

REVIEW

Bipolar Depression: Overview and Commentary

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Depressive phases are the most prevalent component of bipolar disorders, even with modern treatment. Bipolar depressive morbidity is often misdiagnosed and is limited in response to available treatments. These conditions are especially debilitating and are associated with psychiatric comorbidity, substance abuse, functional disability, and increased mortality owing to early suicide and accidents, and later medical illnesses. There is growing awareness that bipolar depression is one of the greatest challenges in modern psychiatry. It is essential to differentiate various forms of depression, dysthymia, and dysphoric mixed states of bipolar disorders from the clinical features of more common, unipolar major depressive disorders. In bipolar depression, antidepressant responses often are unsatisfactory, and these agents probably are overused. Emerging treatments, including several anticonvulsant and modern antipsychotic drugs, as well as lithium—alone or in selected combinations—are partially effective for bipolar depression. Interest in recognizing bipolar depression and seeking more effective, specific, and safer treatments for it are growing. (HARV REV PSYCHIATRY 2010;18:143–157.)

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This article identifies emerging trends in understanding bipolar depression and highlights remaining challenges to its adequate diagnosis and treatment. It includes findings arising from the authors' research along with representative, but not systematic, citations of relevant research reports and reviews. Literature was identified in the PubMed-MEDLINE database through August 2009 (search terms: bipolar disorder, depression, and specific treatments). The basic premise of this overview and commentary is that depression in patients diagnosed with bipolar disorder differs from common (unipolar) major depressive disorders in clinical and epidemiological characteristics and treatment responses.^{1–4} We consider bipolar depression to be a leading, unsolved, clinical and public-health challenge for contemporary psychiatry.^{2,3}

CHARACTERISTICS AND RECOGNITION OF BIPOLAR DEPRESSION

Initial diagnoses of type I bipolar disorder, especially among patients presenting in mania or mixed manic-depressive states, as defined by the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; DSM-IV)⁵ or *International*

Classification of Diseases (10th ed.),⁶ are among the most stable of all major psychiatric diagnoses over time.^{7,8} Diagnosis of bipolar disorder presenting as a depressive episode, dysthymia, or dysphoria requires ascertaining a history of mania (for DSM-IV type I), or hypomania only (for type II), which often is overlooked. Bipolar depression is initially considered or misdiagnosed as unipolar major depressive disorder in various proportions of cases of depression, ranging from 10% to 40%.^{2,9–14} Misdiagnosis is especially likely early in the illness course and if a patient is evaluated without corroborating information. Bipolar disorder patients typically are very concerned about, and seek to avoid, the depressive phases of the illness. They may not recognize hypomania or mania-related episodes of unusually increased mood, energy, activity, or libido as abnormal, and may even prefer such states. Since family members or close friends may be more aware than the patient of mood cycles, and particularly of periods of hypomania, their corroboration can be helpful.^{2,3}

To add further complexity, even in episodes considered by routine clinical assessment to represent pure depression, more than two-thirds of depressed bipolar disorder patients have at least subtle mania-like features.¹⁵ Mild-moderate *mixed* manic-depressive states of overarousal with dysphoria are especially likely to be underdiagnosed or to be considered depressive states, owing partly to a narrow DSM-IV definition of mixed bipolar states as requiring diagnosis of simultaneous mania and major depression.⁵ Mixed states, with symptoms of both depression and mania of varying severity and duration, are common in both types I and II bipolar disorders.^{16–20} Their treatment is poorly studied, but they appear both to predict inferior responses to standard treatments and increased risk for emotional destabilization with antidepressants. Destabilization can include increased agitation or switching into mania or psychosis, sometimes with rapid fluctuations or cycling of mood and activity. Some therapeutic trials include patients in mixed states with those in acute mania, but mixed states appear to be far more strongly associated with later depression or additional mixed states than with mania or psychosis.²¹

Uncertain divisions between bipolar and unipolar forms of major depression have been debated at least since the time of Emil Kraepelin.²² He recommended against distinguishing between recurrent unipolar forms of melancholia and cases with manic, hypomanic, or even cyclothymic phases, preferring to include them all in his category of *manic-depressive illness*. Following identification of a bipolar type within this broad category in the mid-1900s,²² the separation of major depression and bipolar disorder evolved and was reified in standard international diagnostic systems by the 1980s.^{5,6} Currently, there is considerable uncertainty about how far to expand the diagnosis of bipolar disorder, and how to subdivide unipolar major depression into cat-

egories that may better support prognosis and treatment. Manifestations of this uncertainty include current efforts to better define the status of all major mood disorders in children,^{23–26} and to define and delimit a possible spectrum of bipolar-like conditions with even less prominent hypomanic trends than now suffice to diagnose bipolar II disorder or cyclothymia.^{3,17,20}

