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CYP2C19 GENETIC POLYMORPHISMS ON ESCITALOPRAM TREATMENT OUTCOME IN SOUTH INDIAN POPULATION WITH MAJOR DEPRESSIVE DISORDER

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ABSTRACT:

Various CYP2C19 mediated metabolizer groups may arise as a result of inter-individual variability, which potentially influences the efficacy and safety of escitalopram. The aim of this study is to classify MDD patients into various CYP2C19 metabolizer groups and to determine the association between phenotype and treatment outcome. A prospective, open label, observational study of patients with MDD was conducted in the Department of Psychiatry, SVIMS, Tirupati, India. The study enrolled 119 escitalopram monotherapy-treated MDD patients aged 18–58. MADRS, HDRS-17, and CGI were used to measure efficacy at baseline, weeks 4, 8, and 12. Safety and tolerability outcomes were examined from occurring ADRs. Clinical outcomes were compared among phenotype based on changes in HDRS-17, and CGI scores from week 4 to week 12. The statistical analysis was conducted using SPSS software. Subjects were categorized by CYP2C19 genotype: 20 poor (PM), 64 intermediate (IM), 24 extensive (EM), and 11 ultra rapid (UM) metabolisers. Response and remission occurred in 67.2% and 26.8% of the 119 subjects at the end of 12th week study. The response rate in PM was much lower (21.6%) compared to EM. There were 312 adverse drug reactions (ADRs) and 88 (73.94%) individuals had at least one. There were no severe ADRs. The study found that the reduced ability of PM to metabolize escitalopram is probably associated with the decreased efficacy and tolerance shown in PM compared to EM and IM.

Keywords: Major Depressive Disorder; efficacy; safety; escitalopram; genotype; phenotype

1. INTRODUCTION

Major Depressive Disorder (MDD), is a chronic, recurrent disabling mental disorder that causes symptomatic and functional impairment leading to affect individuals' capacity to manage daily responsibilities (Sadock et al., 2015). Globally, more than 300 million individuals of all ages suffer from depression. The National Mental Health Survey in India has revealed that over 23 million individuals could potentially need treatment for depression at any given point in time (Arvind et al., 2019). Not only does MDD have a high suicide incidence (up to 15%), but it also has stress-related problems and associated adverse effects on the cardiovascular system (Dhar and Barton, 2016; Xin et al., 2018). According to the World Health Organization, statistical data suggests that MDD is expected to become the second leading cause of disability and global disease burden by 2030 (Global Burden of Disease Study, 2017; Mathers and Loncar, 2006).

In recent years, escitalopram (ESC) has become one of the most often prescribed SSRIs for the treatment of depression, and is mainly metabolized by CYP2C19 (Maity N et al., 2014) It is a genetically polymorphic drug-metabolizing enzyme with large interindividual metabolic variability (Enhance or diminish function) (Uckun et al., 2015). These polymorphic variants are associated with different phenotypes, including extensive metabolizers (EM; CYP2C19*1/*1), intermediate metabolizers (IM; CYP2C19*1/*2, *1/*3 or *2/*17), poor metabolizers (PM; CYP2C19*2/*2, *2/*3, or *3/*3), and ultra-rapid metabolizers (UM; CYP2C19*17/*17 or *1*17) (Spina and De Leon, 2015; He et al., 2017; Hicks et al., 2015). In contrast to the fully functioning CYP2C19 enzyme encoded by the wild-type allele CYP2C19*1, the majority of people i.e., 25% of ethnic Chinese and 23.5% of Japanese with poor CYP2C19 metabolism carry the variant alleles CYP2C19*2 or CYP2C19*3 (Zohu, 2002; Horai et al., 1989; Yu et al., 2003). A novel CYP2C19*17 variant increases fast antidepressant metabolism (Rudberg et al., 2008).

