ETHICAL ISSUES OF PHARMACOGENETICS OF ANTI-RELAPSE THERAPY IN PATIENTS WITH ALCOHOL DEPENDENCE SYNDROME

Lileeva EG[1] ✉,Speshilova SA[1], Zinoveva MA[1,2]

[1] Yaroslavl State Medical University, Yaroslavl, Russia

[2] Yaroslavl Regional Clinical Narcological Hospital, Yaroslavl, Russia

Alcohol currently contributes to 5% of the overall global burden of diseases and injuries. Alcohol consumption results in death and disability at young age. Medicinal products approved for treatment of alcohol dependence syndrome include disulfiram, Naltrexone, Cyanamid and nalmefene. Variability of a patient-to-patient pharmacotherapy therapeutic effect can also be associated with genetic causes. Examination of the system of pharmacogenetic markers in narcology will be used to provide for preliminary prognosis of effectiveness and tolerance of medicinal products during personalized anti-relapse (supporting) therapy to support and prolong remission in patients with alcohol dependence.

Key words: alcohol dependence syndrome, anti-relapse therapy, pharmacogenetic testing

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✉ **Correspondence should be addressed:** Elena G. Lileeva
Revolutsionnaya Str., 5, Yaroslavl, 150000, Russia; elileeva2006@yandex.ru

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ЭТИЧЕСКИЕ ВОПРОСЫ ФАРМАКОГЕНЕТИКИ ПРОТИВОРЕЦИДИВНОЙ ТЕРАПИИ У ПАЦИЕНТОВ С СИНДРОМОМ ЗАВИСИМОСТИ, ВЫЗВАННЫМ УПОТРЕБЛЕНИЕМ АЛКОГОЛЯ

Е. Г. Лилеева[1] ✉, С. А. Спешилова[1], М. А. Зиновьева[1,2]

[1] Ярославский государственный медицинский университет, Ярославль, Россия

[2] Ярославская областная клиническая наркологическая больница, Ярославль, Россия

В настоящее время алкоголем обусловлено 5% общего глобального бремени болезней и травм во всем мире. Потребление алкоголя приводит к смерти и инвалидности в молодом возрасте. Лекарственные препараты, одобренные для лечения синдрома зависимости от алкоголя, включают дисульфирам, налтрексон, цианамид и налмефен. Вариабельность терапевтического эффекта фармакотерапии от пациента к пациенту может быть также связана с генетическими причинами. Изучение системы фармакогенетических маркеров в наркологии будет использовано для предварительного прогноза эффективности и переносимости препаратов в рамках персонализации противорецидивной (поддерживающей) фармакотерапии для поддержания и продления сроков ремиссии у пациентов с синдромом зависимости, вызванным употреблением алкоголя.

Ключевые слова: синдром зависимости, вызванный употреблением алкоголя, противорецидивная терапия, фармакогенетическое тестирование

Вклад авторов: авторами проведен обзор литературных данных по тематике исследования в области фармакогенетических исследований у пациентов с синдромом зависимости, вызванным употреблением алкоголя. Авторы внесли равный вклад в написание статьи.

✉ **Для корреспонденции**: Елена Георгиевна Лилеева
ул. Революционная, д. 5, г. Ярославль, 150000, Россия; elileeva2006@yandex.ru

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Alcohol is the most actively used psychoactive substance in the world. Its consumption occupies a special place in the list of leading risk factors of population health. Alcohol dependence is still one of the most essential issues whereas basic social losses in the society are mainly associated with this disease and its prevalence [1].

According to the World Health Organization, harmful use of alcohol results in 3.3 million deaths every year, representing 5.9% of all deaths. Excessive alcohol intake is the reason for over 200 health disturbances associated with diseases and injuries. Almost 25% of all death cases among people aged 20–39 years old are associated with alcohol consumption.

Basic alcohol-associated causes of death include poisoning, liver and heart diseases, cancer and car accidents. About 1.38% of global population suffers from alcohol-related diseases. According to the National Medical Research Center named after Serbsky VP of the Ministry of Health of Russia, 1.3% of Russian population is diagnosed with drug intoxication [2].

