Effects of CYP2D6 activity on the efficacy and safety of mirtazapine in patients with depressive disorders and comorbid alcohol use disorder

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Funding. The research was supported by the Russian Science Foundation under grant No. 18-75-10073.
Conflict of interest. The authors declare that there is no conflict of interest regarding the publication of this article.

Abstract

The objective of the study was to investigate the effects of CYP2D6 activity on the efficacy and safety of mirtazapine in patients with depressive disorders and comorbid alcohol use disorder who received mirtazapine. The study included 109 Russian patients who received mirtazapine at a dose of 30.0 [15.0; 45.0] mg per day. Genotyping of *CYP2D6*4* (*1846G>A*, *rs3892097*) was performed using real-time polymerase chain reaction with allele-specific hybridization. The activity of CYP2D6 was evaluated by determining the concentration of endogenous substrate of the enzyme and its urinary metabolite – pinoline to 6-hydroxy-1,2,3,4-tetrahydro-beta-carboline ratio, using high-performance liquid chromatography-mass spectrometry. The statistically significant differences between the scores on HAM-D scale in patients with different genotypes were revealed by day 16: (GG) 5.0 [3.0; 6.0], (GA) 1.5 [1.0; 3.2] ($p<0.001$), and for the UKU scale: (GG) 6.0 [6.0; 7.0], (GA) 8.5 [8.0; 10.0] ($p<0.001$). The calculation of `correlation` coefficients between the differences in scale scores and metabolic rate showed the presence of statistically significant

weak inverse correlation with the efficacy indicator evaluated by HAMD scale ($r = -0.278$, $p<0.05$), but not by the UKU scale ($r = 0.274$, $p>0.05$). This study demonstrated that an increased CYP2D6 activity reduces the efficacy of treatment with mirtazapine.

Keywords: *pharmacogenomics, mirtazapine, personalized medicine, CYP2D6, pinoline.*

Introduction

It is known that substance use disorders are often comorbid with other mental disorders (Zanger et al. 2004), worsening the prognosis of the course and outcome of both diseases (Zarkin et al. 2010). The most common comorbid diagnoses inpatients with alcohol use disorder are affective disorders and depressive disorders (Boschloo et al. 2011). Treating these patients is a challenge, because one disorder worsens the course of another one.

Mirtazapine is recommended for the treatment of patients with depressive disorders (Gautam et al. 2017). At the same time, studies demonstrate that pharmacoresistance occurs in up to 40% of patients with depressive disorder (Spear et al. 2001).

To date it is proven that CYP2D6 is encoded by the gene that evidences a high level of polymorphism (Shen et al. 2007). It allows distinguishing four main groups of carriers of different genetic polymorphisms depending on CYP2D6 isoenzyme activity: normal (extensive), poor, intermediate and ultrarapid metabolizers. The most common allele variants associated with poor metabolizer phenotype are *CYP2D6*3*, *CYP2D6*4*, *CYP2D6*5*, and *CYP2D6*6*. Ultrarapid metabolism is typical for individuals having duplication and multiplication of the wild-type allele variants, *(CYP2D6*1)xN* and *(CYP2D6*2)xN*. There is evidence suggesting that CYP2D6 activity affects the individual response to some antidepressants: paroxetine (Charlier et al. 2003; Sawamura et al. 2004; Ueda et al. 2006), fluoxetine (Shen et al. 2007; Charlier et al. 2003; Wang et al. 2014), fluvoxamine (Zastrozhin et al. 2018), nortriptyline (Dalen et al. 2003; Lee et al. 2006), venlafaxine (Eap et al. 2001; Fukuda et al. 2000; McAlpine et al. 2011; Nichols et al. 2009).

A replacement of guanine by adenine at position 1846 of the *CYP2D6* (*CYP2D6*4*, *CYP2D6 1846G>A*, *rs3892097*) gene results in a splicing defect and decreased activity of CYP2D6 isoenzyme, which should lead to lower rates of the isoenzyme substrate elimination from the body (Zanger et al. 2004). Thus, carriers of the mutant allele A show reduced biotransformation and elimination of mirtazapine (Swen et al. 2011).

Although mirtazapine is commonly used in clinical practice, currently there is no data on correlation between the CYP2D6 genetic polymorphisms and efficacy and safety of mirtazapine among the Russian patients. It is equally important to conduct this study in patients with alcohol use disorder, since such patients have an increased risk of comorbid depressive disorders in comparison with general population (Boschloo et al. 2011). Alcohol addiction can have a negative effect on the course of depressive disorder, and conversely, depression can worsen the course of alcohol use disorder. It emphasizes the relevance of conducting the study in this cohort of patients (Zarkin et al. 2010). It provides effective conditions for conducting the study due to genetic profile peculiarities in this population.

The objective of our study was to investigate the effects of CYP2D6 activity on the efficacy and safety of mirtazapine in patients with depressive disorders and comorbid alcohol use disorder.