Inter-individual variations in CYP2C19-mediated metabolism may influence drug concentration/elimination, affecting efficacy and safety (Anderson, 1998; Wilkinson, 2005). In adults, ultra rapid/rapid metabolizers have lower plasma drug concentrations at equal doses, compared with Extensive metabolizers (EMs), while poor metabolizers have increased blood concentrations. Therefore, escitalopram may cause more adverse effects for poor metabolizers and a higher likelihood of treatment failure for ultra rapid metabolizers. However, 35-45% of depressed patients treated with escitalopram have partial clinical remission or major side effects, leading to poor adherence, medication discontinuation, and chronic illness (Rosen et al., 1999; Trivedi etal., 2006). Compared to other SSRIs, side effects of escitalopram were minimal at earlier (Uckun et al., 2015). Escitalopram, on the other hand, has been linked to more common and new side effects that were not seen in the original clinical studies. These have been found through post marketing data and extensive practical experience (Ng et al., 2013). Drug metabolism and enzymatic activity affected by these genetic polymorphisms of cytochrome P450 (CYP) families must be identified to predict treatment response in MDD patients (Hodgson et al., 2014).

The current study was designed to investigate the differences in the escitalopram efficacy, tolerability and safety between different metabolizing groups based on CYP2C19 genotype in outpatients suffering from major depressive disorder (MDD). We also anticipated that poor metabolizers would have more adverse effects and higher response rates than ultrarapid metabolizers, based on exposure trends reported in adults (Chang et al., 2014; Jukic et al., 2018).

2. MATERIAL AND METHODS

Study design

This 12-week, prospective, open label, observational study of patients with MDD was conducted in the Department of Psychiatry, Sri Venkateswara Institute of Medical Sciences (SVIMS), Tirupati, India. The Institutional Ethics Committee (SVIMS, Tirupati) No.1299 approved the study. Written informed consent was obtained from all the patients and legal guardian during participation after explaining the full procedure. Patients were examined at baseline, week 4, week 8, and week 12.

Subjects

A total of 119 MDD patients (78 female and 41 male) attending OPD of Psychiatry was recruited. The participants were on escitalopram monotherapy and those who fulfilled the inclusion criteria mentioned as follows: (1) Patients of either sex, (2) age between 18 to 55 years, (3) patients with escitalopram treatment only and (4) individuals who exhibit depressive symptoms as defined by DSM V.

The exclusion criteria include: (1) patients with diabetes, hypertension, and ischemic heart disease (2) History of receiving antidepressants within the last six weeks; (3) Pregnant or lactating women; (4) History of substance abuse and drug allergies; (5) Chronic illness or taking drugs that cause depression; (7) Neurological disorders, like stroke, dementia, or seizures.

CYP2C19 Genotyping

DNA was extracted from leukocytes in the cellular fraction using phenol:chloroform after centrifugation and plasma separation. The following variables were used in 20 µl PCR reactions: 10 µl of Ex Taq (2X) (Probe qPCR) premix (Takara Bio Inc.), 0.4 µl of primer, 0.8 µl of probe mix, and 1 µl of genomic DNA as template. An Agentech Gentier real-time PCR 48E system with Ianlong® amplification was employed. The procedure included a 30-second pre-incubation at 95°C and a two-step amplification procedure including 5 seconds at 95°C and 30 seconds at 60°C. At 60°C read steps, fluorescence emission was measured. Clinical pharmacogenetic test results were classified in this study according to the CPIC-approved guidelines for CYP2C19 metabolizer phenotypes (Caudle et al., 2017).

Efficacy and safety assessments

Efficacy assessments included HDRS-17, MADRS, and CGI. The main efficacy endpoints were remission and response rates. Remission criteria: MADRS score < 12 and HDRS-17 score < 8. Therapeutic response was 50% HDRS 17 and MADRS total score decrease from baseline. Changes in HDRS-17 and CGI scores from week 4 to week 12 were secondary efficacy outcomes as the reference category was extensive (‘normal’) metabolizers. A baseline evaluation was done after patient recruiting to identify symptoms prior to drug therapy. Safety and tolerability outcomes were examined from adverse effects (AEs). The Udvalg for Kliniske Undersogelser (UKU), often known as the UKU Side-Effect Rating Scale, was used to assess the safety profile. Developed to offer a complete evaluation of side effects with psychopharmacological medications, it is a clinician-rated scale with well-defined elements (Lingjaerde et al., 1987).

