Improving practice – Bipolar disorder

Dr Stuart Pinkerton, MB ChB Dip. Pharm. Med FFPM
GP, Parkbury House Surgery, St Albans, Hertfordshire

Summary

Bipolar disorder is a highly distressing psychiatric disorder that affects the lives of both the patient and their family, and is associated with a particularly high lifetime risk of suicide. Although estimates of the prevalence of bipolar disorder vary, the fact that up to 3.5% of the population is affected means that the majority of GPs in the UK will have to manage several cases as part of their routine workload. However, the diagnosis and subsequent treatment of bipolar disorder are very complex and can be very challenging even for the most experienced clinician. In particular, it is apparent that the rate of misdiagnosis of bipolar disorder is very high, particularly when attempting to differentiate the depressive phase of the condition from unipolar major depression. Failure to do so may mean that inappropriate treatment with antidepressants is initiated, which has the potential to trigger an acute manic episode. As such, treatment initiation and confirmation of a diagnosis is usually made in secondary care after referral from the GP. A variety of treatment options are available to manage the condition, whilst the use of psychological support, behavioural therapy and counselling may also prove useful in certain patients. Guidelines on the management of bipolar disorder have been published, which, it is hoped, will help to simplify the management of this complex condition.

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Introduction

Bipolar disorder is characterised by one or more manic, hypomanic or mixed episodes, usually accompanied by major depressive episodes. The extreme shifts in mood, energy and functioning that characterise bipolar disorder are usually very distressing for the patient and also profoundly disturbing for the patient's family and friends to observe.

Children, adolescents and adults can all suffer from this most distressing psychiatric disorder, but the condition usually first manifests during adolescence. The 'cycles' or episodes of depression, mania, or 'mixed' manic and depressive symptoms, typically recur, and may become more frequent often leading to significant disruption from work, school, family and social life.

Bipolar disorder is a very serious, lifelong medical condition, and is associated in up to 40% of cases with a highly significant lifetime risk of suicide attempts, with 10–20% of patients tragically succeeding in taking their own life. Consequently, bipolar disorder carries with it a huge burden on patients, their carers and their families.

Some of the risk factors and triggers for bipolar disorder include a family history of the condition, attention deficit disorder (ADD), stress, abuse, hypothyroidism and even seasonal factors. Indeed, some patients describe classical depressive symptoms related to decreasing hours of daylight during the winter months (seasonal affective disorder), which is closely related to the depressive cycle seen in bipolar disorder.

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How common is bipolar disorder?

Estimates of the prevalence of bipolar disorder vary, but typically lie within the range of 1–3.5%, evenly distributed between men and women. It is, therefore, a surprisingly common condition, with most GPs having to manage several challenging patients with bipolar disorder as part of their increasingly heavy caseload.

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There is a very high rate of misdiagnosis of both unipolar and bipolar depressive illness, and it is vitally important to differentiate patients with frank bipolar disorder from patients with cyclothymic personalities and rapid mood swings, as their respective management is very different. In this article, I will attempt to outline some practical strategies that may assist the clinician in identifying these patients more readily and to implement appropriate management accordingly.

Course and impact of bipolar disorder

The usual pattern of bipolar disorder is one of increasing intensity and duration of symptoms with an insidious progression over many years.

Early in the course of illness – usually when patients are in their late adolescence or in their early 20s or 30s – episodes of illness may be separated by long periods of good health during which time there may be few or even no symptoms. However, thereafter symptoms tend to become more frequent; when four or more episodes of illness occur within a 12-month period, the person is said to have bipolar disorder with rapid cycling, which is difficult to treat and is associated with a particularly poor outcome. In addition, the presentation of bipolar disorder is often complicated by concomitant alcohol or substance abuse that generates further management problems for the clinician.

