Received: 22 June 2018 | Revised: 15 September 2018 | Accepted: 25 September 2018

DOI: 10.1002/hup.2677

RESEARCH ARTICLE

WILEY

Using a personalized clinical decision support system for bromdihydrochlorphenylbenzodiazepine dosing in patients with anxiety disorders based on the pharmacogenomic markers

Michael S. Zastrozhin[1,2] | Aleksandr S. Sorokin[2] | Tatyana V. Agibalova[2] | Elena A. Grishina[1] | Anastasiya P. Antonenko[2] | Ilya N. Rozochkin[2] | Denis V. Duzhev[2] | Valentine Y. Skryabin[2] | Tatyana E. Galaktionova[2] | Ilya V. Barna[2] | Anna V. Orlova[2] | Albert D. Aguzarov[2] | Ludmila M. Savchenko[1] | Evgeny A. Bryun[1,2] | Dmitry A. Sychev[1]

[1] Russian Medical Academy of Continuous Professional Education, Ministry of Health of the Russian Federation, Moscow, Russia

[2] Moscow Research and Practical Centre on Addictions, Moscow Department of Healthcare, Moscow, Russia

Correspondence
Mikhail Sergeevich Zastrozhin, Moscow Research and Practical Centre on Addictions, Moscow Department of Healthcare, 37/1 Lyublinskaya Street, Moscow 109390, Russia.
Email: mszastrozhin@gmail.com

Funding information
Conducting fundamental scientific research and exploratory research on priority thematic research areas, Grant/Award Number: MK-2460.2018.7; The Russian Science Foundation, Grant/Award Number: 16-15-00227; President of the Russian Federation

Abstract

Introduction: Although pharmacogenetic tests provide the information on a genotype and the predicted phenotype, these tests themselves do not provide the interpretation of data for a physician. There are currently approximately two dozen pharmacogenomic clinical decision support systems used in psychiatry. Implementation of clinical decision support systems capable of forming recommendations on drug and dose selection according to the results of pharmacogenetic testing is an urgent task. Fulfillment of this task may allow increasing the efficacy of therapy and decreasing the risk of undesirable side effects.

Materials and methods: The study included 51 male patients (21 in the main group and 30 in the control group) with alcohol withdrawal syndrome. To evaluate the efficacy and safety of therapy, several international psychometric scales and rating scales to measure side effects were used. Genotyping was performed using real-time polymerase chain reaction with allele-specific hybridization. Pharmacogenetic test results were interpreted using free software PGX2 (www.pgx2.com).

Results: Statistically significant differences between the scores derived from all psychometric scales were revealed. For instance, the total score on CIWA-Ar scale by day 3 was 13.5 [11.2; 16.0] for the main group and 18.0 [17.0; 22.0] ($p < 0.001$) for the control group; by day 5, it was 6.5 [4.2; 8.0] for the main group and 15.0 [14.0; 16.0] ($p < 0.001$) for the control group. The UKU side effect rating scale (UKU) also revealed a statistically significant difference. The total score on UKU scale by day 3 was 6.0 [5.0; 7.0] for the main group and 7.0 [6.0; 8.0] ($p < 0.001$) for the control group; by day 5, this difference grew significantly: 5.5 [3.0; 9.0] for the main group and 14.0 [12.0; 19.0] ($p < 0.001$) for the control group. The groups were representative (there was no difference between the scores at the inclusion of patients).

Conclusion: Pharmacogenetic-guided personalization of drug dose in patients with alcohol withdrawal syndrome can reduce the risk of undesirable side effects and

pharmacoresistance. It allows recommending the use of pharmacogenomic clinical decision support systems for optimizing drug dosage.

KEYWORDS

alcohol withdrawal syndrome, benzodiazepines, clinical decision support system, CYP2C19, pharmacogenetics, tranquilizers

1 | INTRODUCTION

Anxiety disorders are among the most prevalent psychiatric disorders comorbid with alcohol addiction (Bakken, Landheim, & Vaglum, 2005; Grant et al., 2004; Smith & Book, 2010). Benzodiazepines (BDZs) have the largest and the best evidence base in the treatment of alcohol withdrawal syndrome and are considered the gold standard (Sachdeva, Choudhary, & Chandra, 2015). These medications ameliorate or prevent the symptoms and complications of alcohol withdrawal (Weintraub, 2017). Alcohol is a central nervous system (CNS) depressant, influencing the inhibitory neurotransmitter gamma-aminobutyric acid (GABA; Kattimani & Bharadwaj, 2013). Benzodiazepines are cross-tolerant with alcohol and modulate anxiolysis by stimulating GABA-A receptors (Mayo-Smith, 1997).

Pharmacogenomics studies of BDZs are focused on their metabolizing hepatic cytochrome P450 enzymes. Diazepam is primarily metabolized by *CY2C19* and *CYP3A4* to the major active metabolite, desmethyldiazepam. Its other active metabolites include the minor active metabolites temazepam and oxazepam. At therapeutic doses, desmethyldiazepam is found in plasma at concentrations equivalent to those of diazepam while oxazepam and temazepam are not usually detectable. Other *CYP* enzymes involved in diazepam metabolism include *CYP2C9*, *CYP2B*, and *CYP3A5*. Approximately 3% of Caucasians and 15% to 20% of Asians have reduced or absent *CYP2C19* enzyme activity ("poor metabolizers"). In these individuals, standard doses of diazepam may lead to a higher exposure to diazepam (Dean et al., 2012). A number of studies revealed that both *CYP2C19* and *CYP3A4* are major contributors to the N-demethylation of diazepam in human microsomal fractions, whereas *CYP3A4* is mainly responsible for 3-hydroxylation. Recently, it was shown that *CYP2C19* and *CYP3A4* genetic polymorphisms affect the pharmacokinetics of benzodiazepines. Clinical studies conducted in Chinese, Japanese, and Swedish populations had highlighted the effect of *CYP2C19* genetic polymorphism on differences in pharmacokinetics of diazepam and desmethyldiazepam (Inomata et al., 2005). Although *CYP3A4* is also involved in diazepam metabolism, there have been conflicting results from studies of the impact of *CYP3A4* and *CYP3A5* variants on benzodiazepine metabolism. Overall, it is noteworthy that pharmacogenetics of benzodiazepines is poorly studied in patients with alcohol withdrawal syndrome.

