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**Review Article**

# Escitalopram Use in Depression & the Influence of Genetic Variations on Its Safety & Efficacy

**Tahreem Zaheer[1]*, Fatima Shahid[2], Pratima Chhetri[3]**

[1]Department of Biological Physics, Eötvös Loránd University, Pázmány Péter sétány 1/A, 1117 Budapest, Hungary.
[2]Universiti Kebangsaan Malaysia, 43600 Bangi, Selangor, Malaysia.
[3]Heritage Pointe Pharmasave Pharmacy Alberta, Canada.
Correspondence: tahreem@student.elte.hu



## Abstract

Major depressive disorder (MDD) is a common debilitating mental illness marked by sad feelings, depressed mood, and lack of interest in routine chores that persists daily or for a minimum of two weeks. Serotonin-norepinephrine inhibitors, selective serotonin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, and atypical antidepressants are some common classes of drugs used to treat MDD. Despite strenuous efforts by the researchers, hardly any new antidepressant agent has entered the market. Escitalopram, a highly selective serotonin reuptake inhibitor, is the drug of choice for treating MDD. However, although escitalopram is one of the most frequently prescribed antidepressant agents, a large percentage of MDD patients show variable remission and response to escitalopram. Scientists spent decades finding the underlying mechanism responsible for the significant variations in drug response and incidence of adverse effects. These inter-individual variations in therapeutic response serve as a foundation for the inception of the pharmacogenomic. Pharmacogenomics is a field of research that expounds on the impact of gene variation on altered clinical outcomes of drugs. There has been substantial hope and potential that pharmacogenomics will ameliorate the current therapies for MDD and aid in finding novel targets for new drug discoveries. Numerous candidate genes have been identified and implicated in changing drug response, whether at the receptor, transporter, or drug-metabolizing enzyme. In this review, we attempt to compile the studies on the genetic variations associated with escitalopram efficacy and adverse effects and briefly discuss the pathophysiology and currently available treatment options for MDD.

**Keywords:** Depression, escitalopram, single nucleotide polymorphism, efficacy, safety, genetic variation, drug response

## 1. Introduction

Depressed mood, loss of interest, cognitive function impairment, and vegetative symptoms such as loss of appetite or sleep disturbance are the characteristic features of Major Depressive disorder (MDD) (Otte et al. 2016). MDD is a highly prevalent illness, afflicting approximately 3.8% of the global population, of which nearly 5.0% are adults, and 5.7% are adults over 60 years. As per WHO, nearly 280 million people suffer from depression globally (WHO 2022). This number is of great significance since depression is linked to disability, morbidity, increased medical co-morbidities, and fatality (Saveanu and Nemeroff 2012). Despite the devastating consequences of depression worldwide, no reliable diagnostic tests have been available till now. MDD is classically discerned as defects of brain circuitry or neurotransmission implicated in regulating pleasure, mood, and reward or decision-making (Durisko, Mulsant, and Andrews 2015). This understanding accentuates the involvement of three major pathways in

depression; norepinephrine (NE), monoamine systems—serotonin (5-hydroxytryptamine,5HT), and dopamine (DA). Diagnosis of MDD is based on feelings of worthlessness, guilt, lethargy, poor concentration, anorexia, psychomotor retardation or agitation, disturbed sleep, or suicidal thoughts. According to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), in addition to persistent melancholy, at least five of the symptoms mentioned above must be present in an individual to be diagnosed with MDD. However, manic or hypomanic symptoms must be ruled out before MDD is diagnosed. MDD in children and adolescents are evidenced by their irritable behavior (Bains and Abdijadid 2021).

Even with significant improvement in understanding the pathophysiology of MDD, currently available pharmacological treatments are inefficacious in several patients. On the other hand, although many novel compounds are showing promising results in research, classic pharmacological agents are still the mainstay of MDD therapy, and this trend is expected to continue into the foreseeable future (Sanches, Quevedo, and Soares 2021). Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and atypical agents are the classes of antidepressants (Solvason and DeBattista 2009). In western regions, the consumption of SSRIs is significantly increasing. Selective serotonin reuptake inhibitors (SSRIs), despite their limitations, are excessively used as anxiolytic and antidepressant pharmacotherapy (Marin M. Jukić et al. 2018)(Figure 1). SSRIs are well tolerated compared to TCAs, although both classes have comparable efficacy. Escitalopram is one of the most commonly prescribed SSRIs that shows effect by potentiating serotonergic transmission in the central nervous system via inhibiting its neuronal reuptake. As evident from previous studies, the efficacy of escitalopram is found to be superior to other SSRIs (Cipriani et al. 2009) in the treatment of mild to moderate depression. However, the clinical usefulness of escitalopram is limited by its adverse effects or failure to show anticipated responses in some patients. In addition to many other factors, genetic variation in key genes involved in the metabolism, transport, or drug target can contribute to the risk of adverse events or treatment failure of escitalopram. The purpose of this review is to summarize various pharmacogenomic studies of escitalopram to see the effect of gene variation on treatment response as well as side effects along with brief introduction to pathophysiology of depression.

