Reevaluating Therapies for Bipolar Depression

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The most commonly employed pharmacotherapies for bipolar depression include antidepressants, lithium, and anticonvulsants, such as lamotrigine, valproate, and carbamazepine. A combination of these agents, usually an antidepressant and a mood stabilizer, is often required to achieve an optimal response. However, some treatment guidelines still caution that antidepressant exposure should be minimized in patients with bipolar depression, due to concern that they may trigger treatment-emergent mania or cycle acceleration. This advice prevails despite data showing that antidepressants are effective in treating bipolar depression and evidence that coadministration of a mood-stabilizing medication, at least with modern antidepressants, such as the selective serotonin reuptake inhibitors, can reduce the risk of treatment-emergent mania to levels comparable with those observed with mood stabilizer monotherapy. Although the antidepressant efficacy of most mood stabilizers has not been satisfactorily proven, first-line therapy with 1 mood stabilizer alone or a combination of 2 mood stabilizers is still recommended by many guidelines. Inappropriate treatment of bipolar depression may leave patients at high risk of suicide and increased chronicity of symptoms; effective therapy should, therefore, be provided as early as possible. The efficacy and safety of antidepressants for bipolar depression both as monotherapy and when combined with a mood stabilizer should be studied in adequately powered trials in order to revise treatment guidelines. Electroconvulsive therapy remains an option for treatment-refractory patients and those intolerant to pharmacologic treatment, as well as patients who are pregnant or at high risk of suicide. *(J Clin Psychiatry 2005;66[suppl 5]:17–25)*

Despite the substantial burden associated with bipolar depression,[1–4] pharmacologic options for its acute treatment remain limited, and its management poses a major clinical challenge. Lithium, lamotrigine, valproate, carbamazepine, antidepressants approved for the treatment of unipolar depression, and their combinations are often employed. However, few of these approaches can be recommended with substantial clinical confidence because the evidence base for their use in bipolar depression is limited.

The use of antidepressants in bipolar disorder, in particular, continues to be controversial, particularly the relative risk of inducing mania, hypomania, or cycling acceleration versus their potential benefit in the treatment of depressive symptoms.[5,6] Most experts agree that antidepressant monotherapy for bipolar depression is inappropriate.[7–9] When antidepressants are used to treat bipolar depression, coadministration with a mood stabilizer is usually recommended to reduce the risk of treatment-emergent mania.[7–9] Nevertheless, evidence shows that the prescription of antidepressants as monotherapy for bipolar depression is widespread (Figure 1),[10] suggesting a disconnect between expert thinking and general clinical practice. A reason underlying the overprescription of antidepressants may include familiarity with and confidence in their use, especially in view of their widespread use in treating unipolar depression in the primary care setting.

Differences exist in expert opinion and guidelines regarding when, for how long, and in which patients to use antidepressants,[7–9,11] which may be preventing the adoption of more appropriate treatment strategies. There is a need, therefore, for clear guidance regarding the use of antidepressants in bipolar disorder.

This article reevaluates the evidence supporting the role of antidepressants in the management of bipolar depression alongside the key alternatives, namely lithium, valproate, carbamazepine, lamotrigine, and electroconvulsive therapy (ECT). Olanzapine[12] and quetiapine[13]—the only atypical agents to have data from adequately powered trials of efficacy in bipolar depression—are reviewed elsewhere in this supplement.[14]

