O.V.Grigorova, L.V. Romasenko, A.Z. Faizulloev, T.I. Vazagaeva, L.N. Maksimova, Ya.R. Nartsissov

National Research Centre for Social and Forensic Psychiatry named after V.P. Serbsky, Moscow
Institute of Cytochemistry and Molecular Pharmacology, Moscow

The use of glycine in the treatment of patients suffering from adjustment disorder

Manifestations of mental maladjustment play an important role in the diagnosis of the effects of stressful situations, and methods of treatment include a wide range of therapeutic interventions. This paper describes a randomized, placebo-controlled study of efficacy and tolerability of glycine on the basis of a pharmaceutical composition of the microencapsulated glycine, and magnesium stearate for adjustment disorder with a prevalence of violations of other emotions. In the group treated glycine, 82.4% of patients achieved a significant improvement on a scale of CGI, whereas in the placebo group, the rate was 14.3%. Glycine was safe and well tolerated; there was no patient excluded prematurely due to adverse events. Results of the study confirm the efficacy of glycine and its superiority over placebo in this sample of patients with improvement in all measured parameters.

Keywords: *psychological maladjustment, glycine, stress.*

For clinicians, manifestations of mental disadaptation play an important role in the diagnosis of the consequences of stressful situations that do not have the quantitative and qualitative characteristics of extreme stress (somatic illness, incapacity for work, acute and chronic pain, family and work problems, problems in social relationships).

Yu. A. Aleksandrovsky (2000, 2010) identifies several forms of mental disadaptation within the framework of the response to the stressful event with various borderline mental states – from adaptation reactions and accentuation of character which are not fully serious disorders, to neuroses or personality decompensations (psychopathies), pathological personality development and various neurotic or psychopathic conditions which require competent psychiatric judgment and appropriate treatment.

The term "adjustment disorder", as a diagnostic category, appeared in the DSM-II classification in 1968 and was officially admitted in ICD-9 in 1978. Previously, the term "transient situational disorders" was used to refer such health problems. The decision to add the diagnosis of "adjustment disorder" to the ICD resulted from the need for a clearer distinction between concepts of reactive and endogenous depression. As in DSM-IV (American Psychiatric Association, 1994)

so in ICD-10 (World Health Organization, 1992) the “adjustment disorder” category was saved because of its usability as a clinical term.

According to DSM-IV, adjustment disorder is the main diagnosis for 5-20% of patients on outpatient psychiatric therapy. However, according to a number of researchers, this diagnosis is much less common among this people, and its frequency should be approximately 2.3% of cases (Fabrega et al., 1986). A much higher prevalence of this disorder is registered in general medical practice and in the primary medical assistance – 12% (Strain et al., 1998). According to Snyder and colleagues (1990), when examining a group of patients in a general hospital, an adjustment disorder was more often diagnosed than a major depressive disorder, and in the primary health care system the adjustment disorder was the most common diagnosis.

The prognostic validity of the adjustment disorder was also confirmed in a number of adult patients in hospital (Andreasen & Hoenk, 1982) – 79% patients felt well in five years after the first hospitalization. Patients with adjustment disorder had most of their symptoms quickly reduced (Snyder et al., 1990, Despland et al., 1995); chronic adjustment disorder was reported in less than 17% of all cases (Bronisch, 1991; Greenberg et al., 1995).

Despite the high prevalence of adaptation disorders among the population, this category of diseases was pushed into the background whereas researchers paid more and more attention on affective disorders. This situation is fraught with the danger of overstatement of the need for over-priced (and sometimes with unpredictable effects) psychiatric treatment in cases where the disorder can be reduced without it, spontaneously. According to several authors (Casey et al., 2001), the importance of diagnosis of adjustment disorders is in identifying people who do not need treatment, in contrast to patients with similar symptoms and functional disorders who need special therapy. But also it is emphasized that even subsyndromal anxiety disorders, if remaining untreated, have an extremely negative impact on the quality of life of the patient and people around him.

According to the literature, the methods of adjustment disorder treatment include a wide range of therapeutic interventions. So, the professional help of the psychologist can activate the ways of adaptation specific to the patient. In case of short-term adjustment disorder with clinical manifestations of subsyndromal anxiety, soothing herbals (Valeriana, Leonurus) or drugs which contain them are used, or ,in case of more severe symptoms, anxiolytics (Vorobyova O.V., 2009). Benzodiazines are used to relieve acute anxiety symptoms and should not be used for more than 4 weeks because of the possible addiction syndrome. In case of a risk of chronic disorder (disorder progression for more than three months), the

treatment with selective serotonin reuptake inhibitors (SSRIs) should be discussed. In addition, adverse effects which occur on antidepressant therapy (nausea, drowsiness, sexual dysfunction) often lead to refusal of therapy.

