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

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Various CYP2C19-mediated metabolizer groups may arise as a result of inter-individual variability, which potentially influences the efficacy and safety of escitalopram. Hence, it is crucial to establish a comprehensive collection of information relevant to each phenotype regarding the efficacy and tolerability of therapy. This will enable psychiatrists to make optimal decisions for individual patients.

***The aim of the study**. 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.*

***Materials and Methods.** 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 phenotypes based on changes in HDRS-17 and CGI scores from week 4 to week 12.*

***Results.** Subjects were categorized by CYP2C19 genotype: 20 poor (PM), 64 intermediate (IM), 24 extensive (EM), and 11 ultra-rapid (UM) metabolizers. Response and remission occurred in 67.2 % and 26.8 % of the 119 subjects at the end of the 12th week of the 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. In safety data, nervousness was the most common ADR among the four groups 66 (55.4 %), followed by decreased appetite 48 (40.3 %). There were no severe ADRs. Men had more ADRs than women.*

***Conclusions.** CYP2C19 genotyping may help personalize escitalopram medication. 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. The relationship between metabolizer status and treatment response followed the anticipated direction. Our findings should guide future clinical studies that include pharmacokinetic assessments*

***Keywords:** Major Depressive Disorder, efficacy, safety, escitalopram, genotype, phenotype*

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1. Introduction

Major Depressive Disorder (MDD) is a chronic, recurrent, disabling mental disorder that causes symptomatic and functional impairment, leading to affecting individuals' capacity to manage daily responsibilities [1]. 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 [2]. 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 [3, 4]. 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 [5, 6].

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 [7, 8]. It is a genetically polymorphic drug-metabolizing enzyme with large interindividual metabolic variability (Enhance or diminish function) [9]. 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) [10–12]. 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 [13–15]. A novel CYP2C19*17 variant increases fast antidepressant metabolism [16].

Inter-individual variations in CYP2C19-mediated metabolism may influence drug concentration/elimination, affecting efficacy and safety [17, 18]. 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 [8, 19]. Compared to other SSRIs, side effects of escitalopram were minimal at earlier [20]. 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 [21]. 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 [22]. Previous studies stated that poor metabolizers would have more adverse effects and higher response rates than ultrarapid metabolizers, based on exposure trends reported in adults [23, 24].

The aim of this study

The aim of the study is to investigate the differences in the escitalopram efficacy, tolerability and safety between different metabolizing groups based on CYP2C19 genetic polymorphisms in South Indian MDD patients due to their unusual genetic makeup.

2. Planning (methodology) of research

The first stage was aimed at determining the frequencies of CYP2C19 genetic polymorphisms in MDD patients. DNA sequencing, polymerase chain reaction (PCR)-single-strand conformation polymorphism analysis, and polymerase chain reaction (PCR-restriction fragment length polymorphism analysis) were used to detect the allelic and genotypic frequencies of the (CYP2C19*2, *3, and *17) in blood samples from 119 MDD patients of diverse ethnicities within the South Indian population.

The second stage involved investigating the relationship between CYP2C19 metabolizer phenotype influence efficacy. The primary outcome was the change in mean MADRS score from baseline to the end of the study. The secondary outcome are the changes in total HDRS-17 and score of the CGI-I from baseline to the end of the study.

In the third stage, to explore whether there is a relationship between metabolizer phenotype and adverse effects of treatment. The study analyzed the safety and tolerability by assessing the occurrence of adverse drug reactions using the UKU Scale.

Stages of the study:

1. Literature review of publications on CYP2C19 alleles involved in escitalopram metabolism.

2. Submission of protocol and granting of Ethical Committee approval.

3. Selection of MDD patients according to the inclusion criteria.

3. Determination of CYP2C19 genetic polymorphisms using PCR-RFLP.

4. Assessment of treatment efficacy using MADRS, HDRS-17 and CGI-I scores.

5. Assessment of treatment safety using the UKU side effect rating scale.

5. Processing and analysis of obtained results.

6. Identification of promising directions for further research to personalize escitalopram therapy.

3. 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 were recruited. The participants were on escitalopram monotherapy, and those who fulfilled the inclusion criteria mentioned as follows:

1) patients of either sex;

2) ages between 18 to 55 years;

3) patients with escitalopram treatment only;

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.

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.

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

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: l0 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 [25].

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 decreased 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 evalu-

ation 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 [26].

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

4. 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. CYP2C19 ultrarapid metabolizers have significantly lower exposure to escitalopram when compared to extensive metabolizers and, therefore, may have an increased probability of failing therapy. Based on this hypothesis, escitalopram dose was increased to 20 mg/day for UM, 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 IM, 24 patients as EM, 20 patients were PM and 11 patients as UM.

