ORIGINAL RESEARCH

Key Words: escitalopram, CYP2C19, pharmacogenetics, biotransformation, personalized medicine, depressive disorders, alcohol use disorder

Influence of *CYP2C19*17* Genetic Polymorphism on the Steady-State Concentration of Escitalopram in Patients with Recurrent Depressive Disorder

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*ABSTRACT ~ **Introduction:** Escitalopram is commonly prescribed to patients with recurrent depressive disorder. Some of them do not show adequate response to treatment with escitalopram, while many of them experience adverse drug reactions. **Objective:** The objective of our study was to evaluate the impact of −806C>T polymorphism of CYP2C19 (CYP2C19*17) on the concentration/dose ratio of escitalopram in patients with recurrent depressive disorder. **Material and methods:** Our study enrolled 267 patients with recurrent depressive disorder (average age − 40.2 ± 16.4 years). Treatment regimen included escitalopram in an average daily dose of 12.5 ± 5.0 mg per day. The efficacy and safety rates of treatment were evaluated using the international psychometric scales. For genotyping, we performed the real-time polymerase chain reaction. Therapeutic drug monitoring has been performed using HPLC-MS/MS. **Results:** Our findings revealed the statistically significant results in terms of both treatment efficacy evaluation (HAMD scores at the end of the treatment course): (CC) 9.0 [7.0; 11.0], (CT) 4.0 [2.0; 6.0] and (TT) 2.0 [1.0; 4.0], $p < 0.001$; and safety profile (the UKU scores): (CC) 7.0 [7.0; 8.0], (CT) 3.0 [3.0; 4.0] and (TT) 3.0 [2.0; 3.0], $p < 0.001$. We revealed no statistically significant results for the concentration/dose ratio of escitalopram in patients with different genotypes: (CC) 5.762 [3.939; 9.076], (CT) 5.714 [3.485; 8.533] and (TT) 7.388 [4.618; 10.167], $p = 0.268$). **Conclusion:** The CYP2C19*17 genetic variant significantly affected the efficacy and safety profiles of escitalopram in a group of 267 patients with recurrent depressive disorder but did not greatly affect its equilibrium plasma concentration.* Psychopharmacology Bulletin. *2022;52(3):8–19.*

Introduction

Depression is a common mental disorder that affects approximately 300.2 million people worldwide (~3.8% of world population).[1] The COVID-19 pandemic has led to a drastic increase in depressive and anxiety disorders globally in 2020; the overall number of cases of mental disorders rose dramatically, with an additional 53.2 million and 76.2 million cases of anxiety and depressive disorders, respectively.[2] Studies show that depressive disorders are the most common co-occurring psychiatric disorders among people with alcohol use disorders (AUD), and people with AUD are 2.3 times more likely to have a comorbid major depressive disorder in the previous year in comparison with those with no AUD.[3]

Currently, there are six classes of medications approved to treat depression, including selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), norepinephrine and dopamine reuptake inhibitors (NDRIs) and non-competitive N-methyl-D-aspartate receptor antagonists.[4] Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed medications for the treatment of depression.[5] The six major SSRIs that are marketed

in the USA today (fluoxetine, citalopram, escitalopram, paroxetine, sertraline, and fluvoxamine) are a group of structurally unrelated molecules that share a similar mechanism of action.[6] Even though their primary mechanism of action is similar, each SSRI has unique pharmacokinetics, pharmacodynamics, efficacy, and side effect profile. Studies show that SSRIs' efficacy is variable and incomplete: 60%–70% of the patients do not experience remission, while 30%–40% do not show a significant response.[7] With regards to adverse effects, many are shared among all SSRIs to varying degrees, including sexual dysfunction, gastrointestinal distress, prolonged QT interval, and xerostomia.[8]

