Atypical depression: selection criteria, systematics, approaches to therapy

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The paper reviews Russian and foreign literature on atypical depression (AtD). It sets forth the historical aspects of identifying AtD among other depressive disorders: the authors have traced the path from depression with individual atypical manifestations to a syndrome with a clearly defined pattern and inclusion criteria in the international DSM-4 and DSM-5 classifications. The paper gives epidemiological indicators and shows their diversity due to various approaches to the determination and clinical assessment of AtD. It analyzes the results of studying AtD in the presence of various affective disorders, such as recurrent depressive disorder, bipolar affective disorder, and psychogenic depression, and notes their heterogeneity in both symptoms and genesis. The authors present approaches to treating AtD and the results of investigating drug (antidepressant) and non-drug (cognitive-behavioral psychotherapy, increased physical activity therapy) treatments.

History of the term "atypical depression", its definition and epidemiology

The term "atypical depression" (AD) was first used by P.E. Huston and L.M. Locker in 1948 to describe depressed patients with agitation, psychotic episodes, and more responsive to electroconvulsive therapy (ECT), in comparison with patients with typical depression without psychotic episodes [1]. Following them, J. West and Dally identified atypical depression as therapy-resistant depression with severe anxiety, well responding to treatment with iproniazid (a non-selective monoamine oxidase [MAO] inhibitor) and not accompanied by guilt, weight loss and sleep disturbances [2]

Since then, the term "AD" has undergone a number of significant changes in foreign literature: from "depression with atypical symptoms" to a separate syndrome with a definite structure (first in The *Diagnostic and Statistical Manual of Mental Disorders-IV* [DSM-IV], then in DSM-V), requiring such obligatory criterion as mood reactivity and the presence of, at least, two of the following symptoms: increased appetite (hyperphagia) and / or weight gain, hypersomnia, «lead» paralysis (heaviness in the arms and legs) and increased sensitivity to current events and interpersonal communication [3].

Mood reactivity is understood as an increased response to external factors while the ability to have fun and satisfaction in response to positive events is preserved. Increased appetite and accompanying weight gain should be at least 3–5 kg over the past 3 months. Hypersomnia involves sleep more than 10 hours a day, at least 3 days a week for 3 months. «Lead» paralysis refers to a feeling of heaviness or weakness in the arms or legs, lasting more than 1 hour per day, at least 3 days a week for 3 months.

In Russian psychiatry, depression has traditionally been called "atypical", if it differs from typical melancholic depression. The latter is characterized by a depressive triad, lack of mood reactivity, a more depressed mood in the morning, early morning awakenings, decreased appetite and / or weight loss. AD more widely goes beyond the framework of the classical depressive triad and is accompanied by a number of additional signs, such as hypersomnia, anxiety, different kinds of pain and somatic-vegetative manifestations, derealization-depersonalization syndrome, obsessive-compulsive and phobic disorders, hypochondriacal symptoms [4, 5, 6]. Different combinations of these and typical symptoms reflect the variety of depressive syndrome and explain the need for an additional classification of depression: melancholic, anxious, apathetic, hypochondriacal, masked, anesthetic, depression with ideas of self-incrimination and self-abasement, depression with obsessive doubts, thoughts, actions [7,8 , 9, 10].

In ICD-10 atypical depressions are not distinguished. Depression with atypical features belongs to the categories: F32.8 (other depressive episodes), F38 (other mood disorders) and F39 (mood disorder, unspecified), as well as some of the categories F40-48 [11].

Due to various approaches to the definition and diagnosis of atypical depression, its prevalence rates vary greatly. Epidemiological studies using the DSM-V criteria indicate that from 15% to 29% of depressed patients have atypical depression and its prevalence is 18% to 36% [12]. However, most depressed patients present with mixed signs of atypical and melancholic depression. Classical melancholic depression accounts for 25% to 30% of cases, while atypical depression — for 15% to 30% [13].

Neurobiological, clinical and gender characteristics of atypical depression

The ambiguity in the interpretation of AD constantly increases interest in studying its epidemiological parameters, neurobiological, genetic and clinical features.

