Michael S. Zastrozhin, Anastasiya P. Antonenko*, Elena V. Nesterenko, Leyla I. Seyfullaeva, Violetta R. Mustafina, Antonina P. Esakova, Elena A. Grishina, Alexandr S. Sorokin, Valentin Yu. Skryabin, Ludmila M. Savchenko, Evgeny A. Bryun and Dmitry A. Sychev

Effects of CYP2C19*17 polymorphisms on the efficacy and safety of bromodigyrochlorophenylbenzodiazepine in patients with anxiety disorder and comorbid alcohol use disorder

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Abstract

Background: Bromodihydrochlorophenylbenzodiazepine (Phenazepam®) is used in the therapy of anxiety disorders in patients with alcohol dependence. However, Phenazepam therapy often turns out to be ineffective, and some patients develop dose-related adverse drug reactions (ADR): severe sedation, dizziness, headache, dyspepsia, falling, etc. That ensures the effectiveness of this category of patients. Despite the popularity of Phenazepam® as an anxiolytic drug, there is currently no accurate data on its biotransformation, as well as the effect of polymorphism of a gene on the efficacy and safety of bromodihydrochlorophenylbenzodiazepine in patients. The aim of our study was to study the effect of the polymorphism of the *CYP2C19* gene on the efficacy and safety index of Phenazepam® for patients with anxiety disorders, using algorithms for optimizing the therapy of Phenazepam® to reduce the risk of pharmacological resistance and increase the effectiveness of therapy.

Methods: The study was conducted on 86 Russian patients suffering from alcohol dependence. Patients with trauma anxiety disorders received bromdihydrochlorphenylbenzodiazepine in tablets at a dose of 4.0 [2.0; 6.0] mg per day for 5 days. Genotyping was carried out by the method of polymer chain reaction in real time with allele-specific hybridization. Efficiency and safety assessment was carried out using psychometric scales and scales of Hospital Anxiety and Depression Scale (HADS) severity scores.

Results: Based on the results of the study, statistically significant differences in the number of scores on the scale of HADS severity of *CYP2C19* CT on the third day of therapy were the following: (CC) 10.00 [9.00; 11.00], (CT) 14.00 [13.00; 16.00], (TT) 18.00 [17.00; 19.00], $p = 0.00$, and also on the fifth day: (CC) 6.00 [5.00; 7.00], (CT) 17.50 [16.25; 19.75], (TT) 22.50 [20.00; 24.00], $p = 0.00$. ADRs in patients with different genotypes for this polymorphic marker did not differ.

Conclusions: Thus, it has been shown that the polymorphism of the *CYP2C19* gene may influence the effectiveness indices of Phenazepam therapy in patients with anxiety disorders comorbid with alcohol dependence. This should be taken into account in the appointment of this drug in this way in order to increase effectiveness of therapy and improve the quality of life.

Keywords: benzodiazepines; biotransformation; bromodihydrochlorobenzodiazepine; *CYP2C19*; personalized medicine; pharmacogenetics; Phenazepam.

***Corresponding author: Anastasiya P. Antonenko,** Moscow Research and Practical Centre on Addictions of the Moscow Department of Healthcare, 37/1 Lyublinskaya Street, Moscow 109390, Russia, E-mail: aantonenk0@yandex.ru.
http://orcid.org/0000-0002-6121-290X
Michael S. Zastrozhin: Department of Addictology, Russian Medical Academy of Continuous Professional Education of the Ministry of Health of the Russian Federation, Moscow, Russian Federation; and Moscow Research and Practical Centre on Addictions of the Moscow Department of Healthcare, Moscow, Russia
Elena V. Nesterenko, Antonina P. Esakova, Alexandr S. Sorokin and Valentin Yu. Skryabin: Moscow Research and Practical Centre on Addictions of the Moscow Department of Healthcare, Moscow, Russia
Leyla I. Seyfullaeva and Violetta R. Mustafina: Federal State Autonomous Educational Institution of Higher Education I. M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation, Moscow, Russia
Elena A. Grishina, Ludmila M. Savchenko and Dmitry A. Sychev: Russian Medical Academy of Continuous Professional Education of the Ministry of Health of the Russian Federation, Moscow, Russian Federation
Evgeny A. Bryun: Russian Medical Academy of Continuous Professional Education of the Ministry of Health of the Russian Federation, Moscow, Russian Federation; and Moscow Research and Practical Centre on Addictions of the Moscow Department of Healthcare, Moscow, Russia

Introduction

Anxiety disorders are commonly co-occurring in patients with alcohol use disorder [1–4]. Anxiolytics are primarily used to treat anxiety disorders [5]. Although

Table 1: Data from psychometric scales and the side effect score in patients who received Phenazepam® (scores) on the 1st day of the study.

