The Treatment of Bipolar Depression

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Background: The treatment of bipolar depression represents a relatively understudied area in clinical psychiatry. The depressive phases of bipolar disorder can be very disabling, with significant associated comorbidity and suicide risk, impairment in functioning, and infringement on quality of life. We review the current evidence for the management of bipolar depression. ***Method:*** References for this review were obtained through MEDLINE searches of the medical literature on subjects pertaining to the treatment of bipolar depression. Search terms included *bipolar depression*, *antidepressants*, and *bipolar disorder*. Only publications in English are reviewed here. ***Results:*** Lithium is currently the gold standard and most appropriate initial treatment for the depressive phase of bipolar disorder. Other mood stabilizers have demonstrated preliminary efficacy. Of the antidepressants, bupropion and the selective serotonin reuptake inhibitors may be associated with less risk of inducing hypomania, mania, and rapid cycling compared with tricyclic antidepressants. Monoamine oxidase inhibitors should be considered for patients with anergic bipolar depression. Electroconvulsive therapy has been shown to be highly efficacious. Other treatment modalities, including psychotherapy, sleep deprivation, phototherapy, and newer medications, require further research. ***Conclusions:*** Although the treatment of bipolar depression can be a complicated clinical task, the treatment armamentarium is expanding. Further research, especially in the form of randomized controlled trials, is warranted. Clinicians should be familiar with general guidelines for the use of psychopharmacologic agents for treating bipolar depression.
(J Clin Psychiatry 2000;61[suppl 9]:57–67)

Bipolar I and bipolar II disorders affect approximately 0.8% and 0.5%, respectively, of the adult population over the course of a lifetime.[1] The term *bipolar depression* refers to an episode of major depression occurring in a patient who meets criteria for bipolar I or bipolar II disorder.[2] In these disorders, such episodes are often characterized by briefer duration compared with unipolar depressive episodes and may involve more rapid onset, anergia, psychomotor retardation, and reverse neurovegetative symptoms (hypersomnia and hyperphagia). Indicators that a patient with depression may be at risk for a bipolar disorder include antidepressant-induced hypomania or mania, earlier onset of depressive episodes, and family history of bipolar disorder.

The depressive phases of bipolar disorder can be very disabling. Based on a median follow-up of 18 months, Keller et al.[3] found that the probability of remaining ill for at least 1 year was 7% for manic patients compared with 22% for depressed patients. During bipolar depression, symptoms can range from mild physical and mental slowing, with very little distortion in cognition and perception, to profound depressive symptoms, delusions, hallucinations, and clouding of consciousness.[4] Such potential diversity in clinical presentation requires thorough clinical evaluation and tailoring of treatment on an individual basis.

A myriad of studies have revealed that 25% to 50% of bipolar patients attempt suicide at least once. In a review of follow-up studies, 15% of patients committed suicide, at least 30 times the rate one would find in the general population.[4] Bipolar depression is a serious and potentially lethal phase of bipolar disorder, with marked rates of suicidality, when compared with the manic phase. Dilsaver et al.[5] found the rates of suicidality to be 79.3%, 56.3%, and 2.3% in bipolar depression, depressive mania, and pure mania, respectively, in a sample of 129 bipolar patients. The relative risk of suicidality among subjects with bipolar depression compared with those with pure mania was 34.9, and the relative risk of suicidality among subjects with depressive mania compared with those with pure mania was 24.6. Subjects with either bipolar depression or depressive mania were also more likely to have intraepisode panic disorder than those with pure mania.

Although the depressive episodes of bipolar and unipolar disorders are phenomenologically similar,[6] unipolar depression and bipolar depression are considered distinct entities by both clinicians and researchers. Nevertheless, the pathophysiologic distinction between these 2 conditions remains unclear. Patients with bipolar depression

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have been shown to have lower concentrations of urinary norepinephrine and its metabolites, lower platelet monoamine oxidase activity, and higher platelet-free and stimulated intracellular calcium concentrations compared with unipolar depressed patients.[7] However, none of the biological measures yet examined reliably differentiate bipolar depression from unipolar depression with consistency, which may be because of methodological flaws in studies conducted to date, as well as the relatively small number of subjects studied.

Treatment of bipolar depression is a complicated clinical task owing to the complexity and variability of the illness; the frequent use of combinations of medications, including mood stabilizers, antipsychotics, and anxiolytics; and the potential for switching into hypomanic, manic, or rapid-cycling states. The vast literature on the treatment of unipolar depression cannot be easily extrapolated to the treatment of bipolar depression because of these factors, and the treatment of bipolar depression has received inadequate research attention.

In the following sections, we review the current evidence for clinical management of bipolar depression in adults. Although we focus on efficacy of treatment, many other issues must be considered in selecting an optimal treatment plan, including dosing strategies, side effects, adverse events, duration of treatment, continuation treatment, and prophylaxis. Because of the inadequate research database and the sparsity of randomized controlled trials examining the treatment of this disorder, we have also included preliminary impressions from diverse sources including case reports, open trials, review articles, and consensus guidelines. This review is not meant to be a comprehensive analysis of all studies on the various modalities of treatment, but rather an overview of the current state of knowledge in clinical psychiatry for the treatment of patients with bipolar depression.

References for this review were obtained through MEDLINE searches of the medical literature on subjects pertaining to the treatment of bipolar depression. Search terms included *bipolar depression*, *antidepressants*, and *bipolar disorder*. Only publications in English are reviewed here.