This study represents data of efficacy and safety of a solid, non-sterile dosage form based on a pharmaceutical composition of microencapsulated glycine and magnesium stearate (Glycine) in patients that suffer from adjustment disorder with a predominance of emotional disturbance.

The randomized placebo-controlled study of Glycine efficacy and safety for adjustment disorder treatment was performed at the Boundary Psychiatry Department of the V.P. Serbsky National Research Centre for Social and Forensic Psychiatry on two bases: the 1st is the unit of new tools and methods of therapy on the basis of psychiatric hospital №12 (study manager is Prof. A.S. Avedisova); and the 2nd is the Department of psychosomatic disorders on the basis of the Department of Intermediate Level Therapy of the Sechenov Medical University and the IHD Department of A.L. Myasnikov Institute of Cardiology(study manager is Prof. L.V. Romasenko). Patients that included in the study had adjustment disorder with a predominance of emotional disturbance (F43.23 in ICD-10), with mainly anxious symptoms, aged from 18 to 65, with assigned anxiolytic therapy, and with the general severity of disorder of 3 or less points on a Clinical Global Impression – Severity (CGI-S) scale (at the time of including to the study).

Patients were excluded from the study in case of a severe drug allergy or a history of hypersensitivity, or an established hypersensitivity to glycine, as well as patients with a disorder associated with alcohol or psychoactive drug (according to ICD-10 criteria), and also patients with depressive disorder, organic lesion of the central nervous system and schizophrenia. Anxiety level of patients on the Hamilton – Anxiety Scale (HAM-A) did not exceed 25 points.

A total of 64 patients were included in the study. After randomization, they received Glycine or a placebo after a 7-day wash-out period. Glycine was administered as a monotherapy in a dose of 300 mg/day for 28 days. The Glycine was administred in a form of 100 mg sublingual (or buccal) tablets (which contained microencapsulated glycine and magnesium stearate), three times a day. Patients of the placebo group received a placebo in the same regimen.

The condition of the patients was studied on the basis of the HAM-A Scale, the CGI-S scale, and the General Clinical Impression – Improvement (CGI-I) Scale, which scores were estimated by the clinician during the interview with the patient. Also the Sheehan Anxiety Scale (SAS), which shows the patient's subjective assessment of his condition, was used. The scoring was performed for the first time before the inclusion of the patient in the study, and then during the

therapy weekly (7^{th}, 14^{th}, 21^{st} and 28^{th} days of treatment). The Glycine tolerability was evaluated on the basis of the UKU Side Effects Rating Scale, which includes the description of the undesirable effects, the date of its appearance, duration, the association with the drug under study, and also with the assessment of the vital parameters (blood pressure, heart rate) and laboratory tests (general and biochemical blood analysis, urine analysis).

The average age of the patients was 44.5 ± 14.1 years. There were more women (71.9%) among the patients.

The comorbide psychiatric disorders were not diagnosed in the patients. Psychopathologic abnormalities in medical history were found in 7 patients (10.9%): in 4 cases it were depressive disorders, in one case it was anxiety disorder, neurasthenia and adjustment disorder with predominance of emotional disturbance.

Associated somatic diseases were diagnosed in 56 patients (87.5%), and this disorders were the main stress factor for patients. However, only 13 people during this study needed for therapy with somatic drugs (20.3%). One patient before the inclusion in the study received therapy with a psychotropic drug (clonazepam).

Background characteristics of both placebo and Glycine groups are represented in Table 1.

During the therapy, there were following changes in patients: on the 28th day 82.4% of patients who received Glycine marked an improvement of their condition, while in the placebo group there were only 14.3% of such patients. Almost in 40% patients in placebo group there was no any dynamics in a condition (Table 2).

The average HAM-A score at the end of the 4 weeks-long therapy in the Glycine group was 14.97, meanwhile in the placebo group it was 18.54 points. Thus, the reduction of the average total HAM-A score after 4 weeks of therapy in the Glycine group was 6.59 points (31%), whereas in the placebo group it was only 3.16 points (15%) or half as much as during active Glycine therapy. (Figure 1, Table 3).

