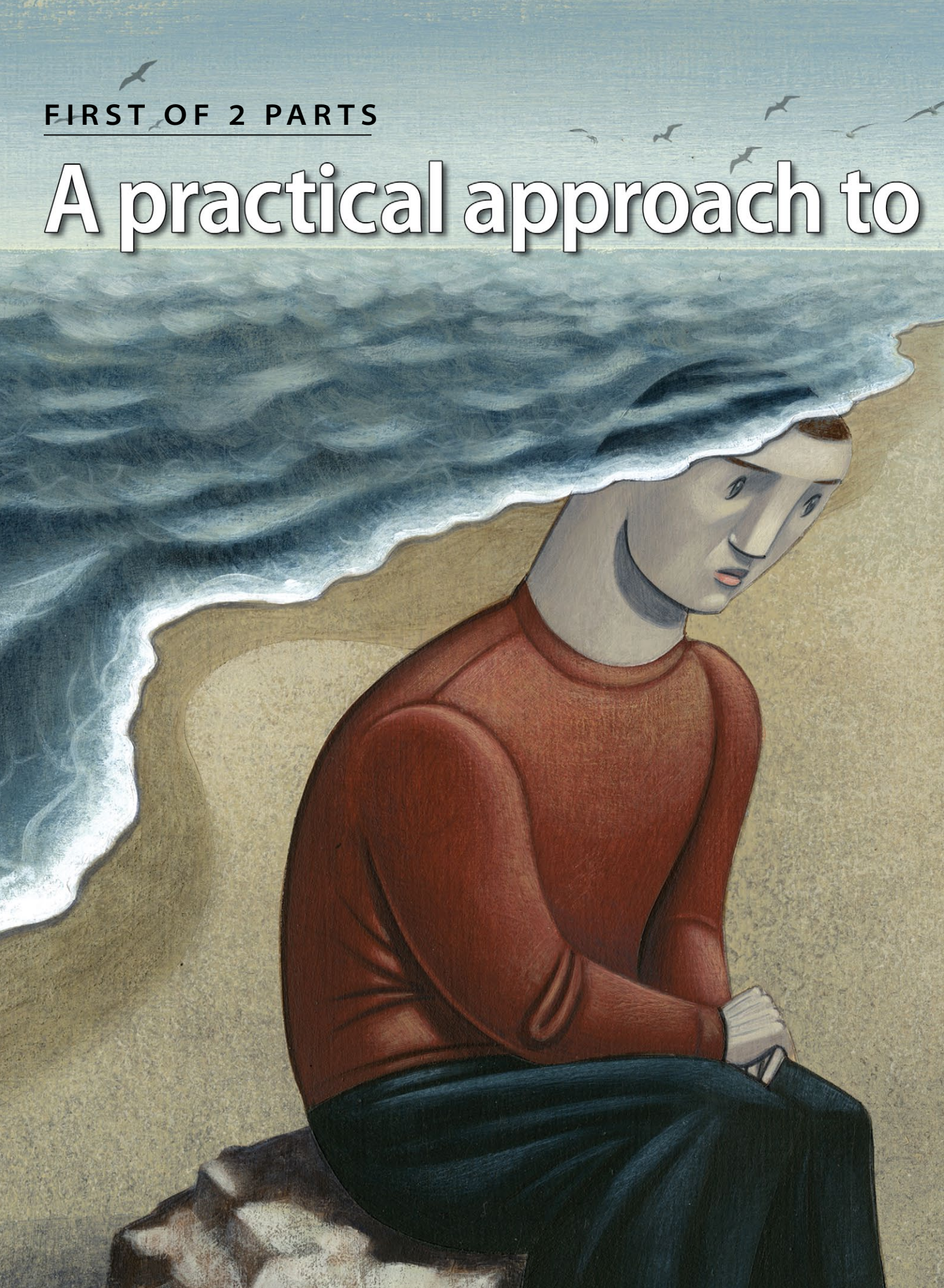
FIRST OF 2 PARTS

A practical approach to



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Dr. Goldberg: Why subtyping can mean better outcomes in depressive disorders

subtyping depression among your patients

Increase treatment success by assessing for the multiple forms that depressive disorders take

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Disclosure
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Depression carries a wide differential diagnosis. Practitioners sometimes think polarity is the fundamental distinction when they conceptualize depression as a clinical entity; in fact, many nosologic frameworks have been described for defining and subtyping clinically meaningful forms of depression, and each waxed and waned in popularity.

