



module 259

Treatment strategies for bipolar disorder

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Bipolar disorder

GOALS AND LEARNING OBJECTIVES

This module explains the treatment strategies for acute mania, acute bipolar depression and longer term treatment. It lists the key symptoms of bipolar disorder and describes how the condition is monitored, possible interactions, and when and how medication should be discontinued, as the risk of relapse remains high even after many years of sustained remission. It will help pharmacy teams support patients with bipolar disorder by explaining the various challenges this group of patients face.

KEY FACTS

Haloperidol, olanzapine, quetiapine and risperidone are the antipsychotics of choice for the treatment of mania

Antidepressants should only be used for treating bipolar depression or long-term treatment if they are prescribed in combination with an antipsychotic

Lithium is the most effective long-term treatment for bipolar disorder, so should be used first-line

Lithium is not recommended for patients with poor adherence as rapid discontinuation may increase the risk of relapse

Sodium valproate should be avoided in women of child-bearing age

If lithium is used, plasma levels, TFT and U&Es should be checked regularly. Patients must have this recorded in a lithium booklet, which pharmacists can check on dispensing

Adherence to medication is crucial in the long-term as the risk of relapse remains high even after many years of sustained remission

If medicines are to be discontinued after careful assessment of the potential dangers, they should be withdrawn over four weeks (three months for lithium). Support for relapse prevention is crucial at this time

Introduction & module overview

Bipolar disorder is a complex condition that has an early age of onset, the first episode usually occurring before the age of 30 years and the peak rate of onset between the ages of 15 and 19 years. There is often a substantial delay between onset and first contact with mental health services.

The incidence per lifetime of bipolar I and bipolar II disorder is around 1 per cent, with 'other' bipolar and related disorders adding a further 2-3 per cent. The prevalence of bipolar disorder is similar in both men and women but, on average, women have a slightly different profile of illness to men.

Bipolar patients have between 10-20 years' premature mortality, partly due to cardiovascular disease, which is driven by weight gain, but also due to suicide, which is amongst the highest for any psychiatric disorder. Approximately 17 per cent of patients with bipolar I disorder and 24 per cent with bipolar II disorder attempt suicide during the course of their illness. Annually, around 0.4 per cent of patients with bipolar disorder will die by suicide – a figure that is more than 20 times greater than the international population average of 0.017 per cent.



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**Table 1: Contributory mechanisms to bipolar disorder**

Genetics	<ul style="list-style-type: none"> • Highly inheritable (up to 80 per cent) • Growing numbers of specific genes for bipolar • The life-time risk of developing bipolar disorder if a first degree relative is affected is five to 10 times greater than the general population and double the risk for developing unipolar major depression
Hypothalamic pituitary adrenal system (HPA)	<ul style="list-style-type: none"> • The adrenal system produces cortisol, known to be a major regulator of the physiological stress response • Both cortisol and thyroid abnormalities have been observed in all stages of bipolar disorder
Neurobiology	<ul style="list-style-type: none"> • The monoamine theory suggests that a lack of monoamines (serotonin, noradrenaline and dopamine) causes depression, while an excess may cause a manic episode. This may explain why antipsychotics are useful in mania
Psychological factors	<ul style="list-style-type: none"> • Childhood maltreatment may act as a predisposing factor for developing the disorder. Both abuse and neglect in childhood have been shown to alter the HPA system • Concurrent factors, such as social class, social support and self-esteem, may act as course modifiers or precipitants for bipolar episodes

The clinical problem

Bipolar disorder is a cyclical mood disorder that involves episodes of disruption to mood and behaviour, interspersed with periods of recovery. These disruptive episodes can either be depressive or manic (either mania or hypomania), and can culminate in psychosis and exhaustion if left untreated. Little is known about the aetiology of bipolar disorder but the different clinical presentations suggest a number of different mechanisms might be involved (see Table 1).

Symptoms

Mania

In mania the mood is elevated to a level out of keeping with the patient's circumstances/character. Symptoms include grandiose ideas and over-confidence, loss of social inhibitions (disinhibited or reckless), increased energy resulting in over-activity, pressure of speech, decreased need for sleep, short attention span and marked distractibility.