Several demographic and clinical characteristics have been proposed to help distinguish bipolar from unipolar depressions.^{1,2,27,28} The sex ratio of risk is close to 1.0 in bipolar disorder—much lower than the female:male risk ratio in unipolar depression.³ Bipolar disorder should be suspected with onset in adolescence or early adult years, especially following a strong family history of mood disorders, “nervous breakdowns,” psychiatric hospitalizations, substance use disorders, postpartum psychiatric illnesses, or other psychiatric conditions.^{2,3} Also, average age of onset is lower in bipolar disorder patients, ranking: bipolar I < bipolar II < unipolar.²⁹ Bipolar disorders have relatively high recurrence rates, often with episodes or substantial mood shifts about once or twice a year,^{3,30} and even more frequently with “rapid cycling” (≥ 4 episodes in a year).^{31,32} Also, particular forms of depression are typical of bipolar depression. Characteristics of bipolar depression include psychomotor retardation (reduced motility, speech, and thought associations) or “leaden paralysis,” as well as additional psychobiological symptoms considered “atypical” in unipolar depression, including *hypersomnia* and *hyperphagia*.²⁸ Sometimes, psychotic features (usually “mood-congruent”) are found. In addition, anxiety disorders, including panic and obsessive-compulsive disorders,^{33,34} and substance abuse,^{35,36} are very prevalent among bipolar disorder patients, and probably characteristic of its early precursor states.^{37,38} Adult unipolar major depression also can include prominent anxiety symptoms.^{2,3} See text box on next page.

Since particular features of bipolar depression are not present in every case or each recurrence, it is sometimes difficult clinically to differentiate unipolar depressive illnesses from bipolar depression, especially based on relatively narrow DSM-IV diagnostic criteria for type II disorders, or on cross-sectional assessment without corroboration.⁷ Diagnostic uncertainties, along with early onset, can delay diagnosis and initiation of sustained treatment. Importantly, however, diagnostic delay or repeated prior episodes may *not* diminish response to mood-stabilizing treatments, despite their potentially severely adverse impact on a patient's life.^{39,40} Additional diagnostic complexity can arise from secondary mood disorders associated with mood-altering drugs, toxins, or a range of neuromedical disorders—in which depression or mania may be a feature.⁶²

In general, depression in its major, subsyndromal-dysthymic, or dysphoric-mixed forms, remains the leading, unresolved, long-term morbidity among both types I and II

Characteristics of Bipolar Depression

- Differentiation from recurrent unipolar major depression requires identification of manic (type I) or hypomanic (type I or II) phases; identification of hypomania can be facilitated by close informants.^{9–14}
- Bipolar depression is suggested by a strong family history (of psychiatric illness or substance-abuse), early age of onset, postpartum psychiatric illness, or psychotic features.^{3,27,28}
- Features considered “atypical” in unipolar depression (hypersomnia, increased appetite, anergy, psychomotor slowing, or “leaden paralysis”), as well as psychotic symptoms, are more common in bipolar than unipolar depression.^{27,28}
- Prevalence is much more similar among women and men than in unipolar major depression.³
- Onset-age ranks: bipolar I < bipolar II < unipolar depression;²⁹ some mood disorders arise in childhood or adolescence.^{23–25,37,38}
- Latency from onset to diagnosis and appropriate treatment averages 5–10 years.^{39,40}
- Recurrence rates exceed those in adult major depressive disorder and can include rapid cycling (≥ 4 episodes/year).^{3,30–32}
- Most cases of bipolar depression include at least mild mania-like elements¹⁵ or mixed states.^{16–21}
- Comorbid anxiety, obsessive-compulsive, and substance-use disorders are prevalent.^{33–36}
- Depressed mood (including major depression, dysthymia, and dysphoric mixed states) is the greatest component of types I and II bipolar disorders, accounting for approximately three-quarters of the 40%–50% of weeks/year unwell in bipolar disorders, even with treatment and from onset.^{21,42–47}
- Cognitive deficits and functional disability are both common in bipolar disorder patients.^{48–56}
- Mortality is increased in types I and II bipolar disorders, especially with severe and highly recurrent depression; high rates of suicide and accidents are associated with youth, and moderate excess mortality with medical comorbidity (especially cardiovascular and pulmonary) in later years, but with similar total numbers of excess deaths versus age.^{57–61}

