УДК 616.895:616.89-008.441.13]-085.214.32
https://doi.org/10.20538/1682-0363-2021-2-79-87

Clinical characteristics and efficiency of antidepressant therapy of mood disorders with comorbid alcohol use disorder

Roshchina O.V.[1], Rozin A.I.[1], Schastnyy E.D.[1], Bokhan N.A.[1, 2]

[1]Mental Health Research Institute, Tomsk National Research Medical Center (NRMC) of the Russian Academy of Sciences
4, Aleutskaya Str., 634014, Tomsk, Russian Federation

[2] Siberian State Medical University
2, Moscow Trakt, 634055, Tomsk, Russian Federation

ABSTRACT

Aim. To determine the nosological and clinical features of mood disorders (MD) with comorbid alcohol use disorder (AUD) and efficiency of antidepressant therapy.

Materials and methods. We examined 88 patients with MD and comorbid AUD – 33 females (37.5%) and 55 males (62.5%). The first group included 31 patients with AUD without comorbid affective symptoms, the second group contained 29 patients with MD without AUD, the third group included 28 patients with AUD and MD. In the study, we applied clinical-psychopathological, clinical-dynamic, and statistical methods with Pearson's χ 2 test, Mann – Whitney *U*-test (for comparison of independent samples), Kruskal – Wallis test (for more than two independent samples), and Wilcoxon test (for comparison of dependent samples). At the level of statistical significance, no differences between the groups according to the gender – age composition were revealed ($p = 0.115$ – according to gender composition, $p = 0.248$ – according to age composition, Pearson's χ 2 test).

Results. The patients with the diagnosis of AUD with comorbid MD showed worse dynamics of the reduction of depressive [from 24.0 (18.3; 33.0) to 9.0 (4.3; 12.0) points according to the Structured Interview Guide for the Hamilton Depression Rating Scale – Seasonal Affective Disorder (SIGH-SAD) ($p = 0.001$, Wilcoxon test)] and anxiety [from 20.5 (12.5; 25.0) to 5.5 (3.3; 8.0) points according to the Hamilton Anxiety Rating Scale (HARS) ($p = 0.001$, Wilcoxon test)] symptoms against the background of the therapy with initially lower indices compared to the group with MD alone [from 27.0 (21.0; 36.0) to 6.0 (5.0; 11.0) points according to SIGH-SAD ($p = 0.001$, Wilcoxon test) (intergroup differences upon admission $p = 0.046$; upon discharge $p = 0.683$, Mann – Whitney *U*-test) and from 21.0 (14.0; 29.0) to 5.0 (3; 10.5) points according to HARS ($p = 0.001$, Wilcoxon test) (intergroup differences upon admission – $p = 0.082$; upon discharge – $p = 0.825$, Mann – Whitney *U*-test)]. The course of AUD is characterized by a larger extent of malignancy in the group with a comorbidity: a decrease in pathological alcohol craving from 31.5 (16.3; 43.5) to 8 (2.3; 14.8) points ($p = 0.001$, Wilcoxon test) in the group with a comorbidity and from 29.5 (21.8; 37.0) to 7 (3.0; 11.3) points with AUD alone ($p = 0.001$, Wilcoxon test) (intergroup differences upon admission – $p = 0.058$; upon discharge – $p = 0.04$, Mann – Whitney *U*-test on the Obsessive Compulsive Drinking Scale (OCDS)).

Conclusion. Clinical-dynamic characteristics of MD with comorbid AUD result in therapeutic difficulties associated with comparatively worse dynamics in reduction of the symptoms of both diseases.

Key words: alcohol addiction, depressive disorders, comorbidity, antidepressant therapy, anti-craving therapy.

Conflict of interest. The authors declare the absence of obvious or potential conflicts of interest related to the publication of this article.

Source of financing. The study was supported by the Russian Science Foundation grant No. 19-15-00023 "Clinical features and search for potential biomarkers of comorbidity of alcohol use disorder and mood disorders".

✉ *Schastnyy Evgeny D.,* e-mail: evgeny.schastnyy@gmail.com.

Conformity with the principles of ethics. All patients signed an informed consent to participate in the study. The study was approved by the local Ethics Committee of Mental Health Research Institute, Tomsk NRMC (Protocol No. 6 of 21.06.2017).

For citation: Roshchina O.V., Rozin A.I., Schastnyy E.D., Bokhan N.A. Clinical characteristics and efficiency of antidepressant therapy of mood disorders with comorbid alcohol use disorder. *Bulletin of Siberian Medicine.* 2021; 20 (2): 79–87. https://doi.org/10.20538/1682-0363-2021-2-79-87.

Клиническая характеристика и эффективность антидепрессивной терапии аффективных расстройств при коморбидности с алкогольной зависимостью

Рощина О.В.[1], Розин А.И.[1], Счастный Е.Д.[1], Бохан Н.А.[1, 2]

[1]Научно-исследовательский институт (НИИ) психического здоровья, Томский национальный исследовательский медицинский центр (НИМЦ) Российской академии наук
Россия, 634014, г. Томск, ул. Алеутская, 4

[2] Сибирский государственный медицинский университет (СибГМУ)
Россия, 634055, г. Томск, Московский тракт, 2

РЕЗЮМЕ

Цель исследования – определение нозологической структуры, клинических особенностей аффективных расстройств (АР) при коморбидности с алкогольной зависимостью (АЗ) и эффективности антидепрессивной терапии.

