

Review Article

Medicating mood with maintenance in mind:
bipolar depression pharmacotherapy

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Objectives: Bipolar depression is a core feature of bipolar disorder, a phase in which many patients spend the majority of time and one that confers a significant degree of burden and risk. The purpose of this paper is to briefly review the evidence base for the pharmacotherapy of bipolar depression and to discuss the recommendations for its optimal management.

Methods: A detailed literature review was undertaken with a particular emphasis on pharmacological treatment strategies for bipolar depression across the acute and maintenance phases of the illness. Electronic library and Web-based searches were performed using recognised tools (MEDLINE, PubMed, EMBASE and PsychINFO) to identify the pertinent literature. A summary of the evidence base is outlined and then distilled into broad clinical recommendations to guide the pharmacological management of bipolar depression.

Results: Partitioning treatment into acute and maintenance therapy is difficult based on the paucity of current evidence. The evidence from treatment trials favours the use of lithium and lamotrigine as first-line treatment in preference to valproate, and indicates that, for acute episodes, quetiapine and olanzapine have perhaps achieved equivalence at least in terms of efficacy. However, the effectiveness of the atypical antipsychotics in maintenance therapy is constrained by the potential for significant side effects of individual agents and the lack of both long-term research data and clinical experience in treating bipolar disorder as compared to other agents. Conversely, lithium and the anticonvulsants are generally slower to effect symptomatic change, and this limits their usefulness.

Conclusions: There has been a tendency for research trials of bipolar depression to differentiate the illness cross-sectionally into the acute and maintenance phases of bipolar depression; however, in clinical terms, bipolar depression invariably follows a longitudinal course in which the phases of illness are inextricably linked, and useful acute treatments are typically continued in maintenance. Therefore, when *medicating mood* in acute bipolar depression it is imperative to keep *maintenance in mind* as it is this aspect of treatment that determines long-term success.

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Another flaw in the human character is that everybody wants to build and nobody wants to do maintenance.

Kurt Vonnegut (1922–2007)

Bipolar disorder, formerly known as manic-depressive illness, has a long history (1, 2) and is one of the top public health concerns worldwide (3). It is defined by the DSM-IV (4) largely on the basis of its manic phase and further subdivided into subtypes I and II. The latter, bipolar II disorder, is characterised by a less severe and shorter phase of mania, termed hypomania, whereas in bipolar I disorder, mania lasts a period of one week or more and features specific changes in mood, energy, and sleep, or culminates in hospitalisation [see DSM-IV-TR (4) for symptoms and signs of bipolar disorder and definitions of its subtypes].

The definition of bipolar disorder, its subtypes, and its partitioning into phases of illness have recently become the subject of much debate because clinically, mania and hypomania do not usually constitute the predominant mood state of the illness, and hypomania is often only detected retrospectively. Indeed, this undue bias toward one aspect of the illness that is reflected in earlier research and current classification systems has caused problems in clinical practice with the detection and diagnosis of bipolar disorder, and unnecessarily skewed the focus of pharmacological management (5, 6).

Bipolar depression

Diagnostic delay

The onset of bipolar disorder is usually insidious and begins with depressive symptoms that are often only recognised retrospectively, once a diagnosis of bipolarity has been made. Typically, the illness begins with nonspecific symptoms, followed by depression, and, on average two years later, hypomania and mania are heralded (7). The initial symptoms of depression usually emerge during adolescence and are understandably difficult to detect because of the tumultuous developmental milieu within which they arise (8). Further, even when depressive symptoms are successfully identified, they are often quite reasonably assumed to be indicative of major (unipolar) depression as opposed to bipolar depression, and hence it is not uncommon for the diagnosis of bipolar disorder to be delayed for up to a decade or more (9). During this period of undetected illness, or misdiagnosis, individuals with bipolar disorder usually receive suboptimal treatment (10, 11). In instances where the delay in diagnosis is considerable, and

especially if during this time conventional antidepressants have been administered, the risk of exacerbating the illness is heightened and its prognosis may be worsened.

In essence, the difficulty in detecting the onset of bipolar disorder stems from our inability to separate bipolar depression from major depression on the basis of symptomatic profile alone. The signs and symptoms of the depressive phase of both phenotypes have undergone detailed comparison, and some features are considered to be suggestive of bipolarity (see Table 1); however, none is pathognomic or sufficiently characteristic (12, 13). To this end, current research is focused on identifying early clinical and biological markers of bipolar disorder. On a probabilistic basis, the phenomenology of bipolar and unipolar depression are subtly divergent (14). Neurocognition has been shown to be compromised in adults with bipolar disorder, not only in the acute phases of illness (depression and mania), but also in euthymia, suggesting a trait deficit (15–19). Indeed, attempts at identifying bipolar cognitive deficits in adolescents and pediatric populations are proving to be promising (20, 21). Similarly, putative functional neuroimaging markers of bipolarity that have been identified in adults (22–24) are being sought in younger bipolar populations (25, 26). However, as yet, no robust or reliable neurobiological marker of bipolar depression has been identified, and clinical diagnosis remains contingent on a history of mania/hypomania (14, 27).

Burden of illness

Even after an accurate diagnosis of bipolar disorder has been made, it is increasingly evident that it is the successful management of bipolar depression that is pivotal to long-term recovery. The majority of patients with bipolar disorder, bipolar II more

Table 1. Comparative features of bipolar depression and major (unipolar) depression showing those that favour a diagnosis of bipolarity

Aspect of illness	Features indicative of bipolarity
Phenomenology	Atypical symptoms Irritability Melancholia Psychomotor retardation/agitation Psychosis
Course of illness	Episodes of depression are <i>brief</i> Occur at an <i>early</i> age Have pattern of <i>recurrence</i> or rapid cycling
Response to antidepressants	More likely to develop: Tolerance Treatment-induced mania Rapid cycling or mixed state

so than bipolar I, spend a considerable proportion of their life suffering from acute episodes of depression and subsyndromal depressive symptoms (11, 28). Therefore, it is no surprise that the disability associated with bipolar disorder is largely attributable to the depressive phase of the illness (27), and it is during periods of bipolar depression that patients are at their most vulnerable. Indeed, the lifetime risk for suicide attempts and completed suicide in bipolar disorder is one of the highest amongst neuropsychiatric illnesses and is particularly high during the depressive phase of the illness (29–31). These observations, and the realization that the treatment of bipolar disorder is essentially the treatment of bipolar depression, underscore the need for its effective and prompt management.

Therefore, in this paper we briefly review the evidence for the use of medications in the treatment of bipolar depression, given that, since the middle of the 20th century, pharmacotherapy has formed the crux of its management and features prominently in contemporary clinical practice guidelines (32–36). Further, we propose that when managing bipolar depression, it is essential to keep *maintenance in mind* and, in particular, to consider the long-term prophylactic efficacy and tolerability of agents when selecting treatment for acute depression.

Methods

A detailed and focused review of the literature on bipolar depression and aspects of bipolar disorder that relate specifically to its depressive phase was conducted by the authors. Electronic library and Web-based searches were performed using recognised tools (MEDLINE, PubMed, EMBASE, and PsychINFO) so as to identify the pertinent literature. In addition, Cochrane reviews, meta-analyses, review articles, randomised controlled trials (RCTs), and other sources of information known to the authors such as books and government reports were scrutinized. Data and material from all of these sources have been discussed and a synthesis of the current evidence base for the treatment of bipolar depression has been graded and summarised in tables and figures using the National Health and Medical Research Council (NHMRC) Levels of Evidence criteria (37) (see Table 2).