bipolar disorder patients, in midcourse or from onset of illness, and even during treatment.^{21,41–48} Depression is also the most prevalent form of bipolar disorder morbidity associated with pregnancy, especially early pregnancy and the postpartum.^{63,64} Overall, among bipolar disorder patients, even with mood-stabilizing treatments, depression and dysthymia account for approximately three-quarters of

the typical 40%–50% of weeks/year in major or minor morbid states.⁴⁷ These treatments are evidently far less effective against depressive than manic morbidity.^{1,3} Moreover, such unresolved depression and the cognitive impairment that is often associated with it appear to contribute importantly to long-term dysfunction and disability in bipolar disorder patients.^{50–55}

Increased death rates in bipolar disorder reflect very high risks of suicide and accidents that may be 20 times above general population rates.^{50–61} Suicide risk is strongly associated with depression and is at least as high in type II as type I bipolar disorder.⁶¹ In addition, older patients experience moderately increased mortality (2–3 times above the general population) arising from cardiovascular, pulmonary, and other highly prevalent general medical conditions.⁵⁸ Due to relative prevalence as well as the risks involved, actual *numbers* of excess deaths in younger versus older bipolar disorder patients are strikingly similar—with violence in the young and excess medical mortality in older patients.⁵⁸

USE OF ANTIDEPRESSANTS FOR BIPOLAR DEPRESSION

Perhaps not surprisingly, given the eagerness of most bipolar disorder patients to avoid or seek treatment for depression, antidepressants continue to be, by far, the leading drugs given to such patients in the United States, both initially and often long term, with little apparent relevance to clinical status or response.^{65,66} International practices vary greatly regarding use of antidepressants for such patients, evidently reflecting perceptions of how similar various forms of clinical depression may be and how they might respond to such drugs. Although the benefit/risk ratio may be more favorable for type II bipolar disorder,^{67–70} antidepressants appear to be limited in efficacy, especially long-term, for bipolar disorder patients and also to be poorly tolerated by many, particularly type I patients.^{71–82} Monoamine oxidase inhibitors may be more effective than other antidepressants for bipolar depression but are rarely employed currently, owing to their risk of adverse effects and potential lethality, and interactions with other drugs.⁸³ Moreover, except for fluoxetine in combination with olanzapine,^{83–88} no other antidepressant or antidepressant drug-combination has been explicitly approved by the U.S. Food and Drug Administration to treat depression in bipolar disorder patients.

Antidepressants perform unevenly in acute bipolar depression. They often fail initially or within several months, and their long-term benefits in protecting against recurrences of bipolar depression, dysthymia, or mixed states are not only limited, but poorly studied.^{77–82} Nevertheless, a range of modern antidepressants is currently favored for use

in treating bipolar depression. They include serotonin reuptake inhibitors and mixed serotonin-norepinephrine reuptake inhibitors, as well as atypical agents such as bupropion and mirtazapine. Despite limited evidence of their efficacy in bipolar depression,^{71–82} such agents appear to be preferred largely for their safety, especially in acute overdoses among patients at high risk for suicide attempts.^{61,89,90}

Aside from questions about their efficacy for bipolar depression, virtually all mood-elevating drugs (antidepressants or stimulants) have variable, but dose-dependent, risks of inducing excited, hypomanic, manic, mixed, or psychotic states—often termed *switching*.^{91–98} A recent, comprehensive review of reports of switching risk found that rates of *spontaneous* mania or hypomania without exposure to an antidepressant averaged about 6% over undefined exposure times, and that the rate with antidepressants was twice as high, suggesting an antidepressant-specific risk of approximately 6%.⁹⁸ Although a common clinical practice, co-treatment with a mood-stabilizing agent has led to inconsistent effects, despite expectation that they can limit mood elevation.^{75,77,98}