Материалы и методы исследования. Обследованы 88 человек с АР и АЗ – 33 женщины (37,5%) и 55 (62,5%) мужчин. Первая группа – 31 пациент с АЗ без коморбидной аффективной симптоматики, вторая – 29 больных с расстройством настроения без зависимости от алкоголя, третья – 28 пациентов с коморбидным течением АЗ и АР. В исследовании использовался клинико-психопатологический, клинико-динамический и статистический методы с использованием критериев χ^2 Пирсона, Манна – Уитни (для сравнения независимых выборок), Краскела – Уоллиса (для более двух независимых выборок), Вилкоксона (для сравнения зависимых выборок). По уровню статистической значимости различий между группами по половозрастному составу не выявлено ($p = 0{,}115$ – по половому составу, $p = 0{,}248$ – по возрастному составу, критерий χ^2).

Результаты. Пациенты с коморбидным диагнозом АЗ и АР демонстрируют худшую динамику редукции депрессивной (с 24,0 (18,3; 33,0) до 9,0 (4,3; 12,0) баллов по шкале SIGH-SAD ($p = 0{,}001$, критерий Вилкоксона)) и тревожной (с 20,5 (12,5; 25,0) до 5,5 (3,3; 8,0) баллов по шкале HARS ($p = 0{,}001$, критерий Вилкоксона)) симптоматики на фоне лечения, при изначально более низких показателях, в сравнении с группой с «чистыми» АР (с 27,0 (21,0; 36,0) до 6,0 (5,0; 11,0) баллов по SIGH-SAD ($p = 0{,}001$, критерий Вилкоксона) (межгрупповые различия при поступлении $p = 0{,}046$; при выписке $p = 0{,}683$, критерий Манна – Уитни) и с 21,0 (14,0; 29,0) до 5,0 (3; 10,5) баллов по HARS ($p = 0{,}001$, критерий Вилкоксона) (межгрупповые различия при поступлении $p = 0{,}082$; при выписке $p = 0{,}825$, критерий Манна – Уитни). Течение АЗ отличается большей злокачественностью в группе с коморбидностью: снижение патологического влечения к алкоголю с 31,5 (16,3; 43,5) балла до 8 (2,3; 14,8) ($p = 0{,}001$, критерий Вилкоксона) в группе с коморбидностью и с 29,5 (21,8; 37,0) до 7 (3,0; 11,3) баллов при «чистой» АЗ ($p = 0{,}001$, критерий Вилкоксона) (межгрупповые различия при поступлении $p = 0{,}058$; при выписке $p = 0{,}04$, критерий Манна – Уитни по обсессивно-компульсивной шкале употребления алкоголя.

Заключение. Клинико-динамические характеристики коморбидного сочетания АР и АЗ ведут к терапевтическим затруднениям, сопряженным со сравнительно худшей динамикой редуцирования симптомов каждого из заболеваний.

Ключевые слова: алкогольная зависимость, депрессивные расстройства, коморбидность, антидепрессивная терапия, антикрейвинговая терапия.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов в связи с публикацией данной статьи.

Источник финансирования. Исследование выполнено при поддержке Российского научного фонда (грант № 19-15-00023 «Клинические особенности и поиск потенциальных биомаркеров коморбидности алкоголизма и аффективных расстройств»).

Соответствие принципам этики. Все пациенты подписали информированное согласие. Исследование одобрено локальным этическим комитетом НИИ психического здоровья, Томский НИМЦ (протокол № 6 от 21.06.2017).

Для цитирования: Рощина О.В., Розин А.И., Счастный Е.Д., Бохан Н.А. Клиническая характеристика и эффективность антидепрессивной терапии аффективных расстройств при коморбидности с алкогольной зависимостью. *Бюллетень сибирской медицины.* 2021; 20 (2): 79–87. https://doi.org/10.20538/1682-0363-2021-2-79-87.

INTRODUCTION

In the current concept of comorbidity of alcohol use disorder (AUD) and mood disorders (MD), co-occurrence of two pathologies is regarded as a synergetic condition, unfavorable for prognosis of each of them [1, 2]. Taking into account the polymorphism of psychopathological symptoms, a personalized therapeutic approach is needed, focused not only on the correction of emotional disturbances but also on the anti-craving therapy for the dependence syndrome.

Among the main factors influencing formation of alcohol addiction and unfavorable prognosis of its course, comorbid mental disorders, primarily of the schizophrenia and affective spectrum, are distinguished [3–6]. In both cases, comorbidity leads to worsening of the disease prognosis [7, 8]. In clinical practice, the comorbidity of MD and AUD is often unrecognized – this can be associated with clinical pathomorphism, when a combination of severe disturbances in one disease and obliterated manifestations of the other often look like manifestations of the first, and the second disorder is either overlooked or ignored [9, 10].

