Current PSYCHIATRY

SECOND OF 2 PARTS

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***.

JON KRAUSE/THE ISPOT.COM

Joseph F. Goldberg, MD
Clinical Professor of Psychiatry
Icahn School of Medicine at Mount Sinai
New York, New York
Director, Affective Disorders Research Program
Silver Hill Hospital
New Canaan, Connecticut

'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

Disclosure
Dr. Goldberg has been a consultant to Avanir Pharmaceuticals and Merck; has served on the speakers' bureau for AstraZeneca, Merck, Novartis, Sunovion Pharmaceuticals, Takeda-Lundbeck; and has received royalties from American Psychiatric Publishing and honoraria from Medscape and WebMD.

Subtyping depression

Clinical Point

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

Table

Evidence- or rationale-based somatic therapy for select subtypes of depression

Treatment	Treatment-resistant	Melancholic	Agitated	Anxious
Atypical antipsychotics	OFC[a] Adjunctive aripiprazole[a] Adjunctive quetiapine[a]	√	√	√
Bupropion	√	No data	No data	√
Deep brain stimulation	√	No data	No data	No data
Electroconvulsive therapy	√	√	√	(-) prognostic factor
Ketamine	Preliminary	No data	No data	No data
Lamotrigine	No data	No data	No data	No data
L-Methylfolate	Adjunctive efficacy after SSRI non-response	No data	No data	No data
Lithium	√ Adjunct to antidepressants	No data	No data	No data
MAOIs	√	√	√	√
Mirtazapine	√	√	√	√
N-Acetylcysteine	No data	No data	No data	No data
Phototherapy	No data	No data	No data	No data
Pramipexole	Preliminary	No data	No data; ill advised	No data
Psychostimulants	Preliminary	Preliminary	No data; ill-advised	No data; ill-advised
Riluzole	Preliminary	No data	No data	No data
Serotonin-norepinephrine reuptake inhibitors	√	√	√	√
SSRIs	√	TCAs might be superior	√	√
Repetitive transcranial magnetic stimulation	√ [a]	(+) open trials	No data	(+) open trials
Tricyclic antidepressants	√	√	√	√
Vagus nerve stimulation	√ [a]	No data	No data	No data
Vortioxetine	No data	No data	No data	No data

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

[a]An FDA-approved indication; all other uses are off-label
[b]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

response syndromes" 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

Discuss this article at www.facebook.com/CurrentPsychiatry

Atypical	Seasonal	Premenstrual dysphoric disorder
No data[b]	No data	No data
+ open trials	√[a]	Inferior to SSRIs
No data	No data	No data
√	No data	No data
No data	No data	No data
No data	No data	No data
No data	No data	No data
No data	No data	No data
√	√	No data
No data	No data	No data
No data	No data	No data
No data	√	Small effect, if any
No data	No data	No data
No data	No data	No data
No data	No data	No data
Open trials	Inconclusive	No data
√	√	√
No data	No data	No data
Inferior to SSRIs and MAOIs	√	Not better than placebo
No data	No data	No data
No data	No data	No data

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.

Treatment-resistant depression

Disease staging models for depression and other psychiatric disorders[a] 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***).

[a]See "Staging psychiatric disorders: A clinico-biologic model," Current Psychiatry, May 2013, at CurrentPsychiatry.com.

continued

Clinical Point

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

Subtyping depression

Clinical Point

High somatic anxiety during depression might predict a poor outcome from ECT

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 loading[5] and 2) structural and functional abnormalities in frontostriatal pathways.[6,7]

Melancholic features do not necessarily recur across successive episodes[8] but carry an increased risk of psychosis[9] 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 antidepressants 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 reactiveness 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.[19] 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.[20]

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[21] or TCAs[22]—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.[23]

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.[b] 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.[24] Small open trials have suggested that MAOIs and TCAs can be efficacious.

Note: Phototherapy lacks demonstrated efficacy in non-seasonal forms of depression.[25]

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.[c] 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.

[b]For further discussion, see "Is a medical illness causing your patient's depression? Current Psychiatry, August 2009, at CurrentPsychiatry.com.

[c]An example is the Research Domain Criteria [RDoC],www.nimh.nih.gov/research-priorities/rdoc/index.shtml.

continued

Clinical Point

In a meta-analysis of depressed patients who abuse alcohol, TCAs and nefazodone were superior to placebo, but SSRIs were not

Subtyping depression

Clinical Point

Treating secondary depression involves addressing the underlying medical condition and might include antidepressants

Related Resources

- Kosinski EC, Rothschild AJ. Monoamine oxidase inhibitors: Forgotten treatment for depression. Current Psychiatry. 2012;11(12):20-26.
- Rodgers S, Grosse Holtforth M, Müller M, et al. Symptom-based subtypes of depression and their psychosocial correlates: a person-centered approach focusing on the influence of sex. J Affect Disord. 2014;156:92-103.