Switching varies with specific drugs and is probably dose dependent. Highest risks are associated with older, less often used, tricyclic-type antidepressants such as amitriptyline, desipramine, imipramine, and nortriptyline.⁹⁸ Such older antidepressants are especially likely to induce switching in adults, but probably less so in juvenile bipolar depression.^{93,98} Since tricyclic antidepressants potentiate neurotransmission with both serotonin and norepinephrine, some modern drugs with similar actions, particularly venlafaxine, may also carry such risks.^{72,75} Risks of switching during treatment with other drugs that potentiate both neurotransmitters, including bicifidine, desvenlafaxine, duloxetine, milnacipran, nefazodone, and sibutramine, remain uncertain.⁸⁹ Risk of switching or destabilizing mood may be lower with selective serotonin reuptake inhibitors (such as citalopram or *S*-citalopram, fluoxetine, paroxetine, and sertraline) and possibly with bupropion,⁹⁸ which is moderately dosed and has mild stimulant-like effects.

Whether mood-elevating agents can induce mania or excitement in otherwise non-bipolar depressed patients (sometimes labeled “type III” or “unspecified [NOS]” bipolar disorder, or as having “secondary,” drug-induced mania) also remains uncertain.^{62,98} Other suggested risk factors for switching include substance abuse⁹¹ and presence of mild hypomanic symptoms or relatively severe bipolar illness.⁹⁷ Moreover, clinical prudence suggests that the presence of known or suspected bipolar disorder is an indication for extra caution in using any mood-elevating agent. Such caution is particularly appropriate among juvenile patients with apparent depressive or attention disorders, who are often given antidepressants or stimulants.^{92,93}

Risk of switching into mania or other excited states from depression may be greater in depressed juveniles than in adults, in part because bipolar disorder often is not recognized in young patients.^{23–26,92,93} This high risk seems paradoxical since antidepressants of all types, including serotonin reuptake inhibitors, have shown inferior efficacy in controlled trials for juvenile, compared to adult, depression.¹⁰⁰ Of note, risk of mood switching with a serotonin reuptake inhibitor may exceed that with a tricyclic antidepressant in juvenile depressed patients below age 14 years, suggesting important, but undefined, developmental changes in pharmacodynamics or susceptibility.^{93,94} Developmental changes also may be reflected in the limited efficacy of antidepressants in pediatric depression⁹⁹ and in the evidently increased risk of self-injurious behaviors, as well as suicidal thoughts, reported to occur in depressed patients below age 25 during treatment with modern antidepressants, in contrast to *lowered* suicidal risk in antidepressant-treated older depressed adults, especially over age 60.^{100,101}

NON-ANTIDEPRESSANT TREATMENTS FOR BIPOLAR DEPRESSION

For depressive phases of bipolar disorders, there is growing interest in alternatives to treatment with antidepressants. This interest reflects various factors: the limited short-term benefits of standard older and modern antidepressants, their poorly established long-term prophylactic value, nontrivial switching and mood-destabilizing risks, and uncertain or age-variable antisuicidal efficacy.^{71–101} Increasingly widely employed are so-called mood-stabilizing agents of all types, often without antidepressants, and in various combinations. These agents typically include certain anticonvulsants, second-generation antipsychotics, and lithium salts.^{102–116}

Lithium Salts

Lithium currently is not favored as a mood-stabilizing treatment in the United States, probably owing to the need for medical monitoring to avoid potential adverse effects, as well as to the lack of commercial promotion of this unpatentable mineral. Nevertheless, lithium carbonate continues to be widely employed internationally, and it remains a standard treatment, including use in moderate, well-tolerated doses to supplement alternative treatments. Lithium appears to have major benefits in protecting against recurrences of many components of bipolar disorders over many years of treatment.^{89,117–123} However, as with virtually all available treatments for bipolar depression, its effectiveness in the depressive, dysthymic, or dysphoric-mixed components of the illness is less clear

than against mania or hypomania. Controlled trials against placebo and active agents provide renewed support for the long-term effectiveness of lithium, including for reducing risk of recurrences of bipolar depression.^{118,120,121,123,124} Moreover, no treatment has outperformed lithium in rapid-cycling bipolar disorders, in which depression is a major component.¹²⁵

Anticonvulsants

Several drugs developed to treat epilepsy have been found useful in treating bipolar disorder patients.^{126,127} As a class, anticonvulsants vary greatly in their psychotropic effects. Only a few have been proved to have substantial antimanic or mood-stabilizing effects, sometimes including protective effects against recurrences of bipolar depression. Their future in the treatment of bipolar depression and its high suicidal risk is made uncertain by evidence from placebo-controlled trials that some anticonvulsants may increase risks of suicidal thoughts or behaviors, at least among epileptic patients.¹²⁸

