A practical approach to subtyping depression among your patients

Improve outcomes by understanding the forms that depressive disorders can take

Depression—sad, empty, or irritable mood accompanied by somatic or cognitive changes—is not a homogeneous condition. Recognizing subtypes of depressive illness can guide treatment and relieve your patient’s suffering. In this 2-part article [April and May 2014 issues], I summarize information about clinically distinct subtypes of depression, as they are recognized within diagnostic systems or as descriptors of treatment outcomes for particular subgroups of patients. My focus is on practical considerations for assessing and managing depression. Because many forms of the disorder respond inadequately to initial antidepressant treatment, optimal “next-step” pharmacotherapy, after nonresponse or partial response, often hinges on clinical subtyping.

The second part of this article examines “situational,” treatment-resistant, melancholic, agitated, anxious, and atypical depression; depression occurring with a substance use disorder; premenstrual dysphoric disorder; and seasonal affective disorder. Treatments for these subtypes for which there is evidence, or a clinical rationale, are given in the Table, page 42.

‘Situational’ depression

In recent decades, the phenomenon of nonsyndromal depression after a life stress has undergone many name changes but little conceptual revision: “situational,” “reactive,” and “neurotic” labels for depression that were used before DSM-III became “adjustment disorders” in DSM-IV-TR and then “stress

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Subtyping depression

“Subtyping depression” in DSM-5. These names all connote presentations of depressed mood after an environmental stressor without either the full constellation of symptoms that define major depression or the chronicity of dysthymic disorder.

Paucity of guidance. There has been little research to identify vulnerability variables for adjustment disorders in the aftermath of particular stressors. Similarly, extensive data are lacking on 1) the likely progression of such disorders to a syndromal form of

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√ = traditional first-line intervention or recommended appropriate first-line intervention

<sup>a</sup>An FDA-approved indication; all other uses are off-label

<sup>b</sup>The effects of atypical antipsychotics on hypersomnia and hyperphagia associated with atypical depression are not well-established

MAOIs: monoamine oxidase inhibitors; OFC: olanzapine-fluoxetine combination; SSRIs: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressant

Clinical Point
Stressful life events more often precede first or early episodes of depression than subsequent recurrences

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Table
Evidence- or rationale-based somatic therapy for select subtypes of depression
depression or 2) protective factors against developing clinically significant depression after a life stress. The extent to which adjustment disorders lie on a continuum with major mood disorders is not well-established, although subthreshold levels of depression can predispose to major depression or suicidal behaviors.1

Models of behavioral sensitization posit that stressful life events more often precede first or early episodes of depression than subsequent recurrences.2 At the same time, nonmelancholic depressions that are preceded by “situational stresses” tend to recur in similar fashion.3

Medical therapy of value? Psychotherapy without medication—apart from occasional sedative–hypnotic drugs as needed for insomnia, anxiety, or distress—is considered the standard of care for treating an adjustment disorder. No drug has demonstrated superiority to placebo for alleviating symptoms of an adjustment disorder, but some clinicians nonetheless sometimes feel compelled to “up-code” the diagnosis of an adjustment disorder to the status of a major affective disorder, even when syndromal criteria for major depressive disorder (MDD) or dysthymia are absent.

T able

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For treatment-resistant depression, repetitive transcranial magnetic stimulation appears to be inferior to ECT

Clinical Point

Disease staging models for depression and other psychiatric disorders2 make note that, elsewhere in medicine, distinct clinical entities often are identified based on their responsivity to treatment (eg, classifying infections as antibiotic-sensitive or -resistant). Within the study and management of mood disorders, “treatment resistance” sometimes is a catch-all description of situations in which past treatment 1) yielded no improvement or partial improvement or 2) was marked by intolerance. Poor outcomes due to past medication intolerance or an aborted trial often are commingled with cases of true lack of improvement after an adequate treatment trial.

It is useful, therefore, to define terminology precisely when describing “treatment-resistant depression” and “treatment-refractory depression.” True past nonresponse to appropriate treatment often carries prognostic importance and bears on future treatment decisions.

