**Title:** Serotonin transporter gene polymorphisms and SSRI tolerability: review of pharmacogenetic evidence

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**Abstract**

Selective serotonin reuptake inhibitors (SSRIs) are first-line pharmacotherapy for mood and anxiety disorders. The common mechanism of drugs in this class is antagonism of the serotonin transporter. Within the serotonin transporter gene, two polymorphic sites termed 5-HTTLPR and STin2, are proposed to have functional consequences and thus have been attractive candidates for pharmacogenetic studies of SSRI efficacy and tolerability studies. This review summarizes approximately 15 years of study of these polymorphisms as they relate to SSRI tolerability phenotypes. Despite some null and occasionally opposite findings, the 5-HTTLPR S allele is generally associated with greater adverse drug reaction burden during SSRI therapy. Phenotypically, the most convincing evidence is in studies of antidepressant-induced mania and gastrointestinal adverse events. Studies of STin2 are sparse and have conflicting findings. Limitations and challenges in interpreting this body of evidence including assay errors, dissimilar grouping of genotypes, and the role of ethnicity in associations, and study methodological differences are outlined. The clinical utility of serotonin transporter genotypes is not yet delineated but will ultimately depend on genotypic effects on tolerability and efficacy of SSRIs as well as alternative treatments.

Selective serotonin reuptake inhibitors (SSRIs) are first-line pharmacotherapy for various affective and anxiety disorders, and are generally considered to have a favorable side effect profile compared with alternative agents such as tricyclic antidepressants.1-3 Nonetheless, SSRIs have a wide range of commonly reported adverse drug reactions (ADRs), including but not limited to drowsiness, nausea, and sexual dysfunction which can lead to treatment discontinuation or necessitate alternative therapy.4 In the era of precision medicine, there is interest in identifying genetic factors that can predict the development of treatment-limiting ADRs. The shared mechanism of SSRIs is antagonism of the serotonin transporter, which is responsible for the reuptake of serotonin from the synaptic cleft. The serotonin transporter gene (*SLC6A4*) has known common polymorphisms and is thus an appealing candidate gene for pharmacogenetic studies of SSRIs.

The majority of studies have focused on an insertion/deletion polymorphism in the 5’ promoter region of *SLC6A4* known as 5-HTTLPR. Functional studies of the promoter region have been recently and comprehensively reviewed.5 This polymorphism leads to short (S) and long (L) alleles, the latter being 44 base pairs longer and conferring greater expression and activity. A single nucleotide polymorphism (rs25531) in the region that subdivides the L allele into LA and LGalleles, indicates the presence of adenine or guanine at the polymorphic site. The LA allele is typically associated with increased expression and activity compared with LG or S alleles.

Another genetic region of interest is a variable number of tandem repeat polymorphism in the second intron, termed STin2. This polymorphism is triallelic with 9-, 10-, or 12-repeat alleles. The 12-repeat allele is associated with increased *SLC6A4* expression.6 Hypothetically, individuals with low expression *SLC6A4* genotypes may have greater saturation of serotonin transporters when exposed to SSRIs, increasing central and peripheral serotonin availability which then manifests as ADRs (see Figure 1).

Some commercially-available genotyping platforms now include 5-HTTLPR, with the intention that this information can be used to inform pharmacotherapy for patients with affective or anxiety disorders. Without large RCTs to support or refute the utility of this information or clinical guidelines (e.g., Clinical Pharmacogenomics Implementation Consortium guidelines) to dictate appropriate use of this information when available, knowledge of existing pharmacogenetic studies and nuances of the polymorphic sites in this gene is key. The present review summarizes the available literature concerning SSRI tolerability phenotypes as they relate to 5-HTTLPR and STin2.

**Methods**

Studies eligible for this review were retrieved by searching MEDLINE on PubMed’s platform, Cochrane Library’s (John Wiley & Sons) Central Register of Controlled Trials, PsycINFO (Ovid SP), and PharmGKB ([www.pharmgkb.org](http://www.pharmgkb.org)) from 1995 to July 19, 2016. A professional clinical research librarian designed the strategies (see supplementary methods). Reference lists of identified articles were screened for additional citations. With duplicates removed, the search yielded 733 articles related to 5-HTTLPR, rs25531, and/or STin2 in patients treated with antidepressants.

Study inclusion criteria were: English language, peer-reviewed published articles, human subjects, *SLC6A4* genetic analysis, and related to antidepressant treatment. Exclusion criteria included: dissertations, conference abstracts, animal studies, reviews, case studies, efficacy or disease- risk only topics without tolerability data, STin2 or 5-HTTLPR not genotyped, and studies of non-SSRI class antidepressants. Although some studies examined other polymorphisms in *SLC6A4*, STin2 and 5-HTTLPR are by far the most frequently studied *SLC6A4* polymorphisms and are thus most suitable for review. If research groups published more than one study using the same population, only the study with the largest sample size was incorporated. If study results were not appropriately stratified (e.g., grouping treatment and placebo populations) or lacked methods to assess or analyze adverse effects, they were excluded. When studies included patients treated with non-SSRI antidepressants, results for the SSRI-treated subgroup were reported, if available.

All articles’ titles and abstracts were independently screened by two authors (JZ and JS) for inclusion and disagreements were arbitrated by discussion, consensus, and if needed, arbitration by a third reviewer (MKF). Full-text of potentially relevant articles were read and notes regarding study design, methods, assessments, and clinical outcomes were collected to construct this review. Figure 2 is a PRISMA flow diagram that describes the deletions and final included studies.