CYP2C19 genetic polymorphism can influence the metabolism of SSRIs, thereby affecting drug efficacy and safety.[9] Thus, patients may be predisposed to poor therapeutic outcomes due to *CYP2C19* genetic polymorphism that alter SSRI biotransformation.[9] Escitalopram is an antidepressant belonging to the selective serotonin reuptake inhibitors (SSRIs) group. In humans, escitalopram is primarily metabolized by CYP2C19 (36%), CYP2D6 (30%) and CYP3A4 (34%).[10] Allele variants in the *CYP2C19* gene (categorized as no function, normal function or increased function) directly modulate the enzyme's efficiency in escitalopram metabolism.[11] The metabolizer status is determined by the two alleles a person carries, and is categorized into poor, intermediate, normal, rapid or ultrarapid metabolizer (UM) status.[12] CYP2C19 poor metabolizers are carriers of the variant alleles *2 and *3, whereas the *17 variant is associated with increased gene transcription and enzymatic activity (rapid or ultrarapid metabolizer).

Most studies have focused on the effects of *CYP2C19*2* and **3* genetic variants, finding that **2* (*G681A*) and **3* (*G636A*) variations reduce enzyme activity.[13,14] Meanwhile, *CYP2C19*17* (*−806C>T)* was found to be associated with increased expression of the *CYP2C19* gene and enzymatic activity.[15] Notably, phenotyping of *CYP2C19* performed in 2015 in 971 Russian patients demonstrated a variable minor allele frequency: *CYP2C19*2* − 0.140, *CYP2C19*3* − 0.006, *CYP2C19*17* − 0.274.[16] A high frequency of *CYP2C19*17* minor allele associated with modified response to medications suggests the preferred choice of this polymorphic marker for the development of pharmacogenetic approaches to prescribing escitalopram.

The objective of our study was to evaluate the effect of *−806C>T* polymorphism of the *CYP2C19* gene (CYP2C19*17, rs12248560) on the concentration/dose ratio of escitalopram in patients diagnosed with recurrent depressive disorder and comorbid AUD.

Material and Methods

Clinical Characteristics of the Study Subjects

The study involved 267 male patients (average age — 40.20 ± 16.38 years). The inclusion criteria were as follows: the dual diagnosis of "Depressive episode (F32.x, according to ICD-10)" and "Mental and behavioral disorders due to use of alcohol. Dependence syndrome. Currently abstinent but in a protected environment (F.10.212)"; signed informed consent, and 8-weeks escitalopram monotherapy. Exclusion criteria were the presence of any other mental disorders; presence of severe somatic disorders (except alcoholic hepatitis and toxic encephalopathy); presence of any other psychotropic medications in treatment regimen; creatinine clearance values <50 mL/min, creatinine concentration in plasma >1.5 mg/dL (133 mmol/L), bodyweight less than 60 kg or greater than 100 kg, age of 75 years or more and presence of any contraindications for escitalopram use.

Therapy Efficacy and Safety Evaluation

In order to assess escitalopram efficacy, several international psychometric scales were used: Hospital Anxiety and Depression Scale (HADS)[17] and Hamilton Depression Rating Scale (HAMD).[18] The safety profile was evaluated using the UKU Side-Effect Rating Scale (UKU).[19] Patients were examined on weeks 1, 4 and 8 of escitalopram therapy.

Genotyping

For genotyping, venous blood samples were collected into VACUETTE® (Greiner Bio-One, Austria) vacuum tubes on week 8 of escitalopram therapy. The single nucleotide polymorphism (SNP) rs12248560 (*CYP2C19*17*) was analyzed by real-time PCR using "Dtlite" DNA amplifiers (DNA Technology, Moscow, Russia) on a CFX96 Touch Real-Time System with CFX Manager software (Bio-Rad Laboratories Inc., Hercules, CA, USA) and the "SNP-screen" sets (Syntol, Moscow, Russia). In every set, two allele-specific hybridizations were used, which allowed simultaneous determination of both alleles of the respective SNP using two fluorescence channels.

Therapeutic Drug Monitoring

For therapeutic drug monitoring (TDM), venous blood samples were collected on week 8 of escitalopram therapy. Both plasma calibration

standards (St) and quality control samples (QC) were made from a stock solution prepared by consistent dissolving of substantial amounts of venous blood in methanol with subsequent dilution to the relevant concentrations. Calibration curve was created using 5, 10, 20, 50, 100, 200, 500, 1000, 2000 ng/mL calibration standards along with 5 ng/mL (LLOQ), 15 ng/mL (Low QC), 1000 ng/mL (Medium QC), and 1500 ng/mL (High QC) quality control samples (QC). Diazepam (250 ng/mL in acetonitrile) was used as the internal standard.