The choice of only one of the existing psychiatric disorders as a therapeutic target negatively affects the effectiveness of therapy, increases its duration, and reduces the duration and quality of remissions. It is important to determine the clinical features and identify suicidal behavior in patients with MD in comorbid mental and somatic diseases [11–13].

MATERIALS AND METHODS

The study included 88 patients admitted to the clinic of Mental Health Research Institute of Tomsk NRMC with a verified diagnosis of AUD (F10.2) or MD (F31.3, F31.6, F32, F33, F34.1) according to ICD-10. Clinical-psychopathological, psychometric, clinical-dynamic, and statistical research methods were used. To evaluate the clinical dynamics, a structured interview for evaluation of depression severity according to HARS (1959) and SIGH-SAD (2002) was used. A risk of alcohol addiction was evaluated according to the Alcohol Use Disorders Identification Test (AUDIT, 1993). The Obsessive Compulsive Drinking Scale (OCDS, 1995) was applied to assess alcohol craving.

Statistical data processing was performed using IBM SPSS Statistics 25 software with the Pearson's χ 2 test, Mann – Whitney *U*-test (for comparison of independent samples), Kruskal – Wallis test (for more than two independent samples), and Wilcoxon test (for comparison of dependent samples). The samples were previously tested for compliance with the law of normal distribution using the Shapiro – Wilk test, which tests the hypothesis that there are no differences between the observed distribution of a trait and the theoretically expected normal distribution. In case of distribution other than normal, quantitative data were presented as the median and the interquartile range *Me* (*Q1*; *Q3*). When testing the hypothesis, the critical level of significance *p* was equal to 0.05.

RESULTS

According to the results of the examination, the patients were divided into three groups. The first group included AUD patients without comorbid affective symptoms (n = 31), 87.1% of them were males, the average age of patients in this group was 44 (40; 53) years. The second group contained MD patients without alcohol addiction (n = 29), 72.4% of whom were females, the average age of patients was 50 (36.5; 57) years. The third group included patients with AUD and comorbid MD (n = 28), among whom 71.4% were males, the average age was 44.5 (36.5; 48.75) years. We did not reveal statistically significant differences

between the groups according to the gender – age composition ($p > 0.05$, Pearson's χ 2 test). The structure of MD in the group without comorbid dependence syndrome was represented by depressive episodes (DE) of various degrees of severity in 34.5% of patients, DE within a recurrent depressive disorder in 31% of individuals, and DE within bipolar disorder (BD) in 24.1% of cases. The comorbid affective pathology was represented equally by dysthymia and DE within a recurrent depressive disorder (32.1% each). Depressive symptoms within BD were revealed in 21.4% of cases. In 14.3% of cases, the comorbid diagnosis was DE of moderate (10.7%) or mild (3.6%) severity. The duration of MD was 5 (2.5; 11.0) years in the group of patients with affective pathology alone and 7.5 (2.25; 13.0) years in patients with a comorbidity ($p < 0.05$, Mann – Whitney *U*-test). The duration of AUD (since the age of formation of the alcohol withdrawal syndrome (AWS)) in the groups with AUD alone and AUD and a comorbidity was 10 (6; 18.5) and 14 (10; 19.75) years, respectively ($p < 0.05$, Mann – Whitney *U*-test).

Based on these terms for disease duration, it can be concluded that in the group with MD with comorbid AUD, substance dependence, as a rule, preceded the MD manifestation. Alcohol use in both groups had a pseudo-binge-drinking nature in 100% of observations. Besides, it is worth noting that the duration of pseudo-binge-drinking and alcohol tolerance were statistically significantly lower in patients with MD and AUD ($p < 0.05$, Mann – Whitney *U*-test). So, the average duration of pseudo-binge-drinking episodes in patients with MD alone was 7 (4; 17) days, and in patients with MD with a comorbidity – 5.5 (3.5; 9.5) days. The tolerance was 16 (11; 23) and 11 (11; 17.75) standard alcohol servings, respectively.

Despite relatively lower volume and duration of alcohol use by patients with dual diagnosis, the duration of AWS was compatible to that in patients with AUD alone: 3 (2; 4) and 3 (2; 5) days, respectively ($p = 0.785$, Mann – Whitney *U*-test). These data indicate poorer tolerance of ethanol effects in patients with MD with comorbid AUD. In the group of patients with MD with comorbid AUD, attention is drawn to the predominance, along with neurovegetative variant of AWS in 78.6% ($n = 22$) of observations, of the psychopathological variant – 14.3% ($n = 4$), which manifested itself predominantly through affective symptoms (depressive, anxious, dysphoric affect). In the group with AUD alone, the second most prevalent variant after the neurovegetative one (83.9%, $n = 26$) was the cerebral variant of AWS (9.7%, $n = 3$), which manifested itself predominantly through cephalgia, dizziness, and muscle twitching. After AWS management, affective disturbances in patients with MD with comorbid AUD not only remained, but also acquired apparent clinical presentation.

