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Review Article

Escitalopram Pharmacogenetics: What Does Evidence Suggest?

Nida Saleem[1]*, Naim-ul-Huda[2]

[1]Shifa College of Pharmaceutical Sciences, Shifa Tameer-e-Millat University, Islamabad, Pakistan.
[2]Shifa College of Medicine, Shifa Tameer-e-Millat University, Islamabad, Pakistan
***Correspondence:** nida.scps@stmu.edu.pk

Abstract

Depression is among the most diagnosed mental health conditions. It affects how a person thinks, feels, and behaves. It can impact anyone at any age and deprive one of physical and emotional life force. In the post-COVID-19 world, depression has become even more prevalent and pervasive. While scientists are actively trying to track the pathophysiology of depression, for now, it remains to be fully understood. Escitalopram, the enantiomer of citalopram, is widely prescribed for treating anxiety, depression, obsessive-compulsive disorder (OCD), etc. It is a potent selective serotonin reuptake inhibitor (SSRI), but its effect is varied in different individuals, as therapeutic failures are common with antidepressants. Pharmacogenomics can help with tailoring effective therapeutic strategies by defining biomarkers to classify responders and non-responders, minimizing the risk of side effects and adverse events. For escitalopram, genes like *SCL6A4* rs25531, *ABCB1* rs1045642, and *CYP2C19**17 rs12248560 were associated with optimal therapeutic response, with better remission rates at lower doses. These findings can be utilized for curating effective patient-centric therapeutic strategies.

Keywords: Depression, escitalopram, SSRIs, pharmacogenetics, personalized medicine

1. Introduction

Depressive disorder, commonly known as depression, is a mental disorder in which a person experiences a loss of pleasure or diminished interest in activities for a prolonged period. It has a deep impact on one's relationships with family as well as friends, and community (WHO 2023). According to the American Psychiatric Association, other symptoms of depression include irritability, significant changes in appetite, unhealthy sleeping patterns, marked increase in purposeless physical activity (inability to sit still, or pacing), difficulty thinking or concentrating, forgetfulness, difficulty making minor decisions, and suicide ideation or attempts (APA 2024). In 2023, the World Health Organization (WHO) reported that around 3.8% of the global population suffered from depression, including 5% of adults, and 5.7% of adults older than 60 years. Notably, women were found to be more likely to have depression than men, with a prevalence of 6% and 4%, respectively (WHO 2023).

According to the analysis 76.2 million additional cases of major depressive disorders (MDD) were reported following the COVID-19 pandemic (Santomauro et al. 2021). While the age-standardized incidence rate (ASIR) slightly decreased by 2.35%, the total number of cases grew exponentially. The COVID-19 pandemic further intensified this trend. High Socio Demographic Index regions like North America and Europe saw the most significant growth in depression rates during the pandemic. Females and older adults, particularly those aged 60-64 years, were most affected, and regions such as central sub Saharan Africa, Greenland, and

Uganda had the highest rates (Wu et al. 2024, Zhou et al. 2025).

A study using data from the Global Burden of Disease (GBD) from 1990 to 2016 found that 3.9% of the population in the South Asian region experienced depression, with some countries like Bangladesh having a slightly higher rate (4.4%) than Nepal (4.0%), India (3.9%), Bhutan (3.7%), and Pakistan (3.0%). The total burden of depressive disorders in South Asia was measured as 9.8 million disability-adjusted life years (DALYs) in 2016 (Ogbo et al. 2018). In a recent analysis on the prevalence of mental health disorders among children and adolescents across South Asian countries, including Pakistan, India, Bangladesh, Sri Lanka, Nepal, Bhutan, moderate depression was observed in 19%, and severe depression in 5.2% (Abbas *et al*. 2024). While the data on depression remains under-reported in Pakistan, a study exploring the mental health status in academic professionals found that 44.3% of the sampled population exhibited moderate to extremely severe depression (Ayesha et al. 2024).

2. Pathophysiology of Depression

The pathophysiology of depression, despite numerous studies, remains elusive. Many explanations, including genetics, neurotransmitters, and hormonal issues, have been put forth to explain the origins of this debilitating condition.

2.1. Neurotransmitter malfunction

Neurotransmitter systems play a crucial role in the etiology of depression. Serotonin (5-HT) is often linked to depression, with low 5-HT levels and altered 5-HT receptors (upregulated 5-HT_2 and downregulated 5-HT_{1A} receptors) observed in depressed patients (Nemeroff 2002). Impairment in 5-HT_{1A} function may arise from factors like social isolation, 5-HT_2 receptor inhibition, or hypercortisolaemia-induced 5-HT_1 neurotransmission inhibition (Deakin and Graeff 1991) (Fig. 1). Morever , Brain derived neurotrophic factor (BDNF) and neurotrophin-3 are important for the growth and function of 5-HT neurons. Any disturbance in these neurotrophic factors could also lead to depression (Xue *et al*. 2021).

Dopamine (DA) is critical for behavioral regulation; any dysregulation in DA neurotransmission could lead to depression. Studies showed that depressed individuals exhibited increased DA reuptake (Duval et al. 2021, Babaev, Cruces-Solis, and Arban 2022).

Glutamate, the primary excitatory neurotransmitter, plays a role in depression. Depressed individuals demonstrated increased glutamate levels, as well as disturbances in N-methyl-D-aspartate receptor (NMDAR) subunits (Gray et al. 2015, Duval et al. 2021).

