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Review Article

Genotype-Related Efficacy and Side Effects of Selective Serotonin Reuptake Inhibitors in Patients with Major Depressive Disorder

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Abstract

Major depressive disorder (MDD) is a major health condition that is amongst the foremost prevailing psychological state disorders worldwide and is extremely perennial and is the fourth foremost cause of disease burden. Despite the common mechanism of action, the drugs from within the same class exhibit variations, reportedly 60-70% of patients do not experience remission, and 30-40% of patients lack adequate response to drug therapy, resulting in non-adherence or discontinuation of therapy and prolongation of disease course. The variability of drug response is believed to be due to an individual's variation in drug metabolism at the genetic level. This review accentuates the *CYP450* enzymes (*CYP2C19*, *CYP2B6*, and *CYP2D6*), their single nucleotide polymorphism (SNPs), and their association with the antidepressants (selective serotonin reuptake inhibitors) efficacy or adverse effects.

Keywords: Major depressive disorder, selective serotonin reuptake inhibitors, single nucleotide polymorphisms, efficacy, adverse effects.

Introduction

MDD is amongst the foremost prevailing psychological state disorders worldwide and is extremely perennial and is the fourth foremost cause of disease burden, expectedly to increase in tendency over the coming decades (Kupferberg, Bicks, and Hasler 2016, Organization 2001). The disease is associated with significant personal and socioeconomic morbidity, with markedly losing functions and increased dependence on service providers concerning workload (Middleton et al. 2005). Major depressive illness is characterized by persistent low moods and loss of interest, accompanied by physical symptoms like weight loss, sleep deprivation, lack of agility, delinquency, and suicidal thoughts in extreme cases (Bell 1994). However, some people also exhibit unusual reactive mood elevation, increased appetite and weight, and excessive sleepiness (Quitkin et al. 1991). Physical symptoms are also not infrequent, and people with severe depressive episodes may develop psychosis (Bell 1994). According to guidelines by the American Psychiatric Association (APA) and the Canadian Network for Mood and Anxiety Treatments (CANMAT), treatment modalities include selective serotonin reuptake inhibitors (SSRIs) as the first-line treatment (Gelenberg et al. 2010, Kennedy et al. 2016). SSRIs such as citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline are the most effective drugs widely being used in the pharmacological management of depression (Marken and Munro 2000). SSRIs are generally well-tolerated, for

example, sertraline is one of the highly efficacious and tolerable agents in this class (Cipriani et al. 2018). The efficacy and safety of these drugs depend on numerous factors, particularly changes in pharmacokinetics that can affect drug metabolism, huge alterations may consequently reduce efficacy or increase adverse effects in the body. Pharmacokinetics of SSRIs also depends on age, sex, body weight, pathophysiological hepatic and renal status, and surgical interventions that may affect absorption, such as gastric bypass (De Vane, Liston, and Markowitz 2002, Edwards and Ensom 2012). Inter-individual variations in drug responses can be explained by pharmacogenetics. The major hepatic enzyme family cytochrome P450 (*CYP450*) plays an important role in oxidative biotransformation and is also involved in the clearance of the majority of SSRIs (Hamdy et al. 2002). *CYP2D6* and *CYP2C19* are the two *CYP450* enzymes that metabolize antidepressants and antipsychotic drugs and are tremendously polymorphic. Genetic variation in the genes of the enzymes results in altered enzymatic activity and hence may demonstrate individual variation in treatment responses as well (Zanger and Schwab 2013, Ingelman-Sundberg 2005). A comprehensive genome-wide association study by Hyed et al. (2016) including 130,620 MDD samples, and 347,620 control samples was the first to identify and report SNP locus associated with MDD (Hyde et al. 2016). In a systematic review of 132 randomized controlled trials (RTCs) comparing fluoxetine with other antidepressants, both dichotomous and continuous outcomes collated that sertraline and venlafaxine were more effective than fluoxetine (Magni et al. 2013).