The main motive for alcohol consumption was the desire for pleasure in the AUD group: hedonistic motivation was observed in 45.2% ($n = 14$) of cases, while in patients with a comorbidity, it was present only in 10.7% ($n = 3$) of individuals. Half of the patients with comorbid MD used alcohol with the aim to correct the emotional state – 50% ($n = 14$), and among patients with AUD alone, there were 9.6% of such patients ($n = 3$). The duration of AUD remissions in patients with a comorbidity reached 12 (3; 24) months, while with comorbid MD, it was 6 (1.25; 34.5) months ($p = 0.037$, Mann – Whitney *U*-test). In cases of MD alone and comorbid MD, these values were 5 (3; 21.75) and 4 (1; 12) months, respectively ($p = 0.048$, Mann – Whitney *U*-test). All patients with a comorbidity noted a pronounced relationship between MD remission and AUD, that is, the cessation of alcohol use led to normalization of the emotional state, and stable emotional background reduced alcohol consumption to a minimum. In this cohort, in 46% ($n = 13$) of cases, failure to achieve AUD remission was preceded by an increase in MD symptoms, and in 32% ($n = 9$) of patients – by resumed alcohol use. Symptoms of both disorders developed simultaneously in 22% ($n = 6$) of the respondents.

Based on the complaints presented by the patient at the time of the initial examination (during the 1st week of hospitalization, after AWS management, in case of seeking medical care in AWS), the leading complaints were identified that characterize the patient's subjective assessment of the condition and determine the therapeutic request when seeking medical care (Table 1).

Table 1

Complaints of the examined patients upon admission

Parameter	Patients with AUD	Patients with MD	Patients with dual diagnosis
Alcohol craving	75.8% ($n = 23$)	–	–
Low mood	16.2% ($n = 5$)	51.7% ($n = 15$)	78.6% ($n = 22$)
Emotional lability, irritability, hot temper	–	10.4% ($n = 3$)	10.7% ($n = 3$)
Anxiety, feeling of inner tension	1.6% ($n = 1$)	37.9% ($n = 11$)	7.1% ($n = 2$)
Anergy, fatigue, asthenia	6.4% ($n = 2$)	–	3.6% ($n = 1$)

Probably, depressive symptoms (decreased mood) in the group of AUD patients were revealed as an obligate component of post-withdrawal syndrome as well as an emotional component of pathological alcohol craving [14]. Asthenic symptoms (anergy, fatigue, asthenia) in both groups of patients who used alcohol could be associated with immediate toxic effect of ethanol on the central nervous system (CNS) [15]. It is worth noting that the patients with AUD with comorbid MD had complaints of the affective spectrum, that is they named correction of the emotional state as the reason for seeking medical care, which, in their opinion, led to excessive alcohol use.

In accordance with the clinical presentation and the leading symptoms, the patients received psychopharmacotherapy with antidepressants and mood stabilizers (Table 2).

Table 2

The main group of psychopharmaceuticals			
Parameter	Antidepressants	Mood stabilizers	No therapy
Patients with AUD	22.5% (n = 7)	64.5% (n = 20)	13% (n = 4)
Patients with MD	79.3% (n = 23)	20.7% (n = 6)	–
Patients with dual diagnosis	60.7% (n = 17)	35.7% (n = 10)	3.6% (n = 1)

For the patients hospitalized in the state of withdrawal, the treatment was administered after management of the withdrawal syndrome, on the 3–5th day of hospitalization. In the groups of AUD patients, there were cases with no maintenance psychopharmacotherapy, which was associated with contraindications to its administration due to comorbid physical pathology. In such a situation, the treatment was focused on symptomatic and psychotherapeutic correction. The patients with AUD were treated with escitalopram (15 mg / day) in 71.4% (n = 5) of cases and agomelatine (25 mg / day) in the remaining 28.6% (n = 2) of cases. Treatment with these drugs cured sleep disorders induced by alcohol dependence, did not affect the parameters of cardiovascular therapy, and did not impair sexual functions. As an alternative to antidepressant therapy, 75.0% (n = 15) of patients were prescribed carbamazepine (400 mg / day), and the remaining 25.0% (n = 5) – topiramate (100 mg / day).

Treatment of patients with MD in 47.8% (n = 11) of cases was carried out with vortioxetine (10 mg/ day), in 21.7% (n = 5) of cases – with sertraline (150 mg / day), in 21.7% (n = 5) of cases – with escitalopram (25 mg / day), in 8.8% (n = 2) of cases – with agomelatine (25 mg / day). The preferential treatment with these modern drugs had high potential for relieving the main symptoms of depression with their excellent tolerance. An alternative strategy for correcting affective disorders in the context of bipolar disorder was the administration of valproic acid sodium salts (750 mg / day) in all cases (n = 6).

