)	0.89 (125)	0.00 (0.13)	1.00 (275)	-1.13 (0.46)	0.015 (107)	0.22 (0.24)	0.36 (217)
NBRS Psychosis[§] , controlling for cognitive impairment ^{**} and burden of physical illness ^{††}	-0.17 (0.49)	0.73 (104)	-0.17 (0.49)	0.73 (104)	-1.12 (0.48)	0.023 (91)	-0.06 (0.30)	0.85 (184)
NBRS Agitation score	0.22 (0.48)	0.64 (131)	-0.27 (0.17)	0.105 (287)	-0.35 (0.54)	0.50 (115)	0.56 (0.27)	0.016^{‡‡} (232)
NBRS Agitation^{**} , controlling for cognitive impairment	-0.18 (0.53)	0.73 (107)	-0.25 (0.19)	0.19 (232)	-0.25 (0.58)	0.67 (91)	0.43 (0.29)	0.14 (184)
Side effects	-0.80 (0.39)	0.040 (132)	-0.55 (0.15)	0.0002 (288)	-0.94 (0.44)	0.036 (115)	0.23 (0.23)	0.31 (232)
Side effects^{**} , controlling for cognitive impairment and diagnosis subtype (Alzheimer vs. Lewy-body dementia)	-1.12 (0.42)	0.0009 (106)	-0.71 (0.17)	<0.0001 (231)	-1.16 (0.48)	0.016 (91)	0.05 (0.27)	0.86 (184)

[†] The **group difference** is the difference between the slopes of the regression lines predicted by the model. A negative group difference indicates less improvement in psychosis or agitation, or more side effects for the S*S*/S*La genotypes compared to the LaLa genotype.

[‡] **NBRS**: Neurobehavioral Rating Scale (29, 30).

[§] Group sizes: citalopram, N=40; risperidone, N=35.

^{**} Measured by the Mini-Mental Status Examination score.

^{††} Measured by the Cumulative Illness Rating Scale adapted for Geriatrics score.

^{‡‡} The effect of 5-HTTLPR on response of agitation symptoms to risperidone was explained by high agitation scores in one participant, who discontinued treatment at week 6. After excluding this participant, this effect was no longer present, while the statistically significant effect of 5-HTTLPR on early response of psychosis symptoms and early adverse effects of risperidone remained.