Bipolar Depression: Specific Treatments

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From the perspective of pharmacologic treatment, bipolar depression is considered in this article as belonging to a spectrum of affective disorders. Insufficient controlled data permit only general recommendations for treatment of the spectrum of affective disorders, except perhaps for the classic form of bipolar I disorder. While the field waits for prospective controlled trials, a wide range of drugs is currently available for the treatment of bipolar depression. The potential advantages of having an increasing number of agents with different mechanisms of actions are suggested by the many small studies claiming some degree of advantage in one or another subgroup of patients with bipolar depression. Several antidepressants and one anticonvulsant have the virtue of clinical experience that contributes to a body of information about side effects and the potential for producing benefit in at least some bipolar depressed patients. By default, and because they appear to have less chance of precipitating mania and are otherwise safe, selective serotonin reuptake inhibitors are probably the most comfortable first-line treatment for bipolar depression.
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Bipolar depression, from the perspective of pharmacologic treatment, will be considered here as belonging to a spectrum of affective disorders (Figure 1).[1] This approach recognizes the fact that many treatments developed for major affective disorder (i.e., unipolar depression) are used to treat bipolar depression and that at least one major treatment for bipolar disorder, lithium, is sometimes used to augment response to antidepressants in nonbipolar patients. Thus, there is no simple match between specific diagnosis and specific treatment. As will become apparent below, surprisingly little definitive data exist on the treatment of any but the classic bipolar I form of manic-depressive illness. For the large number of patients who do not fully respond to monotherapy with the standard mood stabilizer lithium, individualization of treatment is necessary. Principles for individualizing treatment and identification of biochemically unique alternatives are developed below.

As shown in Figure 1, symptoms satisfying criteria for either minor or major depression can be a part of bipolar I, bipolar II, cyclothymic, schizoaffective bipolar type, schizoaffective depressive type, and mixed state disorders, all of which fall into a broadly conceived bipolar spectrum, of which the critical features are a recurrent longitudinal course with presence of hypomanic or manic phases.[2] From a diagnostic point of view, perhaps the most difficult presentation to characterize is that of a mixed state, which is reflected in the widely varying estimates of the prevalence of mixed states from 31% to 67% of inpatients admitted for mania.[2] Even an earlier estimate that required that patients have euphoric manic symptoms in close temporal proximity to depressed ones still reported an incidence of 16%.[3] Subsequent diagnostic criteria for mania do not require the presence of euphoria during an episode.

As discussed in detail by Goodwin and Jamison,[2] the description of patients by Kraepelin[4] early in this century utilized the terms depressed and manic as adjectives to describe the separate dimensions of mood, thought, and activity. This descriptive approach may not lead to a clear diagnosis, but it does capture the range of clinical presentations in mood disorder. The greatest potential for confusion is with what was once called agitated depression and in the DSM-IV[5] is restricted to the modifier "severe with psychotic features" and "if possible, specify whether the psychotic features are mood-congruent or mood-incongruent."[5(p378)] A patient with pressured dysphoric thinking, a high general level of activity, and history of clear hypomania or mania could be relatively easily classified as suffering from a mixed state. A patient who is motorically active (e.g., pacing instead of sitting during waking hours in a quiet, withdrawn state), having difficulty sleeping, extremely worried, irritable and despairing, but not clearly delusional or hallucinating could be in either a severe episode of depression or a mixed state. The final diagnosis would depend on whether he or she suffered from recurrent unipolar depression versus some form of bipolar disorder (i.e., past or subsequent hypomania or mania).