Sample preparation. Sample preparation was carried out by precipitation of proteins. For this, 200 μL of plasma and 600 μL of acetonitrile containing internal standard were introduced into a test tube with a capacity of 1.5 mL. The sample was vortexed for 10 min, then centrifuged for 10 min at 14 500 rpm at 4°C. After centrifugation, the supernatant was transferred into a vial and placed in the autosampler of the HPLC. The study was carried out using an Agilent 1260 high performance liquid chromatography (Agilent Technologies, California, USA) and an Agilent 6460 tandem mass-selective detector (Agilent Technologies, California, USA) with a Jet Stream Electrospray Ionization source.

Conditions for chromatographic analysis. The stationary phase was an Agilent Poroshell 120 EC-C_{18} column (2.7 μm, 3.0 × 50 mm) with an InfinityLab Poroshell 120 EC-C18 guard column (2.7 μm, 3.0 × 5.0 mm) (Agilent Technologies, California, USA). The column oven temperature was 50° C. The mobile phase consisted of eluent A (10 mM aqueous solution of ammonium formate with 0.1% formic acid) and eluent B (methanol with 0.1% formic acid). The flow rate was 0.4 ml/min. Elution took place in a gradient mode (Table 1). Analysis time for each sample was 9.0 min. The volume of the injected sample was 2 μL. Under these conditions, the retention time was 4.75 min for escitalopram and 4.84 min for sertraline.

TABLE 1

Gradient of the Mobile Phase

TIME OF ANALYSIS, MIN	ELUENT A VOLUME RATIO, %	ELUENT B VOLUME RATIO, %
0.00	95	5
0.50	95	5
1.00	50	50
1.50	5	95
3.00	5	95
3.01	95	5
5.00	95	5

Local Ethical Committee

The research was approved by the local ethical committee of the Russian Medical Academy of Continuous Professional Education of the Ministry of Health of the Russian Federation (The protocol No. 6 from 5/16/2017).

Statistical Analysis

Statistical analysis of the results was performed in Statsoft Statistica v. 10.0 (Dell Statistica, Tulsa, OK, USA). The normality of sample distribution was evaluated using the Shapiro-Wilk test and was taken into account for selecting parametric or non-parametric tests. The differences were considered statistically significant at $p < 0.05$ (power above 80 %). Two samples of continuous independent data were compared using the Mann-Whitney U-tests with further correction of the obtained p-value using the Benjamin-Hochberg test, due to the multiple comparison procedure. Several samples of continuous data were analyzed using the Kruskal-Wallis H-test. Correlation analysis was performed using the Spearman nonparametric test, taking into account the abnormal nature of sample distribution. Pearson's Chi^2 test for evaluation of the sampling distribution of the alleles (Hardy Weinberg equilibrium) has been used. Research data are presented in the form of the median and interquartile range (Me [Q1; Q3]), or in case of their normal distribution, as the arithmetic mean and standard deviation (Mean ± SD).

Study Results

In total, 125 out of 267 patients (46.8%) did not carry the *CYP2C19*17* allele, whereas 117 patients (43.8%) were heterozygous for the respective variant. There were 25 carriers of the *TT* (homozygous) genotype (9.4%). Genotype distributions followed the Hardy–Weinberg equilibrium ($Chi^2 = 0.10$, p-value = 0.75).