Psychotic symptoms can be present, for example delusions (usually grandiose), hallucinations (usually voices speaking directly to the patient), excitement, excessive pacing or running around, and moving from one idea to the next (flight of ideas). A diagnosis of mania is made when symptoms last for seven days or more. Hospital admission or intensive community management is always considered in such cases.

Hypomania

Hypomania is an elated state without significant functional impairment (ie. no disruption to work or social rejection). Hypomania is diagnosed when symptoms last for four days or more. Hallucinations and delusions are not experienced.

Depression

Major depressive episodes in bipolar disorder are similar to those experienced in unipolar major depression. Depressive symptoms are commoner than manic symptoms and the risk of suicide is greatly elevated during depressive episodes.

Common symptoms include lowering of mood, reduction of energy and decrease in activity, reduced capacity for enjoyment and interests, poor concentration, marked tiredness after even minimum effort, disturbed sleep (often waking in the morning several hours before the usual time), loss of appetite and weight loss, reduced self-esteem and self-confidence, some ideas of guilt or worthlessness, slowed down thoughts and movements, agitation and loss of libido.

In primary care when adults present with depression, it is important to ask about periods of over-activity or disinhibited behaviour, especially if over four days, as this may alter the diagnosis.

Diagnosis

The Diagnostic and Statistical Manual of Mental Disorders (DSM-V) and the International Classification of Disease (ICD-10) both outline diagnostic criteria for bipolar disorder. According to the DSM-V:

Bipolar I disorder is when at least one manic episode is experienced. Episodes of depression or mixed episodes are not required for a diagnosis

Bipolar II disorder is when at least one major depressive episode and at least one hypomanic episode are experienced.

Mania-like symptoms can be the result of using stimulant drugs, such as cocaine, khat, ecstasy or amphetamine. Since substance misuse is a common comorbidity in bipolar disease, it is important to clarify if any agent has been taken. Medications such as corticosteroids (especially in high doses), levodopa and prescribed stimulants (e.g. methylphenidate) can also cause manic-like symptoms.

Therapeutics/symptom management

The treatment of bipolar disorder includes:

- Management of acute manic episodes
- Management of acute depressive episodes
- Long-term treatment.

Acute manic episodes

Most patients with mania will require short-term medication. The aim of treatment is to reduce the severity and shorten the duration of the acute episode. No psychological treatment currently provides an alternative strategy for the management of mania.

Patients should stop taking any substances known to cause mania when an episode begins. This includes medicines such as antidepressants, cold remedies and decongestants, and stimulants such as illegal drugs and caffeine.

The antipsychotics haloperidol, olanzapine, quetiapine and risperidone are most effective in the short-term reduction of manic symptoms. Lithium, valproate or aripiprazole can be used if antipsychotics are ineffective. Benzodiazepines may also be used short-term to promote sleep for agitated overactive patients.

Patients who experience a manic or hypomanic episode while taking medication should have their dose adjusted based on plasma levels, or doses increased to the maximum in the BNF. If symptoms are inadequately controlled with optimal doses, or the mania is very severe, another medicine is often prescribed.



Reflection exercise 1

The National Confidential Inquiry data for England and Wales (1997-2006) included 1,243 bipolar patients (10 per cent of the sample) who had died from suicide. Only 390 (31 per cent) were adherent with medication at time of death.

- How can community pharmacists contribute to and help with the prevention of suicide?

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Acute depressive episodes

Bipolar depression can be treated with psychological interventions such as family focused therapy (FFT), cognitive behavioural therapy (CBT) or interpersonal and social rhythm therapy (IPSRT). This can include monitoring for signs of mania or hypomania and deterioration of the depressive symptoms. CBT therapy can be used alone; the other psychological therapies should be used with medication.

Antidepressants have not been adequately studied in bipolar depression and they can induce mania in some patients. Only the combination of fluoxetine with olanzapine has shown effectiveness in treating bipolar depression. Despite this evidence, antidepressants are commonly prescribed in bipolar disorder and therefore should always be co-prescribed with an antipsychotic, lithium or valproate in patients with a history of mania.

