Differentiated Approach and Indications for Optimization of Agomelatine Therapy for Endogenous Depression

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Abstract

Objective: Objective of the study was to develop and substantiate differentiated indications for the use of agomelatine (valdoxan) in the treatment of typological variants of endogenous depressions with varying severity on the basis of the analysis of its therapeutic efficacy.

Patients and Methods: An open-label prospective study was conducted, using the clinical-psychopathological, psychometric (The Hamilton Depression Rating Scale (HAMD-21); Udvalg for Kliniske Undersogelser Scale (UKU); the Snaith-Hamilton Pleasure Scale (SHAPS) for assessing anhedonic disorders), and statistical methods. A total of 56 patients (mean age was, 34,9 years) with moderate and severe endogenous depressions were examined within the framework of affective psychosis (n = 42) and shift-like schizophrenia (n = 14) (ICD-10 items F31.3-4; F32.1-2, and F33.1-2). For 4 - 8 weeks the patients received course treatment with agomelatine (valdoxan) in a daily dose of 25 - 50 mg in the evening. The mental status of patients was assessed in dynamics on fixed days according to reduction of Mean Total Score (MTS) of the corresponding scales as insignificant (less than 19% reduction in disorders), moderate (20 - 49%), good (50 - 69%), and significant (70% or more) effects. The effect of agomelatine was analyzed in two groups of patients. In the 1st group (n = 26) specificities of anti-depressive effect and its dynamics in endogenous depressions of different typological structure (melancholic, anxious, and adynamic depressions) were studied. The effect of agomelatine on anhedonic endogenous depressions and manifestations of anhedonia in various spheres of psychic activity (interests, social activity, emotional involvement and eating/drinking) were investigated in Group 2 (n = 30).

Results and Discussion: Good tolerance and a high anti depressive activity of agomelatine were established during the treatment course for moderate and severe endogenous depressions. A significant improvement (84.4% reduction in HAMD-21 MTS) was detected in patients by the 3rd and 4th weeks of the course treatment and consistently persisted during the subsequent follow-up. Agomelatine demonstrated a good effect (a 50% or more reduction in HAMD-21 MTS) already by the 14th day of therapy. Balanced anti-depressive effect of the drug was observed, significant thymoleptic, stimulant, anxiolytic and antianhedonic activities (reductions in the MTS of depressive disorders by 90.83, 84.9, 82.39, and 78.9%, respectively) were noticed.

Conclusion: The universal spectrum of anti-depressive effect of agomelatine, its good tolerability, high efficacy, and rapid improvement makes it the drug of choice in the treatment of a wide range of psychopathological endogenous depressions: melancholic, apathoadynamic, anxious, and anhedonic ones.

Keywords: Agomelatine; Endogenous Depressions; Anhedonia; Therapeutic Effect; Indications for Use

Introduction

The relevance of the development and optimization of anti-depressive therapy methods is due to the significant prevalence of depression. According to WHO (2017), up to 300 million people worldwide suffer from depression; cancer and cardiovascular diseases surpass depression in frequency. The burden of negative consequences of depression in the form of impaired social functioning of patients and the growing economic expenditures of the society is up to 40.5% and is 2-6 times higher than similar indicators for other mental pathologies. Depressions are an important risk factor for suicidal behavior of patients and occupy the second place among diseases, leading to disability and disablement.

All this makes it necessary to conduct studies, devoted to the increase of social adaptation of patients with depressions and improving their quality of life, also by optimization of therapeutic approaches and searching for pathogenetically substantiated treatment methods.

Since the 50-s of the twentieth century the targeted synthesis of "ideal" antidepressants has been carried out, taking into account the pathogenesis of depressive disorders. Several generations of such drugs have already been created. One of the first to be synthesized were "typical" tricyclic antidepressants (TCA), which today are the basic ones in anti-depressive therapy. Their high anti-depressive effect was established (on average in 70% of patients), however, anticholinergic side effects of TCA often complicated antidepressant therapy and led to its cancellation.