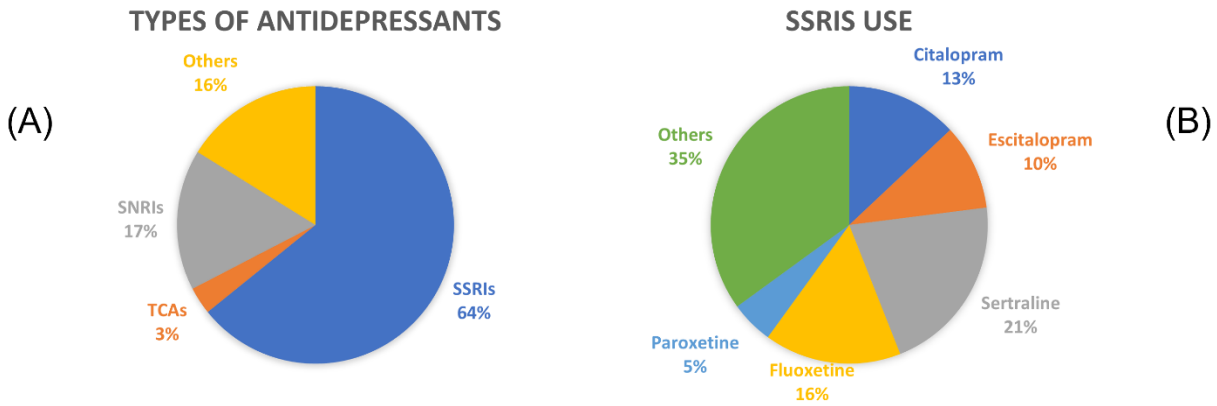


**Figure 1: The figure shows the use of various antidepressants including SSRIs.**

## 2. Pathophysiology of Depression

Several theories have been postulated to explain the underlying pathophysiology of depression (figure 2). The classic monoamine hypothesis suggests that depression is caused by a deficiency or imbalance in monoamine neurotransmitters, particularly serotonin (5-hydroxytryptamine [5HT]) and norepinephrine (NE). Stress, illness, or drug abuse may deplete the neurotransmitters essential for communication between neurons and ultimately lead to depression (Castrén 2005, Buzsáki 2004, Hua and Smith 2004). However, monoamine theory does not fully explain all the effects of antidepressant agents. This led the researchers to propose a chemical theory that states that structural and functional changes of particular molecules in the brain culminate in depression. For many years this theory remained the center of attention for many researchers (Castrén 2005). Chemical neurotransmitters are necessary for the transmission of information between neurons; however, rather than being stored in a chemical form, information in the brain is processed by the complex connections of neurons in neural networks, and this concept formed the basis of network theory (Buzsáki 2004, Hua and Smith 2004). This theory hypothesizes psychiatric disorders as relatively strong networks of interacting symptoms (de Boer et al. 2021). Furthermore, the neurotrophic theory of depression states that a lack of neurotrophic factors leads to reduced hippocampal genesis, neuronal atrophy, and loss of glia, thus ultimately causing depression (Troyan and Levada 2020). Moreover, during clinical studies, plasma concentrations of BDNF are lower in people with bipolar disorder, manic depression, and MDD (Cunha et al. 2006, Palomino et al. 2006). According to the BDNF hypothesis of depression, BDNF deficiency is a major factor in the development of depression (Sawamoto et al. 2016).

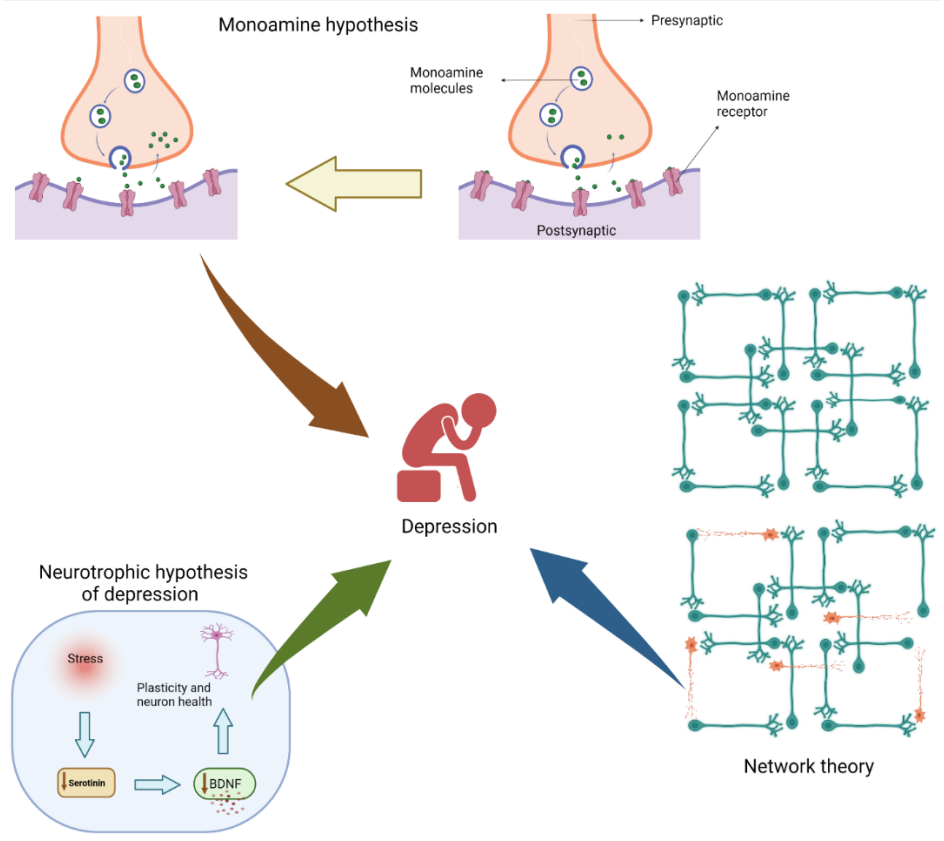


**Figure 2: This figure depicts some of the mainstream hypotheses for developing depression.**

## 3. Current Treatments

### *3.1. Tricyclic antidepressants (TCAs)*

TCAs are among the earliest antidepressants developed in 1959. TCAs produce an antidepressant effect by increasing levels of NE and serotonin in synapses by inhibiting their reuptake. The Food and Drug Administration (FDA) approved TCA for MDD include amoxapine amitriptyline, desipramine, doxepin, nortriptyline, imipramine, protriptyline and trimipramine (Dopheide 2006, Stokes et al. 2020, Boafo et al. 2020).

### *3.2. Monoamine oxidase inhibitors (MAOIs)*

Monoamine oxidase (MAO) is a pre-synaptically situated enzyme in the brain that oxidatively deaminates a broad range of monoamines, including monoamine neurotransmitters (NE, dopamine, serotonin) (McDaniel 1986). MAOIs were the first agents to be introduced for the treatment of depression; however, they are not the first drug of choice due to their undesirable side effects. (Fowler and Ross 1984, Murphy, Sunderland, and Cohen 1984). MAOIs include isocarboxazid, phenelzine, selegiline, and tranylcypromine.

### *3.3. Serotonin and NE reuptake inhibitors (SNRIs)*

In December 1993, the FDA approved the first SNRI (Sansone and Sansone 2014). Since depression is presumed to cause a reduced level of serotonin and NE during neurotransmission, SNRIs are a class of medications that show their effect by blocking serotonin and NE reabsorption back to the neurons that released them (Norris and Blier 2009, Chen et al. 2015) and consequently enhanced postsynaptic receptor activity. However, the affinities of SNRIs for serotonin and NE transporters may vary. Duloxetine and venlafaxine are more potent serotonin reuptake inhibitors, while levomilnacipran and milnacipran inhibit NE reuptake preferentially (Schatzberg and Nemeroff 2017, Nelson 2020, Asnis and Henderson 2015, Auclair et al. 2013).