Results

Phases of illness and treatment

Traditionally, the management of bipolar disorder has been divided according to its phases of illness, namely, acute mania, acute depression, and main-

Table 2. National Health and Medical Research Council (NHMRC) levels of evidence criteria (37)

Level	NHMRC criteria
Level I	Evidence obtained from a systematic review of all relevant randomised controlled trials
Level II	Evidence obtained from at least one properly designed randomised controlled trial
Level III	Evidence obtained from well-designed prospective trial (non-randomised controlled trial), comparative studies with concurrent controls and allocation not randomised, case-controlled or interrupted time series with a control group
Level IV	Evidence obtained from case series, either post-test or pretest/post-test
Level V	Expert opinion

tenance therapy. Further, a notional boundary between acute treatment and maintenance therapy has been drawn on the basis of treatment *response* and *remission*, and all of these terms, along with the terms *relapse* and *recovery*, have been adopted from the management of major depression (38). However, when extrapolating to bipolar depression (39), an additional term is needed to capture the development of treatment-emergent hypomania/mania that is usually referred to as switching (40). This raises additional nosological difficulties that are beyond the scope of this paper; however, in the context of managing bipolar depression, the possibility of inducing a switch is an important consideration that will be discussed briefly when considering the clinical utility of antidepressants. The separate consideration of data pertaining to acute and maintenance treatments is a necessary consequence of the manner in which medication trials have been conducted. However, it is important to note that in practice this dichotomy is often difficult to apply, and that although the efficacy data of medications are considered according to ‘phases’ of treatment, the clinical discussion in this paper regards these as less distinct and proposes a more continuous model for the management of bipolar depression.

Pharmacotherapy

The efficacy of each agent in the treatment of acute bipolar depression and maintenance therapy is discussed and a summary statement is then provided. Important tolerability issues are also noted where relevant, along with side effects. More detailed dosing considerations and adverse effects are provided in Table 3.

Lithium

Acute bipolar depression efficacy. Early placebo-controlled unipolar and bipolar depression trials of

Table 3. Side effects and dosing consideration for pharmacological agents commonly used in bipolar depression^a

Medication	Side effects		Dosing considerations
	Common (incidence ≥1%)	Uncommon or rare (incidence <1%) ^b	
Lithium	<p>GIT: nausea, vomiting, epigastric discomfort, dry mouth, metallic taste, diarrhea, weight gain</p> <p>CNS: fatigue, headache, difficulty concentrating, vertigo, fine tremor</p> <p>Skin: dry skin, exacerbation of psoriasis or acne, rash</p> <p>Metabolic: hypermagnesaemia, hypercalcaemia, hypothyroidism</p> <p>Other: benign ECG changes, leucocytosis</p> <p>Lithium toxicity: signs include loss of balance, increasing diarrhea, vomiting, anorexia, weakness, ataxia, blurred vision, tinnitus, polyuria, coarse tremor, muscle twitching, irritability and agitation. Drowsiness, psychosis, disorientation, seizures, coma and renal failure may occur</p>	<p>Nephrogenic diabetes insipidus, hyperparathyroidism, memory impairment, hair loss, arrhythmias, hyperthyroidism</p>	<p>Recommended therapeutic range 0.5–1.2 mmol/L (lower end of range recommended in maintenance). Risk of toxicity increases markedly >1.5 mmol/L (>3.5 mmol/L is potentially lethal); toxicity can also occur within the ‘therapeutic range’ (particularly in the elderly). Abrupt reduction of >0.2 mmol/L increases risk of relapse. Lithium concentration can be affected by other medications (e.g., ACE inhibitors and NSAIDs) and sodium depletion (e.g., gastrointestinal disturbance). There can be a delay of 6–8 weeks for an antidepressant effect.</p>
Valproate	<p>GIT: nausea, vomiting, abdominal cramp, anorexia, diarrhea, indigestion (especially with nonenteric coated preparations), increased appetite and weight gain</p> <p>CNS: sedation, tremor</p> <p>Skin: transient hair loss</p> <p>Other: thrombocytopenia, elevated liver transaminases, asymptomatic elevations of ammonia</p>	<p>Severe hepatic dysfunction, pancreatitis, extrapyramidal syndrome, hyperammonaemic encephalopathy</p>	<p>Therapeutic range not clearly established, 350–700 mmol/L is suggested as a guide.</p>
Carbamazepine	<p>GIT: dry mouth, vomiting, diarrhea, anorexia, constipation, abdominal pain</p> <p>CNS: dizziness, headache, ataxia, drowsiness, blurred vision, diplopia</p> <p>Skin: rash</p>	<p>Agranulocytosis, aplastic anaemia, severe skin reactions (including Stevens-Johnson syndrome), SIADH, arrhythmias, orofacial dyskinesias, hepatitis</p>	<p>Therapeutic range not clearly established, 20–50 mmol/L is suggested as a guide. Carbamazepine impacts on the p450 (CYP) system and can affect drugs also metabolised by this system (e.g., antidepressants, anticonvulsants, risperidone, haloperidol).</p>
Lamotrigine	<p>GIT: dry mouth, nausea, vomiting</p> <p>CNS: diplopia, dizziness, ataxia, blurred vision, headache, irritability, somnolence, tremor, asthenia, insomnia</p> <p>Skin: maculopapular rash, Stevens-Johnson syndrome (0.3–2.0% in children)^c</p> <p>Other: arthralgia</p>	<p>Hepatic failure, blood dyscrasias, lupus-like reaction. Severe skin reactions including Stevens-Johnson syndrome and Lyell syndrome^c</p>	<p>No demonstrated benefits in measuring serum lamotrigine. To prevent serious skin reaction, initiate at a low dose and increase slowly. Dosage may need to be adjusted if combining with other medications, particularly valproate and carbamazepine</p>
Atypical antipsychotics	<p>Metabolic: weight gain, dyslipidaemia, hyperglycaemia, hyperprolactinaemia</p> <p>Extrapyramidal symptoms: tremor, akathisia, rigidity, slowing, dystonia</p> <p>Anticholinergic reactions: constipation, dry mouth, blurred vision, urinary retention</p> <p>Other: sedation, increased appetite, sexual dysfunction, GI upset, peripheral oedema, nausea, cerebrovascular events, especially in the elderly (stroke, TIA), orthostatic hypotension, tachycardia</p>	<p>Jaundice, neuroleptic malignant syndrome, seizures, tardive dyskinesia, ECG changes (increased QT interval), SIADH, temperature irregularity, blood dyscrasias, arrhythmias, cardiac arrest, seizures, hepatic fibrosis, lupus</p> <p>Clozapine: agranulocytosis (1%), myocarditis, cardiomyopathy, seizures</p>	

Table 3. (Continued)

Medication	Side effects		Dosing considerations
	Common (incidence $\geq 1\%$)	Uncommon or rare (incidence $< 1\%$) ^b	
SSRI antidepressants	<p>GIT: nausea, diarrhea</p> <p>CNS: dizziness, headache, tremor, agitation, insomnia, drowsiness</p> <p>Anticholinergic reactions: dry mouth</p> <p>Other: myalgia, sweating, weakness, anxiety, weight gain or loss, sexual dysfunction, rhinitis</p>	<p>Extrapyramidal reactions: including tardive dyskinesia and dystonia</p> <p>Other: sedation, confusion, palpitations, tachycardia, hypotension, hyponatraemia (as part of SIADH), abnormal platelet aggregation/haemorrhagic complications (e.g., bruising, epistaxis, gastrointestinal and vaginal bleeding), elevated liver enzymes, hepatitis, hepatic failure, galactorrhoea, blood dyscrasias, seizures, akathisia, paraesthesia, taste disturbance</p>	<p>Serotonin toxicity is a potentially life-threatening adverse drug reaction with cognitive, autonomic and somatic effects. Some combinations with other drugs is contraindicated (especially MAOIs or within 14 days of stopping an MAOI and meclobemide or within 2 days of stopping meclobemide) should be avoided.</p>

^aThis table is not exhaustive and when prescribing the reader is advised to consult treatment specific product information and recognised sources of information (34, 210, 211).