Subsequently, different groups of antidepressants, in particular, possessing selectivity of neurochemical action, were successively introduced into practice: selective serotonin reuptake inhibitors (SSRI drugs); noradrenergic and serotonergic antidepressants (NaSSA); specific serotonin and noradrenaline reuptake inhibitors (SNRIs).

These groups of drugs were distinguished by the breadth and universality of the clinical effect, but mainly with mild and moderate depressions. Their strongside was low toxicity owing to the lack of effects on histamine, muscarinic and alpha-adrenergic receptors. However, it was suggested, that the development of depression cannot be explained by the dysfunction of only one monoamine, since all monoamines are associated with certain links of the pathogenetic process, underlying the development of depressive disorders [1].

Currently among the progressive theories of depressive disorders occurrence chronobiological one is singled out, which is based on the concept of desynchronization of biological rhythms in such patients. According to this theory, the chronobiotic hormone melatonin, which is synthesized in the pineal gland during the night phase of the daily rhythm, plays a key role in synchronization of circadian rhythms, including the sleep-wake cycle [2]. The synthesis of melatonin is regulated in the suprachiasmatic nucleus, where it enters from the pineal gland and regulates circadian rhythms. The antidepressant properties of melatonin itself were not confirmed in the clinical trials, but served as the basis for the creation of drugs with similar effects. Thus, in "Servier" laboratory (France) a unique antidepressant drug agomelatine (valdoxane) was synthesized.

The innovative mechanism of its action is realized by influencing the melatonergic and serotonergic systems and, therefore, involves resynchronization of circadian rhythms due to agonism to MT1- and MT2- receptors and selective antagonism to 5-HT2c receptors, which leads to a specific and the indirect release in the frontal cortex of two basic neurotransmitters, norepinephrine and dopamine, which play an important role in the pathogenesis of depression [3-5]. A number of foreign and domestic studies, including placebo-controlled, as well as comparative ones, showed the efficacy of agomelatine in the treatment of depressive states in inpatients and outpatients [6-8]. BP Hasler., *et al.* [9] for the first time pointed out the positive effect of agomelatine in anhedonia, connecting it with the specificities of the melatonergic effect of the drug. It was noted in several comparative studies, that agomelatine led to a significant reduction in psychopathological anhedonic manifestations and positively affected the symptoms of depression in general, improving self-esteem and social functioning of patients [10-13]. The drug was recommended as a means of overcoming resistance in the treatment of apathetic depressions with severe anhedonic manifestations [14]. However, the data on the special features of the clinical action of valdoxan and

its dynamics are insufficiently covered, taking into account the psychopathological structure of endogenous depressions and the degree of their severity.

Aim of the Study

The aim of the study was to develop and substantiate differentiated indications for prescription of agomelatine in typological variants of endogenous depressions of various severity, on the basis of the analysis of its therapeutic efficacy.

Patients and Methods

56 patients were examined (47 females and 9 males, average age was 34.9 years). All patients were diagnosed with moderate or severe endogenous depression within the framework of bi- or monopolar affective psychosis (n = 42), or shift-like schizophrenia (n = 14); according to ICD-10, their condition was classified as F31.3-4; F32.1-2 and F33.1-2.

Exclusion criteria were the presence of medical, neurological and organic brain diseases at the stage of decompensation; the presence of suicidal behavior, substance abuse and alcohol addiction, as well as changes in indices of blood biochemical analysis, especially total bilirubin, aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

An open-label prospective study was carried out; all the patients gave written informed consent to participate in it.

The patients were examined during inpatient treatment in the Department of Endogenous Mental Disorders and Affective States of the Clinic of the Mental Health Research Center according to a single protocol. Clinical-psychopathological and psychometric methods were applied using the international assessment scales HAMD-21 (The Hamilton Depression Rating Scale), UKU (Udvald for Kliniske Undersogelser Scale), questionnaire scales for characteristic of anhedonic disorders (Snaith-Hamilton Pleasure Scale, SHAPS). The patients' conditions were assessed on fixed days.

