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THE ROLE OF NEUROENDOCRINE FACTORS IN THE FORMATION OF ALCOHOL DEPENDENCE AND HUMAN ECOLOGY IN VARIOUS ETHNIC POPULATIONS, NEW APPROACHES TO THERAPY

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Given the biological vulnerability of indigenous peoples to the effects of alcohol and the significant impact of environmental and ethnocultural factors on the clinical and dynamic characteristics of alcohol dependence in people of indigenous nationalities, integrated approaches were used - clinical and clinical-biological in conducting studies to study the disorders caused by alcohol use in people of various ethnicity, which is important for determining effective treatment strategies. The study examined the clinical and dynamic features of the formation and course of alcohol dependence in individuals of Tuvan ethnicity - representatives of the indigenous population of Siberia, especially neuroendocrine metabolism in these patients in comparison with patients of Russian nationality. The therapeutic efficacy of the original anticonvulsant halodif was assessed for the severity of the symptom of alcohol withdrawal syndrome (AAS) and the levels of neuroactive hormones: cortisol and progesterone in the blood of the examined patients. It has been established that the course of alcohol dependence among representatives of the Tuvan ethnic group acquires a highly prodigious character, which indicates a greater vulnerability of representatives of the native Tuvan ethnic group to the effects of alcohol. The index of the ratio of cortisol/progesterone of examined patients with alcoholism of Russian nationality is almost double the index of healthy donors, in patients of Tuvan ethnicity it is almost five times higher than the index of healthy examined persons. The revealed change in the levels of neuroactive hormones and the index of their ratios serves as a prognostic marker in the treatment and rehabilitation of patients, which seems significant in relation to the therapy and rehabilitation of patients of Tuvan nationality, in which hormone levels and their balance largely reflect the severity of the disease compared with Russian patients nationality. The use of the anticonvulsant halodif in basic therapy leads to a dynamic decrease in the total number of points on the Hamilton scale, significantly reduces the level of cortisol and stimulates an increase in progesterone levels, changing the balance of the ratio of hormone levels, closer to that in healthy donors. The ongoing psychopharmacotherapy is pathogenetically directed and increases the effectiveness of treatment, prevents the development of relapse and the progressive dynamics of alcohol dependence, which is especially important for human ecology in the Tuvan ethnic group and, possibly, other populations of the indigenous peoples of the North, Siberia and the Far East.

Keywords: ecology, ethnos, alcohol, addiction, pharmacotherapy, endocrine factors, hormone.

Introduction. In recent decades, considerable attention has been paid to the problem of alcohol consumption and the formation of alcohol dependence among the indigenous ethnic populations of the peoples of the North, Siberia and the Far East. Traditional communities of indigenous northerners in their history of existence have developed specific forms of practice of psychotherapeutic correction - holidays and rituals associated w ith shamanism. The desire for alcohol in people in ethnic populations is often due to the desire to get rid of mental discomfort, to relieve emotional stress caused by the stressful situation associated with a change in the original lifestyle. It is known that representatives of indigenous peoples face the most detrimental consequences of drinking alcohol and have an increased rate of formation of dependence [1, 5, 6]. The individual sensitivity of a person to psychoactive substances includes the effects of ethanol, defined as the possibility of adequate adaptive reactions that are controlled by genetic, social and sociocultural factors in general, reflecting collectively the common features of the human ecology in this population.

Human ecology is “a comprehensive science designed to study the laws of interaction between people and the environment, issues of population development, preservation and development of human health, improving the physical and mental capabilities of a person”, as defined by V.P. Kaznacheeva (1998) [3]. This science has a completely independent value, although it is based on biomedical research. Modern research indicates the biological vulnerability of indigenous populations to the effects of alcohol. In addition, the results of the studies indicate a significant effect of ethnocultural factors on the clinical and dynamic characteristics of alcohol dependence - people of indigenous nationalities have a certain peculiarity of the clinic and the course of alcoholism [1, 2, 4-6].