### *3.4. Selective serotonin reuptake inhibitors (SSRIs)*

SSRIs, or selective serotonin reuptake inhibitors, are antidepressants that are extensively prescribed across the globe owing to their effectiveness in treating various mental illnesses (Gobin et al. 2014, Lin et al. 2017). SSRIs (Citalopram, Escitalopram (Ect), Paroxetine, Fluoxetine, Sertraline) block serotonin presynaptic reabsorption through inhibition of serotonin reuptake transporter, as shown in figure 3 (Slaton, Champion, and Palmore 2015). Depression, anxiety, obsessive-compulsive disorder, migraines, and other neuropathic pain conditions are routinely treated with these drugs (Yilmaz et al. 2010, Mosby 2005).

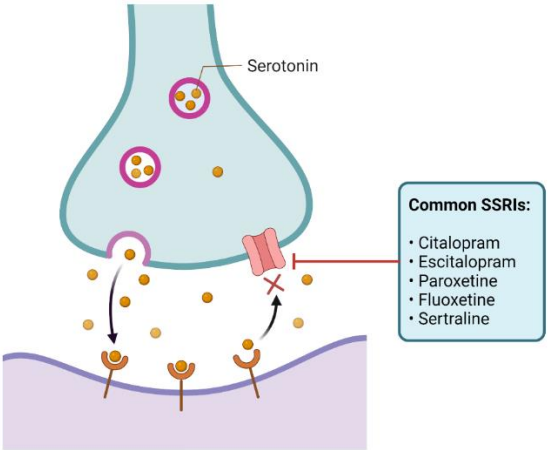


**Figure 3: This figures depicts the mode of action of SSRIs.**

### *3.5. Atypical antidepressants*

Several atypical antidepressants have been discovered as our knowledge of brain neurophysiology progressed (Horst and Preskorn 1998). Patients with severe depression who do not respond well to SSRIs or suffer too many side effects are often prescribed atypical antidepressants (Rush et al. 2006). Atypical antidepressants include Agomelatine, Bupropion, and Mirtazapine.

## 4. Cytochrome P450 enzymes

Cytochromes P450 are the key enzymes responsible for the metabolism of various medications. While more than fifty enzymes belong to this class, 90% of the drugs are primarily metabolized by only 6, with CYP2D6 and CYP3A4 being the most noteworthy. Therefore, any polymorphism in genes encoding these enzymes may alter the anticipated therapeutic outcome of commonly prescribed drugs such as antidepressants.

### *4.1. CYP2D6*

CYP2D6, belonging to the cytochrome P450 mixed-function oxidase system, is responsible for the metabolism and elimination of approximately 25 % of clinically used drugs (Wang et al. 2009). Han and colleagues conducted a study comprising 94 MDD Korean patients, and the symptoms of these patients were assessed by a 21-item Hamilton depression rating scale (HAMD-21). This study evaluated any association between the CYP2D6 P34S (C188T, rs1065852) polymorphism and therapeutic efficacy of escitalopram and any associated adverse effects. No association was found between adverse effects (sleep symptoms, extrapyramidal symptoms, gastrointestinal symptoms, autonomic symptoms, skin reactions, hormonal problems, sexual dysfunction, and headache) and CYP2D6 P34S polymorphism. However, a significant correlation was observed between the P allele of the CYP2D6P34S and treatment response to escitalopram. Furthermore, patients having P alleles of the CYP2D6P34S showed better treatment responses than S allele homozygotes (Han et al. 2013).

In another study, the correlation between the plasma concentration of escitalopram and its efficacy with polymorphism in *CYP2D6* (rs3892097, rs1065852) was evaluated. 100 MDD Asian patients were recruited for the study. As per the results of this study, the severity of disease reduced in CYP2D6 intermediate metabolizers (rs1065852) after eight weeks of treatment, thus showing a positive association between CYP2D6 gene polymorphism and response to treatment with escitalopram (Tsai et al. 2010).

The *CYP2C19* gene encodes for an enzyme found primarily on liver cells in the endoplasmic reticulum, a cell structure involved in protein processing and transport (Organization 2017). Tsai and colleagues also investigated the association of genetic polymorphisms in the CYP2C19 (rs12248560) gene with the treatment response and plasma concentration of escitalopram. HAMD-21 was used to evaluate depressive symptoms. The study found CYP2C19 poor metabolizer (rs4986893) genotypes associated with high serum concentrations of escitalopram and, therefore, more frequent adverse effects (Tsai et al. 2010).

The effect of *CYP2C19 gene variations* on the pharmacokinetics and pharmacodynamics of escitalopram in the Chinese population has been studied (Huang et al. 2021b). The steady-state concentration of escitalopram after a single dose in poor metabolizers (rs.4986893) was higher than in intermediate and extensive metabolizers. This result accentuates to consideration of the genetic profile of patients before initiating treatment with escitalopram.

(Bråten et al. 2021a) designed a study to identify novel CYP2C haplotypes and the impact of CYP2C gene polymorphism on treatment with escitalopram. They identified three novel haplotypes of CYP2C locus (CYP2C:TG, CYP2C:TA, and CYP2C:CG), and by using the genomic DNA of 875 individuals previously treated with

**Table 1: Gene variants affecting efficacy and adverse effects of escitalopram in depression patients**

| Genes | Sample size | Drug | Association/ Correlation | Reference |
|---|---|---|---|---|
| CYP2D6 P34S | 94 | Escitalopram | Associated with the treatment response of escitalopram | (Han et al. 2013) |
| CYP 2D6, 2C19 & 3A4 | 100 | Escitalopram | Associated significantly with serum level of escitalopram | (Tsai et al. 2010) |
| CYP2C:TG, CYP2C:TA & CYP2C:CG | 875 | Escitalopram | Associated with treatment failure with escitalopram | (Bråten et al. 2021b) |
| CYP2C19 | 2087 | Escitalopram | Associated with escitalopram exposure and treatment failure | (Marin M. Jukić et al. 2018) |
| CYP2C19 | 412 | Escitalopram | Associated with escitalopram steady-state plasma concentrations | (Tsuchimine et al. 2018b) |
| CYP2C19 | 166 | Escitalopram | Associated with lower serum concentration of escitalopram | (Rudberg et al. 2008) |
| CYP2C19 | 90 | Escitalopram | Associated with pharmacokinetic parameter of escitalopram | (Huang et al. 2021a) |
| CYP1A2 | 156 | Escitalopram | Associated with escitalopram metabolism | (Kuo et al. 2013) |
| *HTR1A & HTR1B* | 85 | Escitalopram | Not associated with treatment response | (Wang et al. 2018) |
| 5HTTLPR & 5HTTLPR-rs25531 | 148 | Escitalopram | Associated with better treatment response to escitalopram | (Mandal, Bairy, and Sharma 2020) |
| *HTR1A*, *HTR2A* and *SLC6A4* | 55 | Escitalopram | Not associated with escitalopram treatment response and side effects. | (Basu et al. 2015) |
| 5-HTTLPR | 106 | Escitalopram | Associated with treatment in Caucasian patients only. | (Ng et al. 2013) |
| 5-HTTLPR | 125 | Escitalopram | Not associated with treatment response | (Lenze et al. 2010) |
| 5-HTTLPR | 135 | Escitalopram | Associated with a high risk of side effects after treatment | (Maron et al. 2009) |
| 5-HTT and 5HTR2A | 90 | Escitalopram | Not associated with treatment response | (Rajewska-Rager et al. 2008) |
| 5-HTTLPR | 115 | Escitalopram | Associated with treatment response | (Won et al. 2012) |
| TPH1 218A/C and HTR5A 12A/T | 245 | Escitalopram | No association with remission or response to escitalopram | (Kim et al. 2014) |
| ABCB1 | 100 | Escitalopram | Associated with a slower remission rate after treatment | (Lin et al. 2011) |