Bromdihydrochlorphenylbenzodiazepine (Phenazepam®) is commonly used in Russian psychiatric and narcological practice for the treatment of anxiety disorders and alcohol withdrawal syndrome, but reliable papers devoted to clinical pharmacokinetics and pharmacogenetics of this tranquilizer are very limited; probably, it can be correlated with limited distribution of Phenazepam® outside of Russia.

Although pharmacogenetic tests provide information on a genotype and the predicted phenotype, these tests themselves do not provide the interpretation of data for a physician. There are currently approximately two dozen pharmacogenomic clinical decision support systems (CDSSs) used in psychiatry: CNSDose® (Baycrest Biotechnology; Singh, 2015), Genecept Assay® (Genomind Inc.; Fagerness et al., 2014), GeneSight® (Assurex Health; Brener & Holubowich, 2017), YouScript (Genelex; Elliott et al., 2017), and others. Panels used in CDSS invariably include *CYP2D6*, *CYP2C19*, and other loci, depending on the manufacturer, implicated in pharmacokinetics and pharmacodynamics. Meanwhile, only part of such systems has shown the evidence of effectiveness (Bousman & Hopwood, 2016). In particular, a double-blind, randomized study showed that subjects receiving genetically guided prescribing had a 2.52-fold greater chance of remission (Singh, 2015). A prospective double-blind randomized controlled trial to evaluate the benefit of a combinatorial, five gene pharmacogenomic test and interpretive report (GeneSight) for the management of psychotropic medications used in the treatment of major depression in an outpatient psychiatric practice showed that between-group trends were observed with greater than double the likelihood of response and remission in the GeneSight group measured by HAMD-17 at week 10. The authors conclude that pharmacogenomic-guided treatment with GeneSight doubles the likelihood of response in all patients with treatment-resistant depression and allows identifying 30% of patients with severe gene-drug interactions who have the greatest improvement in depressive symptoms when switched to genetically suitable medication regimens (Winner, Carhart, Altar, Allen, & Dechairo, 2013).

Thus, implementation of CDSSs capable of forming the recommendations on drug and dose selection according to the results of pharmacogenetic testing is an urgent task. Fulfillment of this task will allow increasing the efficacy of therapy and decreasing the risk of undesirable side effects.

2 | MATERIALS AND METHODS

2.1 | Clinico-demographic characteristics of patients

The study included 51 male patients (average age—34.64 ± 9.16 years) with alcohol withdrawal state (F10.30, according to ICD-10) who underwent inpatient treatment in Moscow Research and Practical Centre on Addictions of the Moscow Department of Healthcare. Among them, 21 patients started treatment with bromdihydrochlorphenylbenzodiazepine (brand name Phenzitat, 1 mg tablets, JSC "Tatchempharmpreparaty," Russia) in doses recommended by the results of pharmacogenetic testing performed through special software www.pgx2.com (main group). When

prescribing bromdihydrochlorphenylbenzodiazepine to the remaining 30 patients and to exclude the placebo effect, treating physicians received a report containing information that patients had normal genotypes with regard to all of the studied markers and regardless of the patient's real genotype (control group). Physicians were warned that the study would be double-blind by giving them the reports with recommendations based on "ideal" patient genotypes. Thus, physicians knew that some of the recommendations were false and could disregard them. Bromdihydrochlorphenylbenzodiazepine was prescribed using a symptom-triggered regimen (Mayo-Smith, 1997). BDZs were administered according to the withdrawal symptoms as assessed by CIWA-Ar withdrawal rating scale.

Information on clinical and demographic characteristics of the patients is presented in Table 1.

2.2 | Description of the research design

Patients were included in study within 24 hr following hospitalization. Several international psychometric scales were used to measure symptom severity: Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar; Sullivan, Sykora, Schneiderman, Naranjo, & Sellers, 1989), Pennsilvanian Alcohol Craving Scale (PACS; Flannery, Volpicelli, & Pettinati, 1999), Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983), Hamilton Anxiety Scale (HAMA; Hamilton, 1959), Clinical Global Impression—State (CGI-S). Safety profile was evaluated using The UKU Side-Effect Rating Scale (UKU; Lingjaerde, Ahlfors, Bech, Dencker, & Elgen, 1987). Peripheral venous blood (5 ml) was collected for genotyping. A dynamic follow-up lasted for 5 days according to relevant clinical recommendations and guidelines for the treatment of alcohol withdrawal syndrome. In addition to detoxification and vitamin therapy, treatment regimen necessarily included bromdihydrochlorphenylbenzodiazepine. Safety profile was evaluated using The UKU scale on day 6 of the therapy.

TABLE 1 Clinical and demographic characteristics of the patients

Parameter	Main group	Control group	p^a
N (%)	21 (41.2%)	30 (58.8%)	
Age (year)	39.3 ± 16.1	37.4 ± 11.59	>0.999
Weight (kg)	86.3 ± 18.9	84.2 ± 19.36	>0.999
Height (cm)	175.6 ± 28.1	172.3 ± 39.62	>0.999
Body mass index (kg/m^2)	27.9 ± 5.0	28.3 ± 6.8	>0.999
Nationality (Russian), *N* (%)	21 (100%)	30 (100%)	>0.999
Alcoholic steatohepatitis, *N* (%)	21 (100%)	29 (96.7%)	>0.999
Toxic encephalopathy, *N* (%)	18 (85.7%)	27 (90%)	>0.999
Toxic polyneuropathy of the upper extremities, *N* (%)	4 (19%)	6 (20%)	>0.999
Toxic polyneuropathy of the lower extremities, *N* (%)	2 (9.5%)	3 (10%)	>0.999
Viral hepatitis C, *N* (%)	1 (4.8%)	1 (3.3%)	>0.999
Peptic ulcer disease, *N* (%)	3 (14.3%)	4 (13.3%)	>0.999
Duodenal ulcer, *N* (%)	0 (0%)	1 (3.3%)	>0.999
Arterial hypertension, *N* (%)	6 (28.6%)	10 (33.3%)	>0.999
Active smoking, *N* (%)	21 (100%)	29 (96.7%)	>0.999

[a]*p*—*p* value adjusted by the Benjamini–Hochberg procedure (based on results of the Student's *t* test for independent samples with Welch's correction for quantitative variables and the two-tailed Fisher's exact test for qualitative data).