^bIn addition, every medication has the potential to cause a hypersensitivity syndrome (fever, severe skin reactions, lymphadenopathy, hepatitis, haematological abnormalities, facial oedema).

^cRisk is greatest with high initial doses or when combined with valproate.

GIT = gastrointestinal tract; CNS = central nervous system; ECG = electrocardiogram; ACE = angiotensin-converting enzyme; NSAIDs = non-steroidal anti-inflammatory drugs; SIADH = syndrome of inappropriate antidiuretic hormone secretion; TIA = transient ischaemic attack; MAOI = monoamine oxidase inhibitor; SSRI = selective serotonin reuptake inhibitor.

lithium appeared favorable (41–49) despite their small sample sizes and short duration; however, the abrupt cessation of lithium in these studies is thought to have elevated the relapse rate in the placebo group (5). A meta-analysis (50) of unipolar depression studies (45, 48, 51) also identified lithium as superior to placebo (52–57) with bipolarity or a family history of bipolar disorder further predicting a better outcome. Indeed, it has been argued persuasively that the efficacy of lithium is best demonstrated in ‘classic bipolar disorder’ and that the variability of response seen clinically reflects poor patient selection (58, 59).

Contrary to this position, recent data from the EMBOLDEN I trial have failed to demonstrate any differences between lithium (600 mg/d) and placebo in the acute treatment of bipolar depression (60). However, plasma lithium levels have been shown to be critical in determining efficacy and need to be maintained at or above 0.8 mmol/L, suggesting that this may also explain its poor performance in some studies.

Clinically, there is often a 6–8-week delay in the acute antidepressant effect of lithium in the treatment of both bipolar (61) and unipolar depression (50, 56, 62) and this limits its usefulness. Under-

standably, clinicians remain reluctant to use lithium monotherapy as an antidepressant (33) and regard it predominantly as an antimanic agent with prophylactic properties (63). However, on balance, lithium does demonstrate sufficient efficacy in treating acute bipolar depression and hence many guidelines continue to position its use first-line. Studies to identify lithium responder characteristics and further establish its efficacy are warranted so as to better establish its antidepressant role (64, 65).

Maintenance efficacy. The efficacy of lithium in the maintenance of bipolar disorder is well established (66), but as shown by two recent meta-analyses of lithium therapy, it appears to be more effective in preventing recurrences of mania than bipolar depression (67, 68). However, the bias probably reflects poor patient selection, because early research suggests that lithium is effective in treating patients with classic bipolar disorder (69) and that it has prophylactic action in recurrent depression (58, 70).

Tolerability and side effects. Many of the side effects associated with lithium therapy are related to peak serum levels that can be diminished simply

by changing the dosage or frequency of administration. More persistent side effects can be managed with symptomatic medications, such as beta blockers for tremor, topical preparations for skin-related conditions, or diuretics for oedema, polydipsia or polyuria. Further, administering lithium at meal times, changing preparations, or adding dietary fibre may assist with gastrointestinal disturbances. Hypothyroidism is common and occurs in up to a third of patients treated with lithium long term, but can usually be treated with thyroxine. Chronic use of lithium, greater than 10 years, is associated with decreased renal function in 20% of patients, of which a small minority progress to renal failure and necessitate hemodialysis (71).

In summary, in patients with classic bipolar disorder, lithium has discernible efficacy in treating both acute depression and preventing depressive relapse. However, clinically, its effectiveness is limited by its slow onset of antidepressant action and routine administration at subtherapeutic doses that are commonly prescribed to avoid adverse effects (72).

Anticonvulsants

Valproate

Acute bipolar depression efficacy. There are few trials that have specifically examined the use of valproate in the treatment of bipolar depression, but two recent pilot RCTs report its superiority over placebo (73, 74). These findings corroborate the result of an earlier open trial of medication-naïve patients with bipolar II depression who reported a positive response to valproate (75). Like lithium, a comparison of response rates in uncontrolled trials of valproate suggests that it has greater efficacy in treating mania as compared to bipolar depression; however, the data are insufficient to be conclusive (76).

Maintenance efficacy. The widespread use of valproate in bipolar disorder is notable given the paucity of evidence in support of its efficacy as a maintenance agent. In fact, a Cochrane review identified only one randomised, placebo-controlled trial eligible for inclusion (77), which reported equivocal findings (78). However, a post hoc analysis of these data found that in relation to depression, valproate was superior to lithium, particularly in those patients who had responded to valproate during an acute manic phase, or those with a more severe course of illness (79).

Subsequent to this, two randomised comparator trials have included valproate as maintenance

treatment. The results comparing the efficacy of valproate to olanzapine were mixed (80); however, in the second study, valproate was as effective as lithium in the maintenance of rapid-cycling bipolar disorder over a period of 20 months (80, 81).

Side effects. The majority of side effects associated with valproate are dose-related and self-limiting, and can be managed with dose adjustment, change of preparation, or symptomatic treatment (32). Although less dangerous than lithium, valproate can also be toxic in overdose, and fatalities have been reported as a consequence of central nervous system and respiratory depression.

In summary, valproate has shown modest efficacy in the treatment of acute bipolar depression and in the prevention of depressive relapse; however, the evidence base is surprisingly lacking and many of the studies have been criticised for being insufficiently powered and small in sample size.

Lamotrigine

Acute bipolar depression efficacy. Lamotrigine has been shown to be superior to placebo in two early RCTs of bipolar depression (82, 83), but recent findings have prompted its efficacy to be questioned (84). Subsequent to their original trial, Calabrese and colleagues reported on a further four RCTs in which lamotrigine monotherapy did not differ from placebo in the acute treatment of bipolar depression (84). However, a large placebo response across these trials may have contributed to the lack of sufficient separation between lamotrigine and placebo, and it is noteworthy that a recent meta-analysis of lamotrigine bipolar depression studies found a modest effect size in favour of lamotrigine over placebo (85). In practice, its necessarily slow titration over 4–6 weeks to a therapeutic dose delays its antidepressant effect and, perhaps somewhat akin to lithium, this contributes to its perceived diminished efficacy in the treatment of acute depression. Further active comparator and adjunctive therapy studies are warranted, particularly as findings from a recent randomised, double-blind, placebo-controlled trial suggest that lamotrigine may also be effective as an adjunct to lithium (86).

Maintenance efficacy. In contrast to the equivocal data for lamotrigine in the treatment of acute depression, its efficacy in preventing recurrence of mood episodes, particularly depressive episodes, has been demonstrated in two RCTs (87, 88). A pooled analysis of these two studies and a more recent meta-analysis have showed that lamotrigine

is particularly effective in preventing depressive relapse (68, 89).

A recent open randomised trial, designed to mimic clinical practice, found the overall effectiveness of lamotrigine to be comparable to lithium at six months, but, like the aforementioned trials, identified a trend for lamotrigine to outperform lithium in bipolar depression, whereas lithium was more effective in preventing mania (90).

Side effects. Lamotrigine is noted for its potential to cause severe skin reactions, including Stevens-Johnson syndrome, and toxic epidermal necrolysis (Lyell syndrome). The incidence of rashes is approximately 0.3%, and rashes are more likely to occur when the dose of lamotrigine is rapidly escalated or when it is used in combination with valproate (91). Fortunately, not all rashes are serious, but patients should be advised to seek medical attention if a rash appears, and especially if there are concurrent symptoms such as fever and sore throat (32).

