Clinical challenges of bipolar depression

The observation that atypical antipsychotic drugs have some role in treating bipolar disorders has revived interest in the management of bipolar disorder. Given the prevalence of and the disability associated with bipolar depression, current medication is inadequate and new research to help patients with this condition is overdue.

Bipolar affective disorder is characterized by a diverse pattern of symptoms, ranging from mild depression or hypomania (low highs) to severe or rapidly cycling forms of mania and depression with concurrent psychotic symptoms (*Table 1*). It is such a complex disorder with subtle variations that its course and outcome are most often unpredictable. Aretaeus of Cappadocia, the father of bipolar disorders (Marneros and Goodwin, 2005), wrote 2000 years ago: 'There are many different phenomenological types of the illness, but they all belong to one and the same family'. The incidence of bipolar disorder type I is approximately 1% of the world population (Merikangas and Yu, 2002). Bipolar disorder type II is much more prevalent and a spectrum of bipolar disorder that includes states of chronic mild hypomania has been described (Akiskal, 2002). Life course studies have illustrated that some patients go through a short period of rapid cycling followed by periods of less frequent episodes, and vice versa (Coryell et al, 2003).

Diagnostic confusion between bipolar disorder and schizophrenia may occur in the early stages because first rank symptoms of schizophrenia could be present as the illness unfolds initially; in 10–20% of manic patients Schneiderian first rank symptoms are evident. In schizoaffective disorder, mood symptoms and schizophrenic symptoms are both present and approximately in balance – neither type of symptom is sufficiently dominant to justify a diagnosis of either condition. Appropriate management for a particular patient is often complicated by co-morbid conditions, such as substance misuse or attention-deficit hyperactivity disorder, and non-concordance with treatment. Patients with bipolar disorder are depressed three times as often as they are manic. With advancing age depressive episodes outnumber the manic phases. Bipolar depression poses formidable diagnostic and treatment challenges to the clinician. The influence of drug company funding on drug trials is difficult to evaluate and this warrants more independent research.

Table 1. Bipolar disorders

Bipolar disorder type I	Mania or mixed mania and depression
Bipolar disorder type II	Recurrent depression and hypomania without full-blown episodes of either mania or mixed states
Mixed states	Cases where manic and depressive symptoms occur simultaneously
Rapid cycling	At least four episodes of bipolar affective disorder must occur within a period of 1 year

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Bipolar depression

The depressive state of bipolar disorder can be varied and often confusing. Bipolar depression does not only differ from unipolar depression in clinical presentation, there is also a significant difference in optimum treatment. The condition is commonly misdiagnosed because of the similarities between its symptoms and those of major depression. Unipolar depression needs to be differentiated from bipolar depression because inappropriate use of antidepressants may precipitate a hypomanic or manic episode. Bipolar depression differs from other forms of depression because of the high risk both of completed suicide and of psychotic features. For most bipolar patients, depressive symptoms are significantly more debilitating than manic symptoms (Calabrese et al, 2004).

Unrecognized bipolarity

Under-diagnosis and misdiagnosis of depression in bipolar disorder type II as a major depressive disorder is frequently reported. Major depression may be correlated with unipolar depression (recurring attacks of depression only). The severity of depression within the depressive episodes varies, and this needs to be distinguished for treatment purposes. Atypical depressive features are more noticeable in bipolar depressives, as is psychomotor retardation (Mitchell et al, 2001). Bipolar patients may also have a previous history of psychotic depression. The concept of atypical depression emerged in 1959 when a subgroup of depressed patients responded better to treatment with monoamine oxidase inhibitors than with tricylics. The definition of atypical depression has changed over the years and remains unresolved. In addition to the core symptoms of depression, atypical depression may also have reversal of a few of the biological symptoms such as increased appetite and hypersomnia, in addition to heavy, leaden feelings of arms and legs, and a longitudinal pattern of interpersonal rejection sensitivity. From a practical point, atypical depression may be viewed as a variant of bipolar disorder type II, but in a more hypothetical vein, atypicality serves as a nosological bridge between unipolar and bipolar depression (Akiskal and Benazzi, 2005).

