Association of polymorphic variants of genes *(HTR2A, MTNR1A, MTNR1B, CLOCK, DRD2)* and insomnia in alcohol dependence syndrome

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The majority of patients with alcohol dependence syndrome suffer from sleep disorders, particularly insomnia, associated with a number of critical clinical aspects, increased suicide risk, anxiety and depression. The authors of relevant publications indicate associations between polymorphic melatonin genes and melatonin metabolism and symptoms of sleep disorders. However, the literature review failed to reveal any studies on the role of genetic polymorphism of circadian rhythm regulators in sleep disorders in patients with alcohol dependence.

Objective: *to determine the associations of polymorphic variants of genes HTR2A, MTNR1A, MTNR1B, CLOCK, DRD2 with sleep disorders risk in alcohol dependence syndrome.*

Patients and methods. *307 patients with alcohol dependence syndrome were screened, including 61 women (21%) and 246 (79%) men (mean age – 41.92±7.9 years). The presence and severity of sleep disorders were assessed by the Insomnia Severity Index. In addition, 10 ml of venous blood sample was obtained from all participants. Genotyping of single nucleotide variants of HTR2A (rs6313), MTNR1A (rs34532313), MTNR1B (rs10830963), CLOCK (rs1801260), DRD2 (rs1800497) genes was performed using real-time polymerase chain reaction. Statistical analysis of the data was conducted using parametric and nonparametric methods.*

Results and discussion. *The carriage of the *G allele of the polymorphic variant of the MTNR1B (rs10830963) gene, and its genotypes are associated with a greater risk of insomnia than the carriage of *C/*C genotype. The carriage of the *C allele of the polymorphic variant of the CLOCK (rs1801260) gene, as well as the *C/*T genotype, are associated with the presence of sleep disorders. No associations between polymorphic variants of the HTR2A (rs6313), DRD2 (rs1800497) genes and insomnia risk were detected in patients with alcohol dependence syndrome.*

Conclusion. *The found associations reveal prospects for future research on melatonin's role in the pathophysiology of sleep disorders in patients with alcohol dependence and pathogenetic therapy for insomnia.*

Keywords: *sleep disorder; insomnia; single nucleotide variants; melatonin; serotonin; CLOCK.*

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Introduction. Sleep disorders, in particular insomnia, are widespread in patients with alcohol addiction syndrome and are associated with several important clinical aspects of alcohol addiction, increased suicide risk [1, 2], anxiety [3] and depression [4, 5]. Alterations in a number of genes involved in the regulation of sleep processes, particularly in the genes of receptors and enzymes involved in the synthesis and metabolism of melatonin and its precursors, can be one of the prerequisites for insomnia in both healthy and alcohol-dependent individuals [6, 7]. Melatonin is one of the primary regulators of the circadian rhythm; its production in the epiphysis pineal glands depends on light stimulation [8–10]. Regular consumption of ethanol has been shown to affect melatonin metabolism, thereby possibly participating in the development and formation of alcohol dependence [11]. Deirdre A. Conroy et al., studying circadian rhythms by DLMO (dim light melatonin onset), found that patients with alcohol dependence had a slower rate of rising and a smaller maximum amplitude of melatonin rhythm compared with healthy people [12]. K?hlwein E. et al. also observed a decrease in peak values of melatonin secretion in patients with alcohol dependence syndrome compared with healthy individuals [13]. Danel T. et al. (2008) found that in healthy volunteers, in contrast to alcohol-dependent individuals, there is no change in melatonin secretion profile when taking similar doses of ethanol, suggesting that either regular alcohol consumption leads to impaired melatonin metabolism, or the features of melatonin metabolism contribute to the initiation of alcohol dependence [14].

Several authors have described the associations between carriage of polymorphic variants of the melatonin and mela-

tonin metabolism genes and the risk of sleep disturbance symptoms, as mentioned above. Pallesen S. et al. studied the serotonin sodium-dependent transporter and revealed that carriage of the *A/*A genotype of the *SLC6A4* gene (rs25531) is associated with the risk of sleep disorders in mentally healthy individuals [15]. According to the findings of Myung W et al., who studied genetic aspects of depressive disorders in 241 patients from Korea, the *TPH1* gene is involved in the mechanisms of development of moderate insomnia (middle insomnia) during depressive episodes [16]. Park H. J. et al. (2011) also established that carriage of the polymorphic variant of melatonin receptor 1B gene is associated with the risk of sleep disorders in patients with schizophrenia [6]. The association of the polymorphic variant of the melatonin receptor 1B gene (rs10830963) with sleep disorders was reported by Olsson L. et al. (2011). [7]. Apart from the genes involved in melatonin metabolism, a number of researchers point to the role of the carriage of polymorphic variants of the circadian oscillator genes (*CLOCK, PER*, etc.) [17, 18]. Among the published studies, we have not found any works analysing the role of genetic polymorphisms of circadian rhythm regulators in the mechanisms of sleep disorders in patients with alcohol dependence.