In summary, lamotrigine has modest efficacy in the treatment of acute bipolar depression, with meta-analyses suggesting both a lack of separation and some benefit over placebo, though this is somewhat mitigated because of a large placebo response. Further active comparator and adjunctive therapy trials are needed. However, lamotrigine does have a role in the treatment of bipolar depression by virtue of having proven efficacy in maintenance therapy, particularly in preventing relapse into depression, and its relatively benign tolerability profile in comparison to the alternatives, especially with long-term therapy, enhances its utility.

Carbamazepine

Acute bipolar depression and maintenance efficacy. Suitable studies examining the efficacy of carbamazepine in the acute treatment of bipolar depression have not been conducted. Further, randomised maintenance studies comparing carbamazepine to lithium have favoured the latter, suggesting minimal or no efficacy (92–94). However, the unique design of these studies limits the generalizability of their findings.

Side effects. Carbamazepine affects the hepatic, dermatological, and haematological systems, and in practice, tolerability is the most common reason for discontinuation (95). Occasionally, carbamazepine causes serious side effects and can be fatal in overdose.

In summary, there are little data to support the use of carbamazepine as an acute or maintenance treatment for bipolar depression.

Antipsychotics

Acute bipolar depression efficacy. In the treatment of bipolar depression, olanzapine has been shown to be superior to placebo and, in combination with fluoxetine (OFC), superior to both placebo and olanzapine alone (96). OFC is thought to have antidepressant efficacy by virtue of monamine synergism (97) and was the first agent to be approved by the U.S. Food and Drug Administration for the treatment of bipolar depression (98). Further, though an RCT has demonstrated its superiority over lamotrigine (98), it is difficult to compare its efficacy with antidepressant treatments as no trial thus far has included fluoxetine as an active comparator.

With regard to quetiapine, the BOLDER studies (99, 100) and EMBOLDEN data (60, 101) support the efficacy of quetiapine monotherapy in the acute treatment of bipolar I and II depression. Further, pooled data from the BOLDER trials targeting just the bipolar I depressed patients have shown that quetiapine monotherapy is superior to placebo (102). In light of these data, a number of guidelines have positioned quetiapine first-line (103, 104).

There are limited data for the use of risperidone in the treatment of bipolar depression, but available information from open trials and small RCTs lends support to its potential antidepressant effect as an adjunctive treatment (105, 106). This is further supported by its antidepressant augmentation effects in the treatment of unipolar depression (107). Conversely, a randomised, open-label augmentation trial of risperidone for treatment-resistant bipolar depression reported rates of sustained recovery over eight weeks of just 5%. Surprisingly, this recovery rate did not statistically differ from lamotrigine (24%) or inositol (17%), perhaps highlighting the limited statistical power of this study (108).

The use of aripiprazole monotherapy in the treatment of bipolar depression has been examined in two recent RCTs that have failed to report any benefit over placebo at endpoint (eight weeks) (109). However, a small open trial has reported significant antidepressant benefits when aripiprazole is added to existing antidepressant and/or valproate, lithium, or carbamazepine treatment (110).

Maintenance efficacy. Amongst the atypicals, olanzapine has a substantive evidence base, with four RCTs having investigated its use as a maintenance treatment for bipolar disorder. In one trial, the time to next mood episode was significantly longer in patients treated with olanzapine monotherapy (median 174 days) as compared to placebo

(median 22 days), and the relapse rates also favoured olanzapine as compared to placebo (47% versus 80%) (111). Interestingly, compared to lithium, olanzapine has been shown to be significantly more effective at preventing the recurrence of manic or mixed episodes, but both agents are on par with regard to preventing the recurrence of depression (112). Further, no discernible differences in relapse rates were found in comparison to valproate (80). However, in an 18-month placebo-controlled comparison trial, patients who responded acutely to olanzapine added to lithium or valproate demonstrated a longer period of sustained symptomatic remission (but not syndromic remission) when continued on the combination compared to those who were reverted back to lithium or valproate monotherapy (113).

Like olanzapine, quetiapine versus placebo when added to lithium or valproate appears to confer additional benefit and increases the time to recurrence of any event (mania, depression) irrespective of the polarity of the index episode (114–116). Interestingly, preliminary monotherapy maintenance evidence for up to two years suggests that quetiapine may be as effective as lithium in the prevention of relapse into any mood episode (117). It is therefore likely that quetiapine will emerge as an alternative to olanzapine with at least equivalent efficacy in bipolar maintenance therapy.

As yet there are no RCTs of risperidone maintenance treatment in bipolar disorder; however, three- and six-month open-label data suggest that risperidone adjunctive to valproate or lithium improves depressive symptomatology (118, 119). Further, a small two-year open trial of 10 patients provides tentative support for adjunctive depot risperidone in treatment-resistant bipolar disorder (120).

In contrast, aripiprazole has been shown to prevent manic but not depressive episodes (121, 122), and thus far there are no controlled trials of ziprasidone in bipolar depression or maintenance therapy.

Side effects. The atypical antipsychotics have many acute and long-term side effects that significantly limit their tolerability. In the short term, anticholinergic effects and sedation cause problems with adherence; however, it is the long term sequelae, such as metabolic syndrome and extrapyramidal side effects, that are of major concern (123, 124).

In summary, the atypical antipsychotics quetiapine and olanzapine monotherapy and OFC have demonstrated efficacy in the treatment of acute bipolar depression. These same atypicals have emerging efficacy in prophylaxis, with olanzapine

favouring the prevention of mania and quetiapine accumulating evidence with regard to depressive relapse. Adjunctive risperidone has shown some efficacy in the treatment of acute bipolar depression and may have utility in maintenance. Similarly, combinations of atypicals and lithium or valproate are emerging as viable options; however, the long-term use of atypicals in bipolar prophylaxis is constrained by potentially serious side effects and remains a somewhat contentious issue.

Antidepressants

Acute bipolar depression efficacy. Thus far, there has been limited systematic research examining the effects of conventional antidepressants in bipolar depression (5, 125), and that which has been conducted has unfortunately generated equivocal data (126, 127). Indeed, many have questioned the wisdom of using conventional antidepressants in bipolar depression (127–130).

An influential meta-analysis that compared the response rates of antidepressants in bipolar depression to placebo showed that overall, antidepressants were superior (125). However, in a trial that was excluded from this meta-analysis because it did not report response rates, the rates of remission were no better for antidepressants than placebo when added to lithium (131). More recently, the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study (126), which examined patients with bipolar I and II depression, studied the addition of an antidepressant (paroxetine or bupropion) or placebo to either lithium or an anticonvulsant. Remarkably, the response to lithium or an anticonvulsant with an antidepressant was less (23.5%) than that observed with the addition of placebo to lithium or an anticonvulsant (27.3%). Further, in a study of quetiapine compared to paroxetine in bipolar depression, quetiapine but not paroxetine separated from placebo (101).

However, antidepressants do appear to have equally mood-elevating properties in bipolar depression, as evidenced by the occasional precipitation of mania/hypomania. This issue is discussed further under “Clinical considerations”.

Maintenance efficacy. Data on continuation or maintenance phase treatment with antidepressants are limited. A comprehensive review of available studies found no evidence to support the long-term use of antidepressants in bipolar disorder (132), and more recently, preliminary STEP-BD maintenance data suggest only modest benefits with the continuation of antidepressant treatment, noting reduced depressive morbidity and an increased

likelihood of relapse when antidepressants are discontinued. However, antidepressant use does not affect the number of recurrent episodes or severity of episodes and antidepressants do not appear to reduce the severity of any breakthrough episodes (127).