*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. Fig. 1. shows the mean MADRS scores from baseline to week 12 for various metabolizer groups. 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 cohorts were significant (p<0.05) at week 4 and was sustained till week 12.

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. Fig. 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 the 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 are 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 between the UM and EM groups. Overall, CYP2C19 UM showed less improvement in depression symptoms than EM. No significant difference (p>0.05) was observed in efficacy outcomes between sex, age groups and patients experiencing a first episode or a recurrent episode.

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)	Ultrarapid 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 (%)]	41	8	22	7	4
Women [n (%)]	78	16	42	13	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	59	9	34	11	5
Bachelor/Single	21	4	10	4	3
Widowed	27	8	13	5	1
Divorced	12	3	7	0	2
Smoking, n (%)	31	7	18	4	2
Alcohol, n (%)	38	9	19	6	4
Patients experiencing the first episode, n (%)	52	15	25	8	4
Patients experiencing recurrent episodes, 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)

Note: N – total number of study subjects; n – number of variants.

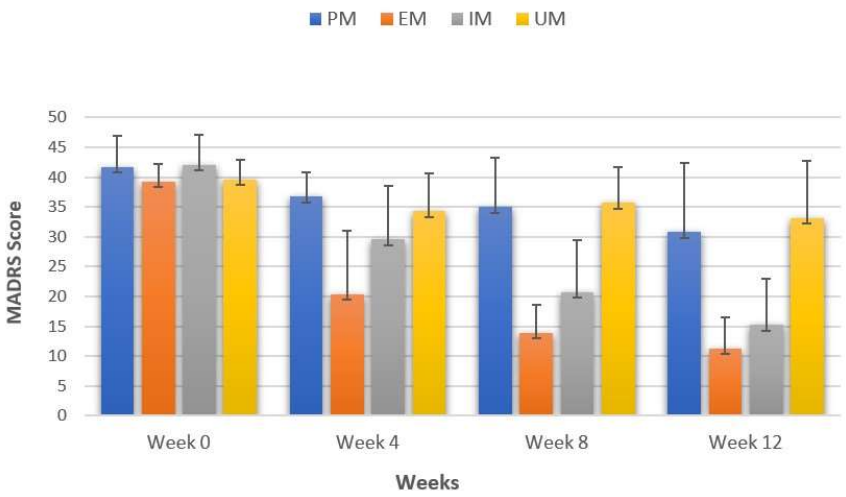

Fig. 1. Mean change from baseline in MADRS scores in four CYP2C19 metabolizer groups. MADRS scores decreased significantly (p<0.05) in EM and IM phenotypes from week 4 to week 12, while there were no significant (p>0.05) differences between the PM and UM. Each column represents the mean+SD (n=119)

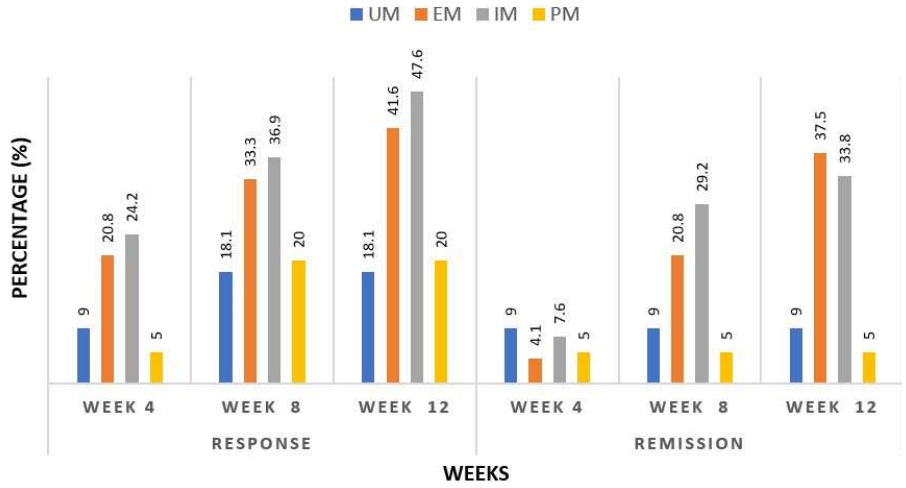

Fig. 2. Percentage of subjects showing response and remission during escitalopram therapy. Escitalopram response and remission rates were lower in UM and PM, respectively, at week 12. Each column represents the percentage (n=119)

