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Serotonin transporter 5-HTTLPR polymorphism and escitalopram treatment response in patients with major depressive disorder

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Abstract

Background There is no doubt that genetic factors have the potential to predict the therapeutic outcomes of antidepressants in patients with major depressive disorder (MDD). This study investigated the association between genetic variants involved in serotonin signaling and brain-derived neurotrophic factor (BDNF) with the response to escitalopram treatment in patients with MDD. We focused on examining the influence of 5-HTTLPR (ins/del), *HTR2A* rs9316233, *BDNF* rs962369, *CYP2C19* and *CYP2D6* on the clinical response to escitalopram.

Methods The patients were recruited from outpatient psychiatric clinics in Košice between 2020 and 2022. Patients received escitalopram for 12 weeks at a fixed dose of 10 mg daily. Clinical assessment was done at baseline and after 4, 8, and 12 weeks using the 21-item Hamilton Depression Rating Scale (HAMD-21).

Results At the end of week 12, 57 (65%) patients were defined as responders to escitalopram treatment, while 31 (35%) patients were non-responders. Genotyping revealed that carriers of the short allele (S) of 5-HTTLPR exhibit a significantly lower therapeutic response to escitalopram measured by HAMD-21 than the long allele (L) carriers ($p=0.01$). Adjusting for *CYP2C19* and *CYP2D6* metabolizer genotypes did not modify the observed relationship between 5-HTTLPR and treatment response. No significant associations were found for *HTR2A* rs9316233 or *BDNF* rs962369 variants and the treatment response.

Conclusions These findings underscore the utility of 5-HTTLPR genotyping in guiding escitalopram therapy for MDD patients. Further research with larger cohorts is warranted to validate these results and elucidate additional genetic determinants of antidepressant efficacy.

Keywords Pharmacogenetics, Depression, Escitalopram, Genetic Polymorphisms, *SLC6A4*

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Introduction

Major depressive disorder (MDD) is a common and severe psychiatric disorder, affecting more than 300 million people worldwide and causing significant impairment in patients' daily lives and a huge burden for society and the healthcare system [1, 2]. Despite the availability of more than 20 available antidepressant drugs, treatment efficacy varies widely among patients, with 30–50% failing to respond to the initial treatment and common antidepressants proving effective in only about 40% of MDD patients [3, 4]. The recurrence of symptoms remains high even among responders [5]. Predicting the most effective antidepressant treatment for an individual remains challenging, and the process of finding an optimal treatment is often a lengthy trial-and-error approach, further complicated by the potential for severe adverse reactions such as suicidal ideation and behaviors [3].

A significant proportion of MDD patients, approximately one-third, are classified as treatment-resistant depression (TRD) with limited therapeutic options available [6]. Given that the molecular targets for psychiatric drugs are currently not fully understood, many of the currently available drugs are likely to remain central role in psychiatric pharmacotherapy for the foreseeable future. Therefore, improving their effectiveness through genetic insights is crucial [7]. Genetic variability accounts for approximately 42% of the variability in antidepressant treatment response, as shown by genome-wide studies [8].

Genetic variants can influence drug response through mechanisms such as single nucleotide polymorphisms (SNPs), gene duplication, deletions, insertions and other alterations that affect gene expression and protein function. Pharmacogenomics plays an important role in predicting responders and non-responders to medications, optimizing drug dose, and avoiding adverse events, thus enabling personalized and effective pharmacotherapy [9].

The role of pharmacogenetics in personalized antidepressant treatment is particularly evident in the metabolism of drugs by cytochrome P450 enzymes, specifically CYP2C19 and CYP2D6. These enzymes play a crucial role in the metabolism of many antidepressants, including selective serotonin reuptake inhibitors (SSRIs) like escitalopram. Genetic polymorphisms in CYP2C19 and CYP2D6 can result in significant inter-individual differences in drug metabolism, influencing both efficacy and safety of antidepressant therapy. For instance, individuals with certain CYP2C19 and CYP2D6 polymorphisms may be classified as poor metabolizers, intermediate metabolizers, or ultrarapid metabolizers. These categories have distinct implications for drug dosing, with poor metabolizers and intermediate metabolizers typically experiencing higher drug exposure and increased risk of adverse

effects, while ultrarapid metabolizers may require higher doses due to rapid drug clearance [10].