Kraepelin, writing in the early 20th century, linked manic-depressive illness with "the greater part of the morbid states termed melancholia,"[1] but many features other than polarity remain important components of depression, and those features often carry implications for how individual patients respond to treatment.

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 first part of this article examines major depressive disorder (MDD), minor depression, chronic depression, depression in bipolar disorder, depression that is severe or mild, and psychotic depression. Treatments for these subtypes for which there is evidence, or a clinical rationale, are given in the ***Table (page 44)***.

The subtypes of depression that I'll discuss in the second part of the article are listed on page 47.

continued

Subtyping depression

Clinical Point

Evidence-based psychotherapy, as an adjunct to drug therapy, further improves outcomes, but with only modest additional effect

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Table

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

Treatment	Major depressive disorder	Chronic/ persistent	Bipolar
Atypical antipsychotics	Olanzapine-fluoxetine combination[a] Adjunctive aripiprazole[a] Adjunctive quetiapine[a]	No data	Olanzapine-fluoxetine combination[a] Lurasidone[a] Quetiapine[a]
Bupropion	√	√	Low risk for polarity switch, but efficacy compared with a mood stabilizer alone is unproven
Deep brain stimulation	√	No data	No data
Electroconvulsive therapy	√ (notably in the setting of high severity, suicidality, or psychosis)	√	√ (notably in the setting of high severity, suicidality, or psychosis)
Ketamine	Preliminary	Preliminary	Preliminary
Lamotrigine	Preliminary; mixed data as adjunct to antidepressants	No data	√
L-Methylfolate	Adjunct to antidepressants	No data	No data
Lithium	√ Adjunct to antidepressants	√ Adjunct to antidepressants	√
Mirtazapine	√ [a]	√	No data
Monoamine oxidase inhibitors	√ [a]	√	Positive data from preliminary randomized trials
N-Acetylcysteine	Preliminary	No data	Positive data from preliminary randomized trials
Phototherapy	If seasonal	No data	If seasonal pattern
Pramipexole	Preliminary	No data	Positive data from preliminary randomized trials
Psychostimulants	Adjunctive to antidepressants	No data	Positive data from preliminary randomized trials of armodafinil and modafinil
Repetitive transcranial magnetic stimulation	√ [a]	Preliminary	Preliminary open trials
Riluzole	Preliminary	No data	Positive data from preliminary open-label trials
Serotonin-norepinephrine reuptake inhibitors	√ [a]	√	No placebo-controlled trials; use with caution because of possible higher switch rate than with other agents
Selective serotonin reuptake inhibitors	√ [a]	√	Positive data from placebo-controlled trials of fluoxetine (bipolar II); positive data from randomized, non-placebo-controlled trials of sertraline
Tricyclic antidepressants	√ [a]	√	Comparable to lithium in randomized trials; possible heightened risk for polarity switch
Vagal nerve stimulation	√ [a]	√	No data
Vortioxetine	√ [a]	No data	No data

Note: Evidence or rationale listed here for these treatments is drawn from the references provided in the text.

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

[a]An FDA-approved indication; use in all other depression subtypes is off-label

Mixed features	Psychotic
√ (extrapolated from bipolar mixed episodes)	√
Ill-advised	√ (with an antipsychotic)
No data	No data
√ (extrapolated from bipolar mixed episodes)	√
No data	No data
No data	No data
No data	No data
√ (extrapolated from bipolar mixed episodes)	√
Ill-advised	√ (with an antipsychotic)
Ill-advised	√ (with an antipsychotic)
No data	No data
No data	No data
No data; ill-advised	No data; ill-advised
Ill-advised	No data, ill-advised
No data	No data
No data	No data
No data	No data
Ill-advised	√ (with an antipsychotic)
Ill-advised	√ (with an antipsychotic)
No data	No data
No data	No data

Major and minor depression

MDD has been the focus of most drug trials seeking FDA approval. As a syndrome, MDD is defined by a constellation of features that are related not only to mood but also to sleep, energy, cognition, motivation, and motor behavior, persisting for ≥2 weeks.

