

# Comparative Evaluation of Psychopharmacotherapy of Atypical Depression in Bipolar and Recurrent Affective Disorder and Psychogenic Depression

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**Objective:** to evaluate the treatment effectiveness for atypical depression (AtD) depending on its nosology: in bipolar affective disorder (BAD), recurrent depressive disorder (RDD) and psychogenic depression (PD).

**Patients and methods.** A total of 250 patients with depression were screened, of which 77 patients with symptoms of AtD were enrolled in the study, 35 of them with BAD, 18 with RDD, and 24 with PD. Patients in all three groups received an antidepressant (AD) or a mood stabilizer (MS) monotherapy, or a combination of AD and antipsychotic (A), AD and A, MS and A, as well as a combination of AD, A and MS. The patients' condition was assessed clinically using a specially designed questionnaire and MADRS and CGI scales at the baseline and the 2<sup>nd</sup>, 3<sup>rd</sup>, 4<sup>th</sup>, 6<sup>th</sup>, 12<sup>th</sup> weeks of treatment. Quality of life satisfaction was assessed with the Q-LES-Q-SF (Scoring the Quality-of-Life Enjoyment and Satisfaction Questionnaire) scale at the treatment onset and after the 12<sup>th</sup> week of treatment.

**Results and discussion.** Treatment regimens that included AD were the most eff in all groups of patients with AtD. The proportion of responders among those who received AD for bipolar disorder (75% or more) was significantly higher than among those who did not receive it (<50%). In the RDD and PD groups, patients responded significantly better to AD monotherapy (RDD – 93.2%; PD – 91.5%) compared to other regimens. Agomelatine was the most frequently used (31.8%) and effective AD in all groups. Also, escitalopram, vortioxetine, and venlafaxine ( $p < 0.05$ ) showed high efficacy, good tolerance, and absence of side effects that aggravate the main symptoms that characterize AtD. Among the antipsychotics in combination with AD, sulpiride was significantly more effective in patients with PD ( $p < 0.05$ ). The highest rates of quality of life satisfaction were achieved in the BAD group, the lowest – in patients with PD ( $p < 0.05$ ), which indirectly indicates the quality of remission, which is determined not only by the degree of reduction of depressive symptoms but also by the patients' subjective perception of their mental state.

**Conclusion.** The inclusion of AD in the AtD treatment regimen significantly increases its effectiveness in patients of all groups, including BAD. AtD treatment should be administered not only taking into account its clinical signs and severity, but also depending on the nosology of the disease, the characteristics of its course. During drug administration, it is necessary to consider the spectrum of side effects, especially those that increase the symptoms of AtD itself.

**Keywords:** atypical depression; recurrent depressive disorder; bipolar affective disorder; psychogenic depression; psychopharmacotherapy; antidepressants; mood stabilizers; antipsychotics.

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The term «atypical depression» (AD) was first used by P.E. Huston and L.M. Locker in 1948 [1] to describe patients with depression accompanied by agitation, psychotic episodes, and a more pronounced positive response to electroconvulsive therapy (ECT), compared with patients with melancholic depression without psychotic episodes. Subsequently, E.D. West and P.J. Dally [2] began to use the term «atypical» to describe therapy-resistant depression with severe anxiety, positively responding to therapy with iproniazid (non-selective monoamine oxidase inhibitor – MAO) and not accompanied by feelings of guilt, weight loss and disturbances of night sleep. The American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-5) criteria are currently used to diagnose AD, where mood reactivity is a mandatory indicator of atypicality, and, in addition, at least two of the following symptoms must be present: increased appetite (hyperphagia) and/or weight gain, hypersomnia, lead palsy (heavy arms and

legs), and hypersensitivity to events and interpersonal communication [3].

