

# Atypical depression: current perspectives

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**Abstract:** The history and present status of the definition, prevalence, neurobiology, and treatment of atypical depression (AD) is presented. The concept of AD has evolved through the years, and currently, in *Diagnostic and Statistical Manual of Mental Disorders* (DSM), Fifth Edition, the specifier of depressive episode with atypical feature is present for both diagnostic groups, that is, depressive disorders and bipolar and related disorders. This specifier includes mood reactivity, hyperphagia, hypersomnia, leaden paralysis, and interpersonal rejection sensitivity. Prevalence rates of AD are variable, depending on the criteria, methodology, and settings. The results of epidemiological studies using DSM criteria suggest that 15%–29% of depressed patients have AD, and the results of clinical studies point to a prevalence of 18%–36%. A relationship of AD with bipolar depression, seasonal depression, and obesity has also been postulated. Pathogenic research has been mostly focused on distinguishing AD from melancholic depression. The differences have been found in biochemical studies in the areas of hypothalamic–pituitary–adrenal axis, inflammatory markers, and the leptin system, although the results obtained are frequently controversial. A number of findings concerning such differences have also been obtained using neuroimaging and neurophysiological and neuropsychological methods. An initial concept of AD as a preferentially monoamine oxidase inhibitor-responsive depression, although confirmed in some further studies, is of limited use nowadays. Currently, despite numerous drug trials, there are no comprehensive treatment guidelines for AD. We finalize the article by describing the future research perspectives for the definition, neurobiology, and treatment. A better specification of diagnostic criteria and description of clinical picture, a genome-wide association study of AD, and establishing updated treatment recommendations for this clinical phenomenon should be the priorities for the coming years.

**Keywords:** hypersomnia, hyperphagia, obesity, bipolar disorder, seasonal affective disorder

## Introduction

Although first described in 1959,<sup>1</sup> depression with atypical features (atypical depression, AD) appeared in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) as a specifier of major depression and dysthymia in 1994 (DSM-IV).<sup>2</sup> Since the issues of AD have been accompanied by controversy, in this review, we discuss the history and the present status of such issues as definition, prevalence, neurobiology, and treatment of AD. In the last part of the paper, we attempt to delineate future perspectives of this clinical phenomenon.

## Definition

The first definition of AD as a preferentially monoamine oxidase inhibitor (MAOI)-responsive depression was introduced by West and Dally in 1959.<sup>1</sup> Prior to such description, the term “atypical depression” was used in 1948<sup>3</sup> for describing depressed patients presenting with agitation, paranoid features, and perplexity, who responded well to electroconvulsive therapy (ECT). In DSM-III, the term was used for depression

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secondary to schizophrenia, for dysthymic disorder with long periods of well-being, and for brief depression (non-adjustment disorder).<sup>4</sup>

In 1982, Davidson et al<sup>5</sup> proposed two types of AD: type A, with predominant anxiety symptoms, and type V, with vegetative symptoms, such as hyperphagia, weight gain, oversleeping, and increased sexual drive.<sup>5</sup> Features shared by both subtypes included early onset, female predominance, outpatient predominance, mildness, and few suicide attempts. Type V was the one frequently seen in bipolar patients.<sup>6</sup>

In 1994, the DSM-IV introduced the criteria for “atypical features” as a modifier of major depression and dysthymia.<sup>2</sup> Diagnosis of AD consists of criteria for depression in major depressive disorder (MDD), a major depressive episode of bipolar disorder, or dysthymia, together with the following specifiers of AD: significant mood reactivity (mood brightness in response to actual or potential positive events) and two or more of the following symptoms: significant weight gain, increase in appetite, hypersomnia, leaden paralysis, and a long-standing pattern of interpersonal rejection sensitivity that results in significant social or occupational impairment. In addition, the patient cannot meet the criteria for melancholic or catatonic depression. Surprisingly, no change in DSM-5<sup>7</sup> in 2013 was introduced, despite substantial remarks presented by some authors many years prior to the introduction of DSM-5.<sup>8,9</sup>

