

Bipolar Depression: Treatment Options

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Objective: To review studies on treatments for bipolar depression and make recommendations for practising clinicians treating patients with bipolar depression.

Method: Studies that examined various treatments for bipolar depression were evaluated and rated for evidence of efficacy using Periodic Health Examination criteria. The rating for classification of recommendation for an intervention was made taking both the efficacy and the side effects into consideration.

Results: Mood stabilizers, cyclic antidepressants, monoamine oxidase inhibitors (MAOIs), and electroconvulsive therapy (ECT) are all effective in treating bipolar depression. Almost all antidepressant treatments with the exception of mood stabilizers have been reported to induce a manic-hypomanic switch and rapid cycling.

Conclusions: Mood stabilizers, lithium in particular, are recommended as the first-line treatment. Addition of a second mood stabilizer or a cyclic antidepressant would be an appropriate next step. Newer agents such as lamotrigine offer considerable promise in treating bipolar depressed patients.

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Key Words: bipolar depression, lithium, antidepressants, mania

Bipolar depression is defined as the occurrence of a major depressive episode in a patient who has had at least one hypomanic or manic episode (1). This condition affects approximately 1% of the general population (2). Depression may be the first affective episode in more than 50% of patients with bipolar disorder (3). In such cases, factors such as bipolar

family history, presence of psychotic features, chronicity of depressive episode, early age at onset, and presence of atypical symptoms, such as hypersomnia, hyperphagia, and a significant psychomotor retardation, may be helpful in predicting a bipolar course (4,5).

This condition is associated with considerable morbidity and mortality. The mean duration of bipolar depressive episodes is considerably longer than manic episodes, and more than 20% of bipolar depressive episodes run a chronic course (6). Despite this, few controlled clinical trials have rigorously examined the effectiveness of specific interventions in treatment of bipolar depression. Most of our current state of knowledge about treatment of depression is derived from clinical trials that systematically excluded bipolar depressed patients. Although no consistent biochemical abnormalities have emerged between unipolar and bipolar depressed patients (7), several other lines of evidence pertaining to symptoms (8-10), course of illness (11-14), and response to treatment (15,16) have accumulated over the past few decades, supporting the bipolar-unipolar dichotomy. Recent long-term follow-up studies examining the course and outcome (17) and the stability of polarity distinction (5) provided further support for the unipolar-bipolar distinction. Effective treatments for unipolar depressed patients, therefore, may or may not be effective for bipolar depressed patients.

In view of the concerns about generalizability of data, the evidence used to formulate treatment recommendations in this paper was based mainly on studies of bipolar depressed

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patients. In cases where data were not available on bipolar depressed patients, data from studies of unipolar depressed patients were used, mainly out of necessity. This necessity is less problematic if the limitations of generalization of data are kept in mind. Apart from a potential difference in the effectiveness of antidepressant treatments for 2 conditions, the treatment of bipolar depression is often complicated by the fact that many antidepressant medications have been reported to induce a manic or hypomanic switch and rapid cycling in this population (18–22). This was the paramount issue in developing an algorithm for the treatment of bipolar depression.

Although extensive data are available on the efficacy of psychosocial treatments in unipolar depression, little is known about their efficacy in bipolar depression. This review will briefly touch on the role of such treatments (see the article by Parikh and others [p 74S] for a more detailed discussion) and then examine the efficacy of various medications in treating bipolar depression. We will then suggest clinical recommendations and an algorithm for a clinician to treat patients with bipolar depression.

Psychosocial Interventions

Bipolar disorder is associated with severe occupational and social deficits. Such deficits may represent residual temperamental disturbances of a “subaffective” nature and/or the psychological sequelae of illness episodes (for example, shame, low self-esteem) (23,24). Mild depressive symptomatology may be successfully treated with cognitive-behavioural or interpersonal therapy, most often in combination with pharmacological interventions. Each of these psychosocial interventions requires some tailoring to the needs of individual patients. Controlled experimental trials of “manualized” interventions (that is, written guidelines for how and when treatment should be administered) are currently being conducted (23). These standardized approaches may optimize the implementation of psychosocial interventions by providing practical and reproducible approaches that have empirically proved effectiveness in bipolar patients. The quality of evidence for psychotherapy was rated as “3,” and recommendation for clinical practice was determined to be “C” (Table 1).