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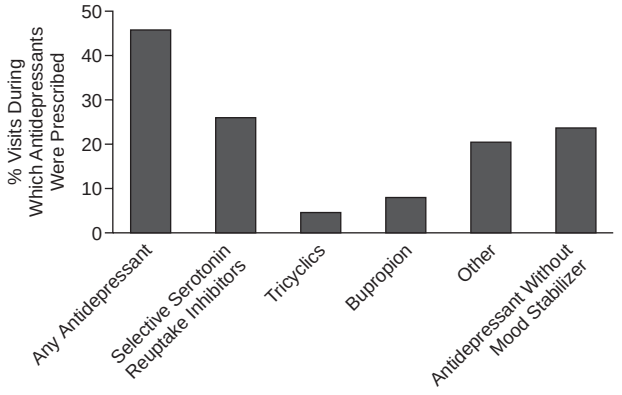
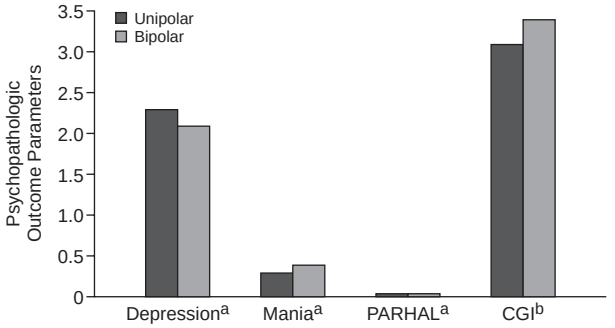
Figure 1. The Prevalence of Antidepressant Monotherapy Prescription for Patients With Bipolar Disorder During the Period 1996–1999[a]



[a]Data from Blanco et al.[10]

Figure 2. Comparison of Treatment Outcome at Discharge Between Inpatients With Unipolar Depression (N = 50) and Bipolar I Depression (N = 50) Treated for an Acute Episode, Matched With Respect to Age, Duration of Illness, and Gender



[a]Data from Bottlender et al.[20] [b]H.G., unpublished data. Outcome parameters included the depressive and manic subscales of the Association for Methodology and Documentation in Psychiatry (AMDP) system, the paranoid-hallucinatory (PARHAL) subscore of the AMDP, and the Clinical Global Impression (CGI).

USE OF ANTIDEPRESSANTS FOR BIPOLAR DEPRESSION

Current Controversies

While most experts believe that, at least in severe cases, antidepressants should be used for bipolar depression, several aspects of their use continue to prompt debate.[11,15] Although a good evidence base exists for the efficacy of antidepressant monotherapy in the treatment of unipolar depression, this is not the case in bipolar depression. Most antidepressant studies exclude patients with bipolar disorder. The relatively few that include patients with bipolar disorder also include those with unipolar depression and do not always include a separate subanalysis.

Uncertainties exist over the relative risk for different antidepressants to induce mania/hypomania or to accelerate cycling. Therefore, any benefit in functioning and reduction in risk of suicide that may be gained from the use of antidepressants cannot be accurately balanced against the risks. The issue is further compounded by the lack of a consistent definition for a treatment-emergent manic episode as opposed to natural cycling, so that delineating the true risk of treatment-emergent mania associated with antidepressant use is difficult. There is also uncertainty over when to discontinue antidepressant medication after response.[16,17] This situation presents a dilemma for physicians treating patients with bipolar disorder, especially in patients at high risk of suicide, who may not respond to first-line treatment. At least in such cases, the use of antidepressant cotherapy appears justified.

This set of issues, reviewed below, has prompted an increased awareness that a reevaluation of the relative benefits and liabilities of antidepressants in bipolar depression is needed.

Efficacy of Antidepressants in Bipolar Depression

Some evidence, albeit observational, for the comparability between antidepressant efficacy in unipolar versus bipolar depression comes from a large, retrospective analysis of 2032 inpatients treated for an acute depressed episode using, in most patients, monotherapy with a tricyclic antidepressant (TCA).[18] Both the Clinical Global Impression ratings and changes in the depressive and manic subscales of the Association for Methodology and Documentation in Psychiatry system[19] found no differences between patients with unipolar and bipolar depression in any outcome parameter (Figure 2).[20] Furthermore, coadministration of a traditional mood stabilizer (usually lithium) did not appear to influence outcome. However, adequately controlled evidence for the efficacy of antidepressants in acute bipolar depression is limited.