Integrated approaches - clinical and clinical-biological in conducting studies to study the disorders caused by alcohol consumption in people of different ethnic backgrounds, are important for determining effective treatment strategies. In this regard, additional studies are needed to identify the clinical and biological features and molecular targets that underlie alcohol-induced dependence. One of the predispositions of the formation of alcohol addiction is a violation of the balance of the processes of excitation and inhibition in the brain, leading to hyper-excitability of the central nervous system, which increases the risk of alcoholism [8,14,18]. Patients with alcoholism are distinguished by impulsivity, extravagant behavior and other disorders associated with this condition [2,9,12]. The effects caused by alcohol associated with changes in the nuclei of the thalamus and limbic regions of the brain lead to disruption of the synchronization processes in the thalamus, a change in the relationship of the functional parameters of the brain and individual differences in behavioral characteristics. An increase in the high-frequency β-activity recorded on the EEG in the deep layers of the frontal cortex of the brain causes the development of relapse in patients with alcoholism [7,8]. The descendants, whose parents were patients with alcoholism, revealed an increase in the fluctuations of beta and gamma frequencies [8]. Sleep disturbance associated with increased excitability due to a decrease in inhibition

processes in the brain caused by chronic alcoholization can play a role in the progression of alcoholism and can be a factor in relapse in these patients.

Alcohol addiction has a similar etiology to other neuropsychiatric disorders, often including dysfunction of the same brain neuronal networks and neurotransmitter systems [14]. The GABAA receptor (GABAAP), as the main mediator of the fast inhibitory effect in the central nervous system [13,16], is modulated by many exogenous compounds, including benzodiazepines (BDZ), barbiturates, alcohol, and endogenous steroids such as progesterone and its metabolites. This non-genomic interaction of neuroactive steroids with GABAAP causes anxiolytic and anticonvulsant effects [13,16,18]. Chronic alcohol consumption and alcohol withdrawal increase levels of cortisol, an anxiogenic neuroactive hormone associated with increased stress function. Dysfunction of GABAR in the brain underlies the pathogenesis of some neurological and mental disorders of a person: epilepsy, insomnia, anxiety, alcoholism and is associated with altered levels of some neuroactive steroids, such as progesterone and cortisol [7,12,15,17,18,21]. The homeostasis control system and the neuroendocrine system are closely connected with such a phenomenon as individual tolerance to alcohol and the level of alcohol dependence of a person, especially from some ethnic groups. Optimization of impaired homeostasis during (or after) acute or chronic ethanol consumption is provided by a specific modulation mechanism of endogenous neurosteroids, which may be a useful pharmacotherapeutic strategy in the fight against alcohol and alcohol abuse [2,10,11,20].

The general basis of the pathogenic mechanisms of epileptic paroxysms and disorders of β-oscillations in the brain associated with hyperactivity of the hypothalamic-pituitary-adrenal axis, causing compulsive craving for alcohol, were prerequisites for a clinical study of the therapeutic efficacy of the original drug galodif1 (a new, highly effective anticonvulsant meta-chloro- benzhydrylurea) and levels of steroid hormones progesterone and cortisol in the treatment of patients with alcoholism.

Purpose: to study the clinical and dynamic features of the formation and course of alcohol dependence in individuals of Tuvan ethnicity, to determine the role of neuroendocrine factors in the formation of alcohol dependence in various ethnic populations: Russians and Tuvans with the aim of further developing effective pathogenetically based therapy.

Materials and methods. During the study, the clinical and dynamic features of the formation and course of alcohol dependence in individuals of Tuvan ethnicity — representatives of the indigenous population of Siberia2, the features of neuroendocrine metabolism in these patients compared with patients of Russian nationality were studied. The therapeutic efficacy of the original anticonvulsant drug, galodif, was evaluated for the severity of the symptom of alcohol withdrawal syndrome (AAS) and the levels of the neuroactive hormones cortisol and progesterone in the blood of the examined patients. Clinical and biochemical studies in patients with alcoholism in withdrawal and postabstinence conditions were carried out in the addictive conditions department of clinics of the Scientific Research Institute of Mental Health of the Tomsk Scientific Research Center and in the Republican Tuberculosis Drug Dispensary, Republic of Tyva, Kyzyl. 68 patients with alcoholism from the Russian ethnic population living in the Tomsk Region and 67 patients from the Tuvan ethnic group were monitored; only men from 24 to 53 years old (mean age: 38.3 ± 8.9 years) with different levels were included in the survey alcohol consumption. The diagnosis of examined patients with alcoholism according to ICD-10 - code F10.201 and F10.202 - mental and behavioral disorders due to alcohol consumption, addiction syndrome, currently - abstinence. The type of course of alcoholism in the examined patients was progressive in nature. The control group included 20 healthy male volunteers (according to the standard set of clinical and laboratory tests). Clinical assessment of the condition of patients was carried out with the traditional clinical description, using clinical, psychopathological, clinical and dynamic methods at different stages of the therapy. Anticonvulsant galodif1 was used in accordance with the recommendations at a dose of 300 mg per day (100 mg x 3) during the course of therapy - 21 days in the post-withdrawal period with varying severity of affective disorders. Quantitative characteristics were evaluated according to Russian versions of HARS - Hamilton's: Anxiety scale and HDRS - Hamilton depression scale. Enzyme-linked immunosorbent assay kits were used to determine serum hormone levels in patients and volunteers. All patients and volunteers examined had no serious liver disease. Blood for the study was taken from the subjects in the morning on an empty stomach. The subjects were informed of the planned studies and agreed. Collected blood serum samples were immediately frozen and stored until analysis at –700 C in a freezer. To determine the levels of hormones (cortisol and progesterone), appropriate kits for enzyme-linked immunosorbent assay of hormones were used; in this work, kits from Bio-Rad were used. The principle of the method is universal; used to determine cortisol, progesterone. Statistical data processing was performed using the standard software "Statistika 10.0" for "Windows", using parametric and non-parametric criteria.