Drug Brand Names

Aripiprazole • Abilify
Bupropion • Wellbutrin
Fluoxetine • Prozac
Ketamine • Ketalar
L-Methylfolate • Deplin
Lamotrigine • Lamictal
Lithium • Eskalith, Lithobid
Methadone • Dolophine
Mirtazapine • Remeron
Nefazodone • Serzone
Olanzapine/fluoxetine • Symbyax
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

1. Fergusson DM, Horwood LJ, Ridder EM, et al. Subthreshold depression in adolescence and mental health outcomes in adulthood. Arch Gen Psychiatry. 2005;62(1):66-72.
2. Mitchell PB, Parker GB, Gladstone GL, et al. Severity of stressful life events in first and subsequent episodes of depression: the relevance of depressive subtypes. J Affect Disord. 2003;73(3):245-252.
3. Coryell W, Winokur G, Maser JD, et al. Recurrently situational (reactive) depression: a study of course, phenomenology and familial psychopathology. J Affect Disord. 1994;31(3):203-210.
4. Slotema CW, Blom JD, Hoek HW, et al. Should we expand the toolbox of psychiatric treatment methods to include Repetitive Transcranial Magnetic Stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. J Clin Psychiatry. 2010;71(7):873-884.
5. Kendler KS. The diagnostic validity of melancholic major depression in a population-based sample of female twins. Arch Gen Psychiatry. 1997;54(4):299-304.
6. Bracht T, Horn H, Strik W, et al. White matter microstructure alterations of the medial forebrain bundle in melancholic depression. J Affect Disord. 2014;155:186-193.
7. Pizzagalli DA, Oakes TR, Fox AS, et al. Functional but not structural subgenual prefrontal cortex abnormalities in melancholia. Mol Psychiatry. 2004;9(4):325, 393-405.
8. Melartin T, Leskelä U, Rytsälä H, et al. Co-morbidity and stability of melancholic features in DSM-IV major depressive disorder. Psychol Med. 2004;34(8):1443-1452.
9. Caldieraro MA, Baeza FL, Pinheiro DO, et al. Prevalence of psychotic symptoms in those with melancholic and nonmelancholic depression. J Nerv Ment Dis. 2013;201(10):855-859.
10. Grunebaum MF, Galfalvy HC, Oquendo MA, et al. Melancholia and the probability and lethality of suicide attempts. Br J Psychiatry. 2004;184:534-535.
11. Roose SP, Glassman AH, Attia E, et al. Comparative efficacy of selective serotonin reuptake inhibitors and tricyclics in the treatment of melancholia. Am J Psychiatry. 1994;151(12):1735-1739.
12. Koukopoulos A, Sani G, Koukopoulos AE, et al. Melancholia agitata and mixed depression. Acta Psychiatr Scand Suppl. 2007;(433):50-57.
13. Fava M, Rush AJ, Alpert JE, et al. Difference in treatment outcome in outpatients with anxious versus nonanxious depression: a STAR*D report. Am J Psychiatry. 2008;165(3):342-351.
14. Regier DA, Narrow WE, Clarke DE, et al. DSM-5 field trials in the United States and Canada, Part II: test-retest reliability of selected categorical diagnoses. Am J Psychiatry. 2013;170(1):59-70.
15. Rush AJ, Trivedi MH, Carmody TJ, et al. Response in relation to baseline anxiety levels in major depressive disorder treated with bupropion sustained release or sertraline. Neuropsychopharmacology. 2001;25(1):131-138.
16. Rasmussen KG, Snyder KA, Knapp RG, et al. Relationship between somatization and remission with ECT. Psychiatry Res. 2004;129(3):293-295.
17. Henkel V, Mergl R, Allgaier AK, et al. Treatment of depression with atypical features: a meta-analytic approach. Psychiatry Res. 2006;141(1):89-101.
18. Husain MM, McClintock SM, Rush AJ, et al. The efficacy of acute electroconvulsive therapy in atypical depression. J Clin Psychiatry. 2008;69(3):406-411.
19. Iovieno N, Tedeschini E, Bentley KH, et al. Antidepressants for major depressive disorder and dysthymic disorder in patients with comorbid alcohol use disorders: a meta-analysis of placebo-controlled randomized trials. J Clin Psychiatry. 2011;72(8):1144-1151.
20. Pedrelli P, Iovieno N, Vitali M, et al. Treatment of major depressive disorder and dysthymic disorder with antidepressants in patients with comorbid opiate use disorders enrolled in methadone maintenance therapy: a meta-analysis. J Clin Psychopharmacol. 2011;31(5):582-586.
21. Pearlstein TB, Stone AB, Lund SA, et al. Comparison of fluoxetine, bupropion, and placebo in the treatment of premenstrual dysphoric disorder. J Clin Psychopharmacol. 1997;17(4):261-266.
22. Freeman EW, Rickels K, Sondheimer SJ, et al. Differential response to antidepressants in women with premenstrual syndrome/premenstrual dysphoric disorder: a randomized controlled trial. Arch Gen Psychiatry. 1999;56(10):932-939.
23. Krasnik C, Montori VM, Guyatt GH, et al. The effect of bright light therapy on depression associated with premenstrual dysphoric disorder. Am J Obstet Gynecol. 2005;193(3, pt 1):658-661.
24. Thaler K, Delivuk M, Chapman A, et al. Second-generation antidepressants for seasonal affective disorder. Cochrane Database Syst Rev. 2011;7(12):CD008591.
25. Thalén BE, Kjellman BF, Mørkid L, et al. Light treatment in seasonal and nonseasonal depression. Acta Psychiatr Scand. 1995;91(5):352-360.

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.