Both an early trial and a more recent placebo-controlled trial indicated that imipramine has some efficacy in treating bipolar depression.[21,22] For newer antidepressants, studies suggest that the selective serotonin reuptake inhibitors (SSRIs) fluoxetine[21] and paroxetine,[22] reversible and irreversible monoamine oxidase inhibitors (MAOIs),[23,24] as well as bupropion[25] are superior to placebo or have similar or higher efficacy compared with imipramine or desipramine in treating bipolar depression. Although venlafaxine and paroxetine have similar efficacy in patients with bipolar depression, they have a differential propensity to induce mania, with paroxetine showing a tolerability advantage over venlafaxine[26] (Table 1). Consequently, the newer antidepressants are used more often for treating bipolar depression. However, the TCAs, such as imipramine and desipramine, may still be useful in treating patients with severe and psychotic depression.[31]

Table 1. Summary of Studies on Antidepressant Use in Bipolar Disorder Discussed in This Review[a]

Clinical Trial	Number of Patients	Comparators and Doses	Duration	Efficacy Parameters	Overall Efficacy	Treatment-Emergent Mania
Amsterdam[27]	17	Once versus twice daily venlafaxine (37.5 to 225 mg/d)	6 wk	Change from baseline HAM-D score	Venlafaxine: 14 points	Venlafaxine: 0%
Amsterdam and Garcia-Espana[28]	15	Once versus twice daily venlafaxine (37.5 to 225 mg/d)	6 wk	Reduction in HAM-D ≥ 50%	Venlafaxine: 63%	Venlafaxine: 0%
Cohn et al[21]	89	Fluoxetine (20 to 80 mg/d) Imipramine (75 to 300 mg/d) Placebo	6 wk	≥ 50% improvement on HAM-D after at least 3 wk of study drug	Fluoxetine: 86% Imipramine: 57% Placebo: 38%	Fluoxetine: 0% Imipramine: 6.7% Placebo: 3.4%
Fogelson et al[29]	11	Bupropion (mean maximum dose 286 mg; range, 100–450 mg)	6 wk	Response evaluated on the GAF	Moderate-to-marked response: 7/11 patients (63.6%) No/minimal response: 4/11 patients (36.4%)	Bupropion: 55%
Himmelhoch et al[23]	56	Tranylcypromine (20–60 mg/d) Imipramine (100–300 mg/d)	6-wk acute treatment + 10-wk continuation phase	Response defined as CGI score of 2/3 sustained for at least 2 wk	Tranylcypromine: 81% Imipramine: 48%	Tranylcypromine: 12% Imipramine: 24%
Nemeroff et al[22]	117	Paroxetine (20–50 mg/d) Imipramine (50–300 mg/d) Placebo	10 wk	Response defined as HAM-D score ≤ 7 or CGI global improvement score ≤ 2	Paroxetine: 45.5% Imipramine: 38.9% Placebo: 34.9%	Paroxetine: 0% Imipramine: 7.7% Placebo: 2.3%
Sachs et al[25]	19	Bupropion (358 ± 62 mg) Desipramine (140 ± 46 mg)	8 wk + 1-y follow-up	Response defined as 2 or more wk during which HAM-D scores were improved by ≥ 50% from baseline	Bupropion: 63% Desipramine: 71%	Bupropion: 11% Desipramine: 50%
Silverstone[24]	156	Moclobemide (450–750 mg/d) Imipramine (150–250 mg/d)	8 wk	HAM-D change from baseline	Moclobemide: 9.9% Imipramine: 13.0%	Moclobemide: 3.7% Imipramine: 11%
Thase et al[30]	16	Tranylcypromine (> 30 mg/d) Imipramine (> 150 mg/d) Crossover study from imipramine to tranylcypromine and vice versa	6-wk continuation phase following Himmelhoch et al[23] (1991)	Beck Depression Inventory; HAM-D score	Imipramine to tranylcypromine: 75% Tranylcypromine to imipramine: 25%	Mania: 1/16 patients (6.3%)
Vieta et al[26]	60	Paroxetine (20–60 mg/d) Venlafaxine (75–450 mg/d)	6 wk	Response: ≥ 50% decrease from baseline to endpoint HAM-D score	Paroxetine: 43% responders Venlafaxine: 48%	Paroxetine: 3% Venlafaxine: 13%

[a]Articles that are mentioned in the text but do not present data specific to a subgroup of patients with bipolar disorder or those that are meta-analyses are not included.
Abbreviations: CGI = Clinical Global Impression, GAF = Global Assessment of Functioning scale, HAM-D = Hamilton Rating Scale for Depression.

