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ORIGINAL RESEARCH

Effects of CYP2D6 genetic polymorphisms on the efficacy and safety of fluvoxamine in patients with depressive disorder and comorbid alcohol use disorder

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Background: Fluvoxamine therapy is used for treatment of patients with depressive disorder, but it is often ineffective, and some patients suffer from dose-dependent undesirable side effects such as vertigo, headache, indigestion, xerostomia, increased anxiety, etc. CYP2D6 is involved in the biotransformation of fluvoxamine. Meanwhile, the genes encoding these isoenzymes have a high level of polymorphism, which may affect the protein synthesis.

Objective: The primary objective of our study was to investigate the effects of *CYP2D6* genetic polymorphisms on the efficacy and safety of fluvoxamine in patients with depressive disorder and comorbid alcohol use disorder, in order to develop the algorithms of optimization of fluvoxamine therapy for reducing the risk of dose-dependent undesirable side effects and pharmacoresistance.

Methods: The study involved 45 male patients (average age: 36.44±9.96 years) with depressive disorder and comorbid alcohol use disorder. A series of psychometric scales was used in the research. Genotyping of *CYP2D6* (1846G>A) was performed using real-time polymerase chain reaction.

Results: According to results of Mann–Whitney *U*-test, statistically significant differences between the efficacy and safety of fluvoxamine were obtained on 9th and 16th days of therapy in patients with *GG* and *GA* genotypes (The Hamilton Rating Scale for Depression: 10.0 [10.0; 23.0] vs 25.0 [24.0; 16.0] ($P<0.001$) on the 9th day and 4.0 [2.0; 5.0] vs 6.0 [6.0; 7.0] on the 16th day; The UKU Side Effect Rating Scale: 6.0 [4.0; 6.0] vs 9.0 [9.0; 10.0] ($P<0.001$) on the 9th day and 5.0 [1.0; 9.0] vs 19.0 [18.0; 22.0] on the 16th day).

Conclusion: This study demonstrated the lower efficacy and safety of fluvoxamine in patients with depressive disorder and comorbid alcohol use disorders with *GA* genotype in *CYP2D6 1846G>A* polymorphic marker.

Keywords: pharmacogenetics, SSRIs, fluvoxamine, biotransformation, personalized medicine, CYP2D6, depressive disorders, alcohol addiction

Introduction

It is known that substance dependence is often comorbid with other mental disorders,[16,20] worsening the prognosis of the course and outcome of both diseases.[24] The most common comorbid diagnoses in patients with alcohol addiction are affective disorders and depressive disorders.[2] Treating these patients is a challenge, because one disorder worsens the course of another one.

A list of antidepressants preferred for alcohol addiction treatment includes mianserin, fluoxetine, fluvoxamine, mirtazapine, and sertraline. In contrast to monoamine

oxidase inhibitors (MAOIs) and tricyclic antidepressants, which enhance the activity of several neuromediators and thereby possess various pharmacological properties (including undesirable ones), the enumerated medications selectively inhibit serotonin reuptake and selectively enhance the activity of this mediator only.[10]

To date, it is proven that CYP2D6 is the primary enzyme responsible for the biotransformation of psychotropic medications.[1,12] This isoenzyme is encoded by the gene, which evidences a high level of polymorphism.[18] It allows distinguishing three main groups of allele variants depending on their possible effects on CYP2D6 isoenzyme activity: functional (extensive metabolizers), low-functional (intermediate metabolizers), and nonfunctional (poor metabolizers). In addition, a group of ultra-rapid metabolizers is identified. These individuals carry more than two copies of functional alleles, causing an increased amount of enzyme to be expressed and resulting in the enhanced biotransformation and elimination rates of drug substrates. The most common allele variants associated with poor metabolizer phenotype are *CYP2D6*3*, *CYP2D6*4*, *CYP2D6*5*, and *CYP2D6*6*. An increased metabolic rate is typical for individuals having duplication and multiplication of the wild-type allele variants, *(CYP2D6*1)xN* and *(CYP2D6*2)xN*. There is evidence for a significant role of *CYP2D6* genotype in the individual response to antidepressants venlafaxine,[5,6,13,14] fluoxetine,[3,18,22] paroxetine,[3,17,21] and nortriptyline.[4,11]