Material and methods

The study included 109 male patients (average age – 36.44±9.96 years) with depressive disorder and comorbid alcohol use disorder who underwent the inpatient treatment in Moscow Research and Practical Centre on Addictions of the Moscow Department of Healthcare. For the therapy of depressive disorder patients received mirtazapine in tablets (Calixta®) at a dose of 30 [15; 45] mg per day from day 5 to day 21 of the inpatient treatment course. An inclusion criterion was 16-days mirtazapine therapy. Exclusion criteria were presence of any other psychotropic medications in treatment regimen except mirtazapine (with the exception of Phenazepam® (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 less than 60 kg or greater than 100 kg, age of 75 years or more and presence of any contraindications for mirtazapine use.

Clinico-demographic characteristics of patients are presented in Table 1. Compared samples of patients were representative due to the absence of statistically significant differences in the studied indicators.

Venous blood samples collected in vacuum tubes VACUETTE® (Greiner Bio-One, Austria) on the sixth day of the mirtazapine 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 "SNP-screen" of «Syntol» (Russia). It was used to determine single nucleotide polymorphism (SNPs) *1846G>A* of the gene *CYP2D6* (*rs3892097*). 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.

The activity of CYP2D6 was evaluated by determining the concentration of endogenous substrate of the enzyme and its urinary metabolite – pinoline to 6-hydroxy-1,2,3,4-tetrahydro-beta-carboline (6-HO-THBC) ratio, using high-performance liquid chromatography-mass spectrometry (HPLC-MS) (Jiang et al. 2009; Sychev et al. 2016; Sychev et al. 2017; Zastrozhin et al. 2017).

To evaluate the mirtazapine efficacy several international psychometric scales were used: The Scale of Pathological Addiction (SoPA), Penn Alcohol Craving Scale (PACS), Visual Analogue Scale (VAS), Clinical Global Impression (CGI), Hospital Anxiety and Depression Scale (HADS), The Hamilton Rating Scale for Depression (HAM-D), The Beck Depression Inventory (BDI). 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 before mirtazapine therapy (day 5 of the inpatient treatment course) and on days 14 and 21 of the inpatient treatment course (days 1, 9 and 16 of mirtazapine therapy). Higher score difference corresponds to greater changes in clinical presentation and to higher efficacy of treatment.

The research was approved by the local ethical committee of Russian Medical Academy of Continuous Professional Education of the Ministry of Health of the Russian Federation (The protocol No. 6 from 5/16/2017), and all patients provided written informed consent.

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, whereas for the dependent groups we used Wilcoxon signed-rank test. To determinate the correlation between quantitative characteristics Spearman rank correlation coefficient was calculated. Correlation coefficient (r_s) from 0,3 to 0,7 means a moderate positive, though reliable between the signs; >0,7 – strong and reliable connection, negative meaning r_s was corresponded to inverse correlation. 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).

Results

The *CYP2D6* genotyping by polymorphic marker *1846G>A* (*rs3892097)* performed in 109 patients have revealed the following:

- The number of patients with *GG* genotype was 81 (74.3%);
- The number of patients with *GA* genotype was 28 (25.7%);
- There were no patients with *AA* genotype.

The distribution of genotypes corresponded to Hardy–Weinberg equilibrium in the European population ($Chi^2 = 2.37$; $p = 0.12$).

The results of data analysis performed for psychometric scales and side-effect rating scale in patients who received mirtazapine are presented in Tables 2-4.

Dynamics of changes in HAMD 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: (*GG*) 13.0 [12.0; 14.0], (*GA*) 13.0 [12.0; 13.0], p = 0.194. By day 9, HAMD scores were statistically significantly different between the compared groups: (*GG*) 7.0 [6.0; 8.0], (*GA*) 4.0 [3.8; 5.0], p<0.001. This difference remained by day 16 also: (*GG*) 5.0 [3.0; 6.0], (*GA*) 1.5 [1.0; 3.2], p<0.001. The scores on other psychometric scales by days 9 and 16 were also statistically significantly different between the patients with different genotypes of *CYP2D6* gene by polymorphic marker *1846G>A*.

Dynamics of changes in the UKU scores across patients with different genotypes are shown in Figure 2. At the beginning of research the compared groups were comparable in the studied parameter: (*GG*) 1.0 [1.0; 1.0], (*GA*) 1.0 [1.0; 2.0], p = 0.774. By day 9, the severity of treatment-related adverse events as assessed by the UKU scale scores was statistically significantly different between the patients with different genotypes:(*GG*) 3.0 [3.0; 3.0], (*GA*) 4.0

[3.8; 5.], p<0.001. This difference increased by day 16: (*GG*) 6.0 [6.0; 7.0], (*GA*) 8.5 [8.0; 10.0], p<0.001.

