Common Selective Serotonin Reuptake Inhibitor Side Effects in Older Adults Associated with Genetic Polymorphisms in the Serotonin Transporter and Receptors: Data from a Randomized Controlled Trial

Lauren D. Garfield, Ph.D., M.P.H., David Dixon, Ph.D., Petra Nowotny, Ph.D., Francis E. Lotrich, M.D., Ph.D., Bruce G. Pollock, M.D., Ph.D., Sean D. Kristjansson, Ph.D., Peter M. Doré, M.A., Eric J. Lenze, M.D.

Objective: *Antidepressant side effects are a significant public health issue, associated with poor adherence, premature treatment discontinuation, and, rarely, significant harm. Older adults assume the largest and most serious burden of medication side effects. We investigated the association between antidepressant side effects and genetic variation in the serotonin system in anxious, older adults participating in a randomized, placebo-controlled trial of the selective serotonin reuptake inhibitor (SSRI) escitalopram.* **Methods:** *Adults ($N = 177$) aged ≥ 60 years were randomized to active treatment or placebo for 12 weeks. Side effects were assessed using the Udvalg fur Kliniske Undersøgelser side-effect rating scale. Genetic polymorphisms were putative functional variants in the promoters of the serotonin transporter and 1A and 2A receptors (5-HTTLPR [L/S + rs25531], HTR1A rs6295, HTR2A rs6311, respectively).* **Results:** *Four significant drug−placebo side-effect differences were found: increased duration of sleep, dry mouth, diarrhea, and diminished sexual desire. Analyses using putative high- versus low-transcription genotype groupings revealed six pharmacogenetic effects: greater dry mouth and decreased sexual desire for the low- and high-expressing serotonin transporter genotypes, respectively, and greater diarrhea with the 1A receptor low-transcription genotype. Diminished sexual desire was experienced significantly more by high-expressing genotypes in the serotonin transporter, 1A, or 2A receptors. There was not a significant relationship between drug concentration and side effects nor a mean difference in drug concentration between low- and high-expressing genotypes.* **Conclusion:** *Genetic variation in the serotonin system may predict who develops common SSRI side effects and why. More work is needed to further characterize this genetic modulation and to translate*

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INTRODUCTION

In the United States, 14.5% of people aged 60 and older take an antidepressant medication.[1] Adherence to antidepressant pharmacotherapy is suboptimal, mainly because of patient intolerance of side effects, even minor side effects.[2] Side-effect burden has improved with the advent of the selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors. However, discontinuation due to adverse reactions is still problematic; almost 40% of patients taking an SSRI experience at least one side effect.[3,4] Antidepressants are increasingly prescribed for older adults with depression and anxiety,[5,6] a population especially vulnerable to side effects.[7,8] Side effects constitute a large public health burden that disproportionately falls on elderly patients. Older adults have less physiologic reserve than younger patients,[7] and SSRI treatment has specifically been associated with weight gain,[9] concentration and attention impairment,[10,11] falls,[12−14] syndrome of inappropriate antidiuretic hormone secretion,[3] and serotonin syndrome[15] in this population. In addition to more severe side effects that happen rarely, common, less severe side effects also play an important role in patient adherence to SSRIs.

One way of addressing side effects of antidepressant treatment is through prevention. Patients with high genetic susceptibility to side effects of a specific antidepressant could be offered a different treatment regimen. This level of treatment personalization is not currently available but is within the sights of pharmacogenomics. Understanding the genetic basis of treatment-emergent adverse events and using this information to improve treatment quality is the goal of this line of research.

Pharmacogenetic effects are variations in drug effect by genotype, in this case the effect being a side effect. Currently, there is no consensus on the pharmacogenetics of SSRI side effects. Available studies lack consistency in samples selected and method of their assessment.[4] The assessment of SSRI side effects is difficult because of individual differences in onset, duration, remission, and recurrence. We addressed these issues through systematic, longitudinal assessment of individual side effects both before and throughout the 12-week treatment trial. Studying side effects within a placebo-controlled trial allows us to distinguish between true drug side effects and placebo symptoms that occur naturalistically. Previous work has shown that some individuals are more likely to experience side effects, regardless of treatment.[16]

Our study examined genetic variation in the serotonin transporter and 1A and 2A receptors in relation to SSRI side effects. The primary aim of this investigation was to determine if SSRIs were associated with genetic variation in the serotonin system. Additionally, our secondary aim was to determine if drug concentration was a moderator of side effects. The serotonin transporter is the main target for all SSRIs, which increase serotonin in the synapse through inhibition of the serotonin transporter. Downstream, this affects serotonergic transmission at proximal targets, including the 1A and 2A receptors.[17] The receptors are located both centrally and peripherally and thus have the potential to influence SSRI side effects through both central nervous system and peripheral changes. The serotonin receptors are known to have functional genetic variation, with high- and low- expressing (gene transcription) genotypes. These functional genotypic differences in expression may influence the occurrence of SSRI side effects phenotypically. We hypothesized that there would be pharmacogenetic differences in SSRI side effects related to genetic variation in these three genes.

METHODS

Data for this study came from a 12-week, double-blind, randomized controlled trial comparing escitalopram and placebo.[18] Participants were ages 60 and older,