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EVALUATION EFFICIENCY OF MODERN ANTIDEPRESSANTS BY MEANS OF QUANTATIVE PHARMACO-EEG

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Abstract

Introduction. Currently, topicality the problem of diagnosis and treatment of depressive disorders (DD) in medical practice is not in doubt. The drugs of choice in the treatment of this affective disease are the selective serotonin reuptake inhibitors (SSRIs). One of the best known and widely used today of representatives a number of SSRIs is fluoxetine. An example perspective way to improve the pharmacotherapy of depression is to combine SSIRs with representatives of other groups of drugs. Great interest from this point of view is the hormone of pineal gland - melatonin (MT), which is an important element of the non-specific antistress system of body. One more potentially significant vector of perfecting therapy is searching/development of the new, more potent and fast-acting antidepressants. In this respect, the attention of researchers attracts agonist to MT_1- and MT_2-receptors and antagonist to 5-HT_{2C}-receptors - valdoxan. **Materials and methods.** In this study, by means of quantitative pharmaco-EEG (QPEEG) was performed a comparative evaluation of pharmacological activity of valdoxan, fluoxetine and combination of fluoxetine with melaxen during rat's experimental depression (ED) and depressive disorder (DD) in patients. Pharmacoeconomic analysis was performed by the method of "cost/effectiveness". **Results and discussion.** It was established that reception of valdoxan and combined fluoxetine with melaxen promotes a more rapid normalization of bioelectric activity of brain than at fluoxetine usage separately. So, on the EEG at rats with ED was registered significant increase of theta-rhythm activity, which dominates in the norm, and at patients with DD this regime of pharmacotherapy normalized the distribution of the alpha-rhythm and reduced slow-wave activity. **Conclusions.** Evaluation efficiency of the above regimes of pharmacotherapy of depressive frustration showed, that the application of valdoxan, and also combination fluoxetine+melaxen favorably affects the course of the disease and contributes to a more rapid normalization of bioelectric activity of brain than fluoxetine in isolation, both experimentally and clinically.

Keywords: depression, rats, patients, valdoxan, fluoxetine, melaxen, pharmaco–EEG.

Introduction. Currently, there is a distinct increase of the DD in the general population [1] and in patients with chronic somatic diseases [2].

According to the principles of evidence-based medicine group of antidepressants – selective serotonin reuptake inhibitors (SSRIs) are considered

as standard and must be included in the plan for the treatment of affective disorders. SSRIs, as we know, have a wide range of pharmacological effects, including: anxiolytic, expressed analgetic and antipanic. Clinical efficiency of this group of antidepressants is proved at treatment of chronic pain, bulimia, obesity, alcoholism, obsessive-compulsive frustration, panic frustration etc. [3, 4].

Among the best known and widely used today of representatives a number of SSRIs reversible type of action is fluoxetine. This drug increases the extracellular concentrations of serotonin, slightly influences on norepinephrine and dopamine and almost not modulates the activity of choline- and histamine H_1-receptors. This explains the absence sedative and cardiotoxic potential of this drug. If we compare fluoxetine with antidepressants of other groups (three- and heterocyclic), it can be described as the drug with a minimum of side-effects, and more secure, even at absolute overdose [5]. However, at the majority of patients, who use fluoxetine, observed anxiety, agitation, sleep disturbances, sexual dysfunction [6, 7].

One of the most perspective ways to improve the pharmacotherapy of depression is to combine SSIRs with representatives of other groups of psychotropic (and other) drugs. Thus, there is evidence on the joint use of antidepressants with antipsychotics in order to improve the treatment of psychosis and drug-resistant forms of depression [8]. But of much greater interest to the combined pharmacotherapy of depression is the hormone of pineal gland - melatonin (MT), which is an important element of the non-specific antistress system of body and control cycle "sleep-wake" [9].

But, one more potentially significant vector of perfecting of antidepressive therapy is searching/development of the new, more potent and fast-acting antidepressants including those with unique mechanisms of action. In this respect, the attention of researchers and practitioners attracts valdoxan, whose action is based on the agonism to MT_1- and MT_2-receptors and antagonism to 5-HT_{2C}-receptors [10].

Purpose of the study.

The main objective of our research was to analyze changes of the indices of bioelectric activity of brain by means of QPEEG dynamics in rats with ED and in patients with ED during treatment by modern antidepressants.

Materials and methods.

The object of the experimental study were 120 white outbred male rats weighing 150-180 g (at beginning of experiment), which were divided into 5 groups (2 - control and 3 - experimental) 30 animals in each. Control groups were as follows: the intact rats (group C) (n=30) and rats, with modelled ED (group D) (n=90). Group D was subsequently divided into 3 experimental groups, in which animals during the experiment had a *per os* treatment by following drugs: fluoxetine in dose of 0.3 mg/kg/day (group F) (n=30); valdoxan in dose of 0.5 mg kg/day (group V) (n=30); fluoxetine - 0.3 mg/kg/day and melaxen 0.05 mg/kg/d (group F+M) (n=30). Modeling rat's ED included 3 stages: stage 1 (the 1st week) - the animals once a day were exposed to a 2-hour immobilization in a plastic container; stage 2 (the 2nd week) - once a day, for 30 minutes induced water-immersion cold stress; stage 3 (3-4 weeks) - was applied 2 above-stated stress factors. Throughout all 4 weeks of experiment the animals were also subjected to chronic exposure to light. EEG recording was made on the 7th, 14th and 21st days of receiving the drugs. According to stereotaxic coordinates to rats of all groups to the area of somatosensory cortex (SSC) and CA_1 region of hippocampus (HC) symmetrically on both sides microelectrodes were implanted, and after 3 days EEG was recorded. Next, the rats of experimental groups for 3 weeks of experiment had a *per os* treatment by studied drugs.

