

ple Yakutsk: Bichik; 2000: 298. (In Russ.).

11. Van Saase J.L.C.M., van Romunde L.K.J., Cats A. [et al.]. Epidemiology of osteoarthritis: Zoetermeer study. Comparison of radiological osteoarthritis in a Dutch population with that in 10

other populations. *Ann. Rheum. Dis.* 1989; 4 (48): 271- 280.

12. Spector T., Champion G.C. Generalized osteoarthritis is a hormonally mediated disease. *Ann. Rheum. Dis.* 1989; №4 (48): 256-261.

13. Altman R., Alarcon G., Apperlouth D. [et al.] The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. *Arthr. Rheum.* 1991; 5 (34): 505 – 514.

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POSSIBILITIES OF PREDICTION OF NEUROTIC, STRESS-RELATED DISORDERS COURSE IN TERMS OF HORMONAL PARAMETERS

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One of the most common and universal disorders of mental adaptation are non-psychotic mental disorders, in which development a large role plays various endocrine and biochemical mechanisms of response to stress. The purpose of the study is to determine the contribution of the endocrine system to the formation of neurotic, stress-related disorders in order to identify the criteria for predicting their protracted course. Material and Methods. A comprehensive clinical-psychopathological and hormonal examination of 43 women (mean age 39.43 ± 7.23 years) inpatient at the first clinical psychiatric unit of the clinic of Mental Health Research Institute of Tomsk NRC with various types of the course of neurotic, stress-related disorders was performed. According to the criteria ICD-10 all patients were divided to clinical groups: adjustment disorders (F 43.2) and enduring personality change after psychiatric illness (F 62.1). Investigation of hormonal status included determination of concentrations of cortisol, prolactin and thyroid-stimulating hormone (TSH) in serum by the method Enzyme Immunoassay (EIA). The hormonal status of 32 healthy women was taken as a control. Results. A psychopathological investigation of patients showed that overexertion of protective mental mechanisms associated with the impact of a stressful situation can lead to a breakdown in adaptation, disturbances of normal functioning and the emergence of various neurotic symptoms that fall into the diagnostic category F 43.2 (adjustment disorders). As the damaging effects of unfavorable factors and stressful co-existence accumulated, the "health resources" decreased, which was a starting point in the formation of persistent personality changes and transition to another diagnostic category F 62.1 Persistent personality change after a mental disorder. The characteristics of the hormonal status of patients with a protracted neurotic, stress-related disorders were: high concentrations of cortisol, prolactin and low serum levels of thyrotrophic hormone, which allows considering them as predictors of persistent personality change at early stage of the diseases. Conclusion We determined the hormonal criteria for predicting a protracted course of neurotic, stress-related disorders with the formation of a persistent personality changes at an early stage of the disease - at the stage of disorder of adaptive reactions.

Keywords: neurotic, stress-related disorders, adjustment disorders, enduring personality change, cortisol, prolactin, thyrotrophic hormone.

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Introduction. One of the most common and universal disorders of mental adaptation are non-psychotic mental disorders, in which development a large role is played by various endocrine and biochemical mechanisms of response to stress [1, 4]. These mechanisms are usually not the cause of the breakdown of adaptation, but its effect, since they are not specific to one or another stress factor and are aimed at achieving early compensation. [18]. Various adverse factors that can lead to maladjustment, accompany a person throughout life. However, in some individuals, adjustment disorders are acute, while others develop chronic forms of neurotic states. The question of why this is happening remains open, despite numerous studies in this field. The relevance of the problem of differentiated prediction of the course of such disorders has been dictated recently by the increasing prevalence of neurotic, stress-related disorders and the need to improve the quality of life, preserve and develop the labor potential of the population, taking into account the tasks and forecasts of the economic, social and psychological development of the country. Highlighting the criteria for

distinguishing between initial and protracted forms of non-psychotic mental disorders helps to identify those suffering from these disorders at the early stages of the disease that helps to prevent an unfavorable trend in the dynamics of neurotic states. Under stress, an increase in the level of hormones is observed, which in physiological quantities are necessary for the normal functioning of all systems of the organism. But if an organism synthesizes an excessive amount of stress hormones for a long time, then undesirable reactions emerge in it, leading to the occurrence of pathological states and the development of various diseases. By additional assessment of the hormonal parameters to the general medical ones, which characterize the adaptation of the organism to the constantly changing environmental conditions, including the mobilization of the organism under the action of stress factors, a differentiated prediction of the course of non-psychotic mental disorders of the neurotic rank is carried out.

