What symptom should be the primary treatment target in depression?

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The treatment of depression remains a mysterious combination of science and art. It is a science insofar as we know plenty about the neurobiology of depression in terms of genetic predisposition, neuroimaging changes, and the biochemical and neuroprotective effects of antidepressants. But it is an art in that we don't really know which therapeutic strategy will work for which individual. Patients' prioritization of their depressive symptoms varies with age, gender, occupation, and other sociodemographic variables. The elderly may emphasize the "meaningless of life," while younger adults identify fatigue or loss of energy as their primary concern. Culture is also important. In Asian societies, somatic symptoms such as headache and poor appetite are perceived as particularly distressing. They occupy much the same position as anhedonia or depressed mood for Western patients. An interesting study in white and Chinese elderly showed that Chinese elderly had a more positive attitude toward weight gain than their white counterparts. In Chinese society, weight gain in the elderly is perceived as "fa-foo" (literally, gaining happiness, ie, a marker of wealth and a happy family). Such people may be fat, but they are "happy fat." Generally speaking, anxiety and sleep disturbance are the most distressing symptoms of depression across all groups and they need to be prioritized in the treatment strategy. However, wise clinicians will always ask their patients which symptom matters to them most. Patients usually list several. The doctor can then work with the patient to identify which comes first. The order of symptom improvement is not only a relevant clinical factor, but also a window onto neural recovery by a depressed brain. No currently available antidepressant offers rapid relief for patients' two main complaints, namely anxiety and sleep disturbance. However, the combination of anxiolytics and hypnotics is invaluable for this purpose. Depressed mood will lift at a later stage, followed by the recovery of interest and pleasure. Damaged brain needs time to recover. The more complex the psychological function, the longer it takes to improve. Even recovered depressives remain psychologically different from healthy controls, in terms of negativity and hesitation. We still don't know whether this represents the residue of a depressive episode or a preexisting personality trait that predisposes to depression. Placebo can achieve improvements rates of up to 35% in depression. Since antidepressant efficacy averages no more than 50%, the margin of pharmacology over placebo is only 15%. Although placebo may be able to relieve all symptoms of depression, there is no evidence that it works better on some symptoms rather than others. True remission rates are much lower on placebo, by a difference well in excess of 15%. In other words, placebo may improve symptoms, but it tends not to eradicate them. Placebo appears particularly effective for somatoform symptoms that are often hard to classify as psychological, cognitive, or physical. But it has no place in long-term strategy, probably because depression is a systemic disease encompassing a constellation of symptoms that can only be cured once the depressive disease is itself cured. Applying the results of scientific research to clinical practice is a constant challenge. A well-designed clinical trial may generate statistically significant data packaged in a beautifully written paper. But the research setting is often too abstracted from clinical reality. It is thus no surprise that some costly studies should have failed to impact clinical behavior. ❐

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Major depressive episode is defined as a period of at least 2 weeks of depressed mood with suicidal ideation and abnormalities of neurovegetative function (altered appetite, weight loss, sleep disturbance [early awakening]), psychomotor activity (loss of energy and interest, agitation, retardation), and cognition (feelings of worthlessness, hopelessness, and inappropriate guilt). A frequent additional feature is diurnal variation (morning depression). While emotional symptoms such as depressed mood and loss of interest have traditionally been viewed as the core symptoms, the prevalence and importance of anxiety and physical symptoms such as pain and fatigue are attracting increasing attention. Antidepressant treatment should be considered for patients meeting diagnostic criteria for depressive episode (ICD-10) *or major depressive episode* (DSM-IV). *Treatment choice depends on the concurrent symptom profile, the disease and treatment history, and patient preference. It should always target the most severe symptoms, ie, those that most endanger the patient and/or others.*

◆ *Suicidality and extreme malnutrition/dehydration are life-threatening conditions requiring priority acute treatment. Suicidality, whether passive (the feeling that life is no longer worth living) or active (ideation, planning, or attempted implementation), is generally an indication for inpatient treatment, in an intensive care unit if acute. Fast-acting benzodiazepines are indicated. Antidepressants that increase activation should be used with caution and the response closely monitored. Hospitalization is mandatory for extreme malnutrition/dehydration since force-feeding may be needed.*

◆ *Psychotic features, particularly delusions of guilt and nihilistic thinking, are a major threat to the patient and others. As such, they require immediate targeting, usually with antipsychotics (including benzodiazepines in the acute state) in an inpatient setting.*

◆ *Anhedonia, a core feature of depression, is a mandatory treatment target since the prolonged inability to experience pleasure substantially increases suicide risk. It requires antidepressants and/or psychotherapy on an inpatient or outpatient basis, depending on severity.*