A subset of patients diagnosed with unipolar depression in fact suffers from bipolar depression (Hirschfeld et al, 2003). When patients fail to respond to even one antide-

pressant, bipolarity should be considered if non-adherence and suboptimal dosing are not the reasons for the antidepressant failure. Co-morbid anxiety symptomatology, feelings of people being unfriendly, a recent diagnosis of depression, a family history of bipolar disorder and legal problems may prove useful indicators of bipolarity. Atypical features, more recurrences and young age of onset are other markers of bipolarity. Most patients with bipolar disorder seek treatment for depression, and not for mania or hypomania. Unrecognized bipolarity can be misdiagnosed as attention-deficit hyperactivity disorder. When depressed patients who have demonstrated reasonable control of their drinking habits start abusing alcohol unexpectedly, bipolarity should be carefully considered. A history of hypomanic or manic episodes strongly indicates a diagnosis of bipolar depression.

Bipolar depression is associated with more mood lability and a relatively acute onset. When a young person presents with psychotic depression or psychomotor retardation, bipolar depression should be considered as a differential diagnosis. Non-specific psychological symptoms and behavioural disturbances may be the precursor of bipolar disorder in young people (Goodwin, 2003). Any patient presenting with depressive symptomatology should be asked about their past history of mood elevation and any family history of affective disorders. Bipolar depression can occur with or without precipitating factors. Bipolar depression should be considered when depressions occur without an identifiable psychogenic stressor. The mood disorder questionnaire is a useful screening tool for identifying the range of bipolar disorder in the general and psychiatric population.

Suicidality

In general, suicide is associated with acute bipolar depression. An earlier statistical analysis of the incidence of suicides in patients with affective disorder estimated a life-time risk of 15% (Guze and Robins, 1970). After reviewing thirteen additional studies, Goodwin and Jamison (1990) concluded that 18.9% of depressed patients would die by suicide. The risk of suicide in those with bipolar disorder is about thirty times higher than that in the general population, and the incidence of suicide is much higher among those in the depressive state than those in the manic phase – 79.3% of inpatients with bipolar disorder have been determined as posing a suicide risk, whereas the suicide risk among the manic patients was 2.3%. The coexistence of bipolar disorder and personality disorder carries a much higher suicide risk than bipolar disorder by itself. Alcohol abuse increases the suicide risk among people with bipolar disorder. Co-existing alcohol abuse is an ominous sign in bipolar disorder. According to one American study 21.7% of those with bipolar disorder make a suicide attempt at some point in their lives, whereas 38.4% of patients with co-morbid bipolar disorder and alcohol misuse make such an attempt (Potash, 2000). The transient disinhibition resulting from alcohol excess serves as the catalyst for making suicide attempts.

Treatment options

Significant variations are often seen in the management of bipolar depression. Ideally, treatment should both ameliorate acute depression and reduce abnormal mood elevation. There are a number of monotherapy and combination therapy options. Treatments in the acute depressive phase and long-term management should be considered separately, although they often involve the same medication, with dose differentiation and omission of an antidepressant for the long term. The National Institute for Health and Clinical Excellence (NICE, 2006) has published recommendations for the treatment of bipolar disorder and offered a guideline for treatment of bipolar depression (*Table 2*).

Antidepressants

There is a plethora of studies examining the efficacy of antidepressants in the management of unipolar major depression, but these do not encompass the treatment of bipolar depression. General findings regarding the efficacies of antidepressants are applicable to bipolar depression. Because of the shortage of trials there is little evidence to assist in the choice of agents to treat bipolar depression. Caution is necessary when prescribing anti-

Table 2. National Institute for Health and Clinical Excellence treatment recommendations for depressive symptoms