Statistical Analysis

For continuous variables, the data was shown as the mean (±standard error), whereas for categorical variables, it was shown as the number and percentage. The quantitative and qualitative data were analyzed using Student's t test. We used Chi-square and Mann-Whitney U tests to analyze thera

py response over time. The assessments relating to ADR were analyzed using descriptive methods. The statistical analysis was conducted using SPSS 22.0. When P value < 0.05, group differences were significant.

3. RESULTS

The study enrolled 119 patients with MDD. Table 1 shows the demographic and clinical data of the patients at baseline, all stratified by CYP2C19 category. The patients age ranged from 18 to 58 years. A total of 78 (65.5%) patients were women, 41 (34.4%) were male. Among the study subjects, 26% reported smoking cigarettes and 31.9% reported consuming alcohol. All patients started escitalopram at 5 mg daily. Escitalopram was increased to 20 mg/day for 11 (83.78%) patients during therapy, while the remainder received the initial dose until the study was completed. The predominant variant allele was CYP2C19*1/*2 (44.5%) followed by CYP2C19*1/*1 (20.1%) and CYP2C19*2/*2 (14.2%). Based on the CYP2C19 genotyping, 64 patients were classified as the IM, 24 patients as EM, 20 patients were PM and 11 patients as UM.

Table 1. Patient's demographic and baseline characteristics of response by CYP2C19 metabolizer phenotypes

Parameters	Total (N=119)	Extensive Metabolizers (N= 24)	Intermediate Metabolizers (N= 64)	Poor Metabolizers (N= 20)	Ultra Rapid Metabolizers (N=11)
Age (Years)	43.2 ± 9.2	40.4 ± 10.2	44.06 ± 9.9	43.45 ± 9.3	43.09 ± 7.7
Sex					
Men [n (%)] Women [n (%)]	41 78	8 16	22 42	7 13	4 7
BMI Mean (SD)	24.8 ± 5.8	24.2 ± 5.35	25.7 ± 6.08	22.62 ± 5.28	24.8 ± 5.36
Marital Status					
Married Bachelor/Single Widowed Divorced	59 21 27 12	9 4 8 3	34 10 13 7	11 4 5 0	5 3 1 2
Smoking n (%)	31	7	18	4	2
Alcohol n (%)	38	9	19	6	4
Patients experiencing first episode, n (%)	52	15	25	8	4
Patients experiencing recurrent episode, n (%)	67	9	39	12	7
CYP2C19 Genotype		*1/*1 (n=24)	*1/*2 (n=53) *2/*17 (n=11)	*2/*2 (n=17) *2/*17 (n=3)	*1/*17 (n=11)

N – Total number of study subjects; n – number of variants

CYP2C19 metabolizer phenotype and efficacy

MADRS mean score change from baseline was the primary efficacy readout, whereas HDRS-17 and CGI scores were secondary readouts. The mean MADRS scores changed throughout escitalopram treatment from baseline to week 12 in various metabolizer groups, as shown in Figure 1. At week 8, PM and UM had 48.5% ($p < 0.05$) and 54.7% ($p < 0.05$) lower MADRS scores than EM. At week 12, PM and UM had 44.9% ($p < 0.05$) and 54.9% ($p < 0.05$) lower MADRS scores than EM. The decline in MADRS scores in the EM and IM cohort were significant ($p < 0.05$) at week 4 and was sustained till week 12.

