Core symptoms of major depressive disorder: relevance to diagnosis and treatment

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The construct of major depressive disorder makes no etiological assumptions about populations with diverse symptom clusters. "Depressed mood" and "loss of interest or pleasure in nearly all activities" are core features of a major depressive episode, though a strong case can be made to pay increasing attention to symptoms of fatigue, sleep disturbance, anxiety, and neurocognitive and sexual dysfunction in the diagnosis and evaluation of treatment outcome. Mood, guilt, work, and interest, as well as psychic anxiety, are consistently identified across validated subscales of the Hamilton Depression Rating Scale as prevalent and sensitive to change with existing treatments. A major limitation of these antidepressant therapies is their narrow spectrum of action. While the core "mood and interest" symptoms have been the main focus of attention, the associated symptoms listed above are often unaffected or exacerbated by current treatments. Careful clinical evaluation should address all of these dimensions, recognizing that improvement may occur sooner in some symptoms (eg, mood) compared with others (eg, sleep disturbance).

 Dialogues Clin Neurosci. 2008;10:271-277.

Core and associated symptoms within the diagnosis of major depressive disorder

The current polythetic approach to diagnostic classification of "Major Depressive Disorder (MDD)" in the *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. *(DSM-IV)*[1] or "Recurrent Depressive Episodes" in *The ICD-10 Classification of Mental and Behavioral Disorders: Clinical descriptions and diagnostic guidelines. (ICD-10)*[2] is devoid of implications about etiopathology or treatment response. Only "depressed mood" (mood) or "loss of interest or pleasure in nearly all activities" (anhedonia) are considered to be essential requirements for the diagnosis of a Major Depressive Episode (MDE) in *DSM-IV*. When these two "core symptoms" were used to screen for MDD using a 2-item version of the Patient Health Questionnaire (PHQ-2), they displayed a sensitivity of 83% and a specificity of 92% for "caseness" based on a Structured Clinical Interview for *DSM-IV* (SCID)[3] and comparable results were obtained in a subsequent European replication.[4]

Confirmatory diagnosis of an MDE, according to *DSM-IV*, requires a minimum of five symptoms (at least one

Keywords: *major depressive disorder; anxiety; sleep; fatigue; cognitive symptom*

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Selected abbreviations and acronyms

MDD	*Major Depressive Disorder*
HAM-D	*Hamilton Rating Scale for Depression*
MDE	*Major Depressive Episode*
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
ICD	*International Classification of Diseases*

being mood or anhedonia) for a minimum of 2 weeks (see *Table I* for *DSM-IV*). It is easy to see how the multiple permutations and combinations of these symptoms contribute to substantial intraclass heterogeneity.

Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either: (1) Depressed mood or (2) Loss of interest or pleasure Note: Do not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations.
(1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, feels sad or empty) or observation made by others (eg, appears tearful). Note: In children and adolescents, can be irritable mood
(2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
(3) Significant weight loss when not dieting or weight gain (eg, a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains
(4) Insomnia or hypersomnia nearly every day
(5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
(6) Fatigue or loss of energy nearly every day
(7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely s elf-reproach or guilt about being sick)
(8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
(9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

Table I. *DSM-IV* criteria for Major Depressive Episode.

Major depressive episode subtypes

Specifiers may be added to imply greater homogeneity within a subpopulation. For example, "with melancholic features" requires at least three of the following symptoms: complete loss of pleasure, lack of reactivity, psychomotor retardation, significant weight loss, excessive guilt, or distinct quality of depressed mood. Some authors have emphasized the presence of psychomotor retardation as a core feature of melancholic depression.[5] The presence of "atypical features" requires two or more of the following symptoms: overeating/weight gain, hypersomnia, leaden paralysis, preservation of mood reactivity, or interpersonal rejection sensitivity. These latter two symptoms (preservation of mood reactivity and interpersonal rejection sensitivity) have been criticized on the basis of poor reliability, and some authors have recommended that only the reverse vegetative symptoms, hypersomnia, and overeating as well as leaden paralysis form the core of atypical depression.[6]

