World ▮ Cultural ▮ Psychiatry ▮ Research ▮ Review
OFFICIAL JOURNAL OF
WORLD ASSOCIATION OF CULTURAL PSYCHIATRY

Original Paper

Clinical-biological peculiarities and efficacy of therapy in alcohol patients of different ethnic groups in Siberia

Tamara V. Shushpanova, Valentin Ya. Semke†, Nikolay A. Bokhan

Abstract. ***Objective*** *Disturbances in exciting and inhibiting functions in brain can induce high nerve excitation laid down in basis of high risk of alcoholism. Alcoholism is associated with abnormal levels of certain neuroactive steroids: progesterone (PG) and cortisol (CS), more severe in different ethnic groups. Drugs that normalize levels of neurosteroid hormones (NS) are perspective in treating of alcohol abstinent patients.* ***Method*** *Clinical evaluation of state of patients was conducted with clinical-psychopathological and clinical-dynamic method. RIA kits from blood serum in examined persons measured assay of cortisol and progesterone before and after treatment with original anticonvulsant Galodif (meta-chlor-benzhydryl urea).* ***Results*** *Using Galodif during 21 days in dose 300 mg daily in alcoholic patients induced reduction of symptoms specific for alcohol withdrawal syndrome (AWS). Dynamic reduction of total scores of Hamilton scales for anxiety and depression was quicker in investigated patients. Galodif decreased level of CS on 138% and increased level of PG on 160%, making it means like in samples from healthy control group. Alterations levels of NS in alcoholic patients suggest the abruption regulation of NS as one of the mechanisms of development of compulsive craving for alcohol. Comparative study of NS levels in blood serum of alcoholic patients showed significant decrease the level of PG, compared with healthy donors; investigations levels of CS showed significant increase of alcoholic patients, especially in patients from Tuvinian ethnic group.* ***Conclusion*** *New approaches in psychopharmacotherapy of alcohol craving and prevention of relapses in alcoholic persons from different ethnic groups are associated with genetic anthropometric peculiarities.*

Keywords: Russian, Tuvinian, ethnic, mental, health, clinical, biological, steroid, hormone, alcohol, alcoholism, anticonvulsant, drug

WCPRR June 2015: 93-99. **© 2015 WACP**
ISSN: 1932-6270

INTRODUCTION Alcohol abuse and dependence according DSM-IV criteria are psychiatric disorders that include ~13% of all population at some point in life. Approximately half of all homicides and motor vehicle-related deaths involve alcohol, as do one fourth of all suicides. Co-morbid psychiatric conditions are common. The estimated social impact of alcohol dependence is $100 billion in public health concern; researchers are studying alcoholism from health care costs, lost wages, and family disruption. It is close associated with social and socio-cultural problems in the society, and it is very significant for us in this time, when we are living to understand this enormous sociological and socio-cultural specificity to the molecular level (a PubMed search on "alcohol" captures more than 68,000 references in the past five years alone).

One of alcoholism development theories supposes alteration in general brain excitability as result of decreased inhibiting processes in CNS. Heightened excitability, impulsiveness, extravagance observed in alcoholic patients are associated with these processes (Yan *et al*, 2010). Disturbances in exciting and inhibiting functions in brain can induce high nerve excitation laid down in basis of high risk of alcoholism (Bauer, 2001; Behar *et al*, 1999; Taber *et al*, 2000). Significant increase of β-oscillation recorded in central-frontal brain regions in alcoholic patients and their children has been revealed

Correspondence to: Tamara V. Shushpanova. Mental Health Research Institute, Tomsk, Russian Federation

mailto: shush59@mail.ru

Received August 8, 2012. Accepted via minor revision on May 5, 2015.

(Rangaswamy *et al*, 2002; 2004) and can induce high-risk development of alcoholism (Haenschel, 2000).