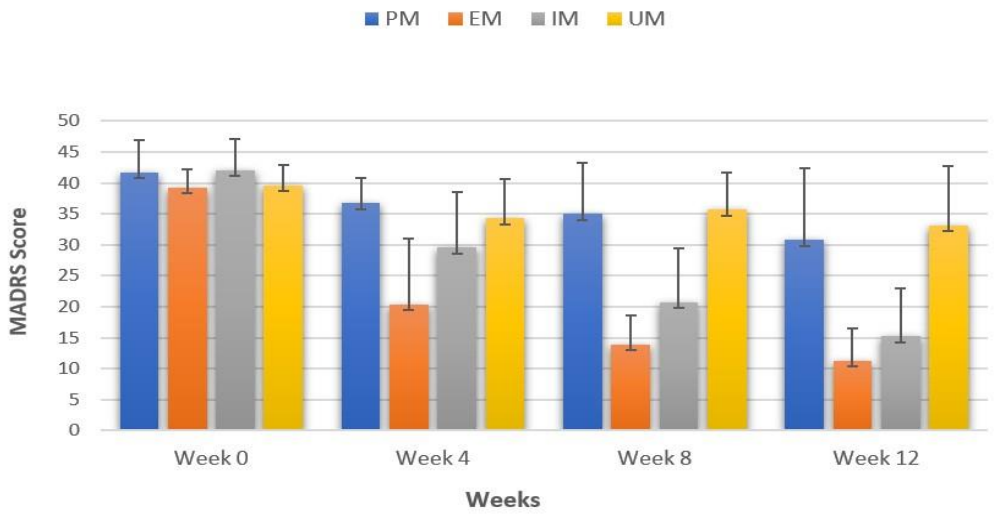

Figure 1. Mean change from baseline in MADRS scores in four CYP2C19 metabolizer groups.

MADRS scores decreased significantly ($p < 0.05$) in EM and IM phenotypes from week 4 to week 12, while there were no significant ($p > 0.05$) differences between the PM and UM. Each column represents the mean + SD (n=119).

After week 12, 39 (32.7%) of 119 study subjects were non-responders and 47 (39.4%) were responders. Remission was achieved by 33 patients (27.7%) of the total. Figure 2 illustrates escitalopram response and remission rates by different CYP2C19 metabolizer status. At weeks 4, 8, and 12, IM and EM had better response and remission rates than PM and UM. Comparing responders and remitters among examined metabolizer groups (EM, IM, PM and UM) using Chi-square test revealed that the association between treatment response and remission was statistically significant. Reduction in HDRS score was seen in all metabolizer groups, however PM & UM had a 42.5% ($p<0.05$) and 49.4% ($p<0.05$) lower reduction than EM at week 12. CGI score of EM was not significantly different from PM at weeks 4, 8, or 12. Changes in CGI-I score from week 4 to week 12 given in Table 2. However, UM and EM were shown to be significantly different. The treatment response was profoundly less among PM, compared to EM patients. Finally, in every visit the highest mean difference was identified in between UM and EM groups.