Pharmacological Treatments

Lithium

An open study (25) and 7 of 8 double-blind, placebo-controlled crossover studies (15,16,26–31) reported lithium to be superior to placebo in treating bipolar depression. In these trials, response rates to lithium ranged from 64% to 100%, and relapse of depressive symptoms ranged from 38% to 70% when switched to placebo. In the only double-blind, placebo-controlled parallel-group trial that compared lithium to imipramine, reductions in mean depressive scores were 32% and 58% for lithium and imipramine, respectively (32). In summary, clinical trials suggest that lithium is superior

Table 1. Quality of evidence and recommendations for treatments: bipolar depression

Treatment	Quality of evidence ^a	Working group classification of recommendation ^b	
		Alone	With mood stabilizer
Psychotherapy	3	C	
Lithium	1	A	
Divalproex	2.3	C	
Carbamazepine	1	C	
Lamotrigine	2.3	C	B
TCA's	1	D	C
MAOIs	1	D	B
SSRIs	1	D	B
Bupropion	1	D	B
Serotonergic noradrenergic reuptake inhibitors (SNRIs)	3	D	C
ECT	2.3	B	B
Light therapy	3	D	C
Sleep deprivation	3	D	C

^aQuality of evidence rating system:

- 1 At least one randomized controlled trial.
- 2.1 Well-designed controlled trial without randomization.
- 2.2 Well-designed cohort or case-controlled studies, preferably multicentre or from more than one research group.
- 2.3 Very significant results from uncontrolled trials from more than one centre comparing results with and without intervention.
- 3 Opinions of respected clinical authorities based on clinical experience, descriptive studies, or reports of expert committees.

^bClassification of recommendations:

- A Good support for the intervention to be considered in clinical practice.
- B Fair support for the intervention to be considered in clinical practice.
- C Poor support for the intervention to be considered in clinical practice.
- D Fair support for the intervention to be excluded from clinical practice.
- E Good support for the intervention to be excluded from clinical practice.

to placebo in treating bipolar depression, but the efficacy of lithium in comparison to antidepressants remains uncertain. Overall, the quality of the evidence for lithium treatment rates as “1,” and the classification of recommendations was determined to be “A” (see Table 1).

MAOIs

Double-blind trials involving subjects with anergic bipolar depression have demonstrated response rates of approximately 75% and 50% with tranylcypromine and imipramine interventions, respectively (33–35). Fewer dropouts and lower switch rates were noted in the tranylcypromine-treated group compared with imipramine-treated subjects. Phenelzine has been reported to be effective in case studies of patients with bipolar depression (36). In the only double-blind trial that examined the efficacy of moclobemide, a reversible inhibitor of monoamine oxidase A, 53% of patients with bipolar depression responded compared with 60% in the imipramine-treated group (37). MAOIs have been reported to cause a switch of mood, but hypomania is more common than mania. Overall, the quality of evidence for MAOI treatment is “1,” and the classification of recommendations was set at “D” in view of the concern about a manic or hypomanic

switch. The use of MAOIs in combination with a mood stabilizer, however, received a "B"-level classification.

Heterocyclic Antidepressants

A number of double-blind trials investigating the efficacy of the tricyclic antidepressant (TCA) imipramine reported an average response rate of 55% (34,35,37–38). The response rate in fluoxetine-treated subjects may be marginally higher than in those treated with TCAs (38,39), with switches reported in both groups. Case reports, as well as results of a double-blind trial, suggest that bupropion may be effective in treatment of bipolar depressed patients (40,41). Although no study directly compared the switch rate in patients on TCAs with those on selective serotonin reuptake inhibitors (SSRIs), data from clinical trials suggest that TCAs more commonly cause a switch into mania (more than 10%) than SSRIs (less than 5%) (21), and TCAs more commonly induce rapid cycling (22). In view of this, there is growing consensus that TCAs should be avoided in bipolar depression. As depression is a common first mood disorder episode in early-onset bipolar disorder, and because there is little evidence for the efficacy of TCAs in adolescents, TCAs should be avoided. The quality of evidence concerning these treatment interventions is strong: "1." The working group classification of recommendations was "D" in view of the concern about a switch into mania or hypomania. When used in combination with a mood stabilizer, however, the rating is "B" for SSRIs and bupropion, and it is "C" for TCAs.