Few interventions are FDA approved for treatment-resistant depression (Table).


continued
Neuromodulation techniques are attracting interest in this area, although repetitive transcranial magnetic stimulation appears inferior to electroconvulsive therapy (ECT) for this indication.4

**Melancholic depression**
Melancholia involves the cardinal symptoms of anhedonia and lack of mood reactivity, alongside such features as distinct quality of mood, diurnal variation, excessive guilt, and severe weight loss. It most closely approximates pre-DSM-III “endogenous depression” and can involve 1) greater genetic loading2 and 2) structural and functional abnormalities in frontostriatal pathways.6,7

Melancholic features do not necessarily recur across successive episodes8 but carry an increased risk of psychosis9 and high-lethality suicidal behavior.10 Melancholia implies necessity for pharmacotherapy or ECT rather than psychosocial treatment alone; some researchers have suggested that tricyclic antidepressants (TCAs) might yield better results than selective serotonin reuptake inhibitors (SSRIs).11

**Agitated depression**
The Research Diagnostic Criteria (a forerunner in the 1970s to DSM-III) described agitated depression, but the disorder was not included in any DSM editions—although it is a “clinical modification” for MDD in the 10th revision of the International Statistical Classification of Diseases and Related Health Problems.

Agitated depression refers to a major depressive episode involving motor or psychic agitation, intense inner tension, and racing or “crowded” thoughts. Some experts believe that it represents a variant of psychotic depression or a bipolar mixed state, but the construct does not specify that criteria for a full manic or hypomanic episode exist.

Recovery from agitated depression tends to be slower than in non-agitated depression. Treatment usually entails an antidepressant plus an antipsychotic, although some believe that antipsychotics can exacerbate, not alleviate, symptoms and, instead, favor antipsychotics, mood stabilizers, or ECT.12

**Anxious depression**
Anxiety symptoms or syndromes occur in at least one-half of outpatients who have major depression, and might account for a substantial percentage of nonresponse to first-line antidepressant therapies.13 The construct of a mixed anxiety–depressive disorder is, in fact, well-represented in the literature, particularly in primary care medicine, but its poor inter-rater reliability in DSM-5 field trials led to its exclusion there as a formal diagnosis.14

Serotonergic antidepressants remain the mainstay of treatment for depression with anxiety, although (contrary to popular perception) bupropion exerts an anxiolytic effect that is comparable to the effect of SSRIs.15 Notably, high somatic anxiety during depression might predict a poor outcome from ECT.16

**Atypical depression**
Often closely linked with early onset and chronicity, the construct of atypical depression has been defined in the literature by the symptom constellation of:
- mood reactivity to environmental circumstances (unlike melancholia)
- heightened interpersonal sensitivity
- hypersomnia
- hyperphagia
- profound fatigue or a sense of physical heaviness.

Some authorities regard atypical features as being especially common in bipolar depression, or in depression among people who have borderline personality disorder.

Particular interest in this construct grew from studies that suggested that atypical depression is more responsive to a monoamine oxidase inhibitor (MAOI) than to a TCA, but also that SSRIs are not clearly superior to MAOIs.17 Response to ECT might also be better in atypical than in typical depression.18

**Depression with a substance use disorder**
Although not a distinct diagnostic entity, depression with a coexisting substance use disorder poses special challenges with regard to the source of symptom emergence (that is, when does depression lead to drug or alcohol use to “self-medicate,” and when
does drug use cause depression?) and treatment. Debate continues about whether 1) medicines that treat depression are effective and worthwhile in the setting of active substance use or 2) aggressive treatment of substance misuse is a prerequisite for subsequent pharmacotherapy for depression that is “uncontaminated” by the psychotoxic effects of concurrent substances of abuse.