Parameter	Genotype CC	Genotype CT	p-Value	Genotype CT	Genotype TT	p-Value	Genotype TT	Genotype CC	p-Value	p-Value (for 3 groups)
SoPA	16.00 [14.50; 19.00]	17.00 [15.00; 20.00]	0.86	17.00 [15.00; 20.00]	17.00 [16.00; 19.00]	0.85	17.00 [16.00; 19.00]	16.00 [14.50; 19.00]	0.69	0.93
PACS	8.00 [8.00; 9.50]	8.00 [7.00; 9.00]	0.88	8.00 [7.00; 9.00]	9.00 [7.00; 10.00]	0.40	9.00 [7.00; 10.00]	8.00 [8.00; 9.50]	0.73	0.68
VAS	41.00 [35.75; 45.50]	46.00 [37.75; 50.00]	0.20	46.00 [37.75; 50.00]	48.00 [42.00; 53.00]	0.19	48.00 [42.00; 53.00]	41.00 [35.75; 45.50]	0.06	0.10
CGI	4.00 [4.00; 4.00]	4.00 [3.00; 4.00]	0.12	4.00 [3.00; 4.00]	4.00 [3.00; 4.00]	0.76	4.00 [3.00; 4.00]	4.00 [4.00; 4.00]	0.02	0.12
HADS	29.50 [26.75; 32.25]	28.00 [26.00; 31.00]	0.69	28.00 [26.00; 31.00]	28.50 [25.25; 31.75]	0.83	28.50 [25.25; 31.75]	29.50 [26.75; 32.25]	0.65	0.88
HAM-A	18.00 [16.50; 18.00]	16.00 [14.25; 18.00]	0.39	16.00 [14.25; 18.00]	16.50 [15.00; 19.00]	0.37	16.50 [15.00; 19.00]	18.00 [16.50; 18.00]	0.77	0.56
UKU	1.00 [1.00; 1.00]	1.00 [1.00; 2.00]	0.14	1.00 [1.00; 2.00]	1.00 [1.00; 1.00]	0.21	1.00 [1.00; 1.00]	1.00 [1.00; 1.00]	0.28	0.19

p, p-Value based on the results of Duncan's test; p (for 3 groups), p-value based on the results of H-test Kruskal-Wallis; SoPA, Scale of Pathological Addiction; PACS, Penn Alcohol Craving Scale; VAS, Visual Analogue Scale; CGI, Clinical Global Impression; HADS, Hospital Anxiety and Depression Scale; HAM-A, Hamilton Anxiety Rating Scale; UKU, Side-Effect Rating Scale.

Table 2: Data from psychometric scales and the side effect score in patients who received Phenazepam® (scores) on the 3rd day of the study.

Parameter	Genotype CC	Genotype CT	p-Value	Genotype CT	Genotype TT	p-Value	Genotype TT	Genotype CC	p-Value	p-Value (for 3 groups)
SoPA	7.50 [6.25; 8.75]	9.00 [9.00; 10.00]	0.02	9.00 [9.00; 10.00]	11.50 [11.00; 12.00]	0.00	11.50 [11.00; 12.00]	7.50 [6.25; 8.75]	0.00	0.00
PACS	3.00 [3.00; 3.00]	4.00 [4.00; 4.00]	0.00	4.00 [4.00; 4.00]	5.00 [5.00; 6.00]	0.00	5.00 [5.00; 6.00]	3.00 [3.00; 3.00]	0.00	0.00
VAS	21.00 [18.75; 21.75]	23.00 [22.00; 25.00]	0.01	23.00 [22.00; 25.00]	29.00 [27.00; 31.00]	0.00	29.00 [27.00; 31.00]	21.00 [18.75; 21.75]	0.00	0.00
CGI	1.00 [1.00; 1.00]	2.00 [2.00; 2.00]	0.00	2.00 [2.00; 2.00]	2.50 [2.00; 3.00]	0.00	2.50 [2.00; 3.00]	1.00 [1.00; 1.00]	0.00	0.00
HADS	10.00 [9.00; 11.00]	14.00 [13.00; 16.00]	0.00	14.00 [13.00; 16.00]	18.00 [17.00; 19.00]	0.00	18.00 [17.00; 19.00]	10.00 [9.00; 11.00]	0.00	0.00
HAM-A	6.50 [6.00; 7.00]	9.00 [8.00; 9.00]	0.00	9.00 [8.00; 9.00]	11.00 [10.00; 11.00]	0.00	11.00 [10.00; 11.00]	6.50 [6.00; 7.00]	0.00	0.00
UKU	1.00 [1.00; 1.00]	1.00 [1.00; 2.00]	0.09	1.00 [1.00; 2.00]	1.00 [1.00; 2.00]	0.51	1.00 [1.00; 2.00]	1.00 [1.00; 1.00]	0.14	0.21