Research and discussion. In the course of the study, we established the clinical and dynamic features of the formation and course of alcohol dependence in persons of Tuvan ethnicity - representatives of the indigenous population of Siberia2. Alcohol dependence in patients of Tuvan nationality differs from alcohol dependence in patients of Russian nationality in a number of clinical and biomedical signs: the first sample of alcohol in Tuvans occurs on average at 18 years old (17.9 ± 2.0), which is much later than in Russians who are familiar with the effects of alcohol from adolescence (15.2 ± 3.0). The systematic consumption of alcoholic beverages develops among Tuvans in adulthood (35.1 ± 9.8), in contrast to Russian men who begin to drink systematically young (24.6 ± 5.9). Accordingly, signs of alcohol dependence in people of Tuvan nationality are formed several years (7-8) later than in Russians: a symptom of loss of quantitative control over use was detected in Tuvans at 36.9 ± 9.9 years, in Russian patients at 29 8 ± 7.5 years; the formation of withdrawal syndrome in Tuvans occurs at the age of 37.7 ± 8.4 years, unlike Russians, in whom the withdrawal syndrome develops on average at the age of 29.6 ± 6.0 years (the level of confidence in all respects is $p = 0.00002$ - $p = 0.00004$). This is due to the ethno-cultural characteristics of the living environment of the indigenous population of Tuva, as well as family and religious relations.

According to the results of the study, we noted that the symptoms of alcohol addiction in Tuvans are formed progressively - on average for 2-2.5 years of systematic drinking, which is on average twice as fast as in people of Russian nationality, and indicates a malignant type of formation of alcoholism. The formation of dependence among Tuvans during the development of psychotic alcoholism has a different dynamics. The onset of systematic alcohol consumption in this case occurs earlier in comparison with the nonpsychotic form (27.9 ± 6.9

years and 35.1 ± 9.8 years, respectively, at p = 0.0007), the main symptoms of the disease are the age of loss of quantitative control over consumption (31.6 ± 6.4), age of manifestation of amnestic forms of intoxication (32.5 ± 6.9), age of withdrawal syndrome (32.4 ± 6.7 and 37.7 ± 8.4 at p = 0.006) - are formed on average five years earlier (differences are significant at the level of p = 0.033; 0.045). According to the clinical and dynamic parameters, Tuvans with a psychotic form of alcoholism are approaching Russians with nonpsychotic alcoholism. Consequently, Tuvans, signs of the formation of alcoholism in which are similar to the age dynamics of the development of alcoholism in Russians (non-psychotic form), have an unfavorable prognosis of the development of the disease - a manifestation of psychotic disorders of 37.4 ± 7.8 years (psychotic alcoholism). Thus, Tuvans reliably later than the Russians first try, and also begin to drink alcohol systematically (35.1 ± 9.8 and 24.6 ± 5.9 years, respectively; p = 0.000007), addiction syndrome forms on average in 2- 2.5 years of systematic drinking, i.e. the course of alcohol dependence among representatives of the Tuvan ethnic group acquires a highly prodigious character, which indicates a greater vulnerability of representatives of the native Tuvan ethnic group to the effects of alcohol.

