# *Effects of different antidepressant treatments on the core of depression*

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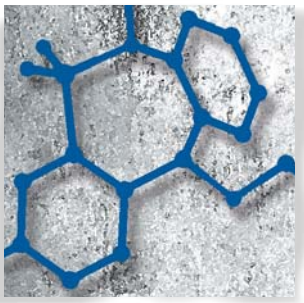

*Core symptoms of depression are a combination of psychological and somatic symptoms, often combined with psychomotor and cognitive disturbances. Diagnostic classification of depression including the concepts of melancholic, endogenous, or severe depression describe severely depressed patients suffering from most of the core symptoms, together with clinical characteristics of a cyclic unipolar or bipolar course, lower placebo response rates, higher response rates to electroconvulsive therapy, to antidepressant treatments with dually or mixed modes of action, or to lithium augmentation. Higher rates of hypothalamic-pituitary-adrenal axis hyperactivity and specific electroencephalographic patterns have also been shown in this patient group. Summarizing the symptomatology of depression in these patients, a broad overlap between the abovementioned subgroups can be suggested. Because the positive diagnosis of those core symptoms of depression may include clinical consequences, it would be of use to integrate all the mentioned concepts in the upcoming new versions of the diagnostic systems DSM-V and ICD-11.*



*Dialogues Clin Neurosci.* 2008;10:309-320.

## Core symptoms of depression in diagnostic classification systems and rating scales

Despite intensive biologically oriented psychiatric research over the last decades, the anatomical and physiological basis of depression is still far from being completely understood. Besides psychological and social factors, biological variables which lead to a generally disturbed central nervous homeostasis apparently play a major role. The so-called catecholamine- and serotonin-deficiency hypothesis,[1] which postulates a deficiency of monoamines (noradrenalin and serotonin) within the synaptic cleft, plays a major role in the understanding of the pathophysiology of depression. In addition, Major Depressive Disorder (MDD) most likely involves the limbic structures (in circuits involving the cingulate-hippocampus-mamillary bodies-anterior thalamus-cingulate), reward circuits (nucleus accumbens, sublenticular extended amygdala, amygdala, ventral tegmentum, cingulate, insula, thalamus, parahippocampal gyrus, and prefrontal cortex), hypothalamus, and anterior temporal cortex.[2] Both deficiencies of neurotransmitters involved in these circuitries, as well as damage to neurons and loss of connectivity, eg, by enduring hypercortisolemia, can be the underlying substrate for what man-

**Keywords:** *antidepressant treatment; depression; melancholia; pharmacological treatment; electroconvulsive therapy*

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## Selected abbreviations and acronyms

| | |
|---|---|
| ***MDD*** | *Major Depressive Disorder* |
| ***DSM*** | *Diagnostic and Statistical Manual of Mental Disorders* |
| ***ICD*** | *International Classification of Diseases* |
| ***HAM-D*** | *Hamilton Depression Rating Scale* |
| ***SSRI*** | *selective serotonin reuptake inhibitor* |
| ***ECT*** | *electroconvulsive therapy* |

ifests clinically as depression. Consequently, influence on neurotrophic factors is also thought to be one possible mechanism of action of antidepressant treatments.[3-6] In addition, a major disturbance of the circadian timing system in depression has been discussed.[7]

Depressive syndromes responsive to specific antidepressant therapies are classified within diagnostic entities using operationalized diagnostic systems such as the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed, Text Revision *(DSM-IV-TR)*[8] or the *The ICD-10 Classification of Mental and Behavioral Disorders (ICD-10)*.[9] Using these diagnostic systems, depressive disorders are characterized by a variety of symptoms, as shown in *Table I*.

To diagnose MDD according to *ICD-10*, a minimum of two main symptoms and two accessory symptoms have to be present (*Table II*, adapted from Bauer et al[11]).

According to *DSM-IV-TR*, five of the nine main criteria of depression have to be present for a diagnosis of an episode of a MDD. This term is often used synonymously with unipolar depression to distinguish it from a major depressive episode as part of bipolar disorder.

The first *DSM-IV-TR* core symptom is depressed mood during most of the day. This can be expressed by sadness, but may also be expressed as a feeling of emptiness or, in children or adolescents, as irritable mood. This draws a clear distinction between depression and grief or bereavement (characterized in *DSM-IV-TR,* V62.82). As with the other core symptoms, this symptom counts towards the diagnosis of depression if it is indicated by patient report or observation. The other psychological core symptoms are: markedly diminished interest or pleasure in all or almost all activities, fatigue or loss of energy every day, and disorders of thought and thinking (both the formal aspects of thinking and the ability to concentrate and make decisions, as well as the content which is often characterized by feelings of worthlessness or inappropriate guilt), perhaps combined with hopelessness and recurrent suicidal thoughts. *DSM-IV-TR* also mentions three somatic or behavioral core symptoms: significant weight loss or decrease in appetite, insomnia or hyposomnia, and psychomotor agitation or retardation.