Phenotyping results can be found in Table 5. We revealed a statistical significance for the metabolic rate indicator 6M-THBC/pinoline: *GA* – 0.30 [0.12; 0.51], *GG* – 0.56 [0.16; 1.29], p = 0.001 (Figure 3).

The calculation of correlation coefficients between the differences in scale scores and metabolic rate showed the presence of statistically significant weak inverse correlation with the efficacy indicator evaluated by HAMD scale ($r = -0.278$, $p < 0.05$, Figure 4). There was no correlation with the UKU scale revealed ($r = 0.274$, $p > 0.05$, Figure 5).

There were no adverse events potentially related to the medical intervention revealed.

Discussion

In the study, it was shown that the efficacy and safety profiles of mirtazapine in patients with depressive disorders and comorbid alcohol use disorder were different across patients with different genotypes of *CYP2D6* gene by polymorphic marker *1846G>A* (*rs3892097*). Patients carrying *GA* genotypes demonstrated faster increase in the UKU scores. This indicates that patients carrying minor allele *A* experience more severe adverse events than patients with allele *A* do. The efficacy of mirtazapine therapy as assessed by the psychometric scales scores was higher in patients with *GA* genotype in comparison with patients carrying *GG* genotype.

The results of our study coincide with the data of meta-analysis of studies conducted in European patients with recurrent depressive disorder published by the Clinical Pharmacogenetics Implementation Consortium (Swen et al. 2011) and the results of some others studies (Kirchheiner et al. 2004; Jiang et al. 2009; Borobia et al. 2009).

Analysing the safety profile of mirtazapine, we assume that patients carrying the minor allele A experience the increased risk of adverse events. Most likely, it correlates with the reduced activity of CYP2D6 isoenzyme, which leads to the reduced biotransformation and elimination rates of mirtazapine with subsequent drug cumulation in these patients and to an increased amount of medication reaching the receptor targets. A similar mechanism can explain the higher efficacy of mirtazapine therapy in patients with depressive disorders.

Genotyping data are partially supported by the results of phenotyping, which takes into account the possible deviations in CYP2D6 activity evaluated by the ratio between the concentration of endogenous substrate (pinoline), and its urinary metabolite due to the comorbid liver disorders. It was shown that an increase in CYP2D6 activity evaluated by the increase in metabolic rate correlates with the reduced efficacy of mirtazapine therapy evaluated by dynamics of changes in psychometric scales scores before and after the treatment.

Unfortunately, we could not confirm the changes in safety profile with phenotyping results, so we cannot claim that CYP2D6 activity affects the safety of mirtazapine therapy in patients with affective disorders comorbid with alcohol use disorder. Nevertheless, we will revert to this issue later, when we will have the results of pharmacokinetic study (plasma levels of the mirtazapine equilibrium concentrations obtained from therapeutic drug monitoring) and

pharmacotranscriptomic study (levels of the microRNA equilibrium concentrations allowing to assess CYP2D6 activity).

The main limitation of our study is the absence of therapeutic drug monitoring results. It allows only suggesting the changes in mirtazapine metabolic rates by the evaluation of the efficacy and safety of therapy.

Conclusions

This study investigated the effects of CYP2D6 activity evaluated by the ratio between the concentration of endogenous substrate (pinoline) and its urinary metabolite, 6-hydroxy-1,2,3,4-tetrahydro-beta-carboline, on the efficacy of mirtazapine therapy. Genotyping results also showed the differences in safety profiles across patients with different genotypes of *CYP2D6* gene by polymorphic marker *1846G>A*.

Acknowledgements

The research was supported by the Russian Science Foundation under grant No. 18-75-10073: “Personalized antidepressant pharmacotherapy of patients with depressive disorders comorbid with alcohol use disorder based on pharmacogenetic, pharmacometabolomic and pharmacotranscriptomic biomarkers”.

References

Borobia A.M., Novalbos J., Guerra-López P., López-Rodríguez R., Tabares B., and Rodríguez V., et al. 2009. Influence of sex and CYP2D6 genotype on mirtazapine disposition, evaluated in Spanish healthy volunteers. Pharmacol Res. 59 (6): 393-8. doi: 10.1016/j.phrs.2009.02.006.

Boschloo L., Vogelzang N., Smit J.H., van den Brink W., Veltman D.J., and Beekman A.T., et al. 2011. Comorbidity and risk indicators for alcohol use disorders among persons with anxiety and/or depressive disorders: findings from the Netherlands Study of Depression and Anxiety (NESDA). J Affect Disord. 131 (1–3): 233–42. doi: 10.1016/j.jad.2010.12.014.

Gautam S., Jain A., Gautam M., Vahia V.N., and Grover S. 2017. Clinical Practice Guidelines for the management of Depression. Indian J Psychiatry. 59 (1): 34–50. doi:10.4103/0019-5545.196973.