p, p-Value based on the results of Duncan's test; p (for 3 groups), p-value based on the results of H-test Kruskal-Wallis; SoPA, Scale of Pathological Addiction; PACS, Penn Alcohol Craving Scale; VAS, Visual Analogue Scale; CGI, Clinical Global Impression; HADS, Hospital Anxiety and Depression Scale; HAM-A, Hamilton Anxiety Rating Scale; UKU, Side-Effect Rating Scale.

Table 3: Data from psychometric scales and the side effect score in patients who received Phenazepam® (scores) on the 5th day of the study.

Parameter	Genotype CC	Genotype CT	p-Value	Genotype CT	Genotype TT	p-Value	Genotype TT	Genotype CC	p-Value	p-Value (for 3 groups)
SoPA	2.50 [2.00; 5.25]	11.50 [11.00; 12.00]	0.00	11.50 [11.00; 12.00]	15.50 [14.00; 17.00]	0.00	15.50 [14.00; 17.00]	2.50 [2.00; 5.25]	0.00	0.00
PACS	2.00 [1.25; 2.00]	6.00 [5.00; 6.00]	0.00	6.00 [5.00; 6.00]	7.00 [6.00; 7.00]	0.00	7.00 [6.00; 7.00]	2.00 [1.25; 2.00]	0.00	0.00
VAS	11.50 [8.25; 14.75]	30.00 [26.00; 33.00]	0.00	30.00 [26.00; 33.00]	38.50 [36.00; 41.00]	0.00	38.50 [36.00; 41.00]	11.50 [8.25; 14.75]	0.00	0.00
CGI	1.00 [1.00; 1.00]	2.00 [2.00; 2.00]	0.00	2.00 [2.00; 2.00]	3.00 [3.00; 3.00]	0.00	3.00 [3.00; 3.00]	1.00 [1.00; 1.00]	0.00	0.00
HADS	6.00 [5.00; 7.00]	17.50 [16.25; 19.75]	0.00	17.50 [16.25; 19.75]	22.50 [20.00; 24.00]	0.00	22.50 [20.00; 24.00]	6.00 [5.00; 7.00]	0.00	0.00
HAM-A	3.50 [2.25; 4.75]	11.00 [9.00; 12.00]	0.00	11.00 [9.00; 12.00]	15.00 [13.00; 15.00]	0.00	15.00 [13.00; 15.00]	3.50 [2.25; 4.75]	0.00	0.00
UKU	1.00 [1.00; 1.00]	1.00 [1.00; 2.00]	0.66	1.00 [1.00; 2.00]	1.00 [1.00; 2.00]	0.14	1.00 [1.00; 2.00]	1.00 [1.00; 1.00]	0.17	0.20

p, p-Value based on the results of Duncan's test; p (for 3 groups), p-value based on the results of H-test Kruskal-Wallis; SoPA, Scale of Pathological Addiction; PACS, Penn Alcohol Craving Scale; VAS, Visual Analogue Scale; CGI, Clinical Global Impression; HADS, Hospital Anxiety and Depression Scale; HAM-A, Hamilton Anxiety Rating Scale; UKU, Side-Effect Rating Scale.