Fluvoxamine is metabolized by CYP2D6 and CYP1A2 isoenzymes. It has no pharmacologically active metabolites.[9] Fluvoxamine is also a strong inhibitor of *CYP1A2*, *CYP2C19*, *CYP3A4*, and *CYP2D6*,[9] which should be considered when prescribing the drug substrates for the listed isoenzymes, including fluvoxamine itself.[9] Studies focused on the effect of *CYP2D6* genetic polymorphisms on fluvoxamine clearance showed contradictory results. Probably these contradictions can be correlated with nonlinear pharmacokinetics induced by phenoconversion. Two studies performed in patients of European and Asian origin suffering from depressive disorder and taking fluvoxamine at doses from 50 to 200 mg/d revealed that individuals with different genotypes of *CYP2D6* polymorphic markers have different fluvoxamine concentration levels.[7,23] Meanwhile, a study conducted by Ohara et al[15] among 46 Japanese patients showed no effect of *CYP2D6*10* genetic polymorphism on fluvoxamine equilibrium plasma concentration level. The effect of *CYP2D6* genotype reduces with the increase of drug dose. The authors correlate it with the inhibitory effect of fluvoxamine on *CYP2D6*. Based on the data acquired for European and Asian populations, it was proposed that a differentiated approach to the dose titration of fluvoxamine in patients with different metabolic rates was required. For poor metabolizers, it is recommended to reduce the medication dose by ~70%, whereas for ultra-rapid metabolizers it is possible to titrate the dose, if necessary, up to 150%, controlling the fluvoxamine plasma concentration level with therapeutic drug monitoring.[19]

Currently, there is no data on correlation between the *CYP2D6* genetic polymorphisms and efficacy and safety of fluvoxamine among Russian patients. Equally important was to conduct this study among the patients with alcohol use disorder as the majority of these individuals, to varying degrees, have liver disorders affecting the biotransformation of xenobiotics. The objective of our study was to investigate the effect of *CYP2D6* genetic polymorphisms on the efficacy and safety of fluvoxamine in the Russian population.

Materials and methods

The study included 45 male patients (average age – 36.44±9.96 years) with depressive disorder and comorbid alcohol use disorder who underwent inpatient treatment in Moscow Research and Practical Centre on Addictions of the Moscow Department of Healthcare. For the therapy of depressive disorder, patients received fluvoxamine in tablets (Fevarin®, Abbott Laboratories, Lake Bluff, IL, USA) at a median dose of 100 [interquartile range: 50; 150] mg/d from day 5 to 21 of the inpatient treatment course. The study subjects were recruited consecutively from October 2016 to June 2017, using inclusion and exclusion criteria. The inclusion criterion was 16-day fluvoxamine therapy. Exclusion criteria were the presence of any other psychotropic medications in the treatment regimen except fluvoxamine (with the exception of Phenazepam®, Cayman Chemical, Ann Arbor, MI, USA) (bromdihydrochlorphenylbenzodiazepine) administered during the treatment of the alcohol withdrawal syndrome, creatinine clearance values <50 mL/min, creatinine concentration in plasma ≥1.5 mg/dL (133 mmol/L), body weight <60 kg or >100 kg, age of 75 years or more, and presence of any contraindications for fluvoxamine 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 (No. 6, September 27th, 2016), and all patients provided written informed consent.

Venous blood samples collected in vacuum tubes, VACUETTE® (Greiner Bio-One, Kremsmünster, Austria) on the 21st day of the fluvoxamine therapy were used for genotyping. 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. (Hercules, CA, USA) and sets "SNP-screen" of Syntol (Moscow, Russia). SNP-screen were used to determine single-nucleotide polymorphisms (SNPs) *1846G>A* of the gene *CYP2D6* (*rs3892097, CYP2D6*4*). In every "SNP-screen" set, two allele-specific hybridizations were used, which allowed the determination of two alleles of the studied polymorphism separately on two fluorescence channels.