Patients prescribed an antidepressant should also be prescribed an antimanic drug	
Start with a low dose of antidepressant and increase gradually if necessary	
If acute depressive symptoms develop while taking antimanic medication monitor dose of antimanic drug and decrease if necessary	
Mild depressive symptoms	If previous episodes of mild depression have not developed into chronic or more severe depression, or patient is judged not to be at significant risk of developing more severe depression, continue assessment for a further 2 weeks (watchful waiting)
	If the patient is judged to be at significant risk of worsening or on review continues unwell, they should be managed as for moderate or severe depression, particularly if functional impairment is evident
Moderate/severe symptoms	Consider prescribing a selective serotonin-reuptake inhibitor antidepressant (or quetiapine where the patient is already taking antimanic medication that is not an antipsychotic)
	If treatment at an adequate dose with adequate compliance does not produce significant improvement, consider psychological treatment focussing on depressive symptoms, problem solving, promoting social functioning and education about medication
Chronic depressive symptoms	Patients with a definite diagnosis of bipolar disorder who are not on prophylactic medication and have no recent history of mania or hypomania should have a long-term selective serotonin-reuptake inhibitor antidepressant in combination with prophylactic medication
	Cognitive behavioural therapy in combination with prophylactic medication, e.g. quetiapine or lamotrigine

From National Institute for Health and Clinical Excellence (2006)

depressants (*Table 3*), and several factors need to be borne in mind. Because antidepressants can cause a manic switch, most guidelines for treating bipolar depression recommend discontinuation of antidepressants in the first 3–6 months after remission (Sachs et al, 2000). If there is a history of a single episode of manic switch owing to treatment with an antidepressant, in conjunction with a history of suicide risk or homicide risk in the manic phase, an antidepressant will not be the right choice of treatment for that particular patient. In patients with bipolar disorder type II – in which hypomania has not caused any untoward incident – antidepressants may be appropriate (Kusumakar, 2002). Antidepressants should be an adjunct to a mood stabilizer; antidepressant monotherapy is not recommended.

Quandary about antidepressant treatment

Clinicians are uncertain as to whether antidepressants shorten the euthymic period or not. Tricyclics are associated with a treatment-emergent affective switch more than other types of antidepressant, but the risk exists with all types. Because of uncertainty about the long-term use of antidepressants, early discontinuation of antidepressants is recommended (Montgomery et al, 2000). An American study has suggested that the risk of depressive relapse in patients with bipolar depression is significantly associated with discontinuing antidepressants soon after remission, and also comments that the risk of manic switch is substantially less than the risk of depressive relapse (Altshuler et al, 2003). Some researchers suggest that antidepressants are being blamed for a process that is an inevitable part of the disease.

Mood stabilizers

Currently the popular mood-stabilizing agents are lithium, carbamazepine, valproate and lamotrigine. There is no consensus definition of an ideal mood stabilizer. Lithium carbonate is essentially an antimanic agent with a modest antidepressant effect. It has been the gold standard for treatment of bipolar disorder for half a century, and is still the mainstay of treatment in UK, even though there are well-observed short- and long-term side effects of lithium treatment (*Table 4*). The therapeutic range of lithium is narrow, and monitoring is required to ensure that a patient remains within the recommended therapeutic plasma levels to avoid toxicity. One third of patients are lithium non-responders and the number of patients discontinuing lithium therapy is quite high (Post, 1990). On the positive side, lithium has been associated with suicide prevention (Tondo et al, 2001). Conversely, overdose with lithium carries a higher mortality than other mood stabilizers. Sudden withdrawal of lithium therapy is frequently associated with rebound manic symptoms.

Treatment with anticonvulsants has a stabilizing effect on mood in epileptic patients, which led to the use of these drugs in treating bipolar depression. There is, however, no clear evidence that depression and epilepsy have a shared aetiology. A number of open and small-scale controlled studies of carbamazepine in depression have suggested a possible antidepressant effect, but the studies are insufficient to come to a conclusion about efficacy in the treatment of depression (Porter et al, 1999). Carbamazepine has been associated with a higher incidence of suicide attempts and of completed suicides (Thies-Flechtner et al, 1996). It remains effective as an antimanic agent.

Open studies of valproate monotherapy have indicated that it has a prophylactic effect against mania, but not against depression. As stated earlier, the use of carbamazepine and valproate in the treatment of acute bipolar depression is not evidence based (Goodwin, 2003).

