Stevenson and Bishop, Clinic Pharmacol Biopharmaceut 2013, 2:2
DOI: 10.4172/2167-065X.1000109

Clinical Pharmacology & Biopharmaceutics

ISSN: 2167-065X

Research Article Open Access

Antidepressant Tolerability and Potential Clinical Implications of Serotonin-2A Receptor Genotypes

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Abstract

Despite the development of new therapeutic agents for the treatment of mood disorders, drug tolerability remains a major barrier to effective treatment for many patients. Pharmacogenomic studies aim to identify genetic markers that moderate drug response and tolerability, with the intention that this information will aid in drug selection and dosing. The serotonin-2A receptor gene (*HTR2A*) is one attractive candidate for pharmacogenomic studies of drugs for mood disorders. Numerous studies have examined associations between polymorphisms within this gene and efficacy and tolerability of drugs for mood disorders. Some of these variants are now being included in some commercially-available platforms with the intent of using them for therapeutic decision making. As these technologies become more widely utilized, clinicians will face decision about what this information means for patients and how/if to apply this information clinically. This review summarizes pharmacogenomic studies of *HTR2A* and tolerability outcomes in a number of adverse drug reaction domains.

Keywords: Antidepressant; SSRI; Tolerability; Adverse drug reaction; Side effects; HTR2A; 5HT2A; Polymorphism

Introduction

Since the introduction of monoamine oxidase inhibitors (MAOIs) in the 1950s, researchers have been searching for antidepressant agents with more favorable tolerability profiles. The introduction of selective serotonin reuptake inhibitors (SSRIs) in the late 1980s provided clinicians with a drug class featuring an improved tolerability profile as compared to MAOIs and tricyclic antidepressants (TCAs), as well as a much wider therapeutic index [1,2].

Despite these considerable advances, side effects from antidepressants greatly affect the treatment course for many patients. A recent study of depressed individuals treated with SSRIs indicated that more than half of the patients reported at least one bothersome side effect from therapy [3]. Approximately one quarter to one third of patients that discontinue antidepressants do so primarily because of side effects [3,4]. Early treatment discontinuation due to side effects is a major barrier to antidepressant therapy as these drugs take a number of weeks to manifest their full positive therapeutic effects [5,6]. And while many patients discontinue antidepressant therapy due to side effects, other patients are able to tolerate them without a need for altering therapy.

Interpatient variability in response to a given drug is a large challenge in psychiatry. Clinically-similar patients often experience vastly different outcomes from the same drug at similar doses. Pharmacogenomic investigations aim to identify how genetic variables may explain a proportion of this variability. It is envisioned that the use of this informationin the clinical setting will improve the likelihood of beneficial therapeutic effects while minimizing likelihood of adverse drug reactions (ADRs). Variants of cytochrome P450 genes have often been associated with abnormal drug concentrations and ADRs [7]. Genes directly or indirectly associated with a given drug's mechanism of action are also attractive candidates for pharmacogenetic studies [8].

The serotonin-2A receptor gene (*HTR2A*) is located on chromosome 13 and encodes the 5-HT2A receptor [9,10]. Activation of this receptor has been postulated to mediate some side effects from serotonergic antidepressants which may directly or indirectly increase signaling through this receptor [11]. Two common single-nucleotide polymorphisms (SNPs) of *HTR2A*, 102 T>C (rs6313) [12] and -1438 A>G (rs6311) [13] are attractive candidate polymorphisms for pharmacogenetic studies. These two SNPs are in almost complete linkage disequilibrium (LD): the T allele of 102 T>C is in almost complete LD with the A allele of -1438 A>G and vice versa for the C and G alleles [14]. The minor allele frequency for both SNPs is approximately 0.43 and allele frequencies do not greatly differ between European, African, and Asian ancestry [12,13]. Another frequently studied SNP, 452 His>Tyr (rs6314) has a much lower minor allele frequency of about 0.07and is more common in Africans than Europeans or Asians [15].