Side effects. The tolerability and side-effect profile of antidepressants specifically in the treatment of bipolar disorder is not known. Compared to other antidepressants, selective serotonin reuptake inhibitors (SSRIs) are generally safer and better tolerated, with a more favourable adverse effect profile, even at high doses (133). Many of the adverse effects of SSRIs, such as gastrointestinal disturbances, tend to be transient and cease within a few days or weeks after commencing treatment (134). The dual-acting antidepressants (venlafaxine, duloxetine, mirtazapine) and noradrenergic agents (reboxetine) have a different side-effect profile; however, like SSRIs, they are considerably safer and better tolerated as compared to tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). The latter often require additional dietary considerations, and like TCAs can be fatal in overdose. There is, however, some evidence, albeit weak, that MAOIs have particular efficacy in bipolar depression (135).

In the context of treating bipolar depression special consideration needs to be given to the potential for developing treatment-emergent antidepressant switching (TEAS) (see below).

In summary, the evidence regarding antidepressant efficacy in acute bipolar depression is inconclusive and long-term data are lacking. At best, antidepressants appear to have limited efficacy in the acute treatment of bipolar depression and, given their potential for inducing mood instability when unchecked, their long-term use in maintenance therapy is questionable. At worst, they confer no benefits in the treatment of depression and may instead be disadvantageous.

Novel medications and complementary agents

Antiglucocorticoids

High cortisol levels have been associated with melancholia, and it has therefore been hypothesised that antiglucocorticoid treatments (e.g., mifepristone, ketoconazole, and metyrapone) may be able to improve the symptoms of depression (136). A Cochrane review of the efficacy and safety of antiglucocorticoids in the treatment of depressive episodes (mainly unipolar) concluded that the use of antiglucocorticoids is still at the 'proof of

concept' stage and that further research is warranted (137). However, in a bipolar disorder trial, the addition of mifepristone to existing treatment resulted in a significant improvement in depressive symptoms and neurocognitive functioning (138).

Celecoxib. Celecoxib, a cox-2 inhibitor, has been investigated for its potential to accelerate the antidepressant effect in bipolar depression. In patients with a bipolar depressed or mixed episode, a small, double-blind, placebo-controlled trial of celecoxib adjunctive to usual treatment showed trends toward an improvement on depression symptoms during the first week of the trial for the celecoxib group overall, and the initial improvement was significant for those subjects who went on to complete the trial (139).

N-acetyl cysteine (NAC). Oxidative stress disrupts glutathione metabolism and has been identified in a number of neuropsychiatric disorders, including bipolar disorder. When prescribed as an adjunct to usual medication, NAC, a precursor of glutathione, has been found to significantly improve depressive symptoms in a placebo-controlled, randomised trial for bipolar disorder (140).

Modafinil. Modafinil is a stimulant medication that is usually used to treat sleep disorders and is now being trialled in the treatment of bipolar depression. A six-week, randomised, controlled study in bipolar I and II depression reported that both response and remission rates for modafinil, in addition to lithium or an anticonvulsant, were superior to adjunctive placebo (141).

Pramipexole. Small RCTs of pramipexole, a dopamine agonist, have demonstrated significant antidepressant effects in preliminary trials for the treatment of bipolar II depression (142) and refractory bipolar I depression (143).

Zonisamide. A small, eight-week, open trial demonstrated significant improvements in depression ratings after the addition of zonisamide, a sulphonamide anticonvulsant, to usual treatment. However, interpretation of the findings is limited by the fact that half of the sample dropped out of the study due to adverse effects (144).

Omega-3 fatty acids. There is increasing interest in the link between omega-3 fatty acid deficiency and the development of bipolar depression. In particular, the long-chain omega-3 fatty acid ethyl-eicosapentaenoate (EPA) that is administered as a supplement has been investigated in three clinical

trials for its antidepressant effect in bipolar disorder. The first clinical trial was conducted by Stoll and colleagues (145), where EPA as an adjunctive treatment significantly delayed the onset of a new depressive episode. More recently, however, there have been mixed findings. A four-month trial of EPA at 6 g/day adjunctive to usual treatment for bipolar depression and rapid-cycling bipolar disorder did not report any significant benefits in either group (146); however, a separate three-month trial of EPA at 1 g or 2 g/day produced a significant improvement in both depression scores and overall functioning as compared to controls (147). The different doses that have been administered across these studies hamper direct comparison; however, unipolar depression research studies suggest that doses of EPA at 1 g/day may be more effective than higher doses (148).

In summary, a number of novel medications and complimentary agents that employ new and different mechanisms of action demonstrate variable efficacy in the treatment of bipolar depression. Preliminary findings appear to be promising but further rigorous studies are needed.

Nonpharmacological management

Psychological interventions

Strong evidence exists for interventions focused on the recognition of early warning signs in bipolar disorder (149). Cognitive and psychosocial functioning have been found to be impaired in bipolar depression and euthymia, possibly because of residual subsyndromal depressive symptomatology (15, 16). Psychological interventions adjunctive to medications appear to have greatest benefit in reducing risk of relapse and can improve social functioning and medication adherence (150–153). The therapeutic effect can be optimised by targeting patients following a depressive episode, and psychological treatments are best instituted early in the course of the illness as they appear to be less effective in those with a high number (>12) of prior mood episodes (152, 154).

When administered adjunctive to pharmacological treatment, psychological interventions that are supported by RCTs include cognitive behavioural therapy (CBT) (155–158), family-focused therapy (153, 159, 160), interpersonal and social rhythm therapy (IPSRT) (161), and group psychoeducation (158, 162). Further, therapeutic gain appears to be sustained at long-term follow-up (154, 157, 163). Specifically, CBT is most effective when instituted early in the course of the illness, and similarly, IPSRT, when administered in the

acute phase, produces longer survival times until a recurrence of an affective episode, whereas family-focused therapy, in addition to improving mood, enhances adherence to medication and results in fewer relapses (153, 159–161, 164).

In summary, psychological treatments, when administered in conjunction with pharmacotherapy, have been shown to be of particular benefit in preventing depressive relapse in bipolar disorder. The timing and type of therapy along with patient selection appear to be important factors when administering psychological interventions.

Physical treatments

Electroconvulsive therapy (ECT). ECT is generally regarded as a safe and effective treatment for both phases of bipolar illness and can be relatively safely administered to treat bipolar depression both during pregnancy and immediately postpartum (165). Further, pursuant of medication, it is useful in the treatment of catatonia (166, 167). The evidence for its efficacy in the treatment of bipolar depression, however, is still somewhat limited, with research mainly having focused on unipolar depression. Open trials and retrospective studies comparing the use of ECT in bipolar and unipolar depression have demonstrated comparable efficacy across the phenotypes, and further, ECT may provide a more rapid response than antidepressants (168, 169).

In the 1990s, a review of bipolar depression identified nine trials relating to ECT, including three controlled trials, and concluded that ECT was superior to placebo and at least as effective as, and in most studies more effective than, antidepressants (170). Further, the speed of response to ECT has been found to be quicker than antidepressant therapy in bipolar depression (171), and a recent retrospective chart review reported superior efficacy of ECT over venlafaxine in treatment-refractory bipolar depression (172). ECT may, however, be less efficacious in bipolar than unipolar depression (173).

Maintenance ECT research consists largely of case series, naturalistic studies, and retrospective reports. The data are methodologically flawed; however, they do support ECT as a valid treatment option in the long-term maintenance of treatment-resistant bipolar disorder (174).

Alternative physical treatments. Alongside ECT, several other physical treatments are currently being investigated as novel therapeutic interventions for treating depressed mood. These studies have been predominantly conducted in unipolar

depressed patients and include vagus nerve stimulation (VNS), repetitive transcranial magnetic stimulation (rTMS), magnetic seizure therapy, and deep brain stimulation (175–177). In bipolar disorder, support for rTMS has been demonstrated in small RCTs and case series data (178, 179), but it may also carry a slight risk of treatment-emergent mania (180). One trial of vagus nerve stimulation has demonstrated similar outcomes for patients with unipolar and bipolar depression both acutely and during follow-up for up to two years (181).