To evaluate the fluvoxamine efficacy, several international psychometric scales were used: The Scale of Pathological Addiction, Penn Alcohol Craving Scale, Visual Analog Scale, Clinical Global Impression, Hospital Anxiety and Depression Scale (HADS), The Hamilton Rating Scale for Depression, and The Beck Depression Inventory. Safety profile was evaluated using The UKU Side Effect Rating Scale (UKU). The specified psychometric scales reflect the clinical presentation of the depressive disorder: higher scores indicate greater depression. Patients were examined a day after fluvoxamine therapy (day 6 of the inpatient treatment course) and on days 14 and 21 of the inpatient treatment course (days 9 and 16 of fluvoxamine therapy). A higher score difference corresponds to greater changes in clinical presentation and to higher efficacy of treatment.

Statistical analysis of the results was performed with nonparametric methods using the "Statsoft Statistica v. 10.0" (Dell Statistica, Tulsa, OK, USA). The normality of samples distribution was evaluated using W-Shapiro–Wilk test and was 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. Research data are presented as median and interquartile range ([Q1; Q3]) or, in the case of normal distribution, as the arithmetic mean and standard deviation (mean ± standard deviation).

Results

The *CYP2D6* genotyping by polymorphic marker *1846G>A* (*rs3892097)* performed in 45 patients with alcohol use disorder revealed the following:

- The number of patients with no mutant *CYP2D6* (genotype *GG*) was 29 (64.4%);
- The number of patients with heterozygous polymorphism *1846G>A* of *CYP2D6* gene (genotype *GA*) was 17 (35.6%);
- There were no patients with homozygous polymorphism *1846G>A* of *CYP2D6* gene (genotype *AA*).

The distribution of genotypes corresponded to Hardy–Weinberg equilibrium in the European population ($\chi^2=2.36$; $P=0.12$).

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

Dynamics of changes in the HADS scores across patients with different genotypes are shown in Figure 1. Dynamics of changes in the UKU scores across patients with different genotypes are shown in Figure 2.

We compared the dynamics of changes in the UKU scale scores across patients with different genotypes. The results of our analysis are presented in Tables 4 and 5.

Dynamics of changes in the HADS scores across patients with different genotypes are shown in Figure 3A and B. Dynamics of changes in the UKU scores across patients with different genotypes are shown in Figure 4A and B.

Discussion

In the study, it was shown that the efficacy and safety profiles of fluvoxamine in patients with affective disorders and

Table 1 The results of psychometric scales and side effect rating scale data analysis (scores) in patients who received fluvoxamine obtained after visit 1 (day 5 of the inpatient treatment course)

Scale	*GG*	*GA*	*P*-value
SoPA	22.000 [20.000; 25.000]	24.000 [22.000; 26.000]	0.059
PACS	11.000 [10.000; 12.000]	10.000 [9.000; 11.000]	0.091
VAS	54.000 [47.000; 59.000]	56.000 [50.000; 62.000]	0.418
CGI	4.000 [4.000; 5.000]	5.000 [4.000; 5.000]	0.716
HADS	36.000 [34.000; 41.000]	37.000 [34.000; 39.000]	0.945
HAM-D	21.000 [19.000; 25.000]	21.000 [19.000; 24.000]	0.819
BDI	55.000 [54.000; 58.000]	58.000 [54.000; 60.000]	0.343
UKU	1.000 [1.000; 1.000]	1.000 [1.000; 1.000]	0.184

Note: Data has been presented in as median and interquartile range.
Abbreviations: BDI, Beck Depression Inventory; CGI, Clinical Global Impression; HADS, Hospital Anxiety and Depression Scale; HAM-D, Hamilton Rating Scale for Depression; PACS, Penn Alcohol Craving Scale; SoPA, Scale of Pathological Addiction; UKU, The UKU Side Effect Rating Scale; VAS, Visual Analog Scale.