The patients with a dual diagnosis received vortioxetine (10 mg / day) in 41.2% (n = 7) of cases, agomelatine (50 mg / day) in 23.6% (n = 4) of cases, escitalopram (25 mg / day) in 17.6% (n = 3) of cases, and sertraline (100 mg / day) in 17.6% (n = 3) of cases. The multi-target and highly selective mechanisms of action of these drugs influenced anhedonia, one of the key symptoms of depressive and addictive disorders, which was associated with suicidal behavior in these patients. Another part of the patients received treatment with carbamazepine (400 mg / day) in 70.0% (n = 7) of cases or valproic acid sodium salts (500 mg / day) in 30.0% (n = 3) of cases to correct affective disorders.

According to the follow-up data, after previous visits for medical care, the majority of patients (68.9%, n = 18), suffering only from affective pathology, received maintenance psychopharmacotherapy. In 62% (n = 18) of cases, it was a drug from the group of selective serotonin reuptake inhibitors (SSRIs): sertraline (n = 8, 100 mg / day), escitalopram (n = 5, 20 mg / day), fluvoxamine (n = 3, 150 g / day), fluoxetine (n = 2, 40 mg / day). 6.9% (n = 2) of patients received a mood stabilizer (valproic acid, 500 mg / day). The average duration of drug intake was 6 (3; 12) months (p = 0.04, Pearson's χ 2 test).

Among the patients with depression associated with AUD, only 21.5% (n = 6) of the respondents received maintenance therapy. The drug from the SSRI group was taken by 17.9% (n = 5) of patients: escitalopram (n = 3, 10 mg / day), sertraline (n = 2, 50 mg / day); 3.6% (n = 1) of patients received a mood stabilizer (carbamazepine, 400 mg / day). The period of independent intake of drugs was 3 (2; 11.25) months (p = 0.03; Pearson's χ 2 test). The presented data indicate low adherence of patients suffering from AUD (both alone and in combination with another pathology) to long-term treatment. Patients do not always follow medical recommendations and tend to stop taking medications earlier than the recommended time [16].

The examined individuals from the group of AUD patients in 98.4% of cases did not receive any maintenance therapy: either the drug was not prescribed by the doctor, or the patients themselves refused to take drugs after discharge from the clinic. Despite the fact that administration of antidepressants is considered to

be the therapy of choice for depressive disorders in the structure of the pathological alcohol craving and suppression of the pathological craving for substances is their independent property, regardless of manifestation of the antidepressant effect, addiction specialists rarely resorted to prescribing antidepressant psychopharmacotherapy [17]. Anticonvulsants, actively used by doctors in substance abuse treatment centers, represent an alternative for benzodiazepine tranquilizers for correction of AWS [18]. However, there are no recommendations on their use in anti-craving therapy for alcohol dependence. Most of the requests for drug treatment ended with implementation of one or another type of subject-mediated hypnosuggestion of a ban on alcohol consumption. Such prevalent techniques as aversion therapy, implanting chemicals under patient's skin, and implanting an anti-alcohol placebo-drug are now an officially recognized anachronism prohibited in state institutions and not included in the Standards for the Provision of Primary Health Care and Specialized Narcological Aid [19, 20].

The examinations carried out upon admission (point 1) and discharge (point 2) using the SIGH-SAD and HARS scales made it possible to objectively assess the severity of depressive (typical and atypical) and anxiety symptoms (Kruskal – Wallis test), and their clinical dynamics (Wilcoxon test) (Tables 3–4).

Table 3

Dynamics of the score on the SIGH-SAD scale

Parameter	Typical symptoms		Atypical symptoms		Total score	
	Point 1	Point 2	Point 1	Point 2	Point 1	Point 2
Patients with AUD	7.0 (3.0; 12.3)*	1.0 (0; 4.0)	2.0 (0; 2.3)*	0 (0; 0)	9.0 (4.0; 14.3)**	1.0 (0; 4.0)
Patients with MD	23.0 (19.5; 29.0)	6.0 (3.5; 11.0)	4.0 (1.0; 7.5)	1.0 (0; 2.0)	27.0 (21.0; 36.0)	6.0 (5.0; 11.0)
Patients with a dual diagnosis	20.0 (16.0; 25.8)	7.0 (4.0; 10.0)	4.0 (1.0; 6.0)	2.0 (0.5; 4.2)	24.0 (18.3; 33.0)**	9.0 (4.3; 12.0)

* $p = 0.001$ (Kruskal – Wallis test) for all cases, ** $p = 0.001$ (Wilcoxon test) for all cases.

Table 4

Dynamics of the score on the HARS scale

Parameter	Point 1	Point 2
Patients with AUD	8.0 (3.8; 14.3)* (**)	1.0 (0; 2.0)
Patients with MD	21.0 (14.0; 29.0)**	5.0 (3; 10.5)
Patients with a dual diagnosis	20.5 (12.5; 25.0)**	5.5 (3.3; 8.0)

* $p = 0.001$ (Kruskal – Wallis test) for all cases, ** $p = 0.001$ (Wilcoxon test) for all cases.