**Results**

General Tolerability

Table 1 summarizes the identified studies examining broad SSRI tolerability and *SLC6A4* genotypes. Six studies in primarily Caucasian populations have found positive associations with the S allele or S/S genotype and worse tolerability.7-12 In 122 primarily Caucasian depressed geriatric patients treated with paroxetine, the 5-HTTLPR S/S genotype was associated with greater severity of ADRs, decreased compliance, lower final dose at the end of the flexible dosing study, and the S allele was associated with study discontinuation.7 Similarly, in 48 non-depressed dementia patients treated with citalopram, the LA/LA genotype was protective from study discontinuation and ADRs as measured by Udvalg for Kliniske Undersøgelser (UKU) scores at 4 weeks and study conclusion (12 weeks) in both crude and adjusted analyses.8 5-HTTLPR S allele carriers were more likely to drop out due to adverse events in a study of 330 PTSD patients treated with sertraline.9 In 100 SSRI-treated Caucasian patients, carriers of the LA allele had lower ADR scale sum scores, although this finding was not statistically significant (p=0.067).10 A prospective study of 44 primarily Caucasian depressed patients treated with antidepressants that block the serotonin transporter (SSRIs, serotonin and norepinephrine reuptake inhibitors, and tricyclic antidepressants) observed that 5-HTTLPR S/S genotype individuals experienced significantly more ADRs than L/S individuals, and L/L individuals reported no ADRs.11 Finally, this association was demonstrated in a much larger sample (n=1131) of white non-Hispanic individuals treated with citalopram in the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) study, in which low expression alleles (S and LG) were associated with higher ADR burden in univariate and multivariate analyses.12

On the contrary, seven studies of Caucasian populations have found no association between 5-HTTLPR and tolerability.13-19 One of the earliest publications examining broad SSRI tolerability by *SLC6A4* genotypes demonstrated no difference in mean number of ADRs by 5-HTTLPR genotype in 36 depressed Caucasian patients treated with fluoxetine, although there were compelling associations between genotype and neuropsychiatric side effects which are covered elsewhere in this review.13 In 74 pediatric patients treated with citalopram, there was no association between 5-HTTLPR genotype and risk of individual ADRs with the exception of agitation.14 Similarly, 5-HTTLPR genotype was not associated with risk of individual ADRs (except headache after dose increase) in a study of depressed adults treated with escitalopram, though it should be noted that investigators examined each of the 32 side effects individually and used a Bonferroni correction for multiple comparisons, which may lead to Type II error.15 In a study of depressed patients receiving paroxetine (n=76), 5-HTTLPR genotype was not associated with patient-reported ADRs, but the low incidence (n=4) results in extremely low power to detect differences by genotype.16 Power is not the sole reason for lack of association between 5-HTTLPR and ADRs, as null associations have been found in larger samples as well. In 214 depressed Caucasian patients treated with various SSRIs, 5-HTTLPR genotype was not significantly associated with overall ADR incidence or any specific ADR domain, although S allele carriers had numerically higher incidence in most domains.17 A study of 234 late-life depression patients treated with SSRIs found no association between 5-HTTLPR genotype and dropout due to ADRs.18 The largest study that failed to show an association between 5-HTTLPR and ADRs or dropout rate was performed using a subset of depressed European ancestry patients treated with escitalopram in the Genome Based Therapeutic Drugs for Depression (GENDEP) project (n=450).19 In addition to these null results, we identified one study which noted a positive association between general tolerability measures and 5-HTTLPR in the opposite direction of other positive studies: the 5-HTTLPR L allele was associated with a higher ADR index in patients with depression secondary to traumatic brain injury-treated citalopram.20

All four studies of 5-HTTLPR and general measures of SSRI tolerability are negative in Asian populations.21-24 Of note, all four studies are small (highest n=136) and 5-HTTLPR is less polymorphic in Asian populations than European populations, with roughly 80% of Asian individuals having at least 1 S allele and 60% with the S/S genotype.5 The combination of low ADR incidence (e.g., study discontinuation), paired with small sample sizes, and reduced genetic variability at this locus results in low statistical power to detect differences in individual studies of Asian populations. This does not necessarily mean that 5-HTTLPR is not clinically important for SSRI therapy in these populations, but much larger studies designed with *a priori* power calculations are needed to investigate this association.

Studies of STin2 are fairly uncommon and inconsistent. One study in Caucasian patients showed that STin2 10/10 individuals were almost four times more likely to suffer from occurrence of ADRs than carriers of the 12 allele (p=0.004).11 A second group found a similarly strong association, but in the opposite direction, with STin2 12/12 individuals demonstrating much greater odds of ADRs (OR 4.3, p=0.0001).10 Meanwhile, null findings have been reported by two other groups studying Caucasian patients, although one had very lower power to detect differences by genotype.16, 17 STin2 was examined in only one Asian general tolerability study we reviewed and the finding was null. In 136 fluoxetine or sertraline-treated elderly Korean patients, there was no association between STin2 genotypes and dropout status or UKU total score.22

In summary, positive studies of 5-HTTLPR in Caucasian populations generally show an association of S alleles and increased risk of ADRs, but there is a similar number of studies showing no association as well as a single study showing an association in the opposite direction (increased risk for the L allele). While differences in disease state, treatment, ethnicity, and ADR assessment undoubtedly contribute to these contradicting findings, there is not a single driving factor that could be identified. Sample sizes were similar on average in studies implicating the S allele and those finding no association (average n=296 and 223, respectively) and larger studies (n>700) have shown both positive12 and null findings.19 Meanwhile, the genotyping of rs23351 does not greatly differ between the groups, with 3/6 studies implicating the S allele and 2/7 studies showing no association genotyping this locus. Associations between 5-HTTLPR and general tolerability measures have not been adequately studied to date, but limited existing evidence does not show a large effect. The body of evidence on STin2 is extremely variable, with studies showing no association, or very strong associations in either direction.

Neuropsychiatric Adverse Events

SSRIs can cause a variety of neuropsychiatric adverse events, including headache, mania, akathisia, agitation, and insomnia, and potentially increase suicidality for some individuals. Table 2 summarizes relevant *SLC6A4* pharmacogenetic studies of these phenotypes. Some of the earliest studies in this domain examined a potential genetic association of *SLC6A4* with antidepressant induced mania (AIM)*.* Of seven studies investigating 5-HTTLPR in relation to AIM, three found significant evidence associating the S allele with increased odds of AIM,25-27, one showed a non-significant trend in that direction,28 and three showed little signal of association.29-31 Studies examining STin2 are consistent in that all three studies failed to show an association between STin2 and AIM.25, 26, 28 One group performed a haplotype analysis of 5-HTTLPR, rs25531, and STin2 and concluded that the L-A-10 haplotype is associated with reduced risk of AIM28 – a finding that is physiologically confusing given the increased expression owed to the 5-HTTLPR and rs25531 genotypes and decreased expression related to STin2 10 repeat allele. Studies examining combined effects of these loci are rare, and the proper methodology for such studies is still debated.32, 33 In addition to these genetic considerations, concurrent use of mood stabilizers may mask AIM and is a potential major confounder between existing studies. Use of mood stabilizers was allowed in some analyses,25, 26, 31 specifically excluded in others,27, 28, 30and was not addressed in one.29 Ideally, future studies will utilize rigorous phenotyping in a more homogenous population in terms of antidepressant and mood stabilizer treatment in addition to controlling for clinical covariates such as age and presence of rapid cycling.