The therapeutic efficacy of valdoxan was studied in dynamics on the basis of the clinical data and reduction in the mean total score (MTS) of the corresponding scales, as compared to the 0th, or previous day of assessment, and was defined as insignificant (up to 19%), moderate (20 - 49%), good (50 - 69%) and significant (70% or more) effect.

Valdoxan in 25 mg tablets was prescribed once a day, in the evening, starting with a dose of 25 mg. In some patients (12.5%) this daily dose was maintained throughout the course of treatment. In most patients (77.5%) with no signs of improvement in their mental state during the first 1 - 2 weeks of treatment, it was increased to 50 mg.

As concomitant therapy, moderate doses of previous antipsychotics, nootropics and normotimics were preserved, any antidepressants and tranquilizers were excluded.

The therapeutic efficacy and safety of agomelatine were analyzed in two groups of patients.

The 1st group included 26 patients (23 females and 3 males), in whom the specificities of anti-depressive activity and its dynamics were studied in endogenous depressions of various types and various degrees of severity, taking into account the leading depressive component. The mean age of the patients was 26.1 ± 13.3 years, the duration of depression made up 7.5 ± 9.3 months. The MTS of severity of depression according to HAMD-21 was initially 24.42 (moderate depression), in 9 patients depression was assessed as severe and in 17 as moderate. The duration of the disease in them reached 11.2 ± 10.4 years, medical history included 5.4 ± 8.1 affective episodes.

The 2nd group consisted of 30 patients (24 females and 6 males), in whom the effect of valdoxan on the manifestations of anhedonia in the structure of varying severity of the typological variety of endogenous depression was determined. The mean age of patients was 35.9 years, the disease duration amounted to 10.4 years, and the number of episodes of depressive episodes suffered was equal to 5.4 ±

8.1. According to the HAMD-21MTS MTS, the severity of anhedonic depressions was initially moderate in 53.3% and severe in 46.7%. The intensity of anhedonia before the start of the study (MTS according to SHAPS) as a whole reached 10.2 points. The severity of anhedonia in different areas of psychic activity was also assessed according to the SHAPS points: in the sphere of interests (points 1, 2, 3, 9), social activity (7, 8, 13, 14), emotional involvement (5, 6, 11, 12) and food/drink (4, 10); before valdoxane prescription, this index was respectively 3.4; 2.4; 3.0 and 1.4 points.

The study was conducted in compliance with the principles of biomedical ethics. The significance of the differences among the obtained parameters was determined according to the Student t-test and Fisher's exact method for a small number of observations (according to p index).

Results

26 patients of the 1st group fully completed a 56-day course of treatment with agomelatine. The course treatment lasted 8 weeks. The dynamics of the condition of the patients was evaluated initially (day 0) and on the 3rd, 5th, 7th, 14th, 28th, 42nd and 56th days of therapy.

If by the beginning of the course therapy of MTS according to HAMD-21 in this group on the whole was equal to 24.42, by the end of the study it decreased by 84.41% (significant effect), and only in 6 (23.1%) patients residual signs of mild depression were noticed. In the remaining 20 (76.9%) patients, the HAMD-21 score ranged from 0 to 6 points, that is, no signs of depression were practically revealed, and the condition met the criteria for complete remission.

It is important, that clinical improvement (normalization of mood, the appearance of psychophysical activity, a decrease in the actuality of sad thoughts, reduction in congruent overvalued ideas of self-humiliation, low value, self-accusation) in patients of the 1st group as a whole was already observed by the 14th day of treatment.

By that time, MTS decreased to 12.08 (by 49.5%), that is, almost to the lower limit of good effect, and by the 21st day it was already 9.0 (decreased by 2.7 times, or 63.15%), which was assessed as a distinct good effect. By the 42nd day of therapy, the good effect, achieved by the 3rd week in the group as a whole, increased to significant, while the MTS decreased by 77.17% and by the 56th day reduced by 84.41%. It is characteristic that after the 4th week of course therapy, the significant effect of agomelatine remained stable, or increased insignificantly in percentage terms, which was confirmed by the assessment on the 42nd and 56th days of treatment.