Epidemiology of Depression

Depression is found to be 20% incidence as a lifelong disorder, with a female to male ratio of about 5:2 throughout the world. Presumably, one-third of the affected population is under treatment, merely not due to negligence, but due to symptoms that are not indistinctive from the routine experience. The disease is predominantly recurrent; however, patients recover from MDD episodes mostly [17]. Nonetheless, the disease is chronic in a considerable proportion of patients, with prospective follow-up of 5 and 10 years, 12% and 17% are found depressed respectively (Keller, Hirschfeld, and Hanks 1997). Despite the recovery from MDD, about 75% of patients may present a recurrent episode within 10 years (Angst 1992, Lavori et al. 1994). The risk of mortality in depression is substantially due to suicide, which has a higher incidence between the age of 15 and 24 years (Wong and Licinio 2001). Evidence demonstrates a vital relationship between depression and cardiovascular illness, alongside expanded mortality rates. Some studies have illustrated that depression can enhance the predisposition to cardiovascular disorders, especially coronary artery disease, and declines the treatment forecast after myocardial infarction (Musselman, Evans, and Nemeroff 1998). The prevalence is 2-21% with a higher incidence in Europe and the lowest in Asia (Gutiérrez-Rojas et al. 2020). The disease is multifactorial and 35% of the patients are believed to acquire it inherently (Otte et al. 2016). The incidence is also two to three times higher in women than men and is associated with age and comorbidities as well (Luo et al. 2019). Therapeutic approaches, like antidepressants, are at hand though outcomes are suboptimal given roughly inadequate response in about 50% of patients(Thom, Silbersweig, and Boland 2019). According to the statistical data of the World Health Organization (WHO), Depression is designated to be the fourth leading cause of disability, and the prevalence

is estimated to transit to the second by the year 2020 (Murray and Lopez 1996, Murray, Lopez, and Organization 1996). In a study with a response rate of 90%, 142 students of a public sector medical college in Karachi were measured on an anxiety and depression scale, the disease prevalence was found to be 70% in the interviewed candidates (Khan et al. 2006). Another study manifested a high incidence of depressive and generalized anxiety disorders in patients with cardiovascular events in Pakistan. The socio-economic factors such as females, single parents, widows, and financial crisis are major risk factors for developing depression and anxiety in the population (Dogar et al. 2008). Similarly, cancer patients are also on the verge of experiencing depressive illness and/or anxiety to the underpinning pathology in the body, concluded to a study in the cancer out-patient department of a tertiary care hospital in Pakistan (Dogar et al. 2010).

Pathophysiology of MDD

MDD is a recurrent psychiatric disease with prominent morbidity and mortality. Regardless of rigorous research during the past few decades, the neurobiological and pathophysiological basis of depressive illness are obscure. As suggested by family, twin, and adoption studies, genetic factors play crucial roles in the occurrence of MDD, and some of the important pathophysiological mechanisms are revealed. The Association between genetic variation and increased risk of depression has not been yet identified. Genetic variation is thought to be less influential in disease occurrence, however, multiple genetic and environmental factors are likely necessary for the development the MDD. Large-scale studies are required to explain the complex phenotypic etiology of MDD. The disease is attributed to occur from interactions among dysfunctional neurotransmitters. The disease is also caused by social-economic and genetic vulnerabilities(Kupferberg, Bicks, and Hasler 2016), consequences are long-term alterations in neurological functions (Lohoff 2010). Neuroimaging and tissue studies have shown synaptic and structural changes in the brain, especially the frontal cortex and hippocampus in MDD patients(Villanueva 2013). Abnormality or dysfunction of the hypothalamic-pituitary-adrenal axis (HPA axis) is reported to be a stronger neurobiological event in MDD. Moreover, such patients exhibit increased levels of circulating pro-inflammatory cytokines, e.g., interleukin -1 (IL-1), interleukin -6 (IL-6), and tumor necrosis factor-alpha (TNF-α) described in figure 1. (Holsen et al. 2013).