Subsyndromal depression, eg, often presented by elderly patients, does not fulfill the complete diagnostic criteria according to *DSM-IV-TR* or *ICD-10*, but might nevertheless necessitate often antidepressant therapy. In addition, differences in the clinical picture of depressive disorders influence both the choice of specific antidepressant therapies and the probability that antidepressant treatment will be successful. Sometimes also the fact that patients stop eating and lose weight may change the clinical picture of depressive disorders.

In addition to the criteria for depressive disorder included in the *DSM-IV-TR* and the *ICD-10*, traditionally used subtypes were at least partially still of relevance, and some are

| Category of depressive symptoms | Symptom list |
|---|---|
| Affective symptoms | • Depressed mood<br>• Anhedonia<br>• Anxiety |
| Psychomotor disturbances | • Retardation<br>• Agitation<br>• Loss of energy and activity |
| Disturbances of cognition and memory | • Feelings of guilt<br>• Feelings of worthlessness<br>• Mood-congruent and -incongruent delusions<br>• Concentration deficits<br>• Memory deficits |
| Psychovegetative disturbances and somatic complaints | • Sleep disturbances (insomnia, early-morning awakening)<br>• Diurnal changes<br>• Loss of appetite and weight<br>• Sexual dysfunction<br>• Constipation<br>• Pain syndromes<br>• Hypertonia<br>• Tachycardia |
| Biological signs | • Hypercortisolemia<br>• Abnormal thyroid function tests<br>• Sleep EEG abnormalities<br>• Hippocampal atrophy<br>• Genetic risk factors<br>• Enhanced cardiovascular risk |

**Table I.** Symptomatology of depressive disorders.[8-10] EEG, electroencephalogram

described in DSM and ICD concepts, eg, of endogenous vs reactive or neurotic depression,[12] melancholic vs non-melancholic depression,[13] or psychotic vs nonpsychotic depression.[13] These traditional concepts underline the huge heterogeneity of patients suffering from depressive disorder, which might be overseen if only the diagnosis of the global category "depressive disorder" is used. Using the additional subtyping, the treating physician or psychiatrist might be enabled to specifically choose the best treatment option for an individual patient with the highest response probability and the most convenient clinical course for the patients.

It was therefore postulated that symptomatic classifications beyond DSM and ICD may be a necessary diagnostic basis to select more specific treatment options, considerably enhancing response quotes to antidepressant treatments.[12-14] In patients suffering from depression with melancholic features, a variety of authors have described a greater illness severity,[15] greater relevance of genetic determinants, differential altered biological functioning, especially of the hypothalamic-pituitary-adrenal (HPA) axis, together with a superior response to physical treatments such as antidepressants and electroconvulsive therapy (ECT) and, in addition, a lower placebo

| DSM-IV | ICD-10 |
|---|---|
| **Major depressive disorder**<br>**A. single episode (296.2x)**<br>**B. recurrent (296.3x)** | **A. Depressive episode (F32)**<br>**B. Recurrent depressive disorder (F33)**<br>**Severity:**<br>• **mild** (F--.0): at least 2 main symptoms, plus at least 2 accessory symptoms; none of the symptoms intense<br>• **moderate** (F--.1): at least 2 main symptoms, plus at least 3 accessory symptoms; some symptoms marked<br>• **severe** (F--.2): all 3 main symptoms, plus at least 4 accessory symptoms; some symptoms severe with intensity |
| Criteria major depressive episode (abridged):<br>**A** Over the last 2 weeks, 5 of the following features should be present most of the day, or nearly every day (must include 1 or 2):<br>1. depressed mood<br>2. loss of interest or pleasure in almost all activities<br>3. significant weight loss or gain (more than 5% change in 1 month) or an increase or decrease in appetite nearly every day<br>4. insomnia or hypersomnia<br>5. psychomotor agitation or retardation (observable by others)<br>6. fatigue or loss of energy<br>7. feelings of worthlessness or excessive or inappropriate guilt (not merely self-reproach about being sick)<br>8. diminished ability to think or concentrate, or indecisiveness (either by subjective account or as observed by others)<br>9. recurrent thoughts of death (not just fear of dying), or recurrent suicidal ideation, or a suicide attempt, or a specific plan for committing suicide.<br>**B** The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.<br>**C** The symptoms are not due to a physical/organic factor or illness<br>**D** The symptoms are not better explained by bereavement (although this can be complicated by major depression). | Criteria of depressive episode (abridged):<br>Minimum duration of episode: about 2 weeks<br>**Main symptoms:**<br>1. depressed mood<br>2. loss of interest and enjoyment<br>3. reduced energy, increased fatigability<br>**Accessory symptoms:**<br>1. reduced concentration and attention<br>2. reduced self-esteem and self-confidence<br>3. ideas of guilt and unworthiness<br>4. agitation or retardation<br>5. ideas or acts of self-harm or suicide<br>6. sleep disturbances<br>10. loss of appetite. |