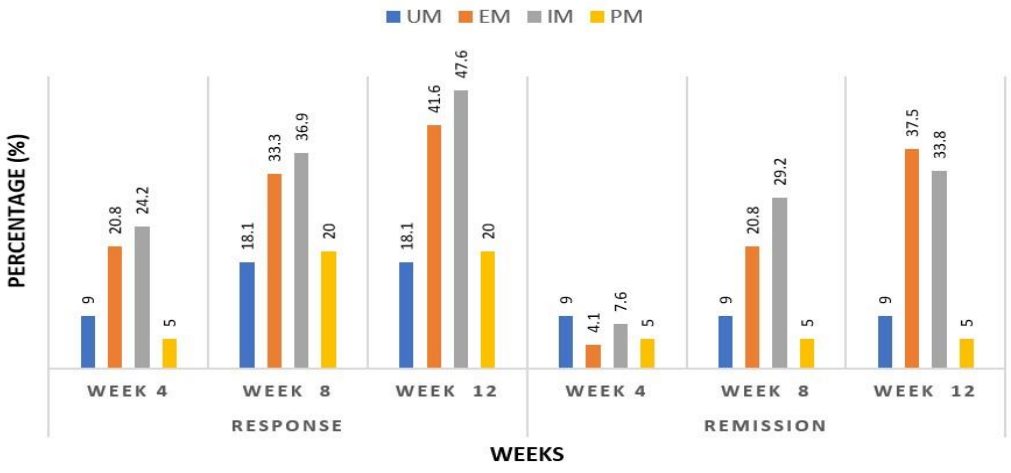

Figure 2. Percentage of subjects showing response and remission during escitalopram therapy. Escitalopram response and remission rates were lower in UM and PM, respectively, at week 12. Each column represents the percentage (n=119).

Overall, CYP2C19 UM showed less improvement of depression symptoms than EM. No significant difference (p >.05) was observed in efficacy outcomes between sex, age groups and patients experiencing a first episode or a recurrent episode.

Table 2. CGI-I changes with different CYP2C19 metabolizer phenotypes (N = 119*)

	Phenotype	N	Mean rank	Sum of ranks	U	P-Value
4 Week	EM IM	24 64	51.42 41.91	1234 2682	602	0.121
	EM PM	24 20	21.6 23.18	526.5 463.5	226.5	0.3064
	EM UM	24 11	15.15 24.23	363.5 266.5	63.5	0.0155
8 Week	EM IM	24 64	40.62 45.95	975 2941	675	0.3843
	EM PM	24 20	20.77 24.58	498.5 491.5	198.5	0.33204
	EM UM	24 11	13.85 27.05	332.5 297.5	32.5	0.0004
12 Week	EM IM	64 24	42.08 50.96	2693 1223	613	0.14475
	EM PM	64 20	19.12 26.55	459 532	159	0.06
	EM UM	64 11	13.92 26.91	334 296	34	0.0005

CGI-I - Clinical Global Impression scale for patients Improvement; *N – Total number of patients

CYP2C19 metabolizer phenotype and Safety

A total of 312 ADRs were reported over the period of 12 weeks. The summary of ADRs in different CYP2C19 metabolizers are shown in Table 3. Nervousness was the most common ADR among the four groups 66 (55.4%), followed by decreased appetite 48 (40.3%), nausea 38 (31.9%), abdominal pain 35 (29.4%), and drowsiness 34(28.6%). However, there were no serious ADRs, and most are mild to moderate. Sexual dysfunction was only reported by men. UKU scale was applied to evaluate the adverse drug reactions in metabolizer groups of patients. When incidence of ADRs compared with the EM, higher rate of ADRs were found in PM and lower in UM. In summary, the PM exhibited lower treatment tolerability than EM, while the treatment tolerability was similar in the EMs and UM.

Table 3. Summary of Adverse drug reactions in different CYP2C19 metabolizers

ADR*	Total (N=119)	Extensive Metabolizers (N= 24)	Intermediate Metabolizers (N= 64)	Poor Metabolizers (N= 20)	Ultra Rapid Metabolizers (N= 11)
Abdominal Pain	35(29.411)	8(33.3)	12(18.7)	14(70)	1(9.09)
Nausea	38(31.9)	6(25)	18(28.125)	13(65)	1(9.09)
Headache	24(20.16)	7(29.166)	7(10.98)	8(40)	2(18.18)
Nervousness	66(55.46)	17(70.83)	22(34.37)	18(90)	9(81.18)
Drowsiness	34(28.57)	9(37.5)	7(10.93)	14(70)	4(36.3)
Weight gain	20(16.80)	4(16.6)	6(9.3)	9(45)	1(9.09)
Irritability	10(8.40)	3(12.5)	5(7.8)	2(10)	0
Dry mouth	48(40.33)	15(62.5)	13(20.31)	14(70)	6(54.54)
Insomnia	14(11.76)	3(12.5)	5(7.81)	5(25)	1(9.09)

Tremor	5(4.20)	(4.16)	1(1.56)	2(10)	1(9.09)
Sexual dysfunction	2(1.60)	0	1(1.56)	1(5)	0
Skin rash	7(5.88)	2(8.33)	1(1.56)	4(20)	0
Urinary frequency	9(7.56)	2(8.34)	4(6.25)	3(15)	0

*ADRs Incidence (% reporting)

4. DISCUSSION

The study showed a significant relationship between genotype-based metabolizing group of CYP2C19 and the possibility of adverse drug reactions with escitalopram. This is the first study to examine the association between CYP2C19 polymorphisms and escitalopram response in South Indian patients with MDD.