The results of data analysis performed for psychometric assessments (HADS, HAMD) and side-effect rating scale (UKU) on weeks 1, 4 and 8 in patients who received escitalopram are summarized in Table 2. Dynamics of changes in HAMD scale scores among the patients with different genotypes are shown in Figure 1. By week 1, there were no statistically significant differences across the compared groups: (*CC*) 22.0 [21.0; 23.0], (*CT*) 22.0 [21.0; 22.0] and (*TT*) 22.0 [21.0; 22.0], p = 0.330. By week 4, we revealed statistically significant differences

TABLE 2

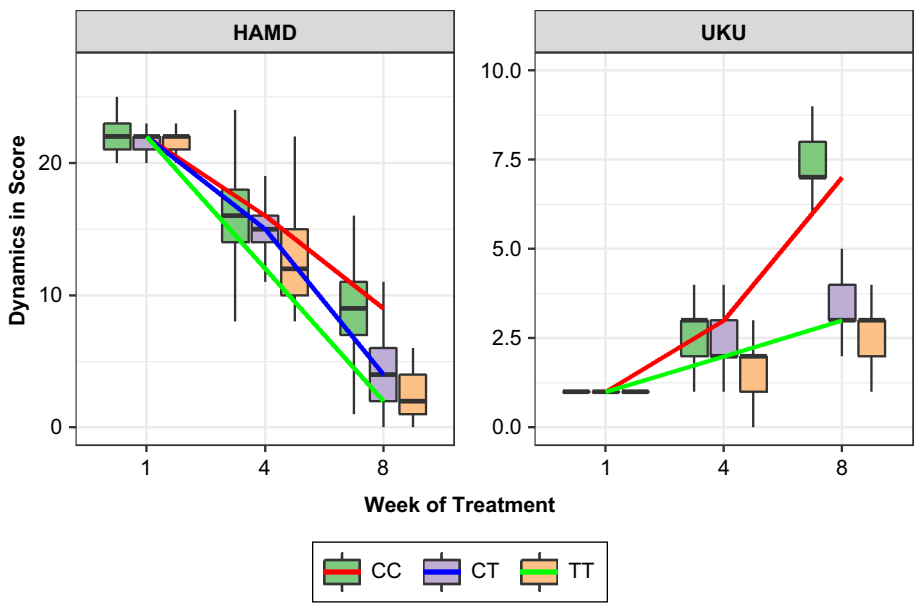
Data from the Psychometric Assessments and Side-Effect Rating Scale in Patients who Received Escitalopram, on Weeks 1, 4 and 8 of the Study

SCALE	*CC*	*CT*	*TT*	P-VALUE
Week 1				
HADS	37.0 [36.0; 38.0]	37.0 [36.0; 37.0]	37.0 [36.0; 38.0]	0.335
HAMD	22.0 [21.0; 23.0]	22.0 [21.0; 22.0]	22.0 [21.0; 22.0]	0.330
UKU	1.0 [1.0; 1.0]	1.0 [1.0; 1.0]	1.0 [1.0; 1.0]	0.359
Week 4				
HADS	27.0 [23.0; 30.0]	26.0 [23.0; 29.0]	20.0 [17.0; 22.0]	< 0.001
HAMD	16.0 [14.0; 18.0]	15.0 [14.0; 16.0]	12.0 [10.0; 15.0]	< 0.001
UKU	3.0 [2.0; 3.0]	2.0 [2.0; 3.0]	2.0 [1.0; 2.0]	< 0.001
Week 8				
HADS	16.0 [12.0; 19.0]	5.0 [2.0; 9.0]	3.0 [3.0; 5.0]	< 0.001
HAMD	9.0 [7.0; 11.0]	4.0 [2.0; 6.0]	2.0 [1.0; 4.0]	< 0.001
UKU	7.0 [7.0; 8.0]	3.0 [3.0; 4.0]	3.0 [2.0; 3.0]	< 0.001

p – p-value obtained in Benjamini-Hochberg multiple testing correction (based on the results of Mann-Whitney U test), Data are presented as Me and IQR.

FIGURE 1

Dynamics of Changes in the HAMD and UKU Scales Scores Across Patients with Different Genotypes by the Polymorphic Marker −806C>T of CYP2C19 (rs12248560)



Data are presented as Me and IQR (colored lines connect the medians on different week of the study).

in patients with different genotypes: (*CC*) 16.0 [14.0; 18.0], (*CT*) 15.0 [14.0; 16.0] and (*TT*) 12.0 [10.0; 15.0], $p < 0.001$. On week 8, the statistically significant differences were also observed: (*CC*) 9.0 [7.0; 11.0], (*CT*) 4.0 [2.0; 6.0] and (*TT*) 2.0 [1.0; 4.0], $p < 0.001$. For other psychometric scales, the same dynamics of changes in scores were obtained.

