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J.Biomed.Transl.Res
ISSN: 2503-2178

JOURNAL OF BIOMEDICINE AND TRANSLATIONAL RESEARCH

Available online at JBTR website: https://jbtr.fk.undip.ac.id

Review Article

The Influence of *CYP2C19* Gene Variants on Selective Serotonin Reuptake Inhibitors in Patients with Major Depressive Disorder: A Pharmacogenetic Prospecting Approach

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Article Info
History
Received: 22 Sept 2023
Accepted: 29 Apr 2024
Available: 30 Apr 2024

Abstract

Major Depressive Disorder (MDD) is a chronic disorder characterized by at least a two-week-long major depressive episode. MDD presents a significant global health burden, often treated with Selective Serotonin Reuptake Inhibitors (SSRIs). However, variable responses to SSRIs, including ineffectiveness and adverse effects, may be attributed to genetic factors influencing drug metabolism, particularly by the CYP2C19 enzyme. This review aimed to assess the impact of *CYP2C19* gene variants on the effectiveness and safety of SSRIs, specifically citalopram, escitalopram, and sertraline, in patients with MDD. A systematic search of databases including PubMed, Google Scholar, and ScienceDirect was conducted using relevant keywords. Articles published between 2013 and 2023 were included. Nine relevant studies from various countries were identified and analyzed. Findings indicated that *CYP2C19* gene variants, notably loss-of-function *(*2, *3)* and gain-of-function *(*17)*, influence the metabolism of SSRIs. Variability in enzyme activity among individuals carrying these variants can lead to significant alterations in drug efficacy and safety profiles. The review underscored the importance of considering genetic factors, particularly *CYP2C19* variants, in tailoring SSRI treatment for MDD.

Keywords: *Major Depressive Disorder; CYP2C19; Gene Variant; Selective Serotonin Reuptake Inhibitors; Drug Metabolism.*
Permalink/ DOI: https://doi.org/10.14710/jbtr.v10i1.20338

INTRODUCTION

Major Depressive Disorder (MDD) is a severe condition marked by at least one major depressive episode that endures for a minimum of two weeks. Distinguished shifts in mood and interest, significant changes in thinking patterns, and conspicuous autonomic symptom alterations accompany it.[1] According to information retrieved from the Institute of Health Metrics and Evaluation in 2023, global depression affects around 280 million individuals. Approximately 3.8% of the global population suffers from depression, with rates varying among different demographics, such as 5% among adults, split into 4% for men and 6% for women, and 5.7% among adults aged 60 years and older.[2] The statistics are influenced by a range of factors including variations in hormone levels among women, the impact of childbirth, varying psychosocial stressors encountered by both men and women, as well as the frequently experienced sense of helplessness among women.[3]

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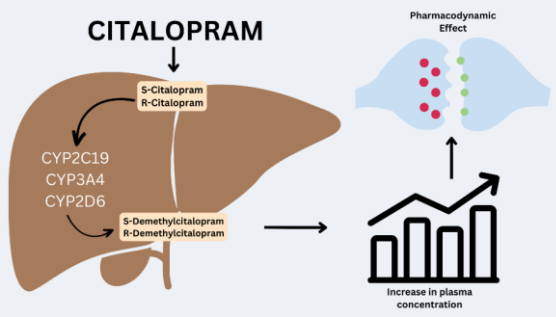

Figure 1. Metabolism of citalopram and escitalopram

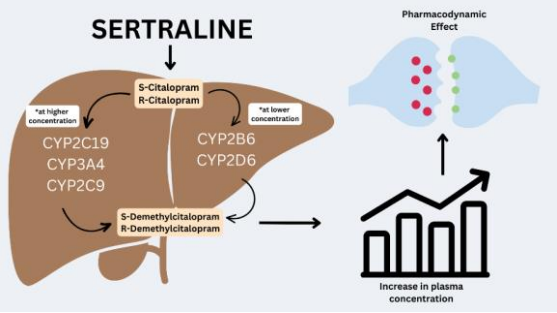

Figure 2. Metabolism of sertraline

MDD is frequently associated with chronic conditions such as diabetes, stroke, and other cardiovascular diseases, thus increasing concerns about this illness. Furthermore, MDD is known to lead to suicide among its sufferers.[4]