The 102 T>C variation does not result in any change to the encoded polypeptide, however, it may be associated with regulatory changes, perhaps due to its close proximity to the gene promoter or a methylation site [16-18]. The -1438 A>G polymorphism is also near the promoter region, which could influence gene expression. The 452 His>Tyr polymorphism alters amino acid sequence and is located in the C-terminal region of *HTR2A*.The substitution of tyrosine, which has a hydrophobic side chain, for histidine, with a positively-charged side chain, may affect receptor conformation and/or function of the gene's product, the 5-HT2A receptor.

Studies with positive findings have associated the 102C and -1438G variants with decreased 5-HT2A expression, and the 452Tyr variant with decreased intracellular signaling. A number of expression studies have failed to replicate these findings, a discrepancy that may be explained by sample size, patient/cell line used, expression assay, or influence from other polymorphisms [19,20]. A recent meta-analysis

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Received April 29, 2013; **Accepted** June 14, 2013; **Published** June 17, 2013

Citation: Stevenson JM, Bishop JR (2013) Antidepressant Tolerability and Potential Clinical Implications of Serotonin-2A Receptor Genotypes. Clinic Pharmacol Biopharmaceut 2: 109. doi:10.4172/2167-065X.1000109

showed a statistically significant association between the -1438 G/G (or 102 C/C) genotype and drug response during SSRI treatment (p=0.04, n=429) [21]. This finding did not hold when studies of non-SSRI antidepressants were included (p=0.69, n=1012).

The present review summarizes available literature on antidepressant tolerability as it relates to *HTR2A* genotype. As a consequence of a number of positive associations between tolerability/efficacy and *HTR2A* genotype, some commercially-available genotyping platforms now include *HTR2A* polymorphisms with the intention that clinical judgments regarding treatment selection, side effect risk, or likelihood of response may be made with this information. The authors intend for this concise review to assist clinicians in therapeutic decision-making as pharmacogenomic concepts become more prevalent in clinical practice.

Materials and Methods

To identify relevant studies for this review, the authors searched Medline/PubMed for original research publications available as of April 2013 regarding antidepressant tolerability and *HTR2A* genotype. This search was performed in a systematic fashion, using the terms 5HT2A, *HTR2A*, serotonin 2A, polymorphism, adverse, side effects, tolerability, discontinuation, tricyclic, TCA, amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, SSRI, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, vilazodone, SNRI, venlafaxine, duloxetine, mirtazapine, trazodone, MAOI, lithium, valproate, carbamazepine, oxcarbazepine, and lamotrigine in all logical iterations. Additional articles were identified by examining the reference lists from articles identified in the initial search. Studies were considered relevant for the present review if they described positive or negative findings in terms of differences in ADRs between genotype groups. If studies had overlapping patient populations, only the study with the larger number of participants was used.

Results

General tolerability

SSRI antidepressants increase synaptic serotonin, which interacts with pre- and post-synaptic serotonin receptors and may contribute to untoward serotonergic effects unrelated to mood [11,22]. A number of studies have reported on the incidence of side effects and/or study drug discontinuation as related the *HTR2A* genotype. Table 1 summarizes the studies included in this review. Potential mechanisms for *HTR2A* influence on specific ADR domains will be discussed.

Murphy et al. studied 246 depressed elderly subjects (age ≥ 65) randomized to treatment with paroxetine (n=124) or mirtazapine (n=122) [23]. The authors examined pharmacogenetic relationships with these two antidepressant treatments due to the differing mechanisms underlying antidepressant action. Paroxetine is a potent selective serotonin reuptake inhibitor, whereas mirtazapine increases noradrenergic and serotonergic transmission and antagonizes 5-HT2 and 5-HT3 receptors [24]. In this 8-week trial, survival analysis showed a strong association between paroxetine treatment discontinuation and the 102 C/C genotype group (n=41). Forty-six percent of paroxetine-treated patients with the C/C genotype dropped out of the study due to adverse events, compared to 16% of those with C/T or T/T genotypes (p=0.001). There were no significant differences between participants with C/C and those with other genotypes in terms of age, gender distribution, ethnicity, plasma drug concentrations, baseline cognition, or baseline depression severity. Furthermore, for paroxetine-treated patients, there was a positive linear relationship between number of C alleles and probability of discontinuation at all assessment points (all p<0.03). In contrast, survival analysis for mirtazapine-treated patients did not show any association between HTR2A genotype and discontinuation at any point in the study.