**Table II.** Classification and criteria of major depressive disorder *(DSM-IV-TR)*[8] and depressive episode *(ICD-10)*.[9]
Table adapted from ref 11: Bauer M, Whybrow PC, Angst J, Versiani M, Möller H-J, WFSBP Task Force on Tretment Guidelines for Unipolar Depressive Disorders. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of unipolar depressive disorder. Part 1: Acute and continuation treatment of major depressive disorder. *World J Biol Psychiatry*. 2002;3:4-43. 

response rate.[14] Therefore the use of a diagnostic system detecting predominantly the core symptoms of melancholic depressive disorders (CORE system, *Table III*) was suggested.[14]

| |
|---|
| • **Mood state items** (eg, guilt, remorse and self-reproach, feelings of unworthiness and hopelessness, greater severity of mood disturbances, non-reactivity of mood, loss of interest, anhedonia, greater suicidal ideation) |
| • **Vegetative items** (eg, loss of appetite and/or weight loss, (terminal) insomnia, diurmal variation with mood, energy worse in the morning ) |
| • **Other features** (eg, retardation, agitation, concentration difficulties, psychotic features) |

**Table III.** "CORE" Symptoms of Depression.[14]

*Atypical depression* including predominantly an increase in appetite and weight gain together with hypersomnia *(Table IV)* seems to be located at the other end of the spectrum. Patients suffering from atypical depression show not only a specific clinical picture including peculiarities regarding the symptomatology and the clinical course of the disease,[16] but also a differential response pattern to specific antidepressants.[17]

| |
|---|
| • Depressed mood |
| • Guilt |
| • Work and interests |
| • Retardation |
| • Psychic anxiety |
| • General somatic symptoms |

**Table IV.** HAM-D6 melancholic subscale.[20]

A completely different approach is the analysis of depression rating scales such as the Hamilton Depression Rating Scale (HAM-D)[18] using multidimensional scaling procedures.[19] A distinction between primary components of depression, which are related directly to core symptoms of major depression, secondary components focused on dysthymic disorders and components related to more accessory symptoms has been made.[19] On the basis of probabilistic test models 6 out of 17 items of the HAM-D17 scale *(Table V)* were classified as a melancholia subscale suitable for quantitative comparisons; the original HAM-D17 scale was considered to be without adequate consistency during treatment course with andidepressant medication.[20]

The factor-analytic approach confirmed that solely the abovementioned items of the HAM-D scale can be combined as a valid indicator for the severity of depression.[19] This was confirmed in a recently published paper analyzing a randomized controlled trial (RCT) comparing the treatment of depression with hypericum perforatum extract vs placebo.[21] It was concluded that the HAM-D6 subscale should be used as a primary outcome measure in antidepressant trials rather than the HAM-D17 scale. In addition to the described symptomatology predominantly distinguishing between core symptoms of depression including melancholic features and other symptoms, depressive syndromes can be subdivided clinically according to the clinical course (unipolar and bipolar depression), the clinical severity of depression (eg, measured using depression rating scales or subdividing in in- and outpatients), the clinical symptomatology (eg, psychotic vs nonpsychotic depression, retardation, catatonic symptoms) and specific subgroups of depressed patients (eg, atypical depression). Some scientific evidence from RCTs and clinical evidence derived from broad clinical experience and consensus showed differential response to different antidepressant treatment options. Therefore, specific clinical recommendations for subgroups of depressed patients are described in the following sections.