The investigation of the spectrum of agomelatine anti-depressive effect (thymoleptic, stimulating, sedative, or anxiolytic) showed its relatively balanced impact on the symptoms of depression. The thymoleptic effect was determined by the dynamics of MTS signs 1, 2, 3 of HAMD-21 (depressive mood, ideas of guilt, suicidal intentions). Stimulating impact was defined according to a reduction in the MTS signs 7 and 8 (working efficiency and activity, retardation); anxiolytic effect was detected according to the reduction in MTS signs 9, 10, 11 (agitation, anxiety, somatic anxiety).

By the beginning of the treatment of MTS symptoms, reflecting the severity of thymic manifestations of depression were 4.62; apathoadynamic ones equalled 4.08, and anxiety symptoms made up 5.46. By the end of the course treatment, their reduction reached 90.83; 94.91 and 82.39% respectively, that is, improvement in the condition of patients was observed according to all components of antidepressive spectrum, which was regarded as significant effect.

The effect of agomelatine on separate symptoms of depression was characterized not only by a similar high efficiency, but also by similar dynamics of improvement during the course treatment (Figure 1).
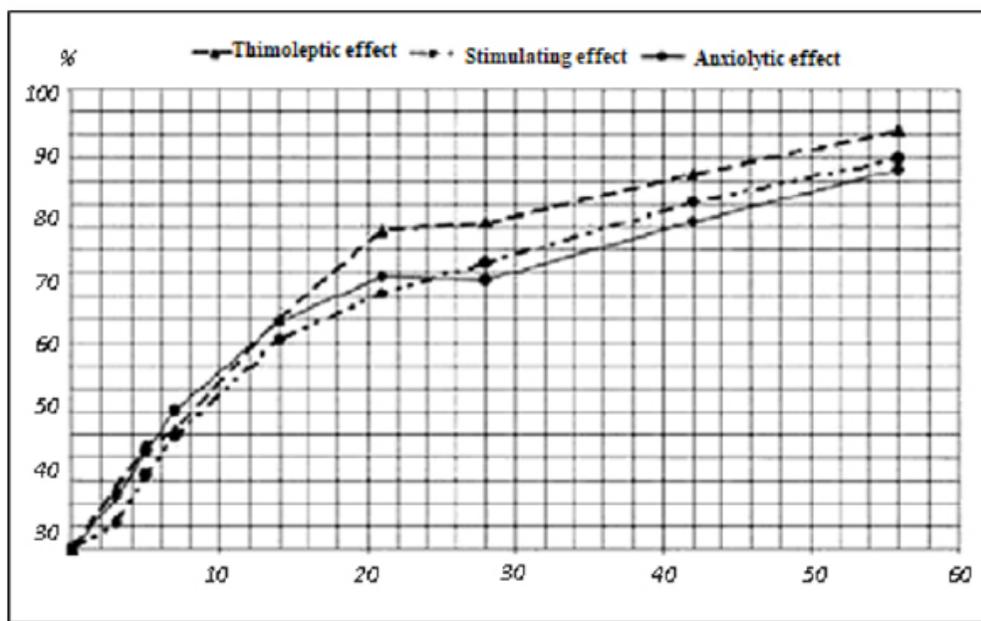
Figure 1: *The dynamics of the thymoleptic, stimulating, and anxiolytic effect of valdoxane (reduction coefficient of MTS HAMD-21, %).*

Already by the 14th day of therapya decrease in MTS, reflecting the intensity of thymic, apatoadynamic, and anxiety symptoms, was 50.0; 49.30 and 45.28%, respectively, that is, it reached the level of good and borderline with its moderate effect.

By the end of the course of treatment, as mentioned above, the drug was highly active in relation to all three components of depression. As to the degree and tempo of symptoms reduction thymoleptic effect clearly predominated (reduction by 90.83%). The intensity of stimulating and anti-anxiety effects was slightly lower (reduction by 84.91 and 82.39%, respectively), but it was also defined as a significant effect.