Objective: to determine the associations of polymorphic variants of genes *HTR2A* (rs6313), *MTNR1A* (rs34532313), *MTNR1B* (rs10830963), *CLOCK* (rs1801260), *DRD2* (rs1800497) with the risk of insomnia in alcohol dependence syndrome.

Materials and methods. The collection of material was carried out based on the Republican Narcological Dispensaries of the Ministry of Health of the Republic of Bashkortostan №2 (Sterlitamak) and №1 (Ufa) between February 2019 and August 2020. Genotyping was performed in the Department of Personalized Psychiatry and Neurology of V.M. Bekhterev National Medical Research Center (Saint Petersburg). The Local Ethical Committee of the Federal State Budgetary Educational Institution of Higher Education Bashkir State Medical University of the Ministry of Health of Russia, Republic of Bashkortostan gave approval (Protocol №2 of 27.02.2019; Protocol №7 of 08.07.2020) to conduct this study.

The following *inclusion criteria* were used to form the group: verified diagnosis F10.2 «Alcohol dependence syndrome» with a period of observation in the narcological service of at least one year; voluntary written informed consent to participate in the study, age 18–55 years; more than 7 days since hospitalization to the narcological hospital and at least 72 hours since the last administration of benzodiazepines. *Non-inclusion criteria* were: the presence of alcohol withdrawal syndrome at the moment of study; the presence of substance dependence criteria other than alcohol or nicotine; other reasons preventing verbal contact; the presence of comorbid psychiatric pathology: schizophrenia, schizotypal conditions, delusional disorders (F20–F29), dementia (F00–F03), mental retardation (F70–F79), severe somatic pathology. *The exclusion criteria* were: refusal to participate in the study after its initiation, identification of non-inclusion criteria during the clinical interview.

307 patients with alcohol dependence syndrome were screened, among whom 21% (61/307) were women, 79% (246/307) were men. The mean age of the subjects was 41.92±7.9 years. This sample can be considered representative of the population studied.

The Insomnia Severity Index (ISI, Bastien et al., 2001, Savard et al., 2005) was used to assess the presence and severity of insomnia [19, 20].

Venous blood samples (10 ml) were taken from all subjects using Vacutainer vacuum systems for molecular genetic and biochemical studies. Venous blood samples for the biochemical study were obtained in the morning on an empty stomach after 10–12 hours of fasting. Venous blood samples for the molecular genetic analysis were frozen (-20°C) and transferred to the Department of Personalized Psychiatry and Neurology of Bekhterev National Research Center for Psychiatry and Neurology. Preparation of blood samples for deoxyribonucleic acid (DNA) extraction was performed with Hemolytic (AmpliSense®) reagent for pretreatment of whole peripheral and umbilical cord blood. DNA extraction was performed with the Ribo-PREP kit (AmpliSens®). Genotyping for single-nucleotide variants of *HTR2A* (rs6313), *MTNR1A* (rs34532313), *MTNR1B* (rs10830963), *CLOCK* (rs1801260) genes, *DRD2* (rs1800497) was performed using real-time polymerase chain reaction (RT-PCR) on a RotorGene 6000 amplifier (Quigen, Germany) using a reagent kit manufactured by Syntol (Moscow).

All statistical processing was performed using STATISTICA 6.1 (Stat. Soft, USA, Serial number AXXR902E261711FAN4), Microsoft Excel, and IBM SPSS Statistics 22. Shapiro–Wilk criterion was applied to determine the normality of the distribution of quantitative variables. Pearson's chi-square criterion (χ^2) was used in frequency analysis. The Mann–Whitney nonparametric U-criterion was applied to compare quantitative variables in two independent groups, and the Kruskal–Wallis test was used to compare quantitative variables in several independent groups. Spearman rank correlation coefficient was also used to study associations between quantitative variables. Linear regression analysis was employed to assess the relationship between the phenomena. Nonparametric methods were chosen according to the distribution of some of the quantitative variables in the sample, different from the normal distribution.

Results. Among the alcohol dependence syndrome sample, 223 subjects complained of sleep disorders: 94% reported problems falling asleep, 86% reported interrupted sleep, and 74% reported waking up too early. 136 (44%) patients met the criteria for insomnia, including sleep disturbance complaints, 10 points or more on the Insomnia Severity Index (ISI). A cut-off threshold of 10 points was proposed by one of the original Morin CM technique authors, which is the most sensitive for detecting insomnia [19]. The structure of insomnia disorders according to the Insomnia Severity Index is shown in Table 1.