Other treatments for bipolar depression include quetiapine, lurasidone, olanzapine (without fluoxetine) or lamotrigine (the latter is often combined with an antipsychotic, lithium or valproate to protect against mania).

Patients with bipolar depression currently taking lithium, valproate or antipsychotics should have their doses and plasma levels checked to see if

they are within the usual target. If treatment is still not effective, quetiapine, olanzapine (with or without fluoxetine) or lamotrigine can be added as concomitant therapy.

Long-term treatment

Long-term treatment, which includes both psychological and pharmacological options, is aimed at preventing either manic or depressive episodes.

Structured psychological interventions (individual, group or family) are designed to prevent relapse by improving knowledge of bipolar disorder through psycho-education (an umbrella term that includes illness awareness, treatment adherence, self-monitoring of mood, early detection of prodromal symptoms and recurrences, and lifestyle advice). Group psycho-education appears to be a highly effective adjunct to pharmacotherapy in relapse prevention.

Tools to aid psycho-education are available through Bipolar UK (bipolaruk.org.uk) and the Depression Alliance (depressionalliance.org).

Medication that has been effective during episodes of mania or bipolar depression is often continued as long-term therapy. Lithium, the most effective long-term treatment for bipolar disorder, is associated with a reduced risk of suicide and is the treatment of choice for most patients. Lithium is not recommended for patients with poor adherence as rapid discontinuation may increase the risk of relapse. When lithium is ineffective, poorly tolerated or used in patients who are unlikely to be adherent, valproate or an antipsychotic may be prescribed.

Patients primarily affected by mania should be treated with the predominantly antimanic medicines lithium, olanzapine, quetiapine, risperidone long-acting injection or valproate. Those primarily affected by depressive episodes should be prescribed lamotrigine, lithium or quetiapine.

In bipolar I disorder, lamotrigine is usually used in combination with an antipsychotic medicine. Lamotrigine and quetiapine may be effective monotherapies in patients with bipolar II disorder.

Some of the medications used to manage bipolar disorder do not have a product licence for a specified indication as recommended by NICE and the British Association for Psychopharmacology, but there is good evidence supporting their use. Semisodium valproate (Depakote) is the only valproate preparation with a licence for the treatment of manic episodes associated with bipolar disorder. And lurasidone currently only has a licence in the UK for schizophrenia.

Antipsychotics

The main mode of action of antipsychotics is antagonism at dopamine D₂ receptors but there are other pharmacological differences between the antipsychotics, hence their use in different phases of bipolar disorder.

All the second generation antipsychotics also have antagonism of serotonin 5-HT_{2A}. Quetiapine additionally has an active metabolite (norquetiapine), which inhibits noradrenaline reuptake. Lurasidone also is an antagonist at 5HT₇ and aripiprazole a partial agonist at D₂ and 5-HT_{2A} receptors. Antipsychotics' affinity at histamine and muscarinic receptors gives rise to side-effects.

Lithium

Lithium modifies the production and turnover of neurotransmitters, particularly serotonin, and may also block dopamine receptors. Patients receiving lithium must be monitored closely and plasma levels should be between 0.4 and 1.0mmol per litre (levels above 1.0mmol/L should always be queried). Levels will usually be monitored every three months and monthly when they are between 0.8 and 1.0mmol/L.

If the current blood level is above the target range and the patient has symptoms of toxicity, he/she should be immediately referred to their doctor or A&E.

Lithium has side-effects affecting the kidneys and the thyroid gland, so renal and thyroid function need to be assessed prior to starting it and repeated every