LITHIUM

Lithium is currently considered the first-line, most appropriate agent for the treatment of acute bipolar depression. In the Expert Consensus Guidelines[8] for the treatment of bipolar disorder, which surveyed 61 leading experts on bipolar disorder and asked them to rate a set of mood stabilizer regimens to achieve direct antidepressant effects without other medications, lithium monotherapy was the only first-line recommendation. In a review of available studies on the acute treatment of nonpsychotic bipolar depression, Zornberg and Pope[9] reported that 9 studies compared treatment with lithium to placebo. Eight of these 9 studies, comprising 145 patients, found lithium more effective than placebo. The response rate to lithium is approximately 79%, with a clearly unequivocal response in 36%.

For patients maintained on lithium therapy, the initial management of breakthrough depression should include evaluation of serum lithium concentration and thyroid function.[10] The lithium dose is generally titrated upward to achieve a serum concentration of 0.5 to 1.2 mEq/L.[1] Patients may require 6 to 8 weeks or longer before a complete response is attained. Given the convincing evidence for lithium's efficacy in treating bipolar depression, it is often considered the clinician's first treatment choice unless individual patient circumstances warrant beginning with another medication or modality. Baldessarini and Tondo[11] recently noted that lithium is unmatched in research support for long-term clinical effectiveness against morbidity and mortality associated with depression and mania in bipolar I and II disorders.

ANTICONVULSANTS

Carbamazepine

The clinical use of carbamazepine is compromised by its unusual property among drugs used to treat psychiatric disorders to induce its own metabolism as well as that of various other medications metabolized by the 3A4 isoenzyme of the cytochrome P450 microsomal enzyme system (including birth control pills, phenytoin, valproate, and many other psychotropics), but some evidence suggests its efficacy for the treatment of bipolar depression. During dose titration, serum levels established for the treatment of seizure disorders are generally applied, from 4 to 15 µg/mL.[1]

Results of several case series indicate that carbamazepine might have both antimanic and antidepressant effects, either as monotherapy or in combination with lithium or unimodal antidepressants.[12,13] In an open study[14] of 36 patients with bipolar depression or depressive mania who received carbamazepine for up to 21 days, the mean ± SD reduction in the Hamilton Rating Scale for Depression (HAM-D) scores was 23.7 ± 10.9 for patients with bipolar depression, a decrease of 72.7%. Seventeen (63.0%) of the 27 patients with bipolar depression entered remission, defined as a HAM-D score ≤ 8, the absence of psychotic features, the absence of need for anxiolytics, the absence of signs of mania, and clinical status allowing discharge.

In a double-blind, placebo-controlled trial,[15] 5 of 13 bipolar depressed patients showed significant improvement in depression ratings, and 3 additional patients experienced partial relapse when placebo was substituted. Although neither plasma nor cerebrospinal fluid (CSF) levels of carbamazepine are significantly correlated with the magnitude of clinical response, improvement in depres-

sion has been shown to correlate with the carbamazepine-10,11-epoxide metabolite CSF level.[16] Preliminary evidence suggests that carbamazepine may have prophylactic efficacy, reducing the number of manic and depressive episodes in refractory patients.[17]

Thirty-five patients with relatively treatment-resistant major depression (24 patients with bipolar depression and 11 with unipolar depression) were studied in a double-blind trial of the acute antidepressant effects of carbamazepine.[18] Improvement in depression ratings became significant by the second week of carbamazepine treatment and remained so throughout the course of the clinical trial. Fifteen (62%) of 24 bipolar patients responded.

Lithium may potentiate the antidepressant response to carbamazepine as it has been shown to do for other antidepressants. In 15 depressed patients (13 had bipolar depression, 2 had unipolar depression, and 8/15 experienced rapid cycling) who had not responded to double-blind treatment with carbamazepine, 8 (53%) responded rapidly (with moderate-to-marked improvement) to the blind addition of lithium to carbamazepine.[19] The majority of these responders (6/8; 75%) improved, essentially to clinical remission. The onset of antidepressant response occurred earlier in responders to lithium potentiation of carbamazepine than in a separate group of depressed patients who responded to lithium alone.

Denicoff et al.[20] designed a 3-year study to compare the therapeutic effects of lithium or carbamazepine in the first year, a crossover to the other drug in the second year, and treatment with the combination of both drugs in the third year. Thirty-three patients (63.5%) had bipolar I disorder, and 19 (36.5%) had bipolar II disorder. More than half (31/51; 60.8%) of the patients had a past history of rapid cycling. Blood levels were targeted for 0.5 to 1.2 mmol/L for lithium and 4 to 12 mg/L for carbamazepine. Twenty-nine patients were evaluable in all 3 treatment phases. As rated by the Clinical Global Impressions (CGI) scale, the percentage of patients with a good treatment response (marked or moderate improvement) was comparable for the monotherapies (33.3% with lithium and 31.4% with carbamazepine) and was 55.2% for the patients taking the combination (differences across the 3 treatment phases were not significant). The authors concluded that lithium and carbamazepine have roughly equal but less-than-adequate prophylactic efficacy in overall bipolar illness; that lithium is superior to carbamazepine in the prophylaxis of mania; that the combination is better than either monotherapy, especially in rapid cyclers; and that despite the use of adjunctive antidepressants, none of the 3 treatment groups exhibited significant improvement in depression.

