

Pharmacotherapy of Bipolar Depression: An Update

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Bipolar affective disorder is a virulent illness with high rates of recurrence, disability, social impairment, and suicide. Although the manic or hypomanic episodes define the disorder, the depressions are more numerous and less responsive to treatment. As the initial depressive episodes are commonly misdiagnosed, initiation of therapy with mood stabilizers is often delayed, increasing the likelihood of treatment-emergent affective switches on antidepressant monotherapy. The empirical basis for selecting treatments for people with bipolar depression is weak, and only the combination of olanzapine and fluoxetine has received US Food and Drug Administration (FDA) approval. Conventional mood stabilizers are preferred for first-line therapies, although atypical antipsychotics are increasingly used, and FDA approval of quetiapine is pending. Antidepressants—particularly selective serotonin reuptake inhibitors and bupropion—are indicated when mood stabilizers are ineffective and for “breakthrough” depressions.

Introduction

Bipolar affective disorder is one of the world's 10 greatest public health problems [1]. For most, bipolar disorder begins in adolescence or young adulthood and runs a recurrent course; more often than not, it is a life-altering illness that is characterized by difficulties with relationships, periods of vocational disability, increased medical morbidity, and reduced longevity [2–4]. Although the disorder is distinguished by the manias, there is increasing evidence that it is the depressions that more typically dominate the longitudinal course disorder and are more difficult to treat [5•]. Suicide, which eventually may end the life of one in 10 people with bipolar disorder, primarily

occurs during depressed or mixed illness episodes [6]. For all of these reasons, optimal treatment of bipolar depression is a topic of considerable importance to psychiatrists. This article will provide a brief overview of the phenomenology and course of bipolar depression and an update on recent developments in therapeutics.

Bipolar disorder is more common than previously appreciated

As the lifetime incidence of mania is only approximately 1% [7], it was once widely believed that bipolar disorder was a relatively uncommon condition, accounting for between 5% and 10% of all mood disorders. However, more recent evidence suggests that hypomania is much more common than mania, with up to 6% of the population meeting criteria for bipolar II disorder [8,9]. If true, up to one half of all people seeking treatment for “depression” may have conditions that fall within a broader bipolar spectrum [10].

Bipolar depressions are often misdiagnosed

As will be discussed subsequently, the differential diagnosis between bipolar and nonbipolar depressions has critical prognostic and therapeutic implications. Of greatest importance, whereas it is the standard of care to prescribe an antidepressant alone for treatment of major depressive disorder (MDD) or dysthymia, antidepressant monotherapy is widely considered to be contraindicated for treatment of bipolar depression because of the risk of treatment-emergent affective switches (TEAS) and induction of rapid cycling. Thus, in order to avoid these complications, early recognition and accurate diagnoses are essential to proper management of bipolar depression. Although this statement may seem to most psychiatrists to be so self-evident as to border on banality, there is strong evidence that bipolar disorder is frequently misdiagnosed. For example, more than two thirds of the membership of the National Depressive and Manic-Depressive Association (now known as the Depression and Bipolar Support Alliance) reported that they initially had been diagnosed with—and treated for—other different mental disorders, with an average time between onset of symptoms and correct diagnosis of approximately 9 years [11]. Not surprisingly, MDD was by a large margin the most common misdiagnosis in this survey [11]. Such a protracted delay in initiation of appro-

appropriate therapy can have devastating effects for younger patients with bipolar disorder, who—with an average age of onset of 19—are often in the midst of making the transition from adolescence to young adulthood. As illustrated by the histories of the early-onset patients in the Systematic Treatment Evaluation Program for Bipolar Disorder (STEP-BD), the largest descriptive study of bipolar disorder ever undertaken, the consequences included reduced educational and subsequent vocational attainment, increased likelihood of comorbid substance abuse, and delays of developmental milestones such as emancipation from one's family of origin or engaging or maintaining stable intimate adult relationships [4].

Depression often dominates the course of bipolar disorder

Although there is no dispute that manic and hypomanic episodes can be more florid and more often warrant urgent clinical attention, it also is true that the average person with bipolar disorder suffers more numerous depressive episodes and that these episodes are typically longer in duration. In fact, in the STEP-BD project's 2-year follow-up, depressive relapses were about four times more likely during preventive therapy than manias and hypomanias. Similarly, in a 10-plus-year naturalistic follow-up study, bipolar I patients spent three to five times more days depressed than they spent manic or hypomanic [12]. For the participants with bipolar II disorder, the ratio of days spent depressed to days spent hypomanic was on the order of 9:1 [13]. When projected across a lifetime, people with bipolar disorder will “lose” 15 years to depression.