Charlier C., Broly F., Lhermitte M., Pinto E., Ansseau M., and Plomteux G. 2003. Polymorphisms in the CYP2D6 gene: association with plasma concentrations of fluoxetine and paroxetine. Ther Drug Monit. 6 (25): 38–42. PMID: 14639062.

Dalen P., Dahl M.L., Roh H.K., Tybring G., Eichelbaum M., and Wilkinson G.R., et al. 2003. Disposition of debrisoquine and nortriptyline in Korean subjects in relation to CYP2D6 genotypes, and comparison with Caucasians. Br J Clin Pharmacol. 6 (55): 630–634. doi: 10.1046/j.1365-2125.2003.01804.x.

Eap C.B., Bondolfi G., Zullino D., Savary-Cosendai L., Powell-Golay K., and Kosel M., et al. 2001. Concentrations of the enantiomers of fluoxetine and norfluoxetine after multiple doses of fluoxetine in cytochrome P4502D6 poor and extensive metabolizers. J Clin Psychopharmacol. 3 (21): 330–334. PMID:11386497.

Fukuda T., Nishida Y., Zhou Q., Yamamoto I., Kondo S., and Azuma J. 2000. The impact of the CYP2D6 and CYP2C19 genotypes on venlafaxine pharmacokinetics in a Japanese population. Eur J Clin Pharmacol. 2 (56): 175–180. PMID: 10877013.

Jiang X.L., Shen H.W., and Yu A.M. 2009. Pinoline may be used as a probe for CYP2D6 activity. Drug Metab Dispos. 37 (3): 443–446. doi: 10.1124/dmd.108.025056.

Kirchheiner J., Henckel H.B., Meineke I., Roots I., and Brockmöller J. 2004. Impact of the CYP2D6 ultrarapid metabolizer genotype on mirtazapine pharmacokinetics and adverse events in healthy volunteers. J Clin Psychopharmacol. 24 (6): 647-52. PMID: 15538128

Lee S.Y., Sohn K.M., Ryu J.Y., Yoon y., Shin J., and Kim J.W. 2006. Sequence-based CYP2D6 genotyping in the Korean population. Ther Drug Monit. 3 (28): 382–387. doi: 10.1097/01.ftd.0000211823.80854.db.

McAlpine D.E., Biernacka J.M., Mrazek D.A., O'Kane D., Stevens S., and Langman L., et al. 2011. Effect of cytochrome P450 enzyme polymorphisms on pharmacokinetics of venlafaxine. Ther Drug Monit. 1 (33): 14–20. doi: 10.1097/FTD.0b013e3181fcf94d.

Nichols A.I., Lobello K., Guico-Pabia C.J., Paul J., and Preskorn S.H. 2009. Venlafaxine metabolism as a marker of cytochrome P450 enzyme 2D6 metabolizer status. J Clin Psychopharmacol. 4 (29): 383–386. doi: 10.1097/JCP.0b013e3181acc4dd.

Sawamura K., Suzuki Y., and Someya T. 2004. Effects of dosage and CYP2D6-mutated allele on plasma concentration of paroxetine. Eur J Clin Pharmacol. 8 (60): 553–557. doi: 10.1007/s00228-004-0792-6.

Shen H., He M.M., Liu H., Wrighton S.A., Wang L., and Guo B., et al. 2007. Comparative metabolic capabilities and inhibitory profiles of CYP2D6.1, CYP2D6.10, and CYP2D6.17. Drug Metab Dispos. 8 (35): 1292–1300. doi: 10.1124/dmd.107.015354.

Spear B.B., Heath-Chiozzi M., and Huff J. 2001. Clinical application of pharmacogenetics. Trends Mol Med. 7 (5): 201-204. PMID:11325631.

Swen J.J., Nijenhuis M., de Boer A., Grandia L., Maitland-van der Zee A.H., and Mulder H., et al. 2011. Pharmacogenetics: from bench to byte – an update of guidelines. Clin Pharmacol Ther. 89 (5): 662-73. doi: 10.1038/clpt.2011.34.

Sychev D.A., Zastrozhin M.S., Grishina E.A., Savchenko L.M., Bryun E.A., and Smirnov V.V. 2016. The correlation between CYP2D6 isoenzyme activity and haloperidol efficacy and safety profile in patients with alcohol addiction during the exacerbation of the addiction. Pharmacogenomics Pers Med. 9: 89-95. doi: 10.2147/PGPM.S110385

Sychev D.A., Zastrozhin M.S., Miroshnichenko I.I., Baymeeva N.V., Smirnov V.V., and Grishina E.A., et al. 2017. Genotyping and phenotyping of CYP2D6 and CYP3A isoenzymes in patients with alcohol use disorder: correlation with haloperidol plasma concentration. Drug Metab Pers Ther. 32 (3): 129-136. doi: 10.1515/dmpt-2017-0021.