Valproate

The spectrum of efficacy of the anticonvulsant and mood stabilizer valproate in the acute and prophylactic settings was studied in 55 refractory rapid-cycling patients treated with valproate either as monotherapy or in combination therapy.[21] Results suggest that valproate possesses potent antimanic and mixed-state properties in both the acute and prophylactic settings but minimal-to-moderate antidepressant properties. For rapid-cycling patients in a depressed episode, 63.6% (7/11) of patients treated with valproate monotherapy responded, and 47.1% (16/34) of patients in the total group (monotherapy plus combined regimens) responded, with response defined by a moderate or marked improvement. These results were extended in an additional 23 patients from the same center.[22] Pattern analysis suggested that patients who have a marked antidepressant response to valproate are likely to do well longitudinally. In the setting of a good antidepressant response, the global efficacy of the agent appeared adequate. However, in the setting of a marked antimanic response, global efficacy remains questionable, and the prospects for periodic depressive breakthroughs may remain high. Given the treatment-resistant status of these subjects, such improvement may indicate significant potential efficacy in bipolar depression.

Another case series of rapid-cycling bipolar patients documented moderate or marked improvement in affective symptoms shortly after the addition of valproate, as well as a marked reduction in the frequency and severity of cycling on follow-up at 3 to 25 months.[23] In a retrospective study[24] of 35 patients who received valproate after failing to respond adequately to conventional treatment for depressive, bipolar, or schizoaffective disorders, 7 of 9 depressed patients showed improvements in Global Assessment Scale (GAS) scores, which represented a level of improvement sufficient to elevate the majority of these patients into the mild symptom range or the virtually asymptomatic state after a mean of 12 to 15 months.

In a retrospective chart review[25] of 32 depressed bipolar patients treated with lithium, divalproex, or carbamazepine for at least 4 weeks prior to being randomized for a double-blind trial, of 6 patients treated with divalproex, 4 responded (defined as no longer meeting criteria for depression). Larger randomized trials are clearly needed to clarify these initial impressions. Studies to date support the conclusion that valproate may be more effective for mania than for depression, as both an acute and a prophylactic treatment,[26] with estimated weak-to-moderate antidepressant effects.[27] Clinically, the dose of valproate is generally titrated upward for a serum concentration between 50 and 100 μg/mL.[1]

Lamotrigine

Lamotrigine has been reported to enhance the efficacy of valproate in the treatment and prophylaxis of bipolar disorder.[28] In an open, naturalistic study that examined the efficacy of lamotrigine in the treatment of refractory bipolar depression in 22 patients on monotherapy with di-

valproex sodium, 16 patients (72%) responded by week 4 when response was defined as ≥ 50% reduction in HAM-D score compared with baseline.[29] Differences in scores became significant at week 1 and remained significant throughout the study. Fourteen (63%) of 22 were considered to have entered remission by week 6 when remission was defined as a HAM-D score of ≤ 6. No subjects switched to mania or hypomania during the 6-week trial period, and none developed a rash or Stevens-Johnson syndrome, the latter a severe, potentially lethal side effect of lamotrigine. Lamotrigine may be useful in the treatment of the depressed phase of refractory bipolar disorder and rapid cycling, as indicated by case reports[30] and preliminary naturalistic trials.[31–34]

Calabrese et al.[35] conducted a double-blind, placebo-controlled study to evaluate the efficacy and safety of lamotrigine in the treatment of major depressive episodes in 192 outpatients with bipolar I disorder. Lamotrigine doses of both 50 and 200 mg/day caused a mean 13-point improvement in HAM-D scores, which was significantly better than the effects of placebo. The rate of response to 200 mg/day of lamotrigine was statistically significant compared with that of placebo for both the Montgomery-Asberg Depression Rating Scale (MADRS) and CGI-Improvement scale. Clinical improvement became evident as early as the third week of treatment. The frequency of development of combined manic, hypomanic, or mixed episodes was not significantly different between lamotrigine and placebo groups. Adverse events were similar across treatment groups, except for a higher rate of headache in the lamotrigine group.

Lamotrigine appears to be a promising agent for the treatment of bipolar depression and seems to have a growing role in the current armamentarium.[36] The risk of rash may increase when coadministering it with valproate, exceeding the recommended initial dose of lamotrigine, or exceeding the recommended dose escalation for lamotrigine.[35]

Gabapentin

A case series[37] of 15 outpatients receiving open-label usual clinical treatment and gabapentin provides preliminary support for its potential efficacy in the depressed phase of bipolar disorder. Subjects received gabapentin orally 2 or 3 times daily with dose adjustment based on clinical response and treatment-emergent side effects. The dose of mood stabilizers was continued but not increased during the 6 weeks of treatment. Eight subjects (53%) responded (3 with a 50% reduction in HAM-D score, 5 with 25% to 50% reduction in HAM-D score). There was, however, no clear relationship between dose and response. At least one report[38] has described a case of apparent hypomania induced by treatment with gabapentin. Further research is required before gabapentin is accepted as a proven appropriate treatment for bipolar depression. However, gabapentin may be an acceptable second-line alternative mood stabilizer in bipolar depression.[36]

STANDARD ANTIDEPRESSANTS

In the Expert Consensus Guidelines,[8] the use of a mood stabilizer in combination with an antidepressant was the first-line treatment for patients with acute bipolar I depression that is severe but nonpsychotic. When asked to rank possible antidepressants for severe or milder bipolar I or II depression, the experts selected bupropion and selective serotonin reuptake inhibitors (SSRIs) as first-line treatment. Although not selected as first line, monoamine oxidase inhibitors (MAOIs) appear to be preferred over traditional tricyclic antidepressants (TCAs). The TCAs were not recommended when a switch to mania or accelerated cycling was a concern.