Anticonvulsants and Benzodiazepines

Double-blind, placebo-controlled trials report an approximate 70% response rate to carbamazepine and a 50% relapse rate with placebo substitution in the treatment of bipolar depression (42–44). In patients with rapid-cycling bipolar disorder, 47% had antidepressant response to divalproex sodium in an open prospective trial (45). Despite the optimistic report of a small case series (46), there is little robust current evidence to support the use of divalproex in acute bipolar depression. In 2 large open-labelled series from at least 3 centres (47,48), lamotrigine has been reported to be a promising agent in the treatment of bipolar depression, although in a significant number of the cases, lamotrigine was added to either divalproex or lithium. Double-blind controlled studies are currently under way to test the efficacy of lamotrigine in bipolar depression. There is no published literature on gabapentin, although studies are currently being conducted with this compound.

Although a double-blind trial has demonstrated a response rate of 60% in adinazolam-treated bipolar depressed patients, the use of this agent as an antidepressant is not recommended given the risk of abuse potential and dependency and the availability of other effective agents with a more favourable risk-to-benefit profile (49). There is little or no evidence that other benzodiazepines have any efficacy in bipolar depression. Overall, the quality of evidence for carbamazepine is

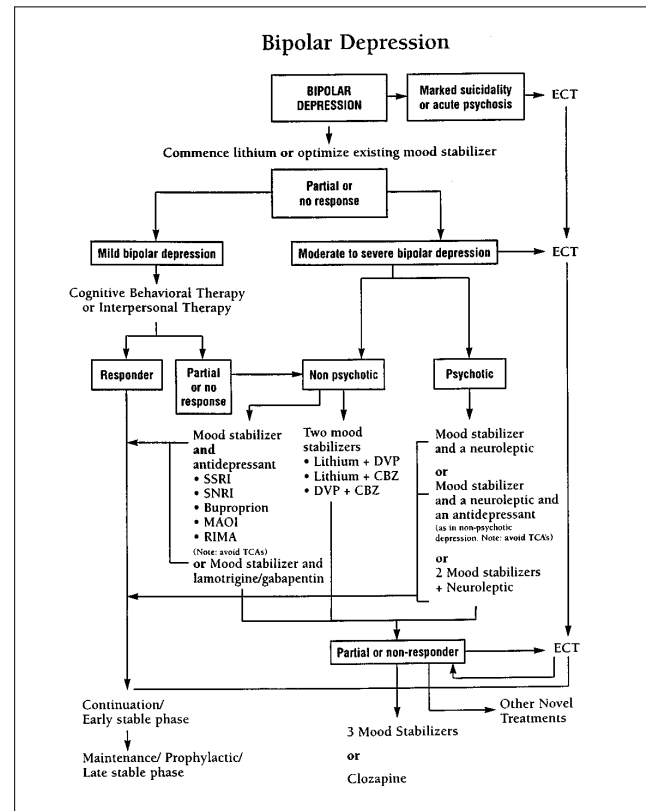


Figure 1. Treatment algorithm for bipolar depression reproduced courtesy of the Canadian Network for Mood and Anxiety Treatments (CANMAT).

"1" and for divalproex and lamotrigine is "2.3." The working group recommended a classification for all 3 agents of "C," but the recommendation would be "B" for lamotrigine if used in combination with another mood stabilizer such as lithium or divalproex sodium.

Miscellaneous Treatments

A small double-blind trial reported levosulpiride to have a comparable response rate (90%) to that of amitriptyline in bipolar depressed patients (50). Much less robust evidence of varying rates of response to dopamine receptor agonists (51,52), total (53) and partial sleep deprivation (54,55), and light therapy (56) have also been reported. Dopamine receptor agonism has been associated with a high switch rate into hypomania or mania (51,52). Clozapine has been reported to be effective in bipolar depression in multiple case series studying refractory bipolar depression (57). Studies with olanzapine are currently being conducted, but as yet there is no published literature with this compound.

Pharmacological Augmentation and Combinations

Lithium augmentation of TCA- (58) and carbamazepine-resistant patients (59) is reported to have led to marked improvement in 36% and 46% of study subjects, respectively. The use of TCAs is not advisable, however, because they

carry a risk of switch into mania and induction of rapid cycling. Although the superiority of bupropion augmentation of mood stabilizers has been inconsistent, conversion of nonresponder to responder rates has exceeded 60% in 2 open studies (60,61) and a double-blind trial (41). Further, bupropion appears to have a lower risk of switching patients into mania or accelerating cycles. Case reports involving subjects receiving antidepressants suggest that carbamazepine administered concurrently with lithium may be effective in lithium-resistant bipolar depressed patients (62,63).