◆ *Severe agitation stresses the patient and must be targeted with benzodiazepines and/or antipsychotics.*

◆ *Anxiety is common in depressive episodes and contributes to the suicidal phenotype. Panic disorder in particular increases the risk of suicidal behavior.*[1,2] *Depending on acuteness and severity, benzodiazepines and antidepressants are indicated in combination with psychotherapy.*

◆ *Rapid relief of sustained insomnia stress enhances mood and provides resources for recovery. Standard options are sedating antidepressants, eg, amitriptyline or mirtazapine, or antipsychotics and short-term benzodiazepines.*

Outside the well-recognized influence of demography, disease history, and somatic/psychiatric comorbidity, antidepressant response has not been clearly shown to differ with psychopathological symptom profile. However, evidence suggests that tricyclic antidepressants are more potent than selective serotonin reuptake inhibitors (SSRIs) in severely depressed inpatients.[3] *Indirect meta-analysis showed the dual-action serotonin-norepinephrine reuptake inhibitor venlafaxine, introduced in 1993, to be more effective than the SSRI fluoxetine.*[4] *Monoamine oxidase inhibitors may be preferable for atypical features, eg, mood reactivity, overeating and hypersomnia.*[5] *Electroconvulsive therapy is an option in life-threatening situations or when otherwise appropriate drugs are contraindicated. Depressive symptoms do not respond to treatment at the same rate or to the same degree. With some drugs, eg, the SSRI sertraline,*[6] *this can be explained by individual pharmacodynamics. Whether the order of symptom improvement is relevant to episode outcome is currently unknown. Recent review suggests that residual symptoms (eg, subthreshold depressive symptoms, cognitive impairment, and sexual dysfunction) influence long-term outcome: they increase the risk of relapse, impede the return to psychosocial and occupational functioning, favor chronification, and increase suicide risk.*[7] *As such, they are major targets of long-term treatment in depressive disorders. Thus, symptoms that are life-threatening to the patient and/or others must be the primary target of depressive episode treatment, bearing in mind that not all symptoms respond at the same rate or to the same degree. Residual symptoms are common and must not be overlooked in long-term treatment.*[8] ❐

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Depression is a prevalent and devastating disorder with a complex etiology involving a variety of neurobiological and socioeconomic factors.[1] It is also multifaceted in its phenomenology, manifested in shifting constellations of symptoms and severities. High recurrence rates and comorbid anxiety often impair functional capacity and quality of life. Melancholia has been recognized since the fourth century BC. Its key symptoms were long regarded as the core of clinical depression, although they have recently been portrayed as aligned more closely with bipolar states.[2] Melancholic symptoms have classically been the primary target for antidepressants and electroconvulsive therapy. They show a significantly lower placebo response, and may also be less responsive to various forms of psychotherapy.[3] They have been widely tested using instruments such as the Beck Depression Inventory, via such items as sadness, past failure, loss of pleasure, guilty feelings, punishment feelings, loss of interest, irritability, and sleep and appetite changes,[4] and the Mini International Neuropsychiatric Interview. A major obstacle when assessing the efficacy of antidepressants against their primary targets is the remarkably high placebo response rate in clinical trials. This has been ascribed to the intrinsic therapeutic effect of the intensive monitoring involved.[5] Placebo response is inversely related to depression severity, being more marked in the case of noncore symptoms or milder, nonmelancholic disease. Although no consistent difference has been found between melancholic and nonmelancholic patients, most studies record that only 20% to 30% of melancholic patients respond to placebo. Low mood reactivity is closely related to other core symptoms in melancholia, and may thus be regarded as the primary treatment target. In some studies, tricyclic antidepressants are more effective in this regard than selective serotonin reuptake inhibitors, but this is not a consistent finding.[3] Total remission should be the treatment target, as partial response carries a high risk of relapse. ❐