Although antidepressants remain crucial in addressing moderate to severe MDD, their effectiveness varies. A significant portion of individuals do not achieve optimal response or even discontinue treatment due to early side effects. Research shows that around 60-70% of individuals with depression do not attain remission, and approximately 30-40% either do not show a notable improvement or encounter medication-related adverse effects leading to discontinuation of treatment, non-adherence, and the emergence of chronic conditions. One significant factor contributing to variations in drug response is the varying activity levels of drug-metabolizing enzymes among individuals, leading to differences in drug exposure.[5,6]

Selective Serotonin Reuptake Inhibitors (SSRIs) constitute a commonly prescribed class of medications primarily utilized for treating depression. Their mode of action involves the inhibition of the serotonin transporter (SERT) at the presynaptic axon terminal. This inhibition results in a prolonged presence of serotonin (also known as 5-hydroxytryptamine or 5-HT) within the synaptic cleft, thereby extending stimulation of postsynaptic receptors. Due to their favorable safety profile, effectiveness, and tolerability, these drugs are recommended as the initial pharmacotherapeutic approach for depression and other mental disorders. Unlike other antidepressant categories, SSRIs have limited impacts on neurotransmitters such as dopamine or norepinephrine. Additionally, SSRIs tend to induce fewer side effects in comparison to Tricyclic Antidepressants (TCAs) and Monoamine Oxidase Inhibitors (MAOIs), mainly owing to their reduced influence on adrenergic, cholinergic, and histaminergic receptors.[7] Nevertheless, despite their extensive utilization, research conducted in the early 2000s indicated that one out of every three patients did not exhibit a positive response to SSRI therapy.[8] Subsequently, this observation garnered validation from other studies, highlighting that SSRIs, predominantly metabolized by the CYP2C19 isoenzyme, displayed susceptibility to variations attributable to many genetic variants.[9,10] SSRIs primarily metabolized by CYP2C19 include escitalopram, citalopram, and sertraline.[11,12] This study will review the influence of *CYP2C19* gene variant on the metabolism of SSRIs (escitalopram, citalopram, and sertraline).

MATERIALS & METHOD

The review process involved searching for relevant articles in Google Scholar, PubMed, and Science Direct databases. The search was conducted using keywords such as "CYP2C19 gene variants," "SSRIs," "major depressive disorder," "pharmacogenetics," "polymorphism," and "variants." Articles within the range of 2013-2023 were included in the review, resulting in the identification of 9 articles that matched the title.

METABOLISM OF CITALOPRAM AND ESCITALOPRAM

Citalopram (CIT) and escitalopram (ESC), both classified as selective serotonin reuptake inhibitors (SSRIs), are frequently recommended for addressing depression. Citalopram and its N-demethylated metabolite comprise a racemic combination encompassing S-enantiomer and R-enantiomer forms. In contrast, escitalopram is the S-enantiomer derived from the racemic citalopram compound.[13] Both enantiomers of citalopram undergo metabolism in the liver through the cytochrome P450 system. As depicted in Figure 1, the formation of R/S-demethylcitalopram is primarily facilitated by the isoenzymes CYP2C19, CYP3A4, and CYP2D6. In vitro and in vivo investigations consistently showed that the effects of citalopram and N-demethylcitalopram are primarily associated with their S-enantiomers, S-citalopram, and S-demethylcitalopram. These S-enantiomers exhibit significantly higher potency in inhibiting serotonin reuptake compared to their respective R-enantiomers, with S-citalopram being about 167 times more potent and S-demethylcitalopram being 6.6 times more potent. Furthermore, the conversion of citalopram to R/S-didesmethylcitalopram involves the action of CYP2D6. In vitro studies on human liver microsomes demonstrated that CYP2C19, CYP3A4, and CYP2D6 were responsible for the transformation of the biologically active S-enantiomer. Due to the racemic nature of citalopram, its administration results in separate steady-state concentrations of R- and S-stereoisomers. Additionally, processes involving N-oxidation and deamination, mediated by CYP2D6, create R/S-citalopram N-oxide and citalopram propionic acid metabolites.[14]

METABOLISM OF SERTRALINE

Sertraline is an effective and widely used antidepressant. Studies have found that sertraline metabolism occurs in the liver, primarily through N-demethylation. Moreover, research suggested that among the CYP450 enzyme family, CYP2C19 plays a

significant role in the sertraline metabolism process.[15,16] Majority of studies on sertraline metabolism asserted that the key metabolic pathway involves demethylation, converting sertraline into desmethylsertraline, which is the sole active metabolite of sertraline. In vitro studies suggested that when sertraline concentrations were higher, the primary contributors to its metabolism were CYP2C9, CYP3A4, and CYP2C19, with CYP2D6 and CYP2B6 making minor contributions (see Figure 2). However, when sertraline concentrations are lower, CYP2D6 and CYP2B6 assume a more prominent role in the formation of desmethylsertraline, while the impact of CYP3A4 on this process diminishes.[17]