Table 2

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

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

*Note: 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 is 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 were mild to moderate. Sexual dysfunction was only reported by men. UKU scale was applied to evaluate the adverse drug reactions in patients with metabolizer groups. When the incidence of ADRs was compared with the EM, higher rates 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

Note: ADRs Incidence (% reporting)

5. Discussion

The study showed a significant relationship between a 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., the white race's CYP2C19*17 allele frequency was 24.2 %, whereas Rudberg et al. found 23.6 % and 15.3 % prevalence in Norway. Rudberg et al., observed 22 %, 18.1 %, and 59.3 % frequencies of CYP2C19*17, CYP2C19*2, and CYP2C19*1. Aynacioglu et al., found 12 % and 0.4 % of CYP2C19*2 and *3 among 404 Turkish people. Like our sample, most research participants were depressed women [19, 27–29].

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 [30].

Except for UM, CYP2C19 metabolizers received the same escitalopram dose. Titrating to 20 mg/day gave UM enough drug exposure and plasma levels to achieve a response by the end of the study. From baseline to week 12, dosage escalation reduced the MADRS score, and the CGI score increased the response rate from week 4 to week 12. Furthermore, PM had more drug exposure and severe adverse effects, which would explain worse tolerability and poor patient compliance that outweighed the clinical benefits.

Analysis of sensitivity revealed that treatment efficacy persists even with CYP2C19 substrate medications. Conversely, PM has lower tolerability than EM, although the magnitude remained the same after sample reduction. This result was also found in the subgroup analysis of the 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. Strumila et al. (2021) found that CYP2C19 IM had higher MADRS scores and were more likely to be diagnosed with MDD than EM [31].

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 [32]. Two large retrospectives found similar results to ours.

Twenty-four individuals had extensive, and twenty had poor metabolizer genotypes. The 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, the 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 [33].

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 [34].

Practical relevance. Clinical findings indicate that poor metabolizers have a higher risk of adverse effects, whereas ultrarapid metabolizers need higher escitalopram doses for MDD remission.

Research limitations. Some limitations exist in this investigation. To start, there was not 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 [35].

Prospects for further research. Pharmacogenetic recommendations for CYP2C19 polymorphisms on antidepressant response are infrequently used by healthcare professionals. South Indian populations have a unique genetic composition, and there is strong evidence that genetic polymorphisms have a significant influence in deciding the antidepressant response and adverse effects of escitalopram. In order to confirm this concept, more large-scale genetic association studies involving treatment response and candidate genes related to pharmacokinetics and pharmacodynamics are necessary.

6. 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.

Conflict of interest

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

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Data availability

Data will be made available on reasonable request.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the current work.

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References

1. Sadock, B. J., Sadock, V. A., Ruiz, P. (2015). Mood disorders. Kaplan and Sadock's synopsis of psychiatry: Behavioural sciences/Clinical psychiatry. Indian Journal of Psychiatry, 11, 347–350.

2. Arvind, B. A., Gururaj, G., Loganathan, S., Amudhan, S., Varghese, M., Benegal, V. et al. (2019). Prevalence and socioeconomic impact of depressive disorders in India: multisite population-based cross-sectional study. BMJ Open, 9 (6), e027250. https://doi.org/10.1136/bmjopen-2018-027250

3. Dhar, A. K., Barton, D. A. (2016). Depression and the link with cardiovascular disease. Front Psychiatry, 7. https://doi.org/10.3389/fpsyt.2016.00033

4. Xin, L.-M., Chen, L., Su, Y.-A., Yang, F.-D., Wang, G., Fang, Y.-R. et al. (2018). Risk Factors for Recent Suicide Attempts in Major Depressive Disorder Patients in China: Results From a National Study. Frontiers in Psychiatry, 9. https://doi.org/10.3389/fpsyt.2018.00300

5. Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study (2017). Lancet, 392 (10159), 1789–1858.