Treatment-emergent extrapyramidal symptoms, agitation, and insomnia have been studied with conflicting findings. Enhancement of locomotor activity by SSRIs appears to be dependent on the serotonin transporter, based on knockout studies in animal models.34 Thus, polymorphisms affecting serotonin transporter number or activity may likewise influence risk of these adverse events. A study found an increased risk of agitation for the low expression 5-HTTLPR S/S genotype,13 while another study reported significantly *decreased* odds in their sample.14 These opposite findings are perhaps partially explained by very different study populations – the first study13 was conducted in adults of Caucasian ancestry whereas the second study14 was conducted in children and adolescents of Jewish ancestry. Curiously, another small study found a non-significant trend toward higher agitation score (p=0.159) for individuals with the high expression L/L genotype.35 The same study described increased nighttime motor activity for individuals with the L/L genotype. On the contrary, another group described no association between 5-HTTLPR genotype and extrapyramidal symptoms.36 With positive findings in both directions as well as negative studies, no confident conclusions can be made regarding 5-HTTLPR and SSRI-related movement, sleep, and agitation phenotypes. STin2 has not been examined in this regard. Notably, all existing studies are small (n<100), so future studies will need to be mindful of statistical power to help conclusively demonstrate the association between these phenotypes and *SLC6A4* or lack thereof.

Additional neuropsychiatric phenotypes have been examined in single studies. Elderly patients may demonstrate an increased duration of sleep on SSRI therapy, but this phenotype was not associated with 5-HTTLPR in one study.37 SSRI discontinuation syndrome (characterized by dizziness, vivid dreams, fatigue, nausea, and paresthesia after discontinuation of treatment) shows high interpatient variability and is thought to be related to serotonergic neural pathways, but showed no association with 5-HTTLPR in a single study.38 One study found an increased risk of headache and a trend toward increased tremor after dose increase (not significant after correction for multiple comparisons) for individuals carrying S alleles.15 SSRIs carry a black box warning for emergence or worsening of suicidal ideation in the United States, but a single study found no significant association between 5-HTTLPR genotype and increased suicidal thoughts.39 A previously described study of children and adolescents attempted to examine the same phenotype, but all participants demonstrated reduced suicidal ideation, resulting in the inability to study this phenotype in that sample.14

In summary, AIM is the best-studied neuropsychiatric phenotype and shows fairly consistent increased odds of AIM with the 5-HTTLPR S allele, although there is significant heterogeneity in study methodology. STin2 studies of AIM have been negative. Evidence is less clear for other neuropsychiatric phenotypes, many of which have only been examined in single and/or small studies. Data are surprisingly conflicting regarding extrapyramidal and agitation phenotypes, with larger and more conclusive studies needed before applying this information to a patient’s treatment regimen.

Sexual Dysfunction Adverse Events

Sexual dysfunction is a common and troubling adverse effect of SSRIs, with reported prevalence varying widely from 10% to 80%. The incidence of sexual dysfunction in SSRI-treated individuals is influenced by factors such as assessment tool, age, sex, and illness severity, and is typically reported more frequently with SSRIs than non-SSRI antidepressants such as bupropion, mirtazapine, and nefazodone, suggesting an integral role of serotonin signaling in the development of sexual dysfunction.40, 41 Numerous pharmacogenetic studies have attempted to identify individuals at greater risk for this adverse effect and *SLC6A4* is a leading candidate gene.41 Literature suggests SSRI-related sexual dysfunction may be dose dependent and improve on drug holidays, so it is feasible that polymorphisms affecting serotonin transporter saturation through serotonin availability to pre- and post-synaptic serotonin receptors may modify risk of this adverse drug reaction. Table 3 summarizes studies of SSRI-related sexual dysfunction by *SLC6A4* genotypes.

In an early study of this phenotype, sexual dysfunction was assessed by the Changes in Sexual Functioning Questionnaire (CSFQ) in 115 depressive patients treated with SSRIs.42 The 5-HTTLPR L/L genotype was significantly associated with the presence of sexual dysfunction in crude analysis and after adjusting for patient sex and depressive symptoms (crude OR 2.7 p=0.02, adjusted OR 2.8 p=0.03), but STin2 genotype was not associated with sexual dysfunction in crude or adjusted analyses. Similar findings were noted in a study of 85 older adults treated with escitalopram.37 Carriers of the 5-HTTLPR LA allele were significantly more likely to report diminished sexual desire (p<0.05). On the contrary, in an analysis of 494 depressed patients treated with escitalopram or nortriptyline, there was no association between 5-HTTLPR genotype and sexual dysfunction (p=0.945), although frequency of sexual dysfunction was low in this study and sexual functioning actually improved on average after treatment.43

Because delayed orgasm is a common ADR of SSRIs, these drugs are sometimes prescribed off-label for the treatment of premature ejaculation. Pharmacogenetic studies of SSRI efficacy for this indication may provide insight into SSRI tolerability in patients treated for more traditional indications. In 69 patients with premature ejaculation treated with paroxetine, the 5-HTTLPR S allele was more common in responders (i.e. more frequent delayed ejaculation, p<0.05).44 To the contrary, in a study of 54 Dutch men with premature ejaculation treated with paroxetine, 5-HTTLPR genotype was not associated with fold change in intravaginal ejaculator latency time (p=0.83).45

It is not surprising that results for this phenotype are conflicting, as sexual functioning is a complex phenotype, with potential for dysfunction in desire, arousal, orgasm, or satisfaction. Of the aforementioned studies, many examine only one sexual function domain and furthermore, SSRI effects and perhaps pharmacogenetic associations with sexual functioning manifest differently between men and women, which data from one study suggest.42 Additional variables may confound results, including use of oral contraceptives and an additional pharmacogenetic variant in the gene encoding the serotonin 2A-receptor.42 Importantly, sexual functioning may improve with resolution of depressive symptoms, which may confound associations with 5-HTTLPR, which has been reported to modulate SSRI efficacy.46 Further, structured assessments of sexual functioning changes after SSRI initiation, ideally stratified by sex and adjusted for confounding clinical and genetic factors, are needed before a pharmacogenetic effect of 5-HTTLPR on SSRI-related sexual dysfunction can be confirmed or rejected.