Randomization was performed by assigning random numbers generated using "=RANDBETWEEN()" function in Microsoft Excel 2016 (Microsoft Corp., USA).

The inclusion criteria were the following: a diagnosis of "Mental and behavioral disorders due to psychoactive substance use. Withdrawal state, uncomplicated (F10.30, according to ICD-10)"; signed informed consent; treatment with bromdihydrochlorphenylbenzodiazepine throughout the period of alcohol withdrawal syndrome. Exclusion criteria were 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 except bromdihydrochlorphenylbenzodiazepine; 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.

An initial dose of bromdihydrochlorphenylbenzodiazepine was 4.0 [2.0; 6.0] mg per day.

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). Before inclusion in the study, all patients were given a full explanation of the purpose of the study, the procedures to be carried out and the potential hazards; they received the study protocol and brochure, and all their questions were answered. Then, the written informed consent approved by the local ethics committee was obtained.

2.3 | Genotyping

Saline samples collected in plastic containers during the day of admission 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 "SNP-screen" sets of "Syntol" (Russia). It was used to determine single nucleotide polymorphisms (SNP's) *CYP2D6*4* (*1846G>A*, *rs3892097*), *CYP2C19*2* (*681G>A*, *rs4244285*), *CYP2C19*3* (*636G>A*, *rs4986893*), *CYP2C19*17* (*-806C>T*, *rs12248560*), *CYP3A5*3* (*6986A>G*, *rs77646*), and *ABCB1*6* (*3435C>T*, *rs1045642*). In every "SNP-screen" set, two allele-specific hybridizations were used, which allowed to determine two alleles of studied polymorphism separately on two fluorescence channels.

2.4 | Description of the CDSS operation principle and the way of decision support system implementation

Pharmacogenetic test results were interpreted using free software PGX2 (www.pgx2.com). This software allows creating the report on results of pharmacogenetic testing instantly, with recommendations understandable to the physician. Pharmacogenetic test results are used as the input data. Algorithms for preparing the recommendations were based on Clinical Pharmacogenetics Implementation Consortium Guideline (Weintraub, 2017). For instance, in patients carrying homozygous polymorphism

1846G>A of *CYP2D6* gene (genotype AA), it was recommended to reduce an initial fluvoxamine dose by 25–50% from the one intended by the physician according to the clinical presentation of the patient.

An example of the resulting report with recommendations (pages 1 and 6) is shown in Figure 1.

Upon admission, patient's biomaterial was collected and DNA was isolated. Then, genotyping at the above mentioned loci was carried out, and the results were loaded to the fields corresponding to data for available polymorphic markers requested in step 1 "Enter genotyping data" in the "Genotypes are known" section of PGX2. In Step 2, "Selecting Drug Groups," the "Tranquilizers (anxiolytics)" group was selected, in relation to which, based on the description of the step, recommendations for personalization should be formed. At Step 3, "Information on the patient and organization" "Moscow Research and Practical Centre on Addictions" was selected as an organization and patient data were entered in the appropriate field. The fields "patient's name" and "date of birth" were not filled in order to anonymise the patient. In Step 4, the English language of the report was selected. The generated PDF file containing the recommendations on personalization of therapy with tranquilizers based on pharmacogenetic testing was printed out to physicians on the same day as biomaterial was sampled. Based on the recommendations, as well as the clinical picture of disease, the physicians chose the dose of phenazepam. All physicians followed the recommendations of CDSS, and it was checked by the general investigator.

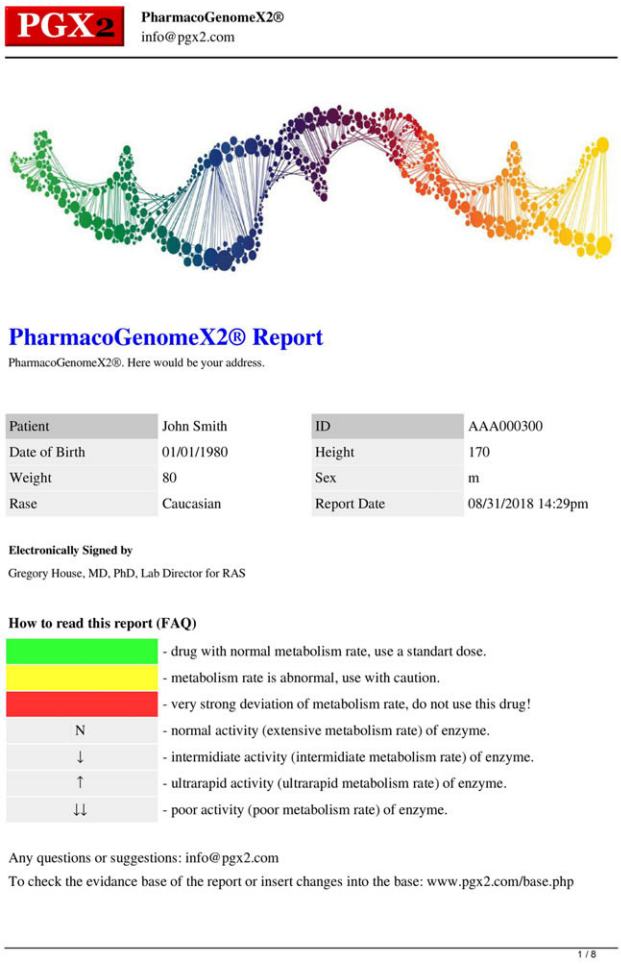
2.5 | Statistical analysis

Statistical analysis was performed using R, a statistical programming language, through Microsoft R Application Network (R version 3.3.2 [2016-10-31]) with the checkpoint package installed to control the versions of the statistical packages used. The development environment RStudio version 1.0.136 was used for programming. 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, Mann–Whitney U test was used with Benjamini–Hochberg multiple testing correction. Research data are presented as mediana and interquartile range (Me [Q1; Q3]) or, in case of normal distribution, as the arithmetic mean and standard deviation (mean ± *SD*). Pearson's χ^2 test was used to compare the frequencies of genotypes and undesirable side effects.