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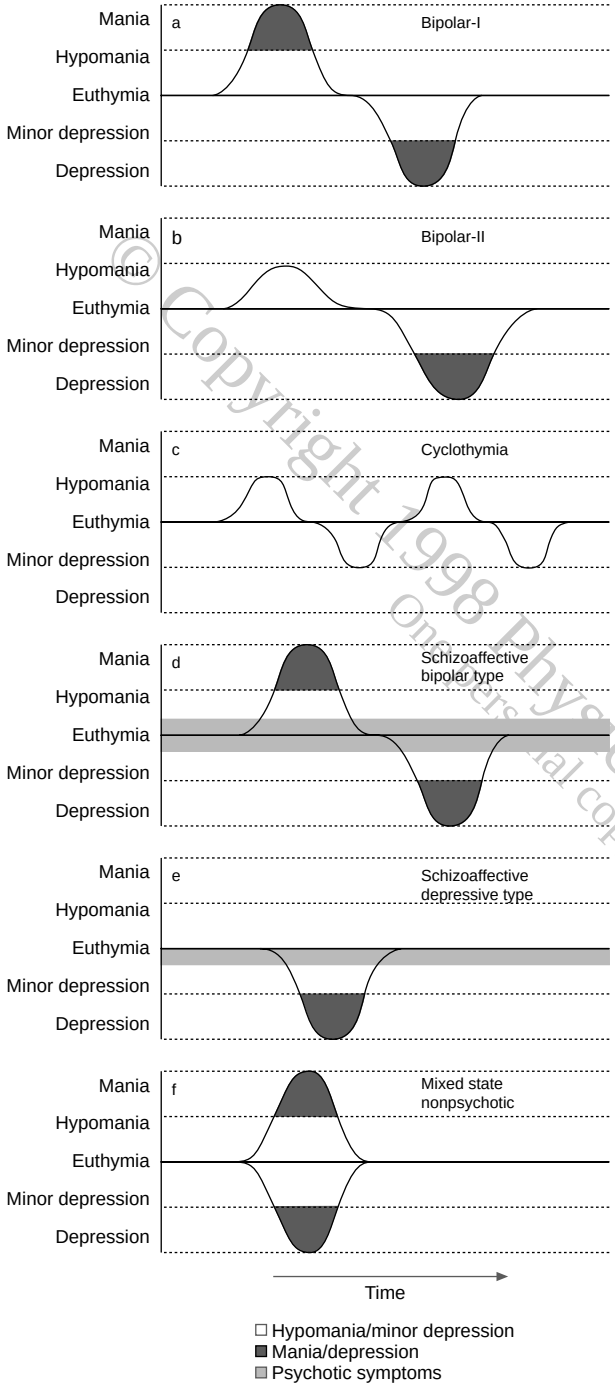
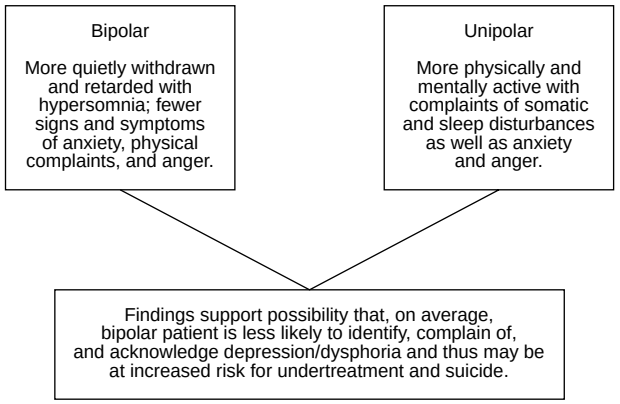
Figure 1. A Diagrammatic Representation of the Spectrum of Affective Disorders*



*From reference 1, with permission.

Figure 2. Clinical Differences in Bipolar vs. Unipolar Depression



Sometimes, only longitudinal history and/or observation can resolve such diagnostic questions. Figure 2 describes the clinical differences in bipolar versus unipolar depression.

This is not simply an academic point since, depending on the diagnosis, one would reach different treatment decisions. If a mixed state is present, monotherapy with an antidepressant is unlikely to be effective and may even make a patient worse.[6–8] Even in a simple pure depressed bipolar phase, monotherapy with antidepressants carries a significant risk of switching patients into mania (see below).

Sometimes, only the experience of an apparent paradoxical worsening of a mixed state or switch into mania from a simple depression after starting an antidepressant uncovers an underlying bipolar condition. A patient may start with an episode of what appears to be a classic retarded, withdrawn depression that seems to respond well to a traditional antidepressant and later experience a very activated, irritable depressive episode that is aggravated by the same drug. In other words, it would be classified as a mixed episode which, in the absence of a history of full mania, might best fit a diagnosis of bipolar II, mixed state. There is, however, no such formal diagnosis in the DSM-IV. Akiskal[9] has argued persuasively that we should broaden our prospective to include such presentations because of the treatment indications.

As revealed in a recent attempt to generate expert agreement on algorithms for treating any form of bipolar depression, there is insufficient controlled data to permit general recommendations except perhaps for treatment of the classic form of bipolar I disorder.[10] One is left with many patients such as the hypothetical one described above falling into an area of imprecise diagnosis and uncertain treatment standards. For such patients, when a first treatment is ineffective, one might consider an individualized sequence based on knowledge of the potential provided by the availability of pharmacologically unique classes of antidepressants and antimanic (sometimes called mood-stabilizing) agents.