In addition to genes involved in drug metabolism, genetic variations in serotonin-related genes are also critical in determining response to SSRIs. Serotonin receptors and transporters are primary targets of SSRIs, making them logical candidates for pharmacogenetic studies. Among these, the 5-hydroxytryptamine receptor 1A (*HTR1A*) and 2A (*HTR2A*) genotypes were studied concerning possible association with antidepressant efficacy. While no significant associations between SNPs in *HTR1A* and the response to antidepressants [11–13] were found, several *HTR2A* have been linked to more favorable outcomes with SSRI treatment [3, 14, 15].

One of the most studied variants is insertion/deletion polymorphism 5-HTTLPR in the gene encoding serotonin transporter *SLC6A4*. A meta-analysis of multiple studies, including data from over 1,400 subjects has demonstrated significant associations between 5-HTTLPR polymorphism and antidepressant response, particularly with respect to the short (S) allele. Carriers of the S allele, particularly those homozygous for the S variant (S/S) have been found to have lower remission rates and poorer responses to SSRI [16].

In addition to serotonin signaling, the brain-derived neurotrophic factor (BDNF) gene has also been implicated in the variability of antidepressant response. BDNF plays a crucial role in the survival, development and differentiation of neurons and synapses in the central nervous system. Mutation in *BDNF* gene can lead to alterations in the structure and function of BDNF and ultimately result in a difference in antidepressant efficacy in individuals [17]. We have recently demonstrated an association of *BDNF* rs962369 with the development of recurrent MDD [18]. In our previous study, we have shown a significant increase in the risk of single-episode MDD with *BDNF* rs962369 [19]. Most antipsychotics and antidepressants undergo metabolism by the polymorphic enzymes CYP2C19 and CYP2D6. According to the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline, treatment with SSRIs should consider CYP2C19 and CYP2D6 metabolizer status [20].

Even though pharmacogenomics of antidepressant drugs has been studied for at least 15 years, there are only a few strong data with outcomes to the clinical practice. The main reason is that the majority of performed studies were on a relatively small sample of patients with reduced statistical power. There is a lack of replication of the results of these small studies, and only a few genome-wide studies have been performed. Moreover, some pharmacogenetic studies included more types of antidepressant drugs. Based on the inconsistency of the data published so far, our study aimed to evaluate the

association between genetic variants involved in serotonin signaling and BDNF with the response to escitalopram treatment in patients with MDD. We focused on examining the influence of 5-HTTLPR (ins/del), *HTR2A* rs9316233, and *BDNF* rs962369 on the clinical response to escitalopram treatment in patients with MDD. The impact of metabolizer status, particularly *CYP2C19* and *CYP2D6*, on the response to escitalopram treatment was also investigated. We hypothesized that genetic variations in genes related to serotonin signaling, particularly 5-HTTLPR, and *HTR2A*, as well as in the *BDNF* gene, will significantly influence the response to escitalopram treatment in patients with MDD. Specifically, carriers of the S allele in 5-HTTLPR and certain variants of *HTR2A* will exhibit a poorer response to escitalopram compared to individuals carrying other alleles. Additionally, we hypothesized that specific variants in *BDNF*, particularly rs962369, will also impact the therapeutic response to escitalopram.

Methods

Subjects and study design

The group of 88 subjects with MDD (both males and females), who were medication-free for at least 1 year before entry into the study, were enrolled. The patients were recruited from outpatient psychiatric clinics in Košice between 2020 and 2022. All patients met ICD-10 criteria for a depressive episode at the time of recruitment (severe depressive episode without psychotic symptoms F32.2 and recurrent depressive disorder, current episode severe without psychotic symptoms F33.2). Clinical diagnosis was made and confirmed by two board-certified psychiatrists. All participants were of Slovak origin.