In contrast, γ-aminobutyric acid (GABA), an inhibitory neurotransmitter, helps balance excitatory transmission and is linked to symptoms of MDD (Zhang et al. 2021, Hasler et al. 2007). MDD patients often face defects in GABA neurotransmission, with lower GABA levels in the brain (Duman, Sanacora, and Krystal 2019). As revealed by autopsy studies of depressed patients, an imbalance between GABA and glutamate systems may contribute to depression (Karolewicz et al. 2010).

2.2. Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs inhibit 5-HT reuptake, thereby increasing serotonergic activity. These drugs exert this effect by inhibiting the serotonin transporter (SERT) at the presynaptic axon terminal. In the aftermath of this action, 5-HT accumulation in the synaptic cleft stimulates postsynaptic receptors for an extended period (Fig. 2).

Compared to other antidepressant, SSRIs do not have much influence on neurotransmitters, such as DA or norepinephrine. Moreover, these drugs have fewer side effects compared to Tricyclic antidepressants (TCAs) and Monoamine Oxidase Inhibitors (MAOIs) due to limited interaction with adrenergic, cholinergic, and histaminergic receptors (Chu and Wadhwa 2020).

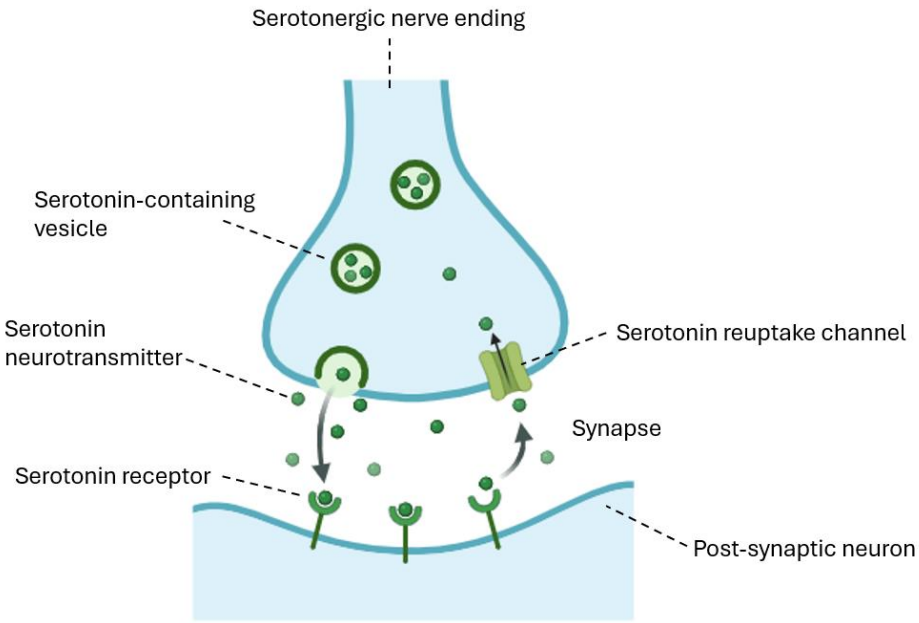

Figure 1: Pathophysiology of Serotonergic Depression (highly active reabsorption of serotonin or 5-HT$_2$ receptor inhibition leads to depression (Wnuk 2019).

Escitalopram, which is an (S)-enantiomer of citalopram, is a potent SSRI. It is approved by the U.S. Food and Drug Administration (FDA) for treating MDD in adolescents and adults for both acute and maintenance phases. The human serotonin transporter (hSERT) is a critical target for antidepressant drugs, and its allosteric modulators, such as escitalopram. In a study, both conventional molecular dynamics (cMD) and steered molecular dynamics (SMD) simulations were employed to elucidate the mechanism of escitalopram's allosteric modulation of hSERT.

Escitalopram binding at the allosteric site enhances its interaction at the orthosteric site, suggesting a cooperative binding mechanism. Furthermore, the occupation of the allosteric site by escitalopram hinders its dissociation from the orthosteric site, indicating a stabilizing effect and enhanced efficacy (Xue et al. 2022). According to a systematic review and meta-analysis, escitalopram's activity was superior in terms of efficacy and tolerability than other antidepressant drugs for the acute phase treatment of MDD (Yin et al. 2023). Moreover, this drug was found to be effective and safe for treating post-stroke depression (PSD). In addition to preventing PSD and it also possibly aided in motor recovery, although more research is needed on that front (Feng et al. 2022).

Escitalopram was also approved by the FDA for the treatment of generalized anxiety disorder (GAD) in both adults and children. Its clinical effectiveness and tolerability are influenced by interindividual variability in pharmacokinetics and pharmacogenetic factors. In addition, escitalopram is widely used off-label for a range of other psychiatric and medical conditions. These include social anxiety disorder, obsessive-compulsive disorder (OCD), panic disorder, posttraumatic stress disorder (PTSD), and premenstrual dysphoric disorder (PMDD). Moreover, it is sometimes prescribed for the management of vasomotor symptoms associated with menopause, such as hot flashes and night sweats, reflecting its broader therapeutic potential beyond mood and anxiety