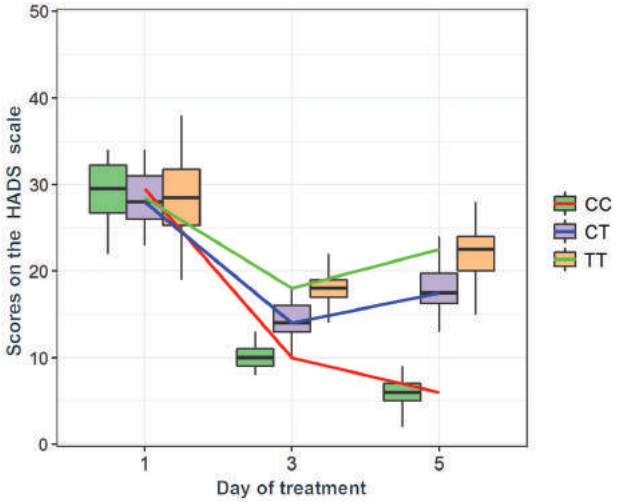

Figure 1: The dynamics of anxiety and depression symptoms (according to HADS evaluation) in patients with different genotypes.
Data are presented as Me and IQR. HADS, Hospital Anxiety and Depression Scale; Me and IQR, median and interquartile range.

benzodiazepines belong to one pharmacological group, their pharmacokinetics varies due to different chemical properties, especially lipophilicity [6].

There are two common biotransformation pathways involving p-450 mycrosomal oxidation: n-alkylation and glucuronidation [7]. Benzodiazepines metabolites are excreted mainly by kidneys.

Bromdihydrochlorphenylbenzodiazepine (Phenazepam®) is often used for anxiety disorder and alcohol withdrawal syndrome therapy in Russia, although there is not

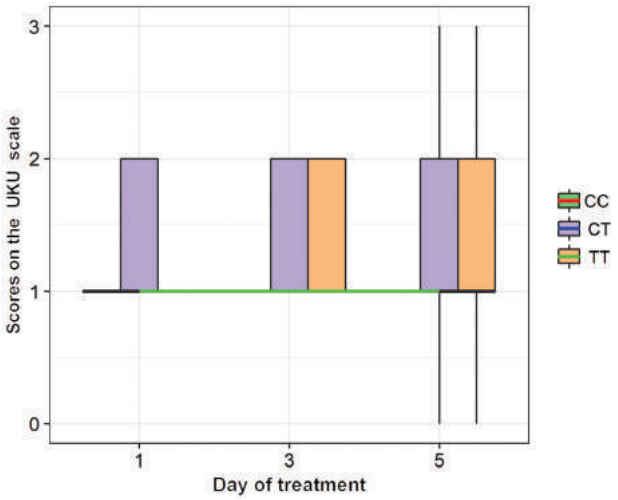

Figure 2: The dynamics of symptoms in the UKU side effect rating scale in patients with different genotypes.
Data are presented as Me and IQR. UKU, Side-Effect Rating Scale.