Severe depression or mania may be accompanied by symptoms of frank psychosis. In this acute phase, it can be very difficult to distinguish the patient's thought disorder, mood and behavioural disturbances from patients with a schizophrenic illness. Symptoms of psychosis may include hallucinations (e.g. hearing, seeing, or otherwise sensing, the presence of stimuli that are not actually there) and delusional ideas (e.g. false and unshakeable personal beliefs, not subject to reason or contradictory evidence, and not explained by a person's cultural concepts). Psychotic symptoms associated with bipolar disorder as opposed to schizophrenia typically reflect the extreme mood state at the prevailing time, be that mania or depression.

Both the nature and the severity of symptoms usually vary significantly between individuals, which further complicates diagnosis. For example, bipolar disorder can be severe and disabling and follow a long-term disease course, or it can be mild with infrequent episodes. Patients can also experience periods of mixed symptoms. There is no reliable marker that predicts the likely prognosis for individual patients, further complicating long-term management plans and making the condition even more challenging to treat. This also means that it is very difficult to advise patients, their carers and families on the likely outcome in any one particular case.

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Common clinical manifestations and diagnostic challenges

Manifestations of mania often include:

- periods of grandiosity with frank delusions of grandeur
- a decreased need for sleep, with boundless and seemingly unremitting energy levels
- loquaciousness with pressured racing thoughts, 'flight of ideas' and distractability
- psychomotor agitation and excessive involvement in pleasurable activities that can have painful consequences (e.g. gross overspending)

In marked contrast, depressed symptomatology is usually characterised by:

- the presence of a persistent sad mood with frequent outbursts of unexplained crying or sobbing
- a loss of interest or sense of any pleasure in activities once enjoyed
- episodes of irritability and agitation compounded by feelings of being physically slowed down
- a loss of energy, listlessness and fatigue, with increased or decreased sleep
- difficulty with thinking and concentrating (patients frequently complain that they simply cannot be bothered and do not have the energy nor the inclination to perform relatively simple tasks such as eating, drinking, reading the newspaper or watching a TV programme)
- significant changes to appetite and body weight
- feelings of inappropriate guilt and worthlessness
- at the severe and most dangerous end of the spectrum, recurrent thoughts of death or suicide, with or without a specific action plan for implementation.

In practice, however, patients rarely demonstrate these classical signs and symptoms, making a definitive diagnosis at first presentation extremely difficult. For example, in both bipolar I disorder (a recurrent disorder of mood featuring one or more manic or mixed episodes, or both manic and mixed episodes, with at least one major depressive episode) and bipolar II disorder (one or more major depressive episodes accompanied by at least one hypomanic episode), it may be very difficult to differentiate the presentation of the depressive phase from patients who present with symptoms and signs of major depression. This is vitally important because treatment strategies for these distinct disorders differ profoundly. Patients with major depression usually respond well to selective serotonin reuptake inhibitors (SSRIs), whilst in contrast these drugs are relatively ineffective in depressed patients with bipolar disorder, regardless of whether this is of type I or type II.

Indeed, misdiagnosis of a depressive phase of bipolar disorder as an episode of major depression followed by the prescription of either a tricyclic antidepressant (TCA) or monotherapy with an SSRI can both have disastrous consequences, potentially inducing a totally unexpected acute manic episode. Furthermore, as patients with bipolar disorder usually spend the vast majority of their symptomatic time in the depressive phase of their illness, the risk of a misdiagnosis of major depression is heightened even further. If an SSRI is to be prescribed for patients in the depressive phase of bipolar disorder then it should be used only in combination with an antimanic agent such as lithium, valproate or an antipsychotic.

Getting the diagnosis right, with appropriate early referral to a secondary care specialist centre, is therefore absolutely essential. For this reason, in my opinion, care protocols and drug treatment should be initiated in the secondary care setting unless there is need for immediate treatment, with possible sectioning of the acutely psychotic patient.