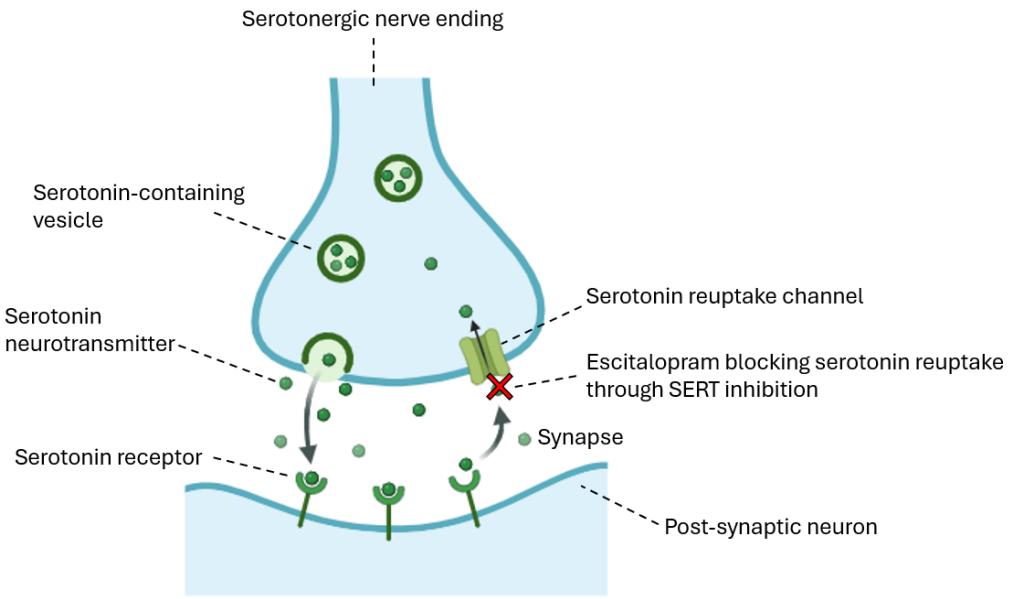

Figure 2: Escitalopram Mode of Action (SERT inhibition and serotonin accumulation in the synapse (Wnuk 2019).

disorders (Landy, Rosani, and Estevez 2023). Another study found strong evidence that escitalopram also has therapeutic potential for treating hepatocellular carcinoma (HCC). Both *in vitro* and large-scale population data suggested escitalopram-mediated autophagy of liver cancer cells, which might reduce the overall risk of developing HCC (Chen et al. 2022).

Furthermore, escitalopram appeared to be an effective treatment option for functional gastrointestinal disorders, improving symptoms across Irritable bowel syndrome (IBS), heartburn, and globus sensation (Alkhowaiter et al. 2023).

3. Pharmacogenetics of Escitalopram

Approximately 25,000 patients per year in the USA seek emergency aid due to antidepressant-related adverse effects (Hampton et al. 2014). Pharmacogenetics plays a crucial role in personalizing antidepressant treatment by helping select the right drug and adjust dosages based on individual genetic profiles, especially for drugs having a narrow therapeutic window. Pharmacogenomic screening is valuable for reducing variability in drug exposure and minimizing risks of side effects or inadequate responses, particularly for patients with extreme phenotypes, such as ultra-rapid metabolizers and poor metabolizers. Cytochrome p450 (CYP) genotyping is particularly useful at the start of treatment, as after long-term use, the most suitable drug is often identified through trial and error, with dosage adjustments made based on effects. Recent studies, such as those on *CYP2C19* and escitalopram response, demonstrate growing evidence for the utility of pharmacogenetic testing (Eap *et al*. 2021).

3.1. SLC6A4

The *SLC6A4* gene, which encodes the serotonin transporter (5-HTT), is located on chromosome 17 (17q11.1–q12) and plays a key role in regulating serotonergic neurotransmission by facilitating the reuptake of serotonin from the synaptic cleft.

A well-characterized functional polymorphism within this gene, known as the 5-HTT gene-linked promoter region (5-HTTLPR), involves an insertion-deletion of two 22-base pair repeat elements in the promoter region. This polymorphism results in two primary allelic variants: the short (S) allele, which is associated

with reduced transcriptional efficiency and lower serotonin transporter expression, and the long (L) allele, which promotes higher transcriptional activity (Kenna et al. 2012). A study exploring the impact of genetic polymorphism on escitalopram efficacy in 88 patients suffering from MDD found that the S allele of the 5-HTTLPR polymorphism carriers demonstrated a significantly lower response to escitalopram compared to individuals with the L allele ($p = 0.01$). Importantly, this association remained significant even after adjusting for the influence of *CYP2C19* and *CYP2D6* genotypes, suggesting an independent effect of 5-HTTLPR on treatment efficacy (Jarčušková et al. 2024).

Another study observed a significant relationship between escitalopram plasma levels and treatment response, particularly in patients with the LS genotype, suggesting that both plasma concentration and *SLC6A4* promoter variation can influence therapeutic outcomes (Canbolat et al. 2021).

Similarly, researchers noticed that patients with the 5HTTLPR S/S genotype had a greater tendency to develop adverse effects compared to those with the L/L genotype. However, this difference was not statistically significant. In conclusion, the study suggests that the 5HTTLPR polymorphism and the *SLC6A4* intron 2 polymorphism are associated with a better response to SSRI treatment (Ramesh, Venkatesan, and Ramasamy 2022).

A south Indian observational study, conducted in 148 MDD patients receiving escitalopram at doses ranging from 10 to 20 mg/day, also concluded that *5HTTLPR*-rs25531 was associated with a better treatment response to escitalopram ($p < 0.001$) (Mandal, Bairy, and Sharma 2020). On the other hand, a study in adolescents aged 12–17 years with a first-degree family history of bipolar disorder treated with escitalopram found no significant associations between the adverse effects and *SLC6A4* genotype (Honeycutt et al. 2024). Similarly, a double-blind, placebo-controlled trial found no statistically significant association between *SLC6A4* (rs25531) and an influence on the efficacy of escitalopram in treating MDD (Brunoni et al. 2020).