The SSRIs have been evaluated in only a small number of controlled clinical trials involving patients with bipolar depression. In a 6-week, double-blind, placebo-controlled study,[21] patients (N = 89) with acute bipolar I depression who were receiving fluoxetine (20–80 mg/day) showed a significantly greater response rate (improvement of ≥ 50% on Hamilton Rating Scale for Depression [HAM-D]) compared with those receiving imipramine (75–300 mg/day) or placebo (86%, 57%, and 38%, respectively; $p \leq .04$). The discontinuation rate was also significantly greater with imipramine than fluoxetine (30% vs. 7%; $p = .02$). Although no treatment effect was established in the primary analysis of a double-blind, placebo-controlled, but underpowered (N = 117) study by Nemeroff and colleagues,[22] in which paroxetine, imipramine, or placebo were added to lithium treatment, a secondary analysis found that in patients with low plasma lithium levels, paroxetine was significantly better than placebo and was better tolerated than imipramine.

The MAOIs have been shown to be effective in treating acute bipolar depression in a limited number of trials and to be at least as effective as the TCAs imipramine or desipramine.[23,24,30,32] However, safety and tolerability issues limit the utility of irreversible MAOIs in patients with bipolar disorder.[33]

The novel antidepressant bupropion has not been well studied in acute bipolar depression. In a double-blind study of 19 patients by Sachs et al.,[25] bupropion was comparable to desipramine as an initial therapy, achieving a response rate of 63%, compared with 71% for desipramine. A similar response rate was observed in an open trial of 11 patients with bipolar I disorder after 6 weeks of therapy.[29] Despite the limitations of these small studies, bupropion often ranks highly in treatment algorithms, probably due to some evidence for a low risk of treatment-emergent mania, as described later.

A recently reported large, randomized, controlled study directly compared the modern antidepressants venlafaxine, bupropion, and sertraline in terms of their antidepressant response—both acutely (10 weeks) and during a 1-year continuation phase for responders—when administered in combination with a mood stabilizer.[34] In the acute phase, patients on sertraline treatment had the highest (55.3%) response rate, where response was defined as "much improved" or "very much improved" on the Clinical Global Impression Bipolar Version (CGI-BP) depression improvement score. The response rates for trials of bupropion were 48.0% and for venlafaxine 43.0%. Approximately 38% of antidepressant trials resulted in the patients entering the continuation phase, and around two thirds of these patients sustained their antidepressant response.

Overall, therefore, the available evidence suggests that standard antidepressants have efficacy in bipolar depression. This finding has recently been confirmed by a Cochrane meta-analysis conducted by Gijsman et al.,[35] which systematically assessed the evidence from 12 randomized, controlled trials involving 1088 patients. The authors concluded that antidepressants are effective in the short-term treatment of bipolar depression. However, the relative lack of controlled evidence for their use in bipolar depression compared with unipolar depression is a justifiable barrier to their general acceptance as first-line monotherapy option for bipolar depression. Further prospective, rigorously controlled trials need to be conducted to confirm the efficacy of the antidepressants in this group of patients. However, until effective alternatives are developed, the limited evidence for the efficacy of antidepressants in bipolar depression should not be a premise on which to dismiss them from the treatment portfolio for bipolar depression.