Leaving aside the question of how to treat mixed states, as noted above, there is an absence of definitive data on long-term treatment approaches to bipolar depression except for that subgroup of patients who enjoy full remission on maintenance lithium.[2,11] More recent studies show that sustained remission on lithium therapy occurs in no more

Table 1. Somatic Treatments Used in Bipolar Depression

Lithium
Anticonvulsants
Valproate
Carbamazepine
Possibly lamotrigine
Antidepressants
Heterocyclics
Monoamine oxidase inhibitors
Bupropion
Selective serotonin reuptake inhibitors
Nefazodone
Venlafaxine
Mirtazapine
Atypical antipsychotics
Electroconvulsive therapy

than 50% of even classic bipolar I patients.[12–15] Three critical but unresolved questions are relevant to the treatment of bipolar depression in those patients whose depressions do not respond to or are not prevented by lithium:

1. Are certain classes of antidepressants better than others in the treatment of manic-depressive illness?
2. If depressions recur when a patient is on therapeutic concentrations of lithium (or any putative mood-stabilizing agents), should an antidepressant be added as a long-term maintenance treatment?
3. What is the proper duration of a trial to assess whether an antidepressant is really working?

Raising these questions is not meant to argue against the remarkable short-term improvement produced by a wide variety of antidepressant agents alone or in combination with a mood stabilizer. Studies of antidepressants in the late 1950s and 1960s frequently included manic-depressive patients who were reported to have a characteristic retarded, hypersomnic depression that showed excellent responses within 3 to 6 weeks to classic tricyclic antidepressants (TCAs) such as imipramine.[2] Many of these responses, however, were later viewed as switching a patient into hypomania or mania or accelerating the underlying mood cycle.[16] Indeed, in some patients, TCAs (and by implication, other antidepressants) may actually worsen the long-term course of bipolar illness.[17]

There has been some controversy over the extent to which TCAs precipitate mania.[17] As reviewed by Goodwin and Jamison,[2] although no single report involves more than 40 patients, the reports are consistent in revealing a substantial switch (24%–70%) into hypomania or mania when antidepressants are used alone or in combination with lithium in bipolar I subjects. Evidence that lithium substantially reduces antidepressant-associated switch rates[18] is countered by other data arguing against a significant protective effect of lithium.[11] Later reviews support the interpretation of a clinically relevant risk of switches and acceleration of mood cycles from antidepressant treatment.[19] In the case of bipolar II outpatients, there appears to be a minimal rate (3%) of switching into hypomania when very strict criteria for identifying a switch are applied.[20] Independent of the question of efficacy, in the predominantly unipolar outpatients entered into controlled clinical trials, switch rates on selective serotonin reuptake inhibitor (SSRI) treatment are in the 3% to 4% range versus 11% to 12% on TCA treatment.[21]

These considerations bring us to the first of the 3 questions raised above and the only one that has been directly evaluated: Is one class of antidepressants better than another in bipolar depressions? Table 1 summarizes possible treatments, most of which are supported by case reports, but not prospective controlled studies. One exception is provided by Himmelhoch and colleagues[22–24] who, more than 2 decades ago, found tranylcypromine to be superior to imipramine in bipolar patients with anergic depression who were not taking or did not require maintenance mood stabilizers. Many experts agree that monoamine oxidase inhibitors (MAOIs) may have special utility in bipolar and/or other severe depressions, especially when combined with lithium or another mood stabilizer.[25–28]

In controlled studies to evaluate lithium's effectiveness in treating depression compared with placebo, an average of 79% of bipolar patients responded to the drug whereas only 36% of unipolar patients showed improvement (reviewed by Goodwin and Jamison[2]). In relatively larger studies (N = 30 to 45) of populations including both bipolar and unipolar patients, lithium appeared to be as effective as imipramine.[29,30] Interestingly, however, in the single prospective controlled study limited to bipolar patients, subjects showed a significantly greater antidepressant response to imipramine than to lithium.[31] Switches into mania or hypomania were not reported in this relatively early study carried out 3 decades ago.

Given the absence of any definitive series of controlled studies spanning the subsequent decades, it is impossible to make broad general recommendations concerning any advantage of lithium for bipolar depression nor any disadvantage for the TCAs. Many experts do discourage use of TCAs,[32] at least for maintenance, on the basis of earlier reports of poorer long-term outcomes with this class of drugs.[18] Current opinion therefore answers question 2, which concerned maintenance use of an antidepressant in bipolars, with a negative, at least as regards TCAs. Available data argue by default for individualization of treatment, i.e., some bipolar depressions will acutely respond better to lithium, some to TCAs, and some to MAOIs. The question of maintenance treatment with antidepressants will be reconsidered after reviewing arguments for trying newer antidepressants in bipolar depression.