The longer duration of bipolar depressive episodes (as compared with manias or hypomanias) has been known for decades and was demonstrated in observational studies dating back to the time of Kraepelin (see Goodwin and Jamison [14]). However, this phenomenon may actually be exacerbated in the modern era because bipolar depressive episodes also tend to be less responsive to standard therapies than manias [5•]. For example, in a treatment study of bipolar I disorder conducted by our group at the University of Pittsburgh Medical Center, it took approximately twice as long for patients presenting with depressive episodes to remit than it did for those whose index episode was mania, despite treatment by expert psychiatrist/psychotherapist teams following well-characterized treatment algorithms [15,16]. Not only were depressive episodes slower to respond to treatment, they also were associated with a greater likelihood of treatment resistance, as reflected by failure to remit across at least 1 year of continuous treatment [15,16].

Improving recognition of bipolar disorder

Although not yet proven prospectively, it is hoped that better recognition and more vigorous treatment early in the course of bipolar depressive episodes will improve longer-term outcomes, including lessening the likelihood

of disability and lowering the risk of premature death. With respect to achieving more accurate diagnosis of bipolar disorder, there is a paradox: Whereas a majority of patients report that their illness was initially misdiagnosed—sometimes repeatedly—modern psychometric studies have demonstrated that mania can be diagnosed with high reliability (for example, see American Psychiatric Association [17]). The problem of incorrect diagnosis is partly the result of the natural history of the illness: Depressive episodes precede manias more often than not, sometimes by years. Without some sort of clinical “sixth sense,” it may not be possible to divine that that teenager or young adult experiencing a first or second episode of major depression will subsequently experience a manic or hypomanic episode. As such, until sensitive and specific biomarkers are developed that distinguish bipolar from unipolar depression, some number of cases of “misdiagnosis” will be unavoidable.

Another source of diagnostic unreliability is diagnosis of bipolar II disorder. Whereas mania is widely recognized as a pathologic state (ie, principal differential diagnoses are other severe mental disorders, including schizophrenia and acute substance-induced psychotic episodes), hypomania can be much more subtle. In fact, bipolar individuals almost never seek treatment for hypomania, and many perceive hypomanic states as their “best,” most productive times. As such, asking depressed patients about a history of “mood swings” often misses the point. When there is no history of clear-cut mania, clinicians need to ask about behavioral indicators that are indicative of behavioral excess or disinhibition, which can be viewed as proxies of bipolarity [10,18]. Suggested behavioral constellations or clusters include signs of intemperance, such as polysubstance abuse (ie, alcohol and two or more drugs) or multiple affairs or divorces, as well as multiple comorbid anxiety and/or personality (especially the *DSM-IV* Cluster B) disorders [19].

Clinical features of the index depressive episode also can be suggestive of an increased likelihood of bipolarity. Early-onset depressions are more likely to fall within the bipolar spectrum, as are those that appear to have a rapid or “out-of-the-blue” onset [14]. The so-called “atypical” or reverse neurovegetative features (eg, increased appetite, weight gain, and hypersomnolence)—which are hardly atypical features in early-onset depressions—also are more common in bipolar depression [5•,20]. When an early-onset depression is accompanied by psychotic features such as delusions and hallucinations, there is an even greater risk that the patient will eventually experience a manic episode [21]. Clinically discrepant features within the depressive episode, such as racing thoughts or increased libido, similarly are associated with a greater risk of switching from nonbipolar to bipolar disorder over time [19,22,23].

Recognition of “latent” bipolarity also can be increased by interviewing the depressed patient's spouse,

parents, or other significant others. Although their impressions should not “trump” the history provided by the depressed patient, hypomanic episodes often are mood congruent, and significant others may be better able to differentiate these as distinct from the patient’s so-called “best” or usual way of functioning. Parents and siblings also can be helpful in completing a comprehensive family history. This can be particularly important because, all other things being equal, a positive family history of bipolar disorder was a powerful predictor of bipolarity in early-onset depressions [24]. Beyond a family history of clear-cut bipolar I disorder, clinicians should be looking for other psychiatrically relevant events that increase the index of suspicion, including multiple family members with treated episodes of depression, suicide or suicide attempts, and psychiatric hospitalizations for “nervous breakdowns” or episodes thought to be schizophrenia.