A second study examined fluvoxamine tolerability as related to *HTR2A*-1438 A>G in a Japanese Major Depressive Disorder (MDD) population (n=100) [25]. Survival analysis did not show a difference in onset rate for all side effects, nor was there a difference in the total number of side effects between genotype groups. There was no difference in incidence of study discontinuation between genotype groups. Of note, these authors assessed outcomes separately across *HTR2A*-1438 genotype groups (A/A, A/G, G/G). A trend was observed where patients with the G/G genotype had faster onset of side effects and at a lower dose, but these findings were not statistically significant.

The association of *HTR2A* genotype and SSRI tolerability may be more pronounced in elderly patients than the general population. The study by Suzuki et al. [25] with less compelling findings was not only in a younger study population, but also used fluvoxamine, which is a less potent SSRI than paroxetine. A study by Kato et al. [26] examined both paroxetine and fluvoxamine efficacy and ADRs as related to the *HTR2A*-1438 A>G polymorphism in a non-elderly study population of 100 Japanese patients with MDD randomized to either study drug. Paroxetine-treated subjects with the G/G genotype (n=10) had greater severity of ADRs (p=0.04). HTR2A genotype did not affect fluvoxamine tolerability. In the combined group of patients treated with paroxetine or fluoxetine, the G/G genotype had a numerically higher percentage of patients discontinuing due to side effects (16 vs. 8%), reporting severe nausea (20 vs. 6.7%), and reporting any side effect (52 vs. 34.7%), though these findings were not statistically significant.

Further evidence of an association between *HTR2A* and paroxetine ADRs comes from Wilkie et al. [27]. This study examined 166 patients with unipolar depression, many of whom were taking an antidepressant at baseline. First, investigators optimized the dose of their pre-enrollment antidepressant. Over half the participants were treated with SSRIs during this phase. *HTR2A* 102 T>C and 452 His>Tyr were not associated with ADR incidence (both p>0.5) during this initial dose optimization phase. Non-responders that were not initially treated with an SSRI were switched to paroxetine for the second phase of the trial. In these paroxetine-treated patients, the *HTR2A* 102 C/C genotype was associated with increased overall ADR incidence (17% vs. 0%, p=0.01). It should be noted that only four participants experienced ADRs with paroxetine; all of these participants had the C/C genotype. *HTR2A* 452 His>Tyr genotype was not associated with ADR incidence during paroxetine therapy.

Lanctot et al. [28] examined this association with citalopram response and tolerability in 90 subjects with depression secondary to traumatic brain injury. Subjects were genotyped for six candidate genes, including *HTR2A* -102 T>C and the serotonin transporter promoter polymorphism (5HTTLPR). The authors performed a backward stepwise linear regression for adverse event index; only 5HTTLPR significantly explained variability in the adverse event index.

A recent meta-analysis of pharmacogenetic markers for treatment response and side effects examined *HTR2A* among other serotonergic and neurotrophic candidate genes [21]. Pooling seven studies (n=801) resulted in a very significant association between the -1438 A>G G/G genotype and side effects (OR 1.91, 95% CI 1.32-2.78, p=0.0006).