The frequencies of CYP2C19*1, CYP2C19*2 and CYP2C19*17 were 24.5%, 27.35%, and 48.05%. EM, IM, PM and UM were 37.7%, 24.5%, and 20.8% of patients. When compared to extensive metabolizers, intermediate metabolizers have higher and ultrarapid metabolizers have lower mean frequency of ADRs, but the difference was not statistically significant. Due to a small sample size in this study, the difference was not significant.

According to Huezo-Diaz et al. (2012) the white race's CYP2C19*17 allele frequency was 24.2%; whereas Rudberg et al. (2008) found 23.6% and 15.3% prevalence in Norway. Rudberg et al. (2008) observed 22%, 18.1%, and 59.3% frequencies of CYP2C19*17, CYP2C19*2, and CYP2C19*1. Aynacioglu et al. (1999) found 12% and 0.4% of CYP2C19*2 and *3 among 404 Turkish people. Like our sample, most research participants were depressed women.

The results showed that CYP2C19 EM had better clinical outcomes than CYP2C19 PM with MDD, although there were no significant differences in therapeutic outcomes between IM and EM. Several clinical psychometric instruments, including the MARDS, HAMD, and CGI-I, which were utilized as objective indicators of the patients' clinical improvement, demonstrated that the PM state significantly impacted the escitalopram efficacy. In PM and UM, our study found lower response and remission rates. In contrast, the response and remission rates at week 12 were over 50% and 40%, respectively (Pinto et al., 2007).

Furthermore, it was observed that CYP2C19 PM significantly affected treatment tolerability. All groups of CYP2C19 metabolizers were given the same dose of escitalopram, it stands to reason that PM led to increased exposure to the drug and, ultimately, more severe side effects. The reduced efficacy in PM might be due to worse tolerability, which would explain poor patient compliance or by the risk of ADRs were they outweighed the clinical benefits. Analysis of sensitivity revealed that treatment efficacy persists even with CYP2C19 substrate medications. Conversely, PM have lower tolerability than EM, although the magnitude remained the same after sample reduction. This result was also found in the subgroup analysis of first episode versus recurring MDD.

The efficacy of amitriptyline, citalopram, escitalopram, and venlafaxine has not been clearly linked to CYP2C19 polymorphism in previous studies, and there is little evidence that CYP2C19 genotype affects the response to fluoxetine. Similarly, there is a lack of definitive data on the impact of CYP2C19 polymorphism on the tolerability of antidepressants. Strumila et al. (2021) found that CYP2C19 influences antidepressant response in a patient cohort with MDD severity. This finding is consistent with our study findings. Also, found that CYP2C19 IM had higher MADRS scores and were more likely to be diagnosed with MDD than EM.

The CYP2C19 enzyme plays a role in the breakdown of natural chemicals like steroid hormones. If the capacity of the CYP2C19 enzyme is diminished, it can disrupt the balance of these molecules and affect the body's ability to maintain homeostasis in processes such as stress

response and inflammation. This is the potential rationale for why individuals with reduced CYP2C19 capability exhibited greater severity of Major Depressive Disorder (MDD) in our study population. Similarly, Fabbri et al. (2018) reported higher ADRs in CYP2C19 PM, indicating poor tolerance. Two large retrospectives found similar results like us.