3 | RESULTS

Genotyping results are shown in Table 2. Genotype distribution of polymorphisms obeyed Hardy–Weinberg equilibrium.

The results of data analysis performed for psychometric scales and side-effect rating scale in patients of both main and control



PGX2 PharmacoGenomeX2®
info@pgx2.com

PharmacoGenomeX2® Report

PharmacoGenomeX2®. Here would be your address.

Patient	John Smith	ID	AAA000300
Date of Birth	01/01/1980	Height	170
Weight	80	Sex	m
Rase	Caucasian	Report Date	08/31/2018 14:29pm

Electronically Signed by

Gregory House, MD, PhD, Lab Director for RAS

How to read this report (FAQ)

	- drug with normal metabolism rate, use a standart dose.
	- metabolism rate is abnormal, use with caution.
	- very strong deviation of metabolism rate, do not use this drug!
N	- normal activity (extensive metabolism rate) of enzyme.
↓	- intermidiate activity (intermidiate metabolism rate) of enzyme.
↑	- ultrarapid activity (ultrarapid metabolism rate) of enzyme.
↓↓	- poor activity (poor metabolism rate) of enzyme.

Any questions or suggestions: info@pgx2.com

To check the evidance base of the report or insert changes into the base: www.pgx2.com/base.php

1 / 8

PGX2 PharmacoGenomeX2®
info@pgx2.com

1. Antipsychotics

Drug	Standart Dose	Decrease Dose	Increase Dose	Do not use	Reason
Chlorpromazine				+	CYP2D6(↓) CYP1A2(N) UGT1A3(N) UGT1A6(N)
Levomepromazine	+				CYP3A4(N) CYP1A2(N) CYP3A5(N)
Promazin			+		CYP1A2(N) CYP3A4(N) CYP2C19(↑) CYP2C9(N)
Cyamemazine	+				CYP1A2(N) CYP3A4(N) CYP3C9(N) CYP2C8(N)
Fluphenazine				+	CYP2D6(↓)
Perphenazine				+	CYP2D6(↓)
Prochlorperazine				+	CYP2D6(↓) CYP3A4(N) CYP3A5(N)
Trifluoperazine	+				CYP1A2(N) UGT1A4(N)
Thioridazine		+			CYP2D6(↓) CYP1A2(N) CYP3A4(N) CYP2C19(↑)
Periciazine				+	CYP2D6(↓)
Promethazine				+	CYP2D6(↓) UGT1A3(N) UGT1A4(N)
Bromperidol	+				CYP3A4(N) CYP3A5(N)
Droperidol	+				CYP3A4(N) CYP3A5(N)
Haloperidol				+	CYP2D6(↓) CYP1A2(N) CYP3A4(N) CYP3A5(N)
Flupentixol				+	CYP2D6(↓)
Chlorprotixene				+	CYP2D6(↓)
Tiothixen	+				CYP1A2(N) CYP3A4(N) CYP3A5(N)
Zuclopentixol				+	CYP2D6(↓) CYP3A4(N) CYP3A5(N)
Olanzapine		+			UGT1A4(N) CYP1A2(N) CYP2D6(↓)
Quetiapine		+			CYP3A4(N) CYP2D6(↓) CYP3A5(N) CYP1A2(N) CYP2C9(N)
Asenapine		+			CYP1A2(N) UGT1A4(N) CYP2D6(↓) CYP3A4(N) CYP3A5(N)
Clozapine		+			CYP1A2(N) CYP2D6(↓) CYP3A4(N) CYP2C9(N)
Sertindole				+	CYP2D6(↓) CYP3A4(N) CYP3A5(N)
Ziprasidone	+				CYP3A4(N) AOX1(N) CYP3A5(N)
Lurasidone	+				CYP3A4(N) CYP3A5(N)
Tiaprid	+				
Sulpiride	+				
Amisulpride	+				
Aripiprazole				+	CYP2D6(↓) CYP3A4(N) CYP3A5(N) DRD3(N)
Risperidone				+	CYP2D6(↓) CYP3A4(N) CYP3A5(N) ABCB1(N)
Iloperidone				+	CYP2D6(↓) CYP3A4(N) CYP3A5(N)
Paliperidone				+	CYP2D6(↓) CYP3A4(N) CYP3A5(N)
Zotepin		+			CYP3A4(N) CYP1A2(N) CYP3A5(N) CYP2D6(↓)

4 / 8

FIGURE 1 Sample report with recommendations on the personalization of tranquilizers, formed with PGX2 (1 and 4 pages)

TABLE 2 Genotyping results in patients of the main group

Allelic variant	Polymorphism	rs	"Wild type" allele (AA)	Heterozygotes (AB)	Homozygous mutants (BB)	Hardy–Wainberg equilibrium	
						χ^2	p^a
CYP2D6*4	1846G>A	rs3892097	17 (81.0%)	4 (19.0%)	0 (0.0%)	0.23	0.62
CYP2C19*2	681G>A	rs4244285	18 (85.7%)	3 (14.3%)	0 (0.0%)	0.12	0.72
CYP2C19*3	636G>A	rs4986893	20 (95.2%)	1 (4.8%)	0 (0.0%)	0.01	0.91
CYP2C19*17	-806C>T	rs12248560	11 (52.4%)	9 (42.9%)	1 (4.8%)	0.25	0.61
CYP3A5*3	6986A>G	rs77646	0 (0.0%)	3 (14.3%)	18 (85.7%)	0.12	0.72
ABCB1*6	3435C>T	rs1045642	11 (52.4%)	9 (42.9%)	1 (4.8%)	0.25	0.61

[a]p—p value based on the results of Pearson's χ^2 test.

groups are presented in Table 3. Dynamics of changes in CIWA-Ar scores and UKU scores across patients of both main and control groups are shown in Figure 2.