Spontaneous Switching

Polarity switching occurring during the natural course of the illness may confound the assessment of risk of treatment-emergent mania and cycle acceleration. A prospective evaluation of the long-term symptom status among 156 patients with bipolar I disorder showed that the polarity of symptoms changed more than 3 times per year in 54.1% of patients, more than 5 times per year in 34.9% of patients, more than 10 times per year in 11.6% of patients, and more than 20 times per year in 5.5% of patients.[36]

Distinguishing between treatment-emergent mania and mania due to other causes, including spontaneous switching, is made difficult by the lack of an agreed and consistently applied definition for what constitutes a hypomanic/manic episode and the maximum time period after beginning antidepressant treatment during which emergence of mania/hypomania can be attributed to an effect of medication. Definitions are also needed to help clinicians recognize cycle acceleration brought about by medication. Longitudinal data on the natural switch rate and cycle frequency should facilitate more accurate estimates of the frequency by which antidepressants induce these events. Until these issues are resolved and further studies are performed, it is difficult to compare switch rates for different antidepressants. Studies must employ consistent definitions, and any comparisons between studies should take into account differences in study populations, duration of follow-up, and concomitant use of mood-stabilizing agents. There is some suggestion that the severity of antidepressant-induced mania may differ between antidepressant classes, but this requires further study.[37–39] In addition, a fair estimate of the proportion of patients switching with an antidepressant compared to placebo can only be made for the responders, as treatment outcome and switch probability are dependent variables. This factor has generally been neglected in reports on switch rates.[40]

Treatment-Emergent Mania

Core to the controversy surrounding the use of antidepressants in bipolar depression is the risk of treatment-emergent mania or cycle acceleration.[15] Although all antidepressants appear to carry this risk to some extent in patients with bipolar depression,[15] antidepressants seem to differ in their propensity to induce mania. Rates of up to 70% have been reported in patients with bipolar disorder treated with antidepressants without a mood-stabilizing medication.[41,42] However, at the time when these rates were reported, first-generation TCAs, heterocyclics, and MAOIs were the only options.

More recently, several studies have concluded that SSRIs appear to have a much lower risk of treatment-emergent mania compared with TCAs and MAOIs[42–44] and that the risk can be sufficiently controlled, but not completely eliminated, by the addition of a mood-stabilizing medication.[45] In particular, low switch rates have been reported for paroxetine.[26,46] The use of MAOIs is often limited by side effects and, for irreversible MAOIs, by the requirement to adhere to a tyramine-free diet. The SSRIs are often chosen instead of MAOIs due to their relative ease of use (simple dosage titration), good tolerability, low toxicity in overdose, and apparently lower risk of inducing a switch to mania or hypomania.

Bupropion is an alternative to SSRIs and has a relatively low risk of weight gain and sexual side effects. Bupropion also appears to have a lower risk of switch to mania. After over a year of double-blind treatment, Sachs et al.[25] reported significantly less mania with bupropion (1/9; 11%) than with desipramine (5/10; 50%), but comparable antidepressant efficacy. However, not all studies have confirmed this lower rate of switching with bupropion.[29]

In a randomized trial comparing paroxetine and venlafaxine in the treatment of patients with bipolar (I or II) depression taking mood stabilizers, there was an apparent increased risk for treatment-emergent mania/hypomania with venlafaxine.[26] This potentially higher risk of treatment-emergent mania associated with venlafaxine compared with an SSRI (e.g., sertraline) and bupropion was also confirmed in the study by Leverich et al.[34]

On the other hand, reasonable and substantiated doubt has been raised regarding whether the switch risk with antidepressants is a true finding or a myth, and more related to the natural course of illness and statistical issues.[40,41] In addition, the withdrawal of antidepressants has also been associated with mania.[47] If a switch risk exists at all, it appears lowest with the SSRIs, MAOIs, and bupropion and highest with TCAs, but may be in most instances statistically, but not clinically, significant.[43] A recent meta-analysis could also not establish a significant switch risk,[35] but the low number of studies that have examined antidepressant-induced mania and the small size of some of the studies limit confidence in any conclusions and underline the need for further controlled, prospective studies.

Antidepressants for Bipolar II Depression

The treatment of bipolar II disorder with antidepressants is another understudied area, and most recommendations for the treatment of bipolar II depression are derived from findings of studies that have included patients with bipolar I depression. Two studies that provided some evidence of the efficacy and safety of venlafaxine in bipolar disorder included patients with bipolar II depression[27,28] and suggest that venlafaxine may have potential in the treatment for bipolar II depression with a low rate of treatment-emergent mania (Table 1). Amsterdam and Brunswick[48] have suggested that for some patients with bipolar II depression, antidepressant monotherapy may be permissible. As bipolar II depression is diagnostically distinct from bipolar I depression, adequately powered, controlled, prospective trials are needed to decipher the best treatment approaches for bipolar II depression.