## Clinical subtypes of depressive disorders and effectiveness of antidepressant treatment options

### Influence of core symptoms and the severity of the disease on treatment outcome

*Melancholic depression*

According to *DSM-IV-TR*, melancholic features are characterized by a loss of the ability to feel pleasure and a variety of somatic symptoms *(Table I)* and psychomotor alterations. Other authors conceptualized melancholia as a categorical entity within a variety of different subgroups of depressive disorder,[14] leading to a clinical syndrome including specific psychopathological characteristics *(Table III)*,

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|---|
| • Increase in appetite and weight gain |
| • Hypersomnia |
| • Leaden paralysis |
| • Long-standing pattern of interpersonal rejection sensitivity |

**Table V.** Atypical depression according to DSM-IV.[20]

together with a greater overall severity of disease, episodic courses of the illness, a positive family history for depression, the lack of high comorbidity with *DSM-IV-TR* axis 1 and axis 2 disorders and a high rate of biological abnormalities including HPA axis hyperactivity.[13,14,22] In addition, a low likelihood of placebo response together with high responsiveness to tricyclic antidepressants (TCA), lithium augmentation and ECT was postulated.[13,14] Also lower response rates to psychotherapeutic approaches were described.[23] Nevertheless, data supporting this view are derived predominantly from subgroup analyses of clinical trials and clinical observations. Up to now, head-to-head comparisons of different antidepressant classes in melancholic and nonmelancholic depression are lacking.[23] Therapeutic consequences of the presence of melancholic features are therefore very similar to that for severe depression, described more in detail in the next section. It can be summarized that electroconvulsive therapy (ECT), dually acting antidepressants, and lithium augmentation in case of nonresponse can be recommended for patients suffering from melancholia.

*Severity of the disease*

Depressive episodes can be classified as mild, moderate, or severe depressive disorder (according to *ICD-10*). Subsyndromal depression may enhance the risk of developing a syndromal depressive disorder according to *ICD-10* or *DSM-IV-TR* requiring antidepressant treatment. Besides the clinical judgment, eg, using the diagnostic criteria according to *ICD-10* or to the *Clinical Global Impression scale* (CGI-S, Item I, severity of disease),[24] severity groups can be separated using depression rating scales such as the HAM-D18 or the Montgomery-Åsberg Rating Scale for Depression (MADRS).[25] Patients suffering from *severe depression*, for example, reach a score of at least 25 on the HAM-D17 scale[26] or 30 on the MADRS.[27] The subdivision according to the severity of depression is of clinical importance because for example, the NICE (National Institute for Clinical Excellence) guidelines[28] recommend antidepressant treatments in primary care in moderate and severe, but not mild, depression. For patients suffering from mild depression, NICE recommends "watchful observation" or psychological intervention as first-line treatment, and antidepressants only in the case of refractoriness.[28]

In moderate depression, nonbiological treatments are also the first choice in some guidelines although, in reality, most moderately depressed patients do require additional antidepressant medication. Furthermore, there is a distinct probability of response using phytotherapeutics such as *hypericum perforatum* (St Johns wort)[29-32] or benzodiazepines without antidepressants (even if this option is not recommended due to their potential for causing dependency and addiction)[33] only in people with mild-to-moderate depression. Moreover, it has been suggested that drug-placebo differences after treatment with antidepressant medication are relatively small and increase as a function of baseline severity of depression.[34] However, according to other reports about the effectiveness of antidepressants, eg, duloxetine[35] or fluoxetine,[36] in mild-to-moderate depression, the treatment of those subgroups of depressed patients also has been recommended.[37] Nevertheless, there is some evidence that especially severe depressive syndromes show a better response to ECT, to tTCAs[38] (TCA) and to dually acting substances[39] such as venlafaxine, duloxetine, or mirtazapine. Especially in severely depressed and hospitalized patients, mixed serotonergic and noradrenergic TCAs compared favorably with selective serotonin reuptake inhibitors (SSRIs)[38,40] and the reversible monoamine oxidase-A inhibitor (RIMA) moclobemide[41] However, escitalopram has also shown good results in severe depression[42] (Montgomery et al, unpublished data). Summarizing published study results of recent years, in spite of the discouraging meta-analytic results of Kirsch et al,[43] it has to be stated that there is an overall worldwide consensus that antidepressants are efficacious in the treatment of depression, regardless of the severity of the disease.[44]