Pharmacotherapy of Bipolar Depression: State of the Art

For a variety of reasons, it is much more difficult to follow the principles of evidence-based medicine to treat bipolar depression than it is to treat MDD or mania [5•]. For starters, there are few comparative randomized controlled trials (RCTs) of various first-line treatments for bipolar depression (see, for example, reviews by Thase [5•] or Gijnsman et al. [25•]). In fact, until recently, there was much less activity in development of novel therapies for all aspects of bipolar disorder when compared with schizophrenia (which is about as common as bipolar I disorder) or MDD. For example, lithium was the only medication specifically approved by the US Food and Drug Administration (FDA) for treatment of bipolar disorder between 1970 and 1994. The landscape changed dramatically following the FDA approval of enterically coated valproate (divalproex) for treatment of mania in 1994, and during the past decade, all five of the widely used atypical antipsychotics (olanzapine, quetiapine, risperidone, ziprasidone, and aripiprazole) and an extended-release formulation of carbamazepine have been approved for treatment of mania, with the anticonvulsant lamotrigine approved for prevention of depressive and manic episodes in bipolar I disorder. By contrast, only a single therapy—the proprietary (fixed-dose) combination of olanzapine and the antidepressant fluoxetine (hereafter referred to as olanzapine-fluoxetine combination [OFC])—has been approved for acute treatment of bipolar depression.

As I have discussed elsewhere, the scarcity of efforts to establish effective treatments for bipolar depression largely resulted from the now-revised FDA policy to view antidepressants as broadly effective for all forms of clinical depression. Thus, without a specific indication for bipolar depression, it was far easier for the pharmaceutical industry to focus its registration studies on establishing

efficacy for MDD [5•]. It also is true that studies of bipolar depression are more difficult to execute, and few studies were conducted by investigators without industry support. With growing recognition that identification of better treatments for bipolar depression is one of psychopharmacology’s greatest unmet needs, the FDA approval of OFC for the specific indication of bipolar depression has set the stage for a new generation of research.

Although only a handful of RCTs on bipolar depression have been completed, there is no shortage of consensus-based expert treatment guidelines for management of bipolar depression. In the United States, for example, clinicians may consult the documents prepared by the American Psychiatric Association [26], the Expert Consensus Guideline Series [27], or the Texas Consensus Panel on Medication Treatment of Bipolar Disorder [28]. However, the recommendations of these guidelines provide only a starting point, and as studies of novel therapies begin to emerge, revising practice strategies to incorporate new evidence is an ongoing process. For the sake of efficiency, the review will first focus on treatment of bipolar I depressions, followed by the more limited evidence on bipolar II depressions.

Mood Stabilizers

Monotherapy with mood stabilizers is widely considered to be the foundation of treatment for bipolar I depression. A mood stabilizer was traditionally defined as a medication that treats mania, prevents manic and/or depressive relapses, and does not induce TEAS. Lithium salts, valproate, and carbamazepine are the three conventional mood stabilizers. More recently, the definition of mood stabilizer was expanded to take into account the unique therapeutic profile of lamotrigine, which apparently prevents manic and depressive relapses without treating acute mania [29]. Although none of these medications has received FDA approval for treatment of bipolar depression, lithium and valproate are recommended as first-line choices for milder episodes of bipolar I depression in all three US practice guidelines, and for depression-prone patients, there is growing enthusiasm for lamotrigine [26–28].

The “mood stabilizer-first” strategy largely reflects the fact that although there is only limited evidence from RCTs of bipolar I depression, mood stabilizers sometimes treat depression and, when effective, are not associated with an increased risk of TEAS (unlike antidepressants) and subsequently will be needed for preventive therapy [26–28]. However, despite almost uniform agreement that mood stabilizers should be the foundation for treatment of bipolar disorder, there is evidence that clinicians often opt for other strategies. In fact, in a survey conducted by the American Psychiatric Association’s research practice network, approximately one third of the bipolar patients were not prescribed a mood stabilizer [30].

Lithium

Although lithium is certainly an “old” medication, there are several important reasons for continuing to consider it to be the mood stabilizer of first choice for treatment of bipolar I depression, and it may well continue to be the standard of comparison for years to come. Beyond its 40-plus-year track record of clinical use for treatment of bipolar disorder, lithium is the only member of the mood stabilizer class with established efficacy in bipolar depression, as determined by multiple positive, placebo-controlled RCTs [31]. In one of the few modern studies to evaluate lithium alone versus the combination of lithium and an antidepressant, combined therapy was not significantly more effective than lithium alone, and monotherapy did particularly well among the treated patients with blood levels of at least 0.8 mEq/L [32]. Perhaps most importantly, lithium also is the only treatment of bipolar disorder that has been shown to decrease the risk of suicide and suicidal behavior [6]. In the study of Goodwin et al. [33] that examined the health care utilization patterns of more than 21,000 patients with bipolar disorder, lithium-treated patients were significantly less likely to attempt suicide, require hospitalization for suicidal behaviors, or complete suicide than were bipolar patients treated with either valproate or carbamazepine.