The biological mechanisms of AD, like any depression, are associated with disruption of the noradrenergic, serotonergic and

dopaminergic systems. Depressed mood, motor lethargy, anergia, slowing thinking, impaired attention, fatigue and pain are commonly associated with dysfunction of the brain noradrenergic system. Decreased mood, anxiety, phobias, panic attacks, obsessions and compulsions, food craving and bulimia, pain are the result of serotonin deficiency. Such symptoms as anhedonia, apathy, spontaneity, emotional fencing, flattened affect, difficult abstract thinking, impaired smoothness and logic of thinking are noted with dopamine deficiency [14].

Abroad, the role of leptin and ghrelin in the regulation of eating behavior and their influence on affective pathology have been studied for a long time. It is known that leptin is produced in adipose tissue and is responsible for reduction of appetite. Ghrelin is produced in the stomach and, on the contrary, increases appetite. Both of them modulate the neuromediation of serotonin and dopamine, thus taking a direct part in the formation of depression mechanisms [15, 16].

Clinical studies suggest that AD is more often associated with the female sex [17, 18, 19, 20], younger age of onset of depression, higher frequency and severity of somatic-vegetative symptoms, a larger number of depressive episodes [21, 22, 23, 24] and, most importantly, with adverse life events [17, 25].

AD is also combined with anxiety, various addictions, overeating and psychotic disorders [26, 27]. AD patients have a higher body mass index (BMI) [28], higher levels of biological correlates (components of metabolic syndrome, markers of inflammation and dysregulation of leptin) [29 , 30, 31] and a higher frequency of hereditary predisposition to affective disorders than patients with typical (melancholic) depression. In patients with AD cyclotymic temperament is more common in the premorbid state. This temperament is possibly a diathesis not only for AD, but also for bipolar affective disorder (BAD), anxiety disorders and borderline personality disorder [32]. People with AD showed high comorbidity with narcissistic, hysterical, borderline and dependent personality disorders [33]. The frequency of personality disorders in patients with AD reaches 90%, that can be regarded as a manifestation of AD itself [27]. Also, these patients are characterized by predominance of such qualities as impulsivity, angry aggressiveness and reduced self-control [34].

Depression in women generally occurs twice as often as in men [20]. Atypical symptoms and somatic manifestations of depression are also observed more often [35], which is confirmed by the study of twins and sisters. Assessing the mental state of 94 female twin pairs, typical and atypical depressions were identified [35]. Atypical depression was accompanied by increased appetite, hypersomnia, more frequent but short episodes. However, the lack of comparison with male twin pairs limits the possibility of the conclusion about differences in depressive symptoms in women and men. This study was conducted by the Canadian Epidemiological Community: the symptoms of recurrent depression in 650 patients were analyzed. The authors reported the presence of atypical symptoms in 11% of cases. In both groups (with typical and atypical depression) women constituted the absolute majority − 77% and 75%, respectively [36].

In the study of twin pairs, a high frequency of atypical symptoms (increased appetite, weight gain, hypersomnia, fatigue) was found in women. These patients also noted tearfulness, ideas of guilt, daily fluctuations in well-being with deterioration in the morning, and lethargy. Sisters, compared to brothers, had an earlier onset of the disease and a longer depressive episode [37].

An important social aspect that deserves attention is suicidal risk to which patients with AD can be exposed. According to several studies, patients with AD in the structure of recurrent depression and bipolar affective disorder type II (BAD II) show higher suicidal risks compared with patients with a typical clinical picture of depression [17]. Moreover, atypical depression in such patients is more often associated with personality disorders, anxiety disorders, female gender, mixed condition and hereditary affective pathology [23, 32]. In addition, in a number of studies a higher risk of suicide (12–60%) was found in patients with BAD II, compared with patients having recurrent depression [38, 39, 40, 41] [23, 32, 38, 39, 40, 41]. The issue of suicidal risks in depressed patients with BAD I does not currently have sufficient evidence, since it has not been comprehensively studied and requires further investigation.