Inclusion criteria included age 18–65 years, diagnosis of MDD by two board-certified psychiatrists. Depressive symptomatology was assessed using the Hamilton Depression Scale Hamilton Rating Scale for Depression, 21-item version (HAMD-21) [21]. In most cases, this was the first psychiatric examination for the patient. Exclusion criteria were no current or lifetime diagnosis of psychotic disorder, bipolar disorder, personality disorder, eating disorder, or history of alcohol or substance abuse/dependence within the six months prior to assessment (nicotine and caffeine dependence were not exclusionary), current suicidal ideation or history of suicide attempt or intentional self-harm in the past. Patients with thyroid disease, cognitive deficits (Mini-Mental State Examination—MMSE above 25) [22], active suicidal ideation, and pregnancy were excluded from the study. Participation in the study was voluntary, and any individual could withdraw during the study. The study was approved by the Ethics Committee of the Louis Pasteur University Hospital in Košice, Slovakia, and all subjects

provided their written informed consent. The research was conducted in accordance with the principles of the Declaration of Helsinki.

At the time of first visit (week 0), initial psychiatric examination and evaluation of the patient using the HAMD-21, and MMSE was performed. Sample of venous blood for genotyping was collected. The treatment of patients started with escitalopram at a fixed dose of 10 mg daily. Benzodiazepines were permissible as temporary adjunctive therapy to manage the acute condition. This treatment lasted a minimum of 4 weeks. After 4 weeks, patients underwent a psychiatric follow-up examination. The treatment of somatic diseases remained unchanged.

Patients were assessed with the HAMD-21 scale at weeks 0, 4, 8, and 12 during the study to monitor dynamics in antidepressant treatment. Remission was defined as a score ≤ 7 points on HAMD-21 at week 12. Response was defined as $\geq 50\%$ HAMD-21 score reduction and those patients were classified as "responders". In this group of patients, treatment with escitalopram continued. Otherwise, we classified patients as "non-responders" and changed their antidepressant therapy. No other psychotropic medication was allowed in the responder group except for symptomatic treatment with low-dose benzodiazepines for a minimal period. The secondary treatment of choice was venlafaxine, trazodone, sertraline, quetiapine, vortioxetine, mirtazapine.

Genotyping

Genomic DNA was extracted from peripheral blood samples using the QIAamp DNA Blood Mini QIAcube Kit. The extraction process was automated on the QIAcube platform (QIAGEN, Hilden, Germany), adhering to the manufacturer's guidelines.

Detection of alleles *CYP2C19**2 (rs4244285) and *CYP2C19**3 (rs4986893) was realized by using LightMix® Kit *CYP2C19**2 and *CYP2C19**3 (version 201111; TIB MOLBIOL GmbH, Berlin, Germany). Genotyping of *CYP2D6**3 (rs35742686), *CYP2D6**4 (rs3892097) and *CYP2D6**5 (gene deletion) was performed with LightMix® Kit for detection of *CYP2D6* alleles *3, *4, and *5/*5 (version 150626; TIB MOLBIOL GmbH, Berlin, Germany). Alleles *CYP2C19**17 (rs12248560) and *CYP2D6**41 (rs28371725) were detected with single pre-designed LightSNiP assays (TIB MOLBIOL GmbH, Berlin, Germany). The amplification and subsequent melting analysis were performed according to the manufacturer's instructions on LightCycler 1.5 Instrument (Roche Diagnostic GmbH, Mannheim, Germany).

5-HTTLPR polymorphism in the *SLC6A4* gene was assessed using PCR amplification followed by electrophoretic analysis. The PCR reaction was carried out using

AmpliAq Gold 360™ Master Mix (Applied Biosystems™, Waltham, MA, USA) in a 20 µL reaction volume. The PCR products were electrophoresed in a 2% agarose gel.