escitalopram, their functional activity was assessed. A novel CYP2C-haplotype defined by rs2860840T and rs11188059G associated with ultra-rapid metabolism of escitalopram was identified. Results of this study indicated that individuals with CYP2C:TG haplotype are at high risk of treatment failure with the standard recommended dose of escitalopram.

In Japan, a study was conducted consisting of 412 patients diagnosed with depression (DSM-IV). The study aimed to investigate the influence of CYP2C19 gene polymorphism (rs4986893, rs12248560) on plasma concentration and the therapeutic outcome of escitalopram. The study concludes that steady-state plasma concentration is significantly influenced by gene variation of CYP2C19 and necessitates dose adjustment in poor metabolizers (rs4986893) (Tsuchimine et al. 2018a).

Another study was conducted to investigate the association of CYP2C19*7 with the serum concentration of escitalopram in psychiatric patients. 166 MDD patients on escitalopram treatment were divided into six subgroups according

to CYP2C19 genotype CYP2C19*17/*17, CYP2C19*1/*17, CYP2C19*1/*1, CYP2C19*17/def, CYP2C19*1/def, and CYP2C19def/def (def¼ defective alleles, i.e., CYP2C19*2 or *3). Results indicated that CYP2C19*17 is associated with a lower serum concentration of escitalopram and may play a role in the failure of treatment (Rudberg et al. 2008).

A member of the cytochrome P450 mixed-function oxidase system, CYP1A2 is involved in the metabolism of xenobiotics in the human body (Nelson et al. 2004). A study investigates the association of genetic polymorphism in the *CYP1A2* gene with escitalopram treatment, and a significant association was found between CYP1A2 SNPs rs2069521, rs2069526, rs4646425, and rs4646427 and escitalopram metabolism. It is suggested that the *CYP1A2* gene may be an indicator of escitalopram metabolism and side effects during the early stages of treatment (Kuo et al. 2013).

### 4.2. *5-Hydroxytryptamine Receptor 1A (HTR1A) and 5-Hydroxytryptamine Receptor 1B (HTR1B)*

HTR1A encodes a G protein-coupled receptor for 5-hydroxytryptamine (serotonin) and belongs to the 5-hydroxytryptamine receptor subfamily. It plays a role in the regulation of 5-hydroxytryptamine release and in the regulation of dopamine and 5-hydroxytryptamine metabolism, thereby affecting neural activity, mood and behavior.

HTR1B is a G-protein coupled receptor that activates a second messenger cascade to mediate inhibitory neurotransmission and regulate the brain's release of serotonin, dopamine, and acetylcholine. HTR1B has been suggested to be associated with multiple emotional and psychiatric problems, including attention deficit hyperactivity disorder (ADHD) (Guimarães et al. 2009).

A study comprising 85 MDD patients investigated the association of (*HTR1A rs6294*, *rs116985176; HTR1B rs6296*, *rs6298*, *rs1228814*, *rs1778258)* with escitalopram antidepressant response. Genotyping was done by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Results showed no association between the treatment response of escitalopram and HTR1A and HTR1B gene variations (Wang et al. 2018).

### 4.3. *Serotonin-transporter-linked promoter region (5HTTLPR)*

The serotonin transporter (5-HTT) in humans is encoded by the gene (*SLC6A4*) having locus on chromosome 17q11.1–17q12. 5-HTT is the main target for SSRIs. 5-HTT is present on nerve terminals as well as cell bodies of serotonergic neurons. Therefore any variation in gene encoding 5-HTT receptors may influence the pharmacological activity of SSRIs (Won et al. 2012).

A study designed to investigate the association between serotonin-transporter-linked promoter region (5HTTLPR) gene variant (rs25531) with escitalopram treatment response in 148 depression patients. 17-item Hamilton Depression Rating Scale (HDRS-17), Montgomery-Asberg Depression Rating Scale (MADRS), and Clinical Global Impression Scale (CGI) were used for the clinical assessment of depression patients. A significant association was observed between LL genotype, LALA haplotypes, and 2 LA functional group with better treatment response to escitalopram (Mandal, Bairy, and Sharma 2020).

Another study, in which 55 patients of depression participated, investigated the association of *HTR1A* (rs6295), *HTR2A (rs6311 and rs6313),* and *SLC6A4* (44 base-pair insertion/deletion at *5-HTTLPR*) with escitalopram treatment. No association was found between these SNPs with escitalopram treatment response and side effects, except memory loss was found to be correlated with rs6311 (Basu et al. 2015).

A prospective multi-site study consisted of 106 patients with depression of Caucasian and Han Chinese ethnicity. Clinical assessment was done with a 17-item Hamilton Depression scale

(HDRS), Clinical Global Impression Scale, and an adverse event scale (UKU). Results suggest that 1/1 allele for 5-HTTLPR has an association with a robust response to escitalopram treatment in Caucasian patients only (Ng et al. 2013).

Another study recruited 125 patients with depression and divided them into escitalopram and placebo groups to investigate the association of 5HTTLPR gene polymorphs (rs25531) with escitalopram efficacy. They were haplotyped with La combination, i.e., haplotype (La-) and haplotype (La+). La+ was found to be associated with escitalopram's therapeutic outcome. Results showed that escitalopram has no efficacy in La- group compared with La+ group (Lenze et al. 2010). Another study comprised 135 depression patients and evaluated the effect of 5HTTLPR gene variation (rs25531) on escitalopram treatment outcomes. Results showed that individuals having the S allele of 5HTTLPR have a high risk of side effects induced by escitalopram (Maron et al. 2009).

