THE TURKISH JOURNAL ON ADDICTIONS
www.addicta.com.tr

ORIGINAL ARTICLE

Optimizing Antipsychotic Therapy in Acute Alcoholic Hallucinosis through Pharmacogenetic Testing

Valentin Skryabin[1,2], Anton Masyakin[1], Sergei Pozdniakov[1], Igor Shatokhin[1], Svetlana Sokolova[1], Valentina Ivanchenko[1]

[1]Moscow Research and Practical Centre on Addictions of the Moscow Department of Healthcare, Moscow, Russia
[2]Russian Medical Academy of Continuous Professional Education of the Ministry of Health of the Russian Federation, Moscow, Russia

ORCID iDs of the authors: V.S. 0000-0002-4942-8556, A.M. 0000-0002-9614-7343, S.P. 0000-0002-5198-6637, I.S. 0000-0003-2078-3842, S.S. 0009-0005-7352-4686, V.I. 0000-0002-8509-8531.

Main Points

- Pharmacogenetic testing reduces ADRs: Personalized antipsychotic treatment using pharmacogenetic testing significantly decreased ADRs in patients with acute alcoholic hallucinosis.
- Safety improvement on day 6: By the sixth day of treatment, patients in the pharmacogenetic-guided group showed a substantially lower UKU Side-Effect Rating Scale score, highlighting better tolerability.
- Pharmacogenetic testing supports safer therapy: Pharmacogenetic testing can optimize safety in alcohol-induced psychosis treatment without compromising efficacy, advocating its broader clinical use.

Abstract

This study evaluates the effectiveness and safety of pharmacotherapy personalized through pharmacogenetic testing for patients with acute alcoholic hallucinosis (ICD-10 code F10.52). Psychotic disorders triggered by alcohol consumption, such as hallucinations and delusions, require antipsychotic treatment, though standard therapy often results in adverse drug reactions and variable efficacy. Pharmacogenetics, which examines gene variants affecting drug metabolism, may improve treatment outcomes by guiding medication selection and dosage. Fifty patients undergoing inpatient treatment for acute alcoholic hallucinosis were enrolled in a randomized clinical trial. The main group ($n = 25$) received treatment adjusted based on pharmacogenetic testing, while the control group ($n = 25$) received standard therapy without genetic data. Patient outcomes were measured using the Positive and Negative Syndrome Scale and the UKU Side-Effect Rating Scale. Although there were no significant differences in treatment efficacy between the groups, patients in the pharmacogenetic group experienced significantly fewer adverse drug reactions, particularly by the sixth day of hospitalization (UKU score: 500 [300; 800] vs. 1200 [1000; 1600], $p < .01$). This demonstrates that pharmacogenetic testing can optimize treatment safety without compromising efficacy, suggesting that personalized therapy based on genetic profiles should be considered for alcohol-induced psychoses. Future studies with larger samples are recommended to validate these findings.

Keywords: Acute alcoholic hallucinosis, antipsychotics, clinical decision support systems, pharmacogenetic testing

Corresponding author:
Valentin Skryabin
E-mail:
sardonios@yandex.ru

Received: September 27, 2024
Revision Requested: November 12, 2024
Last Revision Received: November 14, 2024
Accepted: November 27, 2024
Publication Date: December 27, 2024

Cite this article as: Skryabin, V., Masyakin, A., Pozdniakov, S., Shatokhin, I., Sokolova, S., & Ivanchenko, V. (2024). Optimizing antipsychotic therapy in acute alcoholic hallucinosis through pharmacogenetic testing. *Addicta: The Turkish Journal on Addictions*, 11(3), 374-377.

DOI: 10.5152/ADDICTA.2024.24224

Introduction

Alcohol-induced psychoses can vary greatly in their symptoms, severity, and duration. Among the most severe manifestations is delirium, characterized by marked confusion, while acute alcoholic hallucinosis ranks as the second most common form. Although the overall incidence of alcohol-induced psychoses has declined in recent years, they still account for a significant proportion of psychiatric hospital admissions, particularly in males. Studies estimate that acute alcoholic hallucinosis represents between 14% and 27% of all cases of alcohol-related psychoses (Egorov et al., 2012).

According to the ICD-10 classification, alcoholic hallucinosis falls under the code F10.52 ("Predominantly hallucinatory psychotic disorder due to alcohol use"), while in ICD-11, it is coded as 6C40.60. It refers to psychotic symptoms emerging within 2 weeks of alcohol use and persisting for more than 48 hours. This condition is marked by vivid hallucinations, most commonly auditory, but often involving other sensory modalities as well. Additionally, patients may experience false recognitions, delusions, and psychomotor disturbances, ranging from agitation to stupor. Affect tends to fluctuate significantly, from extreme fear to euphoria, and although consciousness is usually preserved, some confusion may occur. Episodes can last for several weeks or even months (Skryabin et al., 2023).