Individual Susceptibility to Treatment-Emergent Mania

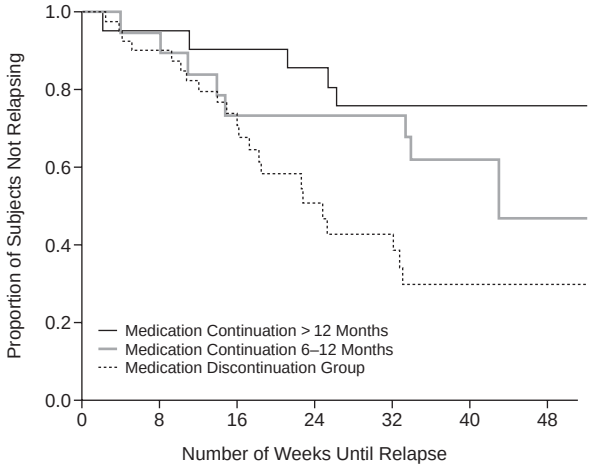
Some patients with bipolar depression may be more susceptible than others to treatment-emergent mania and cycle acceleration during antidepressant use. Potential clinical characteristics considered as predictors of switch susceptibility include female gender, bipolar I versus bipolar II diagnosis, and a known history of antidepressant-induced mania.[15] Future studies are needed to discern these characteristics and to determine whether the contribution of each in predisposing a patient to treatment-emergent mania differs across antidepressant classes. Their findings should help formulate guidelines regarding which class of antidepressant may represent the most effective choice for certain patients.

Optimal Duration of Antidepressant Treatment

Many treatment guidelines recommend that antidepressants be discontinued within the first 2 to 6 months after remission of depressive symptoms.[49] However, recent evidence suggests that antidepressant discontinuation may itself be detrimental because it may increase the risk of depressive relapse.

In a retrospective study of 44 patients with bipolar disorder who were treated for an episode of acute bipolar depression with the addition of an antidepressant to an ongoing mood stabilizer regimen, termination of antidepressant treatment within the first year of remission significantly increased the risk of depressive relapse within that year.[16] Continuation of the antidepressant was not associated with a higher risk of relapse into mania. The findings from this study were replicated in a larger, prospective study that specifically compared antidepressant discontinuation within 6 months of improvement versus antidepressant continuation beyond 6 months of improvement.[17] All patients previously responded on acute antidepressant treatment, and, again, antidepressants were used in combina-

Figure 3. Time to Relapse Among Subjects With Bipolar Disorder Who Discontinued Antidepressant Treatment Within 6 Months of Depressive Episode Remission, Continued for 6–12 Months, or Continued Beyond 12 Months[a]



[a]Reproduced with permission from Altshuler et al.[17]

tion with mood stabilizers. The study found that a shorter duration of antidepressant exposure following successful treatment was associated with a significantly shorter time to depressive relapse (Figure 3). The risk of manic relapse was not significantly associated with continued use of antidepressants and was substantially less than the risk of depressive relapse. Maintenance of combination therapy with a mood stabilizer and an antidepressant may be warranted in patients whose acute bipolar depression was unresponsive to mood stabilizer alone, but was successfully treated with the addition of an antidepressant. An often quoted limitation of the study is that the sample was highly selective for acute antidepressant response and did not include rapid-cycling patients. On the other hand, this implies that the analysis of switch rates is based on responders, which is the statistically correct approach to estimate the true switch rate as discussed by Angst and Gamma.[40] The findings suggest a potential need to reexamine guidelines that recommend discontinuation of antidepressants as early as possible after treatment response.