The $GABA_A$ receptor ($GABA_AR$), as the primary mediator of fast inhibitory input in the CNS (Davies, 2003; Gilman *et al*, 1996; Criswell & Breese, 2005) is modulated by a wide array of exogenous compounds, including benzodiazepines (BDZs), barbiturates, alcohol, as well as endogenous steroids such as progesterone and its active derivate − neurosteroid allopregnanolone. This steroid interaction with $GABA_AR$ induces anxiolytic and anticonvulsant effects (Chen & Fares, 1999). Chronic alcohol consumption and, especially, alcohol withdrawal raise level of cortisol, an anxiogenic neuroactive hormone associated with higher stressogenic function. Abnormal function of $GABA_AR$ in the brain has been implicated in the pathogenesis of some human neurological and psychiatric disorders. They include epilepsy, insomnia, anxiety states and alcoholism appear to be associated with abnormal levels of certain neuroactive steroids, such as progesterone and cortisol (Devaud *et al*, 1995; Reddy, 2004; Strohle *et al*, 2003; Shushpanova & Semke, 2006; 2009; Shushpanova, 2014; Solonsky *et al*, 2011).

Individual human sensibility to psychoactive substances (PAS) includes ethanol effects defined as a possibility to adequate adaptation reactions, which are controlled by genetic and some social and socio-cultural factors. The homeostasis control system and neuroendocrine system are closely connected with such phenomenon as individual tolerance to alcohol and rate of alcohol dependence in persons especially from some ethnic groups.

It is known that optimizing of disrupted homeostasis during (or after) acute or chronic ethanol consumption being provided with specific mechanism by manipulation of endogenous neurosteroid activity may prove a beneficial pharmacotherapeutic strategy in the intervention of alcohol abuse and alcoholism (Gasior *et al*, 1999; Rupprecht & Holboer, 1999; Smith *et al*, 2007; Shushpanova, 2008).

General basis of pathogenic mechanisms of epileptic paroxysms and disruptions of β-oscillations in brain, associated with hyperactivity of hypothalamic-pituitary-adrenal axis, conditioning compulsive craving for alcohol (Haenschel, 2000; Romeo *et al*, 1996; Smith & Woolley, 2004), were preconditions for clinical research of therapeutic efficacy of original drug Galodif® (novel, highly efficient anticonvulsant m-chlor-benzhydryl urea) and levels of steroid hormones progesterone and cortisol in therapy of alcoholic patients from different ethnic groups.

SUBJECTS AND METHODS

We investigated therapeutic efficacy of long-term dozing of original anticonvulsant Galodif® on symptoms of alcohol withdrwal syndrome (AWS) and levels of neuroactive steroid hormones progesterone and cortisol in blood of alcoholic patients from two different ethnic groups (Russian and Tuvinian). Clinical-biochemical investigations in alcoholic patients in withdrawal and post-withdrawal states were carried out at the Addictive State Department of Mental Health Research Institute SB RAMSci and Substance Abuse Treatment Clinic in Republic of Tyva.

Under the observation there were 68 alcoholic patients from Russian ethnic group and 67 patients from Tuvinian ethnic group, men only from 24 to 53 of age (mean age: 38.3 ± 8.9 years) with different levels of alcohol abuse. Type of course of alcoholism in examined patients was of middle-progressing character. Control group included 23 healthy male volunteers.

Clinical evaluation of state of patients was carried out with traditional clinical description, with use of clinical-psychopathological method, clinical-dynamic method at various stages of their treatment. Quantitative characteristics was conducted according to the Russian versions of HAS − Hamilton's Anxiety Scale and HDS - Hamilton's Depression Scale.

RIA kits from blood serum in examined persons measured assay of cortisol and progesterone before and after treatment with Galodif. Preparation was administered according recommendations at dose from 300 mg daily (100 mg up to three times a day) during 15 days in post-withdrawal period, during various degree of severity of affective disorders.

RESULTS Therapy of complicated forms of alcoholism as a whole represents great difficulties because formed organic brain deficiency constrains application of psychotropic preparations in recommended therapeutically effective doses.