Antidepressants (SSRIs) and their indications

SSRIs are the clinically most prescribed drugs in the management of depressive disorders. The United States stands at the top in dispensing 232.7 million antidepressants in 2007 (Thomas and Ellingrod 2009). The efficacy of SSRIs has been proved by several double-blind, placebo-controlled trials for the treatment of depression. Moreover, SSRIs are also been proven effective in the treatment of anxiety, obsessive-compulsive disorder (OCD), and panic disorder (Schatzberg 2000). The mechanism of action of SSRIs is described in figure 2. The first SSRI agent to be approved by FDA for the treatment of depressive disorders was Fluoxetine, particularly for patients of age 65 years and above. (Ables and Baughman III 2003). Fluoxetine also finds its clinical indication in the late luteal dysphoric disorder or premenstrual dysphoric disorder (PMDD) (Steiner et al. 1995). Sertraline, another remarkable SSRI is used in treating post-traumatic stress disorder (PTSD) (Brady et al. 2000, Davidson et al. 2001). Sertraline is also found to ameliorate the quality of life scores in

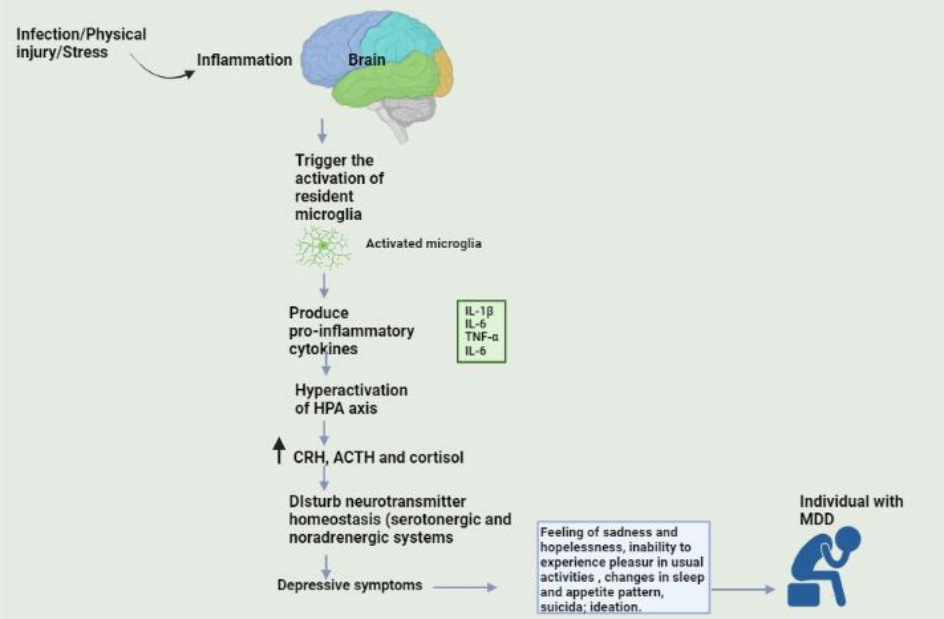

Figure 1. Pathophysiology of MDD. CRH= corticotrophin-releasing hormone, ACTH= adrenocorticotrophin hormone.

psychological and behavioral symptoms in patients with the premenstrual dysphoric disorder (Yonkers et al. 1997, Shah et al. 2008). In 2001, FDA approved Paroxetine in the treatment of social phobia and generalized anxiety disorder (GAD). Escitalopram, the active form of citalopram, is the newest and highly selective SSRI approved by the FDA for the treatment of depression (Ables and Baughman III 2003).

Adverse Effects of Antidepressants (SSRIs)

