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Polymorphism 3435c> t of the *ABCB1* gene (rs1045642) does not affect the mirtazapine efficiency and safety profile in patients with depressive disorders comorbid with alcohol use disorder

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ABSTRACT

Background. Mirtazapine is used to treat patients with depressive disorders. A large proportion of patients in this group do not adequately respond to mirtazapine therapy, while many develop undesirable drug reactions of type A. According to the previous studies, P-gp is involved in the biotransformation of mirtazapine, the activity of which is highly dependent on the polymorphism of the gene encoding it.

Aim. To aim of our study was to study the effect of mirtazapine gene polymorphism on the efficacy and safety of mirtazapine therapy in patients with depressive disorders, comorbid with alcohol dependence.

Materials and methods. The study included 119 male patients with depressive disorders, comorbid with alcohol dependence (age 38.7 ± 16.0 years). As a therapy, mirtazapine was used at a dose of 37.8 ± 13.8 mg / day. Evaluation of the effectiveness profile was carried out using psychometric scales. The safety profile was evaluated using the UKU Side-Effect Rating Scale. Genotyping was carried out by polymerase chain reaction in real time.

Results. In the course of the study, results statistically significant in terms of evaluating efficacy and safety were not obtained (HAMD scores at the end of the course of therapy: (CC) 2.5 [2.0; 4.0], (CT) 2.0 [1.0; 3.0] and (TT) 2.0 [1.0; 3.0], $p > 0.999$; according to the UKU scale: (CC) 3.0 [2.8; 3.0], (CT) 3.0 [3.0; 3.0] and (TT) 3.0 [3.0; 3.0], $p > 0.999$).

Conclusion. The study of 119 patients with depressive disorders comorbid with alcohol dependence showed that 3435C> T polymorphism of the *ABCB1* gene (rs1045642) does not affect the clinical efficacy and safety of mirtazapine.

Key words: mirtazapine, *ABCB1*, pharmacogenetics, biotransformation, personalized medicine, depressive disorder, alcohol use disorder.

Conflict of interest. The authors declare no obvious or potential conflict of interest related to the publication of this article.

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Conformity with the principles of ethics. The study was approved by the local Ethics Committee at the Russian Medical Academy of Continuous Professional Education of the Ministry of Health of the Russian Federation (Protocol No. 6 of 16.05.2017). All patients signed an informed consent.

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Полиморфизм 3435c>T гена *ABCB1* (rs1045642) не влияет на профиль эффективности и безопасности миртазипина у пациентов с депрессивными расстройствами, коморбидными с алкогольной зависимостью

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РЕЗЮМЕ

Введение. Миртазапин используется для лечения пациентов с депрессивными расстройствами. Немалая доля пациентов данной группы не отвечает должным образом на терапию миртазапином, при этом у многих отмечается развитие нежелательных лекарственных реакций типа А. По результатам ранее проводимых исследований показано, что в биотрансформации миртазапина принимает участие гликопротеин Р, активность которого в высокой степени зависит от полиморфизма кодирующего его гена.

Цель. Изучить влияние полиморфизма гена *ABCB1* на эффективность и безопасность терапии миртазапином у пациентов с депрессивными расстройствами, коморбидными с алкогольной зависимостью.

Материалы и методы. В исследование было включено 119 пациентов мужского пола с депрессивными расстройствами, коморбидными с алкогольной зависимостью (средний возраст (38,7 ± 16,0) лет). В качестве терапии использовали миртазапин в дозе (37,8 ± 13,8) мг/сут. Оценка профиля эффективности производилась с помощью психометрических шкал. Профиль безопасности оценивался с помощью валидизированной шкалы UKU Side-Effect Rating Scale. Генотипирование проводилось методом полимеразной цепной реакции в режиме реального времени.

Результаты. По результатам исследования не получены статистически значимые результаты в показателях оценки эффективности и безопасности (баллы по шкале HAMD в концу курса терапии: (CC) 2,5 [2,0; 4,0], (CT) 2,0 [1,0; 3,0] и (TT) 2,0 [1,0; 3,0], $p > 0,999$; по шкале UKU: (CC) 3,0 [2,8; 3,0], (CT) 3,0 [3,0; 3,0] и (TT) 3,0 [3,0; 3,0], $p > 0,999$).

Заключение. Продемонстрировано отсутствие влияния полиморфизма 3435C>T гена *ABCB1* (rs1045642) на показатель клинической эффективности и безопасности миртазапина.