Since the discovery of AD, there has been a continuous search for an effective way to treat it. In addition to ECT, in which, according to different authors, a positive response was observed in more than 80% of patients [1, 4], MAO inhibitor therapy was used with a positive response in 70–80% of patients [5]. The use of irreversible MAO inhibitors (phenelzine, tranylcypromine, nialamide, L-deprenyl – selegelin) turned out to be more effective than reversible MAO inhibitors (pyrazidol, moclobemide) [6]. Some studies have shown positive results of treatment with iproniazid [2, 7], but at present this group of drugs is not practically used in our country due to a large list of restrictions and a high risk of side effects. Several more recent studies have shown a positive and sustained effect when using a combination of psychopharmacotherapy with exercise [8–14]. At the same time, exercises (running, jumping, etc.) were selected

depending on the severity of depression, the psychopharmacotherapy used, as well as the initial body weight or body mass index. The intensity of exercise was calculated taking into account the consumption of kilocalories (from 4 to 16) per 1 kg of body weight. The follow-up period was at least 12 weeks. Based on these results, exercise was recommended for patients with mild to moderate depression. However, the mechanisms responsible for the reduction in depressive symptoms due to exercise need further study. The use of cognitive-behavioral psychotherapy has shown a positive result both in terms of relief of depressive symptoms and as maintenance therapy, especially with regard to autonomic phenomena [15–19]. Treatment using light therapy was not effective enough [20]. The use of transdermal selegiline has shown comparable efficacy and tolerability in patients with both atypical and typical variants of major depression. It should be noted that this method of AD treatment needs additional verification and further research [21].

Currently, more and more preference is given to antidepressants from the group of selective serotonin reuptake inhibitors (SSRIs), which is confirmed by the results of many modern studies [22–27]. A number of domestic works have shown a positive effect of the melatonergic antidepressant agomelatine on AD symptoms [28–32].

The study of AD was previously carried out only within the framework of bipolar affective disorder (BAD) and recurrent depressive disorder (RDD) [33], and the psychogenic form of AD (psychogenic depression – PD) was not distinguished, despite the fact that the main criterion for atypical depressive syndrome is mood reactivity. It seems relevant to develop a differentiated approach to the treatment of AD, depending on its nosological

affiliation, as well as taking into account the possibility of using drugs from different psychopharmacological groups, including modern antidepressants.

The purpose of this study is to compare the effectiveness of AD therapy depending on its nosological affiliation: within the framework of BAD, RDD and PD.

**Patients and methods.** The study was conducted in the period from 2019 to 2021 on an outpatient and inpatient basis at S.S. Korsakov Psychiatric Clinic of Sechenov University. We examined 250 patients aged 18 to 65 years using clinical and clinical-catamnestic methods with a specially developed questionnaire, and selected 77 patients (50 women and 27 men) with symptoms corresponding to the criteria for AD (according to DSM-5). Among them, there were 35 patients with BAD (F31.3–5 according to ICD-10), 24 patients with a diagnosis including PD (F41.0–F41.2, F43.1–2, F45.2–3), 18 patients with RDD (F33.0–3, F33.8–9).

The study did not include patients with decompensated severe somatic pathology, as well as with a depressive state within the framework of schizophrenia spectrum disorders, organic depressions; depressions combined with alcoholism and drug addiction; pregnant and lactating women.

To assess the effectiveness of therapy over time, the following tools were used: Montgomery–Asberg Depression Rating Scale (MADRS), Clinical Global Impression Scale (CGI); for assessing the quality of life and social functioning – the scale for assessing satisfaction with life (quality of life) (Scoring the Quality of Life Enjoyment and Satisfaction Questionnaire, Q-LES-Q-SF). Assessment of the mental state of patients, including clinical and psychopathological examination and determination of indicators of psychometric scales, was carried out before the start of treatment (W0), and on the 2nd (W2), 3rd (W3), 4th (W4), 6th (W6), 12th (W12) week of therapy.