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Issues with accurate diagnosis in different age groups

Diagnosis in children and adolescents can be particularly challenging and distressing for families. Bipolar disorder can present as early as 4 years of age. However, frank major depression in children is relatively rare so symptoms compatible with depressive illness merit early referral to a child psychiatrist for assessment. Young depressed children may feel ashamed and guilty to feel so awful for no apparent reason, and may therefore hide their feelings of profound sadness because they don't understand them. How can an 8-year-old child express in any meaningful way suicidal thoughts? In addition, mania or hypomania may not present in children in the same way as it does in adolescents or adults. Parents may simply think, and indeed wish to think, that they have a hyperactive and very creative young child. Teachers may report hyperactivity and, in the older child, may suspect ADD – an important differential diagnosis. Usually, one or both parents will present to their GP together with their child and report worrying changes in their behaviour, noted both at home and at school. For very young children (i.e. those under 6 years of age), it is well worth involving health visitor colleagues at an early stage to help in the overall evaluation of the case. If bipolar disorder is suspected, or where a diagnosis is uncertain, early referral to a specialist centre is advisable.

Similarly, manic or depressive symptoms presenting in adolescence also merit early specialist referral. The median age of onset of bipolar disorder is relatively young (i.e. 21 years for both genders, with a peak age for first appearance of symptoms of 15–19 years). To establish an accurate diagnosis in this age group requires a high index of suspicion and astute clinical acumen as these patients are usually also experiencing the turbulent mood swings associated with adolescence.

Turning to the elderly, bipolar disorder rarely presents for the first time in this age group and the clinical picture in these individuals is usually very different from that seen in adolescence. For example, onset after the age of 60 years is more likely to be associated with identifiable medical conditions such as stroke and cerebrovascular disease, chronic alcohol abuse and head injuries. There is, therefore, a significant association between acute mania in the elderly and underlying brain disease. Consequently, if elderly patients present for the first time with symptoms compatible with an acute manic episode, underlying organic disease should initially be excluded and specialist referral for acute assessment initiated.

Implications of bipolar disorder for patients and their families

Bipolar disorder usually has a profound impact on a patient's life. Impaired thinking and judgement often leads to poor decision making and impulsive behaviour. This can result in

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disastrous consequences for both their physical and sexual health, and also for the financial and social well-being of patients and their families. During the ‘manic’ phase, patients may lose all sense of financial awareness and indulge in an unconstrained spending spree with disastrous financial consequences. With little or no time for eating and sleeping properly, patients may ultimately be referred to their doctor by other family members in a state of total exhaustion and self-neglect.

At the other end of the spectrum, patients may be so depressed, withdrawn and psychomotor-retarded that there is an equally great risk of self-neglect but with the additional heightened risk of suicide.

In the past, there has been a tendency to romanticise bipolar disorder, particularly within artistic circles. Many artists, musicians and writers have experienced the mood swings associated with the condition, and some even credit the condition for their creativity. Conversely, however, this disease ruins many lives, and there can be no doubt that it is associated with a greatly increased risk of suicide.

A combination of medications and other forms of therapy, including psychological support, can be very helpful. However, they all depend on patients’ acceptance of their disease and the need for lifelong treatment. In this regard, approximately two-thirds of patients are known not to adhere to their treatment regimen. There is, therefore, a major and compelling need for an agent that is both effective and well tolerated across all phases of this devastating disease.

Clinical management

Management challenges in primary care

The longer patients can be maintained in the community, ideally holding down a job and remaining relatively self-sufficient, the better is their likely prognosis and ultimate outcome.

As well as the obvious clinical management issues and frequent intercurrent medical problems, psychosocial and environmental issues are usually profound. Maintaining these patients within the community is therefore a critically important challenge, as they often pose a considerable burden to their families and carers. The longer patients can be maintained in the community, ideally holding down a job and remaining relatively self-sufficient, the better is their likely prognosis and ultimate outcome. Conversely, a need for frequent hospital admission to control rapid-cycling episodes, results in a worse prognosis.