Bupropion

In a study of bupropion[39] in 75 depressed inpatients (patients with bipolar depression comprised 52% and 60% of the placebo and bupropion groups, respectively), bupropion was significantly more active than placebo in reducing depressive and anxiety symptoms after 3 weeks of treatment. In another placebo-controlled study[40] of 66 depressed patients (71% had bipolar depression) over a 28-day period, bupropion-treated patients were significantly improved on the HAM-D and CGI-Improvement and -Severity ratings. The percentage of responders, based on CGI-Improvement termination scores of 1 or 2 (very much or much improved), was 79% for the bupropion group and 13% for the placebo group. Response rates and tolerability for patients with unipolar versus bipolar depression were not reported in these early studies, and frequencies of treatment-emergent mania were also not reported. Case series[41–45] have reported bupropion to be effective for stabilization and maintenance of bipolar depressed patients, rapid cyclers, predominantly depressed bipolar II patients, and patients with depressive mania. Bupropion may have precipitated hypomania or mania in 6 of 11 patients in one report.[44]

In a double-blind trial, 15 patients with bipolar depression receiving concurrent mood stabilizers were randomly assigned to treatment with bupropion or desipramine.[46] Four of the 15 patients crossed over to a second trial on the other medication. Sixty-three percent (5/8) of patients taking bupropion and 71% (5/7) of patients taking desipramine responded to treatment, defined as 2 or more weeks during which 31-item HAM-D scores improved by ≥ 50%. Treatments did not significantly differ for acute efficacy. Over the entire period, including both the acute treatment and continuation phases, the observed rate of hypomania or mania was 50% (N = 5) in the desipramine group and 11% (N = 1) in the bupropion group ($p < .012$). From these preliminary studies, it has been suggested that bu-

propion has similar efficacy as other antidepressants for patients with bipolar depression, but may offer a safer treatment option with respect to risk of inducing mania or cycle acceleration.

Selective Serotonin Reuptake Inhibitors

Although few studies have been conducted with the SSRIs in the treatment of bipolar depression, this class of antidepressants appears to be a promising approach in bipolar depression and may offer fewer side effects[9] as well as less toxicity in overdose compared with TCAs and MAOIs. Some data suggest that SSRIs have a lower propensity to induce switch to hypomania/mania compared with TCAs.[47]

In an open trial[48] involving 16 patients with bipolar II disorder who had been depressed for an average of 5.3 years, fluoxetine was effective in all but 1 patient. This group had a history of poor responses to TCAs, MAOIs, and lithium. Ten of 13 patients who had taken fluoxetine for 10 or more months had a good or very good response, and the other 3 had a fair response.

One 6-week double-blind placebo-controlled comparison of fluoxetine with imipramine in 89 bipolar depressed patients has been reported.[49] A significantly greater number of patients, 86%, responded to fluoxetine treatment compared with 57% for those taking imipramine and 38% for those taking placebo. Completers in the fluoxetine group exhibited greater improvements than those taking imipramine on the HAM-D total score and anxiety/somatization and retardation factors. Endpoint analysis of all patients revealed a statistically significant difference between treatments only on the HAM-D anxiety/somatization factor, which favored fluoxetine.

Nemeroff et al.[50] conducted a double-blind, placebo-controlled study of 117 patients with DSM-III-R bipolar affective disorder, depressive phase. The patients were randomly assigned to paroxetine (N = 35), imipramine (N = 39), or placebo (N = 43) for a 10-week treatment period. All patients received lithium and some received carbamazepine or valproate. Paroxetine and imipramine were superior to placebo in patients with serum lithium levels < 0.8 mEq/L. No such effect was observed in the patients with serum lithium levels > 0.8 mEq/L, because of the antidepressant effect of lithium at these levels. Paroxetine was better tolerated than imipramine and caused no patient to switch into mania.

In another recent study[51] comparing the addition of paroxetine versus a second mood stabilizer in 27 patients with bipolar depression treated with lithium or divalproex sodium, it was suggested that the addition of paroxetine may have greater clinical utility. Both groups showed significant improvement in depressive symptoms during the 6-week trial, but there were significantly more noncompleters in the group being treated with the 2 mood stabilizers than in the group treated with a mood stabilizer and paroxetine. The addition of paroxetine was not associated with the emergence of manic symptoms in this study, although the group size was small, and the study duration was only 6 weeks.

Monoamine Oxidase Inhibitors

Few formal studies have addressed the efficacy of MAOIs in the treatment of bipolar depression. In a controlled, double-blind study of 56 outpatients with anergic bipolar depression (a bipolar depressive episode with fatigue or volitional inhibition, predominant psychomotor retardation, and at least one reversed neurovegetative symptom), Himmelhoch et al.[52] reported that tranylcypromine produced statistically significantly superior outcomes compared with imipramine. Significantly more imipramine patients were withdrawn prematurely from the protocol, and a significantly greater number of patients who completed 4 or more weeks of treatment responded to acute treatment with tranylcypromine. A total of 6 tranylcypromine patients (21%) became hypomanic or manic, as did 7 imipramine patients (25%). Onset of treatment-emergent hypomania/mania tended to occur more quickly in patients treated with imipramine than with tranylcypromine.

Patients who did not respond to the initial treatment in that protocol were, after an appropriate washout period, treated with the other study drug, in a double-blind design.[53] Ten patients were found to be imipramine nonresponders who had been crossed over to tranylcypromine, and only 4 were tranylcypromine nonresponders who had been switched to imipramine. Two patients who had been crossed over because of severe side effects had been taking imipramine during the initial treatment phase. Seventy-five percent (9/12) of patients who had originally failed to benefit from imipramine responded to tranylcypromine crossover treatment. Only 1 of the 4 patients who crossed over from tranylcypromine to imipramine responded.