Atypical depression within BAD

The concept of association of AD with bipolar disorder was put forward by a group of researchers at the University of Pittsburgh at the turn of the XX–XXI centuries. They stated that atypical depression has common features with BAD II [38, 39, 40, 41]. This idea was confirmed by the results of a Polish cross-sectional study, in which a significantly higher frequency of atypical depressive symptoms (hypersomnia and hyperphagia) was found among patients with bipolar depression than in the unipolar group [42].

Studies by many authors also show that high levels of psychomotor retardation, «lead» paralysis (feeling of heaviness in the arms or legs) [35, 36], lability of emotions, hyperphagia accompanied by an increase in body weight, and hypersomnia are more typical of AD within BAD [37, 40, 43]. Also, depression with psychotic symptoms and suicidal behavior are more likely to develop in bipolar patients [44]. Irritability, even without significantly decreased mood, is combined with depressive ideas, especially in teenagers and elderly patients [43]. Bipolar depression is more often associated with a family history of mental illness and an earlier age of onset (< 25 years) [45].

According to an epidemiological study conducted in the United States in 2012 [24], in the general population of depressive patients, the group of patients with AD had significantly higher rates of affinity with depression in BAD I compared to depressive patients who did not have atypical symptoms. Patients with AD and a diagnosis of BAD differed from patients with recurrent depression in a higher frequency of concomitant mental disorders, a younger age at the onset of the disease, a greater number of episodes, higher rates of depression in the family history, anxiety and sensitivity, as well as more frequent suicidal thoughts and suicide attempts. The criteria for atypical depressive syndrome, although common to both disorders, are even more pronounced in BAD than in recurrent disorder with atypical signs [24].

Patients with AD have a lot of comorbidities such as anxiety disorders (panic attacks, social phobia), eating disorders [46], and so-called seasonal depressions. Hypersomnia, hyperphagia and anergia, in turn, are more often registered in seasonal depressive disorder. However, only 10% of patients with atypical depression report seasonal affective episodes. The differences between AD and seasonal depression in terms of symptoms suggest that they form separate subtypes of depression with overlapping symptomatic patterns [47,48].

Atypical depression as part of recurrent depressive disorder

Initially, atypical depression was considered exclusively within the structure of unipolar depression [22], despite the evidence from E. S. Paykel (1977) [46]; T. Detre et al., (1972) [49] that atypical symptoms such as hypersomnia and hyperphagia are more common in bipolar depression. Akiskal H. S., Benazzi F (2005) [50] considered atypical depression either within the structure of BAD II, or as a transitional syndrome, a kind of "bridge" between monopolar depression to bipolar disorder type II [50].

According to Russian researchers [51], AD was detected in 20% of patients with monopolar endogenous depression, mainly in women (95%). The most common symptoms were increased appetite and weight gain, hypersomnia, less frequently − mood reactivity and «lead» paralysis. In most patients with AD aches and senestopathies, as well as atypical panic disorder with the inclusion of conversion symptoms were detected.

The review of individual symptoms and typology of atypical depression in the structure of monopolar and bipolar affective disorders [52] allowed the authors to identify 3 variants of AD: with the predominance of 1) mood reactivity, 2) inverted vegetative symptoms (hyperphagia, hypersomnia), 3) sensitivity to rejection. At the same time, the 1st and 3rd variants were more typical of recurrent depression, and the 2nd − of depression within BAD. These data confirm the assumption of heterogeneity of AD, that requires clarification of its place in the classification of affective disorders.

Atypical depressive syndrome in the framework of psychogenic depressions

It is known that psychogenic depression occurs after an emotionally significant shock resulting from the loss of loved ones, work, property, parental love, moral harassment, bullying, infringement of rights etc. Such depression is divided into neurotic and reactive, based on its severity [53]. The clinical picture of reactive depression is usually characterized by a short period of numbness, sleep disorders, decreased appetite and body weight, followed by an increase in affective disorders, feelings of guilt and remorse in the specific situation that caused the depression. When acuteness of the experience subsides, patients can switch from the psychogenic situation to their health, which often leads to the development of hypochondriac symptoms. In the structure of neurotic depression emotional disorders are less pronounced, do not reach the state of stupor and gloomy hopelessness with unwillingness to live. Suicidal thoughts are usually presented at the verbal level and are caused by a pessimistic assessment of the future and a temporary lack of a comforting perspective. In such patients, sleep is superficial, with awakenings, it is often disturbed due to constant memories associated with a traumatic situation. In women during menopause psychogenic depressions are often accompanied by anxiety, increased appetite and weight gain, and menopausal somatic-vegetative symptoms [53].