The National Service Framework (NSF) for Mental Health and other published guidelines

Any national framework and related management guidelines should provide guidance on patient management, related to both immediate treatment protocols for acute illness and associated care needs, and also ongoing treatment and future care needs, particularly regarding maintenance within the community and patient acceptability of the management plan, including drug therapy. So, with respect to bipolar disorder, to what extent do the NSF for Mental Health and the available published guidelines achieve these objectives?

The NSF for Mental Health

The NSF for Mental Health was a 10-year programme first published in September 1999 focusing on the mental health needs of adults aged up to 65 years and supported by a massive £700m in its first 3 years of implementation. It sets seven specific standards underpinned by a published base of evidence, knowledge and experience, service models and examples of good practice. Particular focus is placed on Standards 4 and 5 – the provision of effective services for people with severe mental illnesses, with all patients receiving a copy of a written care plan with timely access to in-patient care, if required. The objectives are to optimise patient and family engagement, anticipate or prevent any crises and reduce suicide risk.

The central and core common themes in this NSF relate to:

- accessibility – enabling help to be obtainable when and where it is needed
- provision of choice for patients, families and carers, thereby promoting independence
- involvement of service users and their carers in the planning and delivery of care
- empowerment and support for healthcare staff.

These themes are underpinned by ten guiding principles helping to shape decisions on service delivery that all involve promoting the active involvement of healthcare staff, carers and their patients in all decisions regarding management and treatment.

All this sounds fantastic in theory but raises the fundamental question of the practical utility and clinical relevance of the NSF and its impact to clinical practice. For example, there are only four references in the entire 153 pages of the NSF document that relate specifically to bipolar disorder, which contrasts with some 36 references made to schizophrenia. Furthermore, the wording and language employed implies that bipolar disorder is regarded as just another severe mental illness (e.g. page 3: 'psychotic illness such as schizophrenia and bipolar affective disorder'; page 46: 'recurrent and enduring mental illness, for example, schizophrenia and bipolar affective disorder').

The NSF also discusses the need for local implementation groups to agree and implement protocols between primary and secondary care for depression (including post-natal depression), anxiety disorders, schizophrenia, drug and alcohol dependency and patients requiring psychological therapies. Remarkably, there is no mention at all of bipolar disorder. Thus, despite the huge investment in financial and human resources in the NSF for Mental Health, its impact on the clinical management of bipolar disorder has, in my view, been very limited.

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The bipolar guidelines

Have the published bipolar guidelines been any more specific and more useful than the NSF?

The British Association of Psychopharmacology (BAP) issued a consensus statement in 2003 as an evidence-based aid to clinical decision making, derived from an expert consensus meeting and feedback received from other interested parties. It covers issues such as the immediate treatment of episodes, the prevention of relapse and when to withdraw treatment. Like the NSF, it addresses the fundamentals of patient management with respect to diagnosis, access to services, 'safety' and enhanced care, underpinned by the concept of establishing and maintaining a therapeutic alliance between patients, carers, healthcare professionals and all members of the multidisciplinary healthcare team. It also clearly highlights the importance of providing education regarding bipolar disorder, in particular in enhancing adherence to treatment and promoting awareness of stressors and early signs of relapse.

Moreover, in contrast to the NSF, the BAP consensus statement provides us with some specific therapeutic guidance on both short- and longer-term treatment and maintenance therapy, with useful recommendations on the management of patients with rapidly cycling episodes. Importantly, BAP highlights that trials with atypical antipsychotics have demonstrated that antimanic effects can be achieved without inducing extrapyramidal side-effects (EPS) – an important clinical message that should, in the future, influence prescribing practice. BAP concludes that, as for schizophrenia, atypical antipsychotics may be increasingly preferred to typicals because of their superior therapeutic ratio.

Interestingly, in April 2002, the American Psychiatric Association (APA) published very similar evidence-based goals for the management for bipolar disorder and highlighted, like the subsequent BAP consensus statement, the critical importance of establishing and maintaining a therapeutic alliance with the patient, their carers and the broader healthcare team. Specific guidance is also offered on the treatment of acute manic or mixed episodes and maintenance therapy.