Similarly, a study enrolled 90 patients of depression to investigate and find any possible association of ins/del in 5-HTT and T102C in 5HTR2A gene polymorphism with the treatment response of escitalopram. No association was found between escitalopram and alleles polymorphism of 5HTT and 5HTR2A (Rajewska-Rager et al. 2008) homozygote.

(Won et al. 2012) conducted a study consisting of 115 Korean patients diagnosed with MDD and investigated the association between 5-HTTLPR and the clinical outcome of escitalopram treatment. Clinical symptoms were evaluated by HAMD-21. Results showed no significant association of 5-HTTLPR gene polymorphs with remission. Individuals having S allele 5-HTTLPR showed better treatment response than I allele homozygote carriers; however, further investigation still needs to be done.

### *4.4. Serotonin 5A receptor (HTR5A) and tryptophan hydroxylase-1 (TPH1)*

HTR5A, or 5-hydroxytryptamine (serotonin) receptor 5A, is a protein that is encoded by the *HTR5A* gene. HTR5A is found in the central nervous system, where it is expressed by a large number of cortical pyramidal neurons (Goodfellow et al. 2009). TPH1 is a tryptophan hydroxylase isoenzyme that is encoded by the *TPH1* gene in humans. TPH1 was first discovered to synthesize serotonin in 1988 (1988). Until 2003, it was assumed that there was only one TPH gene, but a second version was discovered in the mouse (Tph2), rat, and human brain (TPH2), and the original TPH was renamed to TPH1 (Walther et al. 2003). In a separate study, 245 MDD patients were recruited, and HAMD-17 evaluated clinical symptoms. In addition, the Association of TPH1 218A/C and HTR5A 12A/T polymorphisms and clinical outcomes of escitalopram treatment were evaluated. Results suggested that no association was present with remission or the response to escitalopram treatment (Kim et al. 2014).

### *4.5. ATP Binding Cassette Subfamily B Member 1 (ABCB1)*

*ABCB1* is one of numerous ubiquitous adenosine triphosphate (ATP)-binding cassette (ABC) genes crucial for cellular homeostasis found in all kingdoms of life (Jones and George 2004). In a study, 100 depression patients were enrolled to investigate the association of ABCB1 polymorphism with the effectiveness of escitalopram treatment. The haplotype (rs1882478-rs2235048-rs2235047-rs1045642-rs6949448) of ABCB1 was strongly associated with remission rate, while haplotype T-T-T-C-C was associated with a slower remission rate with escitalopram treatment (Lin et al. 2011).

## 5. Expert Opinion

Escitalopram, the selective serotonin reuptake inhibitor, is the drug of choice in most cases of MDD and is considered superior to other SSRI drugs in terms of efficacy. However, almost 50% of patients treated for MDD with escitalopram do not attain the anticipated functional recovery

and symptomatic remission with this first line of therapy. Antidepressants take almost 2-4 weeks or more to show their efficacy. During this period, the patients may suffer from hopelessness and discontinue treatment before time. Therefore, it becomes imperative to predict the likeliness of the drug to be effective and safe. There is a dire need to identify the underlying mechanisms and, eventually, apply that knowledge to improve diagnosis, treatment, and, ultimately, prevention of MDD. The clinical application of pharmacogenomics to guide the selection of psychotropic medications in the treatment of MDD based on their genetic makeup is gaining popularity, mainly ascribed to the extensive failure of the conventional strategy of treatment selection. One size fits all is an obsolete approach now. Many efforts have been put into translating genetic information to the clinical setting to upgrade prescribing practices for individuals suffering from MDD and other psychiatric disorders. Identifying gene polymorphs that may contribute to altered treatment response by using pharmacogenomic testing provides a promising opportunity to select the appropriate medication for individuals and thus avoid the chances of medication failure and adverse effects. To our knowledge, insufficient data is available regarding the role of genetic variation in relation to escitalopram treatment outcomes in MDD.

Moreover, the findings of these investigations were barely replicated in studies done later. Additionally, MDD patients are often treated with pharmacological and non-pharmacological therapies simultaneously; therefore, it becomes challenging to rule out which treatment is working the best. The power of these pharmacogenomic studies can be increased by increasing the sample size and optimizing the study design to include more severe cases. The cost of genotyping in designing a large pharmacogenomic study is another limiting factor. However, as the cost of genotyping and sequencing is declining, more comprehensive pharmacogenomic studies with larger sample sizes need to be designed.

**Conflict of Interest**

The authors declare that they have no competing interests.

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**Study Approval**

NA

**Consent Forms**

NA.

**Authors Contribution**

TZ conceptualized the study and wrote the final manuscript, FS helped in the literature search and writing the first draft, and PC reviewed the literature and wrote the final manuscript.

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**References**

1988. "Serotonin and Melatonin Synthesis in Peripheral Blood Mononuclear Cells: Stimulation by Interferon-7 as Part of an Immunomodulatory Pathway." *Journal of Interferon Research* 8 (6):705-716. doi: 10.1089/jir.1988.8.705.

Asnis, Gregory M, and Margaret A Henderson. 2015. "Levomilnacipran for the treatment of major depressive disorder: a review." *Neuropsychiatric disease and treatment* 11:125.

Auclair, AL, JC Martel, MB Assié, L Bardin, P Heusler, D Cussac, M Marien, A Newman-Tancredi, JA O'Connor, and R Depoortère. 2013. "Levomilnacipran

(F2695), a norepinephrine-preferring SNRI: profile in vitro and in models of depression and anxiety." *Neuropharmacology* 70:338-347.

Bains, Navneet, and Sara Abdijadid. 2021. "Major depressive disorder." In *StatPearls [Internet]*. StatPearls Publishing.

Basu, Aniruddha, R. K. Chadda, Mamta Sood, Harpreet Kaur, and Ritushree Kukreti. 2015. "Association of serotonin transporter (SLC6A4) and receptor (5HTR1A, 5HTR2A) polymorphisms with response to treatment with escitalopram in patients with major depressive disorder: A preliminary study." *The Indian journal of medical research* 142 (1):40-45. doi: 10.4103/0971-5916.162094.

Boafo, A., S. Greenham, M. Sullivan, K. Bazaid, S. Suntharalingam, L. Silbernagel, K. Magner, and R. Robillard. 2020. "Medications for sleep disturbance in children and adolescents with depression: a survey of Canadian child and adolescent psychiatrists." *Child Adolesc Psychiatry Ment Health* 14:10. doi: 10.1186/s13034-020-00316-8.