SSRIs have shown frequent adverse events in a younger population than in adults, about 5% to 32% of children reported experiencing adverse events when administered SSRIs. (Rynn et al. 2015). The span of adverse effects is also unique in children and is more prone to activation (Cipriani et al. 2016). The common adverse drug reactions (ADRs) occurring from SSRIs are gastrointestinal disorders i.e. constipation, diarrhea, nausea and vomiting, somnolence, sexual dysfunction, and cardiac arrhythmia (QT prolongation and torse de pointes (Westenberg and Sandner 2006). Agitation, insomnia, and neuromuscular dysfunction are common with the use of fluoxetine, probably caused by the relative lack of selectivity of fluoxetine over norepinephrine and serotonin-2C receptors (5-HT2c) (Stahl 1998). These side effects are temporary and dose-related, mitigated by dose reduction or administration of beta-adrenergic blocker or long-acting benzodiazepine (Rosenbaum et al. 2007). In a comparison of side effects, sertraline causes diarrhea more than fluoxetine, but cases of anxiety and insomnia are uncommon. Although sertraline inhibits the *CYP2D6* enzyme at a high dose, however, clinically significant drug interactions are not usual (Ables and Baughman III 2003). Paroxetine has indistinctive side effects to that of other SSRIs, however, exerts a more sedative and constipating effect due to anti-cholinergic activity (Rosenbaum et al. 2007). Citalopram causes transient nausea and is believed to be a lesser cause of insomnia, and anxiety (Mendels, Kiev, and Fabre 1999).

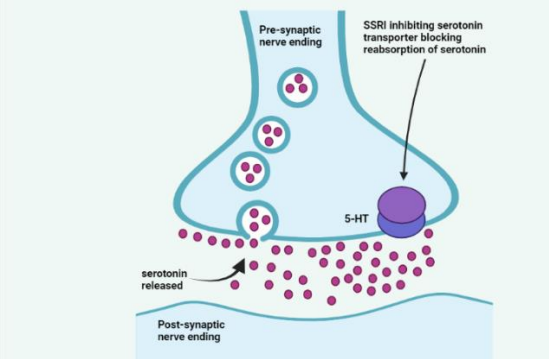

Figure 2. Mechanism of action of SSRIs. These agents inhibit serotonin transporter, causing the blockade of reuptake of serotonin into the neuron, increasing its availability at the receptors and potentiating the serotonergic activity.

Pharmacogenetics

Pharmacogenetics studies the genetic basis of an individual's ability to respond to pharmacotherapy. The variability of this response is a major problem (Steimer et al. 2001). Antidepressant drugs have been a key component in the management of depressive disorders including MDD. However, the efficacy of drugs from the same class is quite variable, reportedly 60-70% of patients do not experience remission, and 30-40of % of patients lack adequate response to drug therapy, resulting in non-adherence or discontinuation of therapy and prolongation of disease course (Ng et al. 2013, Trivedi et al. 2006). Variation in drug response is certainly due to an individual's variability in the drug metabolism (Wilkinson 2005). Large inter-individual changes in treatment outcomes and side effects are not uncommon with antidepressants. The clinical response at recommended doses also varies from a range of good effects to no effect or even worsening of disease course with a higher incidence of adverse effects. Even though a few variables, such as age, sex, body fat, admissions, and nicotine utilization, account for the patient-to-patient differences, there is increasing evidence that genetic variables underline the differences in psychopharmacological drug response(Catalano 1999, Smith and Mendoza 1996). Therefore, the concept of pharmacogenetics as originally defined by Vogel 1959, states heritable differences in metabolic activities of exogenous agents may help to reveal the change in drug response and its pharmacokinetics (Vogel 1959). The genetic polymorphisms of cytochrome P450 families have been studied as a treatment response predictor for antidepressants (Hodgson et al. 2014). In addition to the synthesis and metabolism of various endogenous substances, cytochrome P450 (*CYP450*) is a superfamily of phase-1 enzymes involved in the metabolism of the majority of drugs used clinically (Scott et al. 2012). Despite the familiarity with more than 50 isoenzymes, those mainly involved in antidepressant metabolism and investigated by pharmacogenetics studies are *CYP2C19*, *CYP2D6*, *CYP2B6*, and *CYP2C9*. Due to the high susceptibility of polymorphism in the genes coding for these isoenzymes, the alleles may exhibit defects and alter the metabolic processes partially or wholly (Porcelli et al. 2011). These enzymes are involved in the metabolism of a wide range of therapeutic agents, and polymorphism in their genes causes variable enzymatic processes, consequently leading to inter-individual variation in drug efficacy and adversity (Hamdy et al. 2002). The association of pharmacogenetic markers with Antidepressants (SSRIs) effect are described below in table 1.