In summary, both the BAP and APA guidelines share a common integral theme and highlight the critical importance of patient acceptability of care plans and the associated drug treatments. They are both more useful than the NSF because they offer specific guidance on patient management and highlight three key issues:

- access to immediate care
- promoting recovery/relapse prevention
- the importance of a therapeutic alliance.

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In July 2006, guidelines on the management of bipolar disorder were published by the National Institute for Health and Clinical Excellence (NICE) in an attempt to assist clinicians in the recognition of patients with bipolar disorder and in those at risk of the disorder and also to guide appropriate management with the objective of reducing the numbers of patients who relapse. Again, like the preceding guidelines, NICE calls for the need to fully involve patients and their families in treatment decisions. The guidelines provide clinicians with a set of criteria for specialist referral and also cover diagnosis in adolescents and provide recommendations for appropriate drug treatment.

Rating scales and diagnostic questionnaires in primary care

Diagnostic questionnaires and rating scales are not routinely used in the primary care setting because their use is simply not practical within the constraints of an average 10-minute consultation. In fact, clinical decisions within the primary care environment are usually based on clinical judgement as to how well patients respond to treatment and whether they need further specialist review and assessment.

In contrast, and as we have seen in the preceding sections of this issue of *Drugs in Context*, rating scales are the mainstay of assessment within a clinical trial setting. The Young Mania Rating Scale (YMRS) for the assessment of mania, and the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Clinical Global Impression (CGI) rating scales for assessing depression are the ones with which I have had the most experience. As discussed previously, the majority of GPs, however, will have very little practical need for these rating scales other than a basic understanding of how to interpret them.

Management

Non-pharmacological treatment

We are slowly beginning to discover that natural supplements may play a role in the therapy of bipolar disease. Much has yet to be learned, but there are at least two nutrients that may offer some hope for patients – fish oils and choline. One of the important biochemical abnormalities in bipolar disorder appears to be higher levels of omega-6 and a relative deficiency of omega-3 fatty acids. If this is really the case in practice, then supplementing the diet with fish oils may offer some help. The nutrient, choline, has been shown to be beneficial in patients concurrently treated with the mood stabiliser, lithium, and oral choline decreases purine levels in the brains of lithium-treated subjects with rapid-cycling bipolar disorder.

Psychotherapy, cognitive behavioural therapy (CBT) and counselling have a part to play in the overall management plan of a patient with bipolar disorder, particularly in conjunction with drug therapy. However, historically more experience with these therapy modalities has been gathered in patients with what used to be known as ‘neuroses’ – a group of disorders characterised by anxiety, including situational and phobic anxiety, and reactive depression – rather than in those with bipolar disorder *per se*. Although this terminology and classification has now been updated, there is still relatively more experience of CBT for the management of situational anxiety than there is in the management of bipolar disorder. As such, and for the time being, I prefer to leave the decision to adopt these therapies to the specialist.

Only 60% of patients suffering from bipolar disorder receive appropriate drug therapy.

Pharmacological treatment

Alarmingly, it has been estimated that only 60% of patients suffering from bipolar disorder receive appropriate drug therapy. There is, therefore, a clear need for both effective and well-tolerated agents, preferably given as monotherapy, to treat and prevent the recurrence of episodes of both acute mania and depression.

As a hospital doctor on psychiatric wards some 25 years ago, chlorpromazine and haloperidol were the mainstay of therapies that were prescribed for both acutely manic or schizophrenic patients despite their debilitating side-effect profiles. These ‘typical’ antipsychotics are commonly associated with debilitating EPS and tardive dyskinesia, yet a substantial number of patients are still treated with these older antipsychotics today. Electroconvulsive treatment (ECT) was also commonly used at this time for treating severely depressed patients with evidence of psychomotor retardation, whether or not this was associated with ‘manic-depressive psychosis’ or ‘endogenous depression’ (these terminologies now being superceded by bipolar disorder and major depression, respectively), regardless of the underlying trigger. The problem, however, was that the control of cycling in these patients was very variable and the use of ECT was associated with other short- and longer-term risks. Although ECT is still used in some patients with bipolar disorder today, its use has now become less fashionable.