In a clinical study 45 people were included. Group D (n=45) consisted of patients with a diagnosis of DD moderate; group C (n=17) - practically healthy people; group F (n=15) - patients treated for 42 days fluoxetine in dose of 20 mg/day *per os* once in the morning after food; group V (n=15) - patients treated for 42 days valdoxan in dose of 25 mg/day *per os* once hour before bedtime and, finally, group F+M (n=15) - patients treated for 42 days combination of fluoxetine with melaxen *per os* at doses of 20 mg/day once in the morning after food and 3 mg/day once hour before bedtime, respectively. The criteria take into account the effectiveness of pharmacotherapy EEG data in patients before prescribing medication and on the 14th, 28th and 42th days of treatment.

Register EEG in experiment and clinical study was registered with usage 8-channel encephalograph EEGA-21/26 "Encephalan 131-03" ("Medicom-MTD", Russia), in accordance with the generally accepted rules. We analyzed the relative values of power (RVP) (%) for delta- (δ-), theta- (θ-), alpha- (α-) and beta- (β-) frequency EEG bands.

Pharmacoeconomic analysis was performed by the method of "cost/effectiveness". The outcome of this analysis was the cost-effectiveness ratio, calculated by the formula: CEA = cost of treatment (RUB.) / RVP (%) of α-rhythm in the occipital region.

Results and discussion.

During the analysis of indexes EEG rhythms in the experimental part of our work it was established that for group was characteristic significant dominance of θ-rhythm in all leads, its larger activity was noted in HC, than in SSC. δ-rhythm was

considerably less, and α- and β-rhythms were virtually not registered.

At the ED distribution of power values of EEG rhythms in rats changed in such a way that the θ-rhythm significantly decreased, and began to dominate the δ--rhythm. RVP (%) EEG rhythms of rats at reference state and at the ED are shown in Table 1.

Table 1.

The comparative characteristic of RVP (%) of EEG rhythms of rats at reference state and at the ED.

ELECTRODE LOCALIZATION	EEG RHYTHM	GROUPS OF ANIMALS	
		C	D
HC	δ	22,29±2,71	58,99±4,83**
	θ	60,95±4,06	29,27±3,65**
	α	7,00±0,38	5,61±0,26
	β	9,76±0,38	6,13±0,92
SSC	δ	27,43±2,34	52,80±5,02**
	θ	56,84±5,89	35,34±3,39**
	α	6,74±0,29	5,80±0,33
	β	8,99±0,34	6,24±0,36

Note: *- at p<0.05 as compared to animals of group C; ** - at p<0.01 as compared to animals of group C.

On the 7th day in group F, where rats received fluoxetine, change of EEG rhythms consisted in reliable decrease δ- and a slight increase in θ-activity as compared to indexes at ED.

At introduction of valdoxan (in group V) changes of RVP of EEG rhythms affected mainly δ-rhythm, which decreased significantly in 2 times in the SSC and a little less - in HC, but θ-rhythm, on the contrary, progressively increased in both zones registration. β-activity has also undergone a change in the direction of increasing, exceeding the value of C in the SSC of 1.6 times.

In the study of RVP of EEG rhythms in rats in group F+M, there was a significant decrease in the level of δ- and a slight increase - θ-range compared to the ED. In addition, in both derivations recorded increase β-rhythm, which was to prevail over the performance of C is almost 2 times (Table 2).

Table 2.

The comparative characteristic of RVP (%) of EEG rhythms of rats of groups F, V and F+M on the 7th day of introduction.

ELECTRODE LOCALIZATION	EEG RHYTHM	GROUPS OF ANIMALS		
		F	V	F+M
HC	δ	45,57±3,96**$^{\#}$	27,43±2,57$^{\#\#}$	41,48±3,96**$^{\#}$
	θ	38,05±3,14**$^{\#}$	44,28±3,65**$^{\#\#}$	35,61±1,57**$^{\#}$
	α	7,56±0,64	6,94±0,50	7,11±0,77
	β	8,82±0,63	10,45±0,69$^{\#}$	13,81±2,04*$^{\#\#}$
SSC	δ	43,96±2,84**$^{\#}$	23,90±1,82$^{\#\#}$	37,37±2,19*$^{\#\#}$
	θ	40,54±3,50**	42,36±2,77*	36,32±2,13**
	α	5,85±0,52	6,99±0,45	6,79±0,80
	β	8,65±0,42	14,60±3,67*$^{\#\#}$	16,52±3,69**$^{\#\#}$

Note: *- at p<0.05 as compared to animals of group C; ** - at p<0.01 as compared to animals of group C; $^{\#}$ - at p<0.05 as compared to animals of group D; $^{\#\#}$ - at p<0.01 as compared to animals of group D.