The definition and clinical picture of AD have raised a number of controversies. Researchers from Columbia University established the so-called Columbia criteria for AD as chronic, mild, non-melancholic unipolar depression, with mood reactivity. The significance of mood reactivity reflected the theory that mood non-reactivity was an essential symptom of “endogenomorphic depression”.<sup>10,11</sup> Also, the symptom named by Liebowitz et al<sup>12</sup> as “leaden paralysis”, alternatively defined as lethargy, anergia, or fatigue, was added to the description of AD. The Columbia group pointed out that AD patients, when compared to patients with melancholic depression, had a significantly earlier onset of the illness, much more chronic course of the illness, and less frequently family members with a recurrent and severe depressive illness, but more often family members who were chronically depressed.<sup>13</sup>

The New South Wales University group also defined AD as chronic, mild, non-endogenous (non-melancholic) unipolar depression, but indicated the predominance of anxiety symptoms over mood symptoms and the significance of interpersonal rejection. Parker et al<sup>14</sup> argued that mood reactivity did not show specificity with any other four criterion

symptoms and claimed that anxiety may be more specific and common in AD.

Other studies pointed out an equal probability of mood non-reactivity and mood reactivity with two other associated features of atypical mood.<sup>15,16</sup> According to Thase<sup>9</sup> and Angst et al,<sup>17</sup> mood reactivity is not useful for the diagnosis of AD and should not be regarded as an obligatory symptom. As noticed by O’Keane et al,<sup>18</sup> “it is puzzling that the most controversial symptom in the diagnosis of atypical depression is also the only obligatory one in DSM”. On the basis of the differences in the results of treatment,<sup>19</sup> biology, and family history, a suggestion was also presented by Stewart<sup>20</sup> that depression with atypical features may include at least two types of disorders, one having an early onset and a very chronic illness course and the other with either a later onset or a less chronic course.

The concept that AD is related to bipolar disorder was put forward at the turn of the century. The Pittsburgh University group claimed that AD is a depressive state that can be observed in bipolar disorder and regarded the reversed vegetative symptoms and lethargy as signs of bipolar disorder.<sup>20</sup> According to the bipolar spectrum concept,<sup>22</sup> AD shares features with bipolar II disorder or soft bipolar spectrum disorder.<sup>22–24</sup> That idea was supported by the findings in a Polish cross-sectional study where among depressed patients a significantly higher frequency of atypical depressive symptoms (hypersomnia and hyperphagia) in bipolar than unipolar group was found.<sup>25</sup> Also, in a national survey performed in the general population in the US,<sup>26</sup> individuals with AD had significantly higher rates of bipolar I disorder than those without atypical feature. Patients with AD diagnosed with bipolar disorder differed from those with MDD: bipolar AD patients had more psychiatric comorbidities, younger age of onset, higher number of episodes, higher rates of family history of depression, early-onset anxiety, and rejection sensitivity, and reported more often suicidal thoughts and suicide attempts. The authors concluded that

all those suggested that the characteristics of atypical depression, although common in both disorders, are even more accentuated in bipolar depression than in MDD with atypical features.<sup>26</sup>

Patients with AD have substantial comorbidity with a variety of anxiety disorders (eg, social phobia), eating disorders, and substance-related disorders, which may affect clinical outcomes.<sup>27</sup> Some authors also suggest that AD may be misdiagnosed as personality disorders (borderline,

histrionic, or avoidant).<sup>14,28</sup> According to the review on AD by Silverstein and Angst<sup>29</sup> which focused on comorbid disorders, disordered eating (including bingeing as well as intentional food restrictions), poor body image, pain, insomnia, and fatigue (separately from leaden paralysis) may actually reflect multiple manifestations of a single disorder.

We studied 91 pairs of patients, matched by age, gender, and diagnosis in which one member of the pair was within the normal weight range (body mass index [BMI]  $\leq 25$ ) and the other was either overweight or obese (BMI  $> 25$ ). There were 35 pairs with MDD, 27 with bipolar depression, and 29 with dysthymia. We found that all the symptoms of AD were significantly more pronounced in those depressed patients with a BMI  $> 25$  compared with depressed subjects with a normal weight. Among the diagnostic categories, symptoms of AD were significantly higher in patients with bipolar disorder compared with both MDD and dysthymia.<sup>30</sup>

Hypersomnia, hyperphagia, and loss of energy are also more likely to be reported in the so-called seasonal affective disorder (SAD). However, only 10% of AD patients reported a seasonal pattern of affective episodes, and the differences between AD and SAD in terms of symptoms suggest that they form separate subtypes of depression with an overlapping symptom picture.<sup>31,32</sup>