3.2. CYP2C19

This gene encodes a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins are monooxygenases that catalyze many reactions involved in drug metabolism and the synthesis of cholesterol, steroids, and other lipids (GenBank 2025). Notably, CYP2C19 is among the major metabolizing enzymes for selective serotonin reuptake inhibitors (SSRIs) (Brouwer et al. 2022).

There are 5 phenotypic categories of CYP2C19 activity range: (1) extensive metabolizers carrying normal-function alleles (CYP2C19*1/*1, *2/*17, *4/*17); (2) intermediate metabolizers carrying one loss-of-function allele (*1/*2, *1/*4); (3) poor metabolizers carrying two loss-of-function alleles (*2/*2, *2/*4, *4/*4); (4) rapid metabolizers for alleles (*1/*17); and (5) ultrarapid metabolizers for alleles (*17/*17) (Mahajna et al. 2023). Hyperactive CYP2C19 is expected to lower plasma concentrations of escitalopram, influencing the antidepressant effect; whereas hypoactive CYP2C19 is associated with elevated plasma levels of escitalopram. Such high plasma concentrations could potentially result in SSRI-induced side effects (Brouwer et al. 2022).

A study found that the *CYP2C19* phenotype significantly influenced the pharmacokinetics of escitalopram in children and adolescents with a family history of bipolar disorder. Specifically, slower CYP2C19 metabolizers exhibited higher dose-normalized 24-hour area under the curve (AUC_{0-24}) values ($p = 0.025$), elevated trough concentrations, and longer elimination half-lives compared to normal or faster metabolizers. This leads to greater systemic exposure to escitalopram. However, the *CYP2C19* phenotype was not associated with escitalopram-related adverse events (Honeycutt et al. 2024). Similarly, a retrospective

longitudinal cohort study observed that with each unit difference in the CYP2C19 activity score, the odds ratio for escitalopram intolerability was lowered by 0.73 (95% credible intervals: 0.56–0.89), adjusting for significant covariates. This indicated better tolerability and potentially better efficacy in patients with higher CYP2C19 activity scores. The study concluded that the *CYP2C19* genotype was a useful predictor in distinguishing patients who were low adherence, low drug tolerance, and low response from those who were high adherence, high drug tolerance, and high response (Mahajna et al. 2023).

Another study, involving the complex interplay between genetics, epigenetics, and clinical outcomes related to antidepressant treatment, noted significant treatment-related weight gain in patients carrying the *CYP2C19* rs424428 variant, which was significantly associated with and adjusted serum concentrations of escitalopram ($q < 0.001$). Patients with the *2/*2 genotype (poor metabolizers) had the highest serum escitalopram levels and did not report weight gain during weeks 2–4 of treatment, while those with *1/*1 and *1/*2 genotypes (normal and intermediate metabolizers) experienced weight gain to varying degrees. Furthermore, causal inference tests suggested that these genetic effects were not mediated through epigenetic mechanisms, reinforcing the functional role of the *CYP2C19* rs4244285 variant in influencing escitalopram pharmacokinetics (Islam et al. 2024). In a Chinese study, among 90 healthy subjects it was observed that population carrying *CYP2C19**2 and *CYP2C19**3 alleles is three times higher compared to Caucasians. Notably, the half-life of escitalopram was 38% longer in poor metabolizers compared to extensive metabolizers ($P < 0.05$). Additionally, the area under the curve (AUC), a measure of drug exposure, was 46% higher in poor metabolizers compared to extensive metabolizers ($P < 0.01$). Steady-state concentration predictions based on single-dose pharmacokinetics indicated that poor metabolizers would likely achieve 49% higher escitalopram levels at steady state than extensive metabolizers ($P < 0.001$) and 34% higher than intermediate metabolizers ($P < 0.05$). These findings suggest that genetic testing before escitalopram administration and dose adjustments for poor metabolizers should be considered in clinical practice to optimize treatment outcomes in the Chinese population (Huang et al. 2021).

A study from Russia checked the impact of the *CYP2C19**17 (−806C>T) (rs12248560) polymorphism on the therapeutic outcomes of escitalopram. This relationship was evaluated in 267 patients with recurrent depressive disorder. The study found that the *CYP2C19**17 variant significantly influenced the safety and efficacy of escitalopram. Specifically, patients with the TT genotype scored significantly lower on Hamilton Depression Rating Scale (2.0 [1.0; 4.0]) compared to those with the CC genotype (9.0 [7.0; 11.0]) and the CT genotype (4.0 [2.0; 6.0]), indicating a better treatment response in the TT genotype group ($p < 0.001$). Similarly, the safety profile, assessed by UKU scores, was significantly better in patients with the TT genotype (3.0 [2.0; 3.0]) compared to the CC genotype (7.0 [7.0; 8.0]) and CT genotype (3.0 [3.0; 4.0]) ($p < 0.001$). However, no statistically significant differences were observed in the concentration-to-dose (CD) ratio of escitalopram across the different *CYP2C19* genotypes. With a p-value of 0.268, it was evident that the *CYP2C19**17 genotype did not notably influence escitalopram's equilibrium plasma concentration (Zastrozhin et al. 2022). In a large real-world cohort study involving 5067 patients, the influence of *CYP2C19* genotype on escitalopram pharmacokinetics was assessed in conjunction with *CYP2D6* metabolic status. Patients were genotyped for *CYP2C19**2 (rs4244285), *CYP2C19**3 (rs4986893) and *CYP2C19**4 (rs28399504), *CYP2C19**17 (rs12248560) variant allele. *CYP2D6* variants