 **Table 2: Summary interactions of the medicines used in bipolar disorder**

Medication	Interactions (significant in bold)
Antipsychotics	<p>Levels increased by: Fluoxetine or lamotrigine</p> <p>Levels decreased by: Antiretrovirals, carbamazepine, phenytoin, rifampicin, cigarette smoke or valproate</p> <p>Other interactions: Anti-arrhythmics, anticonvulsants, antihistamines, antibiotics, antimalarials, ciclosporin and tamoxifen</p>
Lithium	<p>Levels increased by: ACE inhibitors and angiotensin II antagonists, diuretics (particularly thiazides), NSAIDs & COX II inhibitors and topiramate</p> <p>Levels decreased by: Theophylline, high sodium (e.g. diet and some antacids) or dehydration</p> <p>Other interactions: Some antibiotics, antipsychotics, diltiazem, domperidone, methyl dopa, metoclopramide, steroids, SSRIs, triptans or verapamil</p>
Valproate	<p>Levels increased by: Aspirin, erythromycin or fluoxetine</p> <p>Levels decreased by: Carbamazepine, imipenem, phenytoin, phenobarbital, mefloquine, meropenem, tiagabine or topiramate</p> <p>Other interactions: Antidepressants (fluoxetine), benzodiazepines, carbamazepine, lamotrigine, phenobarbital, primidone or phenytoin</p>
Lamotrigine	<p>Levels increased by: Valproate</p> <p>Levels decreased by: Antiretrovirals, carbamazepine, rifampicin, phenobarbital, phenytoin or primidone</p> <p>Other interactions: Oral contraception</p>



Next month's CPD module...

Patient safety in community pharmacy:
incident reporting

Learning scenario 1

Suzanne Clarke has come into the pharmacy to pick up her prescription for sodium valproate MR 1g twice a day, which has been prescribed for bipolar affective disorder and which has kept her well for many years. While collecting her prescription she asks for your advice on which supplements to take as she and her partner have been discussing starting a family.

What advice would you give her?

- To take 400mcg daily of folic acid and continue taking sodium valproate
- To see her specialist doctor before becoming pregnant
- To stop taking her sodium valproate before becoming pregnant
- To change to olanzapine

six months during treatment. Patients with cardiovascular disease or risk factors should have an ECG prior to starting lithium treatment.

Patients on lithium should have a record booklet, which prescribers and pharmacists can use to check that blood tests are monitored regularly and that it is safe to issue a repeat prescription and/or dispense the prescribed lithium. A patient information booklet is also available, which contains important information that a patient can refer to for advice on side-effects.

Valproate

The most likely mode of action for valproate is potentiation of the inhibitory action of gamma aminobutyric acid (GABA) in the brain. There are significant risks associated with taking valproate during pregnancy for the unborn child, including a risk of congenital malformations and developmental delay – so its use should be avoided in women of child-bearing age. Valproate is also associated with polycystic ovary disease, so should not be considered in females under 18 years of age.



Reflection exercise 2

How could you use a patient's lithium record booklet to help them understand more about their treatment and improve their care?

Lamotrigine

Lamotrigine inhibits voltage-sensitive sodium channels in the brain, which may limit cell firing. Lamotrigine can cause a rash, which can lead to serious conditions, such as Stevens-Johnson syndrome.

This side-effect is most common in the first eight weeks of therapy, so the dose should be increased very slowly when treatment is started to minimise the risk of this occurring. When used with valproate, the titration should be even slower at half the rate.

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Learning scenario 2

Anne Sutherland asks to speak to you regarding her dad, who has food poisoning. He has been suffering with diarrhoea and vomiting for the past 48 hours. He currently takes lithium carbonate (Priadel) 1.2g at night. Anne wants to know if there is anything available over the counter that can help alleviate the symptoms or treat the food poisoning.

What would your response be?

- To sell some rehydration salts as loperamide is not advisable for food poisoning
- To advise her that her father must continue taking lithium as there is a risk of his bipolar relapsing, but to ensure that he is well hydrated
- To advise him to stop taking the lithium until symptoms resolve
- To attend his GP surgery or A&E as soon as possible

 **Answers on page vi**



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Discontinuation of treatment

Acute treatment for mania and depression should be continued for four weeks after symptoms resolve (usually between three and six months), at which point long-term drug treatment options should be considered. Bipolar depression tends to be shorter than that of unipolar patients, so discontinuation of medication can be in as little as 12 weeks. Longer treatment is justified if patients relapse on the withdrawal of medication.

Discontinuation of long-term treatment for bipolar disorder must be done carefully as relapses can occur even after many years of sustained remission. Abrupt discontinuation of treatment is associated with an increased risk of