Bråten, L. S., T. Haslemo, M. M. Jukic, M. Ivanov, M. Ingelman-Sundberg, E. Molden, and M. K. Kringen. 2021a. "A Novel CYP2C-Haplotype Associated With Ultrarapid Metabolism of Escitalopram." *Clin Pharmacol Ther* 110 (3):786-793. doi: 10.1002/cpt.2233.

Bråten, Line Skute, Tore Haslemo, Marin M. Jukic, Maxim Ivanov, Magnus Ingelman-Sundberg, Espen Molden, and Marianne Kristiansen Kringen. 2021b. "A Novel CYP2C-Haplotype Associated With Ultrarapid Metabolism of Escitalopram." *Clinical Pharmacology & Therapeutics* 110 (3):786-793. doi: https://doi.org/10.1002/cpt.2233.

Buzsáki, György. 2004. "Large-scale recording of neuronal ensembles." *Nature neuroscience* 7 (5):446-451.

Castrén, Eero. 2005. "Is mood chemistry?" *Nature Reviews Neuroscience* 6 (3):241-246.

Chen, L., W. M. Greenberg, C. Gommoll, J. O'Connor, S. R. Zukin, A. Periclou, and P. Ghahramani. 2015. "Levomilnacipran Pharmacokinetics in Healthy Volunteers Versus Patients with Major Depressive Disorder and Implications for Norepinephrine and Serotonin Reuptake Inhibition." *Clin Ther* 37 (9):2059-70. doi: 10.1016/j.clinthera.2015.07.005.

Cipriani, A., C. Santilli, T. A. Furukawa, A. Signoretti, A. Nakagawa, H. McGuire, R. Churchill, and C. Barbui. 2009. "Escitalopram versus other antidepressive agents for depression." *Cochrane Database Syst Rev* (2):Cd006532. doi: 10.1002/14651858.CD006532.pub2.

Cunha, Angelo B. M., Benicio N. Frey, Ana C. Andreazza, Júlia D. Goi, Adriane R. Rosa, Carlos A. Gonçalves, Aida Santin, and Flavio Kapczinski. 2006. "Serum brain-derived neurotrophic factor is decreased in bipolar disorder during depressive and manic episodes." *Neuroscience Letters* 398 (3):215-219. doi: https://doi.org/10.1016/j.neulet.2005.12.085.

de Boer, Nina S., Leon C. de Bruin, Jeroen J. G. Geurts, and Gerrit Glas. 2021. "The Network Theory of Psychiatric Disorders: A Critical Assessment of the Inclusion of Environmental Factors." *Frontiers in Psychology* 12. doi: 10.3389/fpsyg.2021.623970.

Dopheide, J. A. 2006. "Recognizing and treating depression in children and adolescents." *Am J Health Syst Pharm* 63 (3):233-43. doi: 10.2146/ajhp050264.

Durisko, Zachary, Benoit H Mulsant, and Paul W Andrews. 2015. "An adaptationist perspective on the etiology of depression." *Journal of Affective Disorders* 172:315-323.

Fowler, Christopher J, and Svante B Ross. 1984. "Selective inhibitors of monoamine oxidase A and B: biochemical, pharmacological, and clinical properties." *Medicinal research reviews* 4 (3):323-358.

Gobin, Veerle, Katleen Van Steendam, Damiaan Denys, and Dieter Deforce. 2014. "Selective serotonin reuptake inhibitors as a novel class of immunosuppressants." *International immunopharmacology* 20 (1):148-156.

Goodfellow, Nathalie M, Madhurima Benekareddy, Vidita A Vaidya, and Evelyn K Lambe. 2009. "Layer II/III of the prefrontal cortex: inhibition by the serotonin 5-HT1A receptor in development and stress." *Journal of Neuroscience* 29 (32):10094-10103.

Guimarães, Ana P, Marcelo Schmitz, Guilherme V Polanczyk, Cristian Zeni, Julia Genro, Tatiana Roman, Luis A Rohde, and Mara H Hutz. 2009. "Further evidence for the association between attention deficit/hyperactivity disorder and the serotonin receptor 1B gene." *Journal of neural transmission* 116 (12):1675.

Han, Kyu-Man, Hun Soo Chang, In-Kwang Choi, Byung-Joo Ham, and Min-Soo Lee. 2013. "CYP2D6 P34S Polymorphism and Outcomes of Escitalopram Treatment in Koreans with Major Depression." *Psychiatry investigation* 10 (3):286-293. doi: 10.4306/pi.2013.10.3.286.

Horst, W. D., and S. H. Preskorn. 1998. "Mechanisms of action and clinical characteristics of three atypical antidepressants: venlafaxine, nefazodone, bupropion." *J Affect Disord* 51 (3):237-54. doi: 10.1016/s0165-0327(98)00222-5.

Hua, Jackie Yuanyuan, and Stephen J Smith. 2004. "Neural activity and the dynamics of central nervous system development." *Nature neuroscience* 7 (4):327-332.

Huang, X., C. Li, C. Li, Z. Li, X. Li, J. Liao, T. Rao, L. Chen, L. Gao, and D. Ouyang. 2021a. "CYP2C19 Genotyping May Provide a Better Treatment Strategy when Administering Escitalopram in Chinese Population." *Front Pharmacol* 12:730461. doi: 10.3389/fphar.2021.730461.

Huang, Xinyi, Chao Li, Chaopeng Li, Zhenyu Li, Xiaohui Li, Jianwei Liao, Tai Rao, Lulu Chen, Lichen Gao, and Dongsheng Ouyang. 2021b. "CYP2C19 Genotyping May Provide a Better Treatment Strategy when Administering Escitalopram in Chinese Population." *Frontiers in Pharmacology* 12. doi: 10.3389/fphar.2021.730461.

Jones, PM, and AM George. 2004. "The ABC transporter structure and mechanism: perspectives on recent research." *Cellular and Molecular Life Sciences CMLS* 61 (6):682-699.

Kim, Y. G., H. S. Chang, E. S. Won, B. J. Ham, and M. S. Lee. 2014. "Serotonin-Related Polymorphisms in TPH1 and HTR5A Genes Are Not Associated with Escitalopram Treatment Response in Korean Patients with Major Depression." *Neuropsychobiology* 69 (4):210-219. doi: 10.1159/000362241.