On the 14th day of observation at rats in group F δ-rhythm progressively decreases, the θ-rhythm increased; β-activity strengthening, more expressed in the field of SSC, than in HC.

At rats to whom entered valdoxan the θ-rhythm with excess of its values in all recorded assignments (especially - in HC) in comparison with indexes of norm dominated. The δ-rhythm was below values of group C, and the β-rhythm remained increased in the field of SSC.

At introduction of a combination of MP in the F+M group the δ-rhythm decreased twice in relation to indexes at ED, a θ-rhythm, increased, but did not reach original values. Power of a β-rhythm increased more, than twice in both assignments in comparison with the indicators received and at ED, and is normal (Table 3).

Table 3.

The comparative characteristic of RVP (%) of EEG rhythms of rats of groups F, V and F+M on the 14th day of introduction.

ELECTRODE LOCALIZATION	EEG RHYTHM	GROUPS OF ANIMALS		
		F	V	F+M
HC	δ	36,11±2,22**$^{\#\#}$	14,43±3,57*$^{\#\#}$	30,93±2,01**$^{\#\#}$
	θ	42,86±3,43**$^{\#\#}$	68,28±3,65$^{\#\#}$	49,07±3,75*$^{\#\#}$
	α	6,51±0,55	6,64±0,23	6,87±0,57
	β	16,20±2,36**$^{\#\#}$	11,65±0,69$^{\#}$	13,13±2,70*$^{\#\#}$
SSC	δ	34,80±2,00*$^{\#\#}$	13,90±2,82**$^{\#\#}$	28,14±2,18$^{\#\#}$
	θ	39,87±2,33**	63,46±3,71$^{\#\#}$	47,11±3,91*$^{\#}$
	α	6,26±0,37	5,69±0,68	6,60±0,91
	β	20,79±2,51**$^{\#}$	16,95±3,67*$^{\#\#}$	17,82±2,86**$^{\#\#}$

Note: *- at p<0.05 as compared to animals of group C; ** - at p<0.01 as compared to animals of group C; $^{\#}$ - at p<0.05 as compared to animals of group D; $^{\#\#}$ - at p<0.01 as compared to animals of group D.

The analysis of the EEG parameters at animals in group F for the 21st day of a pharmacotherapy of fluoxetine showed that the θ-rhythm was synchronized and had the exact distribution, but values of its RVP were authentically below norm. In the field of group of companies they decreased in comparison with indexes at ED by 1,5 (p<0,01), and in the field of SSC - by 1,2 (p<0,05). Indexes of RVP of a δ-rhythm did not reach norm and remained increased: in assignment of group of companies - by 1,6 times, and in SSC - by 1,2 times, at the same time having decreased concerning indexes at ED both in group of companies, and in SSC by 1,5 (p<0,01). RVP of a β-rhythm in the field of HC obviously increased in 2 (p<0,01), and in SSC - by 3 times (p<0,01) in comparison with group D, and on comparison by group C. The α-rhythm remained invariable, and corresponded to values of norm (figure 1).

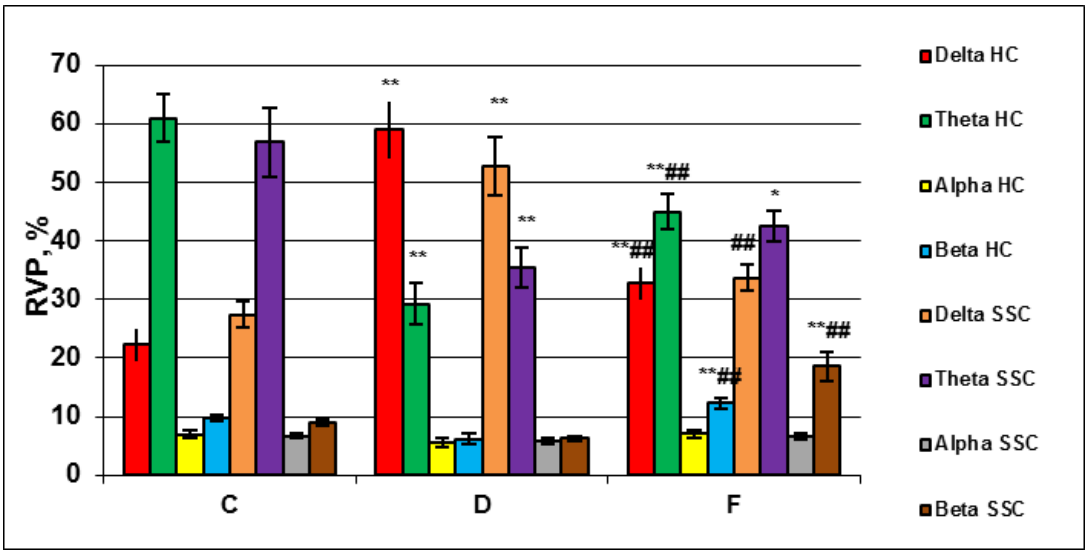

Figure 1. Distribution of RVP of EEG rhythms of rats for the 21st day of introduction of fluoxetine.