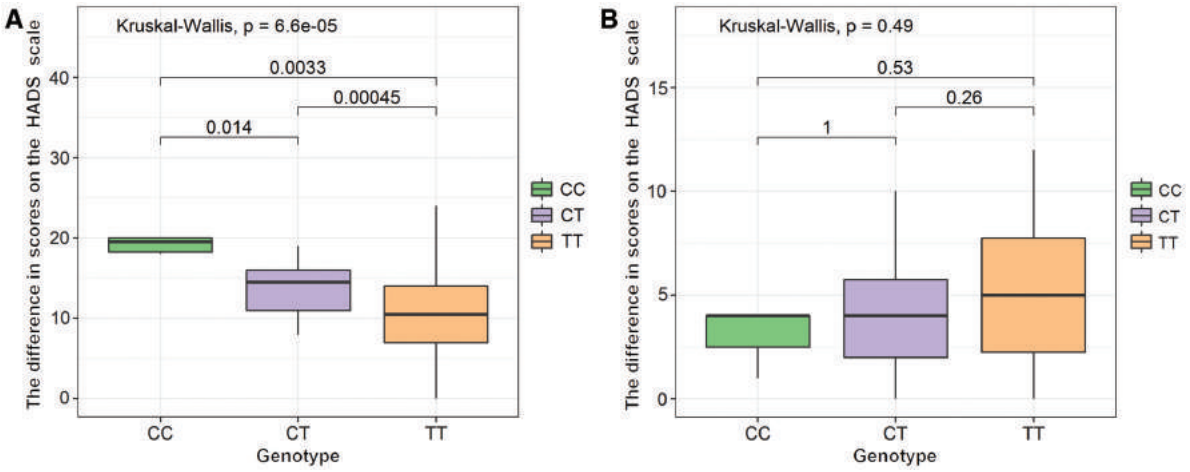

Figure 3: The dynamics of changes in Hospital Anxiety and Depression Scale (HADS) scores.
(A) The dynamics of changes in HADS scores from day 1 to day 3 across patients with different genotypes. Data are presented as Me and IQR. p-Value H-test Kruskal-Wallis. Intergroup comparison – Duncan's test. (B) The dynamics of changes in HADS scores from day 3 to day 5 across patients with different genotypes. Data are presented as Me and IQR. p-Value H-test Kruskal-Wallis. Intergroup comparison – Duncan's test.

enough data about its pharmacokinetics and pharmacogenetics because of limited use of Phenazepam in the US.

Currently there are data on correlation between the *CYP2C19* genetic polymorphisms (including *CYP2C19*2*) and efficacy, but data on safety of bromdihydrochlorphenylbenzodiazepine in Russian population of patients are missing. It was important to conduct this study among the patients with alcohol use disorder as the majority of these patients experience liver disorders affecting the biotransformation of xenobiotics and alcohol-induced gene expression changes.

Materials and methods

Therapy efficacy was evaluated by international psychometric scales: the Scale of Pathological Addiction (SoPA) [8], Penn Alcohol Craving Scale (PACS) [9], Visual Analogue Scale (VAS), Clinical Global Impression (CGI) [10], Hospital Anxiety and Depression Scale (HADS) [11] and the Hamilton Anxiety Rating Scale (HAM-A) [12]. Safety profile was evaluated using The UKU Side-Effect Rating Scale (UKU) [13]. Patients were examined on days 1, 3 and 5 of the therapy.

The study included 86 male patients (average age was 37.16 ± 7.84 years with alcohol use disorder who received treatment in the inpatient facility in Moscow Research and Practical Centre on Addictions of the Moscow Department of Healthcare with the clinical diagnosis of "Adjustment disorders" (F43.2, according to ICD-10) and comorbid "Alcohol dependence in remission (F10.21)".

For the therapy of anxiety disorder patients received bromdihydrochlorphenylbenzodiazepine in tablets at a dose of 4.0 [2.0; 6.0] mg per day for 5 days of the inpatient treatment course.

The inclusion criteria were the following: a diagnosis of "Adjustment disorders (F43.2, according to ICD-10)" with comorbid "Alcohol dependence in remission (F10.21)"; signed informed consent; and treatment with Phenazepam® of 5 days. Exclusion criteria were the following: presence of any other mental disorders; presence of severe somatic disorders (except alcoholic hepatitis and toxic encephalopathy); use 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); body weight less than 60 kg or greater than 100 kg; age of 75 years or more and presence of any contraindications for bromdihydrochlorphenylbenzodiazepine use.

The study was approved by the local Ethics Committee of the Russian Medical Academy of Continuous Professional Education of the Ministry of Health of the Russian Federation (Protocol No.6 from May 16, 2017).

Venous blood samples collected in vacuum tubes VACUETTE® (Greiner Bio-One, Austria) on the fifth day of the bromdihydrochlorphenylbenzodiazepine therapy were used for genotyping. The real-time polymerase chain reaction was performed using DNA amplifiers "Dtlite" of DNA Technology (Moscow, Russia) and CFX96 Touch Real Time System with CFX Manager software of Bio-Rad Laboratories Inc. (USA) and sets of "SNP-screen" of "Syntol" (Russia). It was used to determine single nucleotide polymorphisms (SNPs) *-806C > T* of the gene *CYP2C19* (*rs2248560)*. In every "SNP-screen" set, two allele-specific hybridizations were used, which allowed to determine two alleles of the studied polymorphism separately on two fluorescence channels.

Statistical analysis of the results was performed with non-parametric methods using the "StatsoftStatistica v. 10.0" (Dell Statistica, Tulsa, OK, USA). The normality of samples distribution was evaluated using W-Shapiro-Wilk test and taken into account when choosing a method. The differences were considered as statistically significant at $p < 0.05$ (power in excess of 80%). To compare two independent groups the Mann-Whitney U-test was used. Further Benjamini-Hochberg multiple testing correction was implemented to adjust p-value.

Table 4: The dynamics of changes on psychometric scales and in the UKU side effect rating scale scores from day 1 to day 3 across patients with different genotypes.