Regardless of the treatment used, bipolar disorder is a chronic illness that requires lifelong treatment, and clinicians should consider both the acute and long-term efficacy and safety of a medication when selecting a treatment for an acute episode.

ALTERNATIVES TO ANTIDEPRESSANTS

Lithium

Lithium is recommended as first-line therapy for acute bipolar depression in several guidelines.[9,10] Early studies in bipolar depression indicated that lithium has antidepressant effects superior to placebo and is more effective in bipolar than unipolar depression.[50–53] Although not all patients in those trials achieved a full response, and many of the studies had methodological weaknesses,[54] overall, the research supports the efficacy of lithium over placebo for bipolar depression.[55,56]

However, the clinical effectiveness of lithium treatment for acute bipolar depression is modest. The capacity of lithium to protect patients from suicide during the long term is well established,[57] but this antisuicidal effect is not acute and develops over time, taking 6 to 8 weeks or more.[58] In addition, discontinuation of lithium may cause a significant increase in suicide risk.[59] Thus, lithium monotherapy may not always be sufficient in patients with moderate-to-severe bipolar depression with a high suicide risk. The utility of lithium for bipolar depression is also diminished by untoward side effects, including tremor, thirst, gastrointestinal irritation, and cognitive dulling. In the long term, weight gain and renal, thyroid, and cardiovascular side effects may also occur. These side effects can lead to poor adherence, and patients are often reluctant to continue taking the medication once they feel better. Moreover, lithium has a narrow therapeutic dose range, and routine monitoring of plasma concentrations is required. Recommended levels exceeding 0.8 mmol/L are often needed for maximal effect, but this dose is often associated with a poor tolerability profile. Lithium is associated with neurotoxicity even at doses close to its therapeutic range. A further concern is that abrupt lithium discontinuation may induce relapse,[60] and there is some suggestion that long-term lithium therapy may worsen depressive symptoms.[61] It is also unclear how the antidepressant effect of lithium in bipolar depression compares with that of the newer generation antidepressants, as no controlled head-to-head trials have been published to date.

Lamotrigine

The 2002 revised American Psychiatric Association (APA) practice guidelines recommend lamotrigine as a first-line treatment for bipolar depression, with moderate clinical confidence.[9] This is primarily based on the results of 1 randomized, double-blind clinical trial comparing 2 doses of lamotrigine (50 and 200 mg) with placebo for the acute treatment of 195 patients with bipolar I depression.[62] A clinical response (defined as ≥ 50% reduction in baseline score on the secondary outcome measure, the Montgomery-Asberg Depression Rating Scale [MADRS]) was noted for 48% and 54% of patients treated with low-dose and high-dose lamotrigine, respectively, significantly greater than placebo (29%).[62] These results yielded effect sizes of 0.49 for lamotrigine 50 mg/day and 0.67 for lamotrigine 200 mg/day by week 7 of treatment (G. Evoniuk, Ph.D., written communication).

Studies have demonstrated more convincingly that lamotrigine is effective as maintenance therapy.[63,64] A limita-

tion associated with lamotrigine, however, and an important consideration in the treatment of acute bipolar depression, is the need to slowly titrate the dose upward to avoid rash.[65]

Valproate

Evidence for an acute antidepressant effect of valproate in bipolar disorder is limited. In an uncontrolled, open pilot study[66] involving 19 patients with bipolar II depression, valproate appeared to have antidepressant activity, with 63% (12/19) of patients responding (> 50% decrease in HAM-D ratings). In an 8-week, double-blind pilot study of bipolar I and II patients with major depression, Sachs et al.[67] found that patients treated with valproate had a recovery rate (50% improvement on the HAM-D and a Young Mania Rating Scale [YMRS] score < 10) of 43% compared with a placebo rate of 27%, although the difference was not statistically significant. A further limitation with valproate is that, at doses needed to maximize its antidepressant efficacy, side effects such as nausea, gastrointestinal distress, sedation, and tremor may occur.