In summary, ECT is thus considered an effective treatment option for bipolar depression, particularly if psychotic features are present. Maintenance ECT has also been shown to be effective; however, further research is necessary. Early findings for alternative physical treatments in the management of bipolar depression are promising, but future research is needed.

Clinical considerations in treating bipolar depression

Suicidality and the prevention of suicide

As stated earlier, bipolar patients have elevated risks of both attempted and completed suicide. Rates for the latter are approximately 30–60 times the general population rate of 0.015%, and it is estimated that there is also a lower ratio of attempted suicides to completed suicides in bipolar disorder (3:1) as compared to the general population (35:1) (182). This suggests that suicidal behaviour in bipolar disorder is highly lethal. The risks of suicide also varies according to episode type, and is particularly high during depressive episodes or dysphoric/irritable mixed states (182, 183).

Amongst the pharmacotherapeutic agents used to treat bipolar disorder, lithium is unique, with potent antisuicidal properties. Long-term lithium treatment has been associated with a reduced risk of suicide and suicidal behaviour in both recurrent depression and bipolar disorder, with reviews of RCTs and open studies reporting reductions in risk by as much as 80% (184, 185). However, this must be balanced against its toxicity in overdose and the increased risk of relapse upon rapid discontinuation (186, 187).

In comparison to lithium, the antisuicidal effect of anticonvulsants is not clearly established. While there have been reports of poorer efficacy in preventing suicidal behaviour when compared to lithium (184), more recent findings suggest that anticonvulsants may also reduce the risk of suicidal behaviour. A series of retrospective chart reviews investigated the impact of pharmacological agents on suicidal behaviours in patients with bipolar

disorder over a three-year period (188–190) and found a similar reduction, once medication adherence was considered, in nonlethal suicidal behaviour for valproate, carbamazepine, and lithium; but following discontinuation of any of the three drugs, a sharp 16-fold increase in the risk for suicidal behaviours was observed. However, the reason and rate of discontinuation varied across all instances, and therefore, the cause of this observed increase in suicidal behaviours cannot be established on the basis of these data (188).

In bipolar patients treated with antidepressants, the greatest risk of suicidal behaviour is associated with antidepressant monotherapy (190), whereas the use of antipsychotics is associated with an increased risk in nonlethal suicidal behaviour (189).

In summary, only lithium has convincing antisuicidal properties in the treatment of bipolar disorder.

Antidepressants and TEAS

Historically, antidepressants have been implicated in treatment-emergent switching (antidepressant-induced development of hypomanic/manic symptoms), but the mechanism for this phenomenon and the absolute risk remain unclear. The likelihood of TEAS appears to vary according to antidepressant class, and whether the antidepressant is administered alone or in conjunction with another medication. Tricyclic antidepressants appear to confer a higher risk of TEAS than SSRIs (7–11% for tricyclics and 0–4% for SSRIs), (125, 131, 191, 192) and venlafaxine has also been associated with an increased rate of TEAS (13–15%) as compared to SSRIs and bupropion (3–7%) (193, 194). Recent data further support a differential of the TEAS effect across antidepressant classes (195), however, the risk may be no greater than placebo when antidepressants are used adjunctively in combination with lithium or an anticonvulsant (126). Often TEAS occurs in undiagnosed bipolar depression that is being treated with antidepressant monotherapy. It can usually be managed successfully by withdrawing the antidepressant and initiating treatment with an antimanic agent.

In summary, in the treatment of bipolar depression, the administration of conventional antidepressant monotherapy confers a significant risk of switching that appears to be medication specific; however, the likelihood of TEAS is significantly diminished if an antimanic agent is co-prescribed.

Discussion

The pharmacological management of bipolar depression is somewhat arbitrarily partitioned into

the acute treatment of episodes and the long-term prevention of illness relapse. This notional binary model of treatment creates an artificial and unnecessary separation of management into stage-specific treatments that are administered according to the degree of perceived clinical response and the achievement of remission. In practice, it is often difficult to identify precisely where an episode of bipolar depressive illness ends, and to determine when to transition treatment from acute to maintenance therapy. The need to partition both the illness and its treatments for the purposes of research is understandable, but this should not necessarily dictate the clinical management of bipolar depression. The reasons for this are essentially threefold.

First, in treating bipolar disorder, essentially a recurrent life-long illness, treatments should be chosen not only for efficacy in ameliorating acute depressive symptoms, but also with consideration of which are most likely to prevent recurrence and relapse (196–198). Second, tolerability issues in long-term treatment are an important consideration, and this needs to be balanced against the efficacy data. Third, it is clinically often difficult to confidently identify the respective treatment stages of bipolar illness and thereby accurately map

therapeutic response. In addition, as combination treatments are the rule rather than the exception, the contribution of each individual treatment to the management of the current phase and long-term course is hard to distil. This inevitably generates a gap between the recommendations of most clinical guidelines and what can be realistically implemented in the clinical setting.

In most bipolar disorder guidelines, the evidence and recommendations for the treatment of bipolar depression are presented according to the stage of treatment, but because of the paucity of evidence for maintenance therapy specific to bipolar depression, the recommendations for this phase of treatment are generally less consistent and less specific.

Similarly, it is important to note that the vast majority of studies have focused on bipolar I patients and that earlier studies have often not even attempted to differentiate subtypes (199). Consequently, there is little evidence to instruct the use of pharmacotherapy specifically in the treatment of bipolar II disorder, and recent studies that have examined the effects of anticonvulsants (84, 108) and atypical antipsychotics (99, 100) have yet to find agents with differential efficacy in favour of bipolar II depressive symptomatology.

Table 4. Comparison of first-line pharmacological recommendations for acute bipolar depression

Treatment strategy	RANZCP (2004) (34)	CANMAT (2001, 2009 ^a) (33, 103)	NICE (2006) (212)	BAP (2003) (35)	APA (2002, 2005 ^a) (32, 104)
Monotherapy	Lithium Lamotrigine	Lithium Lamotrigine Quetiapine Quetiapine XR	Lithium Valproate Antipsychotic	Lithium ^b Lamotrigine ^b Valproate ^b Antipsychotic <i>(if depression is mild)</i>	Lithium ^c Lamotrigine Quetiapine
Adjunctive antidepressant	Olanzapine/fluoxetine combination Lithium/lamotrigine + antidepressant	Olanzapine + antidepressant Lithium/valproate + antidepressant Second-line: quetiapine + antidepressant	Antipsychotic + antidepressant Lithium/valproate + antidepressant	Antipsychotic + antidepressant Lithium/valproate + antidepressant <i>(if depression is moderate-severe)</i>	Olanzapine/fluoxetine combination Lithium/valproate + antidepressant ^d
Other combinations	Add lithium Add carbamazepine Add lamotrigine	First-line: lithium + valproate Second-line: lithium/valproate + lamotrigine	Add quetiapine ^e Add lamotrigine ^f		Add lamotrigine ^g Add pramipexole

^aUpdated.

^bLimited evidence exists for these medications in bipolar depression.

^cLithium is not mentioned in updated version of guidelines.

^dModest evidence only.

^eUnless already taking an antipsychotic.

^fAdd lamotrigine (if history of rapid cycling).

^gEspecially if antidepressants cause instability.

RANZCP = Royal Australian and New Zealand College of Psychiatry; CANMAT = Canadian Network for Mood and Anxiety Treatments; NICE = National Institute for Health and Clinical Excellence; BAP = British Association for Psychopharmacology; APA = American Psychiatric Association.