Gastrointestinal Adverse Events

Serotonin is a key signal transducer in the gastrointestinal tract. Extracellular serotonin, which interacts with serotonin receptors in the gut, initiates secretory functions and peristaltic reflexes which can manifest as nausea, vomiting, and diarrhea if exaggerated.47 Indeed these are common ADRs that are seen with initiation of SSRI therapy. Individuals with low expression *SLC6A4* genotypes could theoretically be at increased risk of these ADRs.

Table 4 summarizes *SLC6A4* pharmacogenetic studies of gastrointestinal adverse events during SSRI treatment. One study of gastrointestinal cluster symptoms demonstrated a protective effect of the LA allele. No association was observed with STin2.10 Two studies examined diarrhea specifically, with one study showing double the risk of diarrhea for S allele carriers48 while the other found no association between genotype and incidence.37

Incidence of nausea was examined in 3 studies of Japanese populations. Strangely, nausea has not been specifically examined in Caucasian populations to date. Of the three studies, two showed evidence of a positive association between S/S genotype and increased risk of nausea although the association was not statistically significant in either individual study (p=0.126 and 0.095).49, 50. On the other hand, Kato et al. failed to demonstrate an association between 5-HTTLPR genotype and nausea in a small study (n=100) with low nausea incidence (10%).21 Takahashi et al. also examined STin2 and nausea risk but detected no association.49

Taken together, the evidence is fairly suggestive of an association between 5-HTTLPR S alleles and increased risk of gastrointestinal ADRs, consistent with physiologic understanding of serotonin function in the gut. Notably, studies in this area have been relatively small, with the largest study (n=261) showing a positive association with the S allele and diarrhea.48 STin2 has only been examined in two studies, neither of which showed evidence of association.

Other Adverse Events

Some SSRI ADRs have only been studied in one or two studies of *SLC6A4* (summarized in Table 5). Serotonin helps to regulate weight via food intake modulation.51 Thus, individuals with lower expression *SLC6A4* genotypes may show greater weight loss after SSRI initiation due to greater transporter saturation. Two studies have examined weight changes and *SLC6A4*.48, 52 The aforementioned study found that 5-HTTLPR S/S individuals had greater decrease in weight during sertraline monotherapy (p=0.047).48 A study using weight *gain* after medication initiation as a phenotype found no association between 5-HTTLPR and weight gain greater than 4 kg (p=0.679) in patients treated with a variety of antidepressants (SSRI monotherapy in 45%).52 One previously mentioned study investigated the association between 5-HTTLPR and dry mouth and found decreased risk in individuals with the high expression LA allele.37

Another important ADR of SSRIs is bleeding. The serotonin transporter is found on platelets and serotonin is a mediator of platelet aggregation.53 Differences in serotonin transporter saturation by SSRIs may modulate bleeding risk and this has been examined in two studies of *SLC6A4*.54, 55 One study found no influence of 5-HTTLPR on platelet function analyzer (PFA) closure time (with collagen and epinephrine used as agonists), or reported bruising or bleeding in patients treated with paroxetine.54 On the contrary, another study of patients before and after starting paroxetine found greater changes in bleeding and PFA closure time in carriers of at least one low-expression 5-HTTLPR allele (LG or S) while LA/LA carriers saw no change after treatment initation.55 These discrepant results may be due to differences in agonists used in the PFA assays or the differentiation of L alleles via rs25531 in the latter study.55

**Discussion**

Pharmacogenetic studies of *SLC6A4* and SSRI tolerability are difficult to summarize due to vast differences in disease state, ethnicity, inclusion/exclusion criteria, phenotyping strategy, genotyping methods, data analysis methods, and adjustment for potentially confounding variables. Despite these challenges, some trends in the data are apparent. Considerations of study heterogeneity and limitations of our review are discussed below.

It has been suggested that the effects of 5-HTTLPR or STin2 on SSRI outcomes may be dependent on race or ancestry.46 Indeed, of the 5-HTTLPR studies covered in this review, positive associations were identified in a greater number of studies performed in Caucasian populations compared with those primarily performed in Asian populations. This phenomenon is not necessarily due to a race x genotype interaction. The L allele frequency is much lower in Asian populations compared with white European populations. Thus, small studies of this variant in Asian populations may not be adequate to detect more subtle effects. On the other hand, pooled data in meta-analyses help to overcome this power issue and do not rule out the possibility of differential effects in different populations.46

Technical issues related to assay validity may also explain some of the discordant findings in studies of 5-HTTLPR. Lack of Hardy-Weinberg Equilibrium is one indicator of potential assay bias. Allele-dependent, non-random genotyping errors – that is, problems with the assay that differentially effect L vs S alleles – have been extensively reported at this locus and has led to altered study conclusions and subsequent retractions of manuscripts.56, 57 Biased assays of 5-HTTLPR typically present as an apparent paucity of heterozygotes (S/L) and a preponderance of S/S homozygotes and may be related to magnesium concentration during polymerase chain reaction.56, 57

Study of 5-HTTLPR is further complicated by the inclusion or exclusion of rs25531 genotype, subdividing L alleles into LA or LG. Typically, the LA allele is shown to confer greater expression and activity versus LG or S alleles, though this finding is not universal and there are differing viewpoints on how the repeat polymorphism and rs25531 should be interpreted together.5, 32 If LA alleles are indeed functionally different from LG alleles, studies in which rs25531 is not genotyped have a large number of functionally misclassified alleles, diluting any potential association. Indeed, more positive associations were observed in the present review in studies that considered rs25531 genotype. Notably, many commercial pharmacogenetic platforms do not differentiate the L allele via rs25531 despite growing functional data. More recently, an additional polymorphism rs25532 has been described as modulating gene expression in concert with 5-HTTLPR and rs25531, but has not been genotyped in SSRI tolerability studies to date.5