As AD may be a subtype of depression, one should mention the papers presenting negative results on symptom dimensions or subtypes of depression. According to van Loo et al,<sup>33</sup> studies completed to date do not provide conclusive evidence of the existence of depressive symptom dimensions or symptomatic subtypes. Fifteen different subtypes were described in a meta-review of Harald and Gordon,<sup>34</sup> with symptom-based melancholia, psychotic, and atypical subtypes, and also etiologically based and time-of-onset-based subtypes. According to the authors, anxious subtype of depression and gender-based and treatment-based subtypes of depression were judged as too unspecific to qualify as a subtype of depression. They pointed out that there is a substantial overlap across the five categories and 15 subtypes of depression. The history of the definition of AD is depicted in Table 1.

## Prevalence of AD

Since the first attempt to define AD, many studies on its prevalence have been performed. Variable definitions, as well as differences between studies in cutoff scores for rating the features, have greatly influenced the results of epidemiological studies. Prevalence rates of atypical subtype may depend on the criteria, method, and settings of the study.

**Table 1** The history of the description/definition of atypical depression (AD)

Date, author(s)	Description/definition of AD
1948, Huston and Locher <sup>3</sup>	Depressed patients presenting with agitation, paranoid features, and perplexity, who respond well to electroconvulsive therapy
1959, West and Dally <sup>1</sup>	Depression responsive to monoamine oxidase inhibitors; lack of features commonly seen in endogenous depression such as guilt, early waking, weight loss, an improved mood at night, and a good response to electroconvulsive therapy
1980, DSM-III <sup>4</sup>	Depression secondary to schizophrenia, dysthymic disorder with long periods of well-being, and brief depression (non-adjustment disorder)
1982, Davidson et al <sup>5</sup>	Depression responsive to monoamine oxidase inhibitors. Types of AD: type A, with predominant anxiety symptoms, and type V, with vegetative symptoms, such as increased appetite, weight gain, oversleeping, and increased sexual drive (both types share such features as early onset, female predominance, outpatient predominance, mild symptoms, and few suicide attempts)
1984, The Columbia criteria of AD <sup>10-12</sup>	Chronic, mild, non-melancholic unipolar depression, with mood reactivity; "leaden paralysis", alternatively defined as lethargy, anergia, or fatigue; AD patients, compared to patients with melancholic depression, have a significantly earlier onset of the illness, much more chronic course of the illness, and less frequently family members with a recurrent and severe depressive illness, but more often family members who were chronically depressed
1994, DSM-IV <sup>2</sup>	Diagnosis of AD consists of criteria for depression in major depressive disorder, a major depressive episode of bipolar disorder, or dysthymia, together with the specifiers of AD: significant mood reactivity (mood brightness in response to actual or potential positive events) and two or more of the following symptoms: significant weight gain, increase in appetite, hypersomnia, leaden paralysis, and a long-standing pattern of interpersonal rejection sensitivity that results in significant social or occupational impairment. The patient cannot meet the criteria for melancholic or catatonic depression
2013, DSM-5 <sup>7</sup>	As above
2002, The New South Wales University Group <sup>14</sup>	Chronic, mild, non-endogenous (non-melancholic) unipolar depression; predominance of anxiety symptoms over mood symptoms and the significance of interpersonal rejection; mood reactivity does not show specificity with any other four criteria symptoms; anxiety may be more specific and common in AD
2007, The Pittsburgh University Group <sup>22-24</sup>	Depressive state that can be observed in bipolar disorder. Reversed vegetative symptoms and lethargy are regarded as signs of bipolar disorder; AD shares features with bipolar II disorder or soft bipolar spectrum disorder

**Abbreviation:** DSM, *Diagnostic and Statistical Manual of Mental Disorders*.

Most depressed patients present mixed features of AD and melancholic depression, with only 25%–30% presenting with pure melancholic features and 15%–30% with pure atypical features.<sup>35</sup>

In a national survey in the US in early 1990s, 36%–39% of patients with depression had hypersomnia and overeating, identified as AD.<sup>36</sup> Those AD patients differed from those with non-AD in terms of demographic features, psychiatric comorbidities, and drug abuse history. Results from a national epidemiological survey of the US population performed 10 years later<sup>26</sup> showed 10.2% prevalence of lifetime depression with atypical features, while the prevalence of depression without atypical features was 6.3%. Among individuals with atypical features, 43.5% had only hypersomnia, 23.8% only hyperphagia, and 32.5% showed both symptoms. According to the results of that survey, patients with bipolar I (but not II) disorder were more likely to display the atypical features than those with major depression.