Kuo, Hsiang-Wei, Shu Chih Liu, Hsiao-Hui Tsou, Sheng-Wen Liu, Keh-Ming Lin, Shao-Chun Lu, Mei-Chun Hsiao, Chin-Fu Hsiao, Chia-Yih Liu, Chia-Hui Chen, Mong-Liang Lu, Winston W Shen, Hwa-Sheng Tang, Shen-Ing Liu, Liang-Huey Chang, Hsiao-Yu Wu, Yao-Sheng Chang, Teng-Kuang Yeh, Andrew CH Chen, and Yu-Li Liu. 2013. "CYP1A2 genetic polymorphisms are associated with early antidepressant escitalopram metabolism and adverse reactions." *Pharmacogenomics* 14 (10):1191-1201. doi: 10.2217/pgs.13.105.

Lenze, Eric J., Alison M. Goate, Petra Nowotny, David Dixon, Peichang Shi, Robert R. Bies, Francis K. Lotrich, Bruce L. Rollman, M. Katherine Shear, Paul A.

Thompson, Carmen Andreescu, and Bruce G. Pollock. 2010. "Relation of serotonin transporter genetic variation to efficacy of escitalopram for generalized anxiety disorder in older adults." *Journal of clinical psychopharmacology* 30 (6):672-677. doi: 10.1097/jcp.0b013e3181fc2bef.

Lin, K. M., Y. F. Chiu, I. J. Tsai, C. H. Chen, W. W. Shen, S. C. Liu, S. C. Lu, C. Y. Liu, M. C. Hsiao, H. S. Tang, S. I. Liu, L. H. Chang, C. S. Wu, H. H. Tsou, M. H. Tsai, C. Y. Chen, S. M. Wang, H. W. Kuo, Y. T. Hsu, and Y. L. Liu. 2011. "ABCB1 gene polymorphisms are associated with the severity of major depressive disorder and its response to escitalopram treatment." *Pharmacogenet Genomics* 21 (4):163-70. doi: 10.1097/FPC.0b013e32833db216.

Lin, Wan-Tzu, Yi-Jun Liao, Yen-Chun Peng, Chung-Hsin Chang, Ching-Heng Lin, Hong-Zen Yeh, and Chi-Sen Chang. 2017. "Relationship between use of selective serotonin reuptake inhibitors and irritable bowel syndrome: A population-based cohort study." *World journal of gastroenterology* 23 (19):3513.

Mandal, Tatiyana, Laxminarayana Kurady Bairy, and Podila Satya Venkata Narasimha Sharma. 2020. "Association between functional polymorphisms in serotonin transporter gene (SLC6A4) and escitalopram treatment response in depressive patients in a South Indian population." *European Journal of Clinical Pharmacology* 76 (6):807-814. doi: 10.1007/s00228-020-02866-4.

Marin M. Jukić, Ph.D. ,, Tore Haslemo, Ph.D. ,, Espen Molden, Ph.D. ,, and Magnus Ingelman-Sundberg, Ph.D. 2018. "Impact of CYP2C19 Genotype on Escitalopram Exposure and Therapeutic Failure: A Retrospective Study Based on 2,087 Patients." *American Journal of Psychiatry* 175 (5):463-470. doi: 10.1176/appi.ajp.2017.17050550.

Maron, E., A. Tammiste, K. Kallassalu, T. Eller, V. Vasar, D. J. Nutt, and A. Metspalu. 2009. "Serotonin transporter promoter region polymorphisms do not influence treatment response to escitalopram in patients with major depression." *Eur Neuropsychopharmacol* 19 (6):451-6. doi: 10.1016/j.euroneuro.2009.01.010.

McDaniel, Keith D. 1986. "Clinical pharmacology of monoamine oxidase inhibitors." *Clinical neuropharmacology* 9 (3):207-234.

Mosby, DK. 2005. "Mosby's Drug Consult." *St Louis: Elsevier*.

Murphy, Dennis L, Trey Sunderland, and Robert M Cohen. 1984. "Monoamine oxidase-inhibiting antidepressants: A clinical update." *Psychiatric Clinics of North America*.

Nelson, Craig. 2020. Serotonin-norepinephrine reuptake inhibitors (SNRIs): pharmacology, administration, and side effects.

Nelson, David R, Darryl C Zeldin, Susan MG Hoffman, Lois J Maltais, Hester M Wain, and Daniel W Nebert. 2004. "Comparison of cytochrome P450 (CYP) genes from the mouse and human genomes, including nomenclature recommendations for genes, pseudogenes and alternative-splice variants." *Pharmacogenetics and Genomics* 14 (1):1-18.

Ng, C., J. Sarris, A. Singh, C. Bousman, K. Byron, L. H. Peh, D. J. Smith, C. H. Tan, and I. Schweitzer. 2013. "Pharmacogenetic polymorphisms and response to escitalopram and venlafaxine over 8 weeks in major depression." *Hum Psychopharmacol* 28 (5):516-22. doi: 10.1002/hup.2340.

Norris, S, and P Blier. 2009. "Duloxetine and milnacipran." *The American Psychiatric Publishing Textbook of Psychopharmacology. 4th ed. Arlington, VA: American Psychiatric Publishing*:453-464.

Organization, World Health. 2017. Depression and other common mental disorders:

global health estimates. World Health Organization.

Otte, Christian, Stefan M. Gold, Brenda W. Penninx, Carmine M. Pariante, Amit Etkin, Maurizio Fava, David C. Mohr, and Alan F. Schatzberg. 2016. "Major depressive disorder." *Nature Reviews Disease Primers* 2 (1):16065. doi: 10.1038/nrdp.2016.65.

Palomino, A., A. Vallejo-Illarramendi, A. González-Pinto, A. Aldama, C. González-Gómez, F. Mosquera, G. González-García, and C. Matute. 2006. "Decreased levels of plasma BDNF in first-episode schizophrenia and bipolar disorder patients." *Schizophr Res* 86 (1-3):321-2. doi: 10.1016/j.schres.2006.05.028.

Rajewska-Rager, A., M. Dmitrzak-Weglarz, P. Kapelski, M. Skibińska, M. Kaczmarkiewicz-Fass, and J. Hauser. 2008. "[Association between polymorphisms of ins/del in the 5-HTT gene and T102C in the 5HTR2A gene and the drug response for escitalopram and nortriptyline in depressed patients]." *Psychiatr Pol* 42 (6):903-14.

Rudberg, I., B. Mohebi, M. Hermann, H. Refsum, and E. Molden. 2008. "Impact of the ultrarapid CYP2C19*17 allele on serum concentration of escitalopram in psychiatric patients." *Clin Pharmacol Ther* 83 (2):322-7. doi: 10.1038/sj.clpt.6100291.