Similar to rs25531 and rs25532, some evidence indicates that STin2 may have a combined effect with 5-HTTLPR.33 This may present a source of unexplained variability in studies exclusively examining 5-HTTLPR. Few clinical studies examine the combined effect of STin2 and 5-HTTLPR on clinical outcomes. In addition, rare functional variants in *SLC6A4* and epigenetic mechanisms that affect gene expression are rarely accounted for in SSRI pharmacogenetic studies and are a potential source of unexplained variability.5, 58

Aside from these technical aspects of *SLC6A4* genotyping, other genetic and clinical variables likely contribute to SSRI tolerability phenotypes. Of the genetic factors, variation in genes involved in the pharmacokinetics of SSRIs, such as *CYP2C19*, *CYP2D6*, and *ABCB1* as well as genes related to serotonin signaling such as *HTR2A*, encoding the serotonin-2A receptor, may contribute to ADR risk. In research settings, these are potentially important covariates to include in analyses, and a combinatorial approach to using these pharmacogenes has shown promise in clinical research.59

Whether 5-HTTLPR or STin2 affect SSRI efficacy also needs to be considered when using this genetic information in a clinical setting. Meta-analyses suggest that the 5-HTTLPR L allele and perhaps the STin2 12/12 genotype are associated with better efficacy outcomes.46, 60 Substantial between-study heterogeneity, potential for publication bias, the possibility of effect modulation by ethnicity, and lack of studies simultaneously examining multiple polymorphisms (as well as epigenetic factors) in *SLC6A4* are important limitations to the existing literature. Definitive prospective studies demonstrating that single-gene or combinatorial pharmacogenetic approaches to treatment selection improve hard patient outcomes (such as treatment discontinuation) will likely be needed before *SLC6A4* genotyping is used routinely in clinical practice.

**Conclusion**

Relatively consistent evidence suggests that 5-HTTLPR low expression alleles (S) or genotypes (S/S) are associated with decreased SSRI ADR burden. Robust differences in study population, treatment, evaluation of ADRs, genotyping methods, and statistical methods are present in the exiting literature. Regardless, the single largest study of 5-HTTLPR on SSRI ADR burden, utilizing data from the strictly protocolized STAR\*D study, was in agreement with this conclusion even after controlling for clinical variables in a Caucasian American population.12 Evidence is weaker in studies of Asian populations, although the combination of small sample sizes and lower L allele frequency in these groups almost certainly contributes to negative studies. With positive findings in both directions as well as null associations, more research must be done before STin2 can be considered a valid predictor of SSRI tolerability in the clinical setting.

The most consistent associations of 5-HTTLPR and more specific adverse event phenotypes is with the S allele and higher odds of AIM and gastrointestinal adverse events, though conflicting studies exist in both domains. The AIM literature is complicated by differences in study populations and use of mood stabilizers, and most studies did not genotype rs25531. Despite these issues, a meta-analysis of existing studies in patients on antidepressants (not exclusively SSRIs) shows a suggestive association of the S allele with AIM (p=0.059).28 The observed association between gastrointestinal adverse effects and the S allele is not statistically significant in many individual studies, but is fairly consistent in both Asian and Caucasian populations.

Despite the compelling findings suggesting better SSRI efficacy and tolerability for 5-HTTLPR high expression (LA/LA) genotypes, the implications for treatment alternatives need to be considered to determine whether 5-HTTLPR genotypes might be clinically “actionable”. Namely, is this association specific to SSRIs or does it apply to alternative pharmacologic and non-pharmacologic therapy as well? On a more patient-specific level, it is important to remember that alternative treatments such as bupropion having unique contraindications different from SSRIs, may make them unsuitable alternatives for certain patients. Further, attitudes and preferences toward treatment options may affect the actionablility of 5-HTTLPR on an individual patient basis. Finally, critical gaps exist in the available literature, not in the least the complete lack of *SLC6A4* SSRI tolerability studies in populations not broadly defined as Caucasian and Asian. With pharmacogenetic data becoming more prevalent in both research and clinical settings, the aforementioned limitations may soon be addressed in addition to the broader question of whether *SLC6A4* genotypes can help guide antidepressant treatment selection.

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Table 1. Studies of General Tolerability With SSRIs by *SLC6A4* Genotype