Results of clinical trails have shown reliably high activity of Galodif possessing broad spectrum of antiepileptic action. Galodif appeared to be mostly effective regarding grand seizures, focal with simple symptoms, temporal and secondarily generalized seizures. Preparation can prevent development of delirium in alcoholism, and stop it within short terms. Thus, Galodif represents by itself as highly effective, not toxic, well-tolerated antiepileptic preparation with useful additional kinds of pharmacological activity.

Galodif was administered to alcoholic patients according recommendations at dose from 300 mg a day (100 mg up to three times a day), during 21 days against the background of conventional medication as well as in post-withdrawal period during various degrees of severity of affective disorders. Regarding latter part of patients who have completed course of conventional therapy, further monotherapy with investigated preparation was accomplished.

Clinical dynamic of AWS symptoms under therapy with Galodif (asthenia, cranialgia, cardialgia, dissomnia, vegetative-vascular and disco-ordinate disturbances) is a complex target for pharmacotherapeutic efficacy evaluation. Sedative, thymoleptic aspects of action of the preparation were studied in correction of affective disturbances and possibilities of impact of anticonvulsive properties of Galodif on primary pathological craving for alcohol were investigated.

In the structure of affective disturbances dysphoric disorders dominate, that essentially modify actual state (behavior) of patients. A visible place in the continuum of the above-mentioned disturbances is occupied by asthenic-depressive and anxious-phobic manifestations. Vector of normothymoleptic correction of preparation in our investigation was projected, first of all, at the dysphoric roots of affective disturbances and, to a significantly less degree, at the anxious-phobic manifestations. Pharmaco-positive results of Galodif were observed in local muscle-tonic hyperkinesias like crampi, weakening, first of all, painful manifestations of hyperkinesias.

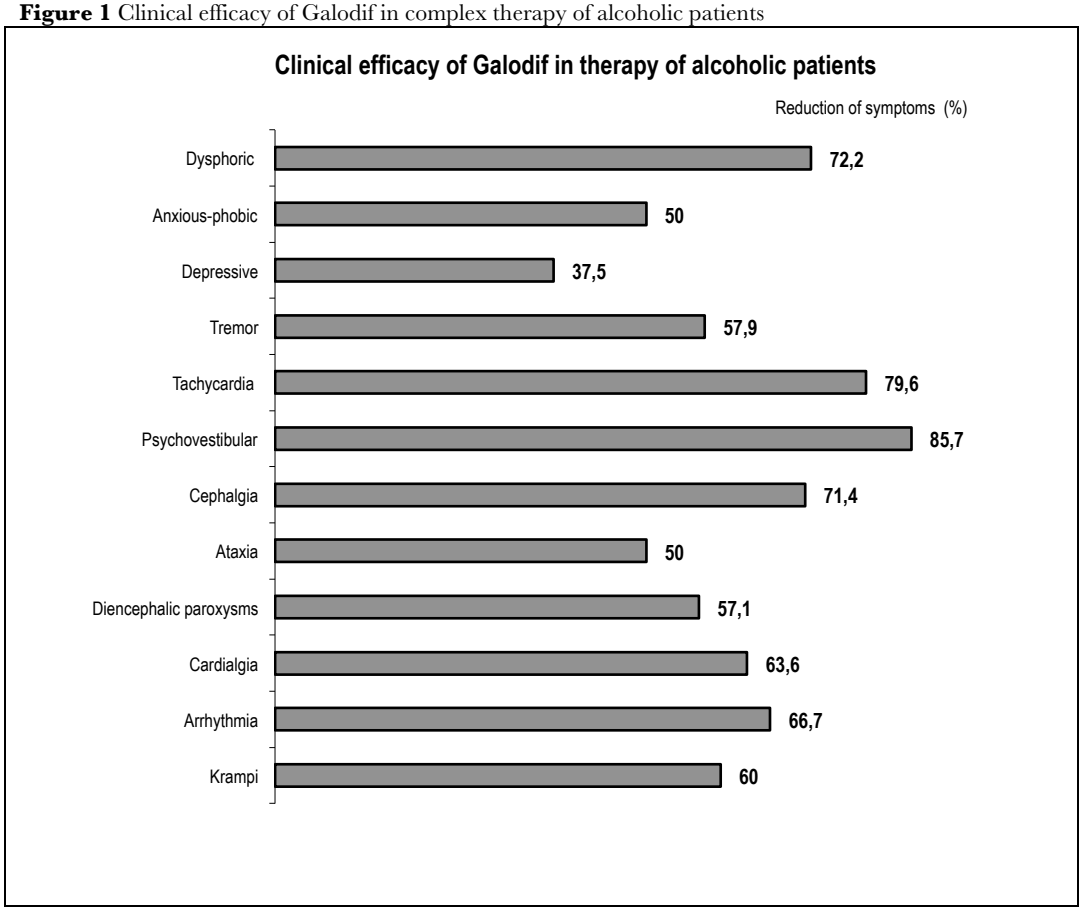
Assessing efficacy of application of Galodif in complicated forms of alcoholism it is necessary to indicate its mild vegetostabilizing action, whose essential component was its balanced sympatocolitic effect with normalization of heart rate and decrease of heightened arterial pressure - in 63% patients. 63.6% of cases were sensitive to the action of Galodif on algical manifestations in structure of cardiovascular disorders, with cardialgia stopping with preparation during 5-6 days at middle degree of severity of AWS.