Carbamazepine (Tegretol[®], Carbatrol[®], and others) has long been used to treat mania and prevent recurrences of acute episodes of bipolar disorder. Long-term use of carbamazepine continues, both internationally and (empirically) also in the United States, despite limited and uneven evidence of its long-term prophylactic benefits, and particularly uncertain efficacy against recurrences of bipolar depression.^{129–131} Carbamazepine was only recently FDA approved for use in treating acute manic or mixed states, but not for long-term prophylaxis. It produces several adverse effects, including complex teratogenic risks. Carbamazepine also is a powerful inducer of hepatic microsomal oxidases, and this property leads to rapid clearance of many drugs, including carbamazepine itself.⁹⁰ Its 10-keto-analogue, oxcarbazepine (Trileptal[®]), which is licensed for the treatment of epilepsy, is somewhat less likely to induce drug clearance and is simpler to use clinically. Oxcarbazepine is sometimes used off-label for the treatment of bipolar disorder, but its research support, especially for bipolar depression, remains very limited.^{132,133} Its active metabolite, *S*-licarbazepine, also remains an experimental agent for bipolar disorder.

In the 1990s valproic acid (Depakene[®]), especially its sodium complex, sodium divalproex (Depakote[®]), became the leading antimanic and putative mood-stabilizing agent in the United States. Its introduction strongly encouraged research on the class of antiepileptic drugs for potential psychotropic properties.^{126,127} It is a highly effective and rapidly acting antimanic agent, especially at high doses (≥ 10 mg/kg/24 hours, on a body-weight basis). It also has been used for long-term treatment of bipolar disorder patients, empirically and off-label, especially in the United States, where it is widely considered a relatively well-

tolerated and easily used alternative to lithium. Nevertheless, valproate has little evidence from controlled trials for any indication in bipolar depression and, in particular, lacks FDA approval for long-term, prophylactic use in bipolar disorders. There is some evidence, however, that it has at least moderate prophylactic efficacy, including for bipolar depression.^{134–138} It is highly teratogenic and has been associated with masculinization of young women.^{136,137}

The efficacy of lamotrigine (Lamictal[®]) as a maintenance treatment for bipolar disorder—in particular, for delaying depressive episodes—is accepted and FDA approved.^{139–143} Lamotrigine is the only agent to have received FDA approval for use in bipolar disorder without initial licensing for acute mania. Indeed, it lacks evidence of antimanic efficacy but appears to have long-term protective effects against recurrences of bipolar depression with weaker effects against recurrences of mania.¹⁴² Studies of the efficacy of lamotrigine as a monotherapy for acute bipolar depression have yielded inconsistent findings,¹⁴² but it may be helpful adjunctively in types I and II bipolar depression.¹⁴³ Its specific effects on other, common, depression-related symptoms in bipolar disorder patients, including dysthymia and the dysphoric component of mixed states, are insufficiently studied. Of note, introduction of this agent as a specific treatment for bipolar depression remains unique and historic—strongly encouraging the search for other treatments for bipolar depression.

Antipsychotics

Antipsychotic drugs, as a class, are potent and rapidly effective antimanic agents, and they have been employed, at least adjunctively, for overall management of bipolar disorder patients for decades.⁸⁹ All second-generation antipsychotic agents, except asenapine and clozapine, have regulatory approval for the treatment of mania.^{115,144–146} By contrast, some older neuroleptics had a clinical reputation for worsening or inducing depression in bipolar disorder patients,^{89,147} and the value of even modern antipsychotics to treat bipolar depression in monotherapy is uneven and inconsistent, suggesting their lack of a “drug-class effect” in that syndrome.^{116,145,146}

One of the most extensively studied of the second-generation antipsychotic agents is quetiapine (Seroquel[®]).^{116,148–158} Unique among antipsychotic drugs, quetiapine is now FDA approved not only for acute mania and mixed states, but also as a monotherapy in acute bipolar depression and as an adjunct in long-term maintenance treatment with lithium or divalproex.^{155,156} Its efficacy in bipolar depression has been supported consistently in several placebo-controlled, short- and long-term trials,^{148,149,153,158} with some evidence of beneficial effects

in bipolar II disorder^{151,156} but not in juvenile bipolar depression.¹⁵⁴

Among other modern antipsychotics, olanzapine (Zyprexa®) has limited evidence of efficacy for short- or long-term treatment aimed at bipolar depression, although it is considered effective in recurrent mania^{116,159,160} and may be effective in preventing recurrences of mixed manic-depressive episodes.¹⁶¹ It has outperformed placebo for acute bipolar depression in one of two short-term trials but lacks research support for long-term benefits in recurrences.^{159–162} In addition, the combination (Symbyax®) of olanzapine with the antidepressant fluoxetine has evidence of short-term antidepressant effects in acute bipolar depression, as noted above.^{84–88}