Moclobemide is a selective, reversible inhibitor of monoamine oxidase A that is available in Europe and Canada for the treatment of depression. A prospective, multicenter, double-blind study[54] compared the antidepressant efficacy of moclobemide with that of imipramine in 381 patients with major depressive episode, including 33 patients with bipolar depression. Both treatments were equally efficacious: 53% and 60% of bipolar depressed patients in the moclobemide and imipramine groups, respectively, responded (as defined by ≥ 50% decrease in HAM-D score at 4 weeks). The tolerability of moclobemide was superior to that of imipramine, mainly due to the lower incidence of anticholinergic side effects with moclobemide.

The burden of the MAOI diet and potential for drug interactions may limit the practical use of the older, nonselective MAOIs in some patients. Nonetheless, these

studies indicate potential utility of MAOIs in the treatment of bipolar depression, especially in patients with the anergic subtype.

Tricyclic Antidepressants

Despite the extensive clinical literature on the treatment of unipolar depression with TCAs, very few studies provide sufficient information to determine their efficacy in bipolar depression. The controlled studies suggest that bipolar depressed patients may be less likely to show an acute response to TCAs than are patients with unipolar major depression, although the difference may not be true for patients with more severe depressions.[4]

Prien et al.[55] randomly assigned 122 patients with recurrent unipolar (N = 78) or bipolar (N = 44) depression to lithium, imipramine, or placebo therapy for 2 years following discharge from hospitalization for acute depression. In bipolar patients, lithium (at serum levels maintained between 0.5 and 1.4 mEq/L) was found to be significantly more effective than imipramine or placebo in preventing manic and depressive episodes requiring hospitalization or supplementary medications. No significant difference was reported between imipramine and placebo. Moreover, there was a relatively high incidence of manic episodes in patients treated with imipramine (67%), compared with lithium (12%) and placebo (33%), during months 5 through 24. Their findings also demonstrated that the bipolar-unipolar dichotomy is a valid clinical distinction that has significance for the treatment of recurrent affective illness. They conclude that depressed patients with a history of manic episodes (bipolar depressed patients) are not good candidates for a treatment regimen including imipramine because the risk of subsequent manic episodes is too great; lithium is more suitable for these patients.

Quitkin et al.[56] randomly assigned 75 patients with bipolar I disorder to treatment with combined lithium and imipramine or lithium and placebo. Infrequent depressive relapse in either treatment group precluded any demonstration of an advantage of adding imipramine to lithium. The rate of depressive relapses in both groups was approximately 10% over an average of 19 months. However, women and manic-prone patients (defined as the most recent episode's being manic) treated with imipramine had an increased risk of mania.

In 1984, a large study[57] was published comparing long-term (2-year) outcome of 117 bipolar and 150 unipolar patients receiving lithium, imipramine, or both conducted in a multicenter collaboration. There was no significant difference in dosage between patients receiving drugs in combination and those receiving the drugs individually. In the bipolar group, lithium and the combination treatment produced a significantly higher percentage of treatment successes (33%) than did imipramine (8%). The combination of lithium and imipramine provided no advantage over lithium alone. The difference between treatments was the high incidence of manic recurrences in the imipramine-treated group. Fifty-three percent of the imipramine-treated patients had a manic or mixed recurrence, compared with 26% in the lithium group and 28% in the combination group. No significant difference was found among treatments in the occurrence of depressive episodes.

Other Antidepressants

The role of second-generation antidepressants, including maprotiline, amoxapine, and trazodone, has not been studied for the treatment of bipolar depression. Third-generation antidepressants, including venlafaxine, nefazodone, and mirtazapine, have not yet been assessed in controlled studies. Nonetheless, the most recent Expert Consensus Guidelines[36] reveal broad support for these agents as second-line treatments or alternate medications in the case of adding or switching agents. Reboxetine has not yet been studied in bipolar depression.

Antidepressant-Induced Hypomania, Mania, and Rapid Cycling

Antidepressant-induced hypomania or mania[58] and rapid cycling[59] are somewhat controversial and unresolved issues that may complicate the treatment of bipolar depression. Reports have described widely varying statistics for these phenomena. All unimodal antidepressants, electroconvulsive therapy (ECT), and sleep deprivation have been reported to cause treatment-emergent switching. Most clinicians do not prescribe antidepressants without concomitant mood stabilizers in depressed patients with bipolar disorder. This is of interest considering the fact that as recently as 20 years ago, many investigators believed that the "switch" process was unrelated to antidepressant therapy and was simply a reflection of the natural course of the illness. There are few doubters currently, although controversy does rage as to whether antidepressants can "switch" bipolar II patients into full-blown mania. Several factors may be predictive of manic reactions to antidepressants, including a past personal history of mania, a family history of mania, a premorbid cyclothymic tendency, early onset, female gender, hypothyroidism, a relatively high frequency of recurrences, and history of drug-induced rapid cycling.[60] TCAs clearly appear to be more likely to induce hypomania or mania and acceleration in cycling, in comparison with MAOIs and newer antidepressants.[61] One retrospective, naturalistic study[62] suggests that TCAs may contribute to the induction or exacerbation of episodes of mania in one third of treatment-refractory bipolar patients and may contribute to cycle acceleration in one quarter of these patients. If rapid cycling or mania/hypomania emerges during antidepressant therapy, the antidepressant should be tapered and discontinued.[63] Further research is needed to clarify these is-

sues, especially as they relate to newer antidepressants and the concurrent use of mood stabilizers.