Citation	n	Population/Diagnosis	Medications	Polymorphisms Studied	Results
Murphy et al. [21]	246	Elderly patients (≥ 65) with major depression	Paroxetine (n=124) or mirtazapine (n=122) with dose escalation protocol	*HTR2A* 102 T>C; *CYP2D6* was also genotyped	102 C allele associated with paroxetine discontinuation. No association for mirtazapine.
Suzuki et al. [23]	100	Japanese outpatients with depressive mood disorders (mostly MDD)	Fluvoxamine with dose escalation protocol	*HTR2A* -1438 A>G; also *HTR3A, HTR3B*, and *CYP2D6*	No association between *HTR2A* and side effect prevalence. -1438 G allele associated with GI ADRs.
Kato et al. [24]	100	Japanese patients with MDD	Paroxetine (n=51) or fluvoxamine (n=49) with dose escalation protocol	*HTRA2A* -1438 A>G; also 5HTTLPR, *HTR3A*, and *HTR3B*	-1438 G allele associated with paroxetine ADR severity. G/G genotype associated with paroxetine-induced nausea. Genotype not associated with fluvoxamine tolerability.
Wilkie et al. [25]	166	Caucasian patients with unipolar depression	Stepwise treatment algorithm with the largest proportion receiving paroxetine	*HTR2A* 102 T>C and 452 His>Tyr; also 5HTTLPR, *SLC6A4* intron 2, *HTR6*, *HTR1B*, and *HTR5A*	102 C/C genotype associated with paroxetine-induced ADRs. No association with 452 His>Tyr or for any other drugs.
Lanctot et al. [26]	90	Post-traumatic brain injury patients with a major depressive episode	Citalopram 20 mg/day fixed-dose	*HTR2A* 102 T>C; also *HTR1A, BDNF, TPH2*, and *MTHFR*	*HTR2A* not associated with ADRs
Yoshida et al. [31]	66	Japanese patients with MDD	Fluvoxamine with dose escalation protocol	*HTR2A* -1438 G>A; also *MAOA*	*HTR2A* not associated with nausea
Tanaka et al. [32]	72	Japanese patients with depressive disorder (n=57) or anxiety disorder (n=15)	Paroxetine with dose escalation protocol	*HTR2A* 102 T>C; also *HTR3A*, *HTR3B*, *CYP2D6*, and 5HTTLPR	*HTR2A* not associated with nausea
Bishop et al. [39]	89	Outpatients with depression	Citalopram, escitalopram, fluoxetine, paroxetine, or sertraline	*HTR2A* -1438 A>G; also *GNB3*	-1438 G/G genotype associated with sexual dysfunction
Perlis et al. [41]	1473	Caucasians with depression from the STAR*D study	Citalopram with dose-escalation protocol	*HTR2A* -452 His>Tyr, and three other *HTR2A* SNPs: rs2770296, rs594242, and rs1928040; also 64 other polymorphisms associated with serotonin, glutamate, dopamine, adrenergic receptors, neurotrophic systems, and antidepressant response	*HTR2A* not associated with sexual dysfunction
Liang et al. [42]	56	Drug-naïve patients with first episode MDD	SSRI (n=43) or venlafaxine (n=2)	*HTR2A* -1438 A>G	-1438 A/A genotype associated with sexual dysfunction
Perroud et al. [44]	796	Patients with MDD	Escitalopram or nortriptyline with flexible dosing	129 polymorphisms related to neurotrophic, serotonergic, and noradrenergic pathways	*HTR2A* polymorphisms not associated with worsening suicidal ideation
Serretti et al. [47]	169	Patients with bipolar disorder type I (n=103) or type II (n=66) with manic switch and 247 matched bipolar controls	A variety of antidepressants (SSRIs, TCAs, MAOIs)	*HTR2A* 102 T>C and -1420 C>T; also 5HTTLPR, *TPH, GNB3, MAOA, COMT, DRD2, DRD4*	*HTR2A* polymorphisms not associated with switching
Murata et al. [51]	56	Japanese patients with MDD (n=37) or anxiety disorder (n=18). One with pain disorder	Paroxetine with an abrupt discontinuation or dose reduction for any reason	*HTR2A*102 T>C and 452 His>Tyr; also *HTR1A, HTR2C, HTR3A, HTR3B*, 5HTTLPR, and *CYP2D6*	*HTR2A* polymorphisms not associated with paroxetine discontinuation syndrome

Table 1: Summary of studies reporting drug tolerability as related to *HTR2A* genotype.

When only SSRI-treated subjects were included, the association was even stronger (OR 2.33, 95% CI 1.53-3.56 p<0.0001).

Taken together, there appears to be an association between the *HTR2A* 102 C (or linked -1438 G) allele and general tolerability as examined by dropout rates, overall ADR incidence, and/or ADR severity in SSRI-treated patients with depression. This finding is only seen in SSRIs based on current literature, and is most evident in patients treated with paroxetine. Chronic administration of SSRIs is associated with 5-HT2A down regulation in animal models [29]. Mechanistically, individuals with lower baseline expression of 5-HT2A due to *HTR2A* variants may be more prone to exaggerated effects from antidepressant therapy leading to higher odds of experiencing ADRs.