However, lithium is far from a perfect treatment, and a significant minority of patients experience unacceptable side effects, and only a small proportion of patients will both adhere to treatment and remain well indefinitely on lithium monotherapy [26–28]. Common side effects include diarrhea and other gastrointestinal side effects, cognitive dulling, tremor, exacerbation of acne, and weight gain; the need for regular blood work and longer-term risks of hypothyroidism and interstitial nephropathy further diminish enthusiasm for lithium therapy. Moreover, although lithium therapy may lessen the risk of suicide, lithium itself has a relatively low safety index in overdose.

Valproate

For largely commercial reasons, valproate has largely replaced lithium as the first-line therapy for bipolar disorder in the United States [33,34]. Despite such widespread use, valproate has not been nearly as well studied as lithium for treatment of bipolar I depression [5•]. In fact, there is only a single, small published positive study of acute phase therapy [35]. Some further evidence of efficacy in bipolar I depression is found in a secondary analysis of patients treated acutely for mixed mania [36] and in the longer-term follow-up of patients receiving preventive valproate therapy following acute phase antimanic therapy [37].

As with lithium, tolerability can be a major limitation of valproate therapy. In addition to nausea and other gastrointestinal side effects, weight gain, changes in hair growth (both alopecia and hirsutism), and men-

strual irregularities can be particularly problematic for younger women. Whether valproate therapy is associated with development of polycystic ovary syndrome, as opposed to an unwanted pharmacologic virilizing effect, is not yet resolved [38]. Blood monitoring is needed, and valproate therapy has been associated with a reduction in platelet count (relatively common), elevated liver function studies (relatively common), and pancreatitis (relatively rare).

Lamotrigine

As previously noted, the therapeutic profile of lamotrigine—which lacks antimanic efficacy—necessitated changing the definition of a mood stabilizer [29]. Although widely believed to have efficacy for treatment of bipolar I depression, the widespread and increasing clinical use of lamotrigine has surpassed the state of the evidence from RCTs. In fact, of the three published studies of acute phase therapy in the literature, only two are positive [39,40]. In the first study, lamotrigine at 200 mg/d was superior to placebo, with the 50-mg/d dose showing evidence of efficacy on some measures. The second trial, which employed a complex crossover design in a predominantly bipolar group of patients with treatment-resistant depression, found lamotrigine—but not gabapentin—to be an effective treatment compared with placebo. Lamotrigine therapy was not associated with an increase in TEAS (as compared with placebo) in either trial.

The one other published RCT found some evidence of lamotrigine in bipolar depression. In this trial, which was conducted by the investigators of the STEP-BD [41], lamotrigine, the atypical antipsychotic risperidone, and inositol (an “active” placebo) were studied as “add-on” therapies in 64 bipolar I and II patients who had not responded to therapy with lithium or valproate in combination with paroxetine and/or bupropion. Treatment was randomized but open label, and patients continued to take mood stabilizers and antidepressants. None of the study therapies was particularly effective, which should not be surprising given the highly treatment-resistant nature of the patient group. The difference between lamotrigine and the comparison groups was not significant on the primary dependent measure, remission rates, which were as follows: lamotrigine, 24%; inositol, 17%; risperidone, 5%. However, the study did not have the statistical power to detect modest between-group differences, and lamotrigine did result in advantages on several secondary measures, including a depressive symptom severity score and a measure of global functioning.

In addition to these trials, the manufacturer has “posted” on its website the results of three more unpublished, placebo-controlled studies of lamotrigine therapy of bipolar depression; all three trials failed on the primary dependent measure. When considered together, the overall evidence base supporting the use of lamotrigine

as a monotherapy for bipolar depression is mixed, and it is my understanding that the manufacturer will not attempt to obtain FDA approval for this indication (ie, two studies with positive results on the primary dependent measure generally have been required for an indication as an antidepressant).

Thus, for the time being, the only official indication of lamotrigine therapy is for prevention of relapse (both depression and mania) in bipolar I disorder. The basis of this indication comes from two 18-month, placebo-controlled RCTs [42•,43•]. In both of these trials—one focused on patients recovering from mania [42•] and the other enrolling patients with resolving bipolar I depressive episodes [43•]—lamotrigine significantly reduced the risk of depressive relapses. In relative terms, the effects of lamotrigine were superior to lithium for protection against depressive relapses and numerically less than lithium for protection against manic relapses [44•]. Nevertheless, in the pooled data set, although the effects for prevention of manic relapse were smaller, a significant protective effect against manic relapses when compared with placebo was found [44•].

One other published study is noteworthy because it evaluated lamotrigine therapy in patients with rapid-cycling bipolar I and II disorders [45]. In this study, patients were stabilized on open-label lamotrigine therapy, and efficacy was evaluated in treatment responders ($n = 182$) utilizing a 6-month, placebo-controlled discontinuation design. The study failed to demonstrate a significant protective effect on the primary dependent measure. Efficacy was apparent on a number of secondary measures, including the proportion that did not relapse during the double-blind phase (relapse rates: lamotrigine, 59%; placebo, 74%). Further, lamotrigine therapy was significantly more effective than placebo in the subset of patients with rapid-cycling bipolar II disorder. The most common interpretation of the latter finding is that lamotrigine was relatively more effective in the bipolar II patients (as compared with bipolar I patients) because of its more limited efficacy for mania.