Claims have been made that bupropion or one or another SSRI may have advantages over TCAs for bipolar depression even in the short term.[28,33–36] Unfortunately, most of these studies have not involved true prospective

randomized trial designs of well-characterized bipolar patients. A decade ago, a trial of fluoxetine versus imipramine included a subgroup of patients diagnosed as having bipolar depression. This prospective blind study reported a remarkable 86% response rate in bipolar patients on fluoxetine versus 57% in bipolar patients on imipramine.[33] To date, there has been no report of any attempt to replicate this finding.

In the most recent double-blind study focused on bipolar depression, bupropion and desipramine were added to ongoing treatment with lithium or an anticonvulsant. Both were effective against the depression, but only 1 of 9 patients on bupropion treatment versus 5 of 10 on desipramine treatment cycled into hypomania or mania.[36] An open study has suggested a beneficial effect of bupropion in rapid cycling bipolar II patients.[35] Prospective controlled studies of bupropion in rapid-cycling patients have not been conducted.

The ideal antidepressant treatment for bipolar disorder would be monotherapy with a mood stabilizer that had no significant side effects and was effective acutely for either pole of the illness, as well as being prophylactic for subsequent episodes. To date, for at least some patients who tolerate it well, lithium has been the agent most closely approximating this ideal. Direct evidence for this is found in observations that in patients who are stable on lithium therapy, abrupt discontinuation produces relapses into hypomania, mania, or depression in 50% of the population within 3 to 4 months.[37] It should also be recalled that lithium maintenance is more successful at plasma concentrations above 0.8 mEq/L, a level not always achieved in routine trials.[38]

As already noted, however, lithium is not consistently effective as an antidepressant, and fewer than 50% of patients on lithium maintenance treatment experience acceptable control of their illness in terms of either symptoms or side effects.[15] And, as previously emphasized, the response rate to lithium monotherapy is even less for mixed states and rapid cycling.[39] Systematic controlled studies of lithium (or any other antimanic agent) combined with a specific antidepressant in the treatment of subtypes of bipolar depression, such as mixed states, are not yet available.

There has been considerable interest in various anticonvulsants as alternatives to lithium with most controlled studies focused on their short-term activity as antimanic agents rather than as maintenance therapies prophylactic for both mania and depression. Specific questions have been raised about the real value of the first of those to be studied, carbamazepine, in the long-term treatment of bipolar disorder.[40] There were earlier reports that carbamazepine had significant antidepressant effects in bipolar depression,[41] but subsequent longer term investigations have shown disappointing results in terms of sustained prevention of future episodes.[42] Many studies of carbamazepine were carried out in patients who were selected as nonresponsive to lithium, and overall data can be interpreted as supporting a unique beneficial role of carbamazepine in selected patients.[43]

Table 2. Compounds With α_2-Adrenoceptor Antagonist Activity*

Compound	α_2	α_1	5-HT_2	H_1	D_2	$I_{1/2}$	NEUI
Yohimbine	++	+	++	?	?++	0	0
Idazoxan	+++	+	++	0	0	++	0
Ethoxyidazoxan	++++	+	+	0	0	0	0
Mianserin	++	++	+++++	++++	0	0	++
Mirtazapine	++	+	+++	+++++	0	?	0
Clozapine	++	+++	+++	+++	++	?	0

*Abbreviations: α_2 = α_2-adrenoceptor, α_1 = α_1-adrenoceptor, 5-HT_2 = serotonin type 2 receptor, H_1 = histamine type 1 receptor, D_2 = dopamine type 2 receptor, $I_{1/2}$ = Imidazoline type 1 and 2 binding sites, NEUI = norepinephrine uptake inhibition Symbols: + to +++++ = relative potency at specified site as an antagonist except in the case of $I_{1/2}$ for which functional consequence of binding remains to be demonstrated (+ = least potent and +++++ = most potent). 0 = no binding at concentrations that block a_2 receptors, ? = unknown.