Table 1. Association of pharmacogenetic markers with Antidepressants (SSRIs) effect.

Year	N	Ethnicity	SNP	Gene	Medication	Outcome measure	Association	Ref.
2016	50	Asian (Turkish)	rs11188072	*CYP2C19**17	Sertraline	Plasma concentrations of SERT and DSERT	No association	(Yuce-Artun et al. 2016)
2016	50	Asian	rs3745274	*CYP2B6*6*	Sertraline	Serum levels of SERT and DSERT	Significant association	(Yuce-Artun et al. 2016)
2016	50	Asian	rs 3745274	*CYP2B6*9*	Sertraline	Serum levels of SERT and DSERT	Significant association	(Yuce-Artun et al. 2016)
2014	290	Asian (Chinese)	rs4986894	*CYP2C19*	SSRIs	50% reduction in HAMD-17 score	No association	(Zhang et al. 2014)
2014	290	Asian	rs1080983	*CYP2D6*	SSRIs	50% reduction in HAMD-17 score	No association	(Zhang et al. 2014)
2014	290	Asian	rs12767583	*CYP2C19*	SSRIs	50% reduction in HAMD-17 score	No association	(Zhang et al. 2014)
2019	150	Caucasian	rs12248560	*CYP2C19**17	Ads	Change CES-D score and MDE	Significant association	(Kanders et al. 2020)
2018	2,087	Caucasian	rs4244285, rs4986893, rs28399504	*CYP2C19**2, *3*,*4	Escitalopram	Escitalopram serum concentrations	Significant association	(Jukić et al. 2018)
2018	2,087	Caucasian	rs12248560	*CYP2C19*17*	Escitalopram	Escitalopram serum concentrations	Significant association	(Jukić et al. 2018)
2018	45	Caucasian	rs3892097	*CYP2D6*4*	Fluvoxamine	SoPA, PACS, VAS, HAM-D, BDI, UKU	Significant association	(Zastrozhin et al. 2018)

CYP450 enzymes (*CYP2C19, CYP2D6, CYP2B6)* SNPs identified and their association with the efficacy and/or adverse effects of SSRIs

CYP2C19

CYP2C19 is an important enzyme from the family of *CYP450*, causing the metabolism of about one-tenth of all clinically indicated drugs including antidepressants, anticonvulsants, proton pump inhibitors, antipsychotics, and antiplatelet drugs (Scott et al. 2012). Inter-individual genetic variations of these enzymatic processes are likely to cause a lack of response or an increase in adverse drug reactions. Based on the intensity of enzymatic activity, the population can be divided into extensive metabolizers (EM) for normal people, and poor metabolizers (PM) for individuals with reduced functions (Ahmed et al. 2021). Among a dozen alleles reported to be reducing the enzyme activity of *CYP2C19*, seven of them produce inactive enzymes. The *CYP2C19* gene consists of nine exons and eight introns located at the locus 10q24.1 to 10q24.3 of chromosome no. 10, having coding sequence 1,473 bp which results in a protein containing 490 amino acid residues. Around 25 genetic variants in the exonic region of the *CYP2C19* have been identified so far, of which the common variants are associated with alteration in drug metabolism, where the presence of the 681 G>A, 636 G>A and 806 C>T polymorphisms result in the *CYP2C19**2, *CYP2C19**3, and *CYP2C19**17 alleles, respectively (Chaudhry, Kochhar, and Kohli 2008, Yin and Miyata 2011). The transition from guanine (G) TO adenine (A) at position 681 in exon 5 (rs4244285) results in variant *CYP2C19**2, causing frequent defects in all populations (Buzoianu et al. 2010). *CYP2C19**2 and *CYP2C19**3 are the most common alleles, encoding enzymes with decreased activity (Beitelshees et al. 2011). *CYP2C19**3(636G>A; rs4986893) is considered the most important allele, in which a point mutation in exon 4 results in a premature stop codon, and therefore nonfunctional protein (Hamdy et al. 2002, Yin and Miyata 2011). The *CYP2C19**17 (rs12248560) is a -806 C>T single nucleotide polymorphism that may cause specific nuclear protein binding to the 5'-flanking region. Subsequently this binding increases gene transcription and enhanced enzymatic activity (Sim et al. 2006).