There have been attempts to dichotomize these two depression subtypes on both treatment responsiveness and psychobiology. Historically, tricyclic antidepressants and electroconvulsive therapy were recommended for the melancholic patient,[7] while patients with atypical features appeared to respond better to classical monoamine oxidase inhibitors[8,9] than to tricyclic antidepressants. These distinctions have been less apparent with the current generation of selective serotonin reuptake inhibitor (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI) antidepressants, and no currently available antidepressant carries a specific indication for either melancholic or atypical symptoms. In fact, Parker's group recently acknowledged that symptom profiles within the "melancholia" population may vary with age. Hypersomnia was noted to be more common in the younger age group, while late insomnia became the dominant sleep disturbance of older patients.[10]

Evidence of core symptoms from rating scales

It is common to evaluate the severity of a depressive episode using classic rating scales, particularly the Hamilton Rating Scale for Depression (HAMD-17)[11] or the Montgomery Asberg Depression Rating Scale (MADRS).[12] Differences in medication type and in the symptom profiles of the population being evaluated may influence outcomes on a rating scale. Among individual

items, the core "depressed mood" item on either the HAMD-17 or the MADRS was more sensitive to drug-placebo separation and to establishing optimal dosing, compared with the full scales in several controlled trials.[13,14]

The sensitivity of some items to differentiate between active drug and placebo can be compromised when a drug has an unfavorable effect on certain items. For example, increased anxiety may occur during the early weeks of SSRI therapy, and activating antidepressants may disrupt some aspects of sleep.[15] The net result is that prevalent items may not emerge on rating scales that are designed to detect improvements during antidepressant therapy. When symptom prevalence and sensitivity to change have been evaluated in large data sets using item analysis or factor analysis, several core symptoms emerge with greater sensitivity to change and less distortion by treatment emergent side effects than with the full versions of the scale.

Three such scales derived from the HAMD-17 are the "Bech 6,"[16] "Maier subscale,"[17] and "HAMD-7"[18] *(Table II)*. Four items are common to each of these scales: mood, guilt, anhedonia, and psychic anxiety. In HAMD-7 and Bech 6, loss of energy (fatigue) was also present, as was psychomotor retardation in Bech 6 and Maier 6, while the HAMD-7 included somatic anxiety and suicidal ideation. All three scales include anxiety symptoms, in contrast to current diagnostic systems.

The prominence of anxiety symptoms and syndromes

Surprisingly, anxiety is not considered as a core or associated symptom of depression according to either *DSM-IV* or *ICD-10* criteria. Neither is "with anxious features" a specifier within *DSM-IV*, yet up to 90% of patients have co-occurring anxiety symptoms, and approximately 50% of depressed patients meet criteria for a comorbid anxiety disorder.[19,20] This lack of syndrome independence on Axis I is a major limitation to the current concept of comorbidity. Comorbid disorders should only exist at a level expected by chance, yet in the case of MDD, comorbidity is the rule and not the exception.[21]

MAIER-6	HAMD-7	BECH-6
Mood	Mood	Mood
Guilt	Guilt	Guilt
Work and interest	Work and interest	Work and interest
Psychic anxiety	Psychic anxiety	Psychic anxiety
Agitation	Energy	Energy
Retardation	*Somatic anxiety*	Retardation
	Suicide	

Table II. Core symptoms from three scales derived from the Hamilton Depression Rating Scale.

A recent proposal for mood and anxiety spectrum disorders, to be considered in DSM-V, has been advanced by Watson[22] who proposes three subclasses of emotional disorders: "bipolar disorders," "distress disorders," (MDD, dysthymic disorder, generalized anxiety disorder, and post-traumatic stress disorder) and "fear disorders" (panic disorder, agoraphobia, social phobia and specific phobia). This reflects a pendulum swing to the unitary position of Mapother[23] and Lewis[24] who viewed states of anxiety along a continuum with depressive disorders, in contrast to the progressive separation of mood and anxiety disorders initiated more than three decades ago.[25,26] It is likely that the inconsistent impact of some antidepressants on anxiety has distorted measurement of anxiety symptoms during treatment.