Ключевые слова: миртазапин, *ABCB1*, фармакогенетика, биотрансформация, персонализированная медицина, депрессивные расстройства, алкогольная зависимость.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

Depressive disorders are among the most frequently reported comorbidities in patients suffering from alcohol use disorder [1]. Antidepressants are commonly used in the depressive disorders treatment, and mirtazapine is a representative of this drug group [2]. Although tetracyclic antidepressants are included in the depressive disorders treatment guidelines, the number of resistant patients and patients with reported adverse drug reactions (ADRs) remains high [3].

Glycoprotein P (P-glycoprotein, P-gp) is involved in the pharmacokinetics of many drugs used for depressive disorders psychopharmacotherapy [4]. The gene encoding *ABCB1* is highly polymorphic, which may affect the interindividual variability in P-gp metabolic activity [5]. Changes in the protein activity may influence the rate of xenobiotic elimination including substrate drugs that, in turn, may have an impact on their effectiveness and safety profiles [6].

There are four groups of metabolizers distinguished by their metabolic rate: extensive metabolizers, poor metabolizers, intermediate metabolizers, and ultra-rapid metabolizers. Extensive metabolizers have normal metabolic rate. Poor metabolizers have mutations in the *ABCB1* gene, which may lead to a decrease in the activity of the encoded protein, as well as a slowdown in the metabolism of substrate drugs, which may lead to an increased risk of adverse drug reactions. Intermediate metabolizers have a mutation in only one of the homologous chromosomes, which reduces the P-gp activity but to a lesser degree than in poor metabolizers. Ultra-rapid metabolizers have the genetically determined increased activity of CYP3A that leads to the accelerated elimination of substrate drugs and reduces treatment effectiveness [7].

The study aimed to determine the influence of *ABCB1* gene polymorphisms on the effectiveness and safety profile of mirtazapine therapy in patients with depressive disorders, comorbid with alcohol use disorder.

MATERIALS AND METHODS

Clinical characteristics of the study subjects. 119 male patients (average age 38.71 ± 15.96 years old) were enrolled in the study. The inclusion criteria were specified as follows: the existence of two comorbid diagnoses: "Depressive episode (F32.x)", and "Mental and behavioral disorders due to use of alcohol. Dependence syndrome. Currently abstinent but in a protected environment (F.10.212)", a signed informed consent, and 16-days mirtazapine monotherapy. Exclusion criteria were specified as follows: 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 mirtazapine use.

Therapy effectiveness and safety evaluation. To evaluate mirtazapine effectiveness several international psychometric scales were used: Penn Alcohol Craving Scale (PACS) [8] and Visual Analogue Scale (VAS) for urge to alcohol assessment [9], and the Clinical Global Impression (CGI) scale [10], Hospital Anxiety and Depression Scale (HADS) [11], and Hamilton Depression Rating Scale (HAMD) [12]. A safety profile was evaluated using the UKU Side-Effect Rating Scale (UKU) [13]. The patients were examined on days 1, 9, and 16 of mirtazapine therapy.

Genotyping. For genotyping, venous blood samples were collected into VACUETTE® (Greiner Bio-One, Austria) vacuum tubes on the 16th day of mirtazapine therapy. The DNA amplifiers "Dtlite" by DNA Technology (Russia), "CFX96 Touch Real-Time System" with CFX Manager software by Bio-Rad (USA), and the "SNP-screen" sets by Syntol (Russia) were used to perform the real-time polymerase chain reaction in order to determine the 3435C>T single-nucleotide polymorphisms (SNPs) of the *ABCB1* gene (rs1045642). The usage of two allele-specific hybridizations in every "SNP-screen" set enabled the determination of two alleles of the studied SNP separately on two fluorescence channels.

Statistical analysis. The data were analyzed with non-parametric methods using the Statsoft Statistica v. 10.0 (Dell Statistica, Tulsa, USA). The normality of sample distribution was evaluated using the Sha- piro – Wilk *W*-test and was taken into account when choosing a statistical method. 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*-test 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. The data is presented in the form of the median and interquartile range *Me* [*Q1*; *Q3*].

RESULTS

The *ABCB1* 3435C>T polymorphic marker (rs1045642) genotyping performed in 105 subjects have revealed the following:

• The number of patients with the CC genotype was 20 (16,8%);

• The number of patients with the CT genotype was 70 (58,8%);

• The number of patients with the TT genotype was 29 (24,4%).

The frequency distribution of genotypes corresponded to the Hardy – Weinberg equilibrium distribution (Chi2 = 4.00; *p*-value = 0.05).

The results of psychometric scales (PACS, VAS, CGI, HADS, HAMD) and side-effect rating scale (UKU) data analysis on days 1, 9, and 16 in patients who received mirtazapine are summarized in Tables 1–3, respectively.