As you know, alcohol abuse and the formation of alcohol dependence is associated with the development of alcohol withdrawal syndrome (AAS) when alcohol is stopped. The development of AAS in patients with alcoholism is accompanied by an increase in anxiety, the occurrence of paroxysms, a compulsive state, increased convulsive activity, developed autonomic symptoms, and a stress reaction. According to the results of modern research, an "epileptogenic concept" of the occurrence of an unmotivated paroxysmal-compulsive craving for ethanol during the period of alcohol withdrawal was formed. Previously repeated "auras" and paroxysmally arising violent memories of pro-alcoholic content are designated as "flashbacks" - a paroxysmal burst of memories. This process can "ignite" and reach a generalized form of attraction with strong excitement, when the craving for alcohol is realized. The process of fomenting a limbic psychotic trigger reaction - a persistent change in the functional state (excitability) of certain areas of the brain - has been defined as "kindling". The Kindling model is considered in the structure of alcoholism as a chronic epileptiform activity, manifested at the behavioral level. With this course of the disease, the use of anticonvulsants is indicated in complex therapy; anticonvulsants pregabalin and carbamazepine are widely used, which are well tolerated by patients, but are imported pharmaceuticals.

The indications for prescribing the anticonvulsant galodif1 in the complex treatment of patients with alcoholism were the clinical manifestations of a pathological craving for alcohol with a distinctly periodic character, richly affective color and signs of paroxysmality. Galodif was prescribed at a dosage of 300 mg per day (100 mg x 3) in the withdrawal and post-withdrawal periods with varying degrees of severity of affective symptoms (compulsive, paroxysmal, dysthymic and dysphoric disorders), the duration of the course was 21 days. The clinical dynamics of the neurotropic toxic effects of ethanol in the structure of alcohol withdrawal syndrome (asthenia, cranialgia, cardialgia, dissomnia, autonomic-vascular and discoordinate-atactic disorders) were analyzed as a symptom-target complex for the pharmacotherapeutic effect of galodif: sedative, timoleptive and timoleptic effects were studied, as well as the effect of galodif on the primary pathological craving for alcohol. The study used the clinical and psychopathological method, the Hamilton anxiety and depression scale.

Our studies have shown that the therapeutic effect of the anticonvulsant galodif was associated with a decrease in the intensity of the ideator component of the pathological craving for alcohol in AAS, a weakening and / or disappearance of craving in the post-withdrawal state. The use of halodif (300 mg / day) in the basic therapy of patients in the withdrawal and post-withdrawal conditions had a normotoleptic effect on the dysphoric component of affective disorders (72.2%), on anxiety-phobic manifestations (50.0%), pronounced effect in sleep disturbance, "psycho-vestibular" dreams (85.7%); with local muscle-tonic hyperkinesis of the "krampi" type (60%); vegetative stabilizing effect in cardiovascular disorders with normalization of heart rate (66.7%) and relief of cardialgia (63.6%); marked effect on cephalgic and diencephalic disorders - a weakening of the intensity of the senestopathic and algic components of cephalgia (71.4%), relief of diencephalic paroxysms (57.1%); a decrease in the pathological craving for alcohol during withdrawal symptoms (88%) and post-withdrawal symptoms (57%); which was expressed in a 5-fold decrease in the total score on the Hamilton Depression Scale (HDRS), and a 6-fold decrease in the Hamilton anxiety scale (HARS) [Fig. one]. The greatest effect of the drug was expressed in patients with a compulsive spontaneous manifestation of a pathological craving for alcohol. The drug did not aggravate discoordinate-atactic manifestations in the structure of AAS and did not cause unwanted adverse reactions.

When conducting a comparative analysis of the levels of steroid hormones in patients with alcoholism and volunteers from the control group, it was found that the level of cortisol was significantly higher than the level of this hormone in the blood of patients with alcoholism, and these changes were significantly more pronounced in patients of the Tuvan ethnic group [Table 1, Fig. 2]. Affective disorders and alcoholism are associated with impaired hormonal metabolism and regulation of the negative feedback mechanism, according to which cortisol released from the adrenal glands inhibits the production of corticotropin-releasing hormone, as a result of which the content of adrenocorticotropic hormone and cortisol increases abnormally. In contrast, the progesterone (PG) content in the blood was significantly lower in

Fig. 1. Therapeutic efficacy of halodif, reduction in the severity of symptoms in% of cases