At the 1st week of treatment, patients in the group with MD alone noted greater severity of both typical and atypical depressive symptoms on the SIGH-SAD scale, as well as anxiety on the HARS scale, compared to the group of patients with a dual diagnosis ($n = 0.046$; Mann – Whitney U-test for SIGH-SAD and $p = 0.082$ for HARS). The levels of anxiety and depression in patients with AUD alone were initially significantly lower than in the other groups ($p = 0.001$; Kruskal – Wallis test for HARS and SIGH-SAD) and were probably detected within the affective component of AWS.

Against the background of psychopharmacotherapy, by the end of the treatment, there was a decrease in the intensity of affective symptoms in the groups of patients with MD ($p = 0.001$; Wilcoxon test) (with and without a comorbidity) to statistically comparable values ($p = 0.683$; Mann – Whitney U-test for SIGH-SAD and $p = 0.825$; Mann – Whitney U-test for HARS), and there were significant intergroup differences compared to the group of patients with AUD alone ($p = 0.001$; Kruskal – Wallis test). Therefore, patients with a dual diagnosis demonstrated comparatively worse dynamics in the reduction of depressive (both typical and atypical symptoms) and anxiety symptoms during treatment with initially lower rates compared to patients with depression alone.

The AUDIT and OCDS scales allowed to assess the subjective severity of AUD. The AUDIT test was developed by the World Health Organization for screening assessment of alcohol use disorders [21]. The sum of the AUDIT scores in the group of patients with AUD alone was 24 (19; 28.25). In AUD with comorbid MD, this score was higher – 26.5 (20.5; 30.5) ($p = 0.03$; Mann – Whitney U-test). In other words, the patients with AUD with comorbid MD showed a tendency to more active alcohol use, as well as a higher risk of adverse events from alcohol abuse.

The OCDS scale is designed for self-assessment of manifestations of attitudes towards alcohol over the past week. According to OCDS scores, alcohol craving was higher at both points of examination in the group with a dual diagnosis (31.5 (16.3; 43.5) and 8 (2.3; 14.8), respectively) than in the group of patients with AUD alone (29.5 (21.8; 37.0) and 7 (3.0; 11.3), respectively) (upon admission – $p = 0.058$; Mann – Whitney *U*-test, upon discharge – $p = 0.04$; Mann – Whitney *U*-test, intragroup dynamics – $p = 0.001$; Wilcoxon test). The analysis of the results of the study following the OCDS and AUDIT tests showed that alcohol addiction with a comorbid affective pathology was characterized by a more malignant clinical course. Pathological alcohol craving was more pronounced and less responsive to therapy, and alcohol consumption was characterized by a more pronounced risk of developing disorders associated with alcohol abuse.

DISCUSSION

Earlier, clinical polymorphism and features of therapy for MD with comorbid AUD were repeatedly pointed out [22–27]. At the same time, there is no consensus regarding the clinical effect of comorbidity on the course of each disease. According to some Russian researchers, AUD, as a rule, accompanies minor depressive disorders, and with an increase in MD, alcohol abuse may stop altogether [28]. Depressions in AUD are often described as "disharmonious", with a large proportion of asthenic-apathetic or dysphoric symptoms [29]. The results of the study also showed that the clinical presentation of MD with comorbid AUD is characterized by lower clinical severity of MD symptoms (according to the SIGH-SAD and HARS scales) compared to the group of patients with affective pathology alone, but by worse dynamics against the background of psychopharmacotherapy.

The commonality of the neurochemical mechanisms in the pathogenesis of the pathological alcohol craving and depressive disorders determines the dependence of actualization or regression of craving on the severity of affective symptoms [30]. Alcohol craving in comorbid patients is much stronger than in the group with AUD alone (according to OCDS). Probably, this should be considered not only as patient's perception of alcohol as a "therapeutic" means for self-treatment to correct the emotional state or reduce side effects of psychopharmacological drugs [31], but also as interest in the formation of symptoms of a wide range of neurotransmitter systems [32]. Such pathogenetic affinity of MD and craving explains its relative persistence in the group of patients with MD with comorbid AUD (according to OCDS), which leads to the conclusion that it is necessary to intensify anti-craving therapy for this cohort of patients.

CONCLUSION

It was found that patients with a dual diagnosis demonstrate the worst dynamics in terms of reduction of depressive (both typical and atypical symptoms) and anxiety symptoms during treatment, with initially lower values compared to the group of patients suffering from depression alone. AUD with comorbid MD is characterized by greater malignancy and worse antidepressant effect during psychopharmacotherapy. In the treatment of AUD, both alone and with a comorbidity, clinicians pay insufficient attention to anti-craving pharmacotherapy with antidepressants.