Twenty-four individuals had extensive and twenty had poor metabolizer genotypes. PM had a higher mean UKU score than extensive metabolizers, but the difference was not statistically significant. There was a substantial correlation between oral escitalopram clearance and adverse drug reactions. Similar outcomes as our study. Expectedly, PM had higher ADR frequency ratings. Similar to Yin et al., PM patients had higher mean ADR scores than EM patients, although at a non-significant level. This may be due to genetic polymorphism diversity across individuals and races (Yin et al., 2006).

Nervousness (55.4%) was the most common adverse effect in our study. The other most frequently reported ADRs were dry mouth (40.3%), nausea (31.9%), abdominal pain (29.4%), drowsiness (28.5%), and headache (20.1%). In 2007, researchers looked at 406 people who had major depressive disorder and were on selective serotonin reuptake inhibitors to determine the frequency of adverse drug reactions (ADRs) and the reason for therapy discontinuation.

Around 90% of individuals had a side effect, with dry mouth being the most common (50.8%). Overall, 42.1% of patients exhibited gastrointestinal symptoms, 39.7% tiredness, 39.4% weight change, 37.2% decreased libido, and 33.3% anxiety. A of patients had GI symptoms (41.7%), tiredness (38.9%), weight change (39.7%), reduced libido (36.5%), and anxiety (32.7%). Compared to Goethe et al., 40.3% of our patients had dry mouth, the second most frequently reported adverse effect. In the other trial, patients received citalopram, which is more likely to have anticholinergic side effects, is the possible reason which may have caused dry mouth (Goethe et al., 2007).

Some limitations exist in this investigation. To start, there wasn't a very big pool of patients to draw from. Second, the study's reliance on single-gene analysis is a major drawback; other enzymes, such as CYP2D6 and CYP3A4, and ABCB1 are involved in the metabolism and transport of escitalopram; these factors might be included when developing a model to predict the success or failure of ESC treatment for individual patients (Tsai et al., 2010; Singh et al., 2012).

5. CONCLUSION

CYP2C19 metabolizer status determines the diverse treatment outcomes among MDD patients prescribed with escitalopram. We concluded that poor metabolizers are associated with an increased risk of adverse effects and ultra rapid metabolizers require higher ESC doses to achieve remission from MDD symptoms. We also noticed that the relationship between metabolizer status and treatment response followed an expected direction. Understanding inter-individual variability, genotype-phenotype relationship, and CYP2C19 polymorphisms helps to optimize personalized drug therapy in clinical practice. Our findings indicate that dosing according to CYP2C19 metabolizer status might improve the response to escitalopram treatment and enhance safety in depressive patients.

Abbreviations

ADR: Adverse Drug Reaction; **BMI**- Body Mass Index; **CGI**- Clinical Global Impression; **CPIC**- Clinical Pharmacogenetics Implementation Consortium; **CYP2C19**- Cytochrome P450 2C19; **DSM**- Diagnostic and Statistical Manual of Mental Disorders; **EM**- Extensive Metabolizer; **HDRS**- Hamilton Depression Rating Scale; **IM**- Intermediate Metabolizer; **MADRS**- Montgomery-Asberg Depression Rating Scale; **MDD**- Major Depressive Disorder; **OPD**- Out Patient Department; **PCR**- Polymerase Chain Reaction; **PM**- Poor metabolizers;

UKU Scale- Udvalg for Kliniske Undersogelser Scale; **UM**- Ultra Rapid Metabolizers; **WHO**- World Health Organization

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Authors Contributions
B.J.K. contributed the concept, design, manuscript preparation, experimental and literature study. V.T.M. design, manuscript analysis, and manuscript review and suggestions. G.K.M. contributed the clinical studies, data acquisition, manuscript review and suggestions.

Declaration of Conflict of Interest
The authors declare that there is no conflict of interest regarding the publication of this article.

Ethical Approval
The study was conducted after obtaining approval from the Institutional Ethics Committee (IEC no. 1299) of Sri Venkateswara Institute of Medical Sciences, Tirupati.

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Informed Consent
Patients included in the study have given their consent to participate in the study.

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