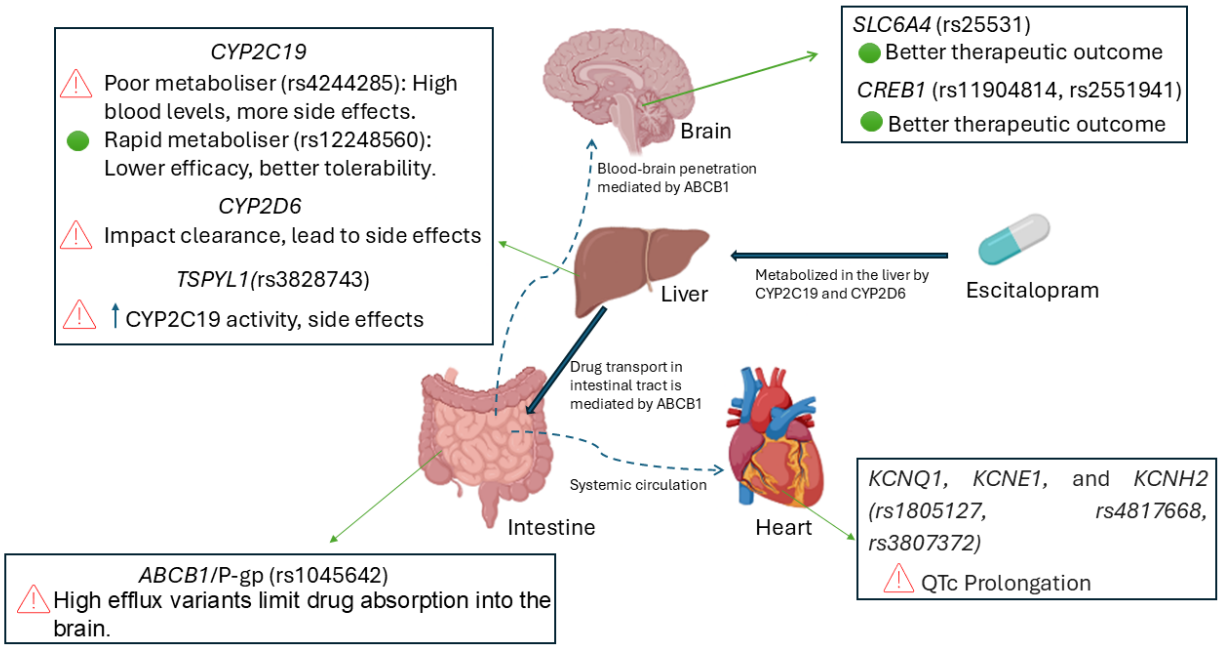

Figure 3. The Effects of Various SNPs on Escitalopram Efficacy. Genetic variants in CYP2C19, CYP2D6, and ABCB1 affect escitalopram metabolism, transport, and brain exposure, while SLC6A4 and CREB1 influence therapeutic response and KCNQ1/KCNE1/KCNH2 variants are associated with QTc prolongation risk.

*CYP2D6**9 (rs5030656), *CYP2D6**10 (rs1065852) and *CYP2D6**41 (rs28371725). The results demonstrated that decreased *CYP2C19* metabolic activity significantly enhanced the impact of *CYP2D6* genotype on escitalopram serum concentrations. Specifically, *CYP2C19* normal metabolizers exhibited a 24% higher escitalopram CD ratio compared to *CYP2D6* normal metabolizers ($p < 0.001$). This effect was more pronounced in *CYP2C19* intermediate metabolizers, where *CYP2D6* poor metabolizers had a 28% higher CD ratio ($p < 0.001$), and in *CYP2C19* poor metabolizers, where the difference reached 31% ($p = 0.04$). Conversely, no significant effect of *CYP2D6* genotype on CD ratio was observed in *CYP2C19* ultra-rapid metabolizers, suggesting that high *CYP2C19* activity may mitigate the influence of *CYP2D6* variation. Furthermore, the metabolic ratio also followed a similar trend, with a stepwise increase in the effect of *CYP2C19* genotype as *CYP2C19* metabolic capacity decreased. These findings underscore the additive and interactive effects of *CYP2C19* and *CYP2D6* genetic variation on escitalopram metabolism (Faraj et al. 2024).

In contrast, despite the established pharmacokinetic relevance of *CYP2C19* variants, according to which the poor metabolizers are expected to have higher plasma concentrations of escitalopram than others, Hippman et al. found no significant association between *CYP2C19* metabolizer status and depression symptom severity during pregnancy. Among the cohort of 83 pregnant women taking SSRIs, including escitalopram, depression scores did not differ significantly across the four predicted metabolizer groups. These findings suggest that, within the context of the second and third trimesters of pregnancy, *CYP2C19* genotype may not meaningfully influence the clinical effectiveness of escitalopram, as measured by depression symptomatology (Hippman et al. 2022). In another study, escitalopram was found to be significantly associated with adverse lipid parameters. However, no statistically significant pharmacogenetic associations were observed between *CYP2C19* metabolic phenotypes and

lipid parameters in participants taking citalopram/escitalopram. While the study stratified metabolic phenotypes into normal, intermediate, poor, rapid, and ultra-rapid metabolizers and used linear regression models adjusted for key covariates, no meaningful differences in lipid levels were attributed to *CYP2C19* variation within this medication subgroup (Richards-Belle et al. 2023).

3.3. CYP2D6

In the Understanding Drug Reactions Using Genomic Sequencing (UDRUGS) study cohort, gene-drug-response pairs involving *CYP2D6* and escitalopram were identified and analyzed. The data revealed that 41% (15 out of 37) of these *CYP2D6*-antidepressant-response pairs were considered actionable (Kee et al. 2023).