High incidence of substance-abuse pathology, disease severity, intensity of medical and social consequences and commonly insignificant effect of a standard complex therapy in patients with psychoactive substance (PAS) dependence syndrome make researchers search for specific markers of various types of disease course attributable to various levels of biological (genetic) risk of its development.

Genetic polymorphism means that different variants of gene structures (polymorphic loci or polymorphisms) within the population constitutes a genetic basis both for individual susceptibility to multifactorial and polygenic diseases of hereditary predisposition and a variety of responses to pharmacological agents, including psychoactive substances [3]. Possible dependence on alcohol due to genetic reasons only is essential for two values:

– prevent dependence on alcohol by assessing the individual genetic risk of the disease;
– therapy and rehabilitation: individual contribution of genetic factors into the pathogenesis of a disease

(genetic radical), assessing the genetic effect on effectiveness of pharmacotherapy and rehabilitation programs.

Stabilization of remission and prevention of recurrences constitute a leading treatment trend of alcoholism. Effectiveness and tolerance of medicinal agents used to treat chemical dependency are associated with polymorphism of genes that determine catabolism of drugs within a body, their binding to specific receptors of neuronal membrane involved in the action of drugs proper and PAS that cause dependence, and with the genes regulating the system of brain remuneration using dopaminergic neurotransmission and the system of endogenic opioid neuropeptides.

It is difficult to detect the genes and gene systems due to he results of association study. They can include genome-wide association studies (GWAS) and candidate-gene association studies (CGAS) constituting the genotype of a disease which produces a significant effect on family burden along with non-specificity and multivariance of disease phenotype. Pharmacological study in narcology is the only way to solve such a complex task and trace a pathogenetic approach to the selection of candidate genes [4, 5].

A schematic task of a pharmacogenetic study suggests to correlate the drug effect or a phenotype ad a genotype. It is a set of genes and their polymorphous variants, which can be contributors of differences in the drug effect. Variability of patient-to-patient pharmacotherapy therapeutic effect can also be associated with genetic causes such as differences in the gene structure of direct and indirect drug targets [6]. To improve therapy effectiveness, three approaches can be used:

1) use of long-acting forms of anti-relapsing drugs;
2) combination with other pharmacological drugs that allow to reduce the symptoms leading to a recurrence;
3) patient stratification based on pharmacotherapy effectiveness taking into account a pharmacogenetic analysis. A genetic panel should include genes controlling the most essential links of DA neuromediation such as SOMT and DBH enzymes, dopamine D2 (DRD2) and D4 (DRD4) receptors, dopamine transporters (DAT1) and genes of opioid receptors (the mu (OPRM1) and kappa (OPRK1) opioid receptor) [6].

Medicinal products approved for treatment of alcohol dependence include disulfiram, naltrexone, cyanamid and nalmefene [7]. Moreover, some products for treatment of alcohol dependence displayed possible effectiveness in clinical studies. The available evidential basis is not sufficient for registration of the products as per the indications. These are some anti-epileptic agents (Topiramate, Pregabalin, Gabapentin) and antidepressants such as serotonin reuptake inhibitors (Sertralin), Baclofen and Ondansetron.

A certain effect of polymorphisms associated with genes of mu-opioid receptors (OPRM1), dopamine D2 (DRD2) and D4 (DRD4) receptors, reverse dopamine transporter (DAT), enzyme of metabolism of catechol-O-methyltransferase catecholamines in the modulation of effective opiate dependence remission stabilization with s/c administration of naltrexone was shown in naltrexone long-acting studies [6]. It was established that irrespective of the type of anti-relapse therapy, a number of polymorphic variants increases the risk of dependence recurrence: allele L (2 repeats with 120 bps), DRD4120bp D4 dopamine receptor, allele C DRD2NcoI D2 dopamine receptor, and 9.9 genotype of DATVNTR40bp dopamine reuptake protein (dopamine transporter). Variants of polymorphism (CC+CT)-(TT)) with a combination of genes (OPRK1-DRD2Ncol) increase the probability of treatment completion. Carriers of the same variants (OPRK1-DRD2Ncol) in the group of naltrexone had a higher probability of treatment program completion. The effect was however reverse in the group of double placeboes, and was not manifested in the group of therapy with naltrexone implant [6].