Table 2 The results of psychometric scales and side effect rating scale data analysis (scores) in patients who received fluvoxamine obtained after visit 2 (day 14 of the inpatient treatment course)

Scale	*GG*	*GA*	*P*-value
SoPA	11.000 [10.000; 12.000]	19.000 [16.000; 20.000]	0.000
PACS	4.000 [3.000; 5.000]	7.000 [7.000; 8.000]	0.000
VAS	35.000 [29.000; 39.000]	43.000 [39.000; 46.000]	0.001
CGI	2.000 [2.000; 3.000]	4.000 [4.000; 4.000]	0.000
HADS	16.000 [15.000; 20.000]	30.000 [29.000; 32.000]	0.000
HAM-D	10.000 [10.000; 12.000]	15.000 [14.000; 16.000]	0.000
BDI	24.000 [21.000; 25.000]	42.000 [39.000; 43.000]	0.000
UKU	6.000 [4.000; 6.000]	9.000 [9.000; 10.000]	0.000

Note: Data has been presented in as median and interquartile range.
Abbreviations: BDI, Beck Depression Inventory; CGI, Clinical Global Impression; HADS, Hospital Anxiety and Depression Scale; HAM-D, Hamilton Rating Scale for Depression; PACS, Penn Alcohol Craving Scale; SoPA, Scale of Pathological Addiction; UKU, The UKU Side Effect Rating Scale; VAS, Visual Analog Scale.

Table 3 The results of psychometric scales and side effect rating scale data analysis (scores) in patients who received fluvoxamine obtained after visit 3 (day 21 of the inpatient treatment course)

Scale	*GG*	*GA*	*P*-value
SoPA	3.000 [2.000; 3.000]	5.000 [5.000; 7.000]	0.000
PACS	2.000 [2.000; 2.000]	1.000 [1.000; 2.000]	0.015
VAS	13.000 [10.000;16.000]	29.000 [24.000; 32.000]	0.000
CGI	0.000 [0.000; 1.000]	2.000 [2.000; 2.000]	0.000
HADS	5.000 [3.000; 6.000]	12.000 [11.000; 15.000]	0.000
HAM-D	4.000 [2.000; 5.000]	6.000 [6.000; 7.000]	0.000
BDI	21.000 [13.000; 28.000]	20.000 [18.000; 22.000]	0.918
UKU	5.000 [1.000; 9.000]	19.000 [18.000; 22.000]	0.000

Note: Data has been presented in as median and interquartile range.
Abbreviations: BDI, Beck Depression Inventory; CGI, Clinical Global Impression; HADS, Hospital Anxiety and Depression Scale; HAM-D, Hamilton Rating Scale for Depression; PACS, Penn Alcohol Craving Scale; SoPA, Scale of Pathological Addiction; UKU, The UKU Side Effect Rating Scale; VAS, Visual Analog Scale.

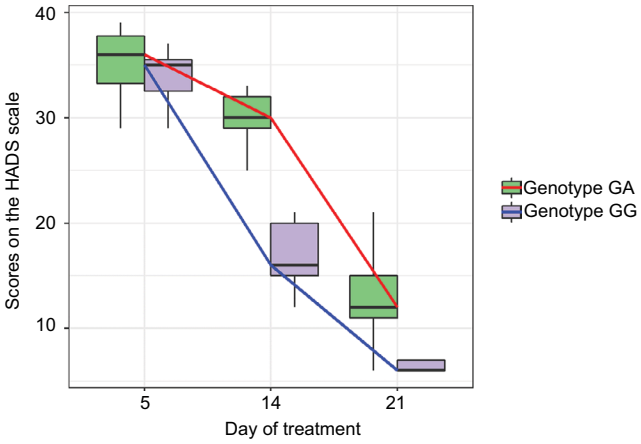

Figure 1 Dynamics of changes in HADS scores across patients with different genotypes on days 5, 14, and 21 of the inpatient treatment course (data are presented as Me and IQR).
Abbreviations: HADS, Hospital Anxiety and Depression Scale; IQR, interquartile range; Me, median.