HTR2A and *BDNF* variants were genotyped using asymmetric real-time polymerase chain reaction (primers ratio 1:10) and high-resolution melting analysis in the presence of an unlabelled probe on the Eco Real-Time PCR System (Illumina, Inc., San Diego, CA, USA). Amplification reactions were set up in 15 µL volumes containing 1× MeltDoctor™ HRM Master Mix (Applied Biosystems™, Waltham, MA, USA), and oligonucleotides designed in our laboratory (Table 1). Genotype identification was carried out using Eco Real-Time PCR system software 4.1.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics V. 20 software (IBM SPSS, Chicago, IL, USA). Comparison of two groups (responders vs. nonresponders) was performed by independent samples t-test for

the comparison of continuous data and by χ^2 -test for the comparison of categorical data. Response to escitalopram treatment was tested using multiple logistic regression models. In those models, the investigated SNPs (5-HTTLPR, *HTR2A* rs9316233, *BDNF* rs962369) were included separately and tested by additive genetic models. In Model 1, age and sex were included as covariates. In Model 2, we also introduced the phenotypes of *CYP2C19* and *CYP2D6* as covariates. Those must be considered where inefficacy of antidepressant treatment is suspected according to the recent CPIC Guideline [20]. Because three SNPs were examined concerning response to escitalopram treatment, the p-value was Bonferroni corrected (0.05/3) to $p = 0.017$, and this value was considered as statistically significant.

Results

Clinical and pharmacokinetic characteristics of responders and non-responders to escitalopram treatment are shown in Table 2. From all subjects investigated, 57 patients responded to escitalopram treatment according to the above-mentioned predefined criteria, while 31 patients were non-responders.

The mean age of non-responders was significantly higher than that of responders (51 vs. 45 years). In both groups, the distribution of male and female subjects was similar.

No significant differences were observed in the distribution of predicted *CYP2C19* and *CYP2D6* metabolizer phenotypes between responder and non-responder groups.

All the investigated variants followed Hardy–Weinberg equilibrium (Table 3).

The main results of the present study are displayed in Table 4. Model 1 shows age and sex-adjusted results of logistic regression. For each S-allele of the 5-HTTLPR

Table 1 Sequence of oligonucleotides for genotyping

Gene (variant)	Oligonucleotide	Sequence 5'-3'
<i>HTR2A</i> (rs9316233)	forward-limit	CTTGGTATTTGCAGGGATCTCTCTTC
	reverse-excess	TTGAAGAATGAGAGGAATCAGCCAT
	unlabeled probe ^a	TATAATTTGCCCAAGCCTTCAA GATGC-Phos
<i>BDNF</i> (rs962369)	forward-limit	GACATTTTATGAGAAGGGTTTAC ATAAG
	reverse-excess	AAAGAATTGCTCACTGTAATGAC
	unlabeled probe ^a	TGCCAAGAGAGTTGAGTCCATGG- Phos
<i>SLC6A4</i> (5HTTLPR)	forward	GGCGTTGCCGCTCTGAATGC
	reverse	GAGGGACTGAGCTGGACAACCAC

^a The underlined nucleotide specifies the major allele for the single nucleotide polymorphism

Table 2 Characteristics of the study population with respect to age, sex, and responder status

Trait		Responder (n = 57)	Non-responder (n = 31)	p
		Mean ± SD / n (%)	Mean ± SD / n (%)	
Age	(years)	44.5 ± 12.4	50.7 ± 15.0	0.040
Sex	men	17 (30%)	11 (35%)	0.586
	women	40 (70%)	20 (65%)	
Metabolizer by <i>CYP2C19</i>	normal	20 (35%)	13 (42%)	0.785
	intermediate/poor	18 (32%)	8 (26%)	
	rapid/ultra-rapid	19 (33%)	10 (32%)	
Metabolizer by <i>CYP2D6</i>	normal	31 (54%)	17 (55%)	0.891
	intermediate	22 (39%)	11 (35%)	
	poor	4 (7%)	3 (10%)	