REFERENCES

1. Roshchina O.V., Rozin A.I., Schastnyy E.D., Bokhan N.A. Clinical value of comorbidity of affective disorders and alcohol dependence. *Bulletin of Siberian Medicine*. 2019; 18 (4): 110–118 (in Russ.). DOI: 10.20538/1682-0363-2019-4-110–118.
2. Vasilieva S.N., Simutkin G.G., Schastnyy E.D., Bokhan N.A. Clinical-dynamic features of affective disorders comorbid with alcohol dependence. *International Journal of Mental Health and Addiction*. 2020. DOI: 10.1007/s11469-020-00234-y.
3. Shytov E.A., Kiselev D.N., Shustov D.I. Comorbidity of mental disorders with alcohol and drug abuse (revue of the problem dual diagnose). *I.P. Pavlov Russian Medical Biological Herald*. 2009; 17 (2): 100–105 (in Russ.).
4. Marusin A.V., Kornetov A.N., Swarovskaya M.G., Vagaitseva K.V. Pavlenyuk E.S., Stepanov V.A. Genetic predisposition to alcoholism, schizophrenia and Alzheimer's disease with psychodiagnostic characteristics in Russian population. *Bulletin of Siberian Medicine*. 2016; 15 (5): 83–96 (in Russ.).
5. Voevodin I.V., Mandel A.I., Abolonin A.F., Belokrylov I.I. Psychological risk factors and variants of addictive, anxiety, and depressive disorders formation among the students. *Siberian Herald of Psychiatry and Addiction Psychiatry*. 2018; 4 (101): 21–27 (in Russ.). DOI: 10.26617/1810-3111-2018-4 (101)-21-27.
6. Andryuschenko A.V., Shulyak Yu.A. Alcohol addiction and depression: approaches to diagnostics and therapy. *Medical Council*. 2016; 19: 28–36 (in Russ.). DOI: 10.21518/2079-701X-2016-19-28-36.
7. Moggi F. Epidemiology, etiology and treatment of patients with psychosis and co-morbid substance use disorder. *Therapeutische Umschau*. 2018; 75 (1): 37–43. DOI: 10.1024/0040-5930/a000964.
8. Grazioli V.S., Bagge C.L., Studer J., Bertholet N., Rougemont-Bücking A., Mohler-Kuo M., Daeppen J.B., Gmel G. Depressive symptoms, alcohol use and coping drinking mo-