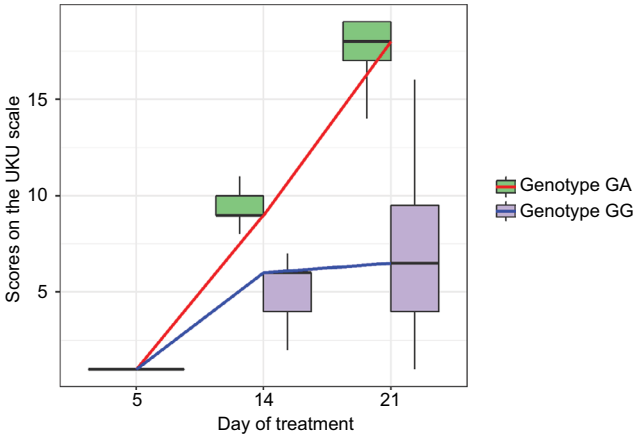

Figure 2 Dynamics of changes in the UKU scale scores across patients with different genotypes on days 5, 14, and 21 of the inpatient treatment course (data are presented as Me and IQR).
Abbreviations: IQR, interquartile rage; Me, median; UKU, The UKU Side Effect Rating Scale.

Table 4 Dynamics of changes in psychometric scales and side effect rating scale scores on days 5 to 14 of the inpatient treatment course in patients with different genotypes of *CYP2D6* gene by polymorphic marker *1846G*>A

Scale	*GG*	*GA*	*P*-value
SoPA	12.000 [10.000; 13.000]	6.000 [3.000; 9.000]	0.000
PACS	7.000 [6.000; 8.000]	3.000 [2.000; 4.000]	0.000
VAS	18.000 [13.000; 27.000]	17.000 [6.000; 22.000]	0.202
CGI	2.000 [1.000; 3.000]	1.000 [0.000; 1.000]	0.000
HADS	17.000 [15.000; 24.000]	7.000 [4.000; 11.000]	0.000
HAM-D	11.000 [10.000; 13.000]	6.000 [5.000; 9.000]	0.003
BDI	32.000 [28.000; 39.000]	16.000 [13.000; 19.000]	0.000
UKU	5.000 [3.000; 5.000]	8.000 [8.000; 9.000]	0.000

Note: Data has been presented in as median and interquartile range.
Abbreviations: BDI, Beck Depression Inventory; CGI, Clinical Global Impression; HADS, Hospital Anxiety and Depression Scale; HAM-D, Hamilton Rating Scale for Depression; PACS, Penn Alcohol Craving Scale; SoPA, Scale of Pathological Addiction; UKU, The UKU Side Effect Rating Scale; VAS, Visual Analog Scale.

comorbid alcohol use disorder correlated with *CYP2D6* genetic polymorphism. The reduced efficacy and worsened safety profile of fluvoxamine therapy were revealed in patients carrying one A allele in *1846G*>A (*rs3892097*). Probably, this correlates with the reduced biotransformation and elimination rates of fluvoxamine and drug cumulation in these patients. This in turn leads to an increased amount of medication reaching the receptor targets of fluvoxamine and to a greater effect on serotonin transport. The acceleration of serotonin transport in the central nervous system neurons results in dose-dependent undesirable side effects (vertigo, headache, indigestion, xerostomia, increased anxiety, etc.) and in reduced efficacy of the depressive disorder therapy, as treatment with any antidepressant given in doses exceeding

Table 5 Dynamics of changes in psychometric scales and side effect rating scale scores on days 14 to 21 of the inpatient treatment course in patients with different genotypes of *CYP2D6* gene by polymorphic marker *1846G*>A

Scale	*GG*	*GA*	*P*-value
SoPA	5.000 [5.000; 6.500]	13.000 [8.000; 15.000]	0.000
PACS	3.000 [3.000; 4.000]	2.000 [1.250; 3.000]	0.000
VAS	16.000 [14.500; 21.500]	30.500 [25.250; 36.500]	0.000
CGI	2.000 [1.000; 2.000]	4.000 [3.000; 5.000]	0.000
HADS	9.000 [7.500; 13.000]	13.500 [9.500; 16.000]	0.000
HAM-D	8.000 [5.500; 9.500]	11.000 [9.250; 13.000]	0.000
BDI	11.000 [8.000; 16.000]	32.000 [29.250; 34.750]	0.000
UKU	5.000 [3.000; 5.500]	10.000 [6.250; 12.000]	0.000

Note: Data has been presented in as median and interquartile range.
Abbreviations: BDI, Beck Depression Inventory; CGI, Clinical Global Impression; HADS, Hospital Anxiety and Depression Scale; HAM-D, Hamilton Rating Scale for Depression; PACS, Penn Alcohol Craving Scale; SoPA, Scale of Pathological Addiction; UKU, The UKU Side Effect Rating Scale; VAS, Visual Analog Scale.