CYP2C19 GENOTYPE

CYP2C19, a vital component of the cytochrome P450 superfamily (CYP450), accounts for approximately 16% of the total liver enzyme composition. This particular enzyme holds a pivotal role in the hepatic metabolism of diverse medications, such as antimalarials (proguanil), antiplatelets (clopidogrel), and antidepressants (amitriptyline, clomipramine). The existance of genetic variants within *CYP2C19* significantly impacts the metabolism of these substrates, thus shaping individual responses to these drugs [18]. Díaz-Ordóñez et al. (2021) successfully identified at least 40 *CYP2C19* variants in their study.[19]

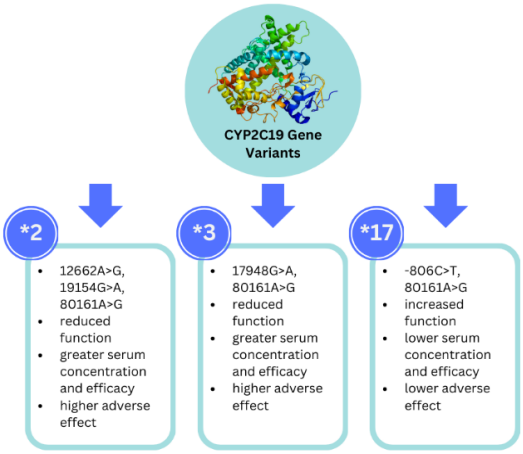

Figure 3. Characteristics of *CYP2C19* gene variant

Table 1. *CYP2C19* Variants diplotype and its enzyme activity[22].

Phenotype	Genotype	Enzyme activity
Ultra-rapid metabolizer	**1/*17* **17/*17*	Increased
Extensive metabolizer	**1/*1*	Normal
Intermediate metabolizer	**1/*2* **1/*3* **2/*17* **3/*17*	Intermediate
Poor metabolizer	**2/*2* **3/*3* **2/*3*	Reduced or none

The *CYP2C19* diplotype and its corresponding enzyme activity are outlined in Table 1. Loss-of-function variant alleles, specifically *CYP2C19*2* and **3*, are grouped as *CYP2C19Null*, whereas *CYP2C19*17* is the sole gain-of-function variant allele recognized. Patients with the Poor Metabolizer (PM) genotype (*CYP2C19Null*/*Null*) lack functional *CYP2C19* enzyme entirely. Intermediate Metabolizers (IM) (*CYP2C19**1/*Null* and *CYP2C19*17*/*Null*) possess one non-functional allele. Patients carrying the *CYP2C19Null*/**17* genotype are categorized as IM because the influence of the *CYP2C19Null* allele on the phenotype is more pronounced than that of the functional *CYP2C19*17* allele. Extensive Metabolizer (EM) or Normal Metabolizer (NM) individuals with the diplotype *CYP2C19*1/*1* have two copies of the wild-type *CYP2C19**1 allele, representing the reference genotype. Ultrarapid metabolizer (UM) denotes individuals who carry either *CYP2C19*1/*17* or *CYP2C19*17*/**17* [20,21]. Figure 3 provides an overview of the characteristics of the three most extensively studied variants, **2*, **3*, and **17*.[22]

The distribution of *CYP2C19* alleles displays a noteworthy trend. The most prevalent non-functional allele, *CYP2C19*2* (c.681G>A; rs4244285), exhibits an occurrence rate of 18% in African and European populations but surpasses 30% in Asian populations. In contrast, other alleles (**3*-**8) are present in limited numbers and lack functionality. *CYP2C19*3* (c.636G>A; rs4986893) possesses a minor allele frequency (MAF) of roughly 7% among East Asian populations. On the other hand, the increased-function allele *CYP2C19*17* (c.-806C>T; rs12248560) has a prevalence of around 23% among Europeans and Africans, with slightly lower occurrence in mixed American and South Asian populations (12%-14%) and nearly absent in East Asians. Consequently, the *CYP2C19* phenotype spans a wide range, from poor metabolism (PM) to ultra-rapid metabolism (UM), with the diversity of these alleles contributing to observed phenotypic variations in different populations.