Table 1. Levels of the neuroactive hormones cortisol and progesterone in patients with alcoholism in various ethnic groups

Type of hormone/marker	Alcoholics Russian nat. (before treatment)	Alcoholics Russian nat. (21 days of therapy galodif)	The control group of the Russian nat. (healthy donors)	Alcoholics Tuvinian nat.
Cortisol (nmol/l)	661.32±108.12*	478.36±97.32	492.07±68.24y	875.00 ±79.54*
Progesterone (nmol/l)	2.66 ± 0.32*	4.28±0.63	4.00 ± 0.54	1.78 ± 0.23*
Index (IR) Cortisol / Progesterone	253.06*	114.44	126.05	499.02*
	n=68	n=66	n=20	n=67

*Уровень значимых различий P <0.005.

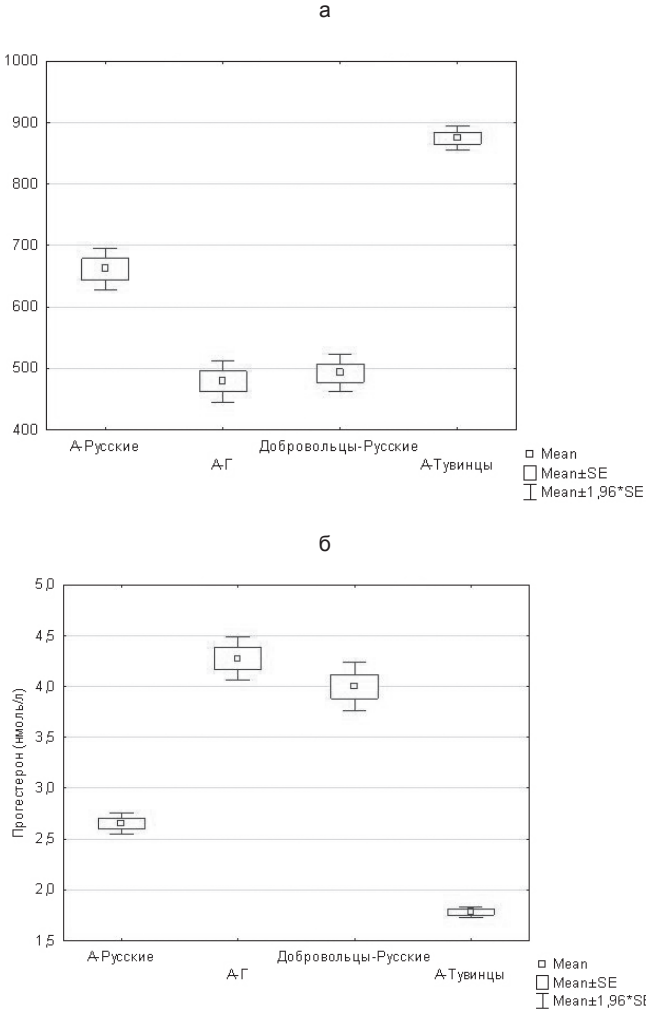

Fig. 2. Statistical analysis of cortisol hormone levels in patients with alcoholism in various ethnic groups
Groups:
A-Rus – Russian patients with alcoholism before treatment;
A+G – Russian patients with alcoholism after treatment with galodif
Volunters –Rus – healthy volunteers
A-Tuv – Tuvan alcoholics

patients compared with the concentration of this hormone in the control group, lower levels of PG were detected in Tuvinian patients [Table 1, Fig. 3]. PG is a precursor in the biosynthesis chain of pregnan, a neurosteroid that modulates GABAergic function in the nuclei of the thalamus and limbic system. PG and its metabolites have an antiglucocorticoid and neuroprotective effect, activates the recovery of myelin, which is especially important for neurotoxic and neurodegenerative lesions of the central nervous system [10,11]. A decrease in the level of PG and its metabolites leads to impaired neuroprotection. Our data indicate that alcohol abuse causes a change in the levels of cortisol and PG, as well as their balance - indices of the ratio of the concentrations of these hormones. The index of the ratio Cortisol / Progesterone (Index Ratio - IR) in the blood of examined patients with alcoholism of Russian nationality is almost twice as high as the IR index in the blood of examined healthy donors; in patients of Tuvan ethnicity, IR is almost five times higher than the IR index of healthy examined individuals [Table 1, Fig. 4]. This fact indicates an imbalance in the ratio of these hormones that regulate the human stress system, as a result of increased levels of cortisol and a decreased level of progesterone, a positive modulator of GABAA, the receptor neurotransmitter system. Moreover, patients of Tuvan ethnicity revealed significantly deeper shifts in the balance of the National Assembly, which are associated with a high risk of developing alcohol dependence and a highly progressive course of the disease.