Among other commonly used second-generation antipsychotics, including aripiprazole,^{116,163–167} risperidone,¹⁶⁸ and ziprasidone,^{169–171} there is little, and generally disappointing, information about their long-term effectiveness for treating bipolar depression. We found no reports of controlled trials of asenapine, clozapine, iloperidone, or paliperidone for treating either acute or recurrent bipolar depression.

Combinations of Drugs

Owing to the difficulty of preventing recurrences of bipolar disorder, especially its depressive phases, it has become a common clinical practice to employ combinations of treatments, or *polytherapy*, empirically. However, other than the combination of fluoxetine with olanzapine,^{84–88} few such combinations are FDA approved or have even been tested for added effectiveness or safety.^{129,130,172–176} Moreover, complex treatment regimens, especially if employed long term, almost surely contribute to inconsistent treatment adherence, increase risk of adverse effects and drug interactions, and generate increased costs—all further complicated by the unknown effects of intermittently altered treatments on the course of bipolar disorders.^{3,66}

Additional Experimental and Nonpharmacological Treatments

A currently popular treatment for bipolar disorder is to add the anti-narcoleptic, mild-stimulant agent modafinil (Provigil®) to mood-stabilizing regimens, although the efficacy and safety of this off-label approach are not clear.¹⁷⁷ There is also inconsistent evidence that adding oils enriched with omega-3 fatty acids (in particular, eicosapentanoic and docosahexaenoic acids) to standard mood-stabilizing treatments may be beneficial, especially for bipolar depression.^{178–180}

In addition to psychotropic drugs, electroconvulsive therapy (ECT), alone or with an antidepressant, has been used to treat various phases of bipolar disorders. The efficacy of ECT in bipolar disorder may be somewhat inferior to that in unipolar depression, particularly with respect to the manic and psychotic components sometimes associated with bipolar depression.^{181–183} Some psychotropic drugs interact with ECT: anticonvulsants can prevent ECT-induced seizures, and ECT can induce cerebral intoxication in the presence of lithium.^{89,181}

Another approach without regulatory approval, and with limited research support, is sleep deprivation as a means of initiating early depression-relieving effects.¹⁸⁴ Studies of psychosocial and rehabilitative efforts aimed specifically at bipolar depression remain strikingly rare.^{185,186} Treatments used or proposed for bipolar depression are summarized in the text box on the next page.

Drug Discontinuation

An important risk of long-term treatment with virtually all psychotropic medicines is that of discontinuation-associated relapses or recurrences of the illnesses being treated. Recurrence of anxiety is well known to follow discontinuing benzodiazepines and many other sedative-hypnotics, as is increased risk of seizures when anticonvulsants are discontinued in epileptic patients.⁹⁰ Much earlier than expected, and possibly more severe, new illness episodes have been documented following discontinuation of lithium,^{187–190} antipsychotics,¹⁹¹ and antidepressants.¹⁹² Rapid discontinuation of antidepressants in patients with bipolar disorder is sometimes followed by mania.¹⁹³ Early recurrence is much more likely when drug discontinuation is abrupt or rapid, as is likely to happen before or early in pregnancy.^{63,189,191}

METHODS OF TESTING NEW TREATMENTS

Patients diagnosed with bipolar disorders present particular challenges for inclusion in treatment trials—challenges that are less common in patients with unipolar major depression. Bipolar disorder patients typically are characterized by clinical complexity, rapid affective and behavioral changes, high risk of relapses and recurrences, and the potential for clinical worsening in response to some treatments, including antidepressants.^{2,3} In addition, high levels of comorbidity, disability, chronic symptoms, and risk of mortality among bipolar disorder patients add further complexity to studies of their treatment.^{194–197} All of these factors need to be considered in the rational design and safe conduct of trials of experimental treatments—including the need for consistent nomenclature for outcomes in experimental treatment trials.¹⁹⁸