The purpose of the study is to determine the contribution of the endocrine system to the formation of neurotic, stress-related disorders in order to iden-

tify the criteria for predicting their protracted course.

Material and Methods. A comprehensive clinical-psychopathological and hormonal examination of 43 women (mean age 39.43 ± 7.23 years) with various types of the course of neurotic, stress-related disorders being under inpatient treatment at the first clinical psychiatric unit of the clinic of Mental Health Research Institute of Tomsk NRMС was carried out. All patients were examined with use of developed at the Borderline States Department of Mental Health Research Institute "Clinical Record Book of Examination of a Patient" adjusted to tasks of the present study. The diagnostic assessment and clinical qualification of neurotic disorders were carried out by psychiatrists of the Borderline States Department in accordance with the International Classification of Diseases of the 10th revision (ICD-10). The diagnosis of neuroses was carried out with regard to accepted criteria, which include a causal relationship with a psychotraumatic situation, neurotic traits of the personality, and neurotic symptoms. 23 patients (group 1) were diagnosed as having adjustment disorders (F 43.2), 20 patients (group 2) – enduring personality change after psychiatric illness (F 62.1). The leading clinical syndrome in both groups was anxiety-depressive one. The study on human subjects was conducted in accordance with Declaration of Helsinki of World Medical Association. All patients upon admission to the clinic gave informed consent for the research.

The study of hormonal parameters – determination of concentrations of cortisol, prolactin and thyroid-stimulating hormone (TSH) in serum was carried out in accordance with the instructions for the use of reagent kits for the immunoenzymatic determination of hormones in serum (JSC "Vector-Best", s. Koltsovo, Novosibirsk Region, Russia).

As a control, data of the hormonal status of 32 practically healthy women were taken, who did not have endocrine diseases at the time of the survey and leading a normal life style.

When performing statistical analysis, STATISTICA version 12.0 for Windows (StatSoft., Inc, USA) was used, the median (Me) and interquartile interval [Q1 — Q3] were calculated. To test the equality of the medians of several samples, Kruskal-Wallis H test was used. The comparison of the studied samples was performed using the Mann-Whitney U test. The critical level of significance was assumed to be 0.05.

Results and Discussion. A psychopathological investigation of patients

showed that overexertion of protective mental mechanisms associated with the impact of a stressful situation can lead to a breakdown in adaptation, disturbances of normal functioning and the emergence of various neurotic symptoms that fall into the diagnostic category F 43.2 (adjustment disorders). According to the ideas of many researchers, the general scheme for the development of neurotic disorders is as follows: in the first years of the development, in the future patient a personality structure is formed that makes contacts in the social environment difficult and leads to emotional tension; further, against this background, disturbances in the somatovegetative domain are added and the adaptive mechanisms overexertion occurs, at the same time the behavior is determined not so much by the requirements of the situation, as by the mechanisms of psychological defense. After the psychotrauma, the system of psychological defense, somatovegetative support and adaptive mechanisms was disrupted. The cause of neurotic disorders was the so-called neurotic conflict – a violation of a person's significant life relationships that go back to childhood and are activated in a psychoinjuring situation. As the damaging effects of infectious and/or existing somatic diseases, various surgical interventions, stressful events, unhealthy habits and unhealthy lifestyles accumulated, the "health resources" decreased that was a trigger link in the formation of persistent personality changes and transition to another diagnostic category – F 62.1 (enduring personality change after psychiatric illness). With a protracted course of neurotic disorder, "flight into illness" deepened and the connection between clinical dynamics and psychogenic influences gradually weakened [11]. With a protracted course of neurosis, the spectrum of neurotic symptoms expanded, the intervals between exacerbations were reduced, the wave-like course disappeared, the psychopathological symptoms stabilized and were hardly reversible.

The outcome of the disease depends on the timeliness and quality of care provided: either full recovery with a transition to a new level of adaptation, or chronicity of the pathological process and the formation of a more serious mental disease, such as panic disorder, depression or enduring personality change.