CYP2C19 Variant and SSRI Metabolism

Several studies that have established a connection between *CYP2C19* variant and the effectiveness of SSRI drugs are presented in Table 2. Jukic et al. (2018) used a retrospective study method on 2087 patients in Norway and found the indications that patients with *CYP2C19* PM and IM genetic profiles would exhibit higher serum concentrations of escitalopram compared to EM.[20] Conversely, patients with UM metabolism status would show lower serum concentrations of escitalopram. The results implied that patients with this metabolism status might face treatment failure. Furthermore, the data suggested that patients with *CYP2C19* UM and PM metabolism conditions are more inclined to switch to other classes of antidepressants in comparison to those with EM metabolic conditions.

Table 2. Research conclusion related to *CYP2C19* variants and their effects on SSRI metabolism.

SSRI	Research type	Genes	Origin of Study	Conclusion	Research
ESC	Retrospective Study	**2, *3, *4, *17*	Norway (n=2087)	PM indicates a tendency for patients to switch medications, while UM shows serum drug concentrations below the therapeutic window.	20
ESC	Clinical Trial	**1, *2, *3*	Japan (n=142)	A significant correlation between *CYP2C19* Variant and ESC concentration can only be found at adjusted doses.	23
ESC	Clinical Trial	**1, *2, *3*	China (n=90)	PM has the highest AUC0-t and AUC0-∞, and the longest half-life. Different Cmax levels were found among the three phenotypic types, but they were insignificant.	21
ESC	Clinical Trial	**2, *3, *17*	Brazil (n=31)	Patients with UM metabolism status show the highest HDRS scale, signifying treatment failure.	5
CIT	Clinical Trial	**2, *17*	Turkey (n=2019)	*CYP2C19*2* variant contributes to inter-individual variability in CIT metabolism in vivo.	24
CIT	Clinical Trial	**2*	Russia (n=130)	Patients with GA genotype status (IM) have lower blood drug concentrations.	25
SET	Clinical Trial	**1, *2, *3, *17*	Scandinavia (n=1202)	*CYP2C19*17* does not significantly impact therapeutic response, whereas increased serum concentrations in PM and IM can elevate the risk of overexposure and adverse drug reactions.	34
SET	Clinical Trial	**2, *17*	Turkey (n=50)	There are no significant differences in plasma concentrations among *CYP2C19* subgroups.	27
ESC, CIT, dan SET	Retrospective Study	**2, *3, *17*	Australia (n=9168)	Participants with RM status show the best tolerability; IM faces a higher risk of side effects, while PM exhibits better efficacy.	6

Huang et al. (2021) studied 90 clinical trial participants in China that investigated the influence of CYP2C19 metabolism on patient pharmacokinetic profiles using the area under the curve (AUC), half-life ($t_{1/2}$), and maximum concentration (C_{max}) data.[21] The data indicated that PM patients had the highest AUC_{0-t} and $AUC0_{-\infty}$, and the most prolonged half-life compared to EM and IM. These AUC results can be interpreted as PM patients potentially having higher therapeutic exposure than EM and IM, which relates to treatment efficacy and safety. While there were differences in C_{max} values among patient profiles, they were not highly significant. UM metabolism status was not included in this study due to a lack of candidates.

In contrast, Tsuchimine et al. (2018) yielded opposing results in Japan.[23] No notable association was observed between *CYP2C19* variant and steady-state escitalopram concentrations when administered at typical doses. This lack of correlation is believed to result from the substantial variability in plasma concentration of escitalopram at a steady state. However, when adjusted for escitalopram doses, a significant correlation was

found. Furthermore, the authors raised the potential involvement of CYP3A4 in the N-demethylation of escitalopram, which could introduce complexity when measuring steady-state plasma escitalopram concentrations.