The clinical picture of acute alcoholic hallucinosis frequently includes severe agitation, overwhelming fear, distressing hallucinations, and suicidal tendencies, which often necessitate inpatient treatment. Most patients require antipsychotic drugs, sometimes in combination with tranquilizers (Soyka, 2008). However, standard antipsychotic treatment is often complicated by adverse drug reactions (ADRs), limiting its effectiveness.

Recent advances in pharmacogenetics, particularly studies focusing on cytochrome P-450 enzymes and drug transport proteins, have highlighted the influence of genetic polymorphisms on drug metabolism. Although pharmacogenetic tests offer insights into patients' genetic profiles and potential drug responses, translating these findings into clinical practice remains challenging. Over two dozen pharmacogenomic clinical decision support systems (CDSS) are currently available in psychiatry, many of which include key loci like *CYP2D6* and *CYP2C19*. However, only a few of these systems have demonstrated clear clinical utility (Bousman & Hopwood, 2016).

The goal of integrating CDSS is to tailor drug selection and dosing based on a patient's genetic profile, ultimately improving treatment safety and efficacy. This study aims to compare the safety and efficacy of pharmacotherapy personalized through pharmacogenetic testing with standard treatment for patients diagnosed with acute alcoholic hallucinosis.

Material and Methods

This study included 50 patients (average age 43.5 $\pm$ 9.6 years) undergoing inpatient treatment at the Moscow Research and Practical Centre on Addictions of the Moscow Department of Healthcare. All patients were diagnosed with acute alcoholic hallucinosis (ICD-10 code F10.52) and identified as being of Russian ethnicity.

Inclusion criteria required a confirmed diagnosis of "F10.52: Mental and behavioral disorders due to alcohol use, predominantly hallucinatory disorder" at the time of enrollment, along with signed informed consent.

Exclusion criteria were as follows: the presence of acute or decompensated chronic somatic or neurological diseases, any recent emergency surgical procedures within the last 30 days, a history of substance dependence (excluding alcohol or nicotine), creatinine clearance below 50 mL/min or plasma creatinine levels of $\geq$ 1.5 mg/dL (133 µmol/L), body weight less than 60 kg or exceeding 100 kg, patients aged 75 or older, and contraindications for haloperidol use.

Eligible patients were randomly assigned to either the main group (n = 25) or the control group (n = 25) using a computer-generated randomization list. Prior to treatment, all patients in both the main and control groups underwent pharmacogenetic testing. Reports based on these results, intended to guide medication selection and dosage adjustments, were made available only to the treating physicians in the main group. Physicians in the control group did not have access to these reports until the end of the study and therefore treated their patients without consideration of genetic data. In both groups, physicians were free to choose the medications, combinations, and dosing regimens they deemed most suitable for each patient, based on clinical judgment. This allowed the main group to receive PGx-guided therapy, while the control group received standard therapy without pharmacogenetic guidance. All patients were admitted within 24 hours of hospitalization.

Treatment efficacy was measured using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987; Zhang & Malhotra, 2011), while treatment safety was evaluated using the UKU Side-Effect Rating Scale (Lingjaerde et al., 1987). Patients were monitored over 5 days, with evaluations conducted at multiple time points.

For genetic testing, venous blood samples were collected using VACUETTE® vacuum tubes (Greiner Bio-One, Austria). Single nucleotide polymorphisms (SNPs) were identified through real-time PCR using "DTprime 5M1" amplifiers (DNA-Technology, Russia) and SNP-Screen kits (Syntol CJSC, Russia), which employed allele-specific probes for detecting both alleles of the polymorphism via fluorescence.

Pharmacogenetic data were processed through the "PGX2" web application, which generated personalized medication recommendations based on genetic findings. These recommendations were presented in a PDF format and provided to the treating physicians for the main group on the day the blood samples were collected.

Upon patient admission, biological material was collected, and DNA was isolated. Genotyping results were entered into the corresponding fields in the PGX2 web application under the "Known Genotypes" section. In Step 2, "Selection of Drug Groups," the "Antipsychotics" category was chosen to generate personalized therapy recommendations. In Step 3, "Patient and Organization Information," the "Moscow Research and Practical Centre on Addictions" was selected, and patient data was entered, omitting