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Major depression, defined according to Diagnostic and Statistical Manual of Mental Disorders Fourth Revision (DSM-IV) *criteria, comprises at least five of the following nine symptoms: depressed mood; loss of interest or pleasure; weight loss; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue; feelings of worthlessness or guilt; difficulty to concentrate; and suicidal ideation.[1] These symptoms have been deemed most specific of the disorder and hence most useful for making valid and reliable diagnoses. Patients diagnosed with depression, however, have many other symptoms, in particular anxiety. This explains why scales designed to rate treatment response, eg, the Hamilton Rating Scale for Depression (HAMD), contain anxiety-related items. To aid differential diagnosis between depressive subtypes and anxiety disorders, studies have attempted to identify the core signs and symptoms of depression, eg, Parker's work on motor retardation[2] or the development of the Newcastle Scales.[3] However, without hard biological markers to validate symptom profiles derived from clinical studies, it is difficult to establish borders between depressive, anxiety and bipolar disorders, or even to identify the true or most important symptoms of depression. Few studies have addressed the effects of drugs on individual depressive symptoms, since the vast majority of clinical trials have used total rating scale scores as outcome variables. Analysis of the outcome of each and every item on a depression rating scale in a single trial would be subject to statistical limitations associated with the issue of multiple comparisons. Even when symptoms are clustered, comparisons are still too many for meaningful statistical analysis. Received wisdom holds that antidepressants only begin to act after 2 or more weeks, with the corollary that any earlier response is evidence of placebo rather than pharmacological effect.[4] Recent contrary data, however, suggest that improvement in major depression may occur much earlier, by the end of the first week.[5] This paradigm shift may encourage more studies on the sequential improvement of depressive symptoms in clinical trials. The therapeutic effects of antidepressants have been differentiated from those of placebo on the basis of the pattern of response over time rather than of individual symptom response.[4] An exception is the depressive subtype melancholia, where symptoms such as lack of reactivity, morning depres-*

sion, terminal insomnia, marked retardation, significant weight loss, and excessive guilt have been shown to predict poor placebo response.[6] In theory there is an urgent practical need to prioritize certain symptoms, in particular suicidal ideation. However, there is disputed evidence that antidepressants are associated with treatment-emergent suicidal ideation and suicide-related behavior, although not with completed suicide, in children, adolescents and adults; on this basis, current antidepressants may be ineffective for securing rapid control of suicidal ideation or suicide attempts.[7] A good case for prioritized treatment could also be made for any symptom whose initial improvement is associated with better subsequent outcome. The few studies of sequential improvement in depressive symptoms suggest that early decreases in anxiety—HAMD 17 anxiety-somatization factor and psychic anxiety—are associated with subsequently higher responder and remitter rates.[8-10] Interestingly, these findings are consistent with current practice in that the effect of antidepressants on anxiety symptoms is the main feature that doctors consider when choosing one drug over another.[11] Thus the main reason why bupropion is less prescribed than other second-generation antidepressants appears to be its lack of anxiolytic effect.[12] Insomnia often fails to respond to antidepressants in clinical trials and may even worsen.[13] Cotreatments targeted at insomnia have therefore been proposed to augment response, remission, and adherence.[14] Novel antidepressants such as agomelatine, which target underlying biorhythm disruption, are more effective in sleep disturbance and may have an important impact in the clinical management of major depression.[15] Antidepressants that differ in their mechanisms of action may differ in the degree and timing of their effects on individual symptoms. Thus, the first symptoms to respond to the norepinephrine reuptake inhibitor desipramine and the selective serotonin reuptake inhibitor paroxetine were psychomotor retardation and anxiety, respectively, while placebo showed no pattern of improvement in association with subsequent remission and response in a clinical trial.[16] In summary, limited evidence suggests that the symptom to be prioritized in the treatment of major depression is not one conventionally classified as depressive, but anxiety, in particular psychic anxiety. ❒

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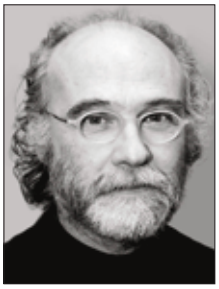

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Why should we need to prioritize target symptoms in the treatment of depression? The question presupposes that some symptoms are more life-threatening or significant than others. Our first task is therefore to hierarchize symptoms along these lines. Depression is commonly viewed as comprising core symptoms (depressed mood and anhedonia) associated with three (emotional, physical, and cognitive) symptom clusters. However, this view is unsupported by any pathophysiological mechanism or mechanisms common to all forms of depression. Until such mechanisms are identified, we have no option but to base our definition of depression, and our resulting treatment options, on the phenomenology of the disorder. If we now analyze the structure of these phenomenological symptom clusters, can we hierarchize certain symptoms in terms of risk or their potential impact on other symptoms, such that successful treatment of one symptom could encompass a spectrum of others? In the absence of hard physical data, we can only base our answer on clinical experience. What that experience teaches us is that if we first treat the core symptoms, we achieve global clinical improvement. This suggests that these symptoms, in some unknown way, play a central role in the pathophysiology of the disorder. They must therefore be considered as treatment priorities. Clinical experience also teaches us that cognitive symptoms are important for informing treatment strategy in depression. They respond quite independently from other symptom clusters. When patients improve in their mood and associated physical symptoms, they often retain the same cognitive disturbance as in the acute phase of the disorder. Clinical experience teaches us that treating cognitive symptoms first has practically no effect on relieving depression, except in its milder forms. The implication is that we must first treat the core symptoms, at least in severe depression, if we are to achieve any global improvement that allows intervention against cognitive symptoms. The conclusion informed by clinical experience is that the core symptoms of depressed mood and anhedonia must be treated first, at least in severe depression, and that cognitive symptoms should be targeted in the second phase of treatment. Clinical experience has shown that improvement in depressive mood is a precondition for obtaining significant benefit from cognitive remediation therapy. ❐