**Depression with psychotic symptoms**

Psychotic features of depression such as hallucinations or delusions, eg, delusional hypochondria, feelings of guilt or nihilistic thoughts, are predominantly mood-congruent, but may also be noncongruent to the depressed mood. Depressive episodes with psychotic symptoms are in most cases an indicator of particular severity of the disease, including a high suicide risk. This additional risk factor has to be taken into account in planning treatment. In patients suffering from psychotic symptoms, usually a combination of the antidepressant therapy with antipsychotic medication is recommended,[45] although it has been reported that there are no advantages of such a combination in specific patient subgroups, eg, in elderly patients.[46] TCAs and selective SSRIs in combination with

antipsychotics are recommended, and amoxapine treatment has shown somewhat lower, but also significant, efficacy.[47,48] In addition, a few reports about good efficacy of SSRI monotherapy during acute and maintenance treatment have been published.[49,50] ECT has been recommended as a possible first-line treatment in such cases because of its high effectiveness during acute-treatment[51] and a more favorable long-term outcome[52] in this subgroup of patients, especially in comparison with pharmacotherapy.[53] In addition, early consideration of lithium augmentation is recommended, especially in this patient group in case of antidepressant treatment failures.[54,55]

*Psychomotor agitation and retardation*

Severe psychomotor retardation, stupor, immobility, and, in contrast, severe agitation (labeled by some authors as catatonic features of depression), can also be seen in depressed patients.[56-58] A relatively high overlap with patients suffering from melancholic and severe depression has been suggested.[13,22] ECT has been reported to have an excellent clinical effectiveness in these cases,[59,60] as well as the administration of benzodiazepines (lorazepam) during the acute-phase treatment, which can lead to immediate relief of catatonic symptoms. In routine clinical use, sedating antidepressants or combinations of nonsedating antidepressants with sedating benzodiazepines are used in agitated patients, whereas activating substances such as SSRIs or noradrenalin reuptake inhibitors (NARIs) are used in patients with predominant psychomotor inhibition.

**Influence of course-related aspects on treatment recommendations**

*Unipolar depression*

A significant proportion of depressive disorders show an episodic course. With the exception of the *recurrent brief depressive episodes* singled out in the *ICD-10*, the threshold for reaching a diagnosis is that symptoms are present for at least 2 weeks. Shorter duration places the episodes into a "subthreshold" group. The differences between threshold and subthreshold depression is feasible but not very helpful in clinical work, since it has been shown that also subthreshold depression causes disability and often requires treatment. In particular, depressive disorders in children and adolescents, as well as depression in old age, comprise a variety of inherent diagnostic problems. In addition, these problems may furthermore be aggravated by specific comorbidities such as anxiety or personality disorders. In the case of the first diagnosis of depression and without knowledge about the future time course of depression, primary unipolar depressive episodes and depressive syndromes showing bipolar features in the future cannot be distinguished clinically. Some authors even postulate that the distinction between unipolar and bipolar depression in modern diagnostic systems may have no clinical relevance for the acute treatment,[13] but of course as described in the following specific risks (switch) of bipolar depression should lead to a modification of the acute treatment to prevent triggering of manic episodes.

*Bipolar depression*

Diagnostic criteria for a depressive episode due to bipolar-I disorder are the same as described already for the case of unipolar depression *(Table II)*. In addition, to diagnose a bipolar disorder, there should have been previously at least one manic or mixed episode including a period of abnormally and persistently elevated, expansive, or irritable mood lasting at least 1 week (or even shorter, if hospitalization is necessary). During this time period, grandiosity or inflated self-esteem are normally present, together with decreased need for sleep, hyperactivity, psychomotor agitation, racing thoughts with flight of ideas, distractibility, and a pressure to keep talking causing marked impairment in social functioning. In case of a mixed episode, these symptoms together with depressive symptoms are present at the same time for at least 1 week. In case of bipolar-II disorder, at least one episode of hypomania, a period of manic symptoms of lesser severity which last at least 2 to 4 days, has been present in the patients´ history. However, shorter hypomanic episodes may also justify treating a patient according to standards for bipolar depression, not unipolar depression.[61,62] In addition, a continuity between bipolar-II disorder and unipolar severe (major) depression has been suggested.[63]

Because bipolar depression has the same symptoms as unipolar depression and at the time of the first depressive episode this information is not yet available, up to 50% of younger patients suffering from depression as the first index episode later receive the diagnosis of a bipolar disorder,[64,65] but these rates remain controversial.[66] Although the evidence for efficacy and effectiveness of

antidepressant treatment of bipolar depression is less than the evidence for the treatment of unipolar depression, the same substances leading to clinical improvement in unipolar depression can be used in bipolar depression. Because of a lower switch risk from depression to hypomania or mania and a proven efficacy, predominantly SSRIs, monoamine oxidase inhibitors (MAOIs),[67] or bupropion[68] in combination with mood stabilizers may be considered as the treatment of choice.[69] Because there is no uniform definition of "switch," the switch rates in scientific publications vary widely. Nevertheless, an up to 3-fold higher switch rate during TCA therapy in comparison with SSRIs has been reported.[70] Therefore it has been suggested that all antidepressants, but especially TCAs, and dually acting antidepressants such as combined serotonin and noradrenaline reuptake inhibitors (SNRIs) are recommended to be combined with mood stabilizers to prevent an enhanced switch risk.