Ueda M., Hirokane G., Morita S., Okawa M., Watanabe T., and Akiyama K., et al. 2006. The impact of CYP2D6 genotypes on the plasma concentration of paroxetine in Japanese psychiatric patients. Prog Neuropsychopharmacol Biol Psychiatry. 3 (30): 486–491. doi: 10.1016/j.pnpbp.2005.11.007.

Wang Z., Wang S., Huang M., Hu H., Yu L., and Zeng S. 2014. Characterizing the effect of cytochrome P450 (CYP) 2C8, CYP2C9, and CYP2D6 genetic polymorphisms on stereoselective N-demethylation of fluoxetine. Chirality. 3 (26): 166–173. doi: 10.1002/chir.22289.

Zanger U.M., Raimundo S., and Eichelbaum M. 2004. Cytochrome P450 2D6: overview and update on pharmacology, genetics, biochemistry. Naunyn Schmiedebergs Arch Pharmacol. 369 (1): 23-37. doi: 10.1007/s00210-003-0832-2.

Zarkin G.A., Bray J.W., Aldridge A., Mills M., Cisler R.A., and Couper D., et al. 2010. The effect of alcohol treatment on social costs of alcohol dependence: results from the COMBINE study. Med Care. 48 (5): 396–401. doi: 10.1097/MLR.0b013e3181d68859.

Zastrozhin M.S., Brodyansky V.M., Skryabin V.Y., Grishina E.A., Ivashchenko D.V., and Ryzhikova K.A., et al. 2017. Pharmacodynamic genetic polymorphisms affect adverse drug reactions of haloperidol in patients with alcohol-use disorder. Pharmgenomics Pers Med. 10: 209-215. doi: 10.2147/PGPM.S140700.

Zastrozhin M.S., Grishina E.A., Denisenko N.P., Skryabin V.Y., Markov D.D., and Savchenko L.M., et al. 2018. Effects of CYP2D6 genetic polymorphisms on the efficacy and safety of fluvoxamine in patients with depressive disorder and comorbid alcohol use disorder. Pharmgenomics Pers Med. 11: 113-119. doi: 10.2147/PGPM.S160763.

Table 1. Clinico-demographic characteristics of patients

Parameter	*GG* (N = 81)	*GA* (N = 28)	p*
Age, years	34.8 ± 7.3	34.7 ± 8.9	>0.05
Body weight, kg	82.9 ± 14.2	85.4 ± 15.34	>0.05
Height, смcm	177.2 ± 19.2	174.6 ± 18.61	>0.05
Body mass index, kg/m^2	27.2 ± 3.4	26.9 ± 3.6	>0.05
Mirtazapine dose, mg/day	32.5±14.3	31.8±14.1	>0.05
Alcoholic steatohepatitis, N (%)	79 (97.5%)	26 (92.9%)	>0.05
Toxic encephalopathy, N (%)	68 (84.0%)	25 (89.3%)	>0.05
Toxic polyneuropathy of the upper extremities, N (%)	16 (19.8%)	7 (25.0%)	>0.05
Toxic polyneuropathy of the lower extremities, N (%)	7 (8.6%)	3 (10.7%)	>0.05
Viral hepatitis C, N (%)	4 (4.9%)	1 (3.6%)	>0.05
Peptic ulcer disease, N (%)	11 (13.6%)	4 (14.3%)	>0.05
Duodenal ulcer disease, N (%)	0 (0.0%)	1 (3.6%)	>0.05
Arterial hypertension, N (%)	22 (27.2%)	9 (32.1%)	>0.05
Active smoking, N (%)	78 (96.3%)	27 (96.4%)	>0.05

Note:

*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).

Table 2. The results of psychometric scales and side-effect rating scale data analysis (scores) in patients who used mirtazapine on the day 1 of study

Scale	*GG* (N = 81)	*GA* (N = 28)	p*
PACS	7.0 [6.0; 7.0]	6.0 [6.0; 7.0]	0.600
VAS	30.0 [27.0; 32.0]	30.5 [29.0; 32.0]	0.373
CGI	3.0 [3.0; 3.0]	3.0 [3.0; 3.0]	0.610
HADS	22.0 [21.0; 24.0]	22.0 [20.0; 23.2]	0.341
HAMD	13.0 [12.0; 14.0]	13.0 [12.0; 13.0]	0.194
UKU	1.0 [1.0; 1.0]	1.0 [1.0; 2.0]	0.774

Note:

*p - p-value based on the results of Benjamini-Hochberg procedure (based on the results of Mann-Whitney U test)

PACS - Penn Alcohol Craving Scale,

VAS - Visual Analogue Scale,

CGI - Clinical Global Impression,

HADS - Hospital Anxiety and Depression Scale,

HAMD - Hamilton Depression Rating Scale,

UKU - Side-Effect Rating Scale.