According to Thase's<sup>21</sup> review presented in 2007, the results of epidemiological studies using DSM-IV criteria suggest that 15%–29% of depressed patients have AD which translates to a 1-year prevalence of 1%–4%. This concurs with clinical studies yielding a prevalence of AD as 18%–36%.

The percentage of AD found in the GENDEP (Genome-based Therapeutic Drugs for Depression study) was 7.4%.<sup>37</sup> In the outpatients studied in the STAR\*D (Sequenced Treatment Alternatives to Relieve Depression) trial, 18.1% had depression with atypical features.<sup>38</sup> In a community sample of young adults (Zurich cohort study), the cumulative incidence rates of various types of depression were as follows: melancholia or AD (in one group), 4.1%; pure melancholia, 7.1%; pure AD, 3.5%; and unspecified depression, 8.2%.<sup>17</sup>

Gili et al<sup>39</sup> studied clinical patterns and treatment outcomes in 1,455 depressed patients. In this group, 16.2% met the DSM-IV criteria for melancholic depression and 24.7% for AD. Compared with melancholic depression, atypical depressive patients were less severely depressed, had fewer depressive episodes, and showed higher rates of comorbid anxiety disorders and substance abuse, and higher rates of remission.

A consistent finding across all studies is that AD is associated with younger age of onset of depression, female preponderance (two to three times more likely in women than in men), occurrence of anxiety, and a history of bipolar II disorder.<sup>8,9,26,40</sup> Also, family history of depression, both unipolar and bipolar, has been found to be more frequent in

AD patients.<sup>26,41</sup> It was even postulated by Stewart<sup>20</sup> to use the diagnosis of depression with atypical features only in the case of patients who report a very early onset (before 20 years of age) and a very chronic course of illness since onset (no spontaneous 2-month period of well-being), and to add those criteria to DSM.

In some studies, it has been noted that diagnostic stability over time, in relation to a given subtype of depression, is present only in about 22%–29% of cases.<sup>17,42</sup> More patients experience fluctuations between melancholic and atypical episodes than continuing with either type consistently over time. Also, observation in the Zurich cohort study (between age 26 and 41) showed that one-third of patients with depression with reversed vegetative syndromes had manifested in the longitudinal course also a typical vegetative syndrome (loss of appetite/weight and insomnia).<sup>24</sup>

## Neurobiology and neuropsychology of AD

A number of neurobiological and neuropsychological studies on the pathogenesis of AD have been performed. They produced interesting results; however, when analyzed, most findings showed an overlap between atypical and non-atypical groups. The family studies have provided some support for the validity of the atypical subtype of major depression. In the twin study of depressive subtypes, higher concordance rates for the atypical subtype in monozygotic (odds ratio [OR] =5.4) than dizygotic (OR =1.0) twins were noted.<sup>43</sup> The community-based family study of the mood disorder spectrum performed by Lamers et al<sup>44</sup> showed greater diagnostic specificity of the familial aggregation of the atypical than the melancholic subtype of major depression.

Changes in the hypothalamic–pituitary–adrenal (HPA) axis are frequently used to suggest the opposing biological features of melancholic depression vs AD. This concept was presented by Gold and Chrousos.<sup>35</sup> Relatively hyperactive HPA axis leading to the symptoms of melancholia and a relatively hypoactive stress response leading to the symptoms of AD have been postulated. They implicate the corticotropin-releasing hormone (CRH) hypersecretion and hyposecretion in the syndromal pattern of melancholic depression and AD, respectively.<sup>35</sup> A meta-analysis of studies on the HPA axis conducted by Stetler and Miller<sup>45</sup> has identified a pattern of relative hypocortisolemia in AD compared to the melancholic spectrum of depressive disorders, but findings of other authors are inconsistent. O'Keane et al<sup>18</sup> suggest that there is a possibility of a “switch” in the regulation of the HPA system from CRH to arginine vasopressin resulting in

an altered homeostasis within the HPA system which may explain the changing profile of depression over time.