What is less in dispute is the impact of anxiety comorbidity on response to the treatment of depression. Patients without anxiety symptoms at the time of remission are significantly more likely to remain well than those patients with residual anxiety.[27] There is also consistent evidence of lower response rates and higher relapse in comorbidly anxious depressed patients. Although there is a strong justification to consider "anxious depression" as a depressive subtype,[28] a case can be made to maintain the separation of Generalized Anxiety Disorder (GAD) from MDD.[29]

Sleep disturbance, apathy, and fatigue

Sleep disturbance

The relationship between sleep and depression is complex. Insomnia is a frequent symptom of depression, and there is evidence to suggest that sleep disturbances are often a prodrome to a MDE.[30] Paradoxically, sleep deprivation has been advocated as an antidepressant therapy[31] while several antidepressant agents actually worsen sleep.[15] Sleep disturbance also lends itself to objective evaluation through polysomnography. Disturbances in the ratio of rapid eye movement (REM) sleep to non-REM sleep, decreased slow-wave sleep, and impaired sleep continuity are among the most robust markers for MDD. Whether reductions in slow-wave sleep and REM latency

are trait or state abnormalities is a controversial issue,[32] and attempts to establish robust diagnostic electroencephalographic markers for MDD have been confounded by the effects of age and gender.[33]

Among the symptoms of depression, sleep disturbance is a prominent symptom that is frequently unresponsive to current antidepressants, or is overtreated with consequent daytime somnolence. In a family practice evaluation of physician diagnosis and patient self-report of depressive symptoms, "insomnia or hypersomnia" along with "depressed mood" were the symptoms most frequently elicited by physicians, although only "suicidal ideation" and "insomnia or hypersomnia" were associated with a statistically significant likelihood of depression diagnosis.[34] Middle (71%), early (62%), and late (55%) insomnia were frequently reported items from the HAMD-17 in a sample of almost 300 depressed clinic patients.[18] However, underscoring the limited effectiveness of current antidepressants to improve sleep, none of these three sleep items were among the seven with greatest sensitivity to change during treatment *(Table III)*. In fact, middle insomnia emerged as the eighth most sensitive item to reflect antidepressant change.[18]

Symptom from HAMD-17	Percent endorsement			Change score Cohen's d
	M	F	All	
Work & interest	99	98	99	1.84
Depressed mood	98	98	98	1.81
Anxiety-somatic	86	92	90	1.03
Suicide	77	72	73	0.88
Energy	98	94	95	0.88
Guilt	86	85	85	0.86
Anxiety-psychaitric	59	90	79	0.83

Table III. HAMD-7: A brief measure of remission. HAMD, Hamilton Rating Scale for Depression
Adapted from ref 20: McIntyre R, Kennedy S, Bagby RM, et al. Assessing full remission. *J Psychiatry Neurosci*. 2002;27:235-239. Copyright © Canadian Medical Association 2002

The importance of sleep disturbance as a residual symptom in MDD has also been highlighted by Nierenberg and colleagues,[35] who examined threshold and subthreshold symptoms among patients who achieved remission (HAMD-17″ 7) after 8 weeks of antidepressant treatment with fluoxetine. The three most prevalent residual symptoms were disturbances in sleep (44%), fatigue (38%), and anhedonia (27%). Since the majority of these patients reported sleep disturbance prior to treatment with fluoxetine it is less likely to have been a treatment-emergent adverse event. The persistence of insomnia is a particular concern, given the propensity for residual sleep disturbance to predict relapse.[36]

Persistent sleep disturbances in SSRI "responders" include prolonged sleep latency (beyond 1 hour), reduced total sleep time, and multiple awakenings. Although coprescription of a hypnotic may have a beneficial effect,[37] concerns about long-term hypnotic use limit this recommendation. Elsewhere, advantages beyond sleep restoration were demonstrated when eszopiclone and fluoxetine were combined in the acute treatment of MDD.[38] Given the role of sleep disruption in predicting relapse, there is a strong argument to consider sleep disturbance as a core symptom in depression, and to emphasize the importance of sleep restoration early in the treatment of an MDE. The daytime effects of persistent sleep disruption should not be underestimated in depressed patients.