Carbamazepine

Similar to the investigation of valproate, very few studies have examined the efficacy of carbamazepine in treating acute depression. A review of several small, double-blind, placebo-controlled studies suggested that carbamazepine does have antidepressant effects, with modest, but statistically significant reductions in depressive symptoms.[53] However, in another study,[68] the response rate for carbamazepine did not appear to be better than that expected for placebo. Thus, carbamazepine is not recommended as monotherapy for acute bipolar depression, but can be a useful option as a prophylactic treatment in combination with other agents. Side effects with carbamazepine use include sedation, tremor, double vision, weight gain, and rash.

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) is an effective nonpharmacologic treatment for bipolar depression and achieves a higher response rate than many pharmacologic options.[52,69] Due to its rapid onset of action, ECT is a valuable alternative in treating patients with severe and psychotic depression, especially those with a high risk of suicide. ECT is also an important and valuable treatment option for bipolar depression accompanied by severe psychomotor retardation, bipolar depression refractory to pharmacologic treatment,[53,70–72] pregnant women with bipolar depression,[58] and patients with drug intolerance.[71] Bilateral ECT appears to be more favorable than unilateral ECT.[73]

Despite its high success rate in treating bipolar depression, ECT is typically not used until after failure with 1 or more antidepressants.[71] Reasons for this include the prohibitive costs associated with its use and patients' and the public's negative perceptions of the effectiveness and safety of ECT. Electroconvulsive therapy is opposed by many consumer groups,[74,75] and public opinion is a likely factor in its variable use between different countries. Levels of perceived benefit differ considerably between patient-led studies and clinical studies. Some patients who receive ECT report memory loss,[76] sometimes severe and persistent. However, it would appear that physicians do not perceive the memory loss to be a substantial problem[77] as it may be wrongly attributed to ECT. Future studies need to be a collaborative effort between patient organizations and clinicians and should investigate patient-valued outcomes, including patient-perceived effectiveness and patient satisfaction, as well as autobiographical perceived memory loss.

SUMMARY AND CONCLUSIONS

Bipolar depression is associated with considerable suffering, disability, and mortality and medical morbidity. Current treatment of acute bipolar depression frequently involves lithium; the anticonvulsants carbamazepine, valproate, and lamotrigine; and antidepressants. However, despite recent evidence derived from a Cochrane meta-analysis, the use of antidepressants in the treatment of bipolar depression appears controversial.

Besides ECT, antidepressants are probably the most efficacious acute treatment options for bipolar depression, particularly in patients who are severely depressed and who express life-threatening behavior. However, their possible, but not unambiguously proven, association with treatment-emergent mania means that they are not universally recommended as first-line therapy for acute bipolar depression.

Large, randomized, controlled trials that should include comparisons with mood-stabilizing medications are needed to further support the safety and efficacy of antidepressants. Appropriate dosage and duration of continuation therapy also need to be defined.

Given the established high risk of suicide in patients experiencing an acute episode of bipolar depression and the consequences of insufficiently treating the attack, there is a need for a treatment strategy with a good safety and tolerability profile that rapidly and effectively resolves the acute episode. It could be argued that many of the currently recommended pharmacotherapies, when given as monotherapy, do not meet these criteria in all patients with acute bipolar depression and leave many patients at risk of poor symptom control, significant functional impairment, long-term relapse, and even suicide. Lithium, carbamazepine, and valproate have relatively weaker antidepressant efficacy than the antidepressants. Moreover, lithium's antidepressant action is delayed by up to several weeks and its use is associated with well-

documented safety and tolerability issues. The antidepressant efficacy of lamotrigine has been suggested by one adequately powered study trial in patients with bipolar I disorder, but it appears to have more efficacy in the prevention of depressive episodes than in the treatment of a current episode of acute bipolar depression.

For patients with bipolar depression who do not respond to antidepressant therapy, ECT remains a valuable option, but controversy between the medical community and patient organizations regarding its actual benefit and some patients' perception of memory loss needs to be resolved.

Drug names: bupropion (Wellbutrin and others), carbamazepine (Tegretol, Carbatrol, and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), sertraline (Zoloft), tranylcypromine (Parnate), venlafaxine (Effexor).

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