Reduction of average score on the mental anxiety subscale (HAM-A) after 28 days of therapy in the Glycine group was 38%, in the placebo group – 18% (Table 4).

Reduction of average score on the somatic manifestation of anxiety subscale (HAM-A) after 28 days of therapy in the Glycine group was 31%, in the placebo group – 10% (Table 5).

Thus, ideational symptoms of anxiety were more reduced compared to somatic symptoms during the therapy by Glycine. But, overall, dynamics is

comparable in both cases, and is significantly higher than reduction of symptoms during the placebo therapy, for both psychotic and somatic manifestations.

According to obtained results, the subjective assessment by patients of their condition and its dynamics was higher than objective data. However, as an objective assessment, patients noted the advantages of active therapy compared to placebo: reduction of symptoms according to the Shihan Self-Assessment Scale in the Glycine group was 74.8%, and in the placebo group – 52% (Figure 2).

Thus, the results of the study confirm the efficacy of glycine and its advantages compared to placebo in this number of patients; Glycine therapy resulted with improvement in all measured parameters. Confirmed improvement was registered in the total scores of the HAM-A scale and its two subscales (somatic and psychic anxiety). The change of the entry average total score of HAM-A was significant (chi-square, $p < 0.0001$). 28 patients (82.4%) treated with Glycine achieved a significant improvement of the score on CGI-I scale, whereas in the placebo group there were 14.3% such patients.

Undesirable effects (AE) were registered in 3 patients in the Glycine group on the 7th day of therapy. In the placebo group AE did not occur. One of the patients had an impaired concentration, asthenia, drowsiness, an increase in the duration of sleep; these phenomena completely disappeared to the 14^{th} day of therapy (this AE was moderately severe). The second patient noticed dry mouth and thirst, it was mild and stopped by the 28^{th} day of therapy. In the third patient there was a moderately severe impaired concentration, which was reduced to the 28^{th} day of therapy. The most frequent adverse event was a concentration disorder (observed in 2 patients out of 3).

There were no clinically significant changes in vital characteristics (blood pressure, heart rate) and results of laboratory tests (general and biochemical blood analysis, general urine analysis) in relation to background research. No AE have been recorded either in the vital characteristics or in the results of laboratory studies.

In order to further study the glycine effect, a placebo-controlled study of its effect on the psychophysiological and neurovegetative parameters of patients with an adjustment disorder with violation of other emotions was made. First of all, the sub-study was conducted in order to assume psychophysiological characteristics of futher list of parameters: sensorimotor activity (based on the dynamics of latent and motor periods of simple and differentiated visual and motor reactions); volume, productivity and time of trace consolidation of short-term and operative memory; stability parameters (volume and concentration) and focus of attention; microcoordinate activity (based on the evaluation of tangencies frequency and

periods of static (resting tremor) and dynamic (tremor of tension) tremorometry). Thus, 14 people were examined, 8 of them received glycine, 6 – placebo.

The vegetative status of the patients was studied by evaluating the vegetative tone parameters (the rest state, without load), vegetative reactivity (eyeball-heart reflex, sinus reflex), and the vegetative activity support (ortho- and clinostatic tests) by variational and vector cardiointervalography. The study was carried out on the basis of KPFK-99 and VNS-Polyspectr – the automatic systems of psychophysiological diagnosis.

On the basis of this psychophysiological and neurovegetative study, the following psychophysiological effects of the drug were revealed:

– glycine had a selective effect on the characteristics of the autonomic (vegetative) nervous system while acting on the segmental part of autonomic regulation by enhancing parasympathetic activation and this way suppressing sympathetic activation (reciprocal effect); but glycine had no effect on suprasegmental vegetative regulation;

– glycine had a positive effect on the pathological element of the resting tremor by reducing its frequency.

Based on the above, it can be assumed that the effects of the drug are caused by its selective M2-cholinomimetic activity, which is indirectly evidenced by changes in psychophysiological and neurovegetative parameters. The drug has a vagotonic effect, which nature is apparently sedative, because at the same time lengthening of the reaction time motor periods and a decrease in the frequency of the pathological component of the resting tremor were registered. The study's design did not include course therapy; however, it can be assumed that the drug has indirect cognitotrophic effect in case of its long-term administration which is associated with the neurometabolic effects of the drug (trophotropic process). In model experimental systems in laboratory animals it was shown that local increase of Glycine concentration leads to reversible dilatation of arterioles of the Pia mater (Podoprigora et al., 2005), this effect also repeated after the second addition of the Glycine solution and can be observed in various tissues (Podoprigora et al., 2009). In addition, a steady increase in fluorodeoxyglucose in the brain of rats, which were pretreated with Glycine, has been observed in PET-CT studies (Blagosklonov et al., 2007a, Blagosklonov et al., 2007b). These observations indicate possible improvements in trophic brain function due to glycine, which leads to an increase of the metabolic responses' lability of neurons and an improvement in patient adaptation.