ECT

Several open prospective trials and a number of retrospective studies have reported the efficacy rate of ECT in bipolar depression to be at least 50% and as high as 100% (64–69). The rate of switch to elevated mood of bipolar depressed patients treated with ECT appears equivalent to that associated with conventional antidepressant treatment (18). ECT is a bimodal treatment, however, and continuing with the course of ECT can produce euthymia. The ratings for quality of evidence and treatment recommendations were “2.3” and “B” for ECT.

Switch into Hypomania or Mania during Treatment for Depression

ECT is no more likely than antidepressants to precipitate a switch into hypomania or mania and to induce rapid cycling, whereas SSRIs may have decreased rates of switch compared with TCAs (18,21). A recent study reported that mania in one-third and rapid cycling in one-fourth of refractory bipolar patients was attributable to antidepressants and not to the expected course of illness (70). There is growing clinical consensus that in patients with depression who have no prior history of bipolar disorder, a switch into mania or hypomania while they are on antidepressants may reflect an underlying bipolar diathesis. Although there is a continuing debate as to the best treatment strategy for such patients, many experienced clinicians and experts in the field treat these patients as suffering from a bipolar disorder, and the guidelines group concurs with such practice.

Clinical Recommendations

The quality of evidence and the working group classification of recommendation for each treatment modality are summarized in Table 1. The working group recommends that the mood stabilizer lithium should be the first choice in the treatment of bipolar depression (Figure 1) (71). In depressions with marked suicidality or severe psychosis, ECT should be considered earlier in the treatment algorithm. TCAs have the greatest predilection to induce a switch into mania and rapid cycling, so they should be avoided in the treatment of bipolar depression. If a patient with bipolar depression has been started on a TCA and appears to be responding well, the

robust use of concomitant mood stabilizers such as lithium or divalproex is advisable.

Should treatment with an antidepressant become necessary to resolve depressive symptoms, SSRIs and bupropion are preferable because they may have a lower propensity to induce a mood switch. Bupropion is available in Canada directly from the manufacturers, although the sustained-release form is expected to be available shortly. There is no evidence that one class of antidepressants is better than another in terms of efficacy in the treatment of bipolar depression. It is inadvisable to use antidepressants without mood stabilizers in bipolar disorder. The consensus of the group was that the antidepressant medication should be gradually reduced and withdrawn completely within 6 to 12 weeks of remission of depressive symptoms. Despite the promising results with lamotrigine in the case series reported, further study of this compound is needed both in monotherapy and in combination with either divalproex or lithium.

Clinical Implications

- Bipolar depression can be treated effectively with medication.
- Switch into mania or hypomania is a common problem with antidepressant medication.
- Antidepressant medication should be withdrawn within 6 weeks of remission of depressive symptoms.

Limitations

- Many studies had a small number of subjects.
- Many antidepressant medications have not been tested in bipolar depressed patients.

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Résumé

Objectif : Examiner des études sur les traitements de la dépression bipolaire et faire des recommandations aux cliniciens en exercice qui traitent des patients atteints de dépression bipolaire.

Méthode : Des études ayant porté sur divers traitements de la dépression bipolaire ont été évaluées et cotées en fonction des résultats relatifs à l'efficacité et au moyen des critères de l'examen médical périodique. On a créé une échelle de classement des recommandations d'intervention en tenant compte à la fois de l'efficacité et des effets secondaires.

Résultats : Les psychorégulateurs, les antidépresseurs cycliques, les inhibiteurs de la monoamine oxydase et l'électrochoc sont tous efficaces afin de traiter la dépression bipolaire. Presque tous les traitements antidépresseurs, à l'exclusion des psychorégulateurs, provoqueraient le passage de la manie à l'hypomanie et des cycles rapides.

Conclusions : Les psychorégulateurs, en particulier le lithium, sont recommandés comme traitement de prédilection. L'ajout d'un deuxième psychorégulateur ou d'un antidépresseur cyclique serait indiqué à l'étape suivante. De nouveaux agents, comme la lamotrigine, sont très prometteurs en vue de traiter les patients atteints de trouble bipolaire déprimé.