Dynamics of changes in UKU scores among the patients are presented in Figure 1. The graph shows that on week 1 the compared groups had no statistically significant differences: (*CC*) 1.0 [1.0; 1.0], (*CT*) 1.0 [1.0; 1.0] and (*TT*) 1.0 [1.0; 1.0], $p = 0.359$. By week 4, a statistically significant difference was obtained: (*CC*) 3.0 [2.0; 3.0], (*CT*) 2.0 [2.0; 3.0] and (*TT*) 2.0 [1.0; 2.0], $p < 0.001$. A statistically significant difference was also observed on week 8: (*CC*) 7.0 [7.0; 8.0], (*CT*) 3.0 [3.0; 4.0] and (*TT*) 3.0 [2.0; 3.0], $p < 0.001$. In addition, the differences were statistically significant when comparing the indicator between individual genotypes.

Table 3 summarizes the data on concentration/dose ratio (C/D) values obtained for escitalopram through pharmacokinetic studies. No statistical significance was revealed for escitalopram C/D ratio in patients with different genotypes: (*CC*) 5.762 [3.939; 9.076], (*CT*) 5.714 [3.485; 8.533] and (*TT*) 7.388 [4.618; 10.167], $p = 0.268$ (Figure 2).

Discussion

This study sought to understand the association between CYP2C19*17 genetic polymorphism and escitalopram efficacy and safety in a sample of Russian patients with recurrent depressive disorder. Our findings did not reveal a statistically significant difference between the values of escitalopram equilibrium concentration in patients with different *CYP2C19*17* genotypes: patients carrying the *C* allele have a lower level of drug equilibrium concentration than those with the *T* allele but no

TABLE 3

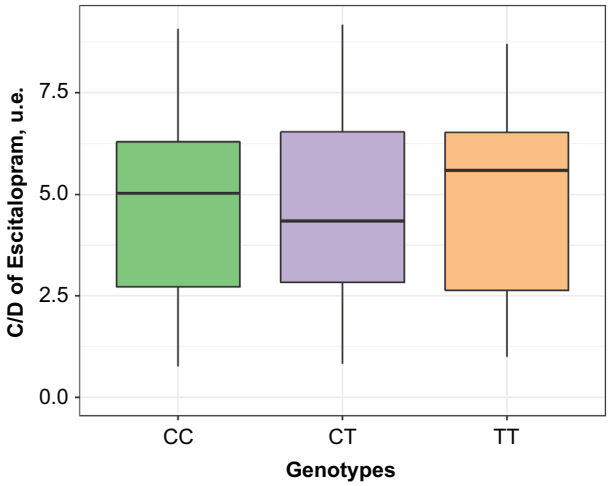
The values of Escitalopram Equilibrium Concentration in Patients with Different Genotypes by the Polymorphic Marker −806C>T of CYP2C19 (rs12248560)

PARAMETER	*CC*	*CT*	*TT*	P-VALUE
Concentration of escitalopram, ng/ml	78.89 [38.51; 118.63]	68.91 [39.89; 93.25]	95.05 [44.12; 134.48]	0.010
C/D of escitalopram, u.e.	5.76 [3.94; 9.08]	5.71 [3.49; 8.53]	7.39 [4.62; 10.17]	0.268

p – p-value obtained in Benjamini-Hochberg multiple testing correction (based on the results of Mann-Whitney U test), Data are presented as Me and IQR.

FIGURE 2

Differences in Escitalopram Concentration/Dose Ratio Values in Patients with Different Genotypes by the Polymorphic Marker *–806C>T* of *CYP2C19* (rs12248560)



Data are presented as Me and IQR (colored lines connect the medians on different week of the study).

statistical significance was found ($p = 0.268$). As a result, carriage of the *T* allele does not lead to a drug accumulation in plasma and an increased risk of adverse drug reactions. Rudberg et al., showed that CYP2C19*17 homozygous phenotype may be associated with lower serum concentrations of escitalopram, which might imply an increased risk of therapeutic failure.[20] In another study, despite the greater escitalopram dosage in the utrarapid group, it was demonstrated that the utrarapid metabolizers only achieved remission of depression symptoms using a pharmacological combination of escitalopram with another antidepressant.[21] This result agrees with the present study where we showed that escitalopram alone does not lead to a drug accumulation in plasma and an increased risk of adverse drug reactions in different genotypes.