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Insomnia is both a symptom and cause of depression. It may even be the worst symptom: to lie awake unable to rest while a prey to pessimistic thoughts is torment. Insomnia is a proven marker for increased suicidality. We recently showed a correlation between sleep disturbance, in particular nightmares, and suicidality and suicide attempts.[1] Sleep disturbance in depression—sleep-onset insomnia, frequent nocturnal awakening, and early morning awakening—reflects underlying circadian dysregulation, mediated by the suprachiasmatic pacemaker. Dysfunctional circadian input may also influence monoaminergic activity, lowering serotonin activity and melatonin levels, with effects on timekeeping and hence sleep. Stress has a major role in the development of depression. Some degree of stress is tolerable, but overload is harmful. Disturbed sleep is the best clinical sign of excessive stress. Stress can be tolerated as long as sleep function is normal. But insomnia is evidence of an overactive hypothalamo-pituitary-adrenal axis. The regulatory peptide corticotropin-releasing factor not only influences the release of adrenocorticotropic hormone, but also the limbic system, inhibiting delta sleep. This dysregulation may also feed back onto the circadian pacemaker. Disruptions in the biological clock mechanism may be both a cause and a consequence of depression. Insomnia is itself a risk factor for the development of depression as shown in several epidemiological studies[2] and borne out in clinical experience. Antidepressants that relieve certain symptoms without correcting sleep disturbance will not achieve a significant response and will incur a high rate of relapse. Patients feel better if their sleep disturbance improves early during treatment. They are otherwise likely to feel worse. The risk that selective serotonin reuptake inhibitors may initially worsen sleep should be counteracted by the addition of hypnotics. The ideal antidepressant is a drug that rapidly improves sleep and resets the circadian system. Sleep disturbance should thus be the primary target in treating depression. This recommendation may appear to conflict with the rapidly positive effect that sleep deprivation may have in melancholia. However, sleep deprivation works by resetting the disrupted circadian system. Other methods that act on the circadian pacemaker can be equally effective. In order to improve sleep as a basis for mood reversal, there are thus sound scientific as well as clinical grounds for prioritizing circadian rhythm in the treatment of depression. ❐

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I would nominate as the priority treatment target one of the so-called core symptoms, such as depressed mood, lack of interest, lack of energy, guilt, psychic anxiety, or somatic anxiety.[1,2] This is because improvement in core symptoms tends to benefit other symptoms and eventually lead to full remission. However, it is difficult to identify the core symptom(s) in an individual patient because depression is heterogeneous in its pathogenesis. Since psychiatric symptoms can be clinically differentiated at multiple levels, phenomenological similarity does not reflect similarity of origin or structure.[3] A further complication is that the symptoms that appear as priorities for the patient may not be those that require priority treatment: our (unpublished) observations indicate that the Beck Depression Inventory (BDI) is less sensitive than clinician rating at identifying responders and remitters, especially in the early treatment period. Thus, at present, clinicians are obliged to choose a core symptom as their priority treatment target because antidepressants have shown no specific differences in their mechanism of action on target symptoms.[2]

Is the order of symptom improvement a relevant clinical factor?

The order of symptom response to antidepressants appears to depend on the drug receptor profile. For example, duloxetine, a serotonin-norepinephrine reuptake inhibitor, improved depressed mood, guilt, suicidal ideation, work/activity, and anxiety in the first week, motor retardation in the second week, motor retardation and hypochondriasis in the third week, and general somatic symptoms, insomnia, and insight after the fifth week.[4] With desipramine, a tricyclic antidepressant that inhibits the reuptake of norepinephrine, early response was shown by motor retardation and depressed mood, while with the selective serotonin reuptake inhibitor paroxetine, anxiety, depressed mood, and distressed expression were the first to improve.[5] As no biological markers for antidepressant treatment have been found and as current practice relies on rating scales, assessment of a patient's treatment has to be based on improvement in the core symptoms, especially during the early treatment period.[1,2,5] Clinically, the degree of symptom response is more relevant than its order, although there does appear to be a characteristic order of symptom response to antidepressants. Residual symptoms are less sensitive to antidepressants and may be more clinically relevant in that they heighten the risk of relapse.[6] Our (unpublished) finding in nonpsychotic major depressive disorder is that the negative self-concept factor in the BDI (items such as feeling of guilt, sense of punishment, self-hate, and self-accusation) is relatively less sensitive to change than observer ratings. This factor may therefore be clinically relevant in treating depression.