The ethnic pharmacogenetics reveals that the occurrence of the *CYP2C19* poor metabolizers (PM) phenotype is 2-5% among Caucasians Africansican, and approximately 15% in Asians (Scott et al. 2011), while *CYP2C19**3 is solely believed to be an Asian mutation (Hamdy et al. 2002). *CYP2C19**2 and *3 alleles have been proposed to explain 90%, of the PM phenotype(Wang et al. 2011). Scott et al concluded in their study that ethnical variation shows higher frequencies of these two alleles in the Asian population at 15% compared to Caucasian and African people at 2-5% The *CYP2C19**2 polymorphism was found to be 29% in prevalence in the Pakistani population (Riaz et al. 2019). *CYP2C19**3 is rarely present in the Caucasian population and is therefore considered exclusive to the Asian population (Hamdy et al. 2002).

The polymorphism in *CYP2C19* had been reported to be associated with depressive symptoms by Sarah et al. (2010) (Sim et al. 2010). Yuce-Artun et al. (2016) also studied that genetic polymorphisms in *CYP2C19* can affect the metabolism of sertraline (SSRI) and its therapeutic outcomes (Yuce-Artun et al. 2016). Moreover, the *CYP2C19* genotype influences the risk for toxicity in patients taking sertraline, citalopram, and escitalopram (Hicks et al. 2017). A Retrospective Study Based on 2,087 patients showed that the *CYP2C19* genotype has a significant effect on the therapeutic response of escitalopram, as assessed by the shift of therapeutic agent (Jukić et al. 2018).

CYP2D6

Some members of CYP families, such as *CYP2D6*, are normal, intermediate, and poor metabolizers because single nucleotide polymorphisms can result in arrest, decrease or increase in enzymatic activity and may have four phenotypes in individuals, including ultra-

rapid metabolizers (Laika et al. 2009). The studies that have been conducted previously have found that the polymorphisms of *CYP2D6* are one of the reasons that cause variation in antidepressant effects in patients with MDD, among which include *CYP2D6* P34S (rs1065852). However, according to our understanding *CYP2D6* may cause a very limited effect on antidepressant efficacy (Zhou 2009), and mixed results have been found from the available accessible studies. Some studies give positive findings which show there is an association between *CYP2D6* polymorphism and antidepressant response. For instance, Zastrozhin et al. conducted a study on 45 male patients with MDD with comorbid alcohol use disorder and the results of the study show a significantly reduced efficacy and safety profile of fluvoxamine (Zastrozhin et al. 2018, Torrellas, Carril, and Cacabelos 2017, Han et al. 2013). Along with positive findings, some studies reported negative findings as well (Ng et al. 2013, Hodgson et al. 2014, Taranu et al. 2017). For example, a study conducted by Hodgson et al. shows that there was no significant association between *CYP2D6* polymorphisms and antidepressant response by analyzing the data from GENDEP (Hodgson et al. 2014).