In the 2nd group, 30 patients with moderate and severe anhedonic endogenous depressions received agomelatine for 30 days. Evaluation of the effect was carried out before the start (day 0) and on the 7th, 14th and 30th days of therapy. In patients of the 2nd group, the special features of anti-depressive activity and the universality of the action of agomelatine on the separate components of depression, which were established in patients of the 1st group, were revealed.

In general, in this group the degree of reduction of MTS on HAMD reached 78.9% by the 30th day of therapy (a distinct significant improvement).

As shown in figure 2, in subgroups with moderate and severe depressive intensity good and significant effects were observed in total in 100 and 92.8% of patients, respectively, but in severe depression, good effect was noticed more often (21.4% versus 18.8% of cases). In turn, significant improvement was registered in a larger number of cases in the subgroup with moderate depression (in 81.2% versus 71.4% of cases).
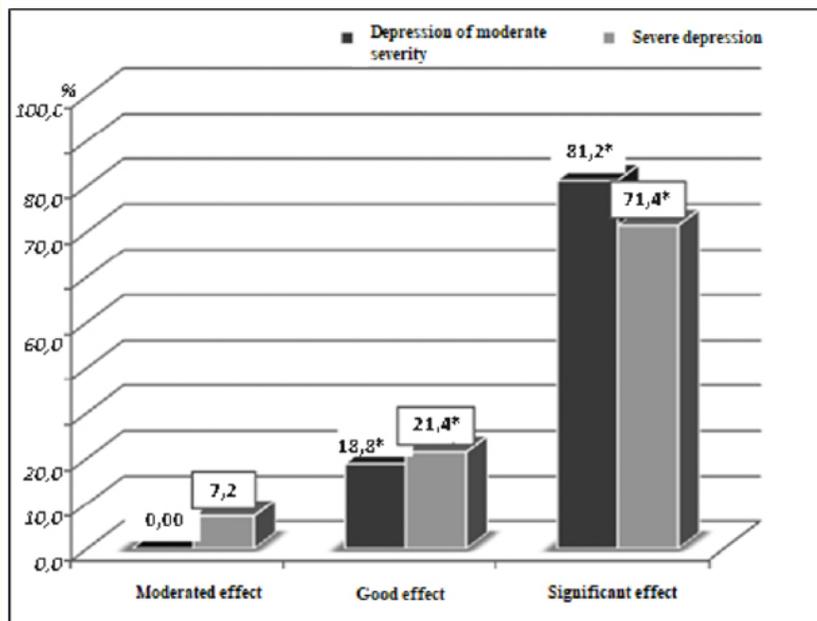
Figure 2: Dynamics of the effect of valdoxan in anhedonic depressions of varying severity (reduction of according to MTS HAMD-21, %) * - p < 0,025.

On average, in the 2nd group, moderate improvement was fixed already by the 7th day of treatment (22.6% of reduction in MTS according to HAMD-21), and by the 14th day the condition of the patients already reached the limit of good effect (48.8% of reduction).

At the same time, in patients with both moderate and severe intensity of depressions the improvement indices on the evaluation days were in the same ranges; however, in the subgroup with moderate depression, the reduction in MTS on HAMD-21 was slightly higher, than in the subgroup with severe depressions, and on the 30th day of treatment it was 81.7 and 76.8%, respectively.

The analysis of the effect of agomelatine on the separate components of anhedonic depression showed, that a decrease in the symptoms of anxiety and depressive affect on the 30th day of treatment corresponded to significant effect (reduction of MTS on HAMD-21 by 76.9 and 82.2%, respectively), with a moderate effect for both components was already achieved by 7th day of treatment, and good effect was reached on the 14th day (Figure 3).

However, despite a slight prevalence of depressive mood over anxiety (1.2 times), in patients of this group the reduction in the severity of depressive mood during these treatment periods was greater than the symptoms of anxiety.