DSM-5 has imposed few changes to the basic definition of MDD:

- bereavement (the aftermath of death of a loved one), formerly an exclusion criterion, no longer precludes making a diagnosis of MDD when syndromal criteria are otherwise fulfilled
- "with anxious distress" is a new course specifier that designates prominent anxiety features (feeling worried, restless, tense, or keyed up; fearful of losing control or something terrible happening)
- "with mixed features" is a new course specifier pertinent when ≥3 mania or hypomania symptoms coexist (that is, might be a subsyndromal mania or hypomania) with a depressive syndrome; the mixed features specifier can be applied to depressed patients whether or not they have *ever* had a manic or hypomanic episode, but MDD—rather than bipolar disorder—remains the overarching diagnosis, unless criteria have ever been met for a full mania or hypomania.

More than 2 dozen medications are FDA-approved to treat MDD. Evidence-based psychotherapies (eg, cognitive-behavioral therapy [CBT] and interpersonal therapy), as adjuncts to pharmacotherapy, further improve outcomes, but with only modest additional effect.[2]

Minor depression. Depressive states that involve 2 to 4 associated symptoms lasting ≥2 weeks but <2 years are sometimes described as minor depression, captured within DSM-5 as "depression not elsewhere defined." The terminology of so-called "minor depression" generally is shunned, in part because it might wrongly connote low severity and therefore discourage treatment—even though it confers more than a 5-fold increase in risk of MDD.[3]

continued

Clinical Point

"Minor depression" confers a more than 5-fold increase in the risk of a major depressive disorder

Subtyping depression

Clinical Point

Nearly all large, randomized controlled trials of antidepressants for bipolar depression show no advantage over placebo

Chronicity

DSM-IV-TR identified long-standing depression by 2 constructs:

- chronic major depression (an episode of MDD lasting ≥2 years in adults, ≥1 year in children and adolescents)
- dysthymic disorder (2 to 4 depressive symptoms for ≥2 years in adults and ≥1 year in children and adolescents), affecting 3% to 6% of adults and carrying a 2-fold increased risk of MDD, eventually.[4]

Depression that begins as dysthymic disorder and blossoms into syndromal MDD is described as "double depression"—although it is not recognized as a unique condition in any edition of the DSM. Subsequent incomplete recovery may revert to dysthymic disorder. DSM-5 has subsumed chronic major depression and dysthymia under the unified heading of persistent depressive disorder.

There are no FDA-approved drugs for treating dysthymia. A meta-analysis of 9 controlled trials of off-label use of antidepressants to treat dysthymia revealed an overall response rate of 52.4%, compared with 29.9% for placebo.[5] Notably, although the active drug response rate in these studies is comparable to what seen in MDD, the placebo response rate was approximately 10% lower than what was seen in major depression.

Positive therapeutic findings (typically, treatment for 6 to 12 weeks) have been reported in so-called "pure" dysthymic disorder with sertraline, fluoxetine, imipramine, ritanserin, moclobemide (not approved for use in the United States), and phenelzine; the results of additional, positive placebo-controlled studies support the utility of duloxetine[6] and paroxetine.[7] Randomized trials have reported negative findings for desipramine,[8] fluoxetine,[9] and escitalopram[10]—although the sample size in these latter studies might have been too small to detect a drug–placebo difference.

In dysthymic and minor-depressive middle-age and older adult men who have a low serum level of testosterone, hormone replacement was shown to be superior to placebo in several randomized trials.[11] Studies of adjunctive atypical antipsychotics for dysthymic disorder are scarce; a Cochrane review identified controlled data only with amisulpride (not approved for use in the United States), which yielded a modest therapeutic effect.[12]

Polarity

In recent years, depression in bipolar disorder (BD) has been contrasted with unipolar MDD based on a difference in:

- duration (briefer in BD)
- severity (worse in BD)
- risk of suicide (higher)
- comorbidity (more extensive)
- family history (often present for BD and highly recurrent depression)
- treatment outcome (generally less favorable).

DSM-5 has at least somewhat blurred the distinctions in polarity by way of the new construct of "major depression with mixed features" (see the discussion of MDD above), identifiable even when a person has never had a full manic or hypomanic episode.