3.4. ABCB1

The *ABCB1* gene, encoding the P-glycoprotein (PGP) transporter, plays a critical role in regulating the central nervous system (CNS) availability of various antidepressants through efflux at the blood–brain barrier. The *ABCB1* gene encodes P-glycoprotein, an efflux transporter that limits antidepressant penetration across the blood–brain barrier.

Another study investigated the association between the *ABCB1* rs1045642 (C3435T) single-nucleotide polymorphism (SNP) and antidepressant treatment response in patients with MDD treated with escitalopram over 8 weeks. Among 113 participants, those with the TT genotype at rs1045642 required significantly lower doses of escitalopram to achieve remission, compared to 24 mg for TC and 19 mg for CC carriers ($p = 0.0001$). This reflects a 2.0-fold greater dose requirement for C allele carriers relative to TT carriers (Singh et al. 2012). A report from the iSPOT-D Trial, examining the role of *ABCB1* genetic variation in antidepressant response, stated that a significant association was found between the rs10245483 SNP and treatment outcomes in patients with MDD treated with escitalopram. Among patients who were homozygous for the common allele of rs10245483, those treated with escitalopram showed a higher remission rate compared to carriers of the minor allele. Specifically, 39.4% of common homozygotes achieved remission, as measured by the 16-item Quick Inventory of Depressive Symptomatology–Self-Rated (QIDS-SR), compared to only 22.2% of minor allele homozygotes ($p = 0.009$).

Additionally, common homozygotes reported significantly fewer side effects, with lower scores on the frequency, intensity, and burden subscales of the side effect rating scale ($p < 0.05$ across all measures). These effects were consistent regardless of cognitive status, indicating that the presence of cognitive impairment did not diminish the predictive value of the rs10245483 genotype (Schatzberg et al. 2015). This study explored the role of genetic variation in the *ABCB1* in influencing the side effect profile of antidepressants, particularly those dependent on the permeability PGP transporter. A total of 789 individuals using antidepressants were included. Among users of PGP-dependent antidepressants, the A-allele of the *ABCB1* gene variant rs2032588 was significantly associated with a reduced number of side effects after adjusting for confounding variables including gender, age, dosage, and duration of use This association was not observed in users of non-PGP-dependent antidepressants, suggesting a specific pharmacogenetic interaction. The rs2032588 SNP remained significantly associated with fewer overall side effects within the PGP-dependent subgroup. These findings suggest a role of *ABCB1* and its variants in determining escitalopram pharmacogenetics. A trend towards a reduced number of serotonergic side effects was observed (FDR-adjusted $q = 0.057$), while no significant associations were found between rs2032588 and cholinergic or histaminergic side effects (Bet et al. 2016). On the other hand, the association between *ABCB1* single-nucleotide polymorphisms (SNPs)

Table 1: Summary of Escitalopram Pharmacogenetic Studies

Gene	rsID(s)	Key association with escitalopram	Reference
SLC6A4	rs25531	Certain allelic variants associated with differential treatment response; findings inconsistent across studies	Kenna et al. 2012; Mandal et al. 2020; Brunoni et al. 2020; Jarčušková et al. 2024
CYP2C19	rs4244285, rs4986893	Poor metabolizer variants associated with higher plasma concentrations, prolonged half-life, and increased exposure	Huang et al. 2021; Islam et al. 2024
	rs12248560	Increased CYP2C19 activity; associated with altered efficacy and tolerability	Zastrozhin et al. 2022
CYP2D6	rs35742686, rs3892097, rs5030655,	Variants jointly influence escitalopram pharmacokinetics when combined with CYP2C19 polymorphisms	Faraj et al. 2024
ABCB1	rs1045642	Genotype associated with dose requirements and treatment response	Singh et al. 2012
	rs10245483	Homozygous variants associated with improved remission rates and fewer adverse effects	Schatzberg et al. 2015
	rs2032588	Variant associated with reduced side-effect burden for P-glycoprotein substrate antidepressants	Bet et al. 2016
TSPYL1	rs3828743	Increased CYP2C19 activity associated with reduced escitalopram response	Qin et al. 2020
CYP1A2	rs2069521, rs2069526,	Variants associated with altered metabolite ratios and increased adverse effects	Kuo et al. 2013
CREB1	rs11904814, rs2551941	Genotypes associated with improved antidepressant response	Yang et al. 2021
KCNQ1 *KCNE1* *KCNH2*	rs1805127, rs4817668, rs3807372	Variants associated with increased risk of QTc prolongation	Chen et al. 2024
PTPRZ1	rs12154537	Associated with anxiety symptom improvement; not significant after correction	Su et al. 2021

rs10245483 and treatment outcomes could not be established. Moreover, none of the investigated *ABCB1* SNPs demonstrated significant associations with response, remission, or changes in depressive symptoms as measured by the Montgomery–Åsberg Depression Rating Scale (MADRS) scores. The overall response and remission rates for all patients were 47.0% and 30.3% in phase I (n=178), and increased to 74.5% and 59.4% in phase II (n=165), respectively (Magarbeh et al. 2023).

3.5. TSPYL

The *TSPYL1* gene encodes the TSPY-like 1 protein, which is active in the brain, testes, and other tissues, though its exact function remains unclear. Based on its link to sudden infant death with dysgenesis of the testes syndrome, the protein is believed to play an important role in the development of the male reproductive system and the brain, particularly the brainstem, which regulates and controls essential functions in the human body like heart rate, breathing, sleeping, and processing sensory information (MedlinePlus 2020).