The purpose of another study was to search for gene OPRM1 polymorphism influencing the response to therapy with peroral naltrexone. Statistically significant differences were found in distribution of patients by genotype within subgroups with good, moderate and bad response to therapy. The most pronounced differences in distribution were detected in relation to two genotypes rs6912029 [G-172T] and rs12205732 [G-1510A] (P = 0,05, Fisher exact test). Thus, the association between OPRM1 G-172T and G-1510A gene polymorphism and response to treatment in case of opioid dependence was shown for the first time. The genotypes were more common among non-responders to naltrexone therapy [8].

In the trial of disulfiram preparations, it was shown that the functional polymorphism of dopamine-beta-hydroxylase gene is associated with an increased risk of adverse effects of therapy with disulfiram [9]. This can be explained by an inhibitory effect of disulfiram on dopamine-beta-hydroxylase of brain neurons.

A study of therapeutic effectiveness and safety of using cyanamide in complex therapy of alcohol dependence performed at the National Scientific Center for Narcology in 2006 as compared with traditional treatment of men aged 25 to 60 years [10] has shown that at the stage of remission the drug displayed good effectiveness. Use of cyanamide allowed to decrease a number of early recurrences significantly and, thus, improve the quality of remission. Remission duration depends on the results of a pharmacogenetic testing. In the study of cyanamide by Krupitsky EM and Kibitova AO, the rs1108580 Bst marker was associated with a greater program retention in the group of disulfiram only (LogRank (Mantel-Cox)=0.053), whereas dopamine receptor type 4 (DRD4 120 bp marker) was associated with the less time to failure in the cyanamide (Log Rank (Mantel-Cox)=0.063) group [11].

In the multi-centered randomized placebo-controlled study, Arias et al (2008) [12] discovered associations between polymorphism of A118G (rs561720) of OPRM1 mu-opiate receptor, polymorphisms of rs2234918 (T921C) and rs678849 gene of delta-opiate receptor (OPRD1) and polymorphism of rs963549 gene of kappa-opiate receptor (OPRK1), on the one hand, and exposure of nalmefene on reduced alcohol consumption.

Antiepileptic agents (topiramate, pregabalin, gabapentin) are second-line therapy medicinal products used to treat patients with the syndrome of dependence due to excessive use of alcohol. A significant number of associations of polymorphisms of various genes with the outcomes of alcoholism therapy with pregabalin was detected during pharmacogenetic studies [13]. 30 polymorphic loci of 19 genes of dopamine, noradrenaline, opioid system, GABA system, glutamate, voltage-dependent calcium channels and neurotrophins were investigated. Pharmacogenetic markers of remission retention included as follows: GG BDNF V66M rs6265 (system of neurotrophins), CC DRD2–141C rs1799732 (system of dopamin), CC GRiK-GluR5 rs2832407 (GABA-glutamate system). The CC DRD2–141C rs1799732 option was a specific predictor of long-term retention within a program, whereas CC GRiK-GluR5 rs2832407 was a specific predictor of successful completion of therapy program. Remission duration (time to recurrence) was associated with GG DRD2 Nco I rs6275 (high risk of fast relapse (dopamine system). On the contrary, LL DRD4 48 bp was a marker of fast relapse low risk (dopamine system) [13, 14].

According to literature, the perspective trends of developing the methods for better effectiveness of remission stabilization in case of alcoholism include a combination of pharmacological agents with various targets of action and therapy personalization based on a pharmacogenetic analysis. Based on the outcomes of genotyping, it is possible to detect patients with high resistance to therapy. Preliminary genotyping allows to improve treatment effectiveness before medicinal preparations are administered and provides for clinically useful standardized individual pharmacological treatment strategies to stabilize alcoholism remission.

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