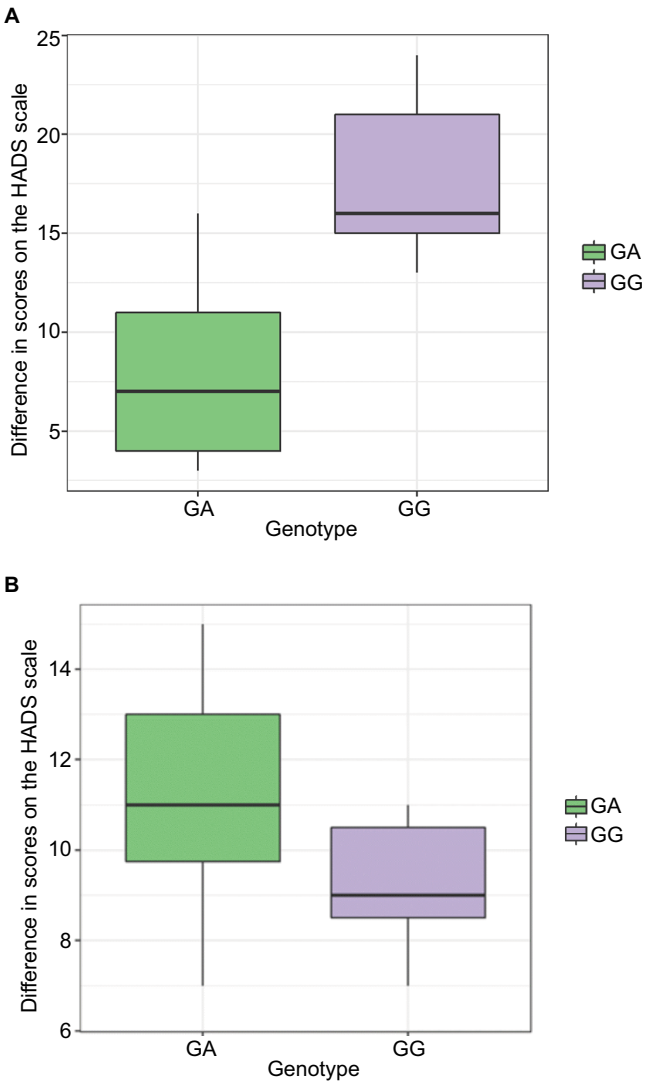

Figure 3 (A) HADS scores across patients with different genotypes of *CYP2D6* gene by polymorphic marker 1846G>A on days 5 to 14 of the inpatient treatment course (data are presented as Me and IQR). **(B)** Dynamics of changes in HADS scores across patients with different genotypes of *CYP2D6* gene by polymorphic marker 1846G>A on days 14 to 21 of the inpatient treatment course (data are presented as Me and IQR).
Abbreviations: HADS, Hospital Anxiety and Depression Scale; IQR, interquartile range; Me, median.

the intended ones and within the toxic concentration range reduces the antidepressive effect of the medication.

The results of our study are in agreement with the results of several previously conducted studies,[7,23] but at the same time are opposite to the results obtained in one study.[15] The most likely reason may be that Ohara et al[15] evaluated the effect of *CYP2D6**10 genetic polymorphism on fluvoxamine equilibrium plasma concentration level, while *CYP2D6**4 genetic polymorphism evaluated in our study probably has a greater effect on *CYP2D6* activity than *CYP2D6**10. Furthermore, the study population was highly heterogeneous in terms of allelic frequencies, leaving the researchers unable to achieve the required statistical power.