Study performed safety of Glycine; the drug was well tolerated by patients, with no premature exceptions due to adverse effects. All adverse events (impaired

concentration, asthenia, drowsiness, prolonged sleep, dry mouth and thirst) were evaluated by researchers as light or moderate. There were no recorded cases of clinically significant changes in laboratory tests and vital signs.

Discussion

Background estimates of the disease severity indicate the mild anxiety affect in the number of patients (in accordance with the average initial scores of CGI-S and HAM-A scales. CGI scores and all other efficacy indicators show improvement in patients who received glycine after a 4-week study period, including total scores of the HAM-A subscale which indicate a reduction in both symptoms of both ideator anxiety and somatic and vegetative symptoms. In this group, 82.4% of the patients showed marked improvement in the CGI score, whereas in the placebo group there were 14.3% patients with improvement. Glycine showed itself as safe and well tolerated drug in this study; none of the patients was excluded prematurely due to adverse effects. All adverse effects (impaired concentration, asthenia, drowsiness, prolonged sleep, dry mouth and thirst) were evaluated by researchers as light or moderate. According to the results of psychophysiological and neurovegetative studies, glycine has a vagotonic effect of sedative nature.

The use of placebo control revealed the superiority of glycine over placebo, in all measured parameters, for the treatment of an adjustment disorder with emotional disturbance.

Conclusion

The results of the study confirm the efficiency of Glycine and its superiority over placebo in this number of patients with improvement of all studied parameters. The vast majority of patients who received glycine (82.4%) achieved a significant improvement in the CGI-I scale, whereas in the placebo group there were only 14.3% of such cases. Glycine was safe and well tolerated by patients in this study, with no premature exceptions to the study due to adverse effects. Not a single case of a clinically significant change in laboratory tests or vital parameters was observed during the administration of glycine.

Thus, this study confirmed the efficacy of a solid, non-sterile dosage form based on a pharmaceutical composition of microencapsulated glycine and magnesium stearate, and also good tolerability of glycine and its superiority over placebo in case of mild anxiety treatment in patients suffering from an adjustment disorder with a predominance of emotional disturbance.

Tables and Figures

Table 1.

Background characteristics

Factor		**Glycine, 34 people**	**Placebo, 30 people**
Average age		**44.4±13.9**	**44.6±14.4**
Sex Number (%)	Female	24 (70.6%)	22 (73.3%)
	Male	10 (29.4%)	8 (26.7%)
Average score on HAM-A scale		21.56±1.7	21.7±2.1
Average score on CGI scale		2.59±0.5	2.63±0.5
Average score on SAS scale		7.7±7.8	7.6±5.8

Table 2.

Patients' dynamics in both groups on CGI scale

Score on CGI scale	**Group**	**Day of therapy**			
		7	**14**	**21**	**28**
5 – slight impairment	Glycine	–	–	–	–
	Placebo	3.3% (1)	3.3% (1)	–	–
4 – no changes	Glycine	8.8% (3)	2.9% (1)	–	–
	Placebo	53.3% (16)	50% (15)	50% (14)	39.3% (11)
3 – slight improvement	Glycine	35.3% (12)	14.7% (5)	5.9% (2)	2.9% (1)
	Placebo	33.3% (10)	30% (9)	21.4% (6)	25% (7)
2 – remarkable improvement	Glycine	44.1% (15)	32.3% (11)	23.5% (8)	14.7% (5)
	Placebo	10% (3)	13.3% (4)	25% (7)	21.4% (6)
1 – significant improvement	Glycine	11.8% (4)	50% (17)	70.6% (24)	82.4% (28)
	Placebo	–	3.3% (1)	3.6% (1)	14.3% (14)
The statistical significance of the differences (chi-square)		$p<0.001$	$p<0.001$	$p<0.001$	$p<0.001$

Table 3.