Gastrointestinal ADRs

A number of gastrointestinal (GI) ADRs are commonly reported with antidepressant use, including nausea, diarrhea, and constipation. These ADRs occur at incidence rates of about 20, 15, and 5%, respectively [1] and are thought to be related to serotonin signaling. Serotonin signaling plays a role in gut motility through 5-HT2A receptors expressed on peripheral smooth muscle [30]. Administration of the 5-HT3 receptor antagonist ondansetron attenuates SSRI-associated nausea [31], providing further evidence of a serotonergic mechanism for at least some SSRI-induced GI ADRs. To reconcile this finding with the current studies of variation in *HTR2A*, serotonin binding to the post-synaptic 5-HTR3 receptor results in depolarization of the postsynaptic membrane, presumably affecting 5-HT2A activation [32].

Four studies specifically reported on GI ADRs as related to *HTR2A* genotype. Yoshida et al. examined incidence of fluvoxamine-induced nausea in respect to *HTR2A*-1438 G>A genotype [33]. Sixty-six Japanese patients with MDD were treated with fluvoxamine for six weeks. Sixteen patients experienced nausea during the study. There was no difference in genotype distribution or allele frequency in participants that experienced nausea versus those who did not.

Tanaka et al. [34] used a similar methodology to evaluate the incidence of paroxetine-induced nausea as related to a number of serotonergic and metabolism related polymorphisms in 72 Japanese patients with depression or anxiety. Twenty-one (29%) subjects experienced nausea, leading to treatment discontinuation in two. The *HTR2A* 102 T>C genotype distribution was not different between those experiencing nausea and those who did not.

Previously described studies by Suzuki et al. and Kato et al. also commented specifically on GI ADRs [25,26]. In the Suzuki et al study of fluvoxamine-induced ADRs, 53 subjects reported GI ADRs. The number of *HTR2A*-1438G alleles was associated with risk for GI ADRs in a Cox regression analysis. In the Kato et al study of paroxetine or fluvoxamine-treated patients with depression, the *HTR2A*-1438 G/G genotype was associated with greater severity of nausea in paroxetine-treated patients (p=0.01). There was no difference between genotypes in fluvoxamine-treated patients. The recent meta-analysis by Kato and Serretti [21] examined GI ADRs in four studies of SSRI-treated patients and found a strong association in the same direction (OR 2.3, 95% CI 1.26-4.21, p=0.007).

Though less robustly studied than general tolerability, a similar trend was observed when focusing on GI ADRs. The two largest studies reporting antidepressant-induced GI ADRs did report some positive findings, though two smaller studies failed to replicate this finding. In positive studies, the lower-expressing -1438G and 102C alleles were associated with ADRs.

Sexual ADRs

Animal studies have associated serotonin agonism at 5-HT2A and decreased sexual arousal and ejaculation [35]. Additional evidence for the involvement of 5-HT2A receptors in sexual side effects comes from human drug studies that have identifieda lower rate of sexual ADRs with 5-HT2A antagonist antidepressants such as nefazodone [36] and mirtazapine [37]. Furthermore, pharmacologic 5-HT2A antagonism attenuates SSRI-induced sexual dysfunction [38-40].

Bishop et al. studied *HTR2A* and sexual side effects as measured with the Changes in Sexual Function Questionnaire (CSFQ) during antidepressant therapy as a primary outcome [41,42]. The initial study sample examined SSRI-associated sexual dysfunction in 81 outpatients treated with citalopram, escitalopram, fluoxetine, paroxetine, or sertraline. Sexual dysfunction was reported in 35% of females and 18% of males. In this study, the *HTR2A*-1438 G/G genotype (n=21) was associated with sexual dysfunction, both in unadjusted analyses and when controlling for age, gender, and anxiety/depression scores. However, the G allele alone was not associated with sexual dysfunction. Women with the G/G genotype had significantly lower scores in arousal and desire/frequency subscores of the rating tool; this association was not significant in males. A follow-up paper by the same research group indicated that use of oral contraceptives may be a strong effect mediator of the *HTR2A*/sexual ADR association [41].