The scientific literature describes social and biological predictors of the favorable and unfavorable course of neuroses. The criteria for unfavorable dynamics of neurotic disorders are as follows: mother's toxicosis, early childhood

psychological trauma, age of onset of the disease (over 40), family history (psychopathological personality traits of parents and alcoholism), presence of accentuated character traits in the patient, presence of a permanent psychoinjuring situation in the family, interpersonal conflicts in the work sphere, mixed psychogenias and other factors [10]. A method for predicting the course of neurotic disorders based on hormonal parameters is proposed. By determining the serum levels of cortisol, dehydroepiandrosterone sulfate (DHEAS), total triiodothyronine (T3), free thyroxine (T4), the authors predict the development in the patient of either an adjustment disorder with the predominance of depressive reactions, or the formation of dissociative (conversion, hysterical) disorder [6]. By calculating the ratio between the immunological and biochemical indicators of homeostasis, a method has been developed for the early diagnosis of an unfavorable course of the psychopathological state in patients with neurotic, somatoform and neurosis-like disorders [8]. We have previously developed a method for predicting a protracted course of neurotic disorders with the transition of an adjustment disorder into an enduring personality change, based on the identification of clinical syndromes of secondary immune deficiency and immunity indicators (level of circulating immune complexes, content of cytotoxic T-lymphocytes and lymphocytes-markers of late activation) [7].

We have proposed a new method that expands the arsenal of well-known methods for predicting the protracted course of neurotic disorders and provides an option in view of the laboratory equipment available at the medical institution. The task was solved by determining the serum levels of hormonal parameters in patients with adjustment disorder. Table presents the results of a hormonal investigation of healthy individuals and patients with adjustment disorder and with enduring personality change after psychiatric illness.

A comparative analysis of the findings revealed differences between all the examined groups (Table). The most significant features in the group of patients with enduring personality change in comparison with patients with adjustment disorders are higher values of concentrations of cortisol (771.23 [506.59 – 867.18] nmol/L and 547.77 [485.18 – 657.44] nmol/L, respectively; $p=0.0422$), prolactin (767.01 [440.20 – 1115.92] mIU/L and 322.74 [166.99 – 615.92] mIU/L, respectively; $p=0.0151$) and lower value of concentration of the thyroid-stimulating hormone – TSH (0.93 [0.60 – 1.57] mIU/mL

Hormonal parameters of the examined groups of patients and healthy persons

Parameters	The examined groups (Me [Q1—Q3])			P ₂
	Healthy individuals (n=32)	Patients with adjustment disorders (n=23)	Patients with enduring personality change	
Cortisol, nmol/L	(n=20)	547.77 [485.18–657.44] p ₁ =0.0016	771.23 [506.59–867.18] p ₁ =0.0001	0.0422
Prolactin, mIU/L	250.46 [186.63–373.50]	322.74 [166.99–615.92] p ₁ =0.1918	767.01 [440.20–1115.92] p ₁ =0.0003	0.0151
TSH, mIU/mL	1.91 [1.63–2.69]	2.63 [1.59–3.18] p ₁ =1.8403	0.93 [0.60–1.57] p ₁ =0.0001	0.0001

Note: p₁ – reliability of differences vs. healthy individuals;
p₂ – reliability of differences between groups of patients.

and 2.63 [1.59–3.18] mIU/mL, respectively; p=0.0001).

The statistical significance of the differences between the hormonal parameters presented in the table is confirmed by Kruskal-Wallis H test for cortisol [H=23.45232; p=0.0000], prolactin [H=9.28387; p=0.0096] and TSH [H=27.25318; p=0.0000].

The choice of hormones cortisol, prolactin and TSH as predictive criteria for the protracted course of neurotic, stress-related disorders at the initial stage of the disease is caused by the following factors. Hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid systems under the control of higher brain regions are the main systems that implement all changes in the body under stress [17]. One of the main stress hormones is undoubtedly cortisol. Its action causes various physiological, cognitive and behavioral changes in the human body that are crucial for successful adaptation to stress [2, 14]. Prolactin is actively involved in the formation of adaptive reactions that occur when various extreme factors act on the body. By regulating mental functions, prolactin influences the body's behavioral responses [15, 16]. The question remains open about the production of thyroid-stimulating hormone of the pituitary gland and the functional activity of the thyroid gland during stress. Most authors believe that under stress, thyroid function is inhibited, and this is attributed to the action of the hypothalamic-pituitary system, namely the suppression of TSH secretion under the influence of high concentrations of adrenocorticotrophic hormone [5, 12]. According to other researchers, during the formation of the response to stress the increase in the secretion of thyroid-stimulating hormone

and increase in the function of the thyroid gland occur according to the following scheme: cortex - hypothalamus - secretion of thyroliberin - anterior pituitary gland - release of thyroid-stimulating hormone - thyroid gland - secretion of thyroid hormones of the thyroid gland [3, 13].