Lamotrigine is an anticonvulsant that has robust antidepressant activity. The mechanism of action of lamotrigine is different from that of other anticonvulsants and mood stabilizers. Its efficacy in the treatment of bipolar depression has been demonstrated in a randomized, double-blind clinical trial comparing lamotrigine 50 mg and 200 mg with placebo. A clinical response was noted for 48% and 56% of patients treated with low- and high-dose lamotrigine respectively, compared with 29% of patients treated with a placebo. Other studies also have yielded favourable results (Bowden et al, 1999; Frye et al, 2000).

Lamotrigine should be titrated slowly as rapid titration increases the risk of developing skin rashes. Other undesirable side effects include delirium, confusion, depression and psychosis (Ferrier, 1998). Because early manifestations of hypersensitivity may occur in the absence of rash, patients with these symptoms should be evaluated immediately. Lamotrigine is more effective against depression than it is against mania in long-term treatment, and is the drug of choice where depression is the major burden of the illness.

Table 3. Caution with antidepressants in bipolar depression

No dual action antidepressants are recommended in bipolar disorder type I
No combination of two antidepressants is recommended in bipolar disorder type I
No antidepressant monotherapy should be given
A shorter course of antidepressant treatment is recommended in bipolar disorder type I
Selective serotonin-reuptake inhibitors are preferred over tricyclics
Selective serotonin-reuptake inhibitors with a shorter half-life are preferred
Avoid antidepressants in rapid cycling bipolar disorders

Table 4. Side effects of lithium

Early side effects	Diuresis, tremor, dry mouth, metallic taste, weakness and fatigue
Later effects	Fine tremor, polyurea, polydipsia, hypothyroidism, impaired memory, electrocardiogram changes
Toxic effects	Nausea and vomiting, diarrhoea, coarse tremor, ataxia, dysarthria, muscle twitching, confusion, coma, convulsion, renal failure, cardiovascular collapse

Second generation antipsychotics

Treatment of bipolar depression originally used traditional antipsychotics for their anxiolytic and hypnotic properties, and to prevent the hypomanic or manic switch, not for their antidepressant properties. As they are available in the depot form, typical antipsychotics are used to ensure medication adherence, even though with the advent of atypical antipsychotics the use of depot preparations has decreased. Co-morbid anxiety symptomatology is a highly prevalent and incapacitating symptom of bipolar depression. This can hinder response to treatment, worsen the course of the illness and increase the rates of suicide and substance abuse. As many as 47–90% of patients are prescribed antipsychotics, either alone or in combination with mood stabilizers (El-Mallakh and Nassir Ghaemi, 2006).

Conventional antipsychotics were thought to be pro-depressants, being more implicated in a switch from mania to depression than is treatment with lithium and valproate. Atypical antipsychotics appear to have a better antidepressant profile than traditional ones (Bowden, 2005; Dunner, 2005). This has been verified in a large double-blind, placebo-controlled clinical trial (Calabrese et al, 2005). The therapeutic response to lithium usually occurs only in the second week of treatment, and is slower than the response to atypical antipsychotic drugs such as quetiapine. The antidepressant properties of atypicals may be related to the fact that they combine 5-HT2A inhibition and down-regulation, as well as D2 antagonism (Yatham et al, 2005). The novel antipsychotics have been approved for acute mania, but their efficacy in acute depression and prophylaxis of depression is under investigation.

Olanzapine has shown a smaller effect, while an olanzapine and fluoxetine combination has shown a moderate effect in patients with bipolar depression type I (Tohen et al, 2003). In an American clinical trial programme known as BOLDER (BipOLar DepRession), quetiapine showed a large therapeutic effect in a group of patients with bipolar depression type I or II (Calabrese et al, 2005). Quetiapine monotherapy was effective and well tolerated, having both antimanic and antidepressant properties in the treatment of bipolar disorder. Quetiapine has anxiolytic and hypnotic properties and this could be an added advantage. Large prospective studies are warranted to test the validity of these findings. So far, these drug trials have been promoted or sponsored by drug companies, a potential weakness of such studies.

Adjunctive therapies

Unfortunately, two thirds of outpatients, even those treated in academic centres, continue to be moderately symptomatic and disabled by depression. They experience residual symptoms quite frequently and generally require combination therapies. In monotherapy, drugs lose effectiveness over time. In general, mood specialists justify the use of combination therapy initially in acute cases, or in the event of monotherapy failure (Bowden, 2004; Post, 2006). The potential benefits of any adjunctive therapy should be balanced against the risk of side effects and interactions. The added drug should be introduced gradually. There are no clear guidelines regarding which agents achieve and sustain remission. The best combination regimen is established by looking at an individual's responsiveness and tolerability.