Out of cerebral clinical manifestations of AWS cephalgical and diencephalic, disorders were most tropic to anticonvulsant action of Galodif. Therapeutic effect of preparation was noticed during stopping of these disorders already at day 3 and in most cases at day 6-7. It is important to underline that application of Galodif did not complicate disco-ordinate-atactic manifestations in structure of AWS. Application of Galodif for correction of dissomnic disorders has shown a purpose effect, especially in combined administration with hypnotics. Self-evident effect of application of preparation has been revealed in qualitative disturbances of sleep – "psychovestibular" dreams. In 85.7% of cases these disturbances of sleep (sensations of "going around and falls" in sleep) were stopped during intake by patients of Galodif. Clinically evident effect of the preparation has been noticed during study of its influence on intensity of vegetoalgic and senestopathic components of headache. An accelerated reduction of cranialgia has been revealed as compared with controls,, decrement or disappearance of senestopathic disorders were observed; in these observations patients were not informed (for exception of suggestive effect) about character of action of administered to them preparation.

Thus, results of clinical efficacy of Galodif in alcoholic patients with co-morbid organic brain impairment have revealed normothymoleptic, analgesic and vegetostabilizing effects of its therapeutic action, in addition to the known anticonvulsant properties. Among affective disturbances, Galodif is effective for correction of dysphoric manifestations. Also preparation has shown greater efficacy in treatment of cerebral (cephalgic, diencephalic paroxysms), cardiovascular (cardialgia) and myofascial (local muscle-tonic hyperkinesias like crampi) sympromocomplexes in structure of AWS. In patients with complicated forms of alcoholism, application of Galodif is effective also in the phase of remission in spontaneously arising symptomocomplex of neurovegetative manifestations of primary pathological

craving for ethanol so called "dry abstinence", for stopping dysphoric disorders. This allows recommending the use of preparation not only under inpatient but also in outpatient conditions as an anti-recurrent and preventive agent. Information about therapeutic efficacy of Galodif has been presented in the diagram:

Figure 1 Clinical efficacy of Galodif in complex therapy of alcoholic patients



Comparative assay of steroid hormones levels (cortisol, progesterone) in blood serum of alcoholic patients and healthy donors showed that content of progesterone was lower in patients (2.65 ± 0.32* nMol/l) compared with control persons (3.99 ± 0.54 nMol/l, $p < 0.05$) from Russian ethnic group.

