Understanding bipolar disorder

Bipolar disorder is a distressing mental illness involving extreme fluctuations of mood. Stephen Bleakley and Rebecca Henry explain how this condition, which affects around one in 100 people, is managed.

BIPOLAR disorder is a distressing and chronic illness which can severely impact on daily functioning and cause social rejection. Although a degree of mood fluctuation is common in everyone, in bipolar disorder the changes can be extreme and interrupt social functioning and everyday performance.

Bipolar disorder was previously called manic depression. It is also known as bipolar affective disorder or simply “bipolar”. Key features of the illness include episodes of mania or hypomania with periods of normal mood (euthymia) or depression (also called bipolar depression). Symptoms of mania include:

- A persistently elevated mood
- Increased energy and activity
- Pressure of speech, distractibility
- A loss of normal social inhibitions, which may result in reckless or inappropriate behaviour

Hypomania presents with similar symptoms but to a lesser severity and without significant disruption to functioning. Symptoms of depression are the same as those seen in unipolar depression and include:

- Low energy
- Lack of interest and enjoyment in everyday activities
- A persistent low mood

Panel 1 presents the diagnostic features of bipolar disorder using the International Classification of Diseases, which is currently in its 10th edition (ICD-10).1

To complicate treatment, however, sufferers can also present in a mixed state, where symptoms of both mania (or hypomania) and depression are seen, or as “rapid cyclers”, where more than four distinct episodes a year are experienced.

For most patients bipolar disorder is chronic and recurrent but the exact course of the illness is subject to large variations. Some will experience mainly episodes of mania or hypomania with few symptoms of depression whereas others may have persistent depression punctuated with occasional hypomanic episodes.

Reflect on knowledge gaps

1. What are the three phases of management of bipolar disorder?
2. How often should lithium levels be measured and what other monitoring is required for patients on lithium therapy?
3. What cautions are required when prescribing an antidepressant to treat bipolar depression and which drugs are preferred?

Before reading on, think about how this article may help you to do your job better.
The lifetime incidence of bipolar disorder is approximately 1 to 2 per cent, depending on the diagnostic criteria used, and the relapse rate is higher than that seen in unipolar depression — 50 per cent within one year of an episode.1

Bipolar disorder occurs equally in men and women and the peak onset of symptoms is in the late teens. The exact cause of the illness is unknown but there is probably a large genetic component, which may account for neurotransmitter and brain structure abnormalities. Adverse social factors are also important and may trigger episodes or cause an earlier age of onset of the illness.2 Physical conditions, such as thyroid disease, can mimic symptoms. Drugs such as antidepressants, L-dopa and stimulants (both prescribed and illicit) can induce symptoms of mania3 and reducing or stopping them can relieve symptoms. Corticosteroids can cause a myriad of psychiatric problems during normal use and on withdrawal. Such medicines should be prescribed with caution for patients with bipolar disorder.

Bipolar disorder is diagnosed following two or more acute episodes of extreme mood changes, one of which must be mania or hypomania. Many patients live with a diagnosis of unipolar depression for many years until they suddenly have one episode of hypomania or mania.

Of great concern is the high suicide rate in patients with bipolar disorder. Fifteen per cent of those diagnosed will commit suicide with the greatest risk during mixed episodes.2

Drug management
The management of bipolar disorder can be split into three phases:

- Treatment of a manic or hypomanic episode
- Treatment of a depressive episode
- Long-term management and prevention of symptoms returning

British guidelines are available from the National Institute for Health and Clinical Excellence,2 the British association of Psychopharmacology (BAP)3 and the Scottish Intercollegiate Guidelines Network (SIGN).4

Panel 1: Diagnostic criteria for bipolar disorder using the ICD-10 criteria

**Bipolar disorder** Diagnosed after two or more episodes of extreme mood change, one of which must be mania or hypomania.

**Mania without psychosis** Symptoms must be present for at least one week. Mood is elevated out of keeping with circumstances from joyfulness to uncontrollable excitement. May include increased energy, resulting in overactivity, pressure of speech, and a decreased need for sleep. Attention cannot be sustained, and there is often marked distractibility. Self-esteem is often inflated with grandiose ideas and overconfidence. Loss of normal social inhibitions may result in behaviour that is reckless, out of character or inappropriate to the circumstances.

**Mania with psychosis** Symptoms as for mania but delusions or hallucinations are usually present.

**Hypomania** Symptoms must be present for at least four days. A persistent mild elevation of mood, increased energy and activity, and marked feelings of well-being. Increased sociability, talkativeness, over-familiarity, increased sexual energy, and a decreased need for sleep are often present but not to the extent that they lead to severe disruption of work or social rejection. Psychotic symptoms are not present.

**Depression** As for unipolar depression.

**Manic or hypomanic episodes** Episodes of mania usually require hospital admission to protect patients from behaviour that may place them, or others, at risk of harm. Any drug that might have contributed to the presentation, such as antidepressants, will need to be stopped to prevent prolonged symptoms.