In foreign literature, there is information that symptoms of AD can appear after high-intensity stress, which can be evaluated as a significant reactive component in the course of AD [54]. AD is considered to occur as a decompensation in response to stressful factors [17, 30, 35, 42, 52]. Therefore, such signs of AD as mood reactivity and increased sensitivity to interpersonal changes require further study and clarification of their role in the structure of AD, especially in the course of psychogenic depressions.

Treatment of AD

Although originally AD included those cases that were better treated with ECT [1], the effectiveness of its application was evaluated ambiguously, since no large-scale comparative studies were conducted in this area. In 2008, Husain and co-authors [55] analyzed the results of treatment of patients with major depressive disorder (DSM-V), divided into typical (n = 453) and atypical (n = 36) groups, using bilateral ECT. Remission was obtained in 67.1% of patients with typical depression and in 80.6% with atypical depression, which confirms the effectiveness of ECT in patients with AD.

As mentioned earlier, AD was characterized by a positive response to IMAO therapy in general, and iproniazid in particular [2]. However, currently, this group of drugs is not practically used in our country due to a number of restrictions and high risks of side effects. In contrast, a group of selective serotonin reuptake inhibitors (SSRI) proved to be effective. The effectiveness of fluoxetine in the treatment of AD is 51−60% [56, 57]. In an open comparative study of fluoxetine and phenelzine, their effectiveness in patients with AD was almost identical [58]. Comparing the effectiveness of fluoxetine and moclobemide in the treatment of patients with AD, a positive dynamic was observed in 60% of patients receiving fluoxetine and in 71% of those receiving moclobemide [59].

Data on the reasonable effectiveness of SSRIs in AD are supported by the results of a study of the auditory evoked potentials (LDAEP), which were registered on EEG and were stronger in patients with AD than in patients without its symptoms. Since LDAEP is considered a biomarker of serotonin activity, these results indicate a relatively low serotonergic activity in patients with AD, which in turn explains the presence of mood reactivity [60], as well as anxiety-phobic disorders, hyperphagia, and various aches in the clinical picture of AD.

There were attempts to treat symptoms of AD, such as overeating and drowsiness, as well as «lethargy» (fatigue), which also characterize seasonal affective disorder (DSM-V), using light therapy, but the results were negative [61].

An increase in physical load in combination with psychopharmacotherapy in patients with depression resulted in a gradual decrease in hypersomnia and body mass index, to a greater extent in atypical depression than in melancholic depression [62].

Psychotherapy, especially cognitive behavioral therapy (CBT), is widely used in the treatment of AD. Its effectiveness was demonstrated in a comparative study of psychotherapy and treatment with phenelzine [63], sertraline − [64, 65, 66]. Fournier and co-authors [67] studied the dynamics of symptoms of depression during a 16-week course of treatment with paroxetine or CBT. Both methods reduced cognitive and suicidal symptoms; however, cognitive therapy had a greater effect on atypical-vegetative symptoms than antidepressants.

Treatment of AD in patients with various disorders requires a personalized approach taking into account the clinical picture, neurobiological substrate, personal characteristics of the patient, as well as gender and age. Since patients with atypical depression are more likely to be obese [68] and have leptin resistance, drugs which do not affect appetite and body weight should be prescribed [69].

Thus, despite numerous studies of AD, there are still no uniform criteria for its isolation in an independent clinical form. Different diagnostic approaches lead to significant dif-

ferences in the results of epidemiological studies and classification of affective disorders. The neurobiological mechanisms of AD, gender characteristics, and the relationship with biological rhythms (diurnal, seasonal) and polarity during affective disorders are insufficiently studied. Clarification and improving knowledge on these issues will contribute to upgrading the diagnosis of depressive disorders, methods of their treatment and prevention.

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