No randomized trials have been conducted to identify the best treatments for such presentations, which has invited extrapolation from the literature in regard to bipolar mixed episodes, and suggesting that 1) some mood stabilizers (eg, divalproex) might have value and 2) antidepressants might exacerbate manic symptoms.

Perhaps most noteworthy in regard to treating bipolar depression is the unresolved, but hotly debated, controversy over whether and, if so, when, an antidepressant is inappropriate (based on concerns about possible induction or exacerbation of manic symptoms). In addition, nearly all of the large, randomized controlled trials of antidepressants for bipolar depression have shown that they offer *no* advantage over placebo.

Some authors argue that a lack of response to antidepressants might, itself, be a "soft" indicator of "bipolarity." However, nonresponse to antidepressants should prompt a wider assessment of features other than polarity—including psychosis, anxiety, substance abuse, a personality disorder, psychiatric adverse effects from concomitant medications, medical comor-

bidity, adequacy of trials of medical therapy, and potential non-adherence to such trials—to account for poor antidepressant outcomes.

Severity

Severity of depression warrants consideration when formulating impressions about the nature and treatment of all presentations of depression.

High-severity forms prompt decisions about treatment setting (inpatient or outpatient); suicide assessment; and therapeutic modalities (eg, electroconvulsive therapy is more appropriate than psychotherapy for catatonic depression).

Mild forms. A recent meta-analysis of 6 randomized trials (each of >6 weeks' duration) of antidepressants for mild depression demonstrated that these agents exert only a modest effect compared with placebo, owing largely to higher placebo-responsivity in mild depressive episodes than in moderate and severe episodes.[13] In contrast, another meta-analysis of subjects who had "mild" baseline depression severity scores found that antidepressant medication had greater efficacy than placebo in 4 of 6 randomized trials.[14] Higher depression severity levels typically diminish the placebo response rate but also reduce the magnitude of drug efficacy.

Psychosis

Before DSM-III, psychotic (as opposed to neurotic) depression was perhaps the key nosologic distinction when characterizing forms of depression. The presence of psychosis and related components (eg, mood-congruence) is closely linked with the severity of depression (high) and prognosis and longitudinal outcome (poorer), and has implications for treatment (***Table***).

Editor's note: *The second part of Dr. Goldberg's review of depression subtypes—focusing on "situational," treatment-resistant, melancholic, agitated, anxious, and atypical depression; depression occurring with a substance use disorder; premenstrual dysphoric disorder; and seasonal affective disorder—will appear in the May 2014 issue of* Current Psychiatry.

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Related Resources

- Goldberg JF, Thase ME. Monoamine oxidase inhibitors revisited: what you should know. J Clin Psychiatry. 2013;74(2):189-191.
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Drug Brand Names

Amisulpride • Amazeo, Amival, Amipride, Sulpitax
Aripiprazole • Abilify
Armodafinil • Nuvigil
Bupropion • Wellbutrin
Desipramine • Norpramin
Divalproex • Depakote, Depakene
Duloxetine • Cymbalta
Escitalopram • Lexapro
Fluoxetine • Prozac
Imipramine • Tofranil
Ketamine • Ketalar
Lamotrigine • Lamictal
Lithium • Eskalith, Lithobid
Lurasidone • Latuda
Mirtazapine • Remeron
Moclobemide • Amira, Aurorix, Clobemix, Depnil, Manerix
Modafinil • Provigil
Olanzapine/fluoxetine • Symbyax
Paroxetine • Paxil
Phenelzine • Nardil
Pramipexole • Mirapex
Quetiapine • Seroquel
Riluzole • Rilutek
Sertraline • Zoloft
Vortioxetine • Brintellix

Clinical Point

High-severity forms of depression prompt decisions about treatment setting, suicide assessment, and therapy

Bottom Line

Depressive disorders comprise a range of conditions that can be viewed along many dimensions, including polarity, chronicity, recurrence, psychosis, treatment resistance, comorbidity, and atypicality, among other classifications. Clinical characteristics vary across subtypes—and so do corresponding preferred treatments, which should be tailored to the needs of each of your patients.

Subtyping depression

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