Table 1.
Genotyping Results for Main and Control Groups

Group	Allelic Variant	Polymorphism	rs	*AA*	*AB*	*BB*	HWE	
							χ^2	*p**
Main	*CYP2D6*4*	*1846G>A*	*rs3892097*	20	5	0	0.31	.58
	*CYP2C19*2*	*681G>A*	*rs4244285*	23	2	0	0.04	.83
	*CYP2C19*17*	*806C>T*	*rs12248560*	17	7	1	0.07	.79
	*CYP3A4*1B*	*392G>A*	*rs2740574*	21	4	0	0.19	.66
	*CYP3A5*3*	*6986A>G*	*rs776746*	0	4	21	0.19	.66
	*ABCB1*6*	*3435C>T*	*rs1045642*	8	14	3	0.69	.4
Control	*CYP2D6*4*	*1846G>A*	*rs3892097*	22	4	0	0.18	.67
	*CYP2C19*2*	*681G>A*	*rs4244285*	22	3	0	0.1	.75
	*CYP2C19*17*	*806C>T*	*rs12248560*	15	8	2	0.38	.54
	*CYP3A4*1B*	*392G>A*	*rs2740574*	24	1	0	0.01	.92
	*CYP3A5*3*	*6986A>G*	*rs776746*	0	4	21	0.189	.67
	*ABCB1*6*	*3435C>T*	*rs1045642*	11	10	4	0.43	.51

Note: **p*, *p*-value based on Benjamini – Hochberg correction (based on Pearson's χ^2 test).

personal identifiers such as "Patient Name" and "Date of Birth" to anonymize the information. In Step 4, the Russian language was selected for the report. The personalized therapy recommendations, generated as a PDF, were provided to the attending physicians on the same day the biological material was collected.

This study was approved by the Ethics Committee of Moscow Research and Practical Centre on Addictions of the Moscow Department of Healthcare (approval no: 12; date: December 06, 2022)

Statistical analyses were performed using non-parametric methods with Statistica v.10.0 software (Dell Statistica, Tulsa, OK, USA). The normality of data distribution was assessed using the Shapiro – Wilk *W*-test. Statistical significance was defined as $p < .05$, and corrections for multiple comparisons were made using the Benjamini – Hochberg test. Differences between groups were analyzed using the Mann – Whitney *U*-test for continuous data, and correlations were examined using Spearman's test. Data are presented as medians and interquartile ranges (Me [Q1; Q3]) or as means and standard deviations (mean ± SD) for normally distributed data.

Results

The genotyping results are presented in Table 1. The distribution of genotypes for all polymorphic markers followed Hardy – Weinberg equilibrium (HWE) for the European population.

The results of PANSS-positive subscale scores and the UKU Side-Effect Rating Scale for the main and control groups on days 1 and 6 of therapy are shown in Table 2.

As shown in the table, at the start of the study, the groups were comparable in terms of PANSS-positive subscale scores (Main: 15.00 [12.00; 17.00] vs. Control: 14.00 [12.00; 16.00], $p > .999$). By the sixth day, no statistically significant differences were observed between the groups in PANSS positive subscale scores (Main: 1.00 [1.00; 2.00] vs. Control: 1.00 [1.00; 1.50], $p = .23$). However, on the UKU scale, the scores differed significantly on the sixth day, with the main group showing lower values (Main: 5.00 [3.00; 8.00] vs. Control: 12.00 [10.00; 16.00], $p < .01$).

Discussion

This prospective study compared the efficacy and safety of pharmacogenetic-guided antipsychotic therapy with standard treatment for patients diagnosed with acute alcoholic hallucinosis. The results revealed no significant differences in treatment efficacy between the groups, as indicated by changes in PANSS positive subscale scores. However, a significant reduction in ADRs was observed in the pharmacogenetic-guided group, as evidenced by lower UKU Side-Effect Rating Scale scores by day 6 of treatment. This suggests that tailoring treatment based on individual genetic profiles can enhance the safety of therapy without compromising its effectiveness.

The findings align with the growing body of evidence supporting the use of pharmacogenetic testing to optimize drug selection and dosage in psychiatric care. Genetic variations, particularly in

Table 2.
PANSS-Positive Subscale and UKU Scores on Days 1 and 6 of Therapy in the Main and Control Groups

Indicator	Main Group (*N* = 25)	Control Group (*N* = 25)	*p**
Day 1 of Hospitalization			
PANSS	15.00 [12.00; 17.00]	14.00 [12.0; 16.00]	> .999
UKU	0 [0; 0]	0 [0; 0]	> .999
Day 6 of Hospitalization			
PANSS	1.00 [1.00; 2.00]	1.00 [1.00; 1.5]	.23
UKU	5.00 [3.00; 8.00]	12.00 [10.00; 16.00]	< .01

Note: *p**, *p*-value based on Benjamini – Hochberg correction (Mann – Whitney *U*-test).

the cytochrome P-450 isoenzymes, play a key role in determining individual responses to psychotropic medications. By identifying patients who are fast or slow metabolizers of these drugs, pharmacogenetic testing allows for more precise dose adjustments, minimizing the risk of ADRs.