In terms of day-to-day side effects, lamotrigine clearly has the most favorable tolerability profile, and it is much less likely to cause sedation, tremor, or weight gain at therapeutic doses than either lithium or valproate. Moreover, therapeutic drug monitoring is not required. However, there is one very serious potential problem: Lamotrigine therapy is associated with a relatively high rate of benign rash (~ 5% to 10%) and an uncommon risk (~ 0.1%) of serious and potentially fatal dermatologic reactions such as Stevens-Johnson syndrome (SJS) [46,47]. It is unfortunate that even experienced dermatologists may not be able to tell the difference between the benign and serious rashes at first, and thus, every new-onset rash must be treated as if it will become SJS, and the medication must be discontinued immediately. This is particularly true because the duration of lamotrigine therapy after the onset of rash is one of the

strongest predictors of which rashes will progress. Prescribers must impress upon patients and their parents that all rashes should be taken very seriously, and lamotrigine therapy must be stopped, at least temporarily, at the first sign of rash. To further lessen the risk of serious rash, lamotrigine therapy must be initiated at a low dose (ie, 25 mg/d unless the patient is taking valproate or carbamazepine, in which case doses of 12.5 and 50 mg/d are initiated to take into account metabolic interactions) and thereafter titrated slowly upward. Additional caution in titration is needed with youths, who are at greater risk. Finally, as a rapid rise in lamotrigine blood levels can trigger the onset of a rash, slow titration is again needed any time there has been a gap in lamotrigine therapy of more than a few days.

Carbamazepine

Although carbamazepine never has been as widely used as lithium or divalproex, clinical interest in it has recently increased somewhat following FDA approval of an extended-release formulation of this compound for treatment of mania. Carbamazepine has been shown to have modest antidepressant effects in several small studies and may have particular utility among patients with rapid-cycling bipolar disorder (see, for example, Post et al. [48]). Less well tolerated than lithium, valproate, and lamotrigine, carbamazepine continues to be recommended in guidelines primarily for patients with treatment-resistant or rapid-cycling forms of bipolar disorder.

Are the Atypical Antipsychotics Also Mood Stabilizers with Antidepressant Effects?

Following the approval of all of the atypical antipsychotics (except clozapine for treatment of mania), the potential utility of this class as mood stabilizers and, more specifically, for treatment of bipolar depression began to be evaluated. Evidence to emerge to date suggests that the definition of what constitutes a mood stabilizer will yet again need to be modified and that at least some of these compounds can exert antidepressant effects without conveying the risk of TEAS.

The efficacy of olanzapine for treatment of bipolar I depression was first evaluated in a large ($n = 833$) placebo-controlled RCT [49•]. In this trial, olanzapine monotherapy was found to have a modest but statistically significant advantage compared with placebo on both continuous and categorical measures of depression, and was not associated with a significant risk of TEAS compared with placebo. However, olanzapine monotherapy was significantly less effective than the combination of olanzapine and fluoxetine; in fact, the advantage of OFC over olanzapine alone was of the same magnitude as the difference favoring olanzapine alone over placebo [49•]. Of note, the advantage of OFC over olanzapine alone was not associated with any greater risk of TEAS. As a result

of this study, OFC—not olanzapine—was approved by the FDA for treatment of bipolar I depression.

The comparative efficacy of OFC and lamotrigine was evaluated in a large ($n = 410$), two-stage, double-blind RCT of patients with bipolar I depression. Results of the 7-week acute phase recently have been published [50•]. OFC was titrated up to 12 to 50 mg/d, and lamotrigine was titrated up to 200 mg/d. Efficacy analyses favored OFC on continuous measures of depressive symptoms and time to response, although final response rates did not differ significantly (OFC, 69%; lamotrigine, 60%). Of note, although neither treatment was associated with a high risk of TEAS, OFC therapy resulted in a significantly larger reduction in mania rating scale scores than lamotrigine therapy. Tolerability indices, by contrast, strongly favored lamotrigine therapy, with lower rates of sedation, tremor, increased appetite, and weight gain, as well as less effect on measures of serum lipids and cholesterol.