6. Mathers, C. D., Loncar, D. (2006). Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med, 3 (11), 2011–2030. https://doi.org/10.1371/journal.pmed.0030442

7. Maity, N., Ghosal, M. K., Gupta, A., Sil, A., Chakraborty, S., Chatterjee, S. (2014). Clinical effectiveness and safety of escitalopram and desvenlafaxine in patients of depression with anxiety: A randomized, open-label controlled trial. Indian Journal of Pharmacology, 46, 433–437. https://doi.org/10.4103/0253-7613.135959

8. Uckun, Z., Baskak, B., Ozel-Kizil, E. T., Ozdemir, H., Ozguven, H. D., Suzen, H. S. (2015). The impact of CYP2C19 polymorphisms on citalopram metabolism in patients with major depressive disorder. Journal of Clinical Pharmacy and Therapeutics, 40 (6), 672–679. https://doi.org/10.1111/jcpt.12320

9. Spina, E., De Leon, J. (2015). Clinical applications of CYP genotyping in psychiatry. Journal of Neural Transmission, 122 (1), 5–28. https://doi.org/10.1007/s00702-014-1300-5

10. He, Q., Yuan, Z., Liu, Y., Zhang, J., Yan, H., Shen, L. et al. (2017). Correlation between cytochrome P450 2C19 genetic polymorphism and treatment response to escitalopram in panic disorder. Pharmacogenetics and Genomics, 27 (8), 279–284. https://doi.org/10.1097/fpc.0000000000000290

11. Hicks, J., Bishop, J., Sangkuhl, K., Müller, D., Ji, Y., Leckband, S. et al. (2015). Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. Clinical Pharmacology & Therapeutics, 98 (2), 127–134. https://doi.org/10.1002/cpt.147

12. Zhou, H.-H. (2002). Genetic polymorphism of CYP2C19 in Chinese ethnic populations. International Congress Series, 1244, 51–61. https://doi.org/10.1016/s0531-5131(02)00455-7

13. Horai, Y., Nakano, M., Ishizaki, T. (1989). Metoprolol and mephenytoin oxidation polymorphisms in Far Eastern Oriental subjects: Japanese versus mainland Chinese. Clinical Pharmacology and Therapeutics, 46, 198–207. https://doi.org/10.1038/clpt.1989.126

14. Yu, B. N., Chen, G. L., He, N., Ouyang, D.-S., Chen, X.-P., Liu, Z.-Q. (2003). Pharmacokinetics of citalopram in relation to genetic polymorphism of CYP2C19. Drug Metabolism and Disposition, 31, 1255–1259. https://doi.org/10.1124/dmd.31.10.1255

15. Rudberg, I., Mohebi, B., Hermann, M., Refsum, H., Molden, E. (2008). Impact of the ultrarapid CYP2C19*17 allele on serum concentration of escitalopram in psychiatric patients. Clinical Pharmacology & Therapeutics, 83, 322–327. https://doi.org/10.1038/sj.clpt.6100291

16. Anderson, I. M. (1998). SSRIs versus tricyclic antidepressants in depressed inpatients: A meta-analysis of efficacy and tolerability. Depression and Anxiety, 7 (S1), 11–17. https://doi.org/10.1002/(sici)1520-6394(1998)7:1+<11::aid-da4>3.0.co;2-i

17. Wilkinson, G. R. (2005). Drug Metabolism and Variability among Patients in Drug Response. New England Journal of Medicine, 352 (21), 2211–2221. https://doi.org/10.1056/nejmra032424

18. Rosen, R. C., Lane, R. G., Menza, M. (1999). Effects of SSRIs on sexual function: A critical review. Journal of Clinical Psychopharmacology, 19, 67–85. https://doi.org/10.1097/00004714-199902000-00013

19. Trivedi, M. H., Rush, A. J., Wisniewski, S. R., Nierenberg, A. A., Warden, D., Ritz, L. et al. (2006). Evaluation of Outcomes With Citalopram for Depression Using Measurement-Based Care in STAR*D: Implications for Clinical Practice. American Journal of Psychiatry, 163 (1), 28–40. https://doi.org/10.1176/appi.ajp.163.1.28

20. Ng, C., Sarris, J., Singh, A., Bousman, C., Byron, K., Peh, L. H. et al. (2013). Pharmacogenetic polymorphisms and response to escitalopram and venlafaxine over 8 weeks in major depression. Human Psychopharmacology: Clinical and Experimental, 28, 516–522. https://doi.org/10.1002/hup.2340

21. Hodgson, K., Tansey, K., Dernovšek, M. Z., Hauser, J., Henigsberg, N., Maier, W. et al. (2013). Genetic differences in cytochrome P450 enzymes and antidepressant treatment response. Journal of Psychopharmacology, 28 (2), 133–141. https://doi.org/10.1177/0269881113512041

22. Chang, M., Tybring, G., Dahl, M.-L., Lindh, J. D. (2014). Impact of Cytochrome P450 2C19 Polymorphisms on Citalopram/Escitalopram Exposure: A Systematic Review and Meta-Analysis. Clinical Pharmacokinetics, 53 (9), 801–811. https://doi.org/10.1007/s40262-014-0162-1