Boerlin and colleagues[64] followed a group of 29 patients with bipolar I depression experiencing 79 depressive episodes who received naturalistic treatment at the UCLA Affective Disorders Clinic. Switch rates for the TCA, MAOI, and fluoxetine subgroups were 32% (7/22), 35% (6/17), and 12% (1/8), respectively, with an average intensity of low-grade mania. Sixty-four percent (14/22) of switches were hypomanic, whereas 36% (8/22) were manic. The only predictor of switching was a greater number of past manic episodes. TCA-induced switches tended to be the most intense, although this finding did not attain statistical significance. The relatively lower switch rates noted in this study, compared with prior estimates of more than 50%, may reflect the consistent use of mood stabilizers in this naturalistic study.

Stoll et al.[65] conducted a blind retrospective study examining clinical differences between a group of 49 consecutive patients admitted to McLean Hospital (Belmont, Mass.) with antidepressant-associated mania and a group of 49 matched patients with spontaneous mania. On virtually every measure of psychopathology, the patients with spontaneous mania had more severe disease when compared with the patients with antidepressant-associated mania. Antidepressant-associated mania was secondary to treatment with TCAs (N = 19), fluoxetine (N = 13), MAOIs (N = 8), bupropion (N = 6), and combinations (N = 3). Patients with MAOI- and bupropion-associated mania had significantly lower overall CGI-Severity ratings on admission and had generally lower scores on individual mental status items, but the latter differences did not attain statistical significance.

OTHER PSYCHOTROPIC MEDICATIONS

Benzodiazepines

Several studies have examined the efficacy of benzodiazepines in treating depressive symptoms in patients with bipolar disorder. In an open-label study[66] of alprazolam in 5 bipolar I depressed patients, 3 patients remitted completely, 1 failed to respond, and 1 responded transiently based on HAM-D and Beck Depression Inventory (BDI) scores. The efficacy and safety of adinazolam, a triazolobenzodiazepine structurally related to alprazolam, was assessed in a study of 80 outpatients with major depression (69%) or bipolar II depression (31%) in a 6-week, double-blind, placebo-controlled study.[67] The number of subjects with a decrease of ≥ 50% on the total HAM-D score was significantly greater for the adinazolam-treated group (60%) compared with the placebo-treated group (38%). Mean scores on several HAM-D clusters (anxiety/somatization, sleep disturbance, and an endogenomorphic cluster) also showed significant differences in favor of adinazolam. No consistently significant differences were observed between subjects whose primary diagnosis was major depression and those with bipolar II depression. In an open trial[68] of 27 inpatients and outpatients diagnosed with unipolar depression (N = 18) or bipolar depression (N = 9), treatment with clonazepam produced significant decreases in HAM-D and BDI scores compared with pretreatment scores. As in earlier studies, the antidepressant action of benzodiazepines appeared to be exceedingly rapid. In this study, 60% of the improvement achieved at the end of 6 weeks of clonazepam treatment had been attained within 1 week after beginning therapy.

Although generally not considered effective antidepressants, some patients may benefit from benzodiazepines for relief of anxiety and insomnia associated with depression.[1] These preliminary reports point to the need for further research with these agents.

Antipsychotics

Antipsychotics are commonly added to the treatment regimen in patients with psychotic bipolar depression. In a double-blind study[69] of 58 patients with psychotic depression, which included 5 bipolar I patients and 4 bipolar II patients, the combination of amitriptyline plus perphenazine was clearly the superior treatment regimen compared with either drug alone. Fourteen (78%) of the 18 patients treated with the combination were responders, compared with 7 (41%) of the 17 patients receiving amitriptyline monotherapy and 3 (19%) of the 16 patients treated with perphenazine alone. The impression that patients with bipolar disorder may be at a greater risk of tardive dyskinesia compared with schizophrenic patients argues for caution in the use of conventional antipsychotics.[4]

Preliminary evidence suggests a possible role for atypical antipsychotics in treating depressive symptoms associated with psychotic and affective disorders. In 1998, Vieta et al.[70] reported results of an open-label pilot study in 10 patients with rapid-cycling bipolar disorder refractory to mood stabilizers who were treated with risperidone. In the 8 patients who completed the 6-month study, HAM-D scores were statistically significantly reduced. This and other preliminary studies[71,72] suggest a possible role for risperidone for depressive symptoms. Approximately 11 reports of risperidone-induced mania have been published, mostly during risperidone monotherapy, although it is difficult to establish whether risperidone treatment was the causative factor.

Two large, multicenter, 6-week studies of olanzapine in the treatment of schizophrenia have reported efficacy in treating depressive signs and symptoms that are commonly present in schizophrenia.[73,74] Path analysis determined that the majority of the treatment effect was directly on depressive symptoms and not solely related to improvements in positive and negative symptoms. Controlled studies are needed to assess these agents and other atypical antipsychotics in bipolar depression. Serotonergic

effects of atypical antipsychotics may be associated with reductions in depression and a broader therapeutic spectrum.[72]

Other Agents

The role of thyroid hormones in the treatment of bipolar disorder continues to be investigated. A recent study[75] evaluated the relationship between changes in thyroid function indices and mood stability during lithium and carbamazepine prophylaxis for bipolar disorder. During the lithium-treatment phase, a low level of thyroxine (T_4) was associated with more affective episodes and greater severity of depression as measured by the BDI. Whether this mood instability can be attenuated with T_4 replacement remains to be studied in a controlled setting. In an earlier study,[76] 11 patients with refractory rapid-cycling bipolar disorder underwent an open trial of high-dose levothyroxine sodium added to a stable regimen of their medications. While taking levothyroxine, severity scores on both depressive and manic symptom rating scales decreased significantly compared with baseline. This improvement was due to the clear-cut response of depressive symptoms in 10 of 11 patients, with manic symptoms responding in 5 of 7 patients who exhibited them during baseline assessment. Nine of the 10 responders showed no improvement until the free T_4 index was approximately 150% above normal. There was no relationship between baseline thyroid status at study entry and clinical response. In depressed patients, low doses of triiodothyronine (T_3), 25 to 50 µg/day, have been reported to accelerate or potentiate antidepressant response.[4]

The roles for calcium channel blockers, topiramate, omega-3 polyunsaturated fatty acids, psychostimulants, opiates, L-tryptophan, dopaminergic agonists, and *S*-adenosylmethionine in the treatment of bipolar depression have yet to be studied in controlled clinical trials.