A second atypical antipsychotic, quetiapine, also has been shown to have antidepressant effects in bipolar depression. In fact, on the basis of two recent, large, positive RCTs, quetiapine may well have become the first monotherapy approved by the FDA for treatment of bipolar depression by the time that this article is published. Both placebo-controlled RCTs examined the efficacy of two doses of quetiapine (300 mg/d and 600 mg/d) in samples including bipolar I (~ two thirds of patients) and bipolar II (~ one third of patients) depressions [51•,52•]. Both studies were positive, with effect sizes for quetiapine monotherapy of approximately the same magnitude (vs placebo) as were observed for OFC (vs placebo). There was no advantage whatsoever for the 600-mg/d dose of quetiapine over the 300-mg/d dose on any outcome measure, and tolerability indices generally favored the lower-dose group. As such, the 300-mg/d dose group clearly had the better efficacy/tolerability profile. Pooling results of the two studies, quetiapine was an effective treatment for patients with bipolar I and bipolar II depressions, including those with a history of rapid cycling and those with high levels of concomitant anxiety.

The major liabilities faced by bipolar patients taking olanzapine and quetiapine are sedation and weight gain and associated metabolic effects, including dyslipidemia and glucose intolerance. Although there have been no comparative studies yet undertaken in patients with mood disorders, there is fairly good evidence from studies of schizophrenia that olanzapine is associated with a greater risk of weight gain than quetiapine [53,54], although differences in grouped data can be small comfort to the individual patient. It also is likely that the effects of these medications on weight are somewhat increased when olanzapine or quetiapine are used in combination with lithium or valproate. In practice, it is imperative to warn patients that weight gain is a real risk—perhaps up to one half of patients will gain an unacceptable amount of weight, and it is equally important to monitor weight closely

during therapy. Generally, patients who do not gain weight during the first 6 to 8 weeks of therapy will not have a significant problem during longer-term therapy. When therapy is effective and there is evidence of weight gain, clinicians must be prepared to either change the medication or require that the patient participate in dietary counseling and regular exercise in order to minimize the chances that a small, “acceptable” amount of weight gain doesn’t become a large and unacceptable problem. Laboratory monitoring of glucose, triglycerides, and other lipids during therapy with these atypical antipsychotics also has become a standard of practice.

With respect to the other atypical antipsychotics, none has yet shown significant antidepressant effects in controlled studies of bipolar depression, although research is ongoing. As previously noted, risperidone was singularly ineffective in one small study of “add-on” therapy of antidepressant-resistant bipolar depression [41], although studies as a first-line therapy would be preferred to assess efficacy in less difficult to treat patients. Aripiprazole, ziprasidone, and—to a lesser extent—risperidone all have more favorable metabolic tolerability profiles than quetiapine and olanzapine, although none of the three is as sedating, and each has unique alternate considerations.

Re-examining the role of antidepressants

Any discussion among experts on the role of antidepressants for treatment of bipolar depression is likely to generate a lively dialogue. Whereas there is clear agreement among US practice guidelines that antidepressants alone are contraindicated for treatment of bipolar I depression [26–28], there is little consensus about how long they should be held in reserve and, if prescribed and apparently effective, how long they should be maintained. Moreover, there is basically no consensus on the proper role of antidepressants for patients with bipolar II depression.

With respect to bipolar I depression, there is some agreement in US guidelines that antidepressants are indicated as “add-on” therapies following nonresponse to mood stabilizers or when a depressive episode has “broken through” during maintenance therapy with a mood stabilizer [26–28]. Many experts also will consider using antidepressants earlier in the course of therapy for treatment of more severe depressive episodes (eg, Keck et al. [27]).

With respect to selecting specific types of antidepressants, there is also wide agreement that tricyclic antidepressants (TCAs) should only be used for treatment of bipolar depressive episodes that have not responded to all of the major classes of newer antidepressants [26–28]. There are two reasons for this recommendation: TCAs are associated with a higher incidence of TEAS in bipolar depression than other antidepressants [25•], and, when compared with newer medications, the TCAs are associated with a substantially greater risk of lethality in overdose [55].

In the United States, the selective serotonin reuptake inhibitors (SSRIs) and bupropion are widely regarded as the antidepressants of first choice [26–28]. The SSRIs (listed in order of FDA approval for MDD: fluoxetine, sertraline, paroxetine, citalopram, and escitalopram) are the most widely prescribed class of antidepressants and, with the single exception of escitalopram, are now available in less-expensive generic formulations. The SSRIs generally are well-tolerated medications (ie, in RCTs of MDD, between 90% and 95% of patients are able to complete a therapeutic trial), and—of particular importance for treatment of bipolar depression—the SSRIs are associated with only a small risk of TEAS, at least when prescribed for patients who do not have a history of rapid cycling [25•,32,49•,56•,57]. The SSRIs also have a relatively broad spectrum of efficacy that includes many of the disorders that are comorbid with bipolar depression, including anxiety disorders and bulimia [5•,26–28].