The inflammatory theory of depression is another concept for a biological basis of depressive psychopathology. Elevated concentrations of pro-inflammatory cytokines, such as interleukin (IL)-6, tumor necrosis factor-alpha (TNF- $\alpha$ ), and C-reactive protein (CRP), are among the most consistent findings in patients with depression.<sup>46</sup> In patients with AD vs non-AD and healthy controls, inflammation appears to be significantly greater in those with AD and AD has different pro-inflammatory cytokine patterns compared to melancholic depression. IL-6 levels were elevated in patients suffering from AD but not in patients with typical depression, compared to normal controls.<sup>47</sup> However, in the paper of Dunjic-Kostic et al,<sup>48</sup> IL-6 was higher in patients with melancholic type of depression compared to healthy controls, and TNF- $\alpha$  was lower in melancholic depression and AD patients compared to healthy controls. AD has been linked to decreased IL-4 and increased IL-2 compared to individuals without atypical features in one study,<sup>49</sup> while another study reported decreased IL-2 in AD compared with controls.<sup>50</sup> Patients with AD had higher CRP levels than those with no depression or with non-AD.<sup>51</sup> As an elevated CRP level has been found to predict coronary artery disease, and increased cytokines are related to metabolic syndrome,<sup>47</sup> AD patients seem to be at an increased risk of developing those somatic conditions. In a 6-year longitudinal study of clinical course of depression,<sup>52</sup> the atypical subtype group had the highest BMI and the highest prevalence of metabolic syndrome. The correlation of IL-6 in AD was found to be significant with glycated hemoglobin, insulin, waist circumference, BMI, and CRP.<sup>47</sup>

Another theory points to the leptin dysregulation (resistance) as the underlying mechanism connecting obesity and depression.<sup>53</sup> Leptin is an adipose-derived hormone involved in the regulation of mood and emotions with presumably antidepressant-like efficacy.<sup>53</sup> In a group of patients with depression, leptin concentration was strongly associated with clinical symptoms of AD, such as hyperphagia, increased weight, and leaden paralysis.<sup>56</sup> Our study demonstrated a higher prevalence of AD symptoms in obese patients compared to non-obese depressed patients.<sup>30</sup>

The neuroimaging studies of depression have shown a variety of abnormalities, particularly in the hippocampus, but also in the white matter. However, the relationship between the severity of symptoms and the hippocampus volume, as well as white matter integrity, is unclear. This may be related to the heterogeneity of depression.<sup>55</sup> In some

studies, an attempt has been made to examine the relationship between structural or functional changes in the brain and depression subtypes. Studies comparing the hippocampus volume between depressed patients with atypical features and those with melancholic features found no significant differences.<sup>56,57</sup> Recently, Ota et al<sup>58</sup> examined differences in white matter integrity assessed with diffusion tensor imaging in AD, melancholic depression, and control group. The results suggest that patients with depression had reduced white matter integrity in some regions; however, there was no major difference between AD and melancholic depression.

Fountoulakis et al<sup>59</sup> compared brain perfusion by using single-photon emission computerized tomography in patients with AD and melancholic depression and in control subjects. When compared with other depressed groups, AD patients had increased frontal, temporal, and parietal perfusion coupled with decreased occipital perfusion. Relative to controls, patients with AD also had increased right frontal perfusion, whereas those with melancholia and undifferentiated depression had decreased perfusion in the majority of non-occipital regions. As summarized by Thase,<sup>9</sup> increased right hemispheric processing was reported in AD patients, compared with both non-AD and healthy controls. Patients with AD showed increased right parietal processing, whereas those with typical depression demonstrated increased left parietal processing.<sup>59</sup> In a review presented by Lee and Kim,<sup>60</sup> the results of studies suggest a pattern where melancholia and undifferentiated depression had similar abnormal brain perfusion that differed from those with AD. This was also confirmed in a study assessing chimeric faces as a measure of perceptual asymmetry where AD patients indicated relatively increased right parietal processing.<sup>61</sup>

Differences between AD and melancholic depression have been demonstrated in neurophysiological studies. In a study of the assessment of the visual evoked potentials using electroencephalogram (EEG) after a visual stimulus, N80 and P100 latencies were significantly shorter in AD and longer in melancholic patients.<sup>62</sup> In another study, the loudness dependence of auditory evoked potentials (LDAEP) recorded in the EEG was stronger in AD patients than in those with non-AD. Since LDAEP has been proposed as a biomarker of serotonin activity, the results suggest a relatively deficient serotonergic activity in patients with AD, which may be connected with their mood reactivity.<sup>63</sup> Recently, Veronezi et al,<sup>64</sup> using the transcranial magnetic stimulation method, found increased motor cortical facilitation and decreased inhibition in AD compared with other depression subtypes. This was related

to gamma-aminobutyric acid A-receptor and glutamatergic activity in the motor cortex.