A population group with similar inclusion criteria was recruited to examine the consistency of genotypes with the Hardy–Weinberg law but dropped from the study later due to the identification of exclusion criteria. Compliance of the genotype distribution with the Hardy–Weinberg law was assessed by Fisher's exact test using the website of the Munich Institute of Human Genetics (https://ihg.gsf.de/cgi-bin/hw/hwa1.pl), as well as by Pearson Chi-square test using Microsoft Excel. The test results are presented in Table 2. Consistency with the Hardy–Weinberg distribution law allows us to conclude that the sample is genetically representative.

Table 1. *Structure of insomnia disorders according to the ISI*

Disorder	Severity of the disorder n (%)					Total
	No	Light	Moderate	Severe	Extremely severe	
Trouble falling asleep	9 (7)	19 (14)	50 (37)	42 (31)	16 (12)	136
Problem with interrupted sleep	17 (13)	16 (12)	61 (45)	35 (26)	7 (5)	136
Problem waking up too early	33 (24)	30 (22)	42 (31)	17 (13)	14 (10)	136

Table 2. *Results of consistency analysis of genotypes with the Hardy–Weinberg law*

Gene (SNV)	Genotypes			F	Chi-square	f_a1	p (Pearson)	p (Llr)	p (Exact)
HTR2A (rs6313)	*C/*C 143	*C/*T 174	*T/*T 47	-0.03	0.27	0.63±0.018	0.6	0.599	0.653
MTNR1A (rs34532313)	*C/*C 181	*C/*T 146	*T/*T 37	0.05	1.3	0.70±0.017	0.350	0.353	0.384
MTNR1B (rs10830963)	*C/*C 148	*C/*G 158	*G/*G 58	0.08	2.066	0.62±0.019	0.151	0.152	0.148
CLOCK (rs1801260)	*T/*T 172	*C/*T 160	*C/*C 32	-0.03	0.366	0.69±0.017	0.545	0.543	0.623
DRD2 (rs1800497)	*C/*C 173	*C/*T 149	*T/*T 42	0.06	1.69	0.68±0.018	0.256	0.259	0.278

Note. F – Inbreeding Ratio; f_a1 – Allele frequency 1 ± standard deviation; p (Pearson) – Pearson's chi-squared test (degree of freedom = 1); p (Llr) – Logarithmic chi-square probability ratio (degree of freedom = 1); p (Exact) – Fisher's exact test.

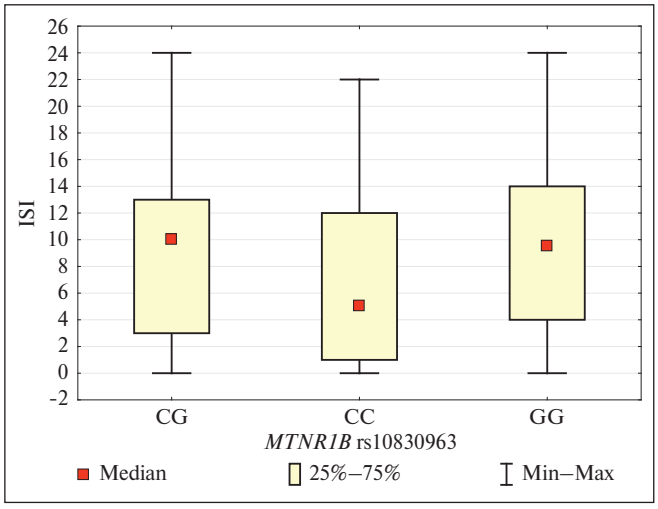
Pearson's χ^2 criterion was used to determine the association of polymorphic gene variants: *HTR2A* (rs6313), *MTNR1A* (rs34532313), *MTNR1B* (rs10830963), *CLOCK* (rs1801260), *DRD2* (rs1800497) and insomnia in patients with alcohol dependence syndrome using frequency analysis. The results are presented in Table 3.

Discussion. An analysis of the association of polymorphic loci rs1801260 of the *CLOCK* gene showed that the frequency of the *T/*T genotype of the *CLOCK* gene (rs1801260) was significantly lower in the group of patients with insomnia (37%) than in the carriers of other genotypes (χ^2=4.888; p=0.027*). A higher incidence of sleep disturbances was not excluded in the carriers of the *C/*T genotype compared with the carriers of other genotypes (p=0.051; χ^2=3.813). Comparing the frequency of alleles in patients with and without sleep disturbance using the Mann–Whitney U-criterion, it was determined that the *C allele was significantly more frequent in patients with insomnia than in patients without sleep disturbance. Thus, we can assume that the *C allele, as well as the *C/*T genotype, are associated with the presence of sleep disorders. The absence of statistical significance in the *C/*C genotype analysis may be due to its relatively low occurrence in the study sample (n=18; 6%).