This study identified a critical role for the *TSPYL1* rs3828743 in modulating both the metabolism and clinical response to escitalopram. Escitalopram is primarily

metabolized by *CYP2C19*, a process that is regulated by *TSPYL1*. The rs3828743 SNP disrupts *TSPYL1*'s ability to suppress *CYP2C19* expression. This leads to increased *CYP2C19* activity. In the Mayo PGRN-AMPS SSRI clinical trial, this variant was significantly associated with lower plasma concentrations of escitalopram after 8 weeks of treatment, indicating enhanced drug metabolism. This effect was particularly prominent in individuals with a normal *CYP2C19* function genotype (*1/*1), where the variant rs3828743 further accelerated escitalopram metabolism, effectively creating a "rapid metabolizer" subgroup within those previously considered normal metabolizers. Clinically, this genetic variation was associated with **poorer treatment response**. Patients carrying the rs3828743 variant, especially those who required dose escalation after week 4, showed significantly lower improvements in depression symptoms based on both the Hamilton Depression Rating Scale (HAMD) and the QIDS-SR scores (Qin et al. 2020).

3.6. CYP1A2

CYP1A2 is involved in the hepatic metabolism of several antidepressants and contributes to interindividual variability in drug exposure and treatment response. A study investigates the association between genetic polymorphisms in the *CYP1A2* gene and the treatment response to the antidepressant escitalopram. Specifically, it examines how genetic variations in *CYP1A2* may influence the metabolism of escitalopram into its primary metabolites, S-desmethylcitalopram (S-DCIT) and S-didesmethylcitalopram (S-DDCIT), and whether these variations correlate with treatment outcomes, including side effects. A total of 158 patients undergoing escitalopram treatment were genotyped for ten SNPs within the *CYP1A2* gene, and serum levels of escitalopram and its metabolites were measured. The results demonstrated significant associations between the SNPs rs2069521, rs2069526, rs4646425, and rs4646427 and the metabolic ratio of S-DDCIT to S-DCIT at week 2 of treatment ($p = 0.002$, 0.018, 0.008, and 0.004, respectively). Furthermore, patients carrying allele types linked to higher S-DDCIT/S-DCIT ratios experienced more severe side effects early in the course of treatment.

These findings suggest that genetic variants in *CYP1A2* may serve as biomarkers for predicting escitalopram metabolism, with fast metabolizers potentially at increased risk for adverse reactions in the initial stages of treatment (Kuo et al. 2013).

3.7. CREB1

The CREB1 gene encodes a transcription factor known as cAMP response element-binding protein (CREB), a basic leucine zipper transcription factor. It is involved in cellular functions, including cell survival. *CREB1* is a member of the *CREB*/*ATF* transcription factor family and plays a role in the dynamic transcriptional regulation of various genes regulating many CNS functions, including neurogenesis, neuronal activation, neuronal survival, and long-term memory (Dinevska et al. 2024). Mounting evidence suggests that the therapeutic effects of SSRIs, such as escitalopram, may involve molecular pathways associated with the CREB. A study investigated the association between SNPs in the *CREB1* and *BDNF* genes and the treatment response to escitalopram in a cohort of 80 patients with panic disorder (PD). Following 8 weeks of escitalopram treatment, clinical assessments were conducted at baseline, week 2, 4, and 8. Four SNPs in the *CREB1* gene (rs11904814, rs6740584, rs2253206, and rs2551941) were genotype. Significant differences in genotype distribution were observed in *CREB1* SNPs rs11904814 and rs2551941 carriers. Notably, subjects with *CREB1* rs11904814 TT and rs2551941 AA responded better to the treatment than others (Yang et al. 2021).

3.8. *KCNQ1, KCNE1,* and *KCNH2*

The *KCNQ* gene family encodes potassium channel subunits with key roles in cardiac,

neural, and sensory function. KCNQ1, co-assembled with KCNE1, forms a cardiac K^+ current essential for repolarization; mutations can cause long QT syndrome and deafness. KCNQ2/3 underlie the neuronal M-current, with mutations linked to juvenile epilepsy (Robbins 2001). In a retrospective study, the association between escitalopram-induced QTc prolongation and genetic as well as clinical factors was evaluated in a cohort of 713 patients who had been prescribed escitalopram and had undergone at least one electrocardiogram (ECG) recording. A subgroup of 135 patients (45 with QTc prolongation and 90 without) was genotyped for 43 SNPs across three key genes implicated in cardiac repolarization: *KCNQ1*, *KCNE1*, and *KCNH2*. Although the mean escitalopram dose was higher in the QTc prolongation group (10.3 mg) compared to the non-prolongation group (9.4 mg), specific genetic variants were found to significantly contribute to increased risk. Carriers of the *KCNE1* rs1805127 C allele and rs4817668 C allele showed a higher likelihood of QTc prolongation. Similarly, individuals with the AG or GG genotypes of *KCNH2* rs3807372 were also at elevated risk (Chen et al. 2024).

3.9. PTPRZ1

PTPRZ1 encodes a member of the receptor protein tyrosine phosphatase family, with genetic expression limited to the CNS. It is thought to be involved in the regulation of specific CNS developmental processes (NCBI 2025). A Chinese research study investigated the potential role of *PTPRZ1* gene variants in predicting SSRI treatment outcomes in MDD patients Cohort 1 (N = 344), which received a variety of SSRIs (including fluoxetine, sertraline, citalopram, escitalopram, fluvoxamine, and paroxetine), and Cohort 2 (N = 160) received only escitalopram for 8 weeks. Furthermore, five *PTPRZ1* SNPs (rs12154537, rs6466810, rs6466808, rs6955395, and rs1918031) were genotyped. In Cohort 2, which had uniform treatment with escitalopram, a statistically significant association was observed between therapeutic outcome and *PTPRZ1* rs12154537 ($p = 0.004$). In the same cohort, a significant association was identified with the G–G–G–G haplotype (rs12154537–rs6466810–rs6466808–rs6955395) ($p = 0.005$). However, no robust association between *PTPRZ1* variants and depressive symptom remission remained after correction for multiple testing, indicating that the genetic influence of *PTPRZ1* may be more specific to anxiety symptom improvement rather than depression (Su et al. 2021).