Beyond the cost difference between escitalopram and the generic formulations of the other SSRIs, the rationale for picking one member of the class over the others is largely based on preference and patient history of response or intolerance. Although it is technically correct to assert that only fluoxetine has received FDA approval for the specific indication of bipolar I depression, it also is true that fluoxetine therapy is only approved for this indication when used in combination with olanzapine. A case for fluoxetine also can be made because of the long elimination half-life of its active metabolite (norfluoxetine), which can lessen the impact of adherence and largely eliminates the risk of discontinuation symptoms following abrupt cessation of therapy. However, a long elimination half-life also can prevent rapid withdrawal of antidepressant therapy, which often is indicated when patients cycle into severe manic states.

Bupropion is a norepinephrine-dopamine reuptake inhibitor (NDRI) that is unrelated to all other antidepressants. Bupropion, like the SSRIs, is available in generic formulations and has not been associated with a high risk of TEAS in studies of bipolar depression [56•,58,59]. Head-to-head trials versus SSRIs in MDD suggest comparable efficacy [60]. In the only study directly comparing bupropion and an SSRI in bipolar depression, the NDRI and sertraline were comparably effective [56•].

Bupropion is primarily distinguished from the SSRIs in terms of tolerability profiles and spectrum of efficacy for associated comorbid disorders. Most importantly, bupropion has a much more favorable sexual side effect profile than any of the SSRIs and, in fact, may be no more likely than an inert placebo to cause anorgasmia, diminished libido, or erectile dysfunction [60]. In contrast to the SSRIs, bupropion does not have established efficacy in any anxiety disorder and is considered by the manufacturer to be contraindicated for treatment of patients with eating disorders (this is because self-

induced vomiting may cause electrolyte imbalances that can lower seizure threshold, which is a concern because bupropion therapy at doses above 450 mg/d has been associated with an increased risk of seizures). With respect to associated comorbidities, bupropion has been approved as an adjunctive therapy for smoking cessation and, unlike the SSRIs, has been found to have some therapeutic activity for attention-deficit hyperactivity disorder [61].

Venlafaxine, the first antidepressant introduced in the United States to be called a serotonin and norepinephrine reuptake inhibitor (SNRI), typically is used for bipolar depression patients who have not responded to SSRIs and bupropion [26–28]. Despite a strong track record of efficacy in comparative studies versus SSRIs [62,63], venlafaxine is generally placed in a second-line slot because of issues of cost (generic formulations are not yet available in the United States) and tolerability. Perhaps most importantly, venlafaxine therapy was associated with higher rates of TEAS—and no greater efficacy—in head-to-head studies of bipolar depression versus paroxetine [64] and sertraline [56•]. It is not yet known if the second SNRI to be introduced in the United States, duloxetine, will be a useful treatment for bipolar depression [5•].

The nonselective, irreversible monoamine oxidase inhibitors (MAOIs), most particularly tranylcypromine [65,66], are held in the highest regard for the most difficult to treat bipolar depressions, as they have the strongest track record of efficacy for difficult-to-treat episodes of bipolar depression. Broader use of these venerable medications is, of course, limited by issues of acceptability, tolerability, and safety, foremost among these being the need for dietary restrictions to avoid hypertensive crises (the so-called “cheese effect”). Another problem stems from the potential for a potentially serious drug-drug interaction with SSRIs and SNRIs affecting central nervous system serotonin neurotransmission known as the serotonin syndrome. As such, the older MAOIs cannot be used in combination with these medications and should not be started without at least a 1-week washout (at least 4 weeks for fluoxetine) [67].

The value of the MAOIs for difficult-to-treat depressions has fostered continued research to try to develop safer medications, which has led to the recent introduction of the patch formulation of selegiline. Although at antidepressant doses, selegiline also is an irreversible, nonselective MAOI, administration via skin patch greatly reduces the potential for dietary interactions. Specifically, the mechanism of the “cheese effect”—inhibition of the A form of the MAO enzyme in the small intestine prevents degradation of tyramine and other vasoactive amines—is essentially bypassed by transdermal administration of the medication. Although the studies of adults with MDD have examined transdermal delivery in doses up to 12 mg/24 h without evidence of hypertensive crises [68], thus far the FDA has only approved the lowest dose for treatment

without dietary restrictions, largely because of insufficient evidence of safety at higher doses. As clinical experience with this “new” medication is limited and there have been no studies in bipolar depression or studies of SSRI nonresponders, it is uncertain if the seligiline patch will replace the older MAOIs, or if there will still be a need for medications such as tranylcypromine for the most difficult to treat bipolar depressions.

Is bipolar II depression really different?