Fatigue and apathy

Particularly in primary care settings, depressed patients are likely to present with complaints of exhaustion or inability to carry out physical or mental work. In fact, fatigue was the commonest depressive symptom in a survey of family practice settings.[39] In the large European collaborative study of almost 2000 depressed patients across 6 countries (DEPRES II), 73% of patients "felt tired"; this symptom was associated with severity of the episode and was more prevalent in women.[40] Although "fatigue or loss of energy nearly every day" is not considered an essential depressive symptom according to *DSM-IV*, it is emphasized within the atypical symptom cluster, with "leaden paralysis" as the extreme variant. However, reduced energy is considered a "core feature" in the definition of depressive episode according to *ICD-10*, emphasizing that marked tiredness may occur after only slight effort.[41] It is a reasonable assumption that sleep disturbance and daytime fatigue are related (as previously reviewed—over 40% of remitters to fluoxetine had sleep disturbance and just under 40% had fatigue), although there are no data to confirm this relationship.

Similarly, apathy may overlap with diminished interest, loss of energy, and even indecisiveness, but this construct is too nonspecific to be considered a core symptom. In fact, apathy has been reported more frequently as a side effect in up to 20% of patients who receive SSRI antidepressants.[42]

Cognitive dysfunction

Subjective neurocognitive disturbance in depression is represented by "diminished ability to think or concentrate" in *DSM-IV*, although broader neurocognitive disturbances can be measured using standardized neuropsychological test batteries. Neuropsychological deficits have most often been detected in older individuals and include disturbances in psychomotor speed,[43] memory,[44] verbal fluency,[45] attention,[45] executive function,[45] and processing speed.[48] Whether restoration of cognitive function occurs with symptom remission in MDD has been a topic of considerable interest in recent years. Mostly in elderly patients, the data suggest enduring deficits in both memory and executive function.[49] Links between recurrent depressive episodes, reduced hippocampal volume and memory deficits have also been reported.[50] Although it is premature to endorse any specific neurocognitive deficit as a core symptom of depression, residual memory disturbance has major implications for functional recovery and deserves ongoing attention in clinical management.

Sexual dysfunction

Sexual dysfunction is also a complex issue among patients with depression. Common complaints include reduction in desire or libido, diminished arousal, a decline in the frequency of intercourse, or an undesirable delay in achieving orgasm. The prevalence of sexual dysfunction in the community is high;[51] it is even higher in untreated depressed patients[52] and may be further exacerbated by antidepressants.[53] In a large European study designed to evaluate sexual function in both treated and untreated depressed patients, more than two thirds of men and women reported decreased libido and the prevalence increased with severity and duration of the depressive episode.[54]

The reluctance among many patients to spontaneously report sexual dysfunction as a disturbing symptom of depression has resulted in a relatively low and misleading prevalence rate. The true importance of sexual dysfunction as a depressive symptom has not been recognized either in diagnosis or during antidepressant therapy. Nevertheless, low libido may contribute to deteriorating interpersonal/marital relations and further exacerbate depression. In the case of SSRI antidepressants, up to 60% of patients report treatment-emergent sexual function.[55,56] Antidepressants that do not stimulate serotonin release are less likely to induce or exacerbate sexual dysfunction.[53,57,58] This has implications for treatment adherence, as sexual dysfunction remains one of the commonest reasons for treatment discontinuation.[53]