Parameter	Genotype CC	Genotype CT	p-Value	Genotype CT	Genotype TT	p-Value	Genotype TT	Genotype CC	p-Value	p-Value (for 3 groups)
SoPA	9.50 [6.50; 12.50]	8.00 [5.25; 11.00]	0.33	8.00 [5.25; 11.00]	6.00 [5.00; 7.75]	0.03	6.00 [5.00; 7.75]	9.50 [6.50; 12.50]	0.04	0.02
PACS	5.00 [5.00; 6.50]	4.00 [3.00; 5.00]	0.21	4.00 [3.00; 5.00]	3.00 [2.00; 4.00]	0.05	3.00 [2.00; 4.00]	5.00 [5.00; 6.50]	0.04	0.03
VAS	19.50 [15.25; 24.50]	20.00 [14.50; 28.00]	0.82	20.00 [14.50; 28.00]	17.50 [13.00; 25.00]	0.10	17.50 [13.00; 25.00]	19.50 [15.25; 24.50]	0.54	0.24
CGI	3.00 [3.00; 3.00]	2.00 [1.00; 2.00]	0.01	2.00 [1.00; 2.00]	1.00 [0.25; 2.00]	0.00	1.00 [0.25; 2.00]	3.00 [3.00; 3.00]	0.00	0.00
HADS	19.50 [18.25; 20.00]	14.50 [11.00; 16.00]	0.01	14.50 [11.00; 16.00]	10.50 [7.00; 14.00]	0.00	10.50 [7.00; 14.00]	19.50 [18.25; 20.00]	0.00	0.00
HAM-A	11.50 [9.50; 12.75]	6.50 [6.00; 10.00]	0.07	6.50 [6.00; 10.00]	6.50 [4.00; 9.00]	0.18	6.50 [4.00; 9.00]	11.50 [9.50; 12.75]	0.01	0.03
UKU	0.00 [0.00; 0.00]	0.00 [0.00; 1.00]	0.03	0.00 [0.00; 1.00]	0.00 [0.00; 1.00]	0.09	0.00 [0.00; 1.00]	0.00 [0.00; 0.00]	0.14	0.04

p, p-Value based on the results of Duncan's test; p (for 3 groups), p-value based on the results of H-test Kruskal-Wallis; SoPA, Scale of Pathological Addiction; PACS, Penn Alcohol Craving Scale; VAS, Visual Analogue Scale; CGI, Clinical Global Impression; HADS, Hospital Anxiety and Depression Scale; HAM-A, Hamilton Anxiety Rating Scale; UKU, Side-Effect Rating Scale.

Research data are presented as median and interquartile range (Me [Q1; Q3]) or, in case of normal distribution, as the arithmetic mean and standard deviation (Mean ± SD). Pearson χ-squared test was applied to frequencies comparison.

Results

The *CYP2C19* genotyping by polymorphic marker *-806C > T* (rs12248560) performed in 86 male patients with anxiety disorder have revealed the following distribution:

- The number of patients with "wild-type" homozygous *GG* genotype was 46 (53.5%).
- The number of patients with heterozygous CT genotype was 33 (38.4%).
- The number of patients with homozygous TT genotype was 7 (8.10%).

Genotypes distribution corresponded to Hardy-Weinberg equilibrium in the European population (Fisher's exact test $\chi^2 = 0.656$; $p = 0.418$).

The results of data analysis performed for psychometric scales and side-effect rating scale in patients who received Phenazepam® are presented in Tables 1–3.

The dynamics of changes in HADS scores across patients with different genotypes are shown in Figure 1. As demonstrated, at the beginning of research the compared groups were comparable in the studied parameter: (CC) 29.50 [26.75; 32.25], (CT) 28.00 [26.00; 31.00], (TT) 28.50 [25.25; 31.75], $p = 0.88$. By day 3, HADS scores were statistically significantly different between the compared groups: (CC) 10.00 [9.00; 11.00], (CT) 14.00 [13.00; 16.00], (TT) 18.00 [17.00; 19.00], $p = 0.00$. This difference remained by day 5 also: (CC) 6.00 [5.00; 7.00], (CT) 17.50 [16.25; 19.75], (TT) 22.50 [20.00; 24.00], $p = 0.00$.