In a now almost classic multicenter study, valproate was shown to be equivalent to lithium in the acute (3 week) treatment of mania.[44] Valproate was equally effective in manic patients who had concomitant depressive symptoms as in those with pure mania, whereas lithium performed best in the latter. A prospective multicenter maintenance study of valproate has been undertaken by its commercial sponsor; results have not yet been published. To date, use of valproate as a first-line treatment for bipolar depression (as opposed to prophylaxis) has not received much support with roughly a 30% average response rate reported even in open studies (reviewed by McElroy and Keck[45]).

Early studies on lamotrigine in bipolar illness have, in contrast, focused as much on the depressed as the manic phase of the illness. An exploratory study of lamotrigine in a relatively substantial number (N = 75) of patients starting when in a depressed, manic, hypomanic, or mixed state reveals it to be well tolerated and suggests that it may prove to be particularly effective in bipolar depression.[46] It should be noted that although carbamazepine, valproate, and lamotrigine are all classified as anticonvulsants, they have different primary biochemical effects. One would not, therefore, expect them to have identical profiles of action in bipolar disorder. Similarly, as noted by authors of many studies cited above, individual bipolar spectrum patients may respond to one anticonvulsant but not to another, further reinforcing the need for individualization of treatment.

Another novel approach to bipolar depression under consideration involves use of agents that inhibit α_2-adrenoceptors. One such compound, idazoxan, was noted to show unexpected efficacy in 2 bipolar inpatients on a National Institute of Mental Health research ward.[47] Subsequent experience with idazoxan in a mixed popula-

Table 3. Specific Pharmacologic Interventions in Bipolar Depression*

Intervention	Advantages	Disadvantages
TCAs	None	Mania; possible rapid cycles; fatal in overdose
SSRIs	Possibly decreased manic switches	Unknown effectiveness; no maintenance data
MAOIs	Efficacy	Side effects
Venlafaxine	Unknown	Possibly like TCAs secondary to norepinephrine
Nefazodone	Possibly sedation	No positive reports for analogue, trazodone
Bupropion	Efficacy	Possible increased mania, dose limits
Lamotrigine	Possible mood stabilizer	Unproven as antidepressant
Mirtazapine	Possible α_2 antagonist	Unknown

*Abbreviations: MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

tion (N = 13) of bipolar and unipolar inpatients involved a 6- to 8-week trial under double-blind conditions. Among the 6 bipolar patients, 5 responded; among the 7 unipolar patients, only 1 responded. In this same group of patients, biochemical changes consistent with α_2-adrenoceptor antagonism could be demonstrated.[48] There remains a possibility, however, that the binding of idazoxan to imidazoline sites may be relevant to its therapeutic effects.[49]

It has not been possible to assess whether a pure α_2 antagonist would be effective. As shown in Table 2, which includes the experimental compound idazoxan and its more potent and selective analogue, ethoxyidazoxan, of the 4 remaining marketed compounds likely to produce some degree of α_2 blockade at clinical doses, none are either that potent or that selective. Yohimbine has been available for some time, but there are no reports of its effects in bipolar patients, and only a negative report of efficacy when added to desipramine in refractory unipolar depression.[50] Interestingly, clozapine is reported to be particularly effective in schizoaffective patients,[51] although no prospective controlled study of clozapine targeted to the depressed phase of either schizoaffective or bipolar depression is available.

Mianserin, which has been available outside of the United States for more than a decade, includes norepinephrine uptake inhibition among its properties[52] and thus may prove indistinguishable from traditional TCAs in terms of effects on bipolar depression. It would, therefore, be of interest to see if mirtazapine, which does not inhibit norepinephrine uptake, shows particular efficacy in bipolar depression, since it includes both α_2 adrenoceptor and 5-HT_2 receptor antagonism,[52] the latter of which seems the most likely basis for the antidepressant effects of another recently introduced antidepressant, nefazodone.

Potential advantages of having the increasing number of agents shown in Table 1 with very different mechanisms of action are suggested by the many small studies claiming some degree of advantage in one or another subgroup of patients with bipolar depression. Unfortunately, no studies with newer agents meet the requirements to draw conclusions: i.e., random allocation of a sufficient number of truly well described and subtyped bipolar depressed patients in prospective double-blind placebo controlled trials.