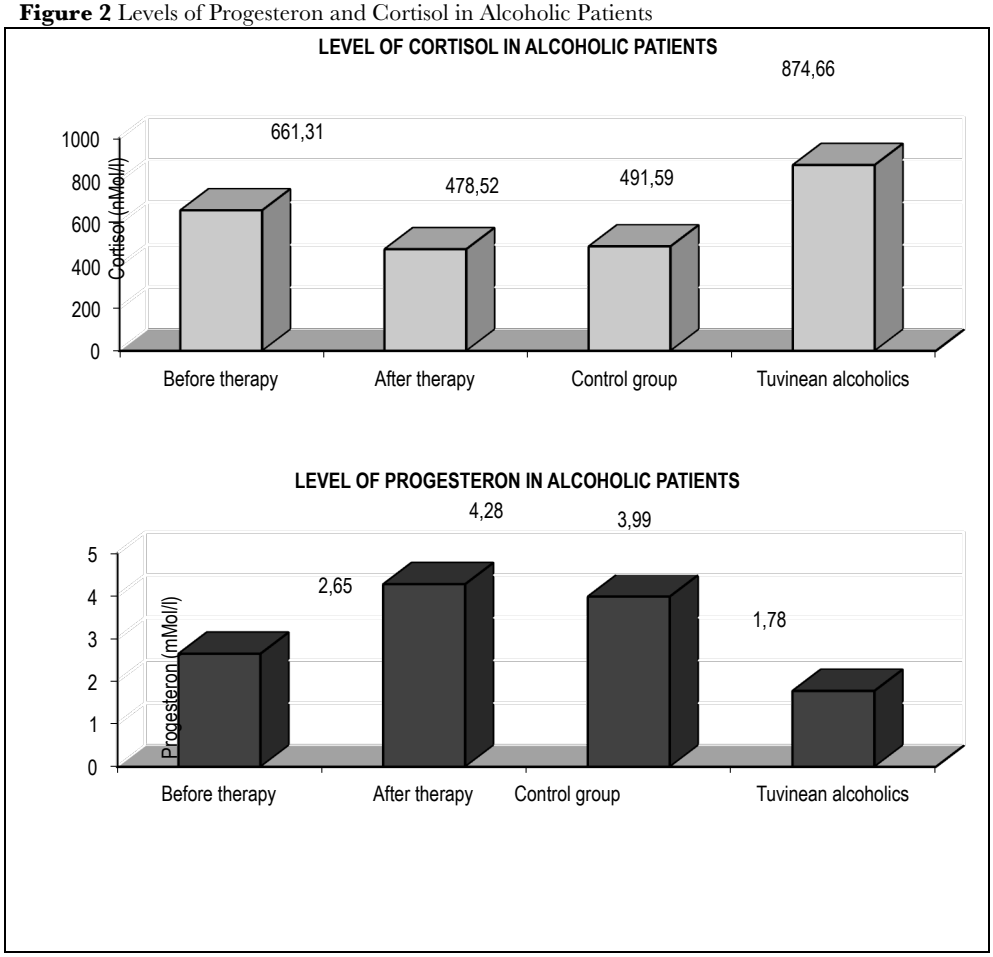
Chronic alcohol abuse significantly decreased concentration of progesterone in blood serum in examined patients as demonstrated in our research. More severe alterations were revealed in alcoholic patients from Tuvinian ethnic group (1.78 ± 0.23* nMol/l, $p<0.05$). Progesterone is a precursor in biosynthesis of its active metabolite – neurosteroid allopregnanolone –, decreased level of progesterone results in decrease of its derivative allopregnanolone possessing sedative and anxiolytic effects. This may cause negative symptoms in alcohol withdrawal and post-withdrawal condition.

Using Galodif therapy during 21 days (300 mg a day) in alcoholic patients induced reduction of severity of AWS symptoms, and led to increase the progesterone level in blood serum to almost control values (4.28±0.63 nMol/l after treatment with Galodif and 3.99±0.54 nMol/l in healthy persons, $p<0.05$).