In addition, it should be mentioned that for bipolar depression there is also reasonably good evidence for monotherapy with the mood stabilizers lithium and lamotrigine, as well as with the atypical antipsychotics olanzapine and quetiapine.[71] However, there is no evidence so far that these treatment regimens may be superior in efficacy when compared with antidepressants.[72]

*Dysthymia and MDD in combination with dysthymia*

Diagnostic criteria for dysthymia and depressive disorders differ in the severity and duration of the symptoms. Dysthymia is characterized by a chronic depressive syndrome of lower intensity of symptoms than severe depression, although it produces very similar levels of disabilities. Also, an additional and superimposing major depressive episode can occur in patients already suffering from dysthymia, then diagnosed as a "double depression" or "double major depressive disorder." The differential diagnosis of both disorders is difficult if a dysthymic episode follows a depressive episode, because the symptoms of dysthymia are then indistinguishable from the (reduced) symptoms of a depressive disorder with only partial remission, which should be diagnosed in this case. Only after a full remission lasting at least 6 months, the subsequent dysthymic symptoms can be diagnosed as dysthymia.

Because the same antidepressant therapies are efficacious in both diagnostic entities, the acute treatment plans can be identical for depressive disorders, dysthymia, and double depression. In addition, treatment with certain antipsychotics such as amisulpride[73,74] predominantly at lower doses, may be of use. Due to the chronic nature of dysthymic disorders, an earlier implementation of psychotherapeutic approaches can be of use. In addition, the treatment goals should be formulated somewhat more cautiously because dysthymia seems to have a lesser probability for a complete recovery.[75]

*Recurrent brief depression*

Recurrent brief depression (RBD) is characterized by at least monthly occurring depressive episodes of short duration that last only a few days.[76] Within *DSM-IV-TR*, recurrent brief depression can only be diagnosed as subthreshold MDD; within ICD-10 it is a diagnostic category of *recurrent depressive disorder*. The combination of severe depressive disorders and RBD is sometimes called "combined depression" (CD).[76] The combination of depressive disorders and RBD shows a relatively high prevalence. The substantially higher risk for suicidal ideations in such cases represents a specific concern. Most trials investigating antidepressant therapies were designed to judge the therapeutic efficacy in major depressive disorders. Different study designs are necessary to investigate the combination of depressive disorders and RBD properly. A variety of negative results after RCTs of SSRIs in the treatment and prophylaxis of RBD have been published (eg, Montgomery et al[77] and Angst et al[78]), but it was hypothesized that methodological problems and highly selected patient samples have been responsible for for these results.[76] Efficacious treatment algorithms for RBD have not been established yet.[79]

*Seasonal affective disorder*

Patients suffering from depression recurring on a regular annual basis during fall or early winter and spring often show subsequent symptoms of bipolar disorder. In addition, depressive syndromes often are characterized by features listed as atypical in *DSM-IV-TR*.

If depressive symptoms are of moderate severity, seasonal forms of depression are treated like other recurrent episodes. Bright-light therapy (phototherapy) can be used as an early augmentation strategy. Because of the proven efficacy,[80,81] bright-light therapy can even be used as a monotherapy in case of mild depression during a

limited treatment trial, but the possibility of occurrence or enhancement of suicidal ideations during phototherapy has to be taken into account.[82]