Perlis et al. [43] examined genetic and clinical predictors of sexual dysfunction in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. The phenotype used in this study was comprised of three items from the Patient-Rated Inventory of Side Effects (PRISE) concerning erectile function, libido, and orgasm. *HTR2A* 452 His>Tyr genotypewas examined, as well as three additional *HTR2A* SNPs: rs2770296, rs594242 and rs1928040. *HTR2A*-1438 G/A was not examined, but is in strong LD with rs1928040. None of the SNPs was associated with sexual dysfunction in this study, either in the cohort as a whole or stratified by gender.

Liang et al. [44] investigated sexual dysfunction via the Arizona Sexual Experience Scale (ASEX) - Chinese version, in previously drug-naive male patients with depression who were beginning therapy with an SSRI (fluoxetine, paroxetine, sertraline, escitalopram n=43) or SNRI (venlafaxine n=2). Sixteen of the 45 subjects experienced sexual dysfunction after drug initiation. The *HTR2A*-1438 A/A genotype was significantly associated with sexual dysfunction. Additionally, G-allele carriers were less likely to experience sexual dysfunction. The authors also note that the sexual dysfunction group had higher mean baseline Hamilton Depression Rating Scale (HAM-D) scores.

Sexual ADRs is the only ADR domain with conflicting positive studies. Explanations for these discordant findings are not easily discernible. For one, there may be a gender effect, as Liang et al. [44] exclusively studied male sexual dysfunction and Bishop et al. [41] mostly observed sexual ADRs in women. Bishop and Liang excluded patients over 40 and 30 years of age, respectively, while the mean age was 41 in Perlis's study. In addition, Bishop et al. used the CSFQ, Liang et al. used the ASEX, and Perlis et al. used a less-robust phenotype of 3 items on a broad side effect questionnaire. Another consideration is that the ethnicity of participants differed between studies, with Bishop et al. and Perlis et al. studying primarily Caucasians and Liang et al. recruiting from a hospital in Taiwan. Conflicting results in subjects with different ethnicities has been observed in *HTR2A*/treatment response studies and may thus be a variable for further investigation in tolerability studies as well [21].

Neuropsychiatric ADRs

A number of studies have examined the potential for an association between HTR2A polymorphisms and suicidality with conflicting results. A review by Serretti summarizes the various lines of conflicting evidence for association with *HTR2A* [20]. A recent meta-analysis of 73 studies showed largely negative measures of association between *HTR2A* genotype and suicidality [45], though this analysis was not specific to suicidality during antidepressant therapy. One study examined increased suicidal ideation during antidepressant treatment [46]. Subjects in the Genome-based Therapeutic Drugs for Depression (GENDEP) study were treated with flexible-dose escitalopram or nortriptyline for 12 weeks. 727 subjects were included in genetic analyses. Of these, 236 had increases in suicidal ideation (a composite score of items on the HAM-D, Beck Depression Inventory, and Montgomery-Asberg Depression Rating Scale), while 491 did not. The authors examined 123 polymorphisms in 9 neurotrophic, serotonergic, and noradrenergic pathways for association with increased suicidal ideation. *HTR2A* polymorphisms were only examined in escitalopram-treated subjects as part of the *a priori* analysis plan due to the drug's mechanism of action. None of the investigated serotonergic gene polymorphisms, including those in HTR2A, was associated with increased suicidality.

Serotonin system genes may predispose individuals to antidepressant-induced mania. The serotonin transporter 5HTTLPR is the most frequently studied polymorphism for this ADR. Two recent meta-analyses examined this association [47,48] while the role of *HTR2A* remains less defined. Serretti et al. [49] examined eight candidate genes in relation to antidepressant-induced mania or hypomania in bipolar disorder in a case-control fashion. Cases (n=169) were defined as bipolar I or bipolar II individuals who presented with at least one acute manic or hypomanic episode within 3 weeks of starting antidepressant therapy, with no interposed euthymic period ("switching"). Controls (n=247) were matched on sex, age, and ethnicity and had a diagnosis of bipolar disorder without a history of

switches. *HTR2A* 102 T>C and *HTR2A*-1420 C>T were not associated with switching in unadjusted analyses or after correcting for potential clinical confounders like mood polarity of onset episode, presence of psychotic features, age, and number of previous manic episodes.