Reduction of an average score on HAM-A scale (2)

Group	**Day of therapy**					
	-7	**0**	**7**	**14**	**21**	**28**
Glycine	21.56 (100%)	21.53 (99.9%)	18.79 (87%)	16.76 (78%)	15.53 (72%)	14.97 (69%)
Placebo	21.7 (100%)	21.83 (100.6%)	20.8 (96%)	20.3 (93.5%)	19.25 (89%)	18.54 (85%)

Table 4.

Reduction of average score on the mental anxiety subscale HAM-A

Group	Day of therapy					
	-7	**0**	**7**	**14**	**21**	**28**
Glycine	100%	100%	84%	73%	65%	62%
Placebo	100%	100.1%	96%	92%	85%	82%

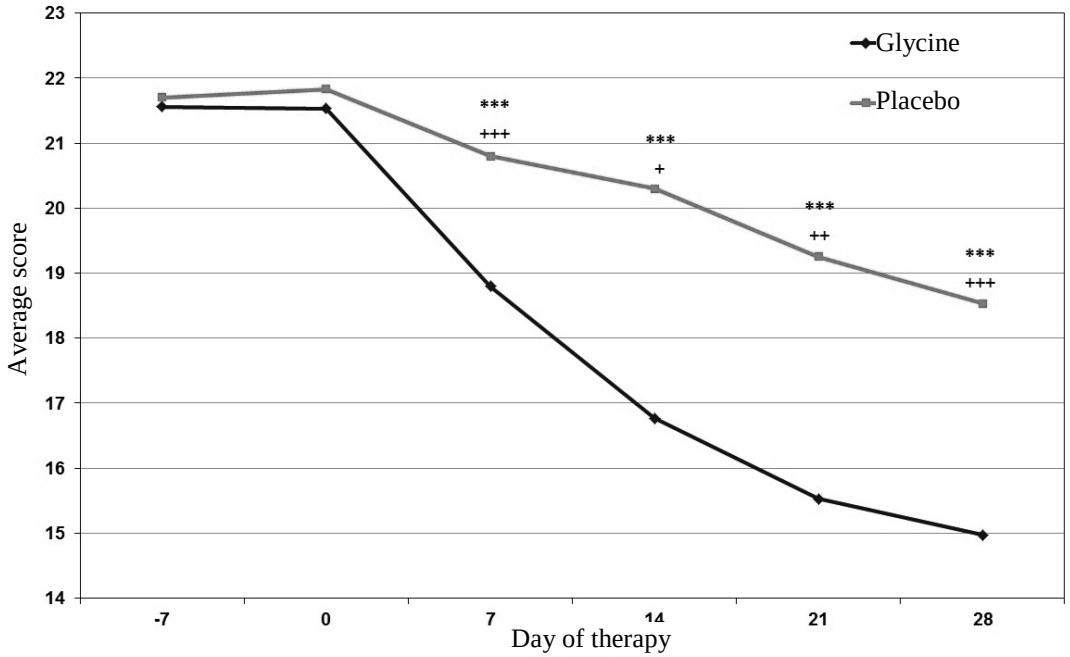
Table 5.

Reduction of average score on the somatic anxiety subscale HAM-A compared to background value

Group	Day of therapy					
	-7	**0**	**7**	**14**	**21**	**28**
Glycine	100%	99.7%	90.7%	84%	80.5%	79%
Placebo	100%	100%	96%	95%	94%	90%

Figure 1.