Data expressed as Mean ± SD / n (%), p

SD Standard deviation, n number, p probability

Table 3 Frequency of alleles in investigated genes

Gene variant	Major Allele homozygotes (n)	Hetero- zygotes (n)	Minor allele homozygotes (n)	CA	VA	MAF (%)	HWE <i>p</i>
5-HTTLPR	40	37	11	L	S	33.5	0.868
HTR2A rs9316233	50	31	6	C	G	24.7	0.925
BDNF rs962369	49	33	6	T	C	25.6	0.990

N Number, CA Common allele, VA Variant allele, MAF Minor allele frequency, HWE Hardy–Weinberg equilibrium, *p* probability

Table 4 Response to treatment with escitalopram by genotypes

Gene variant	VA/CA	Model 1				Model 2			
		OR	95% CI		<i>p</i>	OR	95% CI		<i>p</i>
			low	high			low	high	
5-HTTLPR ins/del	S/L	0.42	0.20	0.85	0.015	0.38	0.18	0.80	0.010
HTR2A rs9316233	G/C	1.68	0.76	3.74	0.201	1.84	0.79	4.28	0.159
BDNF rs962369	C/T	0.62	0.30	1.29	0.202	0.57	0.26	1.24	0.156

VA Variant allele, CA Common allele, OR Odds ratio given per variant allele, 95% CI 95% Confidence interval, *p* probability

Model 1 was adjusted for age and sex. Model 2 was additionally adjusted for CYP2C19 and CYP2D6 metabolizer phenotypes

variant, a significantly decreased response to escitalopram by 58% was observed in the log-additive model (OR 0.42, 95% CI 0.20–0.85, $p=0.015$). The association between the 5-HTTLPR genotype and response to escitalopram treatment was not affected by adjustment for the presence of different metabolizers status of *CYP2C19* and *CYP2D6* (Model 2), the association between the 5-HTTLPR genotype and response to escitalopram treatment remained significant.

No significant relationship between *HTR2A* rs9316233 and *BDNF* rs962369 variants with response to escitalopram treatment was observed.

Discussion

The main finding of the present study is that carriers of the at least one short allele (S) of 5-HTTLPR exhibit a significantly lower therapeutic response to escitalopram measured by HAM-D-21 in comparison with the long allele homozygotes (LL). However, no significant associations were observed between *HTR2A* rs9316233 or *BDNF* rs962369 variants and treatment response.

5-HTTLPR is an insertion (L)/deletion (S) polymorphism in the promoter of the serotonin transporter gene *SLC6A4*. The presence of the S allele was associated with lower transcription of *SLC6A4* [23], pointing to the possibility of lower therapeutic efficacy of SSRIs in S allele carriers. The lower efficacy of SSRI in S allele carriers was observed in several studies [24–26] and a meta-analysis [27]. Some other studies did not find this genetic

diversity in the efficacy associated with 5-HTTLPR variants [28]. The results of two large studies, Sequenced Treatment Alternatives to Relieve Depression (STAR*D) with 1953 participants [29] and Genome Based Therapeutic Drugs for Depression (GENDEP) with 895 participants [3] suggested that the effect of 5-HTTLPR on antidepressant response might be modulated by another polymorphism such as rs2020933 present in the insertion part of L allele [30]. A meta-analysis of 49 studies with different SSRIs showed that the L allele of 5-HTTLPR was associated with better treatment response and higher remission rates. However, the effect was observed only in Caucasians and was not observed in mixed or other antidepressant groups [31]. CPIC Guideline 2023 concluded that the evidence supporting 5-HTTLPR ins/del polymorphism in *SLC6A4* is insufficient to support its clinical utility [20].