As demonstrated, at the beginning of research the compared groups were comparable in the studied parameter (main: 22.0 [19.2; 26.0] vs. control: 21.0 [21.0; 23.0], $p > 0.05$). By day 3, CIWA-Ar scores were statistically significantly different between the compared groups (main: 13.5 [11.2; 16.0] vs. control: 18.0 [17.0; 22.0], $p < 0.001$). This difference remained by day 5 also (main: 6.5 [4.2; 8.0] vs. control: 15.0 [14.0; 16.0], $p < 0.001$).

TABLE 3 The results of psychometric scales and side-effect rating scale data analysis (scores) in patients from the main (guided) and control (unguided) groups

Day	Parameter	Unguided	Guided	p^a
Day 1	CIWA-Ar	21.00 [20.00; 23.00]	22.00 [19.250; 26.00]	1.000
	PACS	10.00 [9.00; 11.00]	10.00 [9.00; 11.750]	1.000
	VAS	61.00 [54.00; 71.00]	60.00 [48.50; 64.50]	1.000
	CGI	5.00 [5.00; 5.00]	5.00 [4.00; 5.00]	1.000
	HADS	34.00 [30.00; 38.00]	34.500 [31.25; 39.75]	1.000
	UKU	1.00 [1.00; 1.00]	1.00 [1.00; 1.00]	1.000
Day 2	CIWA-Ar	18.00 [17.00; 22.00]	13.500 [11.250; 16.00]	<0.001
	PACS	9.00 [7.00; 9.00]	7.00 [6.00; 7.750]	0.001
	VAS	50.00 [40.00; 54.00]	40.500 [33.25; 43.00]	0.029
	CGI	3.00 [3.00; 4.00]	3.00 [3.00; 4.00]	1.000
	HADS	31.00 [28.00; 33.00]	23.00 [21.00; 26.50]	<0.001
	UKU	7.00 [6.00; 8.00]	6.00 [5.00; 7.00]	0.030
Day 3	CIWA-Ar	15.00 [14.00; 16.00]	6.500 [4.250; 8.00]	0.000
	PACS	5.00 [4.00; 6.00]	3.00 [2.00; 3.00]	0.000
	VAS	29.00 [27.00; 33.00]	14.00 [13.00; 17.75]	0.000
	CGI	2.00 [2.00; 2.00]	1.00 [1.00; 1.00]	0.000
	HADS	22.00 [21.00; 24.00]	10.00 [7.00; 13.75]	0.000
	UKU	14.00 [12.00; 19.00]	5.500 [3.00; 9.00]	0.000

Note. CGI: Clinical Global Impression; CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol Scale; HADS: Hospital Anxiety and Depression Scale; PACS: Penn Alcohol Craving Scale; SoPA: Scale of Pathological Addiction; UKU: Side-Effect Rating Scale; VAS: Visual Analogue Scale.

[a]p—p value based on the results of Benjamini–Hochberg procedure (based on the results of Mann–Whitney U test).

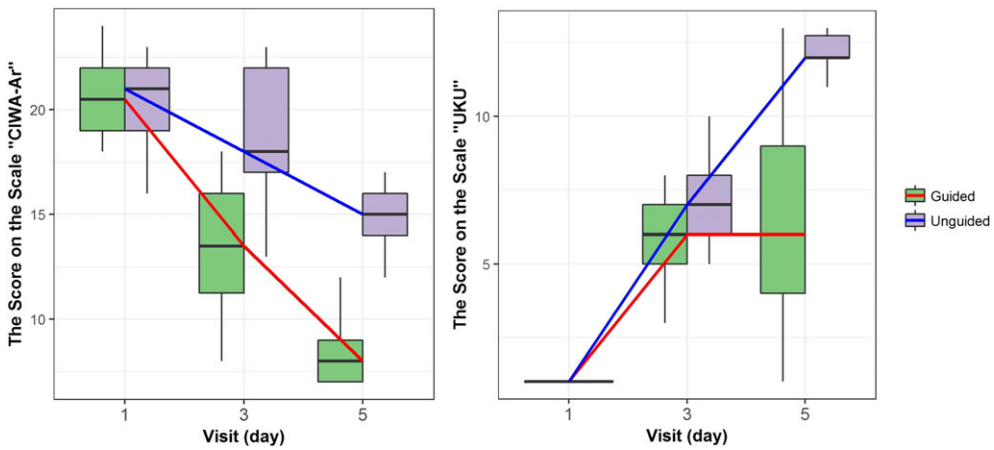


FIGURE 2 Dynamics of changes in Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar) scores and UKU side effect rating scale scores across patients with different genotypes (data are presented as Me and IQR). CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol Scale; UKU: side effect rating scale

As demonstrated, at the beginning of research the compared groups were comparable in the studied parameter (main: 1.0 [1.0; 1.0] vs. control: 1.0 [1.0; 1.0], $p > 0.05$). By day 3, UKU scores were statistically significantly different between the compared groups (main: 6.0 [5.0; 7.0] vs. control: 7.0 [6.0; 8.0], $p < 0.001$). This difference remained by day 5 also (main: 5.5 [3.0; 9.0] vs. control: 14.0 [12.0; 19.0], $p < 0.001$).