4. Discussion and Recommendations

Depression is among the most prevalent psychiatric disorders (Zhang and Yue 2025). Despite decades of research, the exact pathophysiology of depression is not completely understood, although neurotransmitter dysregulation, particularly involving serotonin, dopamine, glutamate, and GABA, emerges as a consistent theme. These findings support the rationale for SSRIs as first-line treatments, while also explaining their variable efficacy (Pandarakalam 2018, Hussain et al. 2020, Lin et al. 2023). Almost 50% of patients fail to respond to initial therapeutic regimens, prompting changes in dose or the prescribed drugs. One of the major culprits behind the collapse of treatment regimens is genetic variation in numerous metabolic enzymes, leading to varied responses to antidepressant agents. Pharmacogenomic or pharmacogenetic testing can potentially optimize antidepressant selection as well as therapeutic outcome, and decrease the risk of adverse events (Vernacchia et al. 2024). Variations in approximately 27 genes are thought to play a role in differences in treatment response to antidepressants. These genetic variations can be in coding and non-coding genomic regions (García-Marín et al. 2022).

Althoug pharmacogenetics is being hailed for its potential to personalize medicine, its utility in routine clinical practice remains challenging. A key barrier has been the lack of clear, actionable guidelines for interpreting and applying

phamacogenetics test results. To counter this constraint, the Royal Dutch Pharmacists Association established the Dutch Pharmacogenetics Working Group (DPWG) in 2005. The DPWG was mandated to develop evidence-based therapeutic recommendations through systematic literature reviews and support healthcare providers by incorporating these guidelines into electronic prescribing, dispensing, and medication surveillance systems.

The current guideline focuses on gene-drug interactions between *CYP2D6* and *CYP2C19* and SSRIs, like escitalopram, aiming to optimize antidepressant therapy through pharmacogenomic insights (Brouwer et al. 2022). Escitalopram is mostly metabolized through CYP2D6 and CYP2C19. Genetic variations in *CYP2D6* and *CYP2C19* could significantly impact escitalopram's efficacy, as research demonstrated (Honeycutt et al. 2024, Mahajna et al. 2023, Kee et al. 2023). However, non-association between *CYP2C19*, encoding the key metabolic enzyme for escitalopram, was also reported (Hippman et al. 2022, Richards-Belle et al. 2023). These contradictory findings could be chalked up to factors like methodology, sample size, and the intended outcomes, ethnic background, polygenicity, and physiological status. While the evidence points to a strong *CYP2C19*-escitalopram association, the results are context-dependent.

Notably, while guidelines show that *CYP2D6* also influences escitalopram's efficacy(Brouwer et al. 2022, Kee et al. 2023), more research is required in that area. Despite being the key regulators of the drug's metabolism, these aren't the only crucial genes; *ABCB1*, *CYP1A2*, *CREB1*, *TSPYL*, *PTPRZ1*, *KCNQ1*, *KCNE1*, and *KCNH2* also exhibited influence on escitalopram's efficacy.

Furthermore, the rise in advanced and high-thoroughput genetic analysis techniques is making it easier to use multi-CYP tests, offering a long-term advantage over conventional techniques. Development in pharmacogenetics, particularly through genome-wide association studies, whole-exome sequencing (WES), and whole-genome sequencing (WGS), may reveal novel genetic variants that affect treatment outcome and guide therapy. Moreover, calculating polygenic risk scores could potentially give insights into depression risk, therapeutic outcomes, and side effects. However, they must be clinically validated.

In addition to pharmacogenetics, the incorporation of epigenetics, therapeutic drug monitoring, drug-drug interactions, clinical evaluations, and brain imaging could significantly optimize depression treatment. A multi-contextual pharmacogenetic knowledge, including pharmacokinetics and pharmacodynamics profile, will be invaluable for refining a personalized treatment plan. However, there is a considerable gap in research and literature focusing on genetic factors involved in the pharmacodynamics of this drug and other antidepressants (Eap et al. 2021).

5. Conclusion

Depression is a debilitating condition that impacts several individuals globally. In addition to lifestyle changes, effective pharmacological intervention is crucial for its management and cure. Incomplete understanding of pathophysiology and manifestations of this disease further challenges the efficacy assessment of antidepressants. One piece to the puzzle can be provided by pharmacogenetics. Particularly, the genetic variants of *SLC6A4*, *ABCB1*, and *CYP2C19* can aid with tailoring effective treatment strategies involving escitalopram. The genetic variants could potentially be utilized as efficacy biomarkers and prevent unnecessary exposure to ineffective therapies and financial losses. One of the main hurdles in fully utilizing these biomarkers is the lack of proper guidelines and genetic databases, especially in low-and-middle income countries. The rise in awareness and fall in costs for pharmacogenetic testing will prove to be beneficial for personalized medicine.

Competing Interests

The authors have no competing interests to declare.

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Ethics Approval

Not applicable, since the work does not involve any study with human participants or animals.

Consent Forms

Not Applicable

Author Contributions

Both authors contributed equally to this study. NS conceptualized the study, and NS and NH drafted the manuscript. Both authors reviewed and approved the final version of the manuscript.

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