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Citation | Sample Size | Ethnicity | Treatment | Genotyping | Phenotypes | Association |
| Murphy et al. 20047 | n=122 depressed outpatients | Primarily Caucasian | Paroxetine (mirtazapine patients excluded for purposes of this review) | 5-HTTLPR | Clinician assessment of adverse event severity, compliance, and time to treatment discontinuation | Number of S alleles associated with increased risk of discontinuation in survival analysis (p<0.05 at all time points)    S/S genotype associated with greater severity of adverse effects (S/S vs L/L, p=0.02), lower final dose (S/S vs S/L and L/L, both p<0.008), and decreased compliance (S/S vs S/L and L/L, both p<0.001) |
| Dombrovski et al. 20108 | n=48 non-depressed inpatients with dementia | 79% Caucasian | Citalopram | 5-HTTLPR, rs25531 | Side effects severity assessed by UKU Side Effect Rating scale and time to treatment discontinuation | 5-HTTLPR S or LG allele carriers discontinued earlier (p=0.029)  5-HTTLPR S or LG allele carriers had greater severity of side effects at 4 weeks (adjusted p=0.0009) and 12 weeks (adjusted p<0.0001) |
| Mushtaq et al. 20129 | n=330 PTSD outpatients | Not described | Sertraline | 5-HTTLPR | Adverse events assessed by dropout rates | S allele carriers had higher dropout rates due to adverse events (18.1%, 15.3%, and 5.9% in S/S, S/L, and L/L groups, respectively, p=0.038) |
| Staeker et al. 201410 | n=100 psychiatric inpatients | Caucasian | Variety of SSRIs | 5-HTTLPR,  rs25531,  STin2 | Adverse events assessed by DOTES | STin2 12/12 genotype associated with greater side effect rate (OR 4.3, p=0.0001)  5-HTTLPR LA allele carriers had lower DOTES sum score, but this was not statistically significant (p=0.067) |
| Popp et al. 200611 | n=44 depressed inpatients | Primarily Caucasian | Variety of SSRIs, SNRIs, and TCAs (mirtazapine pts excluded for purposes of this review) | 5-HTTLPR, STin2 | Moderate-to-severe side effects listed in the DOTES | STin2 10/10 genotype associated with higher side effect incidence (OR 12.78, p=0.004)  5-HTTLPR S/S genotype associated with higher side effect incidence (OR 3.50, p=0.002) |
| Hu et al. 200712 | n=1,131 depressed outpatients | White non-Hispanic | Citalopram | 5-HTTLPR,  rs25531 | Side effects assessed by GRSEB; tolerance as measured by the FIBSER | Low expression alleles (S and LG) associated with greater adverse effect burden (GRSEB > 4) in univariate (OR 1.43, p=0.008) and multivariate (OR 1.63, p=0.002) analyses  5-HTTLPR genotype not associated with tolerance |
| Perlis et al. 200313 | n=36 depressed outpatients | Caucasian | Fluoxetine | 5-HTTLPR | Patient reported side effects | No association with mean number of side effects reported |
| Kronenberg et al. 200714 | n=74 depressed children and adolescents | Jewish | Citalopram | 5-HTTLPR | Side effects reported during clinician interview | Risk of fatigue, decreased appetite, headache, GI discomfort, changes in sleep, sweating, and dry mouth did not differ by genotype |
| Maron et al. 200915 | n=135 depressed outpatients | 96% Estonian | Escitalopram | 5-HTTLPR, rs25531 | Side effects assessed by TSES | No association between 5-HTTLPR genotype and most items on TSES |
| Wilkie et al.  200916 | n=76 depressed outpatients | Caucasian | Paroxetine | 5-HTTLPR,  STin2 | Patient reported side effects occurrence | 5-HTTLPR and STin2 genotype did not influence adverse events rate (p=0.23 and 0.33, respectively) |
| Smits et al. 200717 | n=214 depressed outpatients | Caucasian | Variety of SSRIs (57.9% paroxetine) | 5-HTTLPR,  STin2 | Clinician assessment of adverse events | No significant differences between 5-HTTLPR genotype and general adverse events (although S alleles tend to have higher rates of adverse events compared with L/L genotype carriers)  STin2 not associated with adverse event rates |
| Seripa et al. 201518 | n=234 late-life depressed patients | Caucasian | Variety of SSRIs | 5-HTTLPR | Dropout due to adverse reactions | 5-HTTLPR genotype not associated with dropout due to ADR (p=0.926) |
| Huezo-Diaz et al. 200919 | n=795 depressed outpatients | Caucasian | Escitalopram (n=450) or nortriptyline (n=345) | 5-HTTLPR,  rs25531 | Side effects assessed by UKU Side-effect Rating Scale, Self-Report Antidepressant Side-Effect Checklist and dropout rates | 5-HTTLPR genotype was not related to adverse effects or dropout rate |
| Lanctot et al. 201020 | n=90 post-TBI patients | 52.2% Caucasian, 13.3% Asian, 34.4% others | Citalopram | 5-HTTLPR, rs25531 | Adverse events index consisting of severity and duration | L allele associated with greater adverse events index |
| Kato et al. 200621 | n=100 depressed outpatients | Japanese | Paroxetine (n=51) or fluvoxamine (n=49) | 5-HTTLPR | Clinician assessed mild or severe side effects | No significant differences between 5-HTTLPR genotype and discontinuation due to side effects or reported number of side effects (p>0.31) |
| Kim et al. 200622 | n=241 depressed outpatients | Korean | SSRI (fluoxetine or sertraline; n=136) or nortriptyline, n=105 | 5-HTTLPR,  STin2 | Side effects assessed by UKU Side Effect Rating Scale and dropout status | Genotypes were unrelated to dropout status or summed total score of the UKU Side Effect Rating Scale |
| Ng et al. 200623 | n=45 depressed outpatients | 67.7% Chinese, 33.3% Caucasian | Sertraline | 5-HTTLPR | Side effects assessed by a modified version of the LUNSERS | 5-HTTLPR genotype was not associated with LUNSERS total score (p=0.63) or serotonergic side effects subscale (p=0.62) |
| Aoki et al. 201424 | n=52 panic disorder outpatients; n=88 depressed outpatients | Japanese | Paroxetine | 5-HTTLPR | Discontinuation due to adverse effects within 2 weeks of initiation | Discontinuation due to adverse effects higher but not statistically significant for L/S genotype vs SS in panic disorder (p=0.067)  Discontinuation due to adverse effects not associated with 5-HTTLPR genotype in depression |

ADR = adverse drug reaction; DOTES = Dosage Record and Treatment Emergent Symptom Scale; FIBSER = Frequency, Intensity, and Burden of Side Effects Rating Scale; GI = gastrointestinal; GRSEB = Global Rating of Side Effect Burden; LUNSERS = Liverpool University Neuroleptic Side Effect Rating Scale; OR = odds ratio; PTSD = post-traumatic stress disorder; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TBI = traumatic brain injury; TCA = tricyclic antidepressant; TSES = Toronto Side-Effect Scale; UKU = Udvalg for Kliniske Undersøgelser.

Table 2. Studies of Neuropsychiatric Adverse Drug Reactions With SSRIs by *SLC6A4* Genotype