On the 30th day of therapy, the reduction in symptoms of depression as a whole reached 83.6%, in the subgroup with moderate depression and a decrease in depressive mood and anxiety were approximately the same (by 84.4 and 82, 6%, respectively). In the subgroup with severe depression, these indices were lower, although they were also evaluated as significant effect: 76.0, respectively; 79.7 and 72.3% reduction in disorders, that is, the effect of agomelatine on depressive affect was more pronounced than on the affect of anxiety.
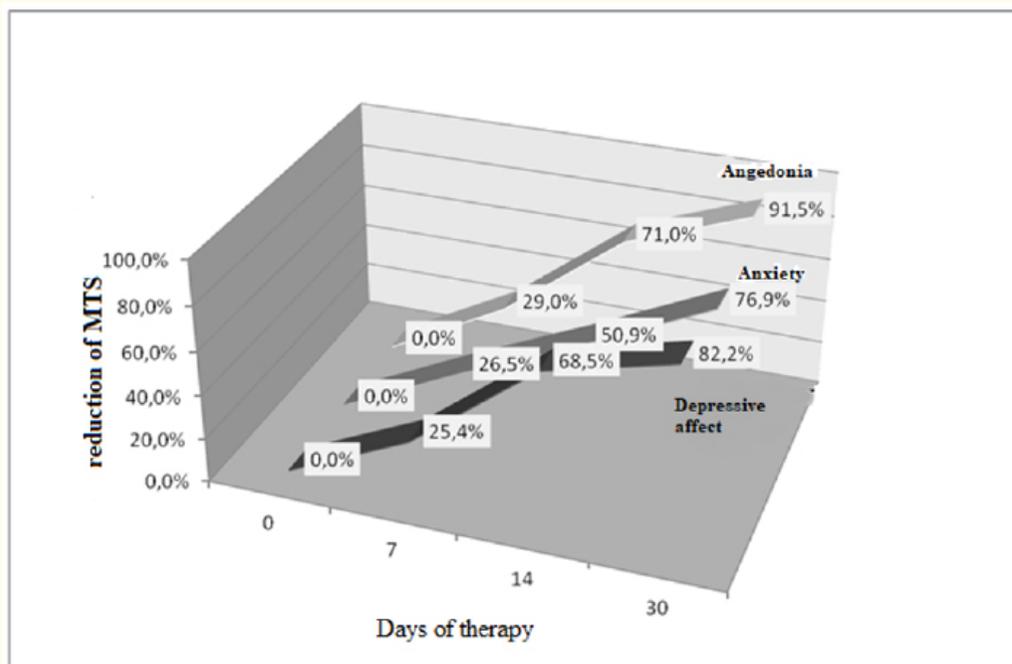
Figure 3: *The dynamics of depressive affect, anxiety, and anhedonia during the treatment with valdoxan (reduction of MTS according to HAMD-21 and SHAPS, %).*

The dynamics of hedonic disorders in the structure of depressive syndrome had the following specificities. At all the stages of treatment, the degree of reduction in the MTS of intensity of anhedonia according to SHAPS both in numerical terms and in gradations of the therapeutic effect exceeded that of depression in general and of its individual components (depressive mood and anxiety).

Significant effect in relation to anhedonic manifestations was already achieved on the 14th day of treatment (decrease by 71%) and by the 30th day the reduction in these disorders was observed by 91.5%, which corresponded to a significant effect, close to the state of recovery.

Equally pronounced effect of agomelatine in relation to the anhedonic component of depression was found, when studying the dynamics of its effect on separate spheres of psychic activity. Only in the sphere of interests the decrease in anhedonia was somewhat lower than in other spheres.

In the sphere of interests, significant effect only appeared by the 30th day of therapy and in percentage terms it was significantly lower than the indices of anhedonia reduction in other spheres of psychic activity (social activity, emotional involvement): 88.2% versus 91.7 - 95.2%, respectively (Figure 4).