The results of data analysis performed for psychometric scales and side-effect rating scale in patients of both main and control groups are presented in Table 4.Dynamics of changes in CIWA-Ar scores across patients of both main and control groups are shown in Figure 3. The decrease of CIWA-Ar scores from days 1 to 3 was 8.0 [5.2; 14.5] in the main group and 3.0 [2.0; 6.0] ($p < 0.001$) in the control group. The decrease of CIWA-Ar scores from days 3 to 5 was 7.0 [6.0; 8.7] in the main group and 3.0 [2.0; 5.0] ($p < 0.001$) in the control group.

Dynamics of changes in UKU scores across patients of both main and control groups are shown in Figure 4. An increase of UKU scores from days 1 to 3 was 5.0 [3.0; 6.2] in the main group and 3.0 [1.0; 4.0] ($p = 0.021$) in the control group. An increase of UKU scores from days 3 to 5 was 3.0 [2.0; 5.7] in the main group and 8.0 [2.0; 5.7] ($p = 0.001$) in the control group.

4 | DISCUSSION

This study investigating the implementation effectiveness of the CDSS based on the principle of generating recommendations on drug and dose selection according to the results of pharmacogenetic testing had a prospective design and was randomized and double-blind. In this study, reports containing recommendations based on normal genotypes have been generated for patients from a control group. It allowed excluding the placebo effect which could inevitably occur in previously conducted studies investigating the implementation of pharmacogenetic algorithms in clinical practice, as treating physicians and patients would know who was subjected to additional testing (pharmacogenetic testing) and who was treated using an empirical dose selection. Thus, this study is the first one in the field of pharmacogenomics that takes placebo-effect into account and is truly double blinded (previously a physician knew, which patients were subjected to pharmacogenetic testing and which were not). It is also important to note that objects of investigation were randomized in main and control groups through nonsurrogate randomization.

We would like to emphasize that physicians who used CDSS provided only positive feedback and stated that they would like to continue using such programs in future. All physicians conducted their own

TABLE 4 Dynamics of changes in psychometric scales and side-effect rating scale scores from days 1 to 3 and from days 3 to 5 in patients from the main (guided) and control (unguided) groups

Interval	Parameter	Unguided	Guided	p^a
From days 1 to 3	CIWA-Ar	3.00 [2.00; 6.00]	8.00 [5.25; 14.50]	0.003
	PACS	2.00 [1.00; 3.00]	4.00 [2.00; 5.00]	0.274
	VAS	20.00 [13.00; 21.00]	21.500 [8.750; 31.75]	1.000
	CGI	2.00 [1.00; 2.00]	2.00 [1.00; 2.00]	1.000
	HADS	6.00 [3.00; 10.00]	10.500 [7.00; 17.50]	0.055
	UKU	6.00 [5.00; 7.00]	5.00 [4.00; 6.00]	0.021
From days 3 to 5	CIWA-Ar	3.00 [2.00; 5.00]	7.00 [6.00; 8.750]	0.001
	PACS	4.00 [2.00; 5.00]	4.00 [3.00; 5.00]	1.000
	VAS	19.00 [10.00; 24.00]	26.500 [19.250; 29.00]	0.054
	CGI	1.00 [1.00; 2.00]	2.00 [2.00; 3.00]	0.001
	HADS	9.00 [7.00; 10.00]	12.500 [8.500; 17.00]	0.131
	UKU	8.00 [6.00; 12.00]	3.00 [2.00; 5.75]	0.001

Note. CGI: Clinical Global Impression; CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol Scale; HADS: Hospital Anxiety and Depression Scale; PACS: Penn Alcohol Craving Scale; SoPA: Scale of Pathological Addiction; UKU: Side-Effect Rating Scale; VAS: Visual Analogue Scale.

[a]p—p value based on the results of Benjamini–Hochberg procedure (based on the results of Mann–Whitney U test).

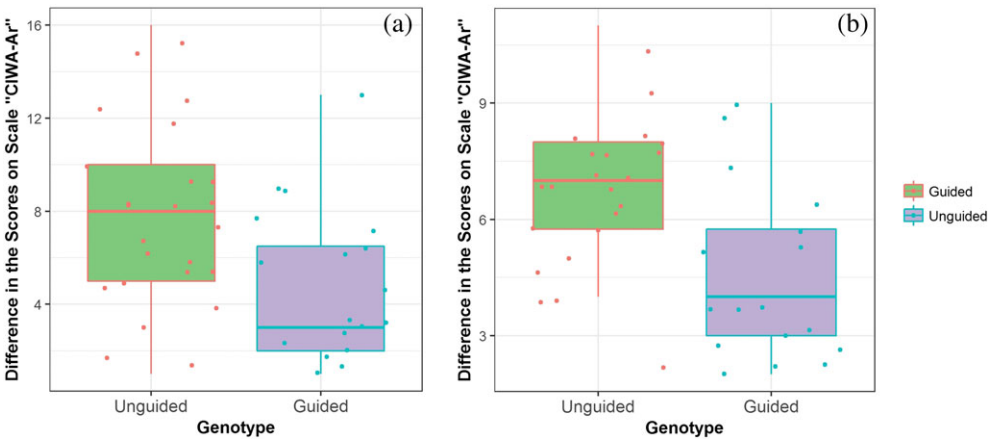


FIGURE 3 Dynamics of changes in Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar) scores from days 1 to 3 (a) and from days 3 to 5 (b) across patients of both main and control groups (data are presented as Me and IQR). CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol Scale