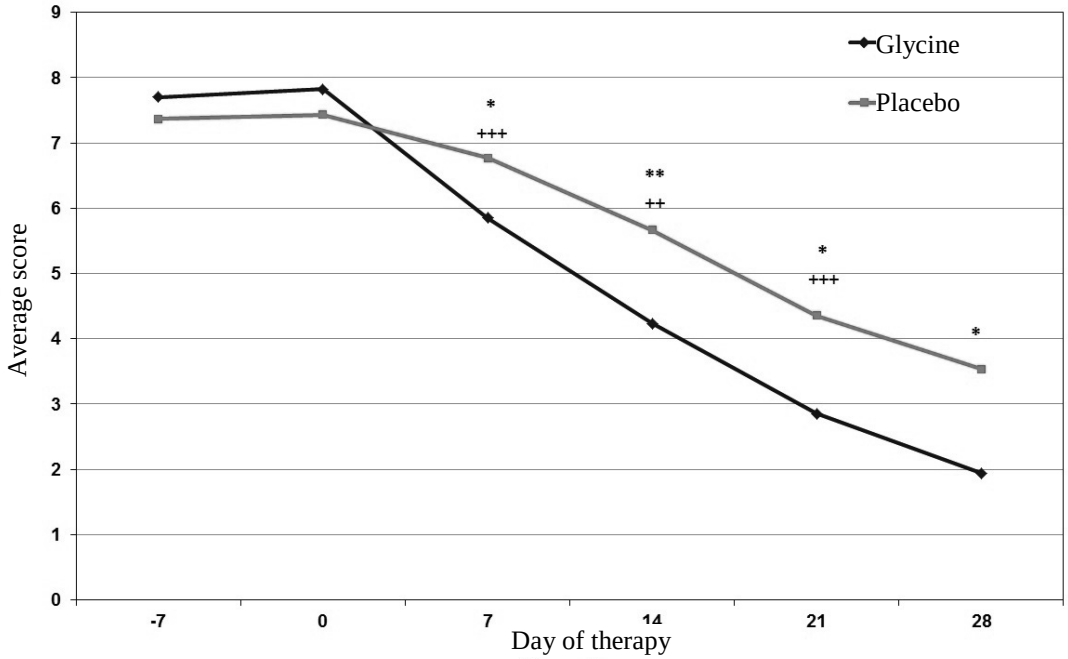
Reduction of an average score on HAM-A scale (1)



Differences compared to background within the group (fig. 1): + $p<0.05$ (placebo — 14th day); ++ $p<0.01$ (placebo — 21st day); +++ $p<0.001$ (glycine — 7th day, placebo — 28th day).

Differences between the groups: ** $p<0.01$ (7th day); *** $p<0.001$ (14th day).

Figure 2.
Reduction of an average score on SAS scale



Differences compared to background within the group (fig. 1): ++ $p<0.01$ (placebo — 21st day); +++ $p<0.001$ (glycine — 7th day, placebo — 21st day).
Differences between the groups: * $p<0.05$ (7th, 21st and 28th days); ** $p=0.01$ (14th day).

Literature

1. Александровский Ю.А. Предболезненные состояния и пограничные психические расстройства. — Литтерра, 2010. — 272 с.
2. Александровский Ю.А., Барденштейн Л.М., Аведисова А.С. Психофармакотерапия пограничных психических расстройств. — М.: ГЭОТАР МЕДИЦИНА, 2000. — 250 с.
3. Воробьева О.В. Стресс и расстройства адаптации. — РМЖ. 2009. — Т. 17, № 1 (350). — С. 789-793.
4. Международная классификация болезней (10-й пересмотр). Классификация психических и поведенческих расстройств (Клинические описания и указания к диагностике). — ВОЗ. — СПб: Адис, 1994.
5. American Psychiatric Association (1980). Diagnostic and Statistical Manual of Mental Disorders, 3d ed. (DSM-III). Washington, DC: American Psychiatric Association.
6. American Psychiatric Association (1994) Diagnostic and Statistical Manual of Mental Disorders (4th edn) (DSM-IV), Washington, DC: APA.
7. Andreasen, N.C. & Hoenk, P.R. (19S2) The predictive value of adjustment disorders: a follow-up study. American Journal of Psychiatry, 139, 584-590.

8. Blagosklonov O., Podoprigora G.I., Davani S., Nartsissov Y. R., Comas L., Boulahdour H., Cardot J.C. (2007). FDG-PET scan shows increased cerebral blood flow in rat after sublingual glycine application. Nuclear Instruments and Methods in Physics Research, Section A: Accelerators, Spectrometers, Detectors and Associated Equipment, 571, 30-32.
9. Blagosklonov O., Podoprigor G.I., Pushkin S.V., Nartsissov Y.R., Comas L., Cardot J.C., Boulahdour H. (2007). Correlation between direct microscopy and FDG-PET in the study of cerebral blood flow in rats. Proc. SPIE Int. Soc. Opt. Eng., 6626, 66260P1-5.
10. Bronisch T. (1991) Adjustment reactions: a long-term prospective and retrospective follow-up of former patients in a crisis intervention ward. Acta Psychiatrica Scandinavica, 94, 86-93.
11. Brugha T.S., Bebbington P.E. & Jenkins R. (1999). A difference that matters: comparisons of structured and semi-structured psychiatric interviews in the general population. Psychological Medicine, 19, 1013-1020.
12. Casey P, Dowrick C, and Wilkinson G Adjustment disorders British Journal of Psychiatry 2001; 179: 479-481.