The analysis of weakening of anhedonia symptoms showed, that with the same dosage regimen, the result of treatment of hedonic disorders on the 30th day in depressions with moderate severity were slightly higher than in severe depressions (reduction of MTS by 93.0 and 89.9%, respectively).
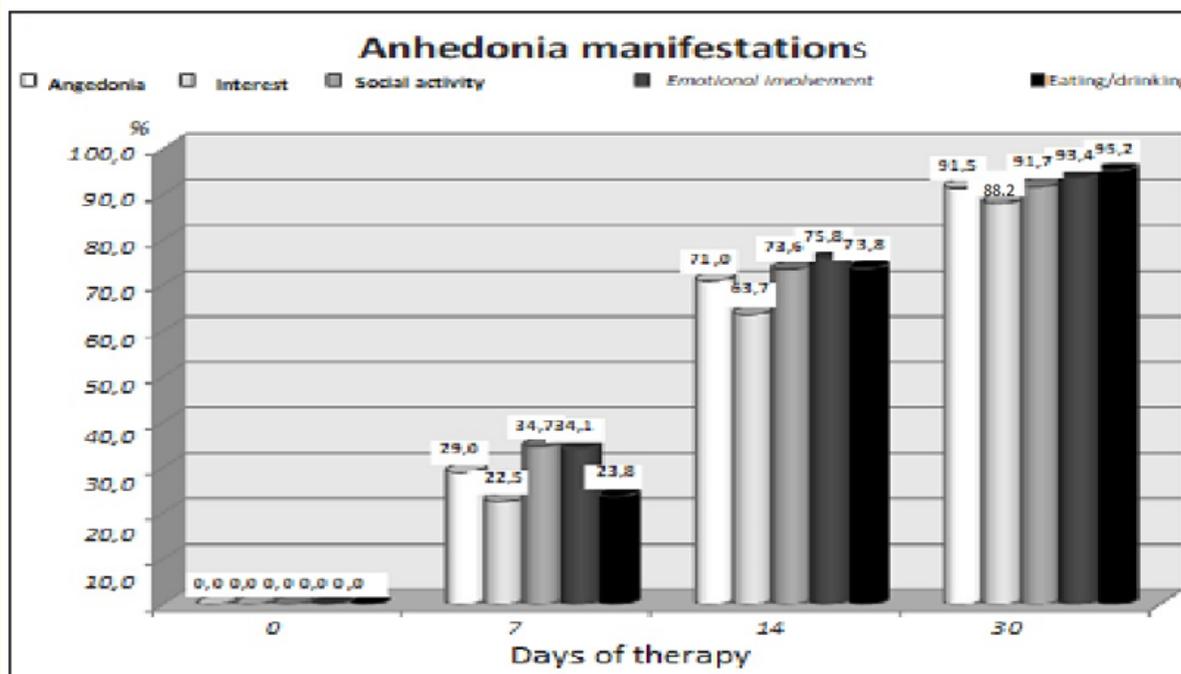
Figure 4: Dynamics of anhedonia in general and its separate manifestations during the treatment with valdoxan (reduction of MTS according to SHAPS, %).

The depth of the agomelatine effect was different in anhedonic depressions of various severity. In severe depression, a more distinct moderate effect was noticed on the 7th day of treatment (reduction in disorders was by 37.6% versus 20.9%), and by the 14th day only the lowest limit of significant effect was reached (decrease in MTS according to SHAPS by 69.1%).

At the same time, with modern spheres of psychic activity, no significant differences in the therapeutic response were noticed on the 30th day of treatment, also in subgroups with depressions of various severity.

However, the same regularity of its formation at different stages of treatment was revealed, as in anhedonia in the general group of patients: in all the spheres more distinct in percentage terms moderate effect was noticed on the 7th day of therapy as well as "lagging" response in reduction of MTS according to SHAPS on days 14 and 30 in severe depression, as compared to moderate one.