Results of our study should be taken into consideration when prescribing fluvoxamine to patients with depressive disorders and comorbid alcohol use disorder since it will allow increasing the efficacy of fluvoxamine therapy and decreasing the risk of undesirable side effects. However, according to the last edition of recommendations by the Clinical Pharmacogenetics Implementation Consortium,[8] fluvoxamine dose should be initialized with the recommended starting dose in patients with intermediate metabolism (ie, *GA* genotype of polymorphic marker *CYP2D6* (*1846G>A*)), whereas in patients carrying homozygous mutant allele (ie, *AA* genotype) it is recommended to replace fluvoxamine with another antidepressant whose

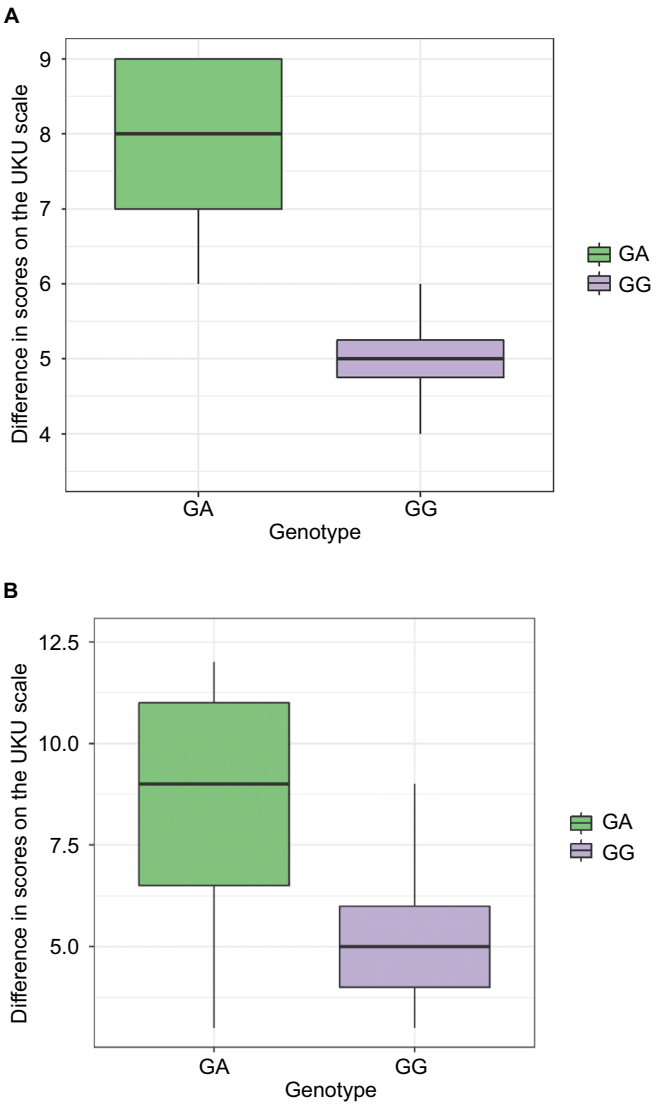

Figure 4 (A) Dynamics of changes in the UKU scale scores across patients with different genotypes of *CYP2D6* gene by polymorphic marker 1846G>A on days 5 to 14 of the inpatient treatment course (data are presented as Me and IQR). **(B)** Dynamics of changes in the UKU scale scores across patients with different genotypes of *CYP2D6* gene by polymorphic marker 1846G>A on days 14 to 21 of the inpatient treatment course (data are presented as Me and IQR).
Abbreviations: IQR, interquartile rage; Me, median; UKU, The UKU Side Effect Rating Scale.

biotransformation is not affected by *CYP2D6* or, in case of impossibility, to reduce the initial fluvoxamine dose by 25%–50%.

Conclusion

The study conducted in 45 patients with depressive disorders and comorbid alcohol use disorder revealed that *CYP2D6* genetic polymorphism could worsen the efficacy and safety profile of fluvoxamine. This should be considered when prescribing fluvoxamine to such patients to reduce the risk of undesirable side effects and pharmacoresistance.

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Disclosure

The authors report no conflicts of interest in this work.

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