Note to figures 1-3: on an axis of ordinates – RVP (%), on an abscissa axis – groups of rats and an EEG rhythms in SSC and HC; * at p<0.05 as compared to animals of group C; ** - at p<0.01 as compared to animals of group C; $^{\#}$ - at p<0.05 as compared to animals of group D; $^{\#\#}$ - at p<0.01 as compared to animals of group D.

At the rats receiving valdoxan, RVP values and θ-and δ-rhythms were restored in the conditions of ED much quicker. Low indicators of δ-activity in comparison with monitoring in 1,4 - 1,9 (p<0,05) in both assignments were noted. The θ-rhythm exceeded input datas both in the field of SSC, and in HC for 16% (p<0,05). Recorded increase in twice RVP of β-rhythm in SSC (p<0,01) (figure 2).

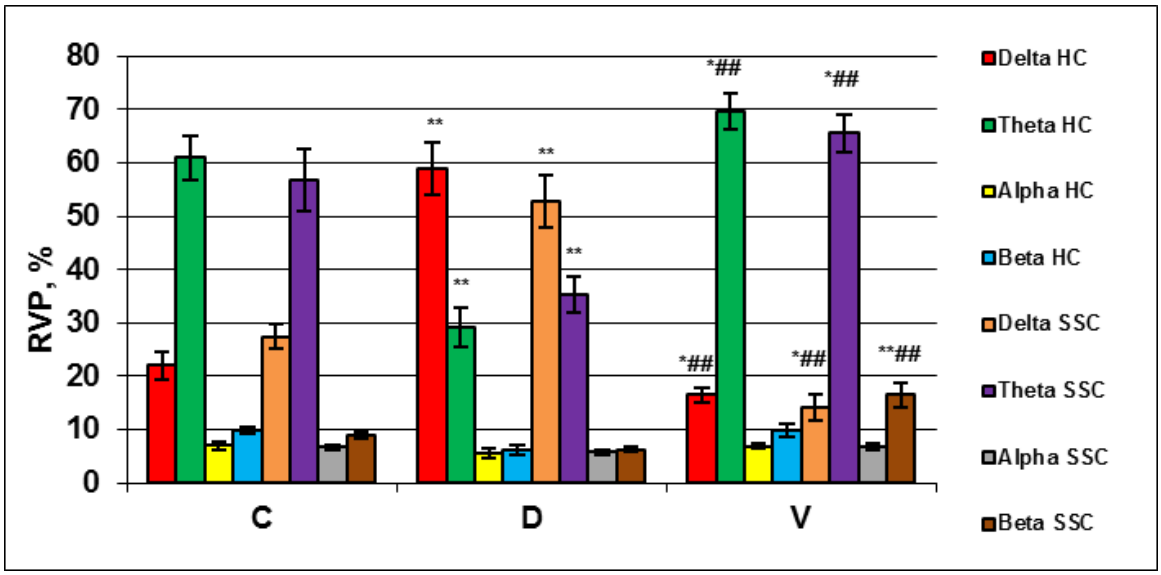

Figure 2. Distribution of RVP of EEG rhythms of rats for the 21st day of introduction of valdoxan.

At animals of the F+M group indexes were similar with group F, except minor changes of activity of a β-rhythm which increased twice ($p<0,01$) in comparison with norm more narrow for the 7th day, and a δ-rhythm which later from the beginning of introduction the combination of drugs corresponded 14 days to monitoring in the field of SSC, but still remained increased by 1,4 times ($p<0,01$) in the field of HC(figure 3).