23. Jukić, M. M., Haslemo, T., Molden, E., Ingelman-Sundberg, M. (2018). Impact of CYP2C19 Genotype on Escitalopram Exposure and Therapeutic Failure: A Retrospective Study Based on 2,087 Patients. American Journal of Psychiatry, 175 (5), 463–470. https://doi.org/10.1176/appi.ajp.2017.17050550

24. Caudle, K. E., Dunnenberger, H. M., Freimuth, R. R., Peterson, J. F., Burlison, J. D., Whirl-Carrillo, M. et al. (2017). Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC). Genetics in Medicine, 19 (2), 215–223. https://doi.org/10.1038/gim.2016.87

25. Lingjærde, O., Ahlfors, U. G., Bech, P., Dencker, S. J., Elgen, K. (1987). The UKU side effect rating scale: A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatrica Scandinavica, 76 (s334), 1–100. https://doi.org/10.1111/j.1600-0447.1987.tb10566.x

26. Huezo-Diaz, P., Perroud, N., Spencer, E. P., Smith, R., Sim, S., Virding, S. et al. (2011). CYP2C19 genotype predicts steady state escitalopram concentration in GENDEP. Journal of Psychopharmacology, 26 (3), 398–407. https://doi.org/10.1177/0269881111414451

27. Rudberg, I., Hermann, M., Refsum, H., Molden, E. (2008). Serum concentrations of sertraline and N-desmethyl sertraline in relation to CYP2C19 genotype in psychiatric patients. European Journal of Clinical Pharmacology, 64 (12), 1181–1188. https://doi.org/10.1007/s00228-008-0533-3

28. Aynacioglu, A., Sachse, C., Bozkurt, A., Kortunay, S., Nacak, M., Schroder, T. et al. (1999). Low frequency of defective alleles of cytochrome P450 enzymes 2C19 and 2D6 in the Turkish population. Clinical Pharmacology & Therapeutics, 66 (2), 185–192. https://doi.org/10.1053/cp.1999.v66.100072001

29. Pinto, C., Trivedi, J. K., Vankar, G. K., Sharma, P. S., Narasimha, V. (2007). An open-label multicentric study of the tolerability and response to escitalopram treatment in Indian patients with major depressive disorder. Journal of Indian Medical Association, 105 (7), 364–368.

30. Strumila, R., Lengvenyte, A., Ambrozaityte, L., Balkeliene, D., Utkus, A., Dlugauskas, E. (2021). CYP2C19 polymorphisms are associated with severity of depression at initial evaluation and after the treatment independently of the prescribed medications: 4 weeks prospective study. Psychiatric Genetics, 31 (5), 177–185. https://doi.org/10.1097/ypg.0000000000000287

31. Yin, O. Q., Wing, Y.-K., Cheung, Y., Wang, Z.-J., Lam, S.-L., Chiu, H. F., Chow, M. S. (2006). Phenotype-genotype Relationship and Clinical Effects of Citalopram in Chinese Patients. Journal of Clinical Psychopharmacology, 26 (4), 367–372. https://doi.org/10.1097/01.jcp.0000227355.54074.14

32. Fabbri, C., Tansey, K. E., Perlis, R. H., Hauser, J., Henigsberg, N., Maier, W. et al. (2018). Effect of cytochrome CYP2C19 metabolizing activity on antidepressant response and side effects: mMeta-analysis of data from genome-wide association studies. European Neuropsychopharmacology, 28 (8), 945–954. https://doi.org/10.1016/j.euroneuro.2018.05.009

33. Goethe, J. W., Woolley, S. B., Cardoni, A. A., Woznicki, B. A., Piez, D. A. (2007). Selective Serotonin Reuptake Inhibitor Discontinuation: side effects and other factors that influence medication adherenc. Journal of Clinical Psychopharmacology, 27 (5), 451–458. https://doi.org/10.1097/jcp.0b013e31815152a5

34. Tsai, M. H., Lin, K. M., Hsiao, M. C., Shen, W. W., Lu, M. L., Tang, H. S. et al. (2010). Genetic polymorphisms of cytochrome P450 enzymes influence metabolism of the antidepressant escitalopram and treatment response. Pharmacogenomics, 11 (4), 537–546. https://doi.org/10.2217/pgs.09.168

35. Singh, A. B., Bousman, C. A., Ng, C. H., Byron, K., Berk, M. (2012). ABCB1 polymorphism predicts escitalopram dose needed for remission in major depression. Translational Psychiatry, 27 (2), e198. https://doi.org/10.1038/tp.2012.115

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