CYP2B6

The human *CYP2B6* gene consists of two known loci, the one is functionally active referred to as *CYP2B6* and the other is its non-functional/inactive pseudogene *CYP2B7* (Hoffman, Nelson, and Keeney 2001, Miles et al. 1990, Yamano et al. 1989). *CYP2B6* enzyme plays a role in the metabolic activation and inactivation of various molecule inhibitors that include anticancer drug molecules (Chang et al. 1993, Granvil et al. 1999, Roy et al. 1999) and also antidepressant drugs (Faucette et al. 2000, Hesse et al. 2000). There are various important genetic variants of highly polymorphic *CYP2B6* gene have been identified to this date that including *CYP2B6**2 (C64T; rs4244285), *CYP2B6**3 (C777), *CYP2B6**4 (A785G; rs2279343), *CYP2B6**5 (C1459T), *CYP2B6**6 (G516T and A785G), *CYP2B6**7 (G516T, A785G, and C1459T), *CYP2B6**8 (A415G), and *9 (G516T; rs3745274) (Lamba et al. 2003, Lang et al. 2001, Zanger and Klein 2013). A study was conducted on 50 Turkish patients with MDD to investigate the effect of genetic polymorphisms of *CYP2B6* (*CYP2B6*6* and *CYP2B6*9*) on the plasma concentrations of sertraline and its metabolite N-desmethyl sertraline (DSERT) in patients with MDD and their findings reveal that genetic polymorphisms in *6 and *9 significantly decrease the effect of sertraline metabolism in patients with MDD. Furthermore, in that study, they also investigated the effects of genetic polymorphisms of *CYP2C19* (*2 and *17) and their findings show that genetic polymorphisms in *2 and *17 do not significantly impact sertraline metabolism (Yuce-Artun et al. 2016).

Conclusions

The antidepressant class of drugs called SSRIs is an essential component in the treatment of MDD. SSRIs inhibit serotonin transporter, causing the blockade of reuptake of serotonin molecule into the neuron, increasing its availability at the receptors and potentiating the serotonergic activity. Despite the common mechanism of action, the drugs from within the same class exhibit variations, reportedly 60-70% of patients do not experience remission, and 30-40% of patients lack adequate response to drug therapy, resulting in non-adherence or discontinuation of therapy and prolongation of disease course. The variability of drug response is believed to be due to an individual's variation in drug metabolism at the genetic level. Although scientists are familiar with more than 50 isoenzymes, those mainly involved in antidepressant metabolism and investigated by pharmacogenetics studies are *CYP2C19*, *CYP2D6*, and CYP2B6. Inter-individual genetic variations of these enzymatic processes are likely to cause a lack of response or an increase

in adverse drug reactions. This review accentuates the CYP450 enzymes (*CYP2C19*, *CYP2B6*, and *CYP2D6*), their SNPs, and their association with the SSRIs efficacy or adverse effects. The polymorphism in *CYP2C19* had been reported to be associated with depressive symptoms, moreover, it can affect the metabolism of sertraline (SSRI) and its therapeutic outcome. Studies also concluded that *CYP2C19*17* polymorphism does not significantly influence sertraline metabolism. On the contrary, *CYP2B6**6 polymorphism has a foremost part and is likely to contribute to interindividual variability in SERT metabolism in vivo at therapeutic doses used in clinical practice. Additionally, the *CYP2C19* genotype influences the risk for toxicity in patients taking sertraline, citalopram, and Escitalopram. Classical studies had revealed the polymorphisms of *CYP2D6* in the variation of antidepressant response among patients with depressive illness, especially including *CYP2D6* P34S (rs1065852). In most psychiatric disorders, the phenotype appears very complex with inconsistent replication in enormous studies. The field of psychiatric genetics is enormously growing despite many hurdles and numerous technological advancements such as whole-genome sequencing have been made for large-scale studies.

Future Perspectives

The variability in the efficacy of antidepressants with reportedly 30-40 % of patients unresponsive to drug therapy, arises the need for the improved efficacy and safety of SSRIs. Advancements in pharmacogenetics testing and tools can certainly help in soaring pharmacotherapy and improving the quality of life in patients with MDD. Future SSRI pharmacogenetics trials should be carried out using a similar research methodology, considering drug concentration measurements and a large group of patients, taking into account ethnic differences to be able to formulate evidence-based screening guidelines. Proposed pharmacogenetics testing should be feasible for the patients, as well as for physicians. Thus, one should struggle to implement medical care with simple, reliable, and economic testing, perhaps only in selective patient populations taking SSRIs.

Conflict of Interest

The authors declare that they have no competing interests.

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Study Approval

NA

Consent Forms

NA

Authors Contribution

FSM conceptualized the study, FSM and AFS carried out the literature search, analysis and wrote the initial draft, FSM supervised the whole project and wrote the final manuscript.

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