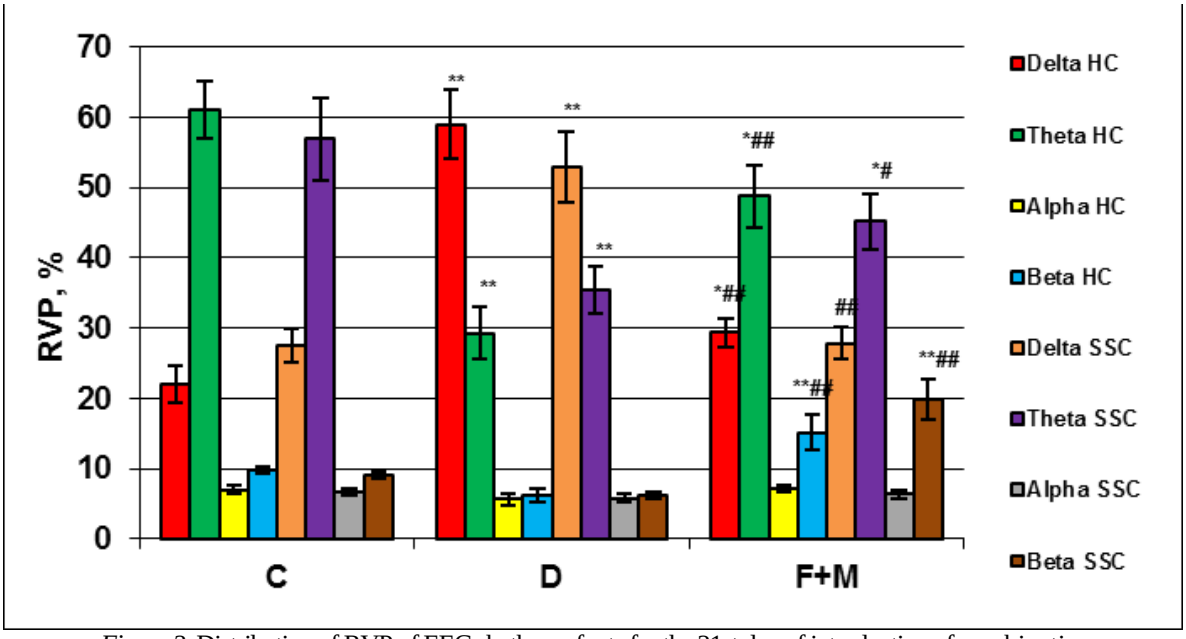

Figure 3. Distribution of RVP of EEG rhythms of rats for the 21st day of introduction of combination of fluoxetine with melaxen.

During the clinical study we defined - how rhythmic activity of the brain at patients with DD of moderate severity and how its parameters are influenced by the carried-out pharmacotherapy antidepressants changes.

In the beginning filing of an EEG at healthy people of group C and patients with DD was carried out (group D). In group C the α-rhythm which was registered in an occipital lead and decreased towards the frontal departments of a brain dominated. The β-rhythm was fixed in the frontal area with gradual decrease to a nape, and δ-and θ-rhythms were a little expressed in all assignments.

When filing an EEG at patients with DD distribution of rhythms significantly changed. The dominating place was taken now by a δ-rhythm, increase in RVP of a θ-rhythm was also noted, and the maximal values of a α-rhythm recorded to the area of a forehead, and in all recorded assignments decrease of RVP of a β-rhythm was observed (table 4).

Table 4.

The comparative characteristic of RVP (%) of EEG rhythms at healthy people and patients with a DD.

ELECTRODE LOCALIZATION	EEG RHYTHM	GROUPS OF PATIENTS	
		C	D
Occipital area	δ	9,28±2,94	41,11±5,69**
	θ	3,47±1,55	15,46±3,69**
	α	76,24±5,55	20,70±2,00**
	β	11,65±4,27	24,37±3,98*
Parietal area	δ	7,36±2,53	37,61±4,68**
	θ	6,17±1,48	16,10±1,52**
	α	59,12±6,87	25,72±3,03**
	β	26,88±2,32	22,19±3,53
Central area	δ	5,20±2,67	30,53±5,97**
	θ	4,54±1,60	8,49±1,78*
	α	33,06±5,38	46,26±6,09*
	β	57,88±7,49	14,80±3,15**
Frontal area	δ	6,21±2,61	36,86±4,34**
	θ	4,09±1,47	7,29±1,81*
	α	25,28±3,85	47,68±6,61**
	β	64,90±7,90	8,17±2,08**

Note: *- at p<0.05 as compared to group C; ** - at p<0.01 as compared to group C.

At the pharmacotherapy of fluoxetine change of EEG rhythms concerned α-rhythm, which began to dominate in occipital area for the 28th day of treatment and was higher in 2,8 (p<0,01) than indexes at a depression. For the 42nd day of a pharmacotherapy of its RVP remained below input datas in 1,3 (p<0,05). The β-rhythm was distributed correctly too, but slightly lagged behind norm in the frontal and central departments for 28% (p<0,05). the δ-rhythm kept authentically high rates of RVP in all recorded assignments (p<0,01), and a θ-rhythm, having reached background values for the 28th day, remained invariable until the end of observation (figure 4).