Treatments for Bipolar Depression	
Treatments	Current Status
FDA-approved indications	
Lithium salts	Long-term: “recurrences” of bipolar I disorder (mania emphasized; depression <i>not</i> specified); may be effective in recurrent and acute types I and II bipolar depression. ^{117–124}
Divalproex	Antimanic only (short term), though often used without regulatory approval (“off-label”) for maintenance treatment. ^{134–138}
Carbamazepine	Antimanic only (short term; may be less effective than other options) ^{129–133}
Lamotrigine	Long-term only (minimally antimanic), with best evidence for protection against depressive recurrences. ^{139–143}
Olanzapine + fluoxetine	For short-term use in acute bipolar depression; its use has a low risk of mania. ^{84–88}
Quetiapine	Short term and adjunctively long term (with lithium or divalproex): for bipolar depression (as well as acute mania or mixed states), with emerging evidence of possible utility in unipolar depression. ^{148–157}
Empirical extensions of indications in unipolar major depression	
Antidepressants	Not specifically approved for bipolar depression (unipolar depression only) but had been used empirically in bipolar disorders despite greatly increased risk of switching, especially over age 14. ^{66–101}
Experimental treatments	
Other antipsychotics	All appear to be antimanic; older agents may worsen or induce bipolar depression; most are poorly tested in bipolar depression. ^{116,159–171}
Omega-3 fatty acids	May be effective (adjunctively) in bipolar depression. ^{178–180}
Modafinil	Limited evidence, but some empirical, for adjunctive use. ¹⁷⁷
Electroconvulsion	Not specifically FDA approved for any indication, but commonly used in otherwise treatment-resistant depression, with extensive empirical evidence of effectiveness in bipolar depression and mania. ^{181–183}
Sleep deprivation	May increase initial response during antidepressant treatment. ¹⁸⁴
Psychosocial	Limited formal study. ^{185,186}

It also needs to be kept in mind that treatments that are effective in treating acute mania or depression, or that are given long term to protect from recurrences, can increase the risk of earlier and possibly more severe new episodes of illness soon after they are *discontinued*, especially if discontinued abruptly or rapidly. In addition to the clinical implications of such discontinuation-induced relapse, this phenomenon probably affects modern trials that include discontinuation to a placebo, as in testing the continued efficacy of an initially effective treatment.¹⁸⁸ The effects of treatment discontinuation on bipolar depression specifically, as well as possible means of limiting its impact on the risk of early relapse or recurrence, remain poorly tested. However, prudence indicates that rapid discontinuation of any apparently successful treatment presents risk of provoking a relapse, especially among (typically) slowly recovering bipolar disorder patients. Discontinuation of treatment—other factors being equal—should be avoided and may represent an ethical challenge by adding clinical risk. The conflict is further complicated by the unwillingness of many

bipolar disorder patients to give up antidepressant treatment or to accept a placebo for fear of potential depressive illness.³

Despite these complexities, most modern antimanic and proved or proposed mood-stabilizing agents have been established as generally and acceptably safe and effective in large, randomized, controlled, experimental treatment trials of various designs. Nevertheless, it is uncertain whether currently standard trial designs can be adapted easily to produce adequate assessments of treatments for bipolar depression. Characteristics of bipolar disorder patients call for innovative trial designs that (1) can assess the degree and timing of improvement or recovery from an acute bipolar-depressive episode, (2) take into account the risks of spontaneous or drug-associated switching into excited states, and (3) evaluate the effects of continued *long-term* treatment to protect against recurrences of major depression or dys-thymia, other affective states, or self-injurious behaviors.¹⁹⁰ In addition, it would be useful to include complex patients commonly encountered clinically, such as those with

comorbid conditions,² so as to provide more generalizable findings. It may also be helpful to consider use of more than one treatment at a time in trials, as is increasingly common in clinical practice.^{172,195} Finally, it remains challenging to select a standard treatment for comparison since none is firmly established for bipolar depression.