In many localities the mood stabiliser, lithium, remains the gold standard for treating patients with stabilised bipolar disorder. Lithium was the first drug to be used as a mood stabiliser but has very little benefit in helping those patients experiencing recurrent depressive episodes. Lithium is also associated with polyuria, hypothyroidism, tremor and cognitive slowing. Regular plasma drug monitoring and tests of thyroid function are therefore essential to optimise drug dosage and minimise the risks of toxicity.

Atypical antipsychotics have gained approval for the treatment of bipolar mania and early clinical experience with these atypicals has been encouraging. Indeed, NICE now recommends that olanzapine should be considered for the long-term treatment of bipolar disorder and also as a potential alternative monotherapy or as a second prophylactic agent if a patient experiences frequent relapses. Recently published data from the USA with quetiapine in patients in the depressive phase of the condition offer the hope that these novel atypical therapies may eventually be approved and licensed by regulatory agencies for use in the treatment of both the manic and depressive components of bipolar disorder. We shall, however, have to await regulatory reviews and updated treatment guidelines before we can routinely offer our bipolar patients atypical antipsychotics for the treatment of both ends of the bipolar disorder spectrum. It should be emphasised that these atypical antipsychotics are not without side-effects. The commonly prescribed atypical, olanzapine, can produce weight gain of up to 12 kg. In addition, according to the manufacturers' own data both EPS and diabetes have been reported, albeit less frequently, over a 1-year treatment period. Although I have no personal experience with the use of risperidone, weight gain has also been reported and the documented association with hyperprolactinaemia, galactorrhoea and menstrual disturbances is of potential concern, and clearly contraindicates its use in breast-feeding women with bipolar disorder. The profile of quetiapine seems to be relatively clean in both these regards, although optimising dose titration to a clinically effective dose and associated early sedation may limit achieving an optimal response.

Future developments in bipolar disorder

Whilst research into other treatments for bipolar disorder is advancing steadily, there do not appear to be any major breakthroughs on the horizon. Despite the profound need for an effective and well-tolerated treatment, there is still currently no approved monotherapy for use in bipolar depressive illness.

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Key points

- Bipolar disorder is a highly distressing condition that usually first manifests during adolescence but which can also onset earlier in childhood.
- Bipolar disorder is a lifelong condition that exerts an enormous burden upon both the patient and their family. It is associated with a very high lifetime risk of suicide, with 10–20% of affected patients being successful in their attempted suicide.
- Bipolar disorder is surprisingly common with up to 3.5% of the population affected. As many patients initially present with symptoms and associated problems to their GP, bipolar disorder is now established as a challenging condition to recognise and manage in the primary care setting.
- Bipolar disorder is often misdiagnosed, which can have a major implication on patients' outcomes from treatment. Misdiagnosis of the depressive phase of bipolar disorder as major depression may mean that the patient is inappropriately prescribed antidepressant monotherapy; this may then trigger an unexpected acute manic episode.
- Treatment for bipolar disorder is normally initiated in secondary care after referral by the GP. A combination of both pharmacological and non-pharmacological therapies (including drug therapy, psychological support and counselling) can be very helpful.
- Maintaining patients in the community should enhance outcomes from treatment. Conversely, those whose disease enters a rapid-cycling course are more likely to be hospitalised and have a poorer outcome.
- Various published national and international guidelines and protocols are available to assist the clinician in both reaching a diagnosis and in making appropriate treatment decisions. They all encourage a stronger therapeutic alliance between the doctor, patients and their families.
- Initiatives such as the NSF for Mental Health, whilst providing useful guiding principles, seem to have overlooked the importance of providing specific advice regarding the management of bipolar disorder.