Previous research has demonstrated the clinical utility of pharmacogenetic-guided therapy. The earlier studies on the implementation of CDSS for personalizing the dosing of bromdihydr ochlorphenylbenzodiazepine in patients with alcohol withdrawal syndrome (Zastrozhin et al., 2020) and in those with affective disorders comorbid with alcohol dependence (Zastrozhin et al., 2018) underscore the importance and feasibility of personalized pharmacotherapy guided by pharmacogenetic testing. The current study extends these findings to patients with acute alcoholic hallucinosis, a population at high risk for adverse effects due to the severity of their symptoms and the intensity of their treatment regimens.

Limitations and Directions / Suggestions for Future Research

The study's limited sample size (25 patients in each group) may have contributed to the lack of statistically significant differences in treatment efficacy. Larger-scale studies are needed to further explore the benefits of personalized therapy in this population.

Another limitation of this study is the absence of phenotyping for cytochrome P-450 isoenzymes. Future research should incorporate additional "omics" biomarkers, such as pharmacometabolomic markers (to assess enzyme activity) and pharmacotranscriptomic markers (for a more precise evaluation of enzyme activity), to further optimize pharmacotherapy.

Finally, the study participants did not include diverse ethnic groups, which limits the generalizability of the results.

This study involving 50 patients demonstrated the value of personalizing therapy for acute alcoholic hallucinosis using pharmacogenetic testing. The results indicate that adjusting medication dosages based on pharmacogenetic algorithms can significantly reduce the risk of ADRs. Although no significant differences in treatment efficacy were observed, the lower incidence of ADRs suggests that pharmacogenetic testing could play a critical role in optimizing treatment safety. Future research should involve larger sample sizes and incorporate additional biomarkers to further refine and enhance personalized treatment strategies.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: This study was approved by the Ethics Committee of Moscow Research and Practical Centre on Addictions of the Moscow Department of Healthcare (approval no: 12; date: December 06, 2022).

Informed Consent: Written informed consent was obtained from the participants who agreed to take part in the study.

Author Contributions: Concept – V.S.; Design – V.S., S.P., S.S.; Supervision – A.M.; Resources – I.S., V.I.; Materials – I.S., V.I.; Data Collection and/or Processing – V.S., S.P., S.S.; Analysis and/or Interpretation – V.S., S.P.; Literature Search – V.S., S.S.; Writing – V.S., S.P., S.S., V.I.; Critical Review – A.M.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The study was funded by the Moscow Department of Healthcare.

References

Bousman, C. A., & Hopwood, M. (2016). Commercial pharmacogenetic-based decision-support tools in psychiatry. *Lancet Psychiatry*, *3*(6), 585 – 590. [CrossRef]

Egorov, A. Y., Aleksin, D. S., & Petrova, N. N. (2012). Specific features of alcoholic psychosis in psychiatric practice. *Vestnik Saint Petersburg Univ. Med*, *1*, 29 – 40.

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, *13*(2), 261 – 276. [CrossRef]

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*, *334*, 1 – 100. [CrossRef]

Skryabin, V. Y., Martinotti, G., Franck, J.,& Zastrozhin, M. S. (2023). Acute alcoholic hallucinosis: A review. *Psychopathology*, *56*(5), 383 – 390. [CrossRef]

Soyka, M. (2008). Pharmacological treatment of alcohol hallucinosis. *Alcohol and Alcoholism*, *43*(6), 719 – 20; author reply 720. [CrossRef]

Zastrozhin, M., Skryabin, V., Sorokin, A., Buzik, O., Bedina, I., Grishina, E., Ryzhikova, K., Shipitsyn, V., Bryun, E., & Sychev, D. (2020). Using a pharmacogenetic clinical decision support system to improve psychopharmacotherapy dosing in patients with affective disorders. *Drug Metabolism and Personalized Therapy*, *35*(4). [CrossRef]

Zastrozhin, M. S., Sorokin, A. S., Agibalova,T. V., Grishina, E. A., Antonenko, A. P., Rozochkin, I. N., Duzhev, D. V., Skryabin, V. Y., Galaktionova, T. E., Barna, I. V., Orlova, A. V., Aguzarov, A. D., Savchenko, L. M., Bryun, E. A., & Sychev, D. A. (2018). Using a personalized clinical decision support system for bromdihydrochlo rphenylbenzodiazepine dosing in patients with anxiety disorders based on the pharmacogenomic markers. *Human Psychopharmacology*, *33*(6), e2677. [CrossRef]

Zhang, J. P., & Malhotra, A. K. (2011). Pharmacogenetics and antipsychotics: Therapeutic efficacy and side effects prediction. *Expert Opinion on Drug Metabolism and Toxicology*, *7*(1), 9 – 37. [CrossRef]