Additional complications for the design of experimental therapeutic studies include the limited ability of standard diagnostic schemes to distinguish clinically important *subgroups* of bipolar disorder patients. DSM-IV currently includes types I and II, and narrowly defined rapid-cycling and mixed-state subgroups.⁵ Furthermore, common conceptions of juvenile bipolar disorder may be overly modeled on typical adult presentations.^{24–26,92} Standard rating scales, developed primarily to score symptoms of unipolar major depression, may not be as well suited for studies of bipolar depressed patients, especially those with minor mania-like features or subtle mixed states. Also lacking are rating methods sensitive to symptoms such as anergy, hypersomnia, or hyperphagia, which are common in bipolar depression but considered atypical in unipolar depression.^{28,199}

Long-term trials—lasting more than a year and testing for prophylactic effectiveness for recurrences of bipolar major depression, dysthymia, or dysphoric mixed states—are rare in the current experimental therapeutics literature.^{109,142} Moreover, their designs may not adequately provide guidance for treating typical bipolar disorder patients at various phases of their illnesses. Many reported studies involve initial “enrichment”: they usually require initial short-term response of acute illness to a particular treatment prior to studying continued treatment versus its discontinuation, often before clinical recovery is secure, and for relatively brief follow-up times that rarely exceed a few months.^{137,141,142} Treatment “effectiveness” typically is considered to be reflected in latency to an endpoint—for example, to a first relapse or recurrence of illness, or to a clinical intervention. Such endpoints are convenient but rely on the statistical method of *survival analysis*, which has not specifically been tested to support time-to-endpoint as an adequate surrogate measure of long-term morbidity.²⁰⁰ Instead, adequate assessments of long-term morbidity in bipolar disorder patients may require many months, if not years.^{3,47,200}

Emerging treatments—notably including some mood stabilizers (especially lamotrigine, lithium, and perhaps valproate) and some second-generation antipsychotic drugs (especially quetiapine), alone or in selected combinations—can be at least partially effective in the treatment or prevention of recurring bipolar depression. Less is known about their long-term effects on dysthymia or the dysphoria of mixed states. These treatments are almost surely more useful and safer than traditional antidepressants, which appear to be grossly overused for bipolar disorder patients, partic-

ularly in the United States.^{65,66,77} Despite a growing list of partially effective treatment options for bipolar depression (see preceding text box on treatment), this syndrome commonly resists satisfactory responses to available mood-altering or -stabilizing treatments. It is therefore not surprising that bipolar disorder patients with prominent and treatment-resistant depression often end up with largely untested, complex combinations of treatments, typically involving mood stabilizers, antipsychotics, antidepressants, stimulants, or sedatives.^{172–176} Such polytherapies are relatively expensive and risk unpredictable drug interactions and adverse effects. Nevertheless, it is a common clinical practice for more difficult-to-treat disorders to involve more complex treatment regimens, despite a lack of evidence to support their effectiveness or safety.

CONCLUSIONS

As a general conclusion, we underscore the points that bipolar depression is very common, often misdiagnosed, and generally poorly responsive to available treatments. Moreover, it is the component of bipolar disorder that most patients find especially troubling and frightening. Bipolar depression is also strongly associated with comorbidity, disability, and premature mortality. It is reassuring that there has been a recent awakening of interest in this important, unsolved challenge for modern psychiatric therapeutics. Finally, it is essential to strive to make appropriate distinctions among various forms of depression, dysthymia, or dysphoric mixed states in bipolar disorder, and to differentiate them diagnostically, prognostically, and therapeutically from ordinary unipolar major depressive disorder.

Declaration of Interest: Dr. Baldessarini has recently consulted to, or collaborated in investigator-initiated research with, Alkermes, AstraZeneca, Auritec, Biotrofix, Eli Lilly, IFI, Janssen, JDS-Noven, Luitpold, Merck, NeuroHealing, Novartis, Pfizer, and Solvay corporations; he is not a member of any corporate speakers' panels; neither he nor immediate family members hold equity relationships with pharmaceutical or biotechnology corporations. Dr. Vieta has received grants, and has been a consultant or speaker for, AstraZeneca, BristolMyers-Squibb, Eli Lilly, Forest, GlaxoSmithKline, Janssen-Cilag, Jazz, Lundbeck, Novartis, Organon, Otsuka, Pfizer, Sanofi-Aventis, Schering-Plough, Servier, UBC, and Wyeth corporations. Dr. Calabrese has received research support from, consulted to, or contributed to continuing medical education activities with Abbott, AstraZeneca, BristolMyers-Squibb, Cephalon, Dainippon-Sumitomo, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Johnson & Johnson, Ortho-McNeil, Repligen, Solvay-Wyeth, and Supernus corporations, as well

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