It is therefore useful, having examined the evidence for the efficacy of individual pharmacological agents for the treatment of bipolar depression, to compare the recommendations of a number of recent international guidelines (see Table 4). The recommendations from five bipolar disorder clinical practice guidelines are tabulated according to treatment strategy in order to allow direct comparison. It is important to note that because each of the guidelines has been produced at different times, the extant evidence upon which they are based has inevitably varied. Further, each of the guidelines has had a different focus and consequently adopted an individual style. The table is therefore a distillation of the guidance provided and has been formatted so as to emphasise commonalities.

Comparing the five guidelines the recommendations for the management of acute bipolar depression can be reduced to two main choices, namely, monotherapy with lithium, lamotrigine, valproate, or quetiapine, or the use of a combination of an antidepressant with any of these agents, including the fixed combination of olanzapine and fluoxetine. Alternatives or subsequent options include combinations of these agents, such as lithium plus valproate or lamotrigine, and the combination of lithium or anticonvulsants with atypical antipsychotics.

The evidence, as summarised in this paper, favours the use of lithium and lamotrigine first-line in preference to valproate, and indicates that, for acute episodes, quetiapine and olanzapine have perhaps achieved equivalence with lithium and the anticonvulsants in terms of *efficacy*. However, the *effectiveness* of the atypical antipsychotics in particular as maintenance agents is constrained by their side-effect profile and the lack of both long-term (a decade or more) research data and clinical experience in treating bipolar disorder as compared to more established agents such as lithium and valproate. Conversely, lithium and the anticonvulsants are generally slower to effect symptomatic change, and this limits their usability; however, when considering the treatment of acute bipolar depression it is important to keep *maintenance in mind* as it is this aspect of treatment that ultimately determines long-term success. Unfortunately, most guidelines and recommendations do not assign sufficient weight to the tolerability of medications when rating effectiveness and instead rank efficacy alone. Further, empirical findings and clinical experience are difficult to factor into evidence-based guidelines and are often captured separately by consensus statements.

The efficacy data for individual medications from research trials have been summarised in

Table 5. Overview of the efficacy^a of pharmacological agents as phase-specific treatments in bipolar disorder based on available evidence

Pharmacological agents	Acute mania	Acute bipolar depression	Maintenance ^b
Lithium	I	II	I ^c
Valproate	I	II ^d	II
Carbamazepine	II	–	–
Lamotrigine	–	I ^e	I ^f
Olanzapine	I	II	I
Risperidone	I	III ^g	III ^g
Quetiapine	I	I	II
Aripiprazole	I	–	II
Ziprasidone	I	–	III
Amisulpride	III	–	–
Clozapine	–	–	IV
Olanzapine/fluoxetine combination	–	II	–
Antidepressants	–	III ^{h,i}	–

^aEfficacy determined using NHMRC levels of evidence (37).

^bIn this instance, maintenance evidence is not specific to bipolar depression.

^cBest evidence for preventing manic episodes, less effective at preventing depressive episodes.

^dData are persuasive but not definitive and trials of sufficient power are required.

^eThere have been mixed findings in relation to the acute efficacy of lamotrigine, with only one meta-analysis reporting modest benefit over placebo. Further, slow titration requirements can delay effect and result in perceived diminished efficacy.

^fEspecially preventing depressive episodes.

^gWhen used as an adjunctively to existing bipolar treatment.

^hMixed findings at Level II has led to downgrading of evidence level.

ⁱRecommended in combination with an antimanic or maintenance agent.

Table 5 using NHMRC levels of evidence (37) (described earlier), and this has then been used as a basis, along with consideration of tolerability profiles, to judge the relative effectiveness of classes of agents in the acute and long-term management of bipolar depression (see Fig. 1). Figure 1 reveals clearly the advantage atypical antipsychotics have ‘on paper’ that positions them favourably as the treatment of choice for acute bipolar depression. However, their long-term efficacy is at best modest, and in light of this, and because this is the more substantial phase of treatment, their actual role both in maintenance therapy and treatment overall needs to be given careful consideration. Further, the relative comparisons as depicted do not take into consideration the issue of tolerability, which again at present tends to favour lithium and the anticonvulsants as compared to the antipsychotics.

In addition to these agents, it is important to consider the role of conventional antidepressants in the treatment of bipolar depression. The guidelines mentioned in Table 4 all advocate the use of antidepressants as adjunctive therapy; however,

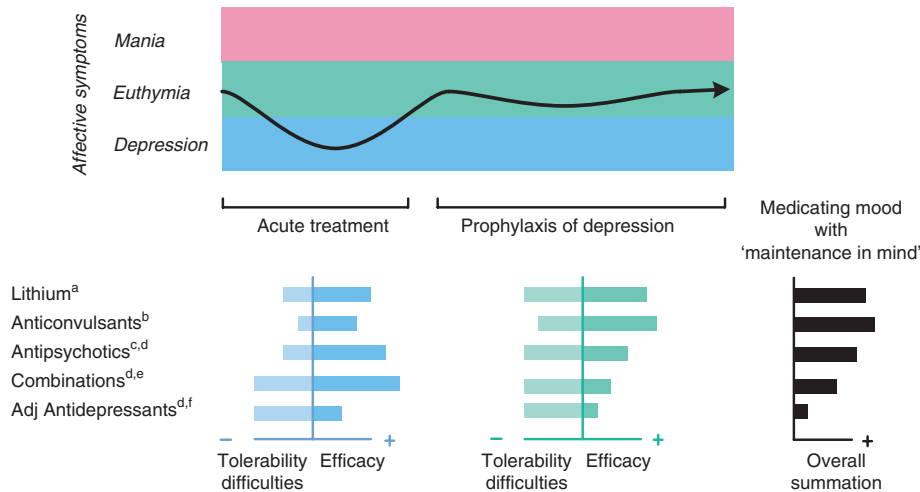


Fig. 1. Effectiveness of pharmacotherapeutic agents in the treatment of bipolar depression. The figure shows the relative efficacy and tolerability of classes of pharmacological agents for both the acute treatment (blue) and prophylaxis of depression (green). Note that the tolerability ratings are deemed to be ‘negative’ and thus are presented in a lighter shade to the left of the efficacy ratings. A summation of the evidence that incorporates the tolerability of agents is captured in the final set of ratings depicted in black that emphasise the need to consider maintenance when prescribing any of the agents, both acutely and long term. Adj = adjunctive. ^aIn maintenance, lithium has demonstrated better efficacy for preventing manic episodes than depressive episodes; however it does have a proven antisuicidal effect. ^bAnticonvulsants: Lamotrigine appears to be particularly effective at preventing depressive episodes, but there is limited evidence available for valproate and no supporting evidence for carbamazepine. ^cThe small efficacy bars for these agents mainly reflect a lack of studies in prophylaxis of bipolar depression. ^dAntipsychotics: Acute efficacy appears to be strongest for quetiapine, followed by olanzapine. Less efficacy evidence exists for long-term maintenance therapy. ^eCombinations: Strongest evidence exists for olanzapine and fluoxetine combination during the acute phase. Other combinations include, but are not limited to, lithium and lamotrigine, lithium and valproate, and olanzapine added to lithium or valproate. In practice, many bipolar patients are managed long term with treatment combinations, but specific maintenance therapy data are lacking and therefore their relative weighting is weaker. Further, clinically monotherapy is the preferred ideal. ^fAdjunctive antidepressants: These have been largely studied in combination with an existing mood-stabilising treatment. Selective serotonin reuptake inhibitors and bupropion are considered the least likely to induce affective switching. Antidepressants are generally not recommended as a maintenance treatment for bipolar depression.

research increasingly points to a lack of efficacy of antidepressants in bipolar depression (126) and in some instances, when prescribed as monotherapy for the treatment of undiagnosed bipolar depression, they may indeed precipitate a worsening of mood rather than achieving stability.