*Statistical processing* of the obtained results was carried out using the Statistica 13.0 software package (StatSoft Inc., USA). Comparison of the three groups on quantitative scales was carried out on the basis of nonparametric Kruskal–Wallis analysis of variance. The significance of differences in the frequency distribution of dichotomous indicators was assessed using Fisher's exact test. The degree of relationship between the indicators was determined by the Spearman's rank correlation coefficient. The level of statistical significance was set at the error probability level of 0.05.

**Results.** The socio-demographic characteristics (Table 1) of the studied groups of patients had both similarities and differences. All groups were dominated by women. The BAD group had the highest average age of patients at the time of inclusion in the study (32.4 years) compared with the PD group (24.5 years;  $p < 0.01$ ). In the BAD group, there were significantly more patients with higher education (60%), in contrast to the PD group (29.2%;  $p < 0.05$ ). In the PD group,

**Table 1. Socio-demographic characteristics of patients**

Indicator	Groups			Total (n=77)
	BAD (n=35)	RDD (n=18)	PD(n=24)	
Average age at the time of inclusion in the study, years, Me [25th; 75th percentile]	32.4 [19.0; 53.0]	27.6 [18.0; 45.0]	24.5 [18.0; 35.0]	28.8 [18.0; 53.0]
Gender, n (%):				
men	17 (48.6)	4 (22.2)	6 (25.0)	27 (31.9)
women	18 (51.4)	14 (77.8)	18 (75.0)	50 (68.1)
Level of education, n (%):				
higher	21 (60.0)*	8 (44.4)*	7 (29.2)	36 (46.8)
incomplete higher	7 (20.0)	7 (38.9)	13 (54.2)*	
secondary	4 (11.4)	1 (5.6)	3 (12.5)	27 (35.1)
vocational				8 (10.4)
incomplete secondary/vocational	3 (8.6)	2 (11.1)	1 (4.2)	6 (7.8)
Employment status, n (%):				
work	16 (45.7)	7 (38.9)	9 (37.5)	32 (41.6)
do not work	19 (54.3)	11 (61.1)	15 (62.5)	45 (58.4)
Marital status, n (%):				
married	15 (42.9)*	5 (27.8)	3 (12.5)	23 (29.9)
lonely	16 (45.7)	13 (72.2)	20 (83.3)*	49 (63.6)
divorced	4 (11.4)	–	1 (4.1)	5 (6.5)

\* $p < 0.05$ .

patients with incomplete higher education prevailed (54.2%;  $p < 0.01$ ). These differences can be explained by the younger age of patients with PD. The BAD group favorably differed in the level of family adaptation: significantly more patients were married (42.9%) than in the group of RDD and especially PD (12.5%;  $p < 0.01$ ), and there were significantly more singles in the PD group, which can also be associated with the younger age of the latter. There were no cases of disability in any group, but the proportion of the unemployed was high (BAD – 54.3%, RDD – 61.1%, PD – 62.5%), which may be due to various factors (social, economic).

As for the clinical and dynamic indicators of depression (Table 2), there were no patients with mild depression in any of the groups, and in patients with PD, moderate depression was relatively more common, especially compared with RDD (79.2% and 50%, respectively;  $p < 0.05$ ), severe depression was more often detected in the RDD group, especially compared with PD (50% and 20.8%, respectively;  $p < 0.05$ ).

For the treatment of depression, various schemes of psychopharmacological drugs were used at the discretion of the attending physician (Table 3).

Antidepressant monotherapy was significantly more commonly used in RDD and not at all in bipolar disorder. The antidepressant + antipsychotic regimen was significantly more often prescribed to patients with PD, and the antidepressant + mood stabilizer was prescribed more often in the bipolar group. Monotherapy with a mood stabilizer and a combination of a mood stabilizer and an antipsychotic were used only in patients with bipolar disorder.

Patients received standard therapeutic doses of mood stabilizers; typical and atypical antipsychotics; SSRI antidepressants, selective serotonin and norepinephrine reuptake inhibitors (SNRIs), the melatonergic antidepressant agomelatine, tricyclic antidepressants, serotonin modulator and stimulant vortioxetine. In some cases, tranquilizers were used to enhance anti-anxiety therapy in a short course of up to 2–3 weeks at the start of treatment.

In all three groups: the antidepressant agomelatine was used most frequently (27.3%), clomipramine was used least frequently (2.6%), no antidepressant was prescribed in 14.3% of cases; the most commonly used antipsychotic was quetiapine (24.7%), the least used were tiapride (1.3%) and clozapine (1.3%), no antipsychotic was prescribed in 37.7% of cases; the most commonly used mood stabilizer was lamotrigine (22.1%), the least used was carbamazepine (2.6%), no mood stabilizer was prescribed in 48.1% of cases; the most frequently used tranquilizer was hydroxyzine (11.7%), and in 79.2% of cases no tranquilizer was used (Table 4).

**Effectiveness of the therapy.** The initial mean score on the MADRS scale in patients of all groups did not differ statistically significantly (29.2; 28.8 and 27.2, respectively;  $p > 0.05$ ). The degree of reduction of symptoms in patients of each of the three groups from the start of treatment to the 12th week was different (Fig. 1), but the differences did not reach statistical significance: in BAD it was 64.6%, in RDD – 73.3%, in PD – 69.5% ( $p > 0.05$ ).

Within each group, a comparison was made of the reduction of symptoms according to the MADRS scale, depending on the treatment

**Table 2. Baseline depression severity, n (%)**

Severity of depression according to ICD-10	BAD (n=35)	RDD (n=18)	PD (n=24)
Mild	0	0	0
Moderate	21 (60.0)	9 (50.0)	19 (79.2)*
Severe	14 (40.0)	9 (50.0)*	5 (20.8)

\* $p < 0.05$ .

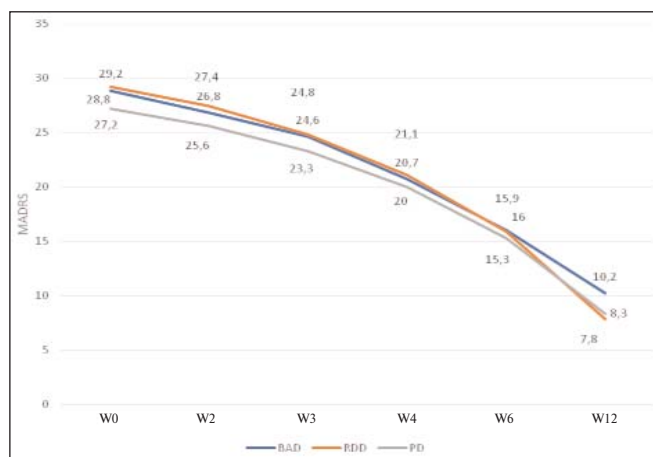
**Table 3. Treatment regimens used in the study, n (%)**

Treatment regimen	Groups		
	BAD (n=35)	RDD (n=18)	PD (n=24)
Antidepressant	–	7 (38.9)**	4 (16.7)
Antidepressant + antipsychotic	2 (5.7)	6 (33.3)	16 (66.7)**
Antidepressant + mood stabilizer	12 (34.3)*	3 (16.7)	1 (4.2)
Antidepressant + antipsychotic + mood stabilizer	11 (31.4)	2 (11.1)	3 (12.5)
Mood stabilizer	3 (8.6)	–	–
Mood stabilizer + antipsychotic	7 (20.0)	–	–

\* $p < 0.05$ ; \*\* $p < 0.001$ .

**Table 4. Drugs and doses used in the study**

Drugs	doses, mg
<b>Antidepressant</b>	
Agomelatine	25–50
Amitriptyline	25–200
Venlafaxine	75–225
Vortioxetine	10–20
Duloxetine	30–120
Clomipramine	75–150
Paroxetine	20–40
Fluvoxamine	50–200
Fluoxetine	20–40
Escitalopram	10–20
<b>Antipsychotic</b>	
Alimemazine	5–20
Aripiprazole	5–10
Quetiapine	6.25–200
Clozapine	50–200
Olanzapine	5–20
Perphenazine	2–8
Sulpiride	50–200
Tiapride	100–200
Thioridazine	10–30
<b>Mood stabilizer</b>	
Acidum Valproicum	300–1000
Carbamazepine	200–400
Lamotrigine	75–250
Lithium carbonic	300–1200
Topiramate	75–200
<b>Tranquilizer</b>	
Bromdihydrochlorphenylbenzodiazepine	0.5–1.5
Hydroxyzine	25–100
Etifoxine	50–200



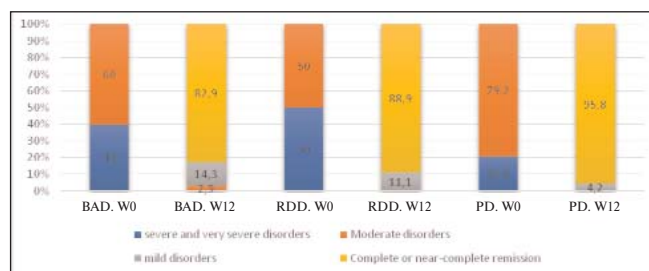
**Fig. 1.** MADRS mean scores in patients of three groups during follow-up

**Note.** W0 – start of treatment; W2 – 2nd week; W3 – 3rd week; W4 – 4th week; W12 – 12th week.

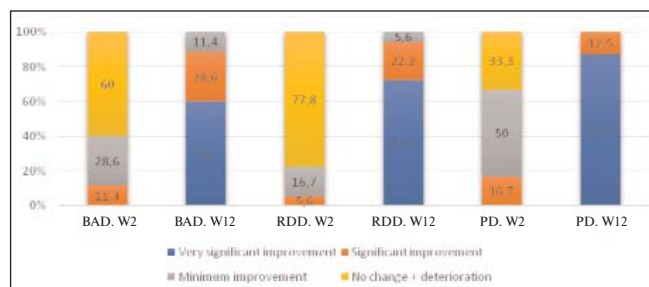
regimen used. In the bipolar group, less efficacy was noted with regimens that did not include an antidepressant, which was detected already from the beginning of the 2nd week of therapy and remained at this level until the end of the study. The average MADRS score for 12 weeks of follow-up decreased in the group receiving the combination of an antidepressant and an antipsychotic to  $7.2 \pm 2.8$ ; antidepressant and mood stabilizer – up to  $6.6 \pm 1.5$ ; mood stabilizer and antipsychotic – up to  $14.8 \pm 1.4$ , in the mood stabilizer monotherapy group – up to  $16.1 \pm 2.3$ ; in the antidepressant, mood stabilizer and antipsychotic group – up to  $6.3 \pm 1.6$ . The number of patients with a MADRS score reduction of  $\geq 50\%$  was significantly higher among the patients treated with an antidepressant: 75.0% with an antidepressant and antipsychotic regimen; 77.1% with an antidepressant and mood stabilizer regimen, and 78.1% with a three-drug combination versus 44.0% with a mood stabilizer monotherapy ( $p < 0.001$ ), and 48.6% with a mood stabilizer regimen and antipsychotic ( $p < 0.05$ ).

In the RDD group, greater efficacy was noted with antidepressant monotherapy. The average MADRS score after 12 weeks of follow-up decreased in the group receiving antidepressant monotherapy to  $2.0 \pm 1.3$ , the combination of antidepressant and antipsychotic – to  $10.1 \pm 1.2$ , antidepressant and mood stabilizer – to  $9.9 \pm 2.5$ , a combination of three drugs – up to  $9.2 \pm 2.0$  points. With antidepressant monotherapy, the decrease in MADRS score  $\geq 50\%$  was significantly higher – 93.2% – compared with 65.4% with the antidepressant and antipsychotic regimen ( $p < 0.05$ ), and also compared with 66.1% with a combination of an antidepressant and a stabilizer ( $p < 0.05$ ) and 68.5% – a combination of three drugs ( $p < 0.05$ ).

In the PD group, the greatest efficacy was also established with antidepressant monotherapy. The average MADRS score after 12 weeks of follow-up decreased in the group receiving antidepressant monotherapy to  $2.3 \pm 1.7$  points, the combination of antidepressant and antipsychotic – to  $9.7 \pm 2.3$ , antidepressant and mood stabilizer – to  $10.9 \pm 1.7$ , in the group, a



**Fig. 2.** CGI-S score before the treatment onset (W0) and at the 12th week of treatment (W12) ( $p < 0.05$ ) in three groups of patients



**Fig. 3.** CGI-I score at the beginning of the 2nd week (W2) and at the end of the 12th week of treatment ( $p < 0.05$ )

combination of three drugs – up to  $10.3 \pm 1.1$ . With antidepressant monotherapy, the incidence of MADRS score reduction  $\geq 50\%$  was significantly higher (91.5%) compared with 64.3% with the antidepressant and antipsychotic regimen ( $p < 0.05$ ), and also compared with 59.9% with an antidepressant and a mood stabilizer ( $p < 0.05$ ) and 62.1% with a combination of three drugs ( $p < 0.05$ ).

The results obtained in the analysis of the reduction of scores on the MADRS scale are confirmed by the dynamics of indicators on the CGI-S and CGI-I scales (Fig. 2, 3). By the end of the 12th week of therapy, no severe depression was registered in any of the groups. Only in the BAD group, moderate disorders were noted in 2.9% of cases. The RDD and PD groups are comparable in terms of the level of improvement achieved upon completion of the therapy.

All groups used antidepressants as monotherapy or in combination with other drugs. The most commonly used were agomelatine, venlafaxine, vortioxetine, and amitriptyline.

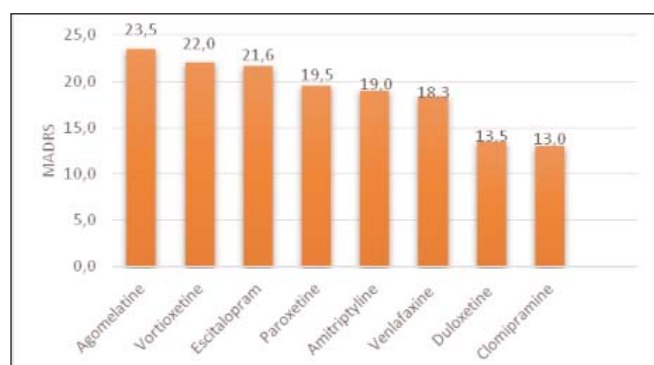
In the bipolar group, when evaluating the effectiveness of the therapy (by comparing the difference in scores on the MADRS scale before and at the end of treatment), depending on the antidepressant used in the regimen (Fig. 4); the most effective was the addition of agomelatine, vortioxetine and escitalopram to the combination ( $p < 0.01$ ).

In the RDD group (Fig. 5), agomelatine, venlafaxine and escitalopram were the most effective ( $p = 0.01$ ).

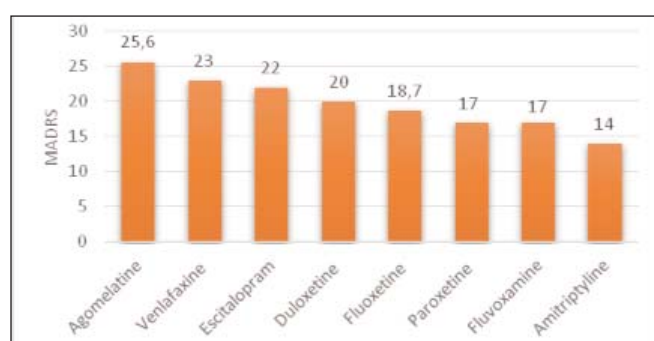
In the PD group (Fig. 6), the highest results were achieved with the use of agomelatine and vortioxetine ( $p < 0.001$ ).

Antipsychotics, unlike antidepressants, were prescribed in all three groups. In the bipolar group, quetiapine, aripiprazole, and olanzapine were most commonly used; in the RDD group, quetiapine and aripiprazole; in the PD group, alimemazine, sulpiride, and quetiapine. In all groups, when comparing the effectiveness of treatment depending on the antipsychotic used, there was no difference, except for cases of adding sulpiride to the

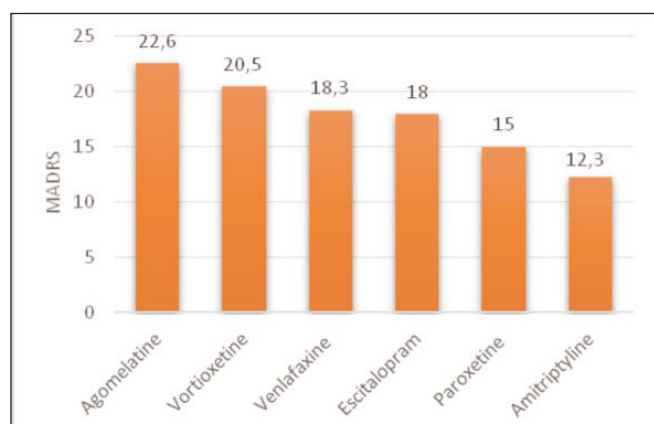




**Fig. 4.** Distribution of the difference in MADRS scores depending on the AD in the bipolar group



**Fig. 5.** Distribution of the difference in MADRS scores depending on the AD used in the RDD group



**Fig. 6.** Distribution of the difference in MADRS scores depending on the AD used in the PD group

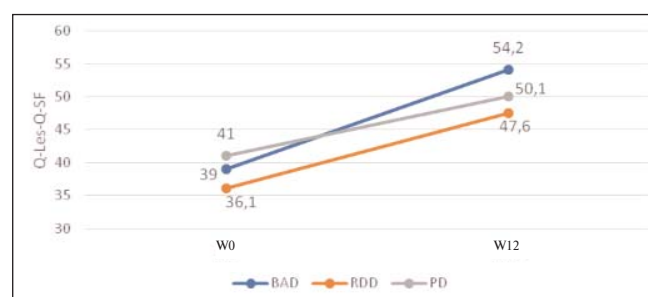
antidepressant treatment regimen in the PD group (compared to no antipsychotic in the treatment regimen;  $p < 0.05$ ).

Also, in all groups, when comparing the effectiveness of treatment, depending on the mood stabilizer used, there was no significant difference. At the same time, in the bipolar group, lamotrigine, valproic acid, and lithium carbonate were most commonly prescribed; in the RDD group, lamotrigine and carbamazepine; in the PD group, lamotrigine and topiramate.

Administration of short-term tranquilizers, up to 2–3 weeks, at the beginning of treatment (in the BAD group – hydroxyzine and bromdihydrochlorophenylbenzodiazepine; in

the RDD group – hydroxyzine; in the PD group – etifoxine and hydroxyzine) did not have a significant effect on the results of the therapy.

No statistically significant difference between the groups was found when assessing the average duration of hospital treatment (BAD – 42.9; RDD – 33.1; PD – 50.6 days;  $p > 0.05$ ), as well as when assessing the average number of hospitalizations per year (BAD – 1.7; RDD – 2.7; PD – 1.3 times;  $p > 0.05$ ). When assessing the quality of life (Fig. 7) after the treatment, there was an increase in the score on the life satisfaction scale in all patients: in the BAD group – from  $39.0 \pm 6.3$  to  $54.2 \pm 2.4$  points, in the RDD group – from  $36.1 \pm 4.1$  to  $47.6 \pm 5.5$ , in the PD group from  $41.0 \pm 2.2$  to  $50.1 \pm 4.1$ . A statistically significant increase in this indicator was noted in the BAD group compared with RDD ( $p < 0.001$ ), as well as in the RDD group compared with PD ( $p < 0.01$ ).



**Fig. 7.** Changes in Q-LES-Q-SF scores in patients of three groups

**Discussion.** In this study, various regimens were used for treatment of AD, including combinations of an antidepressant, a mood stabilizer, and an antipsychotic. The results of treatment indicate that the use of an antidepressant as monotherapy or in combination with other drugs within the framework of RDR and PD is necessary and increases the effectiveness of therapy. For patients from the bipolar group, according to existing foreign and domestic recommendations, antidepressant monotherapy is excluded due to an increased risk of phase inversion, absence of a full remission in the future, and occurrence of relapses. The question of the use of an antidepressant in bipolar disorder, even in combination with a mood stabilizer and an antipsychotic, remains controversial, despite the existing data on their successful use in the treatment of depression in bipolar disorder, especially type II [27, 28]. According to our study, antidepressant monotherapy was the most effective in the RDD and PD groups. In the BAD group, higher rates of MADRS score reduction were also registered in the subgroups of patients who received an antidepressant in combination with other drugs (mood stabilizers and antipsychotics), which is consistent with the results of earlier domestic studies [27, 28].

An important criterion of the effectiveness of treatment of atypical depression is the prescription of drugs that are well tolerated and do not have side effects that increase the symptoms characteristic of AD: increased appetite and body weight, increased anxiety, weakness due to the muscle relaxant effect, drowsiness during the daytime. In our study, the most frequently prescribed antidepressant in all groups was agomelatine – 31.8% of cases, which, along with high antidepressant efficacy, is well tolerated and does not cause the indicated adverse effects [26]. It showed

the best results in comparison with other antidepressants in all groups, which is consistent with the data of other modern studies on the treatment of atypical depression [28–33]. In the bipolar group, along with agomelatine, vortioxetine and escitalopram demonstrated high antidepressant efficacy, in the RDD group, venlafaxine and escitalopram, and in the PD group, vortioxetine and venlafaxine. This is consistent with the results of a comparative study of the efficacy and tolerability of 21 antidepressants based on a meta-analysis of several large studies [34], which showed that agomelatine, citalopram, escitalopram, fluoxetine, sertraline and vortioxetine were better tolerated than other antidepressants.

When comparing the effectiveness of therapy depending on the mood stabilizer or antipsychotic used, no statistically significant difference was obtained. Only the addition of sulpiride to the antidepressant regimen in the PD group was statistically significant. A number of studies confirm the positive effect of sulpiride on depression, anxiety-phobic symptoms, combined with good tolerance [35, 36].

The best indicators of satisfaction with the quality of life were obtained in patients in the bipolar group, the lowest in the PD group, which indirectly indicates the quality of remission, which is associated not only with the objective reduction of depressive symptoms, but also with the patients' subjective perception of their mental state: the appearance of positive emotions, self-satisfaction, restoration of cognitive functions, social functioning.

**Conclusion.** Therapy of atypical depression should be carried out not only depending on its clinical picture, severity and duration, but also taking into account the nosological affiliation of the disease, the characteristics of its course. When deciding on prescribing drugs and their combinations, it is necessary to pay attention not only to the spectrum of action of the drug, its effectiveness and tolerability, but also to the list of possible side effects, especially aggravating the symptoms of AD. The use of antidepressants in bipolar disorder requires special attention in terms of predicting the risk of deterioration due to adverse events in the course of therapy or affect inversion.

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