Is the placebo effect more important for some noncore symptoms?

Recent neurobiological studies suggest that placebo effects are not as simple as previously thought and that they may be clinically relevant by enhancing the effect of specific treatments.[7,8] In the hierarchy of classes of personal illness model proposed in 1975 by Foulds and Bedford,[9] depression occupies a lower hierarchical class. Endogenous depression, on the other hand, especially melancholia and psychotic depression, appears more biologically determined,[10] and does not occupy a lower hierarchical class. Studies from the 1970s suggest that the frequency of placebo effects increases from anxiety disorder, through depressive disorder, to schizophrenia. If we assume that core symptoms are the final common pathway in the pathogenesis of depression and that placebo effects are salient solutions to given stimuli in an individual,[7,8] the noncore symptoms that could be classified in the lowest hierarchical class[9] may be more likely to respond via a placebo effect. ❐

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Prioritizing symptoms in order to optimize treatment strategy is a crucial and complex issue in managing major depression. Depressed patients often overemphasize specific symptoms (eg, cognitive disturbance, loss of interest, sleep difficulties). This may be useful in establishing the diagnosis, but it can be misleading in informing treatment choice. Patients may stress certain persistent symptoms (eg, insomnia, somatic symptoms) at the expense of others that appear less severe, but are more meaningful in terms of drug response. In addition, there are specific populations, such as the elderly, with their own clinical patterns, which tend to be more severe and to carry a poorer prognosis than in nonelderly adult depressives:[1] elderly depressives have more somatization, hypochondriasis, anxiety/retardation, and delusionality, but less guilt, loss of libido, and family history of depression, as well as a less predictable therapeutic response; despite much lower medication doses, side effects are also more troublesome in this age group.[2] Given the symptom heterogeneity, it is mandatory to use standardized rating scales, such as the Hamilton Depression Rating Scale and Montgomery-Asberg Depression Rating Scale, for qualitative and quantitative assessment and for optimizing intervention. In choosing an initial treatment modality, the first consideration is the setting: the choice between hospitalization and outpatient care depends on suicidal ideation and symptom severity, in particular the presence or absence of psychotic features. The second consideration is the choice between pharmacology and electroconvulsive therapy, and if pharmacology, the choice of agent. Life-threatening situations must be addressed as rapidly as possible for the safety of patients and those around them. Less urgently, in order to minimize the development of antidepressant resistance, it is important to consider the duration of certain symptoms and of untreated illness in patients experiencing a first or recurrent depressive episode.[3] Current pharmacological classes of antidepressants allow clinicians to choose the most appropriate agent in light of specific symptom patterns. Certain drugs show symptom specificity. Serotonin norepinephrine reuptake inhibitors (SNRIs), for example, are most effective in cognitive disturbance and/or somatic complaints such as pain.[4] Mirtazapine and trazodone may be particularly useful in sleep disturbance,[5] along with melatonergic agents such as agomelatine.[6] The holy grail of pharmacotherapy is to develop rapid-onset agents that accelerate symptom response and remission. Recent examples include escitalopram, a selective serotonin reuptake inhibitor (SSRI), and the SNRIs venlafaxine and duloxetine. However, rapid onset of effect is not the only factor to consider in a treatment plan, even in severe disease. Tolerability is a critical consideration when efficacy depends on treatment compliance. Therapeutic strategy must therefore be based on a combination of disease factors (symptom severity, profile, and duration, and pattern of recurrence[7]) and pharmacotherapeutic factors (efficacy, tolerability, and time to effect). In prioritizing treatment targets, consideration should be given to the most urgent symptoms, especially if somatic, suicidal, and/or psychotic, followed by the patient's own symptom hierarchy. But the restoration of the fundamental biological rhythms governing sleep, appetite, and other functions must never be neglected. Biorhythm normalization is essential for breaking the vicious cycle of dysregulated affective brain circuits and dysfunctional hypothalamus that can underlie the core biological symptoms of depression. Dysfunctional biorhythms maintain cortical and subcortical circuit imbalance and vice-versa. Drugs designed to normalize biorhythm disruption may be the most promising additions to the pharmaceutical armamentarium against major depression. ❐

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