Future directions

Both *DSM-IV* and *ICD-10* represent descriptive systems of classification. With *DSM-V* in mind, several authors have advocated a role for phenotypic characteristics, genetic data, as well as cognitive or other biological markers.[59,60] Endophenotypes reflect the gap between the gene and the expression of the disease process. In depression, putative biological candidates include disruptions in circadian rhythm, immune function, neurotransmitter-receptor signaling pathways, and neuroendocrine axes, as well as brain structure and function. Studies exploring the influence of gene-environment interactions (involving polymorphisms of the serotonin transporter) on symptom presentation and treatment response in depression have attracted considerable attention.[59,60] Reduction in hippocampal volume has been consistently reported in MDD[63] and linked to duration of untreated depression,[64] as well as deficits in neurocognition.[50] There are also preliminary reports on potential markers for treatment resistance. Lower serotonin transporter binding in the midbrain, medulla, and anterior cingulate cortex was associated with nonremission,[65] while hypermetabolism in the ventral anterior cingulate area brain region was a predictor of nonresponse to both cognitive therapy and venlafaxine.[66] Though provocative, these interesting findings are unlikely to influence diagnostic or treatment selection practices in the near future. In the meantime, a re-examination of core symptoms in depressed patients and careful clinical attention to their response to disparate antidepressant strategies will remain the cornerstone of good clinical practice. ❑

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Síntomas centrales del trastorno depresivo mayor: relevancia para el diagnóstico y el tratamiento

El constructo trastorno depresivo mayor no asume etiologías para las poblaciones con diversas agrupaciones sintomáticas. El "ánimo depresivo" y la "pérdida de interés o placer en casi todas las actividades" son características centrales de un episodio depresivo mayor, aunque han existido buenos argumentos para prestar atención creciente a síntomas como fatiga, alteraciones del sueño, ansiedad, y disfunciones neurocognitivas y sexuales para el diagnóstico y la evaluación de los resultados del tratamiento. El ánimo, la culpa, el trabajo y el interés como también la ansiedad psíquica son identificados consistentemente a través de subescalas validadas de la escala de depresión de Hamilton como prevalentes y sensibles de cambiar con los tratamientos disponibles. Una limitación importante de estas terapias antidepresivas es su limitado espectro de acción. Mientras que los síntomas centrales "ánimo e interés" han sido el principal foco de atención, los síntomas asociados antes señalados a menudo no son afectados o exacerbados por los tratamientos actuales. La evaluación clínica debe ser cuidadosa y orientarse a todas estas dimensiones, reconociendo que la mejoría puede ocurrir más rápido en algunos síntomas (como el ánimo) en comparación con otros (como las alteraciones del sueño).

Symptômes essentiels des troubles dépressifs majeurs : importance pour le diagnostic et le traitement

La constitution des troubles dépressifs majeurs ne présuppose pas d'origine étiologique chez des patients aux symptômes variés. « L'humeur dépressive » et « la perte d'intérêt ou de plaisir dans presque toutes les activités » sont des critères essentiels d'un épisode dépressif majeur, bien qu'il y ait beaucoup à dire sur l'intérêt croissant que suscitent les symptômes de fatigue, les perturbations du sommeil, l'anxiété et les dysfonctions sexuelles et cognitives dans le diagnostic et l'évaluation du traitement. Des sous-échelles validées de l'HAMD (Hamilton Depression Rating Scale*) montrent régulièrement que l'humeur, la culpabilité, le travail et l'intérêt comme l'anxiété psychique sont des symptômes prévalents et susceptibles de variations avec les traitements existants. Ces traitements antidépresseurs sont très limités par leur spectre d'action étroit. Alors que l'attention s'est majoritairement focalisée sur les symptômes majeurs « humeur et intérêt », les symptômes associés cités ci-dessus sont souvent inchangés ou exacerbés par les traitements actuels. Toutes ces questions devraient faire l'objet d'une évaluation clinique soigneuse, certains symptômes (par ex, l'humeur) pouvant être améliorés avant d'autres (par ex, troubles du sommeil).*

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