Antidepressants are usually stopped abruptly in mania but a gradual tapered withdrawal may be appropriate in those with less severe symptoms to avoid antidepressant discontinuation problems (eg, influenza-like symptoms, dizziness and insomnia).

The treatment of choice for a first episode of mania or hypomania includes an atypical antipsychotic, a valproate preparation or lithium if symptoms are less severe.2–4 The four atypical antipsychotics currently licensed for treating mania are aripiprazole, olanzapine, risperidone and quetiapine. These atypical antipsychotics are generally preferred because of their more favourable short-term adverse effects.2–4 A full review of the antipsychotics, including monitoring and adverse reactions, can be found in a previous CPD article on schizophrenia (PJ, 25 July 2009, pp101–4).

Valproate is available in three forms in the UK: sodium valproate, valproic acid and semi-sodium valproate. Sodium valproate and semi-sodium valproate are metabolised to valproic acid, which is responsible for the pharmacological action.2 Although only semi-sodium valproate is licensed for acute mania, it is generally unclear if there is any efficacy or tolerability difference between the preparations.2 What is important is the dose of valproate. For rapid symptom control (ie, within a few days) a loading dose of 20mg/kg/day is occasionally used but at the expense of increased adverse reactions.

Lithium is effective in acute mania but its onset of action is slower than that seen with the antipsychotics or valproate. Added to this is the need for pre-lithium physical health checks, which may be refused by patients who are acutely unwell.

The short-term use of benzodiazepines, such as lorazepam or clonazepam, are also useful in acute mania for their calming and sedative effects.2–4

If a patient presenting with mania or hypomania is already on an appropriate antimanic medicine, clinicians should first check compliance before considering optimising the treatment by increasing the dose. If the response is inadequate then medicines are often combined.2–4 Common combinations include an antipsychotic with either lithium or valproate, or valproate with lithium.
**LEARNING & DEVELOPMENT**

Depressive episodes Most patients with bipolar disorder have far more depressive episodes than manic ones but, until recently, bipolar depression was poorly researched and most of the treatment options were extrapolated from unipolar depression. Bipolar depression often occurs more rapidly, more frequently and with more marked symptoms than unipolar depression and, for many, it is a life-long illness rather than one that occurs in discrete episodes. Antidepressants have a role in treating bipolar depression but should be used with caution because of the risk of causing mania or hypomania (“switching”). They should always be prescribed in conjunction with an antimanic agent to reduce this risk. If an antidepressant is necessary selective serotonin reuptake inhibitors (SSRIs) are recommended because they have a lower risk of switching (3.7 per cent) compared with the tricyclic antidepressants (11.2 per cent) and, probably, venlafaxine. In rapid cyclers and those with a mixed disorder antidepressants are likely to increase the switching rate so should be avoided. In those for whom an antidepressant is not appropriate, quetiapine (at 300mg per day) or lamotrigine (unlicensed in bipolar depression, but the usual dose is 50–200mg per day) are recommended. In contrast to treatment for unipolar depression, antidepressant treatment in bipolar depression is usually short-term. NICE recommends the antidepressant should be tapered off then withdrawn after eight weeks of symptom remission.

Long-term management The goal of long-term treatment is to prevent new mood episodes and to increase the period of stability between episodes. Targeting predominant symptoms and knowing the course of the illness is essential for effective maintenance. NICE recommends long-term treatment should be considered for those who have suffered a manic episode involving significant risk or adverse consequences, those who have had two or more episodes of mania or depression, or sufferers with significant functional impairment, risk of suicide or frequent episodes.

**Panel 2: Specific drug considerations**

**Lithium** Lithium has a narrow therapeutic range so requires close monitoring of plasma levels and other physical health parameters, such as renal and thyroid function. Blood levels should ideally be taken 12 hours after a dose (10–14 hours at most) aiming for a level between 0.6–1mmol/L. Levels above 0.75mmol/L offer additional protection against manic symptoms but come with a greater burden of adverse effects. Lithium toxicity generally occurs above 1.5mmol/L and is associated with symptoms of nausea, diarrhoea, course tremor, drowsiness and ataxia. Because lithium is almost exclusively excreted unchanged in urine any drug that alters renal handling or electrolyte balance can increase lithium levels and hence cause toxicity. This includes angiotensin-converting enzyme inhibitors, thiazide diuretics and non-steroidal anti-inflammatory drugs. Dehydration and a low salt diet can also raise lithium levels rapidly. Erratic compliance or abrupt discontinuation of lithium should be actively discouraged because this may increase the risk of a manic relapse.

Lithium has recently been the subject of National Patient Safety Agency (NPSA) alert in which the importance of regular plasma levels, physical health monitoring and problematic interactions is highlighted (PJ, 5 December 2009, p609). Lithium levels should be measured every three months and, ideally, pharmacists should check them before dispensing. However, GPs currently only get paid to monitor lithium levels annually. The NPSA has developed resources such as a patient record booklet, an information pack and a lithium alert card, which are available to order.