tives: Examining various pathways to suicide attempts among young men. *Journal of Affective Disorders*. 2018; 232: 243–251. DOI: 10.1016/j.jad.2018.02.028.
9. Fein G. Psychiatric comorbidity in alcohol dependence. *Neuropsychology Review*. 2015; 25 (4): 456–475. DOI: 10.1007/s11065-015-9304-y.
10. Turner S., Mota N., Bolton J., Sareen J. Self-medication with alcohol or drugs for mood and anxiety disorders: a narrative review of the epidemiological literature. *Depression and Anxiety*. 2018; 35 (9): 851–860. DOI: 10.1002/da.22771.
11. Lebedeva E.V., Simutkin G.G., Schastnyy E.D., Repin A.N., Sergienko T.N. Particularly disturbing, depressive disorders and suicidal behavior in patients of elderly and senile age with chronic CAD. *Suicidology*. 2014; 5 (5): 69–76 (in Russ.).
12. Vasilieva S.N., Simutkin G.G., Schastnyy E.D., Ivanova S.A., Bokhan N.A. Suicidal behavior of patients suffering from bipolar affective disorder and comorbid mental diseases. *Suicidology*. 2018; 9 (3): 86–92 (in Russ.). DOI: 10.32878/suiciderus.18-09-03(32)-86-92.
13. Lebedeva E.V., Schastnyy E.D., Simutkin G.G., Repin A.N., Nonka T.G. Clinical description of affective disorders and efficiency of antidepressant therapy. *Bulletin of Siberian Medicine*. 2018; 17 (4): 85–93 (in Russ.). DOI: 10.20538/1682-0363-2018-4-85–93.
14. Buzik O.J., Agibalova T.V. Comorbid diseases in alcohol-dependent patients. *I.P. Pavlov Russian Medical Biological Herald*. 2008; 3: 79–86 (in Russ.).
15. Samushia M.A. Monograph review by Bokhan N.A., Korobitsina T.V. "Associated forms of alcoholism in general hospital network". *Mental Disorders in General Medicine*. 2008; 02: 45–47 (in Russ.).
16. Salmina-Khvostova O.I., Zyablitsev D.V. The significance of motivation, stages of readiness to behavior changes, factors of compliance to treatment of alcohol addiction. *Russian Medical Journal*. 2013; 4: 22–25 (in Russ.).
17. Agibalova T.V., Altshuler V.B., Vinnikova M.A., Dudko T.N., Kozyreva A.V., Kravchenko S.L., Nenastieva A.Yu., Utkin S.I. Federal clinical guidelines for the diagnosis and treatment of addiction syndrome. *RSP*. 2014; 57 (in Russ.).
18. Sivolap Yu.P. Alcohol abuse and related disorders treatment of alcohol dependence. *Neurology, Neuropsychiatry, Psychosomatics*. 2014; 3: 7–9 (in Russ.). DOI: 10.14412/2074-2711-2014-3-4-9.
19. Artemyeva M.S., Maydan A.V. Comparative analysis of modern alcoholism treatment concepts. *Health and Education Millennium*. 2017; 19 (9): 19–21 (in Russ.).
20. Krupitsky E.M. Short-term intensive psychotherapeutic narcologic influence as viewed from positions of evidence-based medicine. *Neurological Bulletin*. 2010; 3: 25–27 (in Russ.).
21. Nenastieva A.Yu. Psychometric scales used in modern clinical addiction medicine. *Journal of Addiction Problems*. 2018; 7 (16): 46–71 (in Russ.).
22. Carton L., Pignon B., Baguet A., Benradia I., Roelandt J.L., Vaiva G., Thomas P., Amad Ali., De Philippe T., Naassila M., Geoffroy P.A., Rolland B. Influence of comorbid alcohol use disorders on the clinical patterns of major depressive disorder: a general population-based study. *Drug and Alcohol Dependence*. 2018; 187: 40–47. DOI: 10.1016/j.drugalcdep.2018.02.009.
23. Claycomb E.M., Charak R., Durham T.A., Armour C., Ly C., Southwick S.M., Elhai J.D., Pietrzakde R.H. The 7-factor hybrid model of DSM-5 PTSD symptoms and alcohol consumption and consequences in a national sample of trauma-exposed veterans. *Journal of Anxiety Disorders*. 2017; 51: 14–21. DOI: 10.1016/j.janxdis.2017.08.001.
24. Destoop M., Morrens M., Coppens V., Dom G. Addiction, Anhedonia, and Comorbid Mood Disorder. A Narrative Review. *Frontiers in Psychiatry*. 2019; 10: 311. DOI: 10.3389/fpsyt.2019.00311.
25. Elsayed N.M., Kim M.J., Fields K.M., Olvera R.L., Hariri A.R., Williamson D.E. Trajectories of alcohol initiation and use during adolescence: the role of stress and amygdala reactivity. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2018; 57 (8): 550–560. DOI: 10.1016/j.jaac.2018.05.011.
26. Blum K., Gondre-Lewis M.C., Baron D., Thanos P.K., Braverman E.R., Neary J., Elman I., Badgaiyan R.D. Introducing precision addiction management of reward deficiency syndrome, the construct that underpins all addictive behaviors. *Frontiers in Psychiatry*. 2018; 9: 548. DOI: 10.3389/fpsyt.2018.00548.
27. Wiener C.D., Moreira F.P., Zago A., Souza L.M., Branco J.C., Oliveira J.F., Silva R.A.D., Portela L.V., Lara D.R., Jansen K., Oses J.P. Mood disorder, anxiety, and suicide risk among subjects with alcohol abuse and/or dependence: a population-based study. *Brazilian Journal of Psychiatry*. 2018; 40 (1): 1–5. DOI: 10.1590/1516-4446-2016-2170.
28. Gofman A.G., Oyfe I.A. Alcoholism and endogenous depression; ed. Smulevich A.B. In: Depression and comorbid disorders. Moscow, 1997: 124–136 (in Russ.).
29. Ponizovsky P.A., Gofman A.G. Depression in patients with alcohol dependence. *Korsakov Journal of Neurology and Psychiatry*. 2015; 115 (7): 146–150 (in Russ.).
30. Rozin A.I., Roshchina O.V., Peshkovskaya A.G., Belokrylov I.I. Comorbid combinations of alcohol dependence and depressive disorders. *Siberian Herald of Psychiatry and Addiction Psychiatry*. 2018; 4 (101): 40–45 (in Russ.). DOI: 10.26617/1810-3111-2018-4(101)-40-45.
31. Cooper S., Robison A.J., Mazei-Robison M.S. Reward circuitry in addiction. *Neurotherapeutics*. 2017; 14 (3): 687–697. DOI: 10.1007/s13311-017-0525-z.
32. Mendelevich V.D. Addiction syndrome: evidence-based therapy. *Narcology*. 2014; 8: 94–103 (in Russ.).

Authors contribution

Roshchina O.V., Rozin A.I. – carrying out of the research, statistical analysis and interpretation of data. Schastnyy E.D. – critical revision for important intellectual content. Bokhan N.A. – final approval of the manuscript for publication.

Authors information

Roshchina Olga V., Junior Researcher, Affective States Department, Mental Health Research Institute, Tomsk NRMC, Tomsk, Russian Federation. ORCID 0000-0002-2246-7045.

Rozin Alexander I., Cand. Sci. (Med.), Psychiatrist, Addictive States Department, Mental Health Research Institute, Tomsk NRMC, Tomsk, Russian Federation. ORCID 0000-0001-8617-4754.

Schastnyy Evgeny D., Dr. Sci. (Med.), Professor, Head of the Affective States Department, Mental Health Research Institute, Tomsk NRMC, Tomsk, Russian Federation. ORCID 0000-0003-2148-297X.

Bokhan Nikolay A., Dr. Sci. (Med.), Professor, Academician of RAS, Head of the Mental Health Research Institute, Tomsk NRMC, Head of the Department of Psychiatry, Narcology, and Psychotherapy, Siberian State Medical University, Tomsk, Russian Federation. ORCID 0000-0002-1052-855X.

(✉) **Schastnyy Evgeny D.,** e-mail: evgeny.schastnyy@gmail.com.

Received 29.02.2020
Accepted 29.09.2020