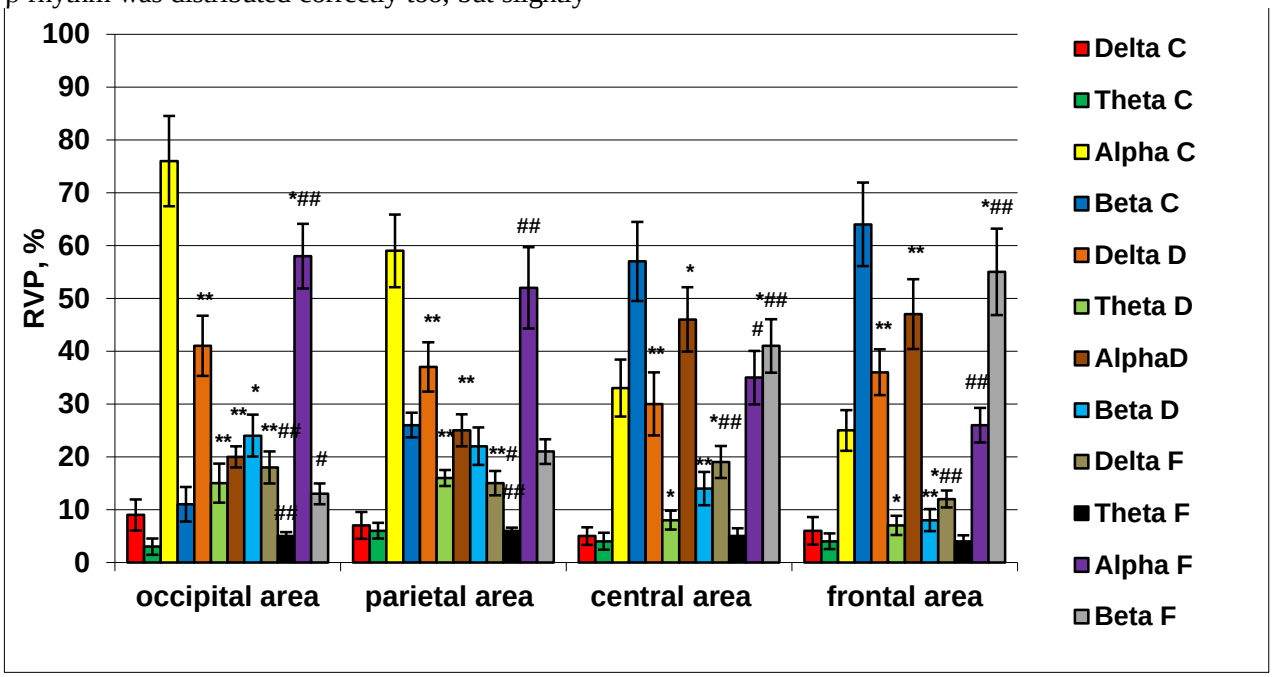

Figure 4. Distribution of RVP of EEG rhythms at patients for the 42nd day of introduction of fluoxetine.

Note to figures 4-6: on an axis of ordinates – RVP (%), on an abscissa axis – the field of registration of EEG rhythms; * at p<0.05 as compared to group C; ** - at p<0.01 as compared to group C; # - at p<0.05 as compared group D; ## - at p<0.01 as compared to group D

Reception of a combination of F+M affected on a rhythmicity, almost similar to that one F. At the 42nd day of a pharmacotherapy α-and β-rhythms did not reach initial indicators, and the δ-rhythm remained increased ≈ 2,5 - 3 in all assignments in comparison with values in group C (figure 5).

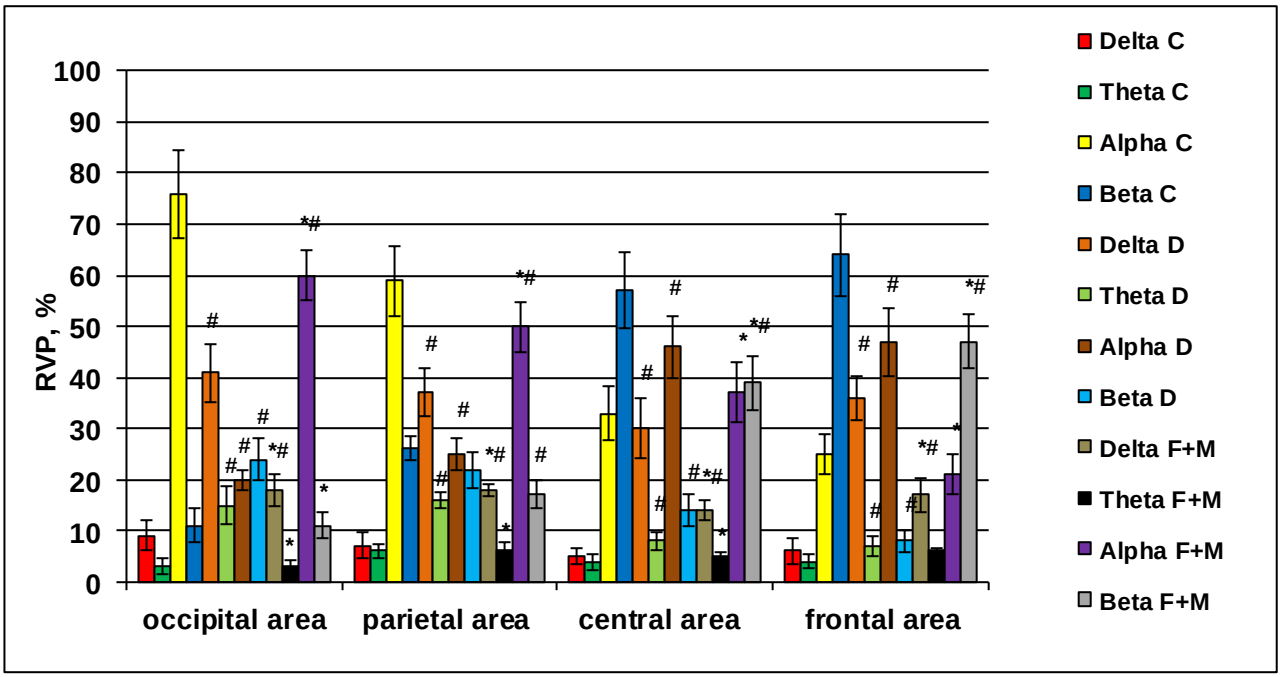

Figure 5. Distribution of RVP of EEG rhythms at patients for the 42nd day of introduction combination of fluoxetine with melaxen.