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Citation | Sample Size | Ethnicity | Treatment | Genotyping | Phenotypes | Association |
| Frye et al. 201528 | n=295 bipolar outpatients | Caucasian | Various antidepressants; subgroup analysis of individuals treated with SSRI or SNRI (n=272) | 5-HTTLPR, rs25531,  STin2 | AIM defined as a manic/hypomanic episode by DSM-IV criteria within 60 days of starting antidepressant or increasing dose | 5-HTTLPR /rs25531 LA allele not significantly associated with AIM (OR=0.74 p=0.097 in an additive model)  STin2 not associated with AIM (OR=1.11 p=0.57 for 12 allele in an additive model)  L-A-10 haploytpe was associated with reduced risk of AIM (p=0.012) |
| Mundo et al. 200125 | n=56 bipolar outpatients | 96% Caucasian; 4% East Asian | Various antidepressants | 5-HTTLPR,  STin2 | Clinician assessment of AIM | 5-HTTLPR S-allele associated with higher incidence of AIM (p<0.001).  STin2 not associated with AIM (p=0.09) |
| Masoliver et al. 200626 | n=103 bipolar outpatients | Not specified | Various antidepressants | 5-HTTLPR, STin2 | History of AIM defined as bipolar diagnosis with at least one manic or hypomanic episode while on an antidepressant | 5-HTTLPR S/S genotype significantly associated with AIM (S/S vs L/L; p=0.04)  S allele borderline associated with AIM (p=0.058)  STin2 not associated with AIM |
| Baumer et al. 200631 | n=47 children and adolescents with or at high risk of bipolar disorder | 81% Caucasian, 8% Hispanic | Variety of SSRIs | 5-HTTLPR | AIM assessed by interview and clinical judgement | No significant association of AIM and 5-HTTLPR alleles (S allele p=0.36) |
| Ferreira et al. 200927 | n=112 outpatient bipolar adults | Caucasian-Brazilian | Venlafaxine, SSRIs, and TCAs; subgroup of n=48 individuals not concurrently treated with mood stabilizers | 5-HTTLPR | AIM defined as a manic or hypomanic episode within 60 days of antidepressant initiation | No significant difference in AIM by 5-HTTLPR genotype for total sample (p=0.34)  In patients that were not concurrently treated with mood stabilizers, S carriers had 4-fold increased odds of AIM (S allele p=0.004) |
| Serretti et al. 200430 | n=380 bipolar outpatients | Caucasian | Various antidepressants | 5-HTTLPR | AIM assessed by clinician review | No significant association in allelic (p=0.35) or genotypic tests (p=0.66) |
| Rousseva et al. 200329 | n=232 bipolar outpatients | Caucasian | Various antidepressants | 5-HTTLPR | History of AIM defined as mood elevation and excitation in 90 days after started on an antidepressant | 5-HTTLPR genotype was not associated with AIM (p=0.63) |
| Perlis et al. 200313 | n=36 depressed outpatients | Caucasian | Fluoxetine | 5-HTTLPR | Patient reported side effects | S/S genotype associated with increased insomnia odds (OR 10.7, p=0.02)  S/S genotype associated with increased agitation (OR 14.0, p=0.01) |
| Kronenberg et al. 200714 | n=74 depressed children and adolescents | Jewish | Citalopram | 5-HTTLPR | Side effects reported during clinician interview  Suicidality measured by CDRS-R | S/S genotype associated with reduced risk of treatment-emergent agitation (6.3 vs 32.8%, p=0.05)  S/S genotype scored higher on CDRS-R than S/L or L/L (p=0.04) but no significant genotype by time interaction was observed (p=0.75) |
| Putzhammer et al. 200535 | n=22 depressed outpatients | Not specified | Paroxetine or citalopram | 5-HTTLPR | Motor activity measured by a 24 hr actograph; clinician scored motor agitation and retardation scale | 5-HTTLPR L/L genotype associated with higher nighttime activity (p<0.001) and non-significant trend toward higher agitation score (p=0.159) |
| Hedenmalm et al. 200636 | n=19 patients | European | SSRIs with extrapyramidal symptoms compared with allele frequencies previously described in European populations | 5-HTTLPR | Clinician-reported extrapyramidal cases in a national database | 5-HTTLPR allele frequencies did not differ between EPS cases and general or depressed population |
| Garfield et al. 201437 | n=85 older adults with generalized anxiety disorder | 80% Caucasian | Escitalopram | 5-HTTLPR,  rs25531 | Adverse events assessed by UKU Side Effects Rating Scale | No association between 5-HTTLPR genotype and increased need for sleep |
| Murata et al. 201038 | n=56 depressed or anxious outpatients | Japanese | Abrupt discontinuation or dose reduction of paroxetine | 5-HTTLPR; STin2 | Clinician assessment patient-reported paroxetine discontinuation syndrome | 5-HTTLPR and STin2 genotypes were not significantly associated with discontinuation syndrome (p>0.17) |
| Maron et al. 200915 | n=135 depressed outpatients | 96% Estonian | Escitalopram | 5-HTTLPR, rs25531 | Side effects assessed by TSES | S allele carriers had more severe headache after dose escalation (corrected p=0.018) and a trend toward higher tremor incidence (uncorrected p<0.05) |
| Perroud et al. 200939 | n=409 adult depressed outpatients | Caucasian | Escitalopram | 5-HTTLPR,  rs25531 | Increase in suicidal ideation as defined by a composite score consisting of items on the HDRS-17, BDI, and MADRS | 5-HTTLPR genotype not associated significantly with suicidal ideation |

AIM = antidepressant induced mania; BDI = Beck Depression Inventory; CDRS-R = Children’s Depression Rating Scale-Revised; DOTES = Dosage Record and Treatment Emergent Symptom Scale; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition); EPS = extrapyramidal symptoms; HDRS-17 = Hamilton Rating Scale for Depression; MADRS = Montgomery-Asberg Depression Rating Scale; OR = odds ratio; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; TSES = Toronto Side-Effect Scale; UKU = Udvalg for Kliniske Undersøgelser.

Table 3. Studies of Sexual Adverse Drug Reactions With SSRIs by *SLC6A4* Genotype

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Citation | Sample Size | Ethnicity | Treatment | Genotyping | Phenotypes | Association |
| Bishop et al. 200942 | n=115 depressed outpatients | 92% Caucasian; 76% female | Various SSRIs | 5HHTLPR, STin2 | Sexual well-being assessed by CSFQ | 5-HTTLPR L/L genotype associated with increased odds of sexual dysfunction in crude and adjusted analyses (crude OR 2.7 p=0.02, adjusted OR 2.8 p=0.03)  STin2 genotype not associated with sexual dysfunction (adjusted p=0.5) |
| Garfield et al. 201437 | n=85 older adults with generalized anxiety disorder | 80% Caucasian | Escitalopram | 5-HTTLPR,  rs25531 | Adverse events assessed by UKU Side Effects Rating Scale | 5-HTTLPR LA carriers had increased risk of diminished sexual desire (p<0.05). |
| Strohmaier et al. 201143 | n=494 depressed outpatients | Primarily Caucasian; 64% female | Escitalopram or nortriptyline | 5-HTTLPR | Sexual dysfunction and depressive symptoms assessed by MADRS, ASEC, UKU Side Effect Rating scale and SFQ | No association detected between 5-HTTLPR genotype and sexual dysfunction (p=0.945) |
| Ozbek et al. 201444 | n=69 premature ejaculation outpatients | Turkish Caucasian | Paroxetine | 5-HTTLPR | Intravaginal ejaculation latency time increase of > 2-fold from baseline | 5-HTTLPR S allele more common in responders (i.e. delayed ejaculation was more common) (p<0.05) |
| Janssen et al. 201457 | n=54 men with lifelong premature ejaculation | Primarily Caucasian Dutch | Paroxetine | 5-HTTLPR | Change in intravaginal ejaculatory latency time | 5-HTTLPR genotype not associated with fold increase of intravaginal ejaculatory latency time (p=0.83) |