Investigation of cortisol level has revealed significant increase of this steroid level compared with control group of healthy persons (661.31±108.27* nMol/l and 491.59±68.23 nMol/l, $p < 0.05$), with more severe alterations being revealed in alcoholic patients from Tuvinian ethnic group (874.66 ±79.53* nMol/l, $p < 0.05$). After therapy with Galodif, the level of cortisol was considerably lower and constituted 478.52±97.13 nMol/l.

Information about levels of steroid hormones (progesterone and cortisol) in alcoholic patients from Russian and Tuvinian ethnic groups has been presented in the diagrams:

Figure 2 Levels of Progesteron and Cortisol in Alcoholic Patients



Therefore, we revealed that treatment with Galodif reduced level of cortisol as low as 138% and increased level of progesterone as low as 160% in blood serum of alcoholic patients, approximating them to values of norm in healthy persons. Alterations of hormone levels in blood serum of alcoholic patients reflects disturbance of regulation of neuroactive hormones as one of mechanism of development and formation of alcoholism.

Consequently, the revealed by us reduction of progesterone level, possessing anxiolytic action on $GABA_AR$ in brain of alcoholic patients, may be a compensatory mechanism under conditions of GABAergic function. These negative processes are promoted by increase of content of cortisol that may be contributed to formation of anxiety, paroxysmal and compulsive disorders, increase of convulsive predisposition, vegetative symptoms associated with deficit of GABAergic neurotransmission in the brain.

CONCLUSIONS Clinical investigations have shown modulator role of neuroactive steroids (PG and CS) in association with effects of chronic consumption of alcohol and its withdrawal. Alterations of neurosteroid levels during Galodif therapy of alcoholic patients may be a perspective for development of new approaches of many aspects of alcoholism with account for genetic and ethnic traits lay down in the basis of these peculiarities. One important finding is that therapy with Galodif appears to restore balance of excitating and inhibiting functions in the brain associated with pathological compulsive alcohol craving (anti-craving effect). This suggests the utility of new approaches in

psychopharmacotherapy of pathological alcohol craving and prevention of relapses in alcoholic persons from different ethnic groups with account for mechanisms having their basis in genetic, biochemical and anthropometric peculiarities of clinical dynamics and course of alcoholism.

REFERENCES

Bauer LO. Predicting relapse to alcohol and drug abuse via quantitative electroencephalography. *Neuropsychopharmacology*, 25: 332-340, 2001

Behar KL, Rothman DL, Petersen KF, Hooten M, Delaney R, Petroff OA, Shulman GI, Navarro V, Petrakis IL, Charney DS, Krystal JH. Preliminary evidence of low cortical GABA levels in localized 1H-MR spectra of alcohol-dependent and hepatic encephalopathy patients. *American Journal of Psychiatry*, 156: 952-954, 1999

Chen HC & Fares Jr RV. Steroid hormones: interactions with membrane-bound receptors. *Current Biology*, 9: 478-481, 1999

Criswell HE & Breese GR. A conceptualization of integrated actions of ethanol contributing to its GABAmimetic profile: a commentary. *Neuropsychopharmacology*, 30: 1407-1425, 2005

Davies M. The role of GABAA receptors in mediating the effects of alcohol in the central nervous system. *Journal of Psychiatry & Neuroscience*, 28: 263-274, 2003

Devaud LL, Purdy RH, Morrow AL. The neurosteroid, 3α-hydroxy-5α-pregnan-20-one, protects against bicuculline-induced seizures during ethanol withdrawal in rats. *Alcoholism Clinical & Experimental Research*, 19: 350–355, 1995

Gasior M, Carter RB, Witkin JM. Neuroactive steroids: potential therapeutic use in neurological and psychiatric disorders. *Trends in Pharmacological Sciences*, 20: 107-112, 1999

Gilman S, Koeppe RA, Adams K, Johnson-Greene D, Junck L, Kluin KJ, Brunberg J, Martorello S, Lohman M. Positron emission tomographic studies of cerebral benzodiazepine-receptor binding in chronic alcoholics. *Annuals in Neurology*, 40: 163-171, 1996