The analysis of RVP of an EEG rhythms at the patients accepting valdoxan showed that for the 28th day the α-rhythm began to correspond to values in group C, except for occipital area where indicators of its RVP increased only for the 42nd days of a pharmacotherapy and exceeded input datas for 14,4% ($p<0,05$). The β-rhythm was not exposed to special modulations unlike a δ-rhythm which underwent reliable regress: in occipital, parietal and central area- by 4,2–3,4 times ($p<0,01$), and in the frontal area - by 5,1 times ($p<0,01$), having also reached the group C RVP level in all assignments, and for the 42nd days corresponded to input datas. The θ-rhythm reached values of norm more narrow for the 14th day. On the person the fact that patients with DD of moderate severity have an increase and normalization of values of fast-wave activity (α-and β-rhythms) in the respective areas of filing of an EEG against the background of reception In occurs quicker, than against the background of F including at a combination of F+M (figure 6).

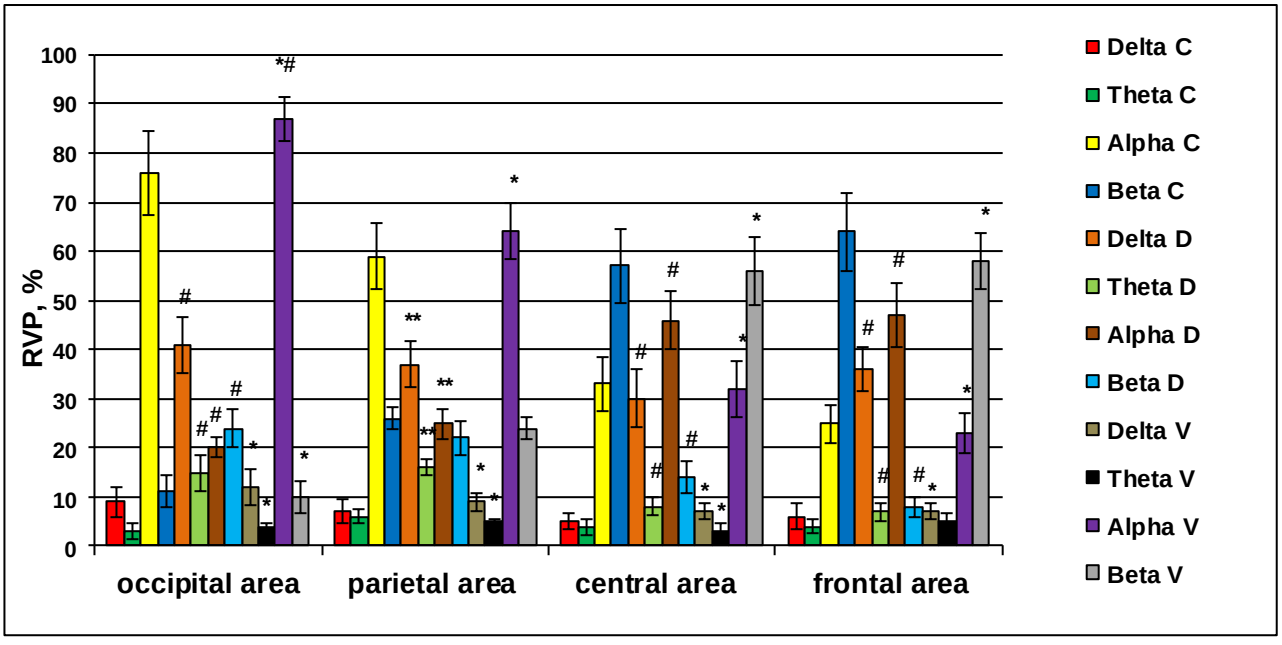

Figure 6. Distribution of RVP of EEG rhythms at patients for the 42nd day of valdoxan.

At finally, the pharmacoeconomic analysis of 2 schemes treatment of DD of moderate severity (valdoxan and a combination fluoxetine + melaxen) by means of the expense/effectiveness method was carried out.

As criterion of effectiveness we accepted a difference (Δ) of RVP values (%) of α-rhythm in occipital area of patients for the 28th and 42nd days of observation in comparison with its indexes at a depression. Data on dynamics of it of an EEG index in groups of comparison are provided in table 5.

Table 5

Dynamics of RVP (%) of α-rhythm in patients comparison groups in the occipital region of the brain

Parameter	Observation time	Group V	Group F+M
RVP (%) of α-rhythm in the occipital area of the brain	Norm	76,24±5,55	
	Depression	20,70±2,00*	
	28 days	60,81±8,95	58,86±6,57*
	Δ by 28 days	40,1±6,2*	38,3±4,3*
	42 days	90,29±4,56*	58,28±5,05*#
	Δ by 42 days	69,6±5,3*	37,6±3,9*#

Note: * - at p<0.05 as compared to original value in this group; # - at p<0.05 as compared to similar value in group V.

Following the results of processing of results it is possible to conclude that the ratio of cost 28 a day course of treatment In to its influence on an indicator of RVP of a α-rhythm exceeds F+M combination, that at application, by 2,2, at the same time this rhythm in both groups does not reach even original values. However, for the 42nd days of a pharmacotherapy this difference became not the so considerable and in group V exceeded the corresponding indicator of the F+M group for 32,5% (i.e. was most of all by 1,4) (figure 7).

