

Agomelatine as a means of Effective Therapy of Anhedonic Endogenous Depressions

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Background: To date depressions, to the optional attributes of which anhedonic manifestations belong, becomes more frequent as for the prevalence of mental pathology.

According to WHO projections for 2020, diagnosis of depressions as to their frequency will come to the fore, being accompanied by negative consequences in the form of impairment of social functioning of patients and the growing economic costs of society to ensure them. This determines the actuality of studies directed at the development of measures of rising social adaptation of patients with depression, improvement of the quality of life, also by means of optimization of therapeutic approaches and the search for pathogenetically grounded methods of treatment.

During the search for "ideal" antidepressive drugs since the 50-ies of XX century their goal-directed synthesis was carried out, associated with the concept of participation of biogenic amines (noradrenaline and serotonin) and their metabolites in the pathogenesis of endogenous depressions.

To date one of the theories of depressive disorders development is chronobiologicalone, based on the concept of desynchronization of biological rhythms in a case of the indicated pathology. According to the studies of Hardeland R., et al. (2008), a key role in synchronization of circadian rhythms, including sleep wake cycle, play chronobiotic hormone melatonin, which is synthesized in pineal gland (its production falls on the night phase of the circadian rhythm). From it melatonin is supplied to

suprachiasmatic nucleus, where it interacts with melatonergic receptors [1]. These discoveries made it possible to create Agomelatine, the drug which possesses agonism towards MT1- and MT2- receptors, as well as it is a selective antagonist towards 5-HT_{2c} receptors. Entering the body, it penetrates the suprachiasmatic nucleus, where it comes into contact with the receptors, mentioned above, which results in specific and indirect release in the frontal cortex of the two basic, playing important role in pathogenesis of depression neurotransmitters: noradrenaline and dopamine.

For the first time Hasler BP, et. al. pointed to therapeutic efficacy of agomelatine in anhedonia, having associated it with the specificities of melatonergic effect of the drug [2]. To date publications about agomelatine efficacy in depressions within the framework of endogenous mental disorders are few in number [3-5].

Objective: of the present study was the analysis of clinical effect of agomelatine on manifestations of anhedonia in the clinical

picture of endogenous depressions, establishing its therapeutic efficacy and tolerance in the dynamics of course treatment of gedonic impairments and substantiation of the effectiveness of the given method of treatment on the basis of the development of differentiated indications for the appointment of the drug.

Patients and methods: The study was carried out as an open prospective research. All the patients signed informed consent for participation in the study. 30 subjects of both genders (24 females, 6 males) aged from 18 to 58 yrs. (mean age – 35.9 yrs.) were examined. All the subjects were in-patients due to endogenous depressive states with the clinical picture of hedonic disorders. In 21 patients depression was diagnosed within the framework of affective psychosis with unipolar (8), or bipolar (13) course, in 9 subjects it was diagnosed within the framework of schizophrenia. According to ICD-10 their diagnoses corresponded to F31.3; F31.4; F33.1; F33.2 and F20.4 items. Mean age of disease manifestation was equal to 26.1 yrs, the duration of illness from the first manifestations made up from one month to 31 yrs (on the average -10.4 yrs). During this period the subjects suffered from 1 to 24 depressive episodes (excluding the present one) per patient (on average of 5.4 ± 8.1 of depression).

All patients underwent examination and treatment according to a single research Protocol. Agomelatine was prescribed as a drug under the trade name valdoxan (manufactured by Servier Laboratory, France), in 25 mg tablets, daily in the evening, initially at a dose of 25 mg, followed by an increase in indications of up to 50 mg: in 5 patients, the daily dose of valdoxan at all stages of the course treatment was 25 mg, in 1 subject - 50 mg; in other cases, the daily dose of valdoxan increased from 25 mg to 50 mg after 1 (11 patients), 2 (13 patients) weeks of taking the drug. The average daily doses of valdoxan

on the days of assessment were 25.8-34.8 - 43.3 - 45 mg. As concomitant therapy, other antidepressants were not allowed, Benzodiazepine tranquilizers; if necessary, the administration of antipsychotics in moderate doses, nootropics, normotimics was allowed (if patients received them before the start of the study). Criteria for not including: - the presence of somatic and organic brain diseases in patients at the stage of decompensation, - suicidal tendencies in behavior, - substance abuse and alcohol dependence, as well as pathological parameters in the biochemical analysis of blood (especially total bilirubin, AST and ALAT).

The following methods were used in the work: clinical, clinical-psychopathological, psychometric (scale-questionnaire for assessing SHAPS hedonic disorders). The severity of symptoms of

anhedonia was assessed in dynamics both by the average total score (ATS) of all SHAPS symptoms as a whole in the picture of depression, and in subgroups of signs grouped by different areas of the prevailing mental activity in which anhedonia occurred, namely: in the field of interests (items 1, 2, 3, 9), social activity (items 7, 8, 13, 14), emotional involvement (n.n.5,6,11,12) and food /drink (n.n.4,10).

The effectiveness of the clinical effect of valdoxan on anhedonic manifestations was determined by the degree of reduction of the average total score (ATS) of the corresponding rating scales in % to 0 or by the previous day of assessment in the following conditional gradations of the treatment effect: when the ATS was reduced by 0-19%, the effect was rated as "insignificant" or "absence" of it; with a reduction of 20-49% - as "moderate"; by 50-69% - as "good", by 70% and more - as "significant". Assessment of the mental state of patients in the dynamics was carried out on 0, 7, 14 and 30 days.

Results: Evaluation of the effectiveness of the course treatment with valdoxan showed that the graduation of the "significant" therapeutic effect of the anhedonic manifestations was achieved already on the 14th day of the course of treatment with a decrease in the average total score of anhedonia according to SHAPS by 71%, and by the 30th day the "significant" treatment effect was approaching the recovery state (by 91.5% reduction in disorders). Equally high rates of formation of the therapeutic effect of valdoxan were found in the framework of the dynamics of indicators of anhedonia in certain areas of mental activity. Thus, by the 14th day of therapy, ATS was reduced by 75.8% in the field of emotional involvement, by 73.5% in the field of food / drink, by 73.6% in the field of social activity, by 71.0% in the field of anhedonia with a lag in the interest field - a reduction of 63.7%. The graduation of the "significant" therapeutic effect of valdoxan in the interest field was achieved only by the 30th day of the course treatment, significantly lower than the SHAPS total reduction in the assessment of anhedonia in other areas of mental activity - 88.2% against 91.7-95.2%.

Conclusion: A course of treatment with agomelatine (valdoxan) may be considered as preferable and highly effective in anhedonic endogenous depressions. It provides a high antidepressant effect on the hedonic disorders proper in its structure, revealing a dominant anti-anhedonic effect. The high therapeutic efficacy of agomelatine in anhedonic depression, the depth, speed and tempo of detection of therapeutic effects, good tolerance make it possible to formulate personalized indications for its purpose, taking into account the established psychopathological features and nosological evaluation of both the depressions themselves and the hedonic disorders in their clinical picture, predicting the best therapeutic response.

References

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