**Other features of MDD influencing course and treatment outcome**

*Atypical depression*

There is no clear agreement about the features that should characterize atypical depression.[83] In French-speaking countries the term "atypical" depression is used for a group of patients with psychotic features. According to *DSM-IV-TR* in atypical depression at least two of the criteria summarized in *Table IV* should be present.
Nevertheless, it was postulated that applying *DSM-IV-TR* criteria for atypical depression represents a valid diagnosis distinct from other forms of depression, but includes a very heterogeneous patient population.[16] Also the *Inventory of Depressive Symptomatology-Clinician Rating* (IDS-C30) is suitable for the diagnosis of atypical depression including an earlier age at onset, a greater comorbidity with anxiety symptoms, and greater symptom severity compared with nonatypical depression.[84] An epidemiological study in primary care found a considerably high proportion of depressed patients suffering from atypical features, suggesting that atypical depression which may contribute to under-recognition of depression in primary care.[85] Patients suffering from atypical depression may have an overall earlier age of onset and a more chronic course of illness in comparison with patients suffering from depression with melancholic features.[16] Nevertheless, those patient groups are also characterized by a high longitudinal association, ie, an overlap of symptoms during the time course of depression: transitions from atypical to melancholic and to nonmelancholic types of depression are described.[86]
Empirical data support the hypothesis that MAOIs and SSRIs represent a first-line treatment option which is superior to other pharmacological treatments.[17,87,88] Due to the need of specific precautions, irreversible MAOIs are not recommended in some countries as a first-line treatment.

*Circadian rhythm disturbances*

Sleep-wake rhythm disturbances, including hypo- or insomnia, are present in a majority of depressed patients suffering from difficulties in falling asleep, interrupted and shortened sleep during the night, and early awakening in the morning. In addition, hypersomnia characterizes most patients suffering from atypical depression (see above). They are rated as criteria for MDD in *ICD-10*, as accessory symptoms in *DSM-IV-TR*, as depressive symptoms within the HAM-D17 scale, and are included in the abovementioned CORE scale for depressive core symptoms.[14] In addition specific sleep EEG patterns, such as reduced slow-wave sleep and shortened REM sleep latency, characterize MDD especially in the presence of melancholic symptoms.[13] Sleep EEG abnormalities are in addition strongly influenced by age and gender of the depressed patients.[89]
From a clinical point of view the use of antidepressants with antihistaminergic and therefore sedating properties, eg, some TCAs or noradrenergic and specific serotonergic antidepressants (NaSSAs) or the use of nonsedating antidepressants in combination with sleep-inducing treatments, are useful. In this case, nonbenzodiazepine hypnotics, benzodiazepines, or sedating atypical antipsychotics which at the same time can augment the antidepressant treatment are suitable. Mirtazapine monotherapy significantly improves sleep parameters in addition to its antidepressant effects[90] without the neceessity of additional hypnotic substances. Unfortunately, initial somnolence and dizziness, together with increased appetite and consecutive weight gain in the long term[91] may represent antihistaminergic side effects which often reduce the patients' compliance and may sometimes even facilitate the development of a metabolic syndrome. While most antidpressants are modifying sleep profiles by suppressing rapid eye movement (REM) sleep, the only dopamine $(D)_2$ and serotonin $(5\text{-}HT)_2$ antagonistic acting substance with antihistaminergic sedating properties without REM suppression is the TCA trimipramine.[92]
An interesting future perspective may therefore be the use of the $MT_1/MT_2$ agonistic and $5\text{-}HT_{2c}$ antagonistic acting antidepressant agomelatine. In healthy older men no effects on normal sleep patterns were found,[93] while in patients suffering from MDD in a pilot dose-finding study[94,95] symptoms related to sleep disturbances such as difficulties in falling asleep, interrupted sleep, shortened sleep, early awakening, and drowsiness decreased substantially, leading to a normalization of sleep/wake rhythms without direct sedation and without REM sleep suppression, indicating that agomelatine contributes to a normalization of disrupted circadian rhythms in depression.

*Depressive syndrome with comorbid pain conditions*

Depressive disorders and predominantly chronic pain are frequent comorbid conditions. Approximately 70% of patients with major depression present physical complaints.[96,97] Severe pain caused by somatic diseases comorbid with depression makes the treatment of depression difficult. Somatoform disorders, fibromyalgia, and similar conditions characterized by pain are often accompanied by depressed mood. Effective treatment of neuropathic pain requires the application of antidepressants with a mixed serotonergic and noradrenergic mode of action such as the TCA amitriptyline.[98] More recently, newer antidepressants have been shown to be useful in the treatment of pain conditions with and without comorbid depression. The efficacy of various pharmacodynamic classes such as SSRIs, NARI, NaSSAs,[99] and SNRIs[100,101] has been shown. It seems plausible that antidepressants with both serotonergic and noradrenergic properties are particularly effective in the treatment of pain and painful physical symptoms. Higher remission rates in these subgroups of depressed patients have been discussed recently.[102] Antidepressants are now seen by many as an essential supplement in a variety of therapeutic regimes for pain control.