On the basis of the data obtained, we have proposed a method for predicting at the early stage of the neurotic, stress-related disorders their protracted course with the formation of an enduring personality change by determining serum levels of hormonal parameters in patients with adjustment disorders. In the group with adjustment disorders, the initial neurotization of the foundation took place in the conditions of everyday family troubles and prepared the conditions for the subsequent development of neurosis. Hormonal parameters in this group differed slightly from those in the group of healthy individuals. Under the influence of the improvement of the micro-social environment, intensive psychotherapeutic work, there was a complete regredient dynamics of neurotic symptoms and a distinct harmonization of personality response.

Earlier, the complex interaction of psychogenic and endocrine links in the development of protracted forms of neurotic states was established. Long-term psychogenic trauma often led to organic changes in somatic functions, i.e., functional changes passed into organic ones. With a massive impact of psychogenic factors, a transformation of the main neurotic symptoms was observed, mixed symptoms appeared: asthenic-depressive, asthenic-hypochondriac, obsessive-phobic. With a protracted course of neurosis, an enduring personality change was gradually formed, a deepening of the "flight into illness", the links between clinical

cal dynamics and psychogenic influences gradually weakened. This dynamic was accompanied by pronounced deviations from the norm in hormone status. With a simultaneous high concentration of cortisol and prolactin and a low concentration of thyroid-stimulating hormone, it is possible to predict the possibility of a protracted course of the disease with the formation of an enduring personality change. A patent for invention has been obtained for this method [9]. The proposed method was tested on 16 patients, is simple to implement and can be implemented in health care and medicine.

Conclusion. Along with general clinical indicators, the determination of the concentration of cortisol, prolactin and thyroid-stimulating hormone allows us to predict a protracted course of neurotic, stress-related disorders with the formation of enduring personality change at an early stage of the disease - at the stage of adjustment disorders. The obtained data expand the arsenal of biomarkers for predicting the course of neurotic disorders at earlier stages of the disease, help develop complex treatment methods, strengthen the impaired system of adaptation and influence all components of neurotic disorder. The advantage of the developed method lies in the fact that it allows reducing the number of days of disability spent by the patient in the hospital by providing adequate timely medical care based on the identification in addition to the clinical laboratory parameters that are objective.

References

1. Баевский Р.М. Проблема здоровья и нормы: точка зрения физиолога. *Клиническая медицина*. 2000; 4: 59-64. [Baevskij R.M. Problema zdorov'ya i normy: tochka zreniya fiziologa. *Klinicheskaya medicina*. 2000; 4: 59-64. (In Russ.)]
2. Козлов А.И., Козлова М.А. Кортизол как маркер стресса. *Физиология человека*. 2014; 2: 123-136. [Kozlov A.I., Kozlova M.A. Kortizol kak marker stressa. *Fiziologiya cheloveka*. 2014; 2: 123-136. (In Russ.)]
3. Кубасов Р.В., Иванов А.М., Барачевский Ю.Е. Клинико-лабораторные особенности секреторной функции тиреоидного звена регуляции у лиц опасных профессий. *Клиническая лабораторная диагностика*. 2017; 2: 103-107. [Kubasov R.V., Ivanov A.M., Barachevskij Yu.E. Kliniko-laboratorny'e osobennosti sekretornoj funkcii tireoidnogo zvena regulyacii u licz opasny'x professij. *Klinicheskaya laboratornaya diagnostika*. 2017; 2: 103-107. (In Russ.)]
4. Малов Ю.С. Пропедевтика внутренних болезней. Учебное пособие для ВУЗов. СПб.: СпецЛит; 2003. [Malov Yu.S. Propedevtika vnutrennix boleznej. Uchebnoe posobie dlya VUZov. SPb.: SpeczLit; 2003. (In Russ.)]
5. Надольник Л.И. Стресс и щитовидная железа. *Биомедицинская химия*. 2010; 4: 443-456. [Nadol'nik L.I. Stress i shhitovidnaya zhele-

za. *Biomeditsinskaya khimiya*. 2010; 4: 443-456. (In Russ..)]