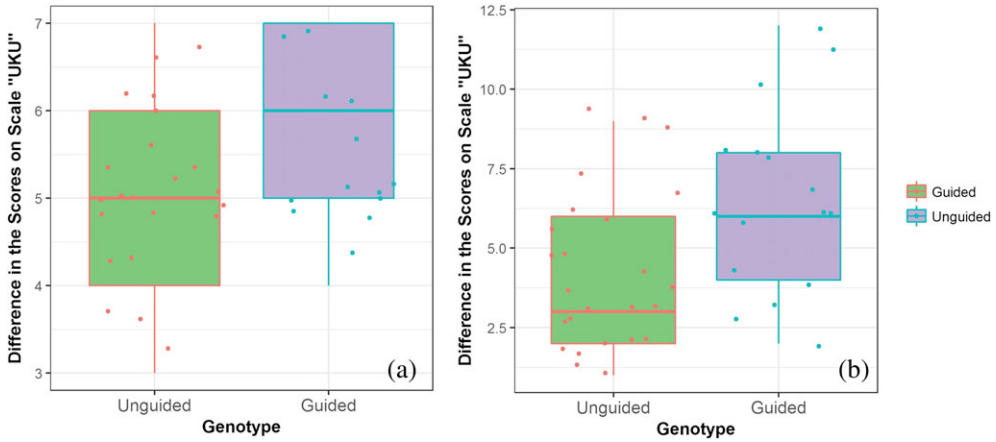


FIGURE 4 Dynamics of changes in UKU scores from days 1 to 3 (a) and from days 3 to 5 (b) across patients of both main and control groups (data are presented as Me and IQR). UKU: Side-Effect Rating Scale

subjective assessment of the extent to which the use of CDSS had an effect on the efficacy and safety of therapy, noting that the adverse drug reactions developed less frequently and were less severe in patients who were prescribed tranquilizers according to the CDSS recommendations. Subjective difference in the therapy effectiveness in patients from the primary and control groups was not noted by the physicians.

The study demonstrated that using algorithms of personalized treatment based on the results of pharmacogenetic testing allows optimisation of the efficacy and safety of therapy in patients suffering from alcohol withdrawal syndrome. In particular, dosage adjustment in patients carrying rapid and slow allelic variants can reduce both pharmacoresistance and risk of undesirable side effects.

Our study has a number of advantages in comparison with other studies investigating the implementation effectiveness of different models of pharmacogenetic testing:

1 This study is the first one comparing the models of treatment with BDZs, which implied the medication prescription both using an empirical dose selection and according to the results of pharmacogenetic testing.
2 As noted above, our study has a control group. It is a generated report based on the genotype data of an "ideal" patient having no deviations in the speed of xenobiotics biotransformation by the cytochrome P-450 isoenzymes and P-glycoprotein.
3 The recommendations were elaborated through free software PGX2 (www.pgx2.com). Its calculation algorithms are based on recommendations of the pharmacogenetic consortiums Clinical Pharmacogenetics Implementation Consortium and The Dutch Pharmacogenetics Working Group (DPWG).
4 The study was conducted in the Russian population. It makes our study more interesting, because previous ones enrolled the patients of the European population.
5 This study was conducted in the inpatient setting. It allowed controlling the use of medication and excluding the cases of missed doses.

Our research has a number of limitations. The first is the absence of phenotyping of cytochrome P-450 isoenzymes. Particularly significant is the absence of phenotyping in patients with alcohol use disorder. Nevertheless, at the time of conducting the research, our team lacked the procedures required to perform the express analyses of cytochrome P-450 isoenzymes and P-glycoprotein activity levels. In justification, we can notice that patients with severe liver disorders (cirrhosis, hepatic failure, presence of jaundice, and scleral icterus) were not enrolled in the study.

Another significant limitation was the absence of therapeutic drug monitoring needed to register the equilibrium of drug concentration. It could allow objectivizing the data of psychometric scales and side-effect rating scale, but the difficulties in financing unfortunately did not allow us to perform it.

5 | CONCLUSION

Despite a number of limitations, this study conducted in 51 patients demonstrated the efficacy of using a personalized pharmacogenomic CDSS for dosing in patients with alcohol withdrawal syndrome. It was shown that pharmacogenetic-guided personalization of the drug dose can reduce the risk of undesirable side effects and pharmacoresistance. It allows recommending the use of pharmacogenomic CDSSs for optimizing drug dosage.

ACKNOWLEDGMENTS

This research was conducted with the financial support of grant from the President of the Russian Federation to assist young Russian scientists holding PhD degrees (project MK-2460.2018.7) and support of The Russian Science Foundation, project 16-15-00227 "Conducting fundamental scientific research and exploratory research on priority thematic research areas."

AUTHOR CONTRIBUTIONS

M. S. Z.—overall supervision, development of the main CDSS code; A. S. S.—genotyping of CYP2C19*2 (681G>A, rs4244285), CYP2C19*3 (636G>A, rs4986893), and CYP2C19*17 (-806C>T, rs12248560); T. V. A. and L. M. S.—assistance in describing the clinical part of the study; E. A. G.—genotyping of CYP2D6*4 (1846G>A, rs3892097), CYP3A5*3 (6986A>G, rs77646), and ABCB1*6 (3435C>T, rs1045642); A. P. A.—assistance in preparing the publication and its submission; I. N. R.—

statistical analysis, assistance in preparing the study design; V. Y. S.—assistance in preparing the study design, translation of the article; D. V. D., T. E. G., I. V. B., A. V. O., and A. D. A.—physicians who agreed to use CDSS (unfortunately, the conditions of our grants do not allow providing any financial support to physicians who agreed to use CDSS, so we promised to include them in the authors list to create a motivation for them); E. A. B.—assistance in describing the clinical part of the study, administrative support; D. A. S.—scientific advisor during the CDSS basis development, assistance in interpreting the study results. All authors participated in the analysis of the obtained data, development of study design, and editing the text of publication.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

ORCID

Michael S. Zastrozhin https://orcid.org/0000-0003-0607-4812
Aleksandr S. Sorokin https://orcid.org/0000-0003-4914-8869
Tatyana V. Agibalova https://orcid.org/0000-0003-4612-4845
Elena A. Grishina https://orcid.org/0000-0002-5621-8266
Anastasiya P. Antonenko http://orcid.org/0000-0002-6121-290X
Ilya N. Rozochkin https://orcid.org/0000-0003-3885-3837
Denis V. Duzhev https://orcid.org/0000-0001-8409-9922
Valentine Y. Skryabin https://orcid.org/0000-0002-4942-8556
Tatyana E. Galaktionova https://orcid.org/0000-0001-6873-3161
Ilya V. Barna https://orcid.org/0000-0002-6097-737X
Anna V. Orlova https://orcid.org/0000-0001-5198-9240
Albert D. Aguzarov https://orcid.org/0000-0001-7664-998X
Ludmila M. Savchenko https://orcid.org/0000-0001-9075-7047
Evgeny A. Bryun https://orcid.org/0000-0002-8366-9732
Dmitry A. Sychev https://orcid.org/0000-0002-4496-3680