The abrupt cessation of SSRI therapy is known to induce discontinuation symptoms in some patients [50]. The severity and occurrence of these discontinuation symptoms appears to differ based on characteristics of the withdrawn medication [51] whereby potent agents with short half-lives such as paroxetine tend to be associated with more significant discontinuation symptoms [52]. Murata et al. [53] examined whether serotonin- or drug metabolism-related polymorphisms influence the incidence and severity of paroxetine discontinuation syndrome. The study population consisted of 56 Japanese patients with diagnoses of MDD or anxiety disorder that were treated with paroxetine for 8 weeks or longer. Participants then had a dose reduction under the direction of a psychiatrist, or abruptly discontinued the drug themselves for psychosocial reasons. Participants were interviewed directly about a number of symptoms that could be associated with paroxetine discontinuation; those expressing at least one new symptom within 7 days of medication reduction/discontinuation were identified as having discontinuation syndrome. Patients were genotyped for the *HTR2A* 102 T>C and 452 His>Tyr polymorphisms. Of the 56 patients, 20 (36%) experienced as least one symptom of paroxetine discontinuation syndrome. The most common symptoms were dizziness, vivid dreams, fatigue, nausea/vomiting, headache, and anxiety. There was no difference between cases in controls in genotype distribution of either *HTR2A* polymorphism. Of note, all cases and controls were 452 His/His.

Limitations of Current Literature

There are a number of limitations to the available literature on *HTR2A* and ADRs. Most studies have focused on two SSRIs, fluvoxamine and paroxetine. It is possible that specific antidepressant agents may modify the *HTR2A*/ADR relationship. For example, Kato et al. [26] identified an association between *HTR2A* and tolerability in patients treated with paroxetine but not fluvoxamine. This nuance of the data makes it difficult to apply findings to other SSRIs or antidepressants of other classes. Furthermore, there were very few studies of non-SRRI antidepressants, and no *HTR2A* studies concerning tolerability for mood stabilizers found in our search.

Additionally, studies were performed primarily in Caucasian and Asian populations. As discordant results between ethnicities have been shown in other genetic studies, this may limit the applicability of current findings to a broader patient population [21]. Other polymorphisms associated with antidepressant tolerability, such as 5HTTLPR [21], were not controlled for in many of the studies summarized in our review, which may also confound the results.

Summary

In summary, there is mounting evidence that *HTR2A* genotype may play a role in the tolerability of SSRI antidepressants. The direction of the finding is mostly consistent, in which patients with the -1438 G or 102 C variant alleles experience greater side effect burden or incidence of events. The magnitude of effect appears clinically relevant, with a recent meta-analysis indicating about twice the odds of side effects for the -1438 G/G genotype [21]. There are insufficient studies addressing 452 His>Tyr. The minor allele frequency for this polymorphism complicates research efforts, though it is plausible that it could influence side effect burden, given studies linking this variant to lower activity, like -1438 A/G and 102 T/C [20].

The strongest and largest body of data supporting the association of *HTR2A* and tolerability comes from studies that examined broad outcomes such as study discontinuation or general occurrence of side effects. Studies of specific side effects are mixed. In studies of GI ADRs, many positive findings were identified with the -1438G or 102C carriers at increased risk for adverse outcomes. While studies of sexual ADRs identified positive associations with genotypes, the direction of association is conflicting. Studies of neuropsychiatric ADRs were negative.

As genetic information becomes commonplace in clinical practice, opportunities will arise to combine clinical and genetic factors to optimize drug selection and dose titration. Based on the findings of this review, practitioners with the benefit of *HTR2A* genetic data available for their patients may consider *HTR2A* genotype, with the most data to support relationships with lower tolerability to paroxetine-associated ADRs in those who are -1438G or 102C allele carriers. Whether prospectively testing patients for these variants decreases the time needed to identify a tolerable treatment and improve quality of life and broad clinical outcomes has not been explicitly tested. Thus while the findings summarized herein are scientifically interesting and appear to represent clinically relevant effect sizes, we must interpret these findings with caution and more explicitly identify how and when to provide genetic analyses in clinical environments. Additionally requiring formal testing is the hypothesis that patients that are historically sensitive to side effects with low-expression *HTR2A* variants may benefit from non-SSRI therapies. In the coming decade, we hope to see prospective data validating a genotype-informed approach to drug selection and titration in mood disorders.

Sources of Support

K08MH083888 (Bishop).

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