ELECTROCONVULSIVE THERAPY

In their review, Zornberg and Pope[9] reviewed 9 studies, comprising a total of 723 patients, evaluating ECT in the depressed phase of bipolar disorder. In the 7 studies that compared ECT with antidepressant drugs, ECT was clearly more effective in 5. In the Expert Consensus Guidelines,[8] ECT or combined mood stabilizer, antidepressant, and antipsychotic were the 2 first-line treatments for the acute treatment of a patient with bipolar I depression with psychosis. ECT has the fastest and probably the highest response rate, but also has the disadvantages of relatively high relapse rates and of being relatively uninformative about what medication treatment would be most helpful in the continuation and maintenance phases.[8] Yet, many patients who are medication resistant not only respond to ECT, but are maintained symptom free by maintenance ECT. ECT should be considered as the initial treatment if the patient is severely ill, especially delusional, at high risk of suicide, or has a history of good response to ECT.[4] Some have suggested that ECT may be preferable to TCAs in treating bipolar depression, because the risk of shortening the cycle or precipitating mania seems to be lower with ECT,[4] although this is not well established. ECT is appropriate for bipolar depression at any time if acceptable to the patient and should not simply be reserved as a treatment of last resort.[6] Lithium treatment is usually discontinued during a cycle of ECT owing to reports of neurotoxicity with the combination.

OTHER NONPHARMACOLOGIC MODALITIES

Psychotherapy

The role of psychotherapy in the treatment of bipolar depression has not been adequately studied. Nonetheless, many clinicians supplement pharmacologic treatment with psychotherapy. In a survey of Canadian psychiatrists,[77] 84.2% of respondents identified a combination of psychotherapy and somatic therapy as their preferred therapeutic intervention. Over half the respondents indicated a preference for the use of a variety of psychotherapeutic strategies rather than adherence to a specific technique.

Differences in response between psychodynamic, cognitive-behavioral, interpersonal, and other psychotherapeutic techniques have not been studied. Interpersonal and social rhythm therapy is a specific psychotherapy currently being studied that addresses medication noncompliance, disruptions in social rhythms, and stressful life events.[78] Adjunctive psychotherapy can help patients come to terms with the repercussions of past episodes and to comprehend the practical and existential implications of having manic-depressive illness.[4] Individual, marital, family, or group psychotherapy and support and psychoeducation groups may be useful to deal with denial, disruption in interpersonal functioning, and fears of recurrences.

Sleep Deprivation

Although the mechanism of sleep deprivation for 1 night or more is unclear, it has been shown to cause a marked but transient improvement in depressive symptoms in bipolar depression. Although studies of total sleep deprivation, partial sleep deprivation, and selective rapid eye movement (REM) sleep deprivation have documented average antidepressant response rates of around 60%,[4] improvement may be transient for most patients, and such an approach is difficult to put into practice. The literature contains several reports that sleep deprivation induces mania in bipolar patients.[4]

In a recent study,[79] 40 patients with bipolar I disorder in a depressive episode were randomly assigned to sleep deprivation plus pindolol or sleep deprivation plus placebo. On days 1, 3, and 5, patients were totally deprived of sleep for 36 hours. Highly significant group effects, time effects,

and time-per-group interaction were noted on the HAM-D scores between the 2 groups. At the end of 10 days of acute treatment, 75% of patients treated with pindolol and sleep deprivation showed complete response, compared with only 15% in the placebo group. One week later, 70% and 5%, respectively, were still rated as responders. Further studies on sleep manipulation techniques and combination strategies with medications are urgently needed.

Phototherapy

Treatment of depression with high-intensity light is another interesting potential treatment for bipolar depression. Response to phototherapy is relatively rapid, but relapses after withdrawal of light are similarly rapid.[4] This treatment may be more effective in patients with a seasonal pattern (winter depression).

Other Treatment Modalities

Several promising treatments for unipolar depression have recently been studied including rapid transcranial magnetic stimulation and vagal nerve stimulation. Their use in the treatment of bipolar depression is an area of intense scrutiny.

CONCLUSIONS

The treatment of depression in bipolar disorder represents an understudied area in clinical psychiatry that needs further research owing to the frequency of depressive episodes in bipolar disorder, the high rates of associated suicidality and comorbid psychiatric and substance use disorders, and the negative impact on psychosocial functioning and quality of life. The depressed phase of bipolar disorder seems to be less responsive to standard treatment than the manic phase.[78] Research is also needed to elucidate the pathophysiologic distinctions between unipolar and bipolar depression. Although antidepressant-associated manic states appear to be less severe than spontaneous mania, they are often quite severe, and the potential for switching to hypomania, mania, or more rapid cycling during the treatment of depression remains an important clinical question requiring further research.