The use of antidepressants in the treatment of acute bipolar depression is therefore being challenged, but it is the almost complete lack of long-term data that is perhaps most worrying. Further, the few studies that report some long-term findings suggest that antidepressants have little if any beneficial effect (127). Therefore the use of antidepressants in the treatment of bipolar depression, even for the acute phase of illness, perhaps needs to be checked.

Based on data that incorporate clinical experience and taking a long-term perspective to managing bipolar depression, it would appear that lithium and anticonvulsants, in particular lamotrigine, should be the treatments of choice. However, simplification to this extent and the limiting of other options is perhaps premature. Data on lithium, arguably the best agent for managing bipolar disorder, show that even lithium has markedly inconsistent evidence that both supports

and advises against its use. This highlights an upstream difficulty that has been discussed earlier in this paper, namely, the lack of accuracy with respect to diagnosis. It is likely that this leads to a lack of specificity of treatments and therefore it is possible that much of the conflicting evidence in the literature actually reflects diagnostic heterogeneity of the disorder. Lithium, for instance, performs well in treating ‘classic bipolar disorder’ but has a much poorer record of efficacy in the management of other patterns of bipolarity (200, 201). It may be that greater sophistication is needed at the outset of treatment, with better definition of supposed bipolar depression ‘subtypes’. This would permit treatments to be matched to the individual pattern of illness and allow the putative strengths of individual agents, or combinations of agents, to be taken into consideration. The limitations of diagnosis in bipolar disorder have already been explicated; however, in addition to a more detailed cross-sectional examination of illness parameters, perhaps a longitudinal perspective that incorporates contextual factors is also needed.

The context of bipolar depression presentations is detailed in Fig. 2. The schematics 1–6 highlight the pertinent information that should ideally be

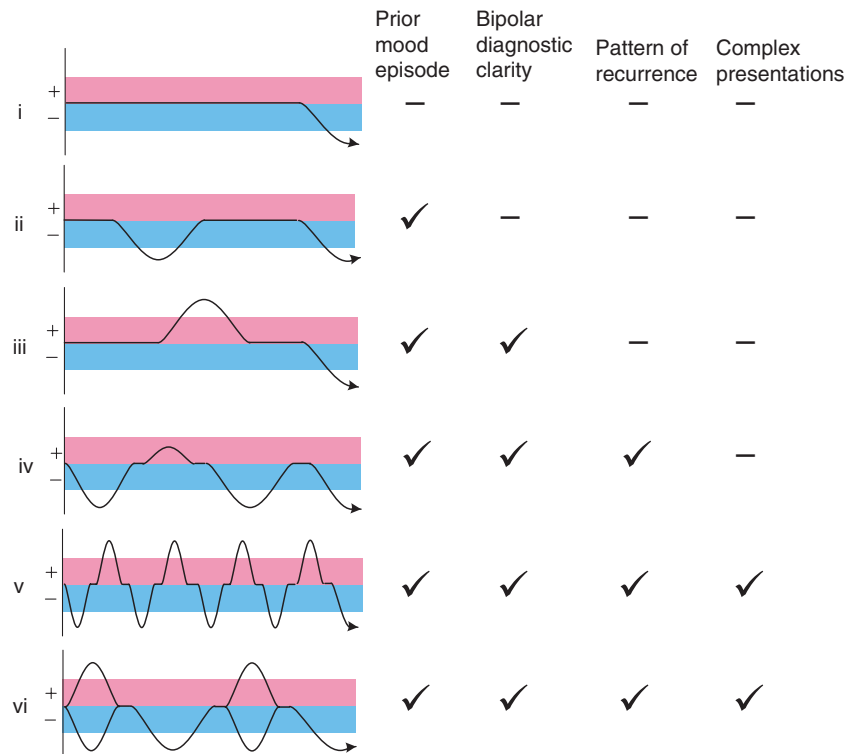


Fig. 2. Contextual aspects of bipolar depression presentations for clinical consideration. + = manic symptoms; - = depressive symptoms; ✓ = feature is present; - = feature is not present. (i). Current depressive episode, initial presentation. (ii). Current depressive episode with a history of depressed episode. (iii). Current depressive episode with a history of a manic episode. (iv). Current depressive episode with a history of depressive and hypomanic episodes, predominantly depressive course. (v). Current depressive episode with a history of rapid-cycling complex presentations. (vi). Current depressive episode with a history of complex mood presentations including predominantly mixed episodes.

considered and can be potentially used to better diagnose likely subtypes of bipolar depression. Knowing, for instance, that an individual has a complex pattern of illness (vi) may preclude the use of lithium. Similarly, having identified a tendency for mood swings (iv) or rapid cycling (v), the use of agents with antimanic potency in addition to antidepressant effects would be preferable. These refinements would perhaps better inform researchers and clinicians alike as to the true therapeutic profile of individual agents. It is unlikely that any one agent, or class of agents, will be capable of treating all the various manifestations of bipolar depression we see today, or that successful lifelong remission can be predictably sustained without resorting to changes in treatment strategy at some point in the course of the illness. However, where possible the aim should be to maintain monotherapy and successfully treat bipolar depression using the minimum number of agents necessary.

With an expansion in the number of medications, the pharmacological management of bipolar depression has become increasingly sophisticated and reflects the complexity of the illness. In addition to medications, however, it has become clear that psychological interventions that enhance

treatment adherence and also exert an independent therapeutic effect are perhaps of equal, if not greater, importance and in chronic lifelong illnesses such as bipolar disorder are fundamental to ensuring long-term maintenance of well-being. A key aspect of psychological therapies includes establishing a healthy therapeutic relationship that also facilitates psychoeducation and permits the involvement of family and partners where necessary (202, 203). Simple measures such as instituting a healthy lifestyle and structured routine (204), along with more sophisticated targeted techniques such as family-focused therapy and IPSRT (150, 151), make considerable differences to overall outcome when combined with optimum pharmacotherapy. Physical activity appears to be of benefit in bipolar disorder (205), and consideration should be given to smoking cessation, as there is a suggestion that smokers have a poorer response to treatment (206, 207).

Complex cases of bipolar depression that show treatment refractoriness often involve mixed episodes or comorbid substance misuse. Not surprisingly, the treatment strategies for these complicated presentations are even less clear than those for typical bipolar depression and often require

multidisciplinary approaches, with trialling of combinations of treatments and novel strategies, including resorting to physical interventions (208, 209). Discussion of these treatments is beyond the scope of this paper, but again, should be envisaged and considered when first embarking upon the treatment of bipolar depression.

Conclusion

Bipolar depression is undoubtedly a heterogeneous entity that has become broader in definition over recent years because of nosological imprecision and uncertainty with regard to its diagnosis. The latter is compounded through onset of the illness typically with depressive symptoms that are usually mistaken for major depression. This lack of diagnostic clarity has meant that treatment studies have yielded inconsistent findings that are reflected in bipolar disorder management guidelines. The artificial separation of treatment into acute and maintenance phases has been essential for therapeutic investigations; however, application of this model to clinical practice is difficult and unnecessary. The pharmacotherapy of bipolar depression acutely should involve long-term consideration of the suitability of that agent for maintenance therapy. Treatment choice should not be predicated on efficacy alone, but instead consider tolerability and overall effectiveness. To this end, the adjunctive use of psychological interventions appears promising and deserves greater prominence.

Finally, many treatments are effective in treating bipolar depression, but greater sophistication is needed in terms of diagnosis and profiling of patients so as to tailor therapy to the needs of the individual and thereby enhance the likelihood of success. Further research into treatment aspects of bipolar depression is urgently needed, but many promising agents and a better understanding of the utility of existing agents bode well for the management of this burdensome illness.

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