6. Пат. 2356059 Российская Федерация, МПК G01N 33/78. Способ прогнозирования течения невротических расстройств [Текст] / Иванова С.А., Гуткевич Е.В., Семке В.Я., Вялова Н.М., Рядовая Л.А., Епанчинцева Е.М., Перчаткина О.Э. Заявитель и патентообладатель Государственное учреждение Научно-исследовательский институт психического здоровья Томского научного центра Сибирского отделения Российской академии медицинских наук (ГУ НИИ ПЗ ТНЦ СО РАМН). – № 2007142885/15; заявл. 19.11.2007; опубл. 20.05.2009, Бюл. № 14. [Pat. 2356059 Rossijskaya Federaciya, MPK G01N 33/78. Sposob prognozirovaniya techeniya nevroticheskix rasstrojstv [Tekst] / Ivanova S.A., Gutkevich E.V., Semke V.Ya., Vyalova N.M., Ryadovaya L.A., Epanchineva E.M., Perchatkina O.E'. Zayavitel' i patentoobladatel' Gosudarstvennoe uchrezhdenie Nauchno-issledovatel'skij institut psixicheskogo zdorov'ya Tomskogo nauchnogo centra Sibirskogo otdeleniya Rossijskoj akademii medicinskix nauk (GU NII PZ TNCz SO RAMN). – № 2007142885/15; zayavl. 19.11.2007; opubl. 20.05.2009, Byul. № 14. (In Russ..)]

7. Пат. 2421727 Российская Федерация, МПК G01N 33/48. Способ прогнозирования затяжного течения невротических расстройств [Текст] / Никитина В.Б., Ветлугина Т.П., Лебедева В.Ф., Мальцева С.Н. Заявитель и патентообладатель Учреждение Российской академии медицинских наук Научно-исследовательский институт психического здоровья Сибирского отделения РАМН. – № 2009143442/14; заявл. 24.11.2009; опубл. 20.06.2011, Бюл. № 17. [Pat. 2421727 Rossijskaya Federaciya, MPK G01N 33/48. Sposob prognozirovaniya zatyazhnogo techeniya nevroticheskix rasstrojstv [Tekst] / Nikitina V.B., Vetlugina T.P., Lebedeva V.F., Mal'ceva S.N. Zayavitel' i patentoobladatel' Uchrezhdenie Rossijskoj akademii medicinskix nauk Nauchno-issledovatel'skij institut psixicheskogo zdorov'ya Sibirskogo otdeleniya RAMN. – № 2009143442/14; zayavl. 24.11.2009; opubl. 20.06.2011, Byul. № 17. (In Russ..)]

8. Пат. 2427841 Российская Федерация, МПК G01N 33/53. Способ ранней диагностики течения и исхода невротических, связанных со стрессом, соматоформных и неврозоподоб-

ных расстройств / Положий Б.С., Вернекина Н.С. Заявитель и патентообладатель Федеральное государственное учреждение «Государственный научный центр социальной и судебной психиатрии им. В.П. Сербского» (ФГУ «ГНЦССП Росздздрав»). – № 2009128933/15; заявл. 28.07.2009; опубл. 27.08.2011, Бюл. № 24. [Pat. 2427841 Rossijskaya Federaciya, MPK G01N 33/53. Sposob rannej diagnostiki techeniya i isxoda nevroticheskix, svyazanny'x so stressom, somatoformny'x i nevrozopodobny'x rasstrojstv / Polozhij B.S., Vernekina N.S. Zayavitel' i patentoobladatel' Federal'noe gosudarstvennoe uchrezhdenie «Gosudarstvenny'j nauchny'j centr social'noj i sudebnoj psixiatrii im. V.P. Serbskogo» (FGU «GNCzSSP Roszdrava»). – № 2009128933/15; zayavl. 28.07.2009; opubl. 27.08.2011, Byul. № 24. (In Russ..)]