REFERENCES

Bakken, K., Landheim, A. S., & Vaglum, P. (2005). Substance-dependent patients with and without social anxiety disorder: Occurrence and clinical differences. A study of a consecutive sample of alcohol-dependent and poly-substance- dependent patients treated in two counties in Norway. *Drug and Alcohol Dependence*, *80*, 321–328. https://doi.org/10.1016/j.drugalcdep.2005.04.011

Bousman, C. A., & Hopwood, M. (2016). Commercial pharmacogenetic-based decision-support tools in psychiatry. *Lancet Psychiatry*, *3*(6), 585–590. https://doi.org/10.1016/S2215-0366(16)00017-1

Brener, S., & Holubowich, C. (2017). Pharmacogenomic testing for psychotropic medication selection: A systematic review of the Assurex GeneSight Psychotropic test. *Ontario Health Technology Assessment Series*, *17*(4), 1–39.

Dean, L. et al. (2012). Diazepam therapy and *CYP2C19* genotype. *Medical Genetics Summaries [Internet]*. Bethesda (MD): National Center for biotechnology information (US). https://www.ncbi.nlm.nih.gov/books/NBK379740/

Elliott, L. S., Henderson, J. C., Neradilek, M. B., Moyer, N. A., Ashcraft, K. C., & Thirumaran, R. K. (2017). Clinical impact of pharmacogenetic profiling with a clinical decision support tool in polypharmacy home health patients: A prospective pilot randomized controlled trial. *PLoS One*, *12*(2), e0170905. https://doi.org/10.1371/journal.pone.0170905

Fagerness, J., Fonesca, E., Hess, G. P., Scott, R., Gardner, K. R., Koffler, M., … Lombard, J. (2014). Pharmacogenetic-guided psychiatric intervention associated with increased adherence and cost savings. *The Amercian Journal of Managed Care*, *20*(5), e146–e156.

Flannery, B. A., Volpicelli, J. R., & Pettinati, H. M. (1999). Psychometric properties of the Penn alcohol craving scale. *Alcoholism, Clinical and Experimental Research*, *23*(8), 1289–1295. https://doi.org/10.1111/j.1530-0277.1999.tb04349.x

Grant, B. F., Stinson, F. S., Dawson, D. A., Chou, S. P., Dufour, M. C., Compton, W., … Kaplan, K. (2004). Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: Results from the National Epidemiologic Survey on alcohol and related conditions. *Archives of General Psychiatry*, *61*, 807–816. https://doi.org/10.1001/archpsyc.61.8.807

Hamilton, M. (1959). The assessment of anxiety states by rating. *The British Journal of Medical Psychology*, *32*, 50–55.

Inomata, S., Nagashima, A., Itagaki, F., Homma, M., Nishimura, M., Osaka, Y., … Toyooka, H. (2005). *CYP2C19* genotype affects diazepam pharmacokinetics and emergence from general anesthesia. *Clinical Pharmacology and Therapeutics*, *78*, 647–655. https://doi.org/10.1016/j.clpt.2005.08.020

Kattimani, S., & Bharadwaj, B. (2013). Clinical management of alcohol withdrawal: A systematic review. *Industrial Psychiatry Journal*, *22*(2), 100–108. https://doi.org/10.4103/0972-6748.132914

Lingjaerde, 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. Supplementum*, *76*(334), 1–100. https://doi.org/10.1111/j.1600-0447.1987.tb10566.x

Mayo-Smith, M. F. (1997). American society of addiction medicine working group on pharmacological management of alcohol withdrawal. Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. *JAMA*, (2), 144–151.

Sachdeva, A., Choudhary, M., & Chandra, M. (2015). Alcohol withdrawal syndrome: Benzodiazepines and beyond. *Journal of Clinical and Diagnostic Research*, *9*(9), 1–7.

Singh, A. B. (2015). Improved antidepressant remission in major depression via a pharmacokinetic pathway polygene pharmacogenetic report. *Clinical Psychopharmacology and Neuroscience*, *13*, 150–156. https://doi.org/10.9758/cpn.2015.13.2.150

Smith, J. P., & Book, S. W. (2010). Comorbidity of generalized anxiety disorder and alcohol use disorders among individuals seeking outpatient substance abuse treatment. *Addictive Behaviors*, *35*, 42–45. https://doi.org/10.1016/j.addbeh.2009.07.002

Sullivan, J. T., Sykora, K., Schneiderman, J., Naranjo, C. A., & Sellers, E. M. (1989). Assessment of alcohol withdrawal: The revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *British Journal of Addiction*, *84*(11), 1353–1357. https://doi.org/10.1111/j.1360-0443.1989.tb00737.x

Weintraub, S. J. (2017). Diazepam in the treatment of moderate to severe alcohol withdrawal. *CNS Drugs*, *31*(2), 87–95. https://doi.org/10.1007/s40263-016-0403-y

Winner, J. G., Carhart, J. M., Altar, C. A., Allen, J. D., & Dechairo, B. M. (2013 Nov). A prospective, randomized, double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder. *Discovery Medicine*, *16*(89), 219–227.

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica*, *67*(6), 361–370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x

How to cite this article: Zastrozhin MS, Sorokin AS, Agibalova TV, et al. Using a personalized clinical decision support system for bromdihydrochlorphenylbenzodiazepine dosing in patients with anxiety disorders based on the pharmacogenomic markers. *Hum Psychopharmacol Clin Exp*. 2018;e2677. https://doi.org/10.1002/hup.2677