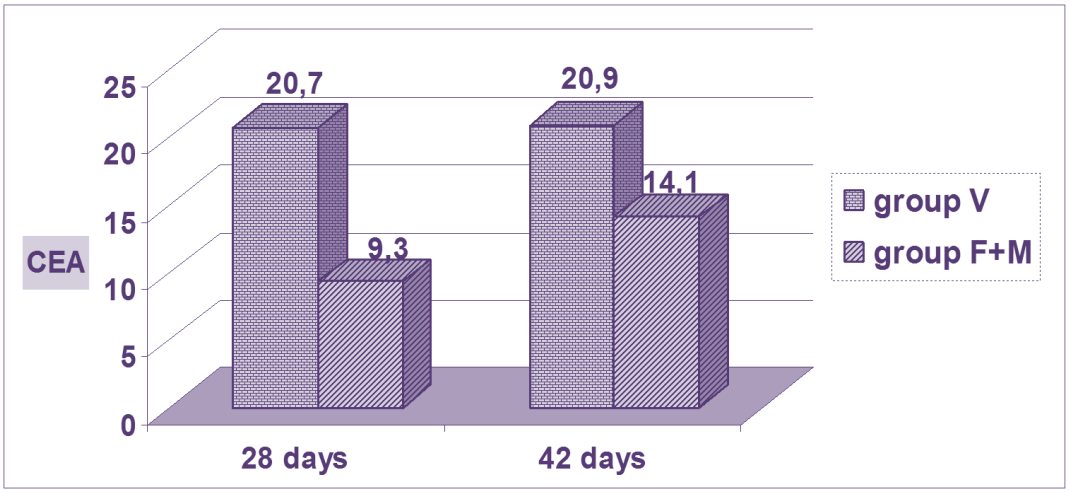

Figure 7. **Cost-effectiveness of pharmacotherapy course at patients surveyed groups on RVP of a α-rhythm of the brain.**

Note: on an axis of ordinates – the drug cost per course of treatment (rub.) / RVP (%) α-rhythm on the 28th and 42th days of observation. On an abscissa axis – the period of observation.

Summary.

According to results of the clinical and experimental study of changes in the bioelectric activity of the brain by means of QPEEG against the background of antidepressant use can be concluded that the low values of θ-rhythm, and also increase δ- and β-activities of brain groups of rats, who received fluoxetine separately or in a combination with melaxen are bound, probably to the presence of this antidepressant anxiogenic effects. The combination of F+M has a similar effect on EEG rhythms in rats with the only difference that the enhancement of β-activity was observed on the first week of introduction of the studied drugs. This, in our opinion, may be associated with the ability melaxen has modulatory effects on subcortical structures of the brain [11].

In turn, valdoxan, not only has a modulating effect on θ-activity detected in all leads, but also reduces the δ-rate increase and β-rate, especially in the SSC. It can be assumed that such changes are associated with a unique mechanism of action of valdoxan, which distinguishes it from other

antidepressants, and, above all, its activating effect on MT_1-and MT_2 – melatonin receptors.

The analysis of RVP of EEG rhythms at patients showed that the main role in modulation of rhythmic activity of a brain at patients of groups F and F+M is played by fluoxetine which, though promotes the exact distribution of a α-rhythm, nevertheless does not allow to be restored to it fully. The same can be told also about β-activity. This drug also promotes preservation of the increased δ-rhythm power in all recorded assignments, that correlates with conclusions of other authors [12, 13].

Based on the above it can be concluded that at pharmacotherapy at valdoxan the rhythmic activity of a brain is characterized by much more rapid positive dynamics of indexes of an EEG from all carried-out treatment options that is explained by the unique mechanism of action of this drug and, in particular, its melatonin-mimetic potential. It is important that unlike the tricyclic antidepressants, SSIRs and inhibitors of MAO valdoxan, according to literature, does not influence serotonin level in the brain [14]. Some importance in realizing the effects of the arrangements may also have antagonism in relation to 5-HT2c-reseptors of serotonin and increased catecholamine (dopamine and norepinephrine) in the frontal cerebral cortex [15].

Thus, summarizing the received results, we can say that the application of a valdoxan, and also combination fluoxetine+melaxen at treatment of depressive frustration of moderate severity, favorably affects the course of the disease and contributes to a more rapid normalization of bioelectric activity of brain than fluoxetine in isolation.

Conclusions.

1. Long-term usage of valdoxan in contrast to the fluoxetine and combination of fluoxetine with melaxen helps to normalize the distribution of EEG rhythms in rats with ED, as evidenced by an increase in RVP of θ-rhythm of 16% in the HC and SSC and increase in RVP of β-rhythm of 2 times in the SSC.

2. QEEG comparative analysis of the results shows that the most favorable effect on the rhythmic brain activity in patients with DD as compared to other circuits has valdoxan therapy, what confirmed, first of all, in the increase of 2.9 times (as compared to the depression) and normalization RVP of α-rhythm EEG already on the 28th day of treatment.

3. By means of pharmacoeconomic analysis was showed that as compared to combination fluoxetine+melaxen for usage valdoxan characterized more favorable values of the coefficient "cost/effectiveness" exceeding those of fluoxetine with melaxen by 32.5% in terms of impact on the bioelectric activity of the brain at patients with depression.

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