Rush, A. J., M. H. Trivedi, S. R. Wisniewski, J. W. Stewart, A. A. Nierenberg, M. E. Thase, L. Ritz, M. M. Biggs, D. Warden, J. F. Luther, K. Shores-Wilson, G. Niederehe, and M. Fava. 2006. "Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression." *N Engl J Med* 354 (12):1231-42. doi: 10.1056/NEJMoa052963.

Sanches, Marsal, Joao Quevedo, and Jair C. Soares. 2021. "New agents and perspectives in the pharmacological treatment of major depressive disorder." *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 106:110157. doi: https://doi.org/10.1016/j.pnpbp.2020.110157.

Sansone, Randy A., and Lori A. Sansone. 2014. "Serotonin norepinephrine reuptake inhibitors: a pharmacological comparison." *Innovations in clinical neuroscience* 11 (3-4):37-42.

Saveanu, Radu V, and Charles B Nemeroff. 2012. "Etiology of depression: genetic and environmental factors." *Psychiatric clinics* 35 (1):51-71.

Sawamoto, Atsushi, Satoshi Okuyama, Kana Yamamoto, Yoshiaki Amakura, Morio Yoshimura, Mitsunari Nakajima, and Yoshiko Furukawa. 2016. "3,5,6,7,8,3′,4′-Heptamethoxyflavone, a Citrus Flavonoid, Ameliorates Corticosterone-Induced Depression-like Behavior and Restores Brain-Derived Neurotrophic Factor Expression, Neurogenesis, and Neuroplasticity in the Hippocampus." *Molecules* 21 (4):541.

Schatzberg, Alan F, and Charles B Nemeroff. 2017. *The American psychiatric association publishing textbook of psychopharmacology*: American Psychiatric Pub.

Slaton, Rachel M, Megan N Champion, and Kayla B Palmore. 2015. "A review of paroxetine for the treatment of vasomotor symptoms." *Journal of pharmacy practice* 28 (3):266-274.

Solvason, Hugh Brent, and Charles DeBattista. 2009. "Antidepressant Dosing for the Acute Treatment of Unipolar Depression." *Primary Psychiatry* 16 (10).

Stokes, P. R. A., T. Jokinen, S. Amawi, M. Qureshi, M. I. Husain, L. N. Yatham, J. Strang, and A. H. Young. 2020. "Pharmacological Treatment of Mood Disorders and Comorbid Addictions: A Systematic Review and Meta-Analysis: Traitement Pharmacologique des Troubles de L'humeur et des Dépendances Comorbides: Une Revue Systématique et une

Méta-Analyse." *Can J Psychiatry* 65 (11):749-769. doi: 10.1177/0706743720915420.

Troyan, Alexandra S, and Oleg A Levada. 2020. "The Diagnostic Value of the Combination of Serum Brain-Derived Neurotrophic Factor and Insulin-Like Growth Factor-1 for Major Depressive Disorder Diagnosis and Treatment Efficacy." *Frontiers in Psychiatry* 11:800.

Tsai, M. H., K. M. Lin, M. C. Hsiao, W. W. Shen, M. L. Lu, H. S. Tang, C. K. Fang, C. S. Wu, S. C. Lu, S. C. Liu, C. Y. Chen, and Y. L. Liu. 2010. "Genetic polymorphisms of cytochrome P450 enzymes influence metabolism of the antidepressant escitalopram and treatment response." *Pharmacogenomics* 11 (4):537-46. doi: 10.2217/pgs.09.168.

Tsuchimine, S., S. Ochi, M. Tajiri, Y. Suzuki, N. Sugawara, Y. Inoue, and N. Yasui-Furukori. 2018a. "Effects of Cytochrome P450 (CYP) 2C19 Genotypes on Steady-State Plasma Concentrations of Escitalopram and its Desmethyl Metabolite in Japanese Patients With Depression." *Ther Drug Monit* 40 (3):356-361. doi: 10.1097/ftd.0000000000000506.

Tsuchimine, Shoko, Shinichiro Ochi, Misuzu Tajiri, Yutaro Suzuki, Norio Sugawara, Yoshimasa Inoue, and Norio Yasui-Furukori. 2018b. "Effects of Cytochrome P450 (CYP) 2C19 Genotypes on Steady-State Plasma Concentrations of Escitalopram and its Desmethyl Metabolite in Japanese Patients With Depression." *Therapeutic drug monitoring* 40 (3):356-361. doi: 10.1097/FTD.0000000000000506.

Walther, Diego J., Jens-Uwe Peter, Saleh Bashammakh, Heide Hörtnagl, Mechthild Voits, Heidrun Fink, and Michael Bader. 2003. "Synthesis of Serotonin by a Second Tryptophan Hydroxylase Isoform." *Science* 299 (5603):76-76. doi: doi:10.1126/science.1078197.

Wang, Bo, Li-Ping Yang, Xiao-Zhuang Zhang, Shui-Qing Huang, Mark Bartlam, and Shu-Feng Zhou. 2009. "New insights into the structural characteristics and functional relevance of the human cytochrome P450 2D6 enzyme." *Drug metabolism reviews* 41 (4):573-643.

Wang, Peipei, Qinyu Lv, Yemeng Mao, Cuizhen Zhang, Chenxi Bao, Hong Sun, Hanmei Chen, Zhenghui Yi, Weimin Cai, and Yiru Fang. 2018. "HTR1A/1B DNA methylation may predict escitalopram treatment response in depressed Chinese Han patients." *Journal of Affective Disorders* 228:222-228. doi: https://doi.org/10.1016/j.jad.2017.12.010.

WHO. 2022. "https://www.who.int/news-room/fact-sheets/detail/depression."

Won, E. S., H. S. Chang, H. Y. Lee, B. J. Ham, and M. S. Lee. 2012. "Association between Serotonin Transporter-Linked Polymorphic Region and Escitalopram Antidepressant Treatment Response in Korean Patients with Major Depressive Disorder." *Neuropsychobiology* 66 (4):221-229. doi: 10.1159/000341876.

Yilmaz, Zeynep, Alessandro Ceschi, Christine Rauber-Lüthy, Oliver Sauer, Uwe Stedtler, Dagmar Prasa, Carola Seidel, Elisabeth Hackl, Petra Hoffmann-Walbeck, and Gabriela Gerber-Zupan. 2010. "Escitalopram causes fewer seizures in human overdose than citalopram." *Clinical Toxicology* 48 (3):207-212.