Table 3. *Frequency analysis of polymorphic gene variants and the presence of sleep disorder*

Gene	Genotypes			Chi-square; p-value
HTR2A (rs6313)	*C/*C 47% (51/108) χ^2=0.865 p=0.352	*C/*T 42% (72/169) χ^2=0.167 p=0.683	*T/*T 37% (11/30) χ^2=0.659 p=0.417	χ^2=1.866 p=0.601
MTNR1A (rs34532313)	*C/*C 41% (68/165) χ^2=0.861 p=0.354	*C/*T 50% (56/110) χ^2=3.674 p=0.055**	*T/*T 31% (10/32) χ^2=2.233 p=0.135	χ^2=5.398 p=0.145
MTNR1B (rs10830963)	*C/*C 35% (52/148) χ^2=8.42 p=0.004*	*C/*G 52%(53/101) χ^2=4.768 p=0.029*	*G/*G 50% (29/58) χ^2=1.173 p=0.279	χ^2=9.160 p=0.027*
CLOCK (rs1801260)	*C/*C 50% (9/18) χ^2=0.314 p=0.575	*C/*T 50% (70/141) χ^2=3.813 p=0.051**	*T/*T 37% (55/148) χ^2=4.888 p=0.027*	χ^2=5.531 p=0.137
DRD2 (rs1800497)	*C/*C 41% (71/172) χ^2=0.028 p=0.867	*C/*T 50% (31/62) χ^2=2.285 p=0.131	*T/*T 31% (13/42) χ^2=2.340 p=0.126	χ^2=6.243 p=0.1

Note: * p < 0.05; ** p trend < 0.09



The severity of sleep disturbances in carriers of different genotypes of the polymorphic variant of the MTNR1B gene (rs10830963)

A number of significant associations were also found in the analysis of polymorphic variants of melatonin receptor genes in patients with and without insomnia. It was found that the frequency of the *C/*T genotype of the *MTNR1A* gene (rs34532313) was likely to be higher in the group of patients with insomnia than in the carriers of other genotypes (p=0.055). The frequency of the *C/*C and *C/*G polymorphic variants of the *MTNR1B* gene (rs10830963) was found to be significantly lower in the group of patients with insomnia. A comparison of allele frequency in patients with and without insomnia applying the Mann–Whitney U-criterion revealed that the *G allele was significantly more frequent in patients with insomnia than in patients without sleep disturbances (p=0.015). A statistically significant difference was obtained by comparing the severity of insomnia in patients with different genotypes, using the Kruskal–Wallis criterion. It was also revealed that the carriers of the *C/*C genotype had lower insomnia severity than the carriers of other genotypes (Figure 1). The C*/C* genotype carriage of the *MTNR1A* gene (rs34532313) was associated with the lowest severity of sleep problems in the structure of insomnia disorders compared with other genotypes carriers, with the highest severity among T*/T* genotype carriers, suggesting an association between the T* allele and sleep problems (p=0.0361). Thus, it was shown that the *G allele as well as the *C/*G and *G/*G genotypes, were associated with a greater risk of insomnia than the *C/*C genotype. Applying the Spearman rank correlation method, we found that the number of *C alleles in the genotype inversely correlated with the severity of problems with falling asleep (R=-0.13; p=0.018), problems waking too early (R=-0.19; p=0.0007), intermittent sleep problems (R=-0.12; p=0.03), Insomnia severity index (R=-0.17; p=0.002). By performing a simple regression analysis, where the dependent variable was the insomnia severity index and the predictor was the carriage of the *C/*C genotype, we could construct a model that explained 2.85% of the variance (b*=-0.168; p=0.0029).

The associations of polymorphic variants of the *HTR2A* (rs6313), *DRD2* (rs1800497), and insomnia genes in patients with alcohol dependence syndrome were not identified.

Conclusions. We found several significant associations between the polymorphic gene variants analysed in this study and sleep disturbances in patients with alcohol dependence syndrome. The carriage of the *G allele of the polymorphic variant of the *MTNR1B* gene (rs10830963) and its genotypes was associated with a greater risk of dyssomnia than the carriage of the *C/*C genotype. The *C allele of the polymorphic variant of the *CLOCK* gene (rs1801260) and the *C/*T genotype was associated with a high risk of sleep disturbance in patients with alcohol dependence syndrome. The detected associations open perspectives for further study of the role of melatonin in the pathophysiology of sleep disorders in patients with alcohol dependence and search for pathogenetic therapies for insomnia.

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Conflict of Interest Statement

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