Meta-analysis of controlled trials of antidepressants for patients who have MDD or a dysthymic disorder plus a comorbid alcohol use disorder found that antidepressants were, overall, superior to placebo unless a patient is actively drinking. Of the various classes of antidepressants, TCAs and nefazodone were found to be superior to placebo but, surprisingly, SSRIs were not. Another meta-analysis of adjunctive antidepressant outcomes for opiate-dependent, depressed patients who are receiving methadone maintenance therapy found no difference between antidepressants and placebo in their effect on depression symptom outcomes.

**Premenstrual dysphoric disorder**
A new category in DSM-5, premenstrual dysphoric disorder (PMDD) represents a variant of premenstrual syndrome that arises during the luteal phase and ends with menstruation. Symptoms include several of those identified with MDD (without duration criteria), as well as mood swings, panic attacks, and physical complaints.

SSRIs—but not bupropion or TCAs—and, sometimes, low-estrogen oral contraceptives are mainstays of treatment; so is cognitive-behavioral therapy, as well as lifestyle modifications (eg, exercise and changes to diet). Phototherapy has not shown robust efficacy for PMDD.

**Secondary depression**
In DSM-5, depressive episodes that arise secondary to a general medical condition (eg, hypothyroidism and other endocrinopathies, cerebrovascular accidents, malignancies) or iatrogenically from medications (eg, corticosteroids, some anticonvulsants, interferon) are viewed as distinct from MDD in regard to risk of recurrence, genetic underpinnings, and possible neurodegenerative pathophysiology. Unlike MDD, patient-specific risk factors are poorly defined for anticipating that a secondary depression is more or less likely to develop in the context of an exogenous substance or medical illness.

Treating secondary depression involves addressing the underlying condition and might include antidepressant medication.

**Seasonal affective disorder**
DSM-5 identifies “with seasonal pattern” as a specifier for recurrent major depression. Phototherapy remains a standard treatment, although a Cochrane Review identified comparable outcomes with fluoxetine, but inconclusive data for other, newer antidepressants. Small open trials have suggested that MAOIs and TCAs can be efficacious.

Note: Phototherapy lacks demonstrated efficacy in non-seasonal forms of depression.

**What does the future hold for classifying depressive disorders?**
Recent initiatives have attempted to classify depression less by traditional clinical signs and more by focusing on possible underlying neurobiological substrates. In the future, subtyping of mood disorders might focus on such constructs as:

- positive and negative valence systems and attentional domains
- treatment-responsivity relative to genotypic variants (for example, the serotonin transporter gene locus [SLC6A4] or prediction of L-methylfolate-responsive depression based on the genotype of the methylenetetrahydrofolate reductase [MTHFR] polymorphism)
- disrupted neural plasticity in brain circuits believed to regulate emotion.

Until robust biomarkers for depression are identified and validated, however, such advances in nosology remain experimental and speculative.
**Related Resources**


**Drug Brand Names**

- Aripiprazole - Abilify
- Bupropion - Wellbutrin
- Fluoxetine - Prozac
- Ketamine - Ketalar
- L-Methylfolate - Depilin
- Lamotrigine - Lamictal
- Lithium - Eskalith, Lithobid
- Methadone - Dolophine
- Mitrazapine - Remeron
- Nefazodone - Serzone
- Olanzapine/fluoxetine - Symbyax
- Paroxetine - Paxil
- Pramipexole - Mirapex
- Quetiapine - Seroquel
- Riluzole - Rilutek
- Vortioxetine - Brintellix

**Editor’s note:** The first part of Dr. Goldberg’s review of depression subtypes—focusing on major and minor depression, chronicity, polarity, severity, and psychosis—appeared in the April 2014 issue.

**References**


**Bottom Line**

Depressive disorders comprise a range of conditions that can be viewed along many dimensions, including “situational,” treatment-resistant, melancholic, agitated, anxious, and atypical depression; depression occurring with a substance use disorder; premenstrual dysphoric disorder; and seasonal affective disorder, among other classifications. Clinical characteristics vary across subtypes—as do corresponding preferred treatments, which should be tailored to the needs of your patients.