Table 3. The results of psychometric scales and side-effect rating scale data analysis (scores) in patients who used mirtazapine on the day 9 of study

Scale	*GG* (N = 81)	*GA* (N = 28)	p*
PACS	4.0 [3.0; 4.0]	2.0 [2.0; 2.0]	<0.001
VAS	17.0 [14.0; 18.0]	11.0 [9.8; 12.0]	<0.001
CGI	2.0 [2.0; 2.0]	1.0 [1.0; 1.0]	<0.001
HADS	12.0 [10.0; 14.0]	7.5 [4.0; 9.2]	<0.001
HAMD	7.0 [6.0; 8.0]	4.0 [3.8; 5.0]	<0.001
UKU	3.0 [3.0; 3.0]	4.0 [4.0; 5.0]	<0.001

Note:

*p - p-value based on the results of Benjamini-Hochberg procedure (based on the results of Mann-Whitney U test)

PACS - Penn Alcohol Craving Scale,

VAS - Visual Analogue Scale,

CGI - Clinical Global Impression,

HADS - Hospital Anxiety and Depression Scale,

HAMD - Hamilton Depression Rating Scale,

UKU - Side-Effect Rating Scale.

Table 4. The results of psychometric scales and side-effect rating scale data analysis (scores) in patients who used mirtazapine on the day 16 of study

Scale	*GG* (N = 81)	*GA* (N = 28)	p*
PACS	2.0 [2.0; 3.0]	1.0 [1.0; 2.0]	<0.001
VAS	11.0 [9.0; 13.0]	4.5 [2.0; 6.5]	<0.001
CGI	1.0 [1.0; 1.0]	0.0 [0.0; 1.0]	<0.001
HADS	8.0 [6.0; 10.0]	4.0 [2.0; 6.0]	<0.001
HAMD	5.0 [3.0; 6.0]	1.5 [0.8; 3.2]	<0.001
UKU	6.0 [6.0; 7.0]	8.5 [8.0; 10.0]	<0.001

Note:

*p - p-value based on the results of Benjamini-Hochberg procedure (based on the results of Mann-Whitney U test)

PACS - Penn Alcohol Craving Scale,

VAS - Visual Analogue Scale,

CGI - Clinical Global Impression,

HADS - Hospital Anxiety and Depression Scale,

HAMD - Hamilton Depression Rating Scale,

UKU - Side-Effect Rating Scale.

Table 5. Difference in concentrations of pinoline and its metabolite and the metabolic rate in patients with different genotypes

Scale	*GG* (N = 81)	*GA* (N = 28)	p*
THBC/pinoline ratio (units)	0.30 [0.12; 0.51]	0.71 [0.42; 1.12]	<0.001
Pinoline (pg/ml)	1518.02 [1237.63; 1802.74]	1402.90 [1159.01; 1752.85]	0.313
6M-THBC (pg/ml)	453.81 [156.77; 816.80]	966.85 [422.68; 1584.07]	0.001

Note:

*p - p-value based on the results of Benjamini-Hochberg procedure (based on the results of Mann-Whitney U test)

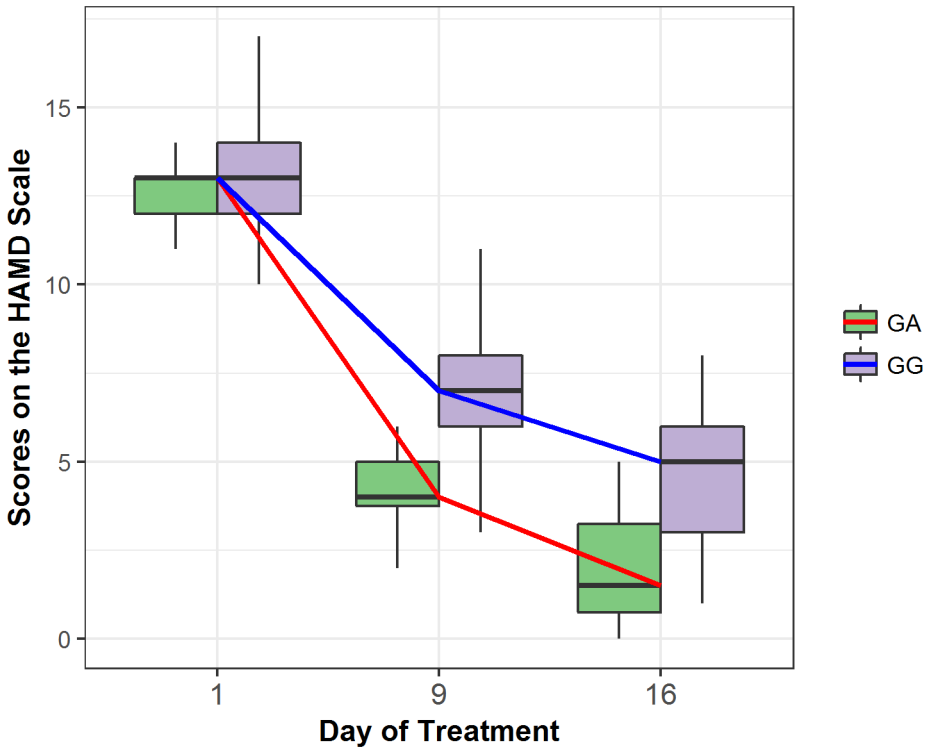

Figure 1. Dynamics of changes in HAMD scale scores across patients with different genotypes