Table 1

Psychometric scales and side-effect rating scale (UKU) data on in patients received mirtazapine, day 1 of the research, *Me* [Q_1; Q_3]

Scale	CC	CT	TT	*p*-value
PACS	11.0 [11.0; 11.0]	11.0 [11.0; 11.0]	11.0 [11.0; 11.0]	$p > 0.999$
VAS	51.0 [50.8; 52.0]	49.0 [46.0; 52.8]	49.0 [47.0; 51.0]	$p > 0.999$
CGI	5.0 [5.0; 5.0]	5.0 [5.0; 5.0]	5.0 [5.0; 5.0]	$p = 0.086$
HADS	37.0 [36.0; 38.0]	36.0 [34.2; 38.0]	37.0 [36.0; 38.0]	$p > 0.999$
HAMD	22.0 [21.0; 22.0]	22.0 [21.0; 23.0]	22.0 [21.0; 22.0]	$p = 0.636$
UKU	0.5 [0.0; 1.0]	1.0 [0.0; 1.0]	0.0 [0.0; 1.0]	$p > 0.999$

Table 2

Psychometric scales and side-effect rating scale (UKU) data on in patients received mirtazapine, day 9 of the research, *Me* [Q_1; Q_3]

Scale	CC	CT	TT	*p*-value
PACS	7.5 [7.0; 8.0]	7.0 [7.0; 8.0]	7.0 [7.0; 7.0]	$p > 0.999$
VAS	32.5 [31.0; 35.2]	32.0 [31.0; 33.8]	32.0 [30.0; 36.0]	$p > 0.999$
CGI	3.0 [3.0; 3.0]	3.0 [3.0; 4.0]	3.0 [3.0; 3.0]	$p > 0.999$
HADS	25.0 [24.0; 26.2]	24.0 [23.0; 25.0]	24.0 [22.0; 25.0]	$p > 0.999$
HAMD	15.0 [14.0; 16.0]	15.0 [13.0; 16.0]	14.0 [14.0; 15.0]	$p > 0.999$
UKU	2.0 [2.0; 2.2]	2.0 [2.0; 2.0]	2.0 [2.0; 3.0]	$p > 0.999$

Table 3

Psychometric scales and side-effect rating scale (UKU) data on in patients received mirtazapine, day 16 of the research, *Me* [Q_1; Q_3]

Scale	CC	CT	TT	*p*-value
PACS	1.0 [1.0; 1.2]	1.0 [1.0; 1.0]	1.0 [0.0; 2.0]	$p > 0.999$
VAS	5.5 [3.5; 7.2]	4.0 [3.0; 5.8]	5.0 [4.0; 6.0]	$p > 0.999$
CGI	0.0 [0.0; 1.0]	1.0 [0.0; 1.0]	1.0 [0.0; 1.0]	$p > 0.999$
HADS	4.0 [3.0; 4.0]	3.0 [1.2; 5.0]	4.0 [2.0; 5.0]	$p > 0.999$
HAMD	2.5 [2.0; 4.0]	2.0 [1.0; 3.0]	2.0 [1.0; 3.0]	$p > 0.999$
UKU	3.0 [2.8; 3.0]	3.0 [3.0; 3.0]	3.0 [3.0; 3.0]	$p > 0.999$

Figure 1 demonstrates the dynamics of changes in the HAMD scale scores among the patients with different genotypes. As shown, by the day 1 the studied groups had already had statistically significant differences: (CC) 22,0 [21,0; 22,0], (CT) 22,0 [21,0; 23,0], and (TT) 22,0 [21,0; 22,0], p = 0,035. By the 9th day of the study, statistically significant differences had ceased to be observed in carriers of different genotypes for the studied polymorphic marker: (CC) 15.0 [14.0; 16.0], (CT) 15.0 [13.0; 16.0], and (TT) 14.0 [14.0; 15.0], p = 0.627. On the last 16th day of the study, as well as on the 2nd visit, no statistical difference was obtained: (CC) 2.5 [2.0; 4.0], (CT) 2.0 [1.0; 3.0], and (TT) 2.0 [1.0; 3.0], p > 0.999. The similar dynamics of changes in scores as in the HAMD scale was obtained by other psychometric scales.

Figure 2 demonstrates the dynamics of changes in the UKU scores among the patients. As shown, by the day 1 of the research no statistically significant differences in scores for carriers of different genotypes for the studied polymorphic marker were obtained: (CC) 0.5 [0.0; 1.0], (CT) 1.0 [0.0; 1.0], and (TT) 0.0 [0.0; 1.0], p = 0.535. By day 9, statistically significant differences disappeared (were not detected): (CC) 2.0 [2.0; 2.2], (CT) 2.0 [2.0; 2.0], and (TT) 2.0 [2.0; 3.0], p = 0.502. Statistically significant differences were not obtained on the 16th day of the therapy: (CC) 3.0 [2.8; 3.0], (CT) 3.0 [3.0; 3.0], and (TT) 3.0 [3.0; 3.0], p > 0.999.