The use of the original anticonvulsant Galodif (meta-chloro-benzhydrylurea) for 21 days at a dose of 300 mg per day in patients with alcoholism caused an induced decrease in symptoms characteristic of AAS. Galodif is safe for use in people with a relatively small number of side effects compared to other anticonvulsants, it has a detoxifying effect, stimulating the monooxygenase system of the liver [20], which is important in case of chronic alcohol intoxication. A dynamic decrease in the total Hamilton score (anxiety and depressive disorder) was faster in the studied patients. Halodif significantly reduced the level of cortisol and stimulated an increase in PG levels, changing the balance of the ratio of hormone levels, bringing the IR index closer to that in healthy donors [Table 1, Fig. 4].

Neuroactive steroid hormones are able to specifically modulate the function of the GABAergic neurotransmitter system of the brain. NS (progesterone and its metabolites) and drugs that have a positive modulating effect on GABAA - receptors that enhance the inhibitory function in the central nervous system, have anxiolytic, analgesic, anticonvulsant, sedative, hypnotic and anesthetic effects, reducing the severity of symptoms in AAS and the primary pathological attraction to ethanol.

In the light of the data obtained, the balance of the NS is considered by us as one of the factors of the pathogenetic mechanism of the development of alcoholism, and the use of galodif in the treatment of patients with alcoholism allows us to correct the levels of NS and their ratio. This leads to positive clinical dynamics, faster and more stable remission, and may be a prospect for the development of new approaches in the treatment of patients with alcoholism.

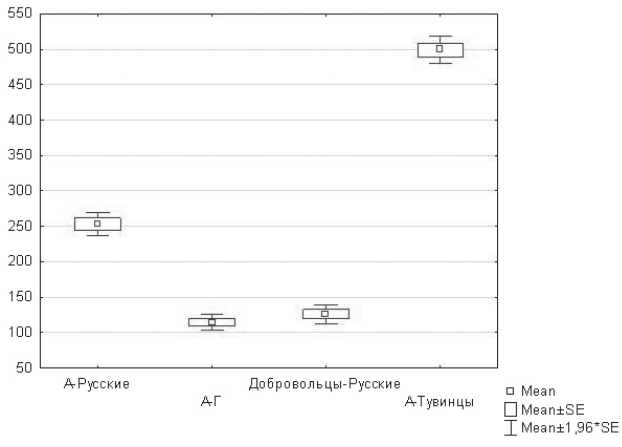

Fig. 4. Statistical analysis of Index Ratio (IR) cortisol/ progesterone in patients with alcoholism in various ethnic groups

Pharmacological drugs that modulate neurosteroid activity can exert clinical effects through their effect on the balance of neuroactive hormones. The development of new pharmaceuticals that affect the metabolism of endogenous NS, taking into account individual ethnic characteristics associated with deeper shifts in the balance of NS and creating a high risk of development and progressive dynamics of alcohol dependence, is one of the significant strategies in the treatment of mental disorders and alcoholism in patients in various ethnic populations.

Conclusion. Thus, based on the results of our work, it can be assumed that the detected change in the levels of NS and the index of their ratios serves as a prognostic marker in the treatment and rehabilitation of patients, which seems significant in relation to the treatment and rehabilitation of patients of Tuvan nationality, whose NS levels and their balance to a large extent reflect the severity of the course of the disease in comparison with patients of Russian nationality.

A study in the Addictive Clinic of the Mental Health Research Institute of Tomsk Scientific Research Center of the Russian Academy of Sciences allows recommending the use of the anticonvulsant galodif as a therapeutic and prophylactic agent in patients with alcoholism with compulsive and paroxysmal disorders associated with impaired levels of neuroactive hormones in various ethnic groups, especially those with sharp changes hormonal balance. Psychopharmacotherapy that corrects this condition is pathogenetically directed and increases the effectiveness of the treatment, prevents the recurrence of the disease and the progressive dynamics of alcohol dependence, which is especially important for human ecology in the Tuva ethnic group and, possibly, other populations of the indigenous peoples of the North, Siberia and the Far East.

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