Different from previously discussed articles, a study by Bernini de Brito & Ghedini (2020) in Brazil utilized the HDRS (Hamilton Rating Scale for Depression) scale to measure indications of depression in patients through a questionnaire. The results showed that patients with *CYP2C19* UM metabolism conditions had higher HDRS scale scores, indicating more severe levels of depression compared to other metabolism statuses.[5]

Furthermore, investigations into the impact of *CYP2C19* variant on the effectiveness of citalopram were carried out by Uckun et al. in 2015 and Zastrozhin et al. in 2021.[24,25] The study by Uckun et al. (2015) indicated a significant role of *CYP2C19* variant in the CIT metabolism process. *CYP2C19*2* variant was crucial in inter-individual variations in in vivo CIT metabolism at therapeutic doses commonly used in clinical practice. Thus, the *CYP2C19*2* variant was predicted to yield better treatment outcomes and a higher risk of adverse drug effects. In contrast, this study found no significant differences in CIT and DCIT plasma concentrations between patients with the *CYP2C19*17* allele and those with *CYP2C19*1* homozygotes.[24]

Zastrozhin et al. (2021) specifically investigated the impact of *CYP2C19*2* variant on the effectiveness of citalopram. The variations were statistically significant in the equilibrium concentrations of citalopram among patients with different *CYP2C19*2* (681G>A) genotypes. Patients carrying the A allele exhibited lower drug equilibrium concentration levels than those with the G allele. This reduction seems to arise from decreased biotransformation processes and a slower elimination rate of citalopram in individuals with the A allele, leading to drug accumulation in the bloodstream. Consequently, there is a potential for an elevated risk of adverse drug reactions and the possibility of developing pharmacoresistance. These findings suggest that carriers of this polymorphic variant may face an increased likelihood of experiencing adverse drug reactions associated with citalopram, likely due to reduced CYP2C19 activity, impaired drug biotransformation processes, decreased elimination rates, and subsequent drug buildup in the bloodstream.[25]

The third SSRI drug primarily metabolized by CYP2C19 is sertraline. A study conducted by Bråten et al. (2020) found that individuals with CYP2C19 PM and IM variants exhibited notably higher serum concentrations of sertraline in comparison to those categorized as normal metabolizers (NM). This increase is attributed to the compromised metabolism of sertraline, a process typically facilitated by the CYP2C19 enzyme in individuals with PM and IM phenotypes. Interestingly, the study results indicated that the *CYP2C19*17* variant did not affect the therapeutic response to sertraline. However, the heightened serum concentrations observed in individuals with CYP2C19 PM and IM phenotypes pose a potential risk of drug overexposure, potentially leading to adverse drug reactions.[26] Based on these findings and using NM individuals as the reference group within a large patient population, it is estimated that the initial sertraline dose could be reduced by 60% for individuals with the CYP2C19 PM phenotype and by 25% for individuals with the CYP2C19 IM phenotype. These estimates are based on the relative differences between the IM and PM phenotypes compared to NM. Nevertheless, the slight variations in the ratio of sertraline to N-desmethylsertraline among different *CYP2C19* phenotype groups suggest that other enzymes may have a more substantial role in the N-demethylation process of sertraline. The result highlights the broader complexity of sertraline metabolism that must be considered when effectively adjusting doses and monitoring drug therapy.

Another study that elucidates the impact of *CYP2C19* variant on sertraline efficacy is the research by Yuce-Artun et al., 2016.[27] The findings from this study support the 2020 study by Bråten et al. that the genetic variant *CYP2C19*17* does not significantly influence sertraline metabolism. Concurrently, this study investigated the relationship between *CYP2B6* variant and sertraline efficacy. However, it was discovered that the *CYP2B6*6* variant has a more pronounced role and appears to contribute to inter-individual variations in SERT metabolism under real-world conditions at therapeutic doses used in clinical practice.

Among the studied articles, Campos et al. (2022) is the only one that discusses all three drugs together, namely escitalopram, citalopram, and sertraline. This research was conducted retrospectively on 9500 participants in Australia. This study indicated that individuals with PM status experience significantly higher antidepressant efficacy than those with normal or rapid metabolism. Furthermore, it was discovered that individuals with Rapid Metabolizer (RM) status have higher tolerability levels. They tend to have a lower risk of discontinuing drug use than individuals with NM status due to side effects. However, individuals with intermediate metabolism, who fall between rapid and slow metabolizers, may have a higher risk of reporting side effects during treatment. These findings indicate that drug tolerability can vary depending on the *CYP2C19* metabolizer status, with RM status showing the best tolerability, IM facing a higher risk of side effects, and PM showing better efficacy.[6]

DISCUSSION

Pharmacogenetics and pharmacogenomics are two fields that have gained significant attention recently, alongside the rise of studies in personalized medicine. Despite appearing similar, these two fields have distinctions. Pharmacogenetics is a research field studying how genetic variations in individuals can affect drug responses. Its focus is on specific genes or particular genetic variations' roles in influencing drug metabolism, transportation, or mechanisms of action. On the other hand, pharmacogenomics utilizes a broader approach, examining the relationship between the overall genetic profile and drug responses.