*Depressive syndrome in adjustment disorders*

Due to the fact that the symptoms of adjustment disorders and depressive disorders may be identical, and due to the fact that depressive episodes often occur after exposure to severe stress, it is justified to offer the same therapeutic regimes to patients suffering from adjustment disorders as to patients suffering from depressive disorders. This is especially true during the period of acute treatment. Controlled efficacy trials in adjustment disorders are rare, but both clinical experience and retrospective studies[103] suggest no crucial difference between depression and adjustment disorder in response rates to treatment. On the contrary, some authors also suggested lower response rates for biological treatments such as ECT in depressive syndromes caused by adjustment disorders.[13] Nevertheless, the use of psychosocial therapies in adjustment disorders may begin earlier and be more intense in comparison with patients suffering from severe MDD and melancholia.

Summarizing the symtomatology of depression in those patients, a broad overlap between the abovementioned three subgroups can be suggested.

Because the positive diagnosis of the core symptoms of depression may lead to clinical consequences for individual treatment plans, it would be of use to integrate all mentioned concepts in the upcoming new versions of the diagnostic systems, DSM-V and ICD-11.

## Conclusion

Core symptoms of depression according to diagnostic systems and rating scales are a combination of psychological symptoms such as depressed mood (sadness or feelings of emptiness are synonymously used), anhedonia, diminished interest or pleasure, and suicidality in combination with somatic symptoms such as disturbed sleep and appetite. Furthermore, psychomotor and cognitive disturbances consitute further core symptoms.

Most diagnostic subdivisions of depressive states according to diagnostic systems or rating scales, eg, the use of concepts such as melancholic depression, endogenous depression, or the subdivision according to the need for hospitalization or to the severity of disease lead to a patient group of predominantly severely depressed patients suffering from most of the core symptoms, together with the clinical characteristics of a cyclic unipolar or bipolar course, lower placebo response rates, higher response rates to ECT, to antidepressant treatments with dually or mixed modes of action, or to lithium augmentation. In addition, higher rates of biological characteristics such as HPA-axis hyperactivity and specific EEG patterns have been shown in this patient group. ❑

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### *Efectos de diversos tratamientos antidepresivos en lo nuclear de la depresión*

*Los síntomas nucleares de la depresión son una combinación de síntomas psicológicos y somáticos que a menudo se asocian con alteraciones psicomotoras y cognitivas. La clasificación diagnóstica de la depresión, que incluye conceptos de melancolía, endogeneidad o gravedad, describe pacientes con cuadros graves que presentan la mayoría de los síntomas nucleares; junto con las características clínicas de un curso cíclico unipolar o bipolar, una baja frecuencia de respuesta a placebo, y una alta respuesta a la terapia electroconvulsiva, a los tratamientos con antidepresivos con mecanismos de acción dual o mixta y a la potenciación con litio. En este grupo de pacientes también se ha observado una alta frecuencia de hiperactividad del eje hipotálamo-hipófisis-adrenal y patrones electroencefalográficos específicos. Al resumir la sintomatología de la depresión en estos pacientes se puede sugerir un amplio traslape entre los subgrupos previamente mencionados. Dado que el diagnóstico positivo de los síntomas nucleares de la depresión puede implicar consecuencias clínicas, sería útil integrar todos los conceptos mencionados en las próximas nuevas versiones de los sistemas diagnósticos del DSM-V y de la CIE-11.*

### *Effets de différents traitements antidépresseurs sur la dépression majeure*

*Les symptômes majeurs de dépression sont une association de symptômes psychologiques et somatiques, souvent combinés à des troubles psychomoteurs et cognitifs. La classification diagnostique de la dépression mélancolique, endogène ou sévère, décrit des patients sévèrement déprimés, présentant la plupart des symptômes majeurs, avec des caractères cliniques uni- ou bipolaires, des taux de réponses plus faibles au placebo, plus élevés à la sismothérapie et aux traitements antidépresseurs (modes d'action doubles ou mixtes) ou à la potentialisation par le lithium. Dans ce groupe de patients, il a été aussi observé des taux plus élevés d'hyperactivité de l'axe hypothalamohypophysaire et des tracés électroencéphalographiques spécifiques. En résumant la symptomatologie dépressive de ces patients, les sous-groupes mentionnés ci-dessus peuvent largement se chevaucher. Le diagnostic positif de ces symptômes majeurs de dépression pouvant avoir des conséquences cliniques, les versions à venir des outils diagnostiques DSM-V et ICD-11 devraient intégrer toutes les notions décrites ici.*


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