The most convincing finding in the research literature on the treatment of bipolar depression is that lithium is markedly more effective than placebo.[9] Lithium has an estimated overall complete or partial response rate of 79% for bipolar depressed patients compared with 36% for unipolar patients,[4] although there is increasing recognition of lithium's high failure rate in many settings.[80] Acute and prophylactic treatment studies reveal that lithium is a moderately effective treatment for acute bipolar depression and provides moderately effective protection against bipolar depressive recurrences.[57]

Although the evidence for their efficacy is less substantial, both carbamazepine and valproate are believed to be bimodal agents possessing both antimanic and antidepressant efficacy, i.e., true mood stabilizers. Although particularly useful in the acute management of mania, their exact antidepressant efficacy remains poorly defined. They likely offer minimal-to-moderate efficacy in the acute treatment of depression.[27,81] Valproate may be more effective than other agents for rapid cycling. Lamotrigine may prove to be particularly effective in bipolar depression,[82] and the preliminary study results are promising. Individual bipolar spectrum patients may respond to one anticonvulsant but not to another, further reinforcing the need for individualization of treatment.[82] Optimizing these mood-stabilizing treatments before introducing antidepressant medications offers good potential for benefit with minimal risk.[6]

According to the most recent Expert Consensus Guidelines,[36] mild depression should be treated with mood-stabilizer monotherapy initially, whereas severe depression should be treated from the start with a mood stabilizer plus an antidepressant. After resolution of a first episode of bipolar depression, antidepressants should be tapered in 2 to 6 months (a much shorter continuation period than is generally advised for unipolar depression).

Many studies of traditional antidepressants were conducted before the bipolar-unipolar distinction became established in clinical psychiatry, and few studies have been conducted with a focus on bipolar depressed patients. The response rates in bipolar depression have been estimated to be approximately 55% with TCAs, 53% to 86% with MAOIs, and 60% to 80% with SSRIs, although these rates represent short-term treatment trials aimed at 50% reduction in symptoms.[78] MAOIs may be considered the treatment of choice for atypical (anergic) bipolar depression.[10]

Monotherapy with unimodal antidepressant agents is generally avoided, primarily because of the risks of induction of hypomania or mania, or acceleration of cycling. Although moderately effective for acute bipolar depression with an average response rate of 55%,[83] the use of imipramine (and presumably other TCAs) for the long-term preventive treatment of bipolar depression is not recommended[57] owing to the increased risk of manic recurrence. Some have recommended discontinuing antidepressants within 2 weeks of achieving remission of depressive symptoms[47] to decrease the risk of inducing hypomania or mania. The use of standard antidepressants along with a mood stabilizer decreases the risk of switching. Preliminary evidence suggests less risk of switching with SSRIs and bupropion.

It may be obvious, but the reader should recognize the inherent difficulty in conducting controlled trials of bipolar depression. Unlike trials of patients with unipolar depression or schizophrenia, the use of multiple pharmacologic agents is unavoidable in conducting these trials in an ethical manner, and as a result, the power analyses demand very large numbers of subjects per group.

The evidence for the efficacy and superiority of ECT over other treatments is clear-cut and convincing, and a substantial proportion of depressed patients who fail to respond to TCAs do respond to a course of ECT.[4] ECT may be especially useful for patients who are more severely ill, patients with psychotic depression, cases of treatment-resistant depression, and as an alternative to drug therapy in pregnant women.

Antidepressants are frequently used in combination with lithium owing to evidence of synergism or potentiation in both unipolar and bipolar depressed patients. That T_3 may potentiate antidepressant response and that T_4 may decrease affective instability in lithium-treated patients are interesting findings that need further clarification. Both sleep deprivation and phototherapy appear to act rapidly, but their action frequently ceases when the treatment stops or shortly thereafter.

In refractory bipolar depression, combination treatment is often required.[80] Although the role of hospitalization has not been addressed herein, this is an obvious consideration for patients who are suicidal or severely depressed.

Side effects of the available therapies (lithium, MAOIs, TCAs, ECT) frequently complicate treatment, and the side effect profiles of various antidepressants should be a crucial determinant in choosing the most appropriate form of therapy for each patient.[47] Symptom profiles of individual patients (e.g., anergic depression, agitated depression) and history of switching into mania may also help in determining the choice and dosage of antidepressants.[84] Noncompliance is a difficult problem, especially in patients who are young, early in their illness, reluctant to give up their hypomanias, or prone to frequent elevated moods and grandiose delusions.[4] Detailed mapping of mood fluctuations during treatment with various medications, such as with the life chart methodology, may optimize and rationalize the treatment regimen.[80] Fostering a therapeutic alliance in which the illness, its treatment, and medication side effects can be openly discussed optimizes compliance and the likelihood of long-term stability and allows new episodes to be identified as early as possible.[1]

Drug names: alprazolam (Xanax and others), amitriptyline (Elavil and others), amoxapine (Asendin and others), bupropion (Wellbutrin), carbamazepine (Tegretol and others), clonazepam (Klonopin and others), desipramine (Norpramin and others), divalproex sodium (Depakote), fluoxetine (Prozac), gabapentin (Neurontin), lamotrigine (Lamictal), levothyroxine (Synthroid and others), mirtazapine (Remeron), nefazodone (Serzone), olanzapine (Zyprexa), paroxetine (Paxil), perphenazine (Trilafon and others), phenytoin (Dilantin and others), reboxetine (Vestra), risperidone (Risperdal), topiramate (Topamax), tranylcypromine (Parnate), trazodone (Desyrel and others), venlafaxine (Effexor).

Disclosure of off-label use: The authors have determined that, to the best of their knowledge, the following agents are not approved by the U.S. Food and Drug Administration for the treatment of depression: adinazolam, alprazolam, carbamazepine, clonazepam, divalproex sodium, gabapentin, lamotrigine, levothyroxine, lithium, L-tryptophan, moclobemide, olanzapine, perphenazine, pindolol, risperidone, S-adenosylmethionine, topiramate, triiodothyronine, valproate.

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