Haenschel C. Gamma and beta frequency oscillations in response to novel auditory stimuli: a comparison of human electroencephalogram (EEG) data with in vitro models. *Proceeding from the National Academy of Science USA*, 97: 7645-7650, 2000

Rangaswamy M, Porjesz B, Chorlian DB, Wang K, Jones KA, Bauer LO, Rohrbaugh J, O'Connor SJ, Kuperman S, Reich T, Begleiter H. Beta power in the EEG of alcoholics. *Biological Psychiatry*, 52: 831-842, 2002

Rangaswamy M, Porjesz B, Chorlian DB, Wang K, Jones KA, Kuperman S, Rohrbaugh J, O'Connor SJ, Bauer LO, Reich T, Begleiter H. Resting EEG in offspring of male alcoholics: beta frequencies. *International Journal of Psychophysiology*, 51: 239-251, 2004

Reddy DS. Role of neurosteroids in catamenial epilepsy. *Epilepsy Review*, 62: 99-118, 2004

Romeo E, Brancati A, De Lorenzo A, Fucci P, Furnari C, Pompili E, Sasso GF, Spalletta G, Troisi A, Pasini A. Marked decrease of plasma neuroactive steroids during alcohol withdrawal. *Clinical Neuropharmacology*, 19: 366-369, 1996

Rupprecht R & Holsboer F. Neuroactive steroids: Mechanisms of action and neuropsychopharmacological perspectives. *Trends in Neuroscience*, 22: 410-416, 1999

Shushpanova TV. Treatment of alcoholic patients with original anticonvulsant alters alcohol motivation and progesterone level in plasma. *European Neuropsychopharmacology*, 18 (Suppl.4): 531, 2008

Shushpanova TV. Influence of maternal alcoholism on the brain benzodiazepine receptor development in human embryo and fetus during ontogeny. *Journal of Alcoholism & Drug Dependence*, 2: 176, 2014

Shushpanova TV & Semke VYa. Peripheral benzodiazepine receptors of thrombocytes in alcoholism [Russian]. *Zhurnal Nevrologii i Psychiatry*, 11: 53-56, 2006

Shushpanova TV & Semke VYa. Peripheral benzodiazepine receptors in platelets of alcoholic patients as a test of efficacy of antialcohol drugs. *European Neuropsychopharmacology*, 19: (Suppl.3): S646, 2009

Smith SS, Woolley CS. Cellular and molecular effects of steroid hormones on CNS excitability. *Cleveland Clinic Journal of Medicine*, 71: S4-10, 2004

Smith SS, Shen H, Gong QH, Zhou X. Neurosteroid regulation of GABA(A) receptors: Focus on the alpha4 and delta subunits. *Pharmacology & Therapeutics*, 116: 58-76, 2007

Solonsky AV**,** Shushpanova TV, Semke VYa, Bokhan NA. Neuromorphologic and neurochemical regularities of prenatal exposure of developing human brain to alcohol. *European Psychiatry*, 26: (Suppl.1): S106, 2011

Ströhle A, Romeo E, di Michele F, Pasini A, Hermann B, Gajewsky G, Holsboer F, Rupprecht R. Induced panic attacts shift gamma-aminobutyric acid type A receptor modulatory neuroactive steroid composition in patients with panic disorder: Preliminary results. *Archives of General Psychiatry*, 60: 161-168, 2003

Taber KH, Hurley RA, Abi-Dargham A, Porjesz B. Cortical inhibition in alcohol dependence. *Journal of Neuropsychiatry and Clinical Neuroscience*, 12: 173-176, 2000

Yan H, Li Q, Madison R, Wilson WA, Swartzwelder HS. Differential Sensitivity of Hippocampal Interneurons to Ethanol in Adolescent and Adult Rats. *Journal of Pharmacological Experimental Therapy*, 335: 51-60, 2010