As noted previously, there is no consensus about the best way to treat bipolar II depression [26–28]. In the absence of controlled studies and expert consensus, I recommend that bipolar II depressions be treated according to the patient’s clinical course and past treatment history [5•]. It is suggested that patients with bipolar II depression should be viewed in relation to a continuum, ranging from a prototypic nonbipolar depressive disorder on one end to a classical bipolar I depression on the other. Thus, if the patient’s hypomanias have been mild and infrequent, and there is no history of antidepressant resistance or TEAS, antidepressant monotherapy may be chosen. Consistent with this approach, several studies have documented successful treatment of bipolar II depressions with antidepressants alone [69–72]. Should the patient’s history suggest clinical problems with hypomania—or if the patient should develop a TEAS or rapid cycling on antidepressant monotherapy—mood stabilizers and, if warranted by severity, atypical antipsychotics should be initiated before considering antidepressants [5•].

Preventing relapse: mood stabilizers alone or combined with antidepressants?

Given the high rate of depressive relapse, as well as the amount of time that bipolar patients spend depressed during longitudinal follow-up, successful acute phase therapy should be viewed as only a starting place. For most, if not all, a preventive treatment regimen will need to be initiated and indefinitely maintained.

Among the mood stabilizers, there is no doubt that lithium has the longest track record and best evidence of efficacy, even though lithium has better efficacy for prevention of mania than depressive episodes [73,74]. After lithium, lamotrigine has the best evidence of preventive efficacy, with two positive relapse-prevention trials (see Goodwin et al. [44•]). The different therapeutic profiles of lithium and lamotrigine also are suggestive of the potential for additive efficacy for patients who relapse despite monotherapy. Although less extensively studied and without formal FDA indication for prophylactic therapy, both valproate and carbamazepine are likely to convey some protection against depressive relapse.

Although both olanzapine and quetiapine have recently been shown to have antidepressant efficacy in bipolar depression, studies of the longer-term relapse prevention effects are still ongoing. Even if prophylactic

efficacy is established, problems with weight gain and other metabolic complications will necessitate careful monitoring to minimize risks.

The evidence supporting longer-term use of antidepressants for relapse prevention in bipolar depression is simply not sufficient to justify routine use [5•]. When antidepressants have been prescribed (in combination with mood stabilizers) for acute phase therapy, there is no consensus as to the recommended duration of preventive therapy [27]. As not a single study of longer-term therapy has been conducted with modern antidepressants, the findings of a prospective naturalistic study conducted by the Stanley Network investigators may well be the most relevant [75•]. Based on the judgment of the treating clinician, patients who respond to acute phase antidepressant therapy could either be withdrawn or remain on medication for a variable length course of preventive treatment. This type of clinician’s choice design typically is biased against the more complex strategy (ie, the patients with the best prognoses typically do better with less-intensive treatments, whereas the more difficult to treat patients typically do worse despite receiving the more intensive therapies). Despite this bias, Altshuler et al. [75•] found that patients who received briefer courses of antidepressants were significantly more likely to relapse than patients who received longer courses of antidepressants. Moreover, the protective benefit of continued antidepressant treatment was associated with a negligible increase in risk of mania [75•]. When response to an antidepressant has been clear cut—and there is no evidence of cycling—maintenance antidepressant therapy may significantly improve the longer-term outcomes of at least a subset of patients with bipolar depression.

Conclusions

One of the world’s greatest public health problems, bipolar affective disorder, often immutably changes the life of the person with the illness and causes significant relationship problems, vocational disability, and impairments of quality of life. Although defined by the manias and hypomania, the more numerous, persistent, and often—treatment-resistant depressive episodes typically exact the greater toll on people with the disorder and their significant others. Recurrent and unremitting depressions also are the proximal cause of suicide, unarguably the most tragic outcome of bipolar disorder. Misdiagnosis and inappropriate treatment conspire to ensure that only a minority of bipolar depression patients actually benefit from available therapies. After decades of relative neglect, treatment of bipolar depression is increasingly recognized as one of the major unmet needs in contemporary psychopharmacology. Until better therapies are identified, milder bipolar I depressions should be treated first with mood stabilizers, including lithium salts, valproate, and lamotrigine. Atypical antipsychotics such as olanzapine

and quetiapine soon may be considered appropriate alternatives to these mood stabilizers for first-line therapy of bipolar I depression, particularly with careful monitoring to minimize weight gain and other metabolic side effects. When mood stabilizers and atypical antipsychotics are ineffective, SSRIs and bupropion are the preferred antidepressants. In fact, the combination of olanzapine and fluoxetine is currently the only form of pharmacotherapy that has received FDA approval for treatment of bipolar I depression. Treatment of bipolar II depression is even less well studied and, until adequate data are available, may be best guided by the patient's history and response to previous courses of antidepressant medication. When antidepressants are prescribed to patients with bipolar I or II depression, ongoing monitoring is necessary to ensure that the risks of TEAS and cycle acceleration are minimized.

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