Statistical analysis of the data on the clinical efficacy profile of escitalopram in patients with different *CYP2C19*17* genotypes revealed the statistically significant differences in the efficacy rates ($p < 0.001$). The analysis of escitalopram safety data also revealed the statistically significant difference ($p < 0.001$). The value of these parameters is statistically significantly lower for carriers of the minor allele than for carriers of the major allele. This may indicate that the carriage of this polymorphic marker may lead to a decreased risk of the adverse drug reactions of escitalopram in comparison with carriers of nonmutant

alleles. It is probably due to an increased CYP2C19 activity in these patients resulting in the increased rate of escitalopram biotransformation and elimination, and decrease in drug plasma level.

Thus, based on the results obtained that the *−806C>T* genetic polymorphism affects the efficacy and safety rates of escitalopram in patients with recurrent depressive disorder, it is possible to assume that it is necessary to take the results of *CYP2C19*17* genotyping into account before prescribing escitalopram to such patients.

This study has some limitations. The study included only one CYP2C19 gene and one polymorphic variant of this gene. Other genetic factors (CYP2C19*2 and *3) were not evaluated. The study did not assess the influence of gender as all subjects were males. Finally, the study did not assess the effect of other molecular biomarkers (serum biomarkers of liver function, micro-RNA, etc.). Regardless, this study can provide individualized assessments of escitalopram metabolism by CYP2C19*17 genetic variant; leading to more personalized medicine strategies for individuals with recurrent depressive disorder.

Conclusion

In summary, we showed that the *CYP2C19*17* genetic polymorphism greatly influenced the efficacy and safety profiles of escitalopram in a group of 267 patients with recurrent depressive disorder but did not affect its equilibrium plasma concentration. ✤

Funding Source

The study was supported by the grant from the President of the Russian Federation for state support of young Russian scientists - PhDs (project MK-3902.2021.3): Personalized pharmacotherapy with tranquilizers for patients with anxiety disorders comorbid with alcoholism, based on pharmacogenetic, pharmacokinetic and pharmacotranscriptomic biomarkers.

Disclosure

The authors report no conflicts of interest in this work.

Author's Contribution

M.S. Zastrozhin – conception and design of the study, recruitment of study participants, biomaterial sampling, carrying out of the genotyping, statistical processing of the obtained data, drafting of the article. V.Yu.

Skryabin, D.S. Horyaev – recruitment of study participants, biomaterial sampling, carrying out of the genotyping, statistical processing of the obtained data, drafting of the article. F. Rwere - analysis of the results of pharmacokinetics, description of methods, revision and editing of the article. A.E. Petukhov – development of a method for determining the equilibrium concentration of escitalopram, revision and editing of the article. E.P. Pankratenko, V.V. Noskov, N.V. Vinokurova – carrying out therapeutic drug monitoring, revision and editing of the article. S.A. Pozdnyakov, V.A. Ivanchenko, I.A. Zaytsev, N.V. Grishina E.A. – design of the laboratory part of the study, carrying out of the genotyping, revision and editing of the article. R.V. Vlasovskih – conception and design of the study, assistance in resolving administrative and ethical issues, revision and editing of the article. E.A. Bryun– conception and design of the study, revision and editing of the article. D.A. Sychev – the idea of the study, conception and design of the study, revision and editing of the article. All authors made a substantial contribution to the research and preparation of the research paper, and were involved in drafting of the article or its critical revision for important intellectual content and gave final approval of the revision to be published.

Funding

This work was financially supported by the project 16-15-00227 entitled "Fundamental research and exploratory research in priority areas of research" of the Russian Science Foundation.

Conflict of Interest

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

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