We have compared dynamics of changes in the UKU scores and psychometric scales scores in groups of patients with different genotypes. The dynamics of changes in the UKU scores across patients with different genotypes are shown in Figure 2. At the beginning of the study the compared groups were comparable in the examined parameter: (CC) 1.00 [1.00; 1.00], (CT) 1.00 [1.00; 2.00], (TT) 1.00 [1.00; 1.00], $p = 0.19$. By day 3 no statistically significant difference occurred in patients with different genotypes: (CC) 1.00 [1.00; 1.00], (CT) 1.00 [1.00; 2.00], (TT) 1.00 [1.00; 2.00], $p < 0.21$. By day 5, the difference remained insignificant: (CC) 1.00 [1.00; 1.00], (CT) 1.00 [1.00; 2.00], (TT) 1.00 [1.00; 2.00], $p < 0.20$.

The dynamics of changes in the UKU scores and psychometric scales across patients with different genotypes are shown in Table 2.

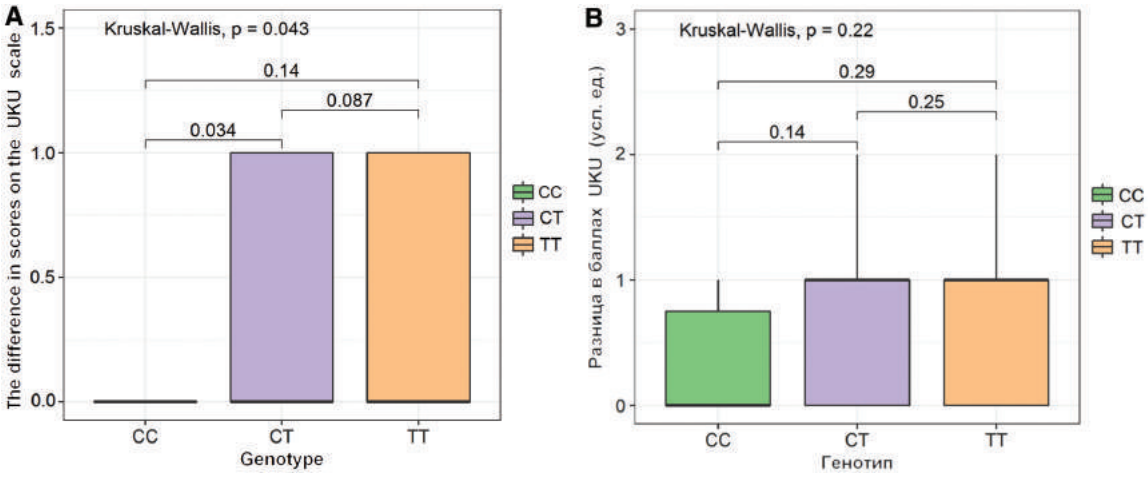

Figure 4: The dynamics of changes in the Side-Effect Rating Scale (UKU) side effect rating scale scores.
(A) The dynamics of changes in the UKU side effect rating scale scores from day 1 to day 3 across patients with different genotypes. Data are presented as Me and IQR. p-Value H-test Kruskal-Wallis. Intergroup comparison – Duncan's test. (B) The dynamics of changes in the UKU side effect rating scale scores from day 3 to day 5 across patients with different genotypes. Data are presented as Me and IQR. p-Value H-test Kruskal-Wallis. Intergroup comparison – Duncan's test.

The dynamics of changes in HADS scores across patients with different genotypes are shown in Figure 3A and B. Changes in the scores from day 1 to day 3 were as follows: CC 19.50 [18.25; 20.00], with genotype CT 14.50 [11.00; 16.00], and genotype TT 10.50 [7.00; 14.00] ($p = 0.00$). Changes in the scores from day 3 to day 5 were as follows: CC – 4.00 [2.50; 4.00], CT – 4.00 [2.00; 5.75], TT – 5.00 [2.25; 7.75] ($p = 0.49$) (Table 4).

The dynamics of changes in the UKU scores across patients with different genotypes are shown in Figure 4A and B. Changes in the scores from day 1 to day 3 were as follows: CC – 0.00 [0.00; 0.00], CT – 0.00 [0.00; 1.00], TT – 0.00 [0.00; 1.00] ($p < 0.04$) 0.00. Changes in the scores from day 3 to day 5 were as follows: CC – 0.00 [0.00; 0.75], CT – 1.00 [0.00; 1.00], TT – 1.00 [0.00; 1.00] ($p < 0.22$) (Table 5).