The antimanic effects of lithium and the superior antidepressant effects of lamotrigine can be taken advantage of if these drugs are given in combination; a promising option that warrants further systematic study (Post, 2006). On the basis of observational findings, combining lamotrigine with other mood-stabilizing agents or an atypical antipsychotic may achieve better mood stability. However, the efficacy of such combinations has not been systematically compared with monotherapy. Combining lamotrigine with lithium or valproate, or an atypical antipsychotic, is theoretically promising, but more prospective studies are warranted. Valproate and lamotrigine have pharmacokinetic interactions; valproate doubles lamotrigine levels. Lamotrigine may have a pharmacodynamic interaction with carbamazepine, leading to neurotoxicity. Combining lamotrigine and quetiapine may be a valuable idea to treat severe bipolar depression. Lithium, lamotrigine and valproate require regular checking of blood levels. There is currently some objection to using heavy-duty antipsychotics to treat bipolar depression type II when antidepressants and mood stabilizers could be given a proper trial.

Electroconvulsive therapy

NICE guidance on electroconvulsive therapy (ECT) and depression indicates that ECT should be held in reserve rather than being an early treatment option. Given the treatments that are currently available, and considering the risk of switching to hypomania or mania, this is a fair position, but where ECT has worked in the past with a particular patient and that patient is actively suicidal, it remains a life-saving option. ECT is also useful in treating bipolar depression during pregnancy and refractory cases of depression. ECT is rapidly effective, and is even more effective in mixed depressive states than in non-mixed depressions. The less frequent use of ECT in recent years coupled with widespread use of antidepressants has worsened the condition of these seriously ill patients and consequently they suffer longer duration of episodes, longer hospitalization and higher suicidal risk (Marneros and Goodwin, 2005).

Co-morbidity

It is unclear whether coffee and alcohol are mood stabilizers or destabilizers but they are unsafe in the hands of people with bipolar disorder. Bipolar patients tend to be heavy smokers and coffee drinkers. Both manic and depressed patients have a tendency to misuse alcohol; in the manic phase there is increased craving for alcohol while in the depressed phase it is used as self-medication. Likewise, bipolar patients are highly vulnerable to sub-

stance misuse. Co-morbidity of bipolar disorder and alcoholism and other substance use disorders are highly prevalent. The so-called 'dual diagnosis' creates clinical challenges in terms of establishing an accurate diagnosis and appropriate treatment strategies. The inter-relationship between these disorders appears to be mutually detrimental. Substance abuse and alcoholism complicate the course and prognosis of bipolar disorder while bipolar disorder may be a risk factor for developing the former disorders. Substance-dependent bipolar patients pose formidable challenges to the mental health team, needing a non-confrontational, non-threatening approach.

Psychosocial management

With bipolar disorder, as with many other conditions, there is a need to treat the whole person that encompasses physical and social needs as well as the psychological state. Psychosocial treatments and environmental triggers operate more powerfully for depression than mania (Johnson et al, 2000). Adjunctive psychosocial interventions keep patients on track, increase clinical stability and enhance pharmacotherapy outcome, reducing re-hospitalization. A variety of psychosocial interventions affect psychosocial functioning (Frank et al, 1994; Bauer et al, 1998; Clarkin et al, 1998). Cognitive behavioural therapy (CBT), psycho-education, family therapy, and interpersonal and social rhythm therapy (designed to help patients develop stable relationships and sleep pattern, and offer awareness of prodromal symptoms both for patients and carers) are the main psychosocial interventions. Given the severity of psychosocial problems in the aftermath of bipolar episodes, such effects are particularly beneficial (Johnson et al, 2000). An interesting case study (Wehr et al, 1998) reveals the success of a rapid cycling patient through psychosocial intervention over a 2-year period to help him maintain bed rest in a dark room for 14 hours each night resulting in sleep and mood stabilization.