ASEC = Antidepressant Side-Effect Checklist; CSFQ = Changes in Sexual Functioning Questionnaire; MADRS = Montgomery-Asberg Depression Rating Scale; OR = odds ratio; SFQ = Sexual Functioning Questionnaire; SSRI = selective serotonin reuptake inhibitor; UKU = Udvalg for Kliniske Undersøgelser.

Table 4. Studies of Gastrointestinal Adverse Drug Reactions With SSRIs by *SLC6A4* Genotype

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Citation | Sample Size | Ethnicity | Treatment | Genotyping | Phenotypes | Association |
| Staeker et al. 201410 | n=100 psychiatric inpatients | Caucasian | SSRIs | 5-HTTLPR,  rs25531,  STin2 | Adverse events assessed by DOTES | 5-HTTLPR LA allele carriers had significantly less gastrointestinal side effects (p=0.0005) in 100 SSRI treated patients |
| Reimherr et al. 201048 | n=261 depressed outpatients | 78.5% Caucasian; 10.5% African American; 5% Asian | Sertraline | 5-HTTLPR | Clinician assessment of adverse events | 5-HTTLPR genotype associated with incidence of diarrhea (p=0.043); S carriers 19% vs L/L 7.3%  5-HTTLPR genotype associated with degree of weight loss (p=0.047) with S/S experiencing the greatest loss |
| Garfield et al. 201437 | n=85 older adults with generalized anxiety disorder | 80% Caucasian | Escitalopram | 5-HTTLPR,  rs25531 | Adverse events assessed by UKU Side Effects Rating Scale | No association between 5-HTTLPR genotype and incidence of diarrhea |
| Takahashi et al. 200249 | n=66 depressed outpatients | Japanese | Fluvoxamine | 5-HTTLPR,  STin2 | Side effects severity (nausea) assessed by UKU Side-effects Rating Scale | 5-HTTLPR S/S genotype not significantly associated with incidence of nausea (p=0.095)  STin2 12/12 genotype not significantly associated with incidence of nausea (p=0.51) |
| Tanaka et al. 200850 | n=81 outpatients with depressive or anxiety disorders | Japanese | Paroxetine | 5-HTTLPR | Nausea assessed by UKU Side Effects Rating Scale | 5-HTTLPR S/S genotype not significantly associated with incidence of nausea (p=0.126) |
| Kato et al. 200621 | n=100 depressed outpatients | Japanese | Paroxetine (n=51) or fluvoxamine (n=49) | 5-HTTLPR | Clinician assessed mild or severe side effects | No association between 5-HTTLPR genotype and  incidence of severe nausea (p=1.0) |

DOTES = Dosage Record and Treatment Emergent Symptom Scale; SSRI = selective serotonin reuptake inhibitor; UKU = Udvalg for Kliniske Undersøgelser.

Table 5. Additional Studies of Adverse Drug Reactions With SSRIs by *SLC6A4* Genotype

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Citation | Sample Size | Ethnicity | Treatment | Genotyping | Phenotypes | Association |
| Reimherr et al. 201048 | n=261 depressed outpatients | 78.5% Caucasian; 10.5% African American; 5% Asian | Sertraline | 5-HTTLPR | Clinician assessment of adverse events | 5-HTTLPR genotype associated with degree of weight loss (p=0.047) with S/S experiencing the greatest loss |
| Secher et al. 200952 | n=165 depressed patients | Danish | Variety of antidepressants (SSRI monotherapy 45%) | 5-HTTLPR | Weight gain of more than 4kg over 4-6 weeks of treatment | 5-HTTLPR genotype not associated with weight gain (p=0.679); data for SSRI-treated subgroup not published |
| Garfield et al. 201437 | n=85 older adults with generalized anxiety disorder | 80% Caucasian | Escitalopram | 5-HTTLPR,  rs25531 | Adverse events assessed by UKU Side Effects Rating Scale | No association between 5-HTTLPR genotype and increased need for sleep |
| Hougardy et al. 200854 | n=43 outpatients with various indications | Caucasian | Paroxetine | 5-HTTLPR | PFA (using collagen and epinephrine as agonists)  Spontaneous bleeding and bruising assessed by questionnaire | No significant association of 5-HTTLPR and PFA or spontaneous bleeding or bruising |
| Abdelmalik et al. 200855 | n=18 depressed outpatients | Not specified | Paroxetine | 5-HTTLPR,  rs25531 | Bleeding time, PFA-ADP, PFA-epinephrine | Greater changes in bleeding time and PFA (with epinephrine or ADP as agonists) in individuals with at least 1 low expression allele (LG or S) (all p<0.04) |

ADP = adenosine diphosphate; PFA = platelet function analyzer closure time; SSRI = selective serotonin reuptake inhibitor; UKU = Udvalg for Kliniske Undersøgelser.

Figure 1. Representation of theoretical consequence of *SLC6A4* polymorphisms in the setting of treatment with selective serotonin reuptake inhibitors (SSRIs). High expression genotypes, represented at left, result in higher serotonin transporter (5-HTT) density. Low expression genotypes, at right, have reduced 5-HTT density, and thus may result in greater increases in synaptic serotonin (5-HT) in the presence of the same SSRI dose. This excess 5-HT interacts with 5-HT receptors resulting in exaggerated serotonergic effects that manifest as adverse drug reactions.

Figure 2. Schematic of the literature search process.