Genetic profiling tests are in high demand due to the evidence of varying treatment outcomes in individuals based on their genetic conditions. One of the most prominent studies involves the *CYP2D6* gene's metabolism in relation to anticancer drug substrates. *CYP2D6* is a gene with numerous variants that often lead

to different therapeutic outcomes in cancer patients. In 2013, Westbrook & Stearns stated that remarkable progress has been made in breast cancer treatment by introducing targeted therapies like aromatase inhibitors (AI) and biological therapies like trastuzumab. Targeted therapy introductions have proven to aid in understanding factors contributing to individual variability in response to various breast cancer treatments, such as the impact of genetic variations on drug metabolism.[28,29] Pharmacogenomic studies are also considered to have great potential in altering asthma treatment regimens in other diseases, such as asthma. Data and findings from pharmacogenomic studies suggest that standard treatment guidelines cannot be uniformly applied to the entire asthma patient population. Understanding the influence of genetic variations on therapy responses can reduce side effects and enhance patient outcomes.[30]

Major depressive disorder is a proven hereditary illness. Individuals with a family history of MDD have a threefold higher risk of experiencing depression. Broadly, the two main options for treating MDD are psychotherapy and pharmacotherapy. Both approaches have demonstrated efficacy in reducing depressive symptoms and overall well-being. A recent study indicated that combining psychotherapy and pharmacotherapy as an initial treatment strategy produced more favorable outcomes than utilizing either treatment in isolation.[4]

The application of genetic profiling to tailor depression therapy has been extensively studied. A meta-analysis conducted in 2018 stated that depressed patients treated with pharmacogenetic guidance had a 1.71 times higher chance of symptom remission compared to patients who did not undergo pharmacogenetic testing.[31] Another systematic study in 2021 also declared that treatment guided by pharmacogenetic testing would positively affect symptom remission and better treatment response.[26]

In Indonesia, the initial investigation into the prevalence of the *CYP2C19* gene was carried out by Ikawati et al. in 2014, focusing on *CYP2C19* variants within the Bugis ethnic group.[32] This research was subsequently expanded upon by Miftahussurur et al. in 2021, encompassing a broader examination of variant distribution in Indonesia and comparing various ethnic groups. The findings revealed that the frequency of recessive genes responsible for diminished CYP2C19 activity (**2* and **3* alleles) stood at 40.7% (135 out of 332). In summary, the prevalence rates for rapid, intermediate, and poor metabolisms in Indonesia were 38.5%, 41.6%, and 19.9%, respectively. This data indicates that more than half (61.5%) of participants exhibited reduced CYP2C19 enzyme activity.[33]

Despite its clear significance, pharmacogenetic and pharmacogenomic studies in Indonesia are still relatively rare. Some private health laboratories offer genetic profiling services, which are considered exclusive. In the future, pharmacogenomic and pharmacogenetic studies are expected to gain more attention, considering Indonesia's diverse demographic, ethnicities, and genetic background. This review, especially, has the potential to shed light on how genetic variations (*CYP2C19*) within the population can influence drug responses (CIT, ESC, and SERT) uniquely. The findings from such research can directly impact clinical practice, helping healthcare providers make informed decisions about medication choices and dosages, ultimately improving treatment outcomes and reducing adverse drug reactions.

CONCLUSION

Variants in *CYP2C19* have been demonstrated to influence the efficacy of SSRIs in treating patients with Major Depressive Disorder symptoms. Patients with UM metabolism status typically exhibit lower plasma serum concentrations, indicating a risk of treatment failure. Conversely, patients with IM or PM metabolism status tend to display higher plasma serum concentrations and an increased risk of adverse drug reactions (ADRs). Hence, it would be beneficial for patients prescribed SSRIs to undergo pharmacogenetic testing prior to treatment initiation, enabling an assessment of their pharmacogenetic profile and the formulation of an appropriate treatment plan. While such studies are still relatively scarce in Indonesia, future challenges may encompass financial constraints, the necessity for specialized infrastructure and expertise, and the integration of pharmacogenetic testing into routine clinical practice. However, considering the importance of this research, it will be necessary to gather all information about human genetic profiles to inform drug choices in Indonesia. This approach can increase the likelihood of treatment success and mitigate the occurrence of adverse reactions.

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