Valproate Valproate is a major human teratogen so should be avoided in pregnancy and, because the fetal abnormalities occur in early pregnancy, ideally it should be avoided in any women of child-bearing potential. If an unplanned pregnancy occurs while a woman is taking valproate she should be advised to seek immediate specialist advice.

**Lamotrigine** Lamotrigine, although useful in treating and preventing bipolar depression, must be titrated slowly to reduce the risk of a serious rash developing. A rash develops in 10 per cent of patients and in 1 per cent can become serious or potentially life threatening, with rare reports of Stevens–Johnson syndrome and toxic epidermal necrolysis. It is usually maculopapular and generally appears within eight weeks of starting treatment. Anyone who develops a rash, for which there is no other obvious cause and which appears to be spreading or worsening should be advised to stop taking lamotrigine and seek immediate medical attention. A rash is more likely if lamotrigine is co-prescribed with valproate (which prolongs the half life and reduces the clearance of lamotrigine).

**Carbamazepine** Carbamazepine is a potent inducer of cytochrome P450 hepatic enzymes so can increase the clearance of many other drugs and potentially cause treatment failure. Medicines affected include most antidepressants, antipsychotics, benzodiazepines, methadone, theophylline and oestrogens.
Where preventing episodes of mania is the main aim of treatment lithium, aripiprazole, olanzapine, quetiapine or valproate are recommended. In patients with mainly depressive episodes quetiapine or lamotrigine would be the initial drug choices, followed by lithium. Treatment should be continued for at least two years after a single acute episode and for up to five years if there are risk factors for a relapse (such as a history of frequent relapses, ongoing stressors etc.) In the event that the initial choices are not fully effective or the patient relapses then combining the above drug choices may be appropriate.

Carbamazepine is occasionally used in long-term prophylaxis of bipolar disorder and in less severe manic episodes after other drugs have proved ineffective. Non-compliance is a real issue in mental health and can result in relapses and hospital admissions. Pharmacists can play a useful role engaging patients in open, honest and non-judgemental discussions around the important of compliance in bipolar disorder. For example, they could explore whether patients have any concerns about their medicines (eg, side effects) which could contribute to poor compliance.

Specific drug considerations are discussed in Panel 2. Treating bipolar disorder in pregnancy must also be given special consideration. Treatment is complex and requires an expert opinion and a multidisciplinary approach. An increase in congenital malformations has been reported with valproate.
carbamazepine, lamotrigine and lithium and all these should ideally be avoided during pregnancy. A mood-stabilising antipsychotic such as those mentioned may be a suitable alternative but come with the caveat of limited supporting evidence and multiple adverse reactions.

All women of child-bearing age who suffer from bipolar disorder should be encouraged to have open and frank discussions about contraception at the time of prescribing and during follow-up appointments.

Monitoring People with bipolar disorder have higher levels of physical morbidity and mortality than the general population. Patients are recommended to have an initial physical health check soon after initial presentation and this should be repeated annually. The initial health check should include a fasting blood glucose, blood pressure, full blood counts, liver and renal function, lipid profile, thyroid function and weight. In addition, many of the medicines used in bipolar disorder have specific physical health monitoring recommendations (see Panel 3, p4).

Panel 4 summarises advice from NICE on the drug treatments for bipolar disorder.

Non-drug treatment options Drug treatment remains the principal therapeutic intervention in bipolar disorder, but a few alternative approaches can help in long-term treatment. Teaching clients to recognise early warning signs (ie, symptoms described in Panel 1, p2) of an acute episode can enable help to be accessed as soon as possible and reduce admission to hospital. The first port of call would be the GP, although some patients may be closely monitored by the local community mental health team and so can directly access specialist services.

Making lifestyle changes, such as reducing stress, practising good sleep hygiene, keeping regular work patterns and reducing alcohol and substance misuse, are also useful. Structured psychological treatments, such as cognitive behavioural therapy and family therapy, are also recommended in mild or moderate symptoms.

Electroconvulsive therapy (ECT) is also occasionally used for severe manic or depressive episodes, if other treatments have failed or the condition is life-threatening.

Signposting
- MDF The Bipolar Organisation is a national user-led organisation and registered charity for people whose lives are affected by bipolar disorder.
  www.mdf.org.uk
- Time to Change is a national campaign aiming to end the stigma associated with mental illness.
  www.time-to-change.org.uk
- The Choice and Medication website offers peer reviewed, patient-friendly advice on all medicines used in mental illness.
  www.choiceandmedication.org

Reference

Act: practice points
Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist’s CPD portfolio.
1. Check your patients on lithium have a recent and appropriate lithium level.
2. Have they also had renal function and thyroid function checks within the past six months?
3. Find out about your local community mental health team. Whom would you contact if you were concerned about an individual?
4. Help reduce the stigma associated with mental illness by downloading materials and a toolkit from the Time to Change website (see Signposting).

Evaluate
For your work to be presented as CPD, you need to evaluate your reading and any other activities. What have you learnt? How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?

Record
Consider making this activity one of your nine CPD entries this year.