9. Пат. 2613111 Российская Федерация, МПК G01N 33/74. Способ прогнозирования течения невротических, связанных со стрессом расстройств / Никитина В.Б., Ветлугина Т.П., Рудницкий В.А., Перчаткина О.Э., Лебедева В.Ф., Бохан Н.А. Заявитель и патентообладатель Федеральное государственное бюджетное научное учреждение «Научно-исследовательский институт психического здоровья». – № 2015149164; заявл. 16.11.2015; опубл. 15.03.2017, Бюл. № 8. [Pat. 2613111 Rossijskaya Federaciya, MPK G01N 33/74. Sposob prognozirovaniya techeniya nevroticheskix, svyazanny'x so stressom rasstrojstv / Nikitina V.B., Vetlugina T.P., Rudniczkij V.A., Perchatkina O.E', Lebedeva V.F., Bohan N.A. Zayavitel' i patentoobladatel' Federal'noe gosudarstvennoe byudzhethoe nauchnoe uchrezhdenie «Nauchno-issledovatel'skij institut psixicheskogo zdorov'ya». – № 2015149164; zayavl. 16.11.2015; opubl. 15.03.2017, Byul. № 8. (In Russ..)]

10. Сарсембаев К.Т. Биологические и социальные корреляты благоприятного и неблагоприятного течения невротических расстройств. *Журнал неврологии и психиатрии им. С.С. Корсакова*. 2003; 5: С. 66-70. [Sarsembaev K.T. Biologicheskie i social'ny'e korrelyaty' blagopriyatnogo i neblagopriyatnogo techeniya nevrozov. *Zhurnal nevrologii i psixiatrii im. S.S. Korsakova*. 2003; 5: S. 66-70. (In Russ..)]

11. Яковлева А.Л., Симуткин Г.Г. Соотношение социальной адаптации и тяжести текущей

депрессии у пациентов с коморбидными аффективными и личностными расстройствами. *Сибирский вестник психиатрии и наркологии*. 2016; 1: 15-18. [Yakovleva A.L., Simutkin G.G. Sootnoshenie social'noj adaptacii i tyazhesti tekushhej depressii u pacientov s komorbidny'mi affektivny'mi i lichnostny'mi rasstrojstvami. *Sibirskij vestnik psixiatrii i narkologii*. 2016; 1: 15-18. (In Russ..)]

12. Stein E.J., da Silveira Filho N.G., Machado D.C., Hipólido D.C., Barlow K., Nobrega J.N. Chronic mild stress induces wide-spread decreases in thyroid hormone $\alpha 1$ receptor mRNA levels in brain-Reversal by imipramine. *Psychoneuroendocrinol.* 2009; 34 (2): 281-286. DOI: 10.1016/j.psyneuen.2008.09.005.

13. Sun Q., Liu A., Ma Y., Wang A., Guo X., Teng W., Jiang Y. Effects of forced swimming stress on thyroid function, pituitary thyroid-stimulating hormone and hypothalamus thyrotropin releasing hormone expression in adrenalectomy Wistar rats. *Exp. Ther. Med.* 2016; 12 (5): 3167-3174. DOI: 10.3892/etm.2016.3790.

14. Erickson K., Drevets W., Schulkin J. Glucocorticoid regulation of diverse cognitive functions in normal and pathological emotional states. *Neurosci. Biobehav. Rev.* 2003; 27 (3): 233-246. DOI: 10.1016/s0149-7634(03)00033-2.

15. Labad J., Stojanovic-Pérez A., Montalvo I., Solé M., Cabezas Á., Ortega L., Moreno I., Vilella E., Martorell L., Reynolds R.M., Gutiérrez-Zotes A. Stress biomarkers as predictors of transition to psychosis in at-risk mental states: roles for cortisol, prolactin and albumin. *J Psychiatr Res.* 2015; 60: 163-169. DOI: 10.1016/j.jpsychires.2014.10.011.

16. Ittig S., Studerus E., Heitz U., Menghini-Müller S., Beck K., Egloff L., Leanza L., Andreou C., Riecher-Rössler A. Sex differences in prolactin levels in emerging psychosis: Indication for enhanced stress reactivity in women. *Schizophr Res.* 2017; 189: 111-116. DOI: 10.1016/j.schres.2017.02.010.

17. Belda X., Fuentes S., Daviu N., Nadal R., Armario A. Stress-induced sensitization: the hypothalamic-pituitary-adrenal axis and beyond. *Stress.* 2015; 18(3): 269-279. DOI: 10.3109/10253890.2015.1067678.

18. Wichers M.C., Maes M. The role of indoleamine 2, 3-dioxygenase (IDO) in the pathophysiology of interferon-alpha-induced depression. *J. Psychiatry Neurosci.* 2004; 29(4): 11-17.