CBT is best introduced in the maintenance phase. CBT involves identifying maladaptive cognition and behaviours that may be barriers for the patient's recovery and ongoing mood stability. Follow-up studies suggest that patients receiving CBT have significantly fewer bipolar episodes and less sub-syndromal mood symptoms if given as an early option. One UK study found that adjunctive CBT was beneficial only for patients with 12 or fewer episodes of bipolar disorder (Scott et al, 2006). More research into the specific cognitive process in bipolar disorder is required to refine and develop CBT intervention unique to this disorder. Family therapy should be directed at resolving the effects of the disorder on family, reducing levels of negative expressed emotions and improving adaptive communication skills. It is important that the patient develops a positive sense of self-esteem; bipolar relapses are an assault on the patient's social dignity and self-image. Psycho-education involves informing the patient and carers about medication adherence and stress management, but it is equally important to educate them about the course of the disorder and treatment options. Recent interest in bipolar disorders has offered enormous opportunity for psychosocial education in the longitudinal course of the illness.

Interpersonal and social rhythm therapy focuses on mood episodes associated with disruptions to social routine and sleep/wake cycles (social rhythm). Constructing a chart of moods and life events may guide both choice of treatment and expectation of outcome of treatment (MacQueen et al, 2002). Monitoring and grading mood is a useful technique to adjust the mood swings.

Psychosocial intervention also includes a component of teaching bipolar patients to cope with prodromal symptoms to prevent full-blown episodes, and a mood chart can reveal such symptoms (Lam et al, 2001). Mania can fuel itself and depression can spiral down. Bipolar patients are able to report prodromal symptoms reliably and it is beneficial to teach patients to monitor their moods systematically and to promote healthy coping strategies. Manic symptoms are seductive, and in the manic prodromal phase patients may have a tendency to give in to the temptation of succumbing to them, whereas in the depressive prodromal stage patients may stay inactive, hoping that symptoms will go away automatically. Early warning signs of depression are subtler than early signs of manic symptoms.

The patient's involvement in his/her treatment programmes is the key predictor of a positive outcome. A negative therapeutic alliance may exist as result of innocent actions and attitudes on the part of mental health staff as well as on the part of patients; this may be attributed to the nature of the illness. Evaluating and managing the suicide risk, and controlling and managing co-occurring substance abuse disorders, are parts of psychosocial management. If found to be effective, psychosocial management could offer benefits in bipolar depression comparable to antidepressants without the side effects or risk of induction of mania or rapid cycling.

Conclusions

Bipolar depression can result in increased morbidity and mortality rates when compared to unipolar depression. It can also lead to decreased productivity and psychosocial functioning, and increased use of mental health resources. The neurobiology of anhedonia and suicidality is different from that of racing thoughts and euphoria, but the treatments of both conditions are inter-linked – depression and mania may be two sides of the same coin. Unmet clinical needs persist in all phases of bipolar disorder. Agents with bimodal activity – which can ameliorate acute depression and reduce abnormal mood elevation – are desirable for the treatment of bipolar depression.

A dearth of authentic research in the management of bipolar depression has resulted in multiple uncertainties. Given the time bipolar patients spend in the depressive phase, new modes and novel approaches to treatment are immensely important. The recognition of the core features of bipolar depression, the threshold symptoms for treat-

ment, and the optimal treatment choices for monotherapy or combination therapy all warrant further investigation. The optimal duration of maintaining antidepressant therapy has not been established empirically and, until better evidence-based guidelines are available, antidepressant therapy should be tailored on an individual basis. **BJHM**

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KEY POINTS

- Bipolar depression involves diagnostic and treatment challenges.
- Bipolarity should be carefully considered for patients who do not respond to antidepressants.
- Uncertainties persist in the use of antidepressants in bipolar depression.
- Mood stabilizers are recommended for prophylaxis of bipolar depression.
- Atypical antipsychotics are approved for use in mania but their role in depression warrants further studies.
- Research is required to set out a more rational approach to combination therapies for bipolar depression.
- Emerging data suggest that lamotrigine and quetiapine are effective treatments for acute bipolar depression.
- The National Institute for Health and Clinical Excellence guidelines clarify some of the confusions in the treatment of bipolar depression.