Table 3 offers a categorization of antidepressants and one anticonvulsant that have either been studied in bipolar depression and/or on mechanistic grounds can be argued to have special potential. TCAs, SSRIs, and MAOIs are considered as classes with the remainder being single compounds. Except for lamotrigine, all agents considered here were developed as antidepressants for the treatment of depression, albeit broadly defined for MAOIs and TCAs (bipolar depressed patients were included in early studies) and more narrowly defined (bipolar patients generally excluded) for those introduced since 1980. The main basis for separation relates to the range of biochemical effects produced by each agent. Venlafaxine, as a newer agent, is considered separately from the SSRIs and TCAs, even though its presumed mode of action involves serotonin and norepinephrine uptake inhibition. It is, however, free of many of the other pharmacologic properties of TCAs, such as antagonism of cholinergic and histaminergic receptors. These actions, however, are unlikely to have any impact on bipolar depression (for good or ill) except for some possible value of antihistaminic sedation in hypomanic or manic phases.

In the absence of definitive studies, one can view the listed drugs as having the virtue of clinical experience, which has generated an appreciation of side effects and the potential of producing benefit in at least some bipolar depressed patients. In any individual bipolar patient, depressions are almost always self-limiting in duration and highly likely to recur. Thus, longitudinally there may be opportunities to try many antidepressants. To assess patients over the long term, tools such as a life chart and/or daily mood chart can be helpful.[32,53]

Given the potential lethality in overdose, uncertain longer term benefits, and apparent relatively high probability of inducing a switch into hypomania or mania, TCAs are not generally recommended as a first choice for bipolar depression. Similarly, the standard MAOIs, despite numerous small studies attesting to their superior potency in some bipolar patients, are an unlikely first-line treatment, given the burden of the MAOI diet and potential for dangerous drug interactions. It would be interesting to have a reversible MAO type A inhibitor available to see how it would perform, since from a safety point of view, such an agent would be far more acceptable than traditional MAOIs.

By default and because they appear to have less chance of precipitating manias and are otherwise safe, SSRIs are probably the most comfortable first-line treatment for use

by most physicians. There seems to be little rationale to turn to venlafaxine except if one believes the addition of norepinephrine uptake inhibition will provide greater efficacy. Although this may ultimately prove to be true in the acute depressed phase, venlafaxine may also carry a risk of a higher switch rate into mania. There is nothing yet to argue for nefazodone in bipolar depression, except perhaps its greater sedative properties, which may not be relevant since its related precursor, trazodone, is very effective as a hypnotic, but has not emerged as particularly useful for bipolar disorder.

The last 3 drugs in Table 3 (bupropion, lamotrigine, and mirtazapine) are the most novel both in terms of mechanism and apparent potential for differential therapeutic action. The warning about increased seizure risk with the standard formulation of bupropion may have limited its use, but the available favorable reports suggest that further studies are warranted. Certainly for those patients taking maintenance valproate (an anticonvulsant), bupropion should be safe. Since bupropion has an unknown primary action but at least secondarily affects norepinephrine and dopamine but not serotonin,[54] it may provide unique therapeutic benefit in some patients. The anticonvulsant lamotrigine may emerge as both antidepressant and antimanic for some patients and should be evaluated for mood stabilization. Unlike the other drugs in Table 3, it was not developed to be used as an antidepressant in unipolar depression, so its antidepressant spectrum of activity is still untested and conjectural.

Mirtazapine has not yet been studied in bipolar depression. It affects both norepinephrine and serotonin function, but in a unique combination (Table 2). It has been argued to be a potent antidepressant based on positive results from inpatient studies,[55] and as noted above shares the property of α_2 antagonism with a class of drugs that may have unique effects. The latter argument is speculative, but is raised by the more general observation that when confronted with the many potential clinical subtypes subsumed under the diagnosis of bipolar depression, a range of biochemically distinct antidepressants is likely to increase the possibilities of effective therapy for any individual patient. And although the present article has focused on pharmacologic treatments, it should not be forgotten that electroconvulsive therapy (ECT) can be an effective intervention in any phase of manic-depressive illness.[2]

While the field waits for more prospective controlled trials, the treating physician can choose among a wide range of drugs that may help bipolar depression. He or she can view each prescription as constituting an individual trial with the understanding that different biochemical mechanisms of action may be associated with differential clinical response. Included in this general approach is a recognition that combinations of agents with widely differing properties are often appropriate and necessary in the acute and long-term treatment of bipolar depression.

Drug names: bupropion (Wellbutrin), carbamazepine (Tegretol and others), clozapine (Clozaril), desipramine (Norpramin and others), fluoxetine (Prozac), imipramine (Tofranil and others), lamotrigine (Lamictal), mirtazapine (Remeron), nefazodone (Serzone), tranylcypromine (Parnate), trazodone (Desyrel and others), venlafaxine (Effexor), yohimbine (Yocon and others).

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