Note:

Data are presented as Me and IQR (colored lines connect medians in different days of study)

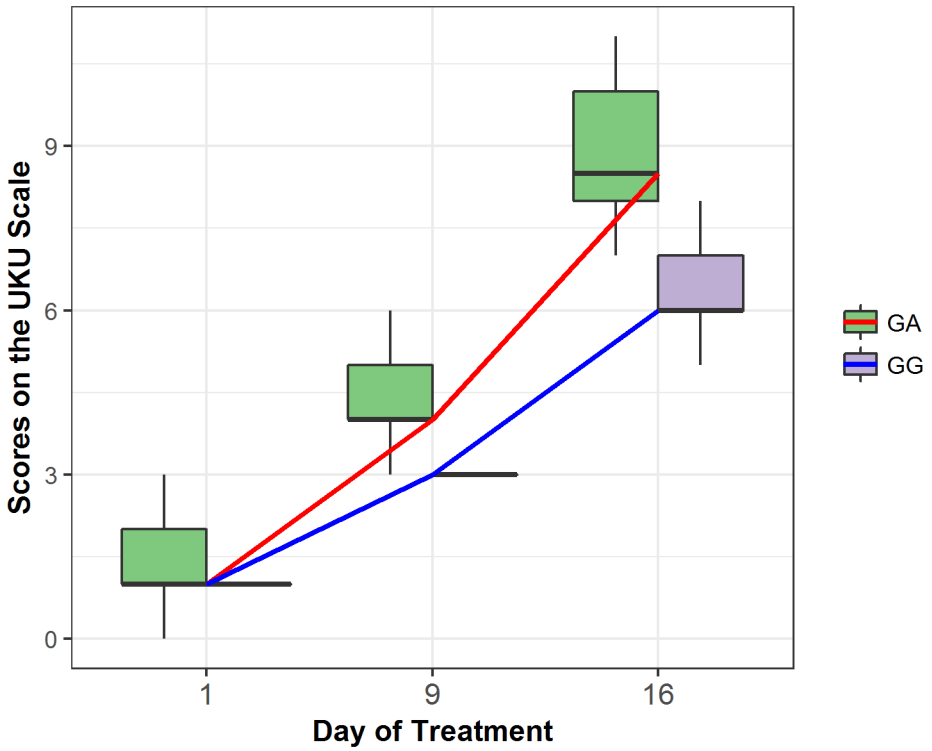

Figure 2. Dynamics of changes in UKU side effect rating scale scores across patients with different genotypes

Note:

Data are presented as Me and IQR (colored lines connect medians in different days of study)

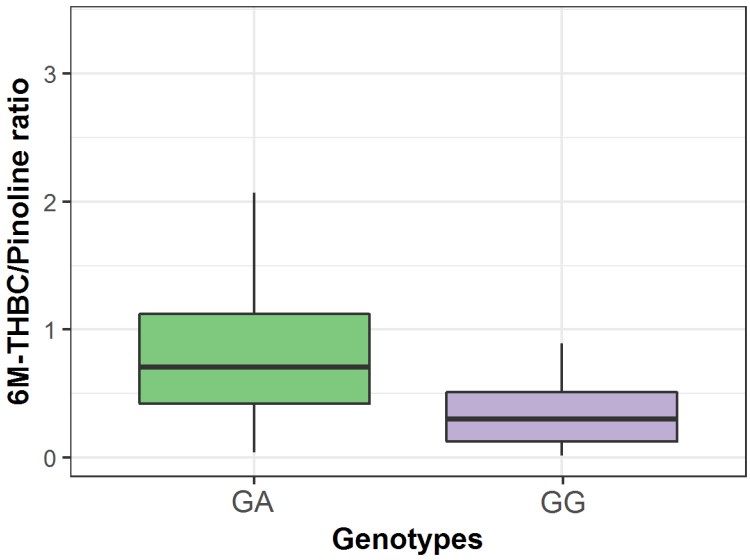

Figure 3. Difference in the ratio of pinoline concentrations and its metabolite in patients with different genotypes

Note:

Data are presented as Me and IQR

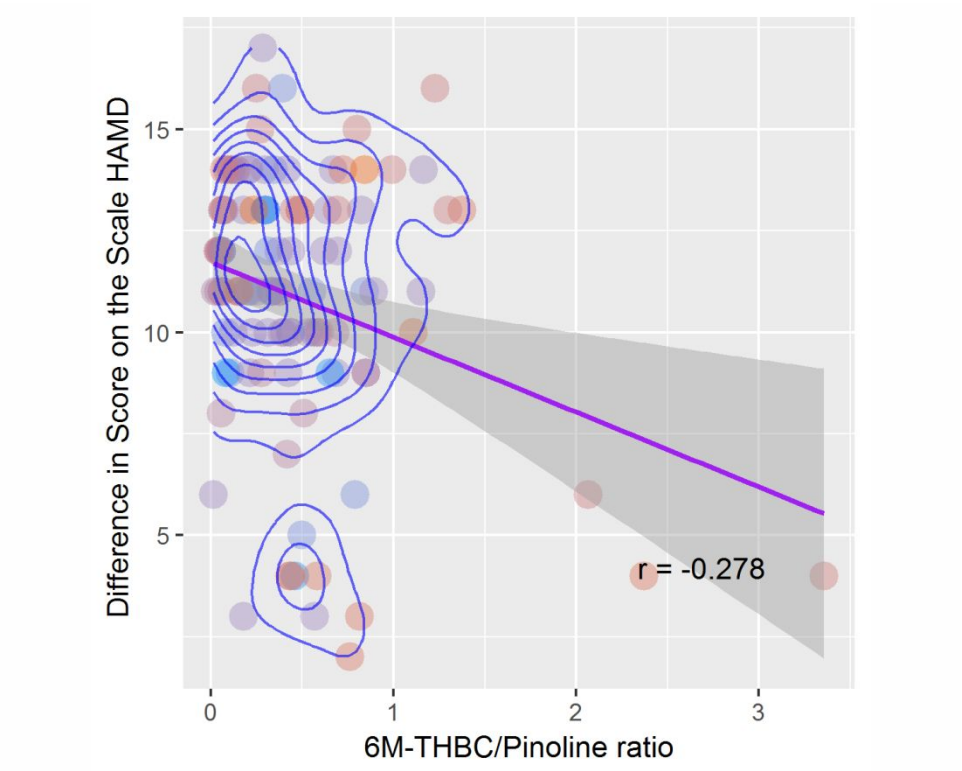

Figure 4. Effects of *CYP2D6* activity evaluated by the ratio between the metabolic rate 6M-THBC/pinoline on the efficacy of therapy evaluated by the dynamics of changes in HAMD scale scores

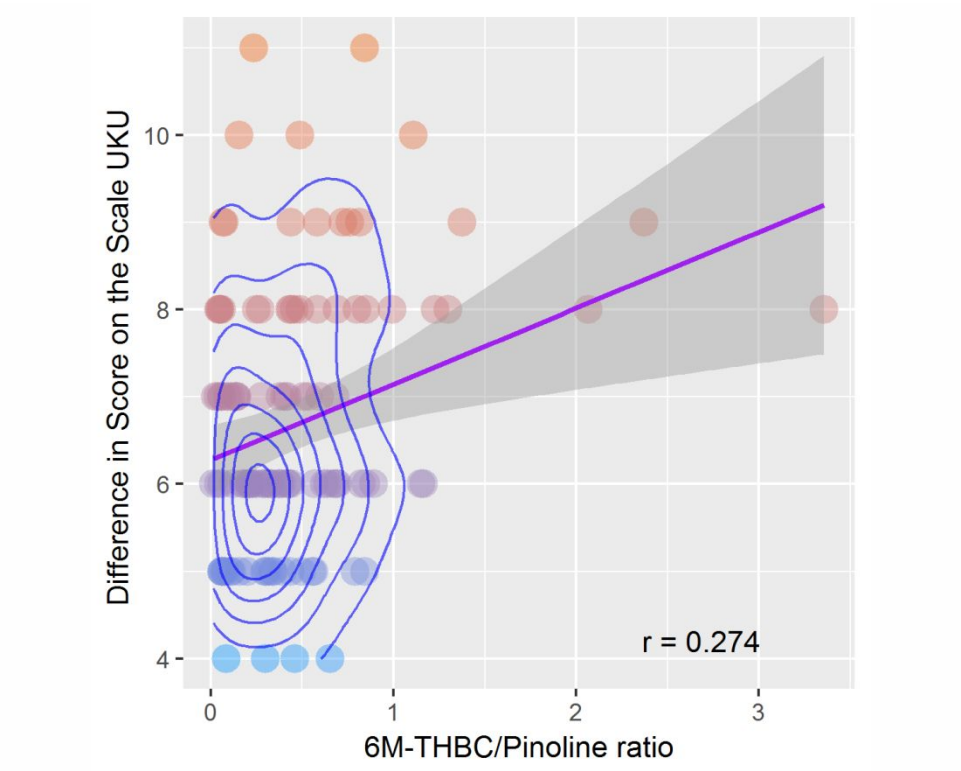

Figure 5. Effects of *CYP2D6* activity evaluated by the ratio between the metabolic rate 6M-THBC/pinoline on the safety of therapy evaluated by the dynamics of changes in the UKU scale scores