Recently, a systematic literature review on neuropsychological studies in melancholic depression and AD was published.<sup>65</sup> The authors compared the results of cognitive tests in melancholic and non-melancholic type of depression (NMD).<sup>65</sup> According to the review, melancholic patients have poorer performance compared to NMD patients when it comes to tasks involving verbal and visual memory, executive function, sustained attention and span, as well as psychomotor speed. In the authors' opinion, verbal fluency tests and psychomotor speed tasks seem to be suitable tools for differentiating AD from melancholic depression, since melancholic patients performed worse and showed more extensive and greater impairments than NMD patients.<sup>65</sup>

A psychological hypothesis about AD takes into account the personality and temperament<sup>40</sup> to distinguish patients with AD from those with typical depression. It was proposed that pathological sensitivity to perceived interpersonal rejection (resulting in social or occupational impairment) forms the main feature of AD. The personal pattern of rejection sensitivity is always accompanied by a variety of dysregulated emotional (exceeded anxiety) and self-consolatory problems (oversleeping and overeating).<sup>14</sup> In this concept, the spectrum of atypical depressive disorder was suggested, viewing it as psychological or reactive in origin.

## Treatment

The concept of AD emerged from the clinical observations of West and Dally in 1959.<sup>1</sup> They noted that some depressed patients did not benefit from imipramine and ECT, the treatments usually effective for what they called "typical" depression, but achieved remarkable benefits when treated with iproniazid, the original MAOI. Therefore, the first recommendation on how to treat AD stemmed from the definition of AD as "a preferentially monoamine oxidase inhibitor-responsive state". Superiority of the MAOI phenelzine over imipramine in depressed patients, meeting the Liebowitz et al<sup>12</sup> criteria of AD, was demonstrated in studies performed at the turn of 1980–1990s.<sup>66–68</sup> The study of Stewart et al<sup>69</sup> in patients with major depression showed a robust therapeutic effect of imipramine in patients without, but not with, atypical features.

Since 1990s, studies have also been performed comparing moclobemide, a reversible inhibitor of monoamine oxidase, with other antidepressant drugs in the treatment of AD. As far as selective serotonin reuptake inhibitors (SSRIs) are concerned, Lonnqvist et al<sup>70</sup> showed a better effect of

moclobemide than fluoxetine. However, in another study, a lack of differences in efficacy was found between moclobemide and sertraline.<sup>71</sup> A comparison of moclobemide and a tricyclic antidepressant, clomipramine, within a project of the DUAG (Danish University Antidepressant Group) Study, showed a better effect of moclobemide than clomipramine in patients with atypical vegetative symptoms, while the reverse was true for patients suffering from typical depression.<sup>72</sup>

Following initial skepticism as to the efficacy of ECT in AD,<sup>1</sup> no controlled studies of ECT in this condition have been performed. In 2008, Husain et al<sup>73</sup> examined the outcomes of patients with MDD divided into the typical (n=453) and the atypical (n=36) group who were treated with acute bilateral ECT. Remission was obtained in 67.1% of typical depressed patients and in 80.6% of atypical ones, and the latter group was 2.6 times more likely to remit than the typical group after adjustment for age, psychosis, gender, and depression severity. Therefore, in the light of modern ECT, these early observations of West and Dally seem unconfirmed.

In 2006, a meta-analysis was published for the pharmacological treatment of depression with atypical features. Only eight publications met the criteria for a double-blind, controlled condition and an operational diagnosis of AD, according to DSM. For the comparison of MAOI (including reversible ones) and tricyclic antidepressants, an effect size was 0.27, suggesting a better efficacy of the former, while for MAOI and SSRI, such an effect was negligible (0.02), indicating a lack of differences in efficacy.<sup>74</sup>

However, nowadays, MAOIs are not widely used, and the treatment guidelines for AD are lacking. The results of newer studies have not produced any clear indications in this respect. Comparing with SSRI, Papakostas et al<sup>75</sup> showed better efficacy of bupropion in improving hypersomnia and fatigue, elements of AD. Another study found that depressed patients with atypical features are less likely to remit with citalopram than those without atypical features.<sup>11</sup> In the GENDEP study, there was no indication that AD may respond better to SSRI than to tricyclic antidepressants as a similar efficacy of escitalopram and nortriptyline was observed.<sup>37</sup> Pae et al<sup>76</sup> in a post hoc analysis of five short-term trials with selegiline (selective MAOI type B) showed equal efficacy of this drug in patients with atypical and non-atypical subtype of depression.