Two studies mentioned above found an association between different *HTR2A* variants and response to SSRIs. In the STAR*D study, rs7997012 was associated both with response to and remission after citalopram treatment in 1,149 participants [32]. In the GENDEP project, clinical (severity of depression, number of previous episodes, duration of episode, age, gender, and type of antidepressant) and genetic variables were studied in response to a serotonin-reuptake-inhibiting and a norepinephrine-reuptake-inhibiting drug. In a multicenter study, 760 adult patients with depression were treated with escitalopram or nortriptyline for 12 weeks.

One hundred sixteen single nucleotide polymorphisms in 10 candidate genes were genotyped. The study found that several variants in the *HTR2A* gene predicted the response to escitalopram, with one marker (rs9316233) explaining 1.1% of variance. However, in GENDEP, the investigators were unable to replicate the association between rs7997012 and the escitalopram response observed in the STAR*D study [3, 29]. In the present study, we did not replicate the association of rs9316233 with escitalopram response.

BDNF may play a role in the antidepressant mechanism within the hippocampus [33]. Specifically, antidepressants are believed to stimulate BDNF expression in the hippocampus, which may counteract neuronal atrophy and cell death, thus fostering an antidepressant response. Complex interactions between BDNF and the serotonin system have been observed. These interactions involve BDNF promoting the function, growth, and sprouting of serotonin neurons, as well as increasing serotonin synthesis and reducing serotonin uptake. Consequently, additional serotonin uptake inhibition by escitalopram might not provide added benefit in depressed patients with sufficient BDNF expression [34].

In the past two decades, *BDNF* variants have also been extensively studied in relation to antidepressant treatment. Several studies reported decreased BDNF levels in patients with MDD before treatment [35, 36]. The non-synonymous variant rs6265, which leads to the substitution of Val66Met, has been studied most comprehensively, with conflicting results. While some studies indicated that the Met variant of rs6265 polymorphism was related to lower responses to SSRIs [37], other studies found quite the opposite evidence. In a recently published study, MDD patients who were carriers of the Met allele showed better responses to antidepressants [38]. In the present study, we choose to evaluate the *BDNF* rs962369 variant because we previously reported its association with MDD [18], but we did not find a significant association with response to escitalopram treatment.

The weakness of the present study is the relatively low number of subjects included. On the other hand, this number corresponds with the number of patients in the majority of previous pharmacogenetic studies with antidepressants. Despite the relatively small sample size, the focus on one SSRI (escitalopram) and adjustment for *CYP2C19* and *CYP2D6* metabolizer status helped to avoid confounding caused by different pharmacokinetics and/or pharmacodynamics of drugs from the SSRI group. Further research with larger cohorts is warranted to validate these findings and elucidate additional genetic determinants of antidepressant efficacy.

Conclusions

Our study confirms the observation of a lower response rate to escitalopram treatment in MDD patients carrying the S-allele of the HTTLPR variant. Specifically, our findings suggest that the presence of one S-allele in a patient's genotype may be associated with a 58% decrease in treatment response. Utilizing this genetic profile can help in selecting antidepressants that are both effective and well-tolerated or in adjusting the dose of them.

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Not applicable

Clinical trial number

Not applicable.

Authors' contributions

DJ: Writing of the original draft, and Review & Editing. IT: Conceptualization, Formal Analysis, Writing of the original draft, and Review & Editing. NH: Writing of the original draft, Review & Editing. ASY: Data Analysis. MK: Review & editing. VH, LK, and JŽ: Genotyping, Writing of genotyping methodology. MJ: Data Analysis and Review & Editing. AB: Conceptualization, Methodology, Formal Analysis, Data collection, Writing of the original draft, and Review & Editing.

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

The authors assert that all procedures used in the conduct of this study conformed to the ethical standards of the relevant national and institutional committees on human experimentation and to the 1975 Declaration of Helsinki, as revised in 2008. The study was approved by the Ethics Committee of the Louis Pasteur University Hospital in Košice, the registration code number 2019/EK/6035, approval date: June 20, 2019. A written consent form was obtained from all participants before entering the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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