Discussion

The study has shown that the safety profile of Phenazepam® (bromdihydrochlorphenylbenzodiazepine) in patients with affective disorders and comorbid alcohol use disorder correlates with *CYP2C19* (-806C > T) genetic polymorphism.

CT and CC genotypes carriers experienced faster anxiety score reduction than patients with TT genotype.

Probably it correlates with the enhanced activity of CYP2C19 isoenzyme in patients carrying TT and CT genotypes of polymorphic marker *CYP2C19* (-806C > T). Increased activity of CYP2C19 leads to the faster biotransformation and elimination rates of Phenazepam® with subsequent lower plasma concentration in these patients and to reduced amount of medication reaching the receptor targets of Phenazepam®.

Nevertheless, despite the fact that CC genotype carriers are less metabolically active and tend to have higher Phenazepam® blood concentration, they did not experience higher rate of adverse drug reaction in comparison to patents with different genotypes.

As mentioned before, Phenazepam® acts less effectively in patients who carry CT and TT genotypes. These patients could suffer from residual anxiety and feel disappointment about their treatment. Treatment optimization (increase dose or replace Phenazepam® with tranquilizer with different metabolical pathway) may be beneficial in T-allele carriers to avoid loss of compliance and prevent relapses.

Conclusions

The study revealed the Phenazepam® safety differences in patients suffering from anxiety disorder and comorbid alcohol use disorders with different genotypes of polymorphic marker *CYP2C19* (-806C > T). This should be considered when prescribing this medication to such patients to enhance therapeutical efficacy and reduce the risk of undesirable side effects and pharmacoresistance.

Table 5: The dynamics of changes on psychometric scales and in the UKU side effect rating scale scores from day 3 to day 5 across patients with different genotypes.

Parameter	Genotype CC	Genotype CT	p-Value	Genotype CT	Genotype TT	p-Value	Genotype TT	Genotype CC	p-Value	p (for 3 groups)
SoPA	3.00 [3.00; 6.75]	3.00 [1.00; 3.00]	0.21	3.00 [1.00; 3.00]	4.00 [3.00; 6.00]	0.00	4.00 [3.00; 6.00]	3.00 [3.00; 6.75]	0.84	0.00
PACS	1.50 [1.00; 2.00]	2.00 [1.00; 2.00]	0.68	2.00 [1.00; 2.00]	1.00 [1.00; 2.00]	0.20	1.00 [1.00; 2.00]	1.50 [1.00; 2.00]	0.82	0.43
VAS	8.00 [2.50; 12.75]	6.00 [4.00; 9.00]	0.63	6.00 [4.00; 9.00]	9.00 [6.00; 12.75]	0.03	9.00 [6.00; 12.75]	8.00 [2.50; 12.75]	0.73	0.10
CGI	0.50 [0.00; 1.00]	0.00 [0.00; 1.00]	0.86	0.00 [0.00; 1.00]	1.00 [0.00; 1.00]	0.04	1.00 [0.00; 1.00]	0.50 [0.00; 1.00]	0.37	0.11
HADS	4.00 [2.50; 4.00]	4.00 [2.00; 5.75]	1.00	4.00 [2.00; 5.75]	5.00 [2.25; 7.75]	0.26	5.00 [2.25; 7.75]	4.00 [2.50; 4.00]	0.53	0.49
HAM-A	3.00 [2.25; 3.00]	3.00 [1.00; 4.00]	0.82	3.00 [1.00; 4.00]	4.00 [2.00; 5.75]	0.00	4.00 [2.00; 5.75]	3.00 [2.25; 3.00]	0.24	0.01
UKU	0.00 [0.00; 0.75]	1.00 [0.00; 1.00]	0.14	1.00 [0.00; 1.00]	1.00 [0.00; 1.00]	0.25	1.00 [0.00; 1.00]	0.00 [0.00; 0.75]	0.29	0.22

p, p-Value based on the results of Duncan's test; p (for 3 groups), p-value based on the results of H-test Kruskal-Wallis; SoPA, Scale of Pathological Addiction; PACS, Penn Alcohol Craving Scale; VAS, Visual Analogue Scale; CGI, Clinical Global Impression; HADS, Hospital Anxiety and Depression Scale; HAM-A, Hamilton Anxiety Rating Scale; UKU, Side-Effect Rating Scale.

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