Recently, the results of the iSPOT-D (International Study to Predict Optimized Treatment in Depression), including patients treated with escitalopram, sertraline, or venlafaxine, were reported. Three subtypes of patients were

delineated: patients with melancholic, atypical (according to DSM criteria), and anxious depression. Thirty-nine percentage of patients exhibited a pure-form subtype, 36% more than one subtype, and 25% could not be classified as any of the subtype groups. Symptom reduction and likelihood of remission did not differ significantly between subtype groups. The authors of the study concluded that subtypes of depression may be of minimal value in antidepressant selection.<sup>77</sup>

Since symptoms like overeating and oversleeping, as well as “lethargy” (fatigue), are characteristic of SAD, an attempt was made to use light therapy for AD, but the results were negative.<sup>78</sup> More promising outcomes were obtained with exercise where hypersomnia and increased BMI had been associated with better response. Rethorst et al<sup>79</sup> studied this procedure in depressed patients, and the results showed that patients with AD had better treatment response to exercise.

Psychotherapy, especially cognitive behavioral therapy (CBT), has been widely used in the treatment of depression, including AD. The efficacy of CBT in AD was demonstrated in a pilot study<sup>80</sup> as well as in subsequent trials.<sup>81–83</sup> In one of them, CBT treatment was found to be equal to the treatment with MAOI, phenelzine.<sup>81</sup> Recently, Cuijpers et al<sup>84</sup> performed a meta-analysis comparing AD and melancholic depression as a predictor of the therapeutic outcome of CBT and did not find any indication that either of these types can be a significant outcome moderator. They also found that these two types are not predictors to antidepressant treatment. Fournier et al<sup>85</sup> point to a different change in specific depressive symptoms during a 16-week antidepressant (paroxetine) or CBT course of treatment. In their study, both treatments reduced cognitive and suicide symptoms; however, cognitive therapy reduced the atypical-vegetative symptoms more than medications, which suggests its usefulness in AD.

## Perspectives

Depression is one of the most prevalent mental disorders, affecting some 121 million people worldwide. It increases the risk of suicide by 20 times and is among the leading causes of disability. According to the World Health Organization (WHO) data, by the year 2020, depression will be the second most common cause of disease and premature death worldwide.<sup>86</sup> Identifying the atypical subtype of depression in terms of clinical and biological features would give patients a chance for personalized treatment.<sup>87</sup> Therefore, studies should be directed at clarifying more issues such as diagnosis, neurobiology, and treatment, described in this article.

Although in 1982 Davidson et al<sup>5</sup> claimed that “atypical depression is poorly defined”, a recent review of Stewart

et al<sup>8</sup> argues for this clinical phenomenon as a valid entity. Better specification of diagnostic criteria and description of the clinical picture of AD taking into account the age of onset and the course would be required. Also, AD should have a proper place in the ICD-11. Further research on the neurobiology of AD is also needed, for example, the genome-wide association study. New pathogenic findings may broaden the biological characteristics of AD which may pave the way to a more specific treatment.

Guidelines for the treatment of AD taking into account the experiences gathered so far should be introduced in not too distant future. The algorithm for using appropriate antidepressants should be created. As the associations demonstrated between AD and bipolar depression may have therapeutic consequences and no pharmacological trials addressing this issue have been performed so far, we propose that, in each AD patient, a test for bipolarity should be performed (eg, by means of the Mood Disorder Questionnaire<sup>88</sup> or Hypomania Checklist-32 scale<sup>89</sup>). In the event of a positive result, an attempt to use a drug with antidepressant and mood-stabilizing properties such as lithium, lamotrigine, quetiapine, or lurasidone can be made. Also, because patients with atypical features of depression become obese more frequently<sup>90</sup> and have a resistance to leptin,<sup>54</sup> drugs which do not influence appetite and body mass should be taken into account.

After nearly 60 years of existence in contemporary psychiatry, AD still remains an intriguing clinical phenomenon where a lot of research should be done for its better understanding and management.

## Disclosure

The authors report no conflicts of interest in this work.

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