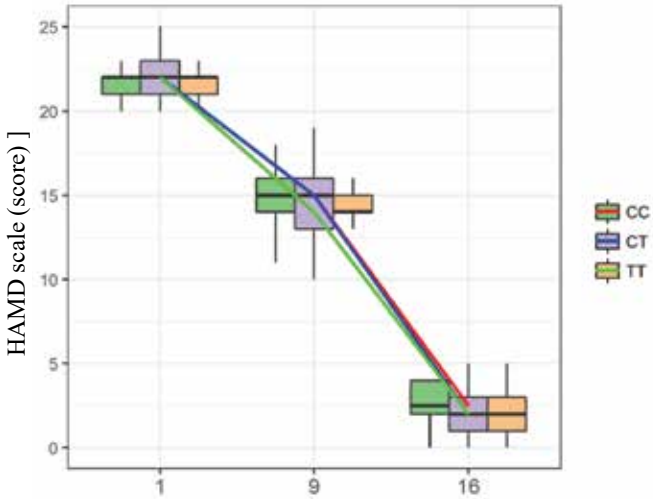

Fig. 1. Dynamics of changes in the HAMD scale scores among the patients with different genotypes in 3435C>T (rs1045642) ABCB1 polymorphic marker

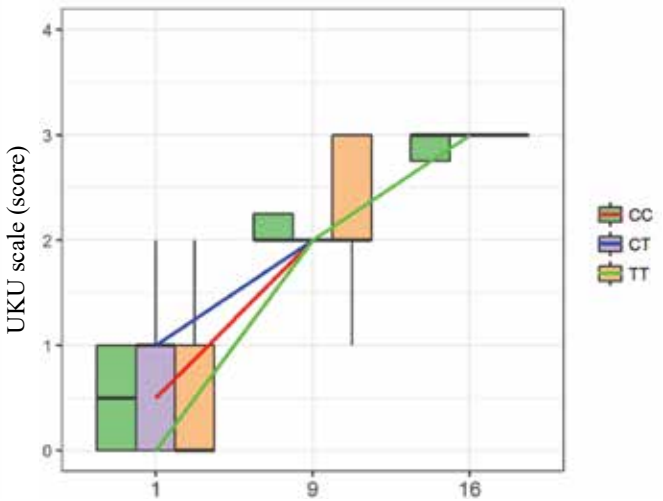

Fig. 2. Dynamics of changes in the UKU scale scores among the patients with different genotypes in 3435C>T (rs1045642) ABCB1 polymorphic marker

DISCUSSION

Statistical analysis of the data on mirtazapine clinical effectiveness and safety profile in patients with different genotypes for the 3435C>T polymorphic marker of the *ABCB1* gene (rs1045642) showed no statistically significant differences in effectiveness and safety (p > 0.999). These results may indicate the absence of the effect of this polymorphic marker on the clinical effectiveness and treatment safety of this group of patients.

Thus, according to the obtained results, which showed that the *ABCB1* gene (rs1045642) 3435C> T genetic polymorphism does not affect the effectiveness and safety rates of mirtazapine therapy in patients with depresssion disorders, comorbid with alcohol use disroder, it is possible to assume that it is not necessary to take into account the results of genotyping by the loci of this gene before prescribing mirtazapine to such patients. At the same time, prior studies manifested that *CYP2D6* gene polymorphisms should be taken into account when administering mirtazapine, as this may have an impact on the mirtazapine effectiveness and safety profile in patients with depressive disorders, comorbid with alcohol use disorder [14–16].

CONCLUSION

The current study conducted on 119 patients with depressive disorders, comorbid with alcohol use disorder, found the absence of the effect of *ABCB1* gene 3435C> T polymorphism (rs1045642) on the clinical effectiveness and safety of mirtazapine.

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Authors contribution

Zastrozhin M.S. – 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. Scryabin V.Yu. – recruitment of study participants, biomaterial sampling, carrying out of the genotyping, statistical processing of the obtained data, drafting of the article. Ryzhikova K.A. – carrying out of the genotyping, revision and editing of the article. Grishina E.A. – design of the laboratory part of the study, carrying out of the genotyping, revision and editing of the article. Koporov S.G. – conception and design of the study, assistance in resolving administrative and ethical issues, revision and editing of the article. Bryun E.A. – conception and design of the study, revision and editing of the article. Sychev D.A. – 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.

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