During the course treatment, good tolerance to valdoxan was established. At all stages of therapy, undesirable (adverse) effects (AE) were observed in half of the patients. On the UKU scale, only 24 names of AEs were recorded, of which 41.7% were mental, 37.5% were autonomous, 29.8% were "other" AEs. neurological AEs were detected. A significant frequency of AEs (41.3%) was noticed already at the initial assessment (day 0), but, subsequently, by the 7th and then by the 21st and 30th days of therapy, a gradual decrease in the number of all the AEs and their severity according to the UKU down to 1 point (respectively down to 38.5 and 20.2%) was observed. These AEs could be considered to be a result of the previous mental condition and/or other therapy. This was especially true for psychic AEs (impaired concentration, fatigue, sleep disorders, emotional indifference, depression), which were not only the most frequent during the initial assessment (41.6%), but also the most severe ones (on the average up to 2.4 points according to UKU with a 3-point rating). A smaller

proportion of AEs, that first occurred, or became more frequent by the 7th day of treatment as compared with the initial index could be associated with valdoxan. These were isolated autonomous symptoms (disturbance of accommodation, hypersalivation, or dry mouth), which significantly decreased and were mildly expressed throughout the entire treatment period, even with an increase in the daily dose of the drug. In no case did AEs require withdrawal of therapy. Such symptom as constipation (in 2 patients) was detected with a stable frequency and had a mild degree of severity (1 point) from the moment the study began, most likely, it could be rightly attributed to somatic symptoms of depression, and not to AE. In 2 female patients, initially suffering from obesity of the II degree, from the 7th to the 30th days of treatment, in addition to other AEs, an increase in body weight (by 1 - 2 kg) was observed, which corresponded to 1 point according to the UKU. During the course of treatment with agomelatine, no somatic AEs were detected; blood pressure, heart rate did not change, blood biochemical parameters (total bilirubin, AST and ALT) from the start of the study until the 30th day of treatment remained within the normal limits.

Discussion

The obtained results confirm the high antidepressant activity of agomelatine during the treatment of endogenous depressions. Already after 1 month of the course of treatment, the patients demonstrated a significant improvement (reduction in MTS of depressive disorders on HAMD-21 upon the average by 84.4%), with subsequent relatively stable preservation of the achieved effect and the development of remission after 5 - 8 weeks of therapy. Already at the 2nd week of treatment, a good effect was recorded in patients (reduction of MTS on HAMD-21 by 50% or more), and a steady significant effect was achieved by the 4th week.

The antidepressive effect of valdoxan includes a balanced thymoleptic, stimulating, anxiolytic and anti- anhedonic effects, which became apparent in the form of significant improvement already by the 3rd and 4th weeks of treatment and the reduction of MTS according to HAMD-21 of the corresponding depressive disorders by 90.83; 84.91; 82.39 and 78.9% by the end of the study. Available reports on the clinical effects of valdoxan have repeatedly emphasized its high efficacy and early (since the 14th day of treatment) development of the anti-depressive effect.

However, these works dealt with the treatment of outpatients with mild to moderate severity of depressions [13], while in our study, inpatients were included not only with moderate, but also with severe depression (respectively 58, 9 and 41.1%), in whom high therapy results were achieved. The efficacy indicators of valdoxan by the end of the course of treatment (8 weeks) were ambiguous: for moderately expressed depressions, HAMD reduction in MTS ranged from 47.7% [10] to 81% and for severe depression, valdoxane was not appointed in these studies. Discussing the balanced spectrum of action of this drug, the authors mainly evaluated the separate components of its psychotropic activity (anhedonia, anxiety, stimulating effect) [10,12].

Our data significantly expand the existing understanding of the spectrum and nature of the anti-depressive effect of valdoxan and allows formulating specific recommendations for its use in various types of depression.

Conclusion

Owing to the universal spectrum of antidepressive effects, valdoxan can be used in various psychopathological types of endogenous depressions: sad (melancholic), apathoadynamic and anxious ones.

The results of our study showed, that treatment with valdoxan is preferable in anhedonic endogenous depressions; the drug has a distinct effect not only on anxiety, but also on hedonic disorders, including various spheres of psychic activity (interests, social contacts, emotional involvement, etc).

High efficacy and good tolerance serve as the basis for choosing this drug as an antidepressant and make it possible to formulate personalized indications for its prescription, taking into account the psychopathological specificities of depressions themselves and hedonic disorders in their clinical picture. At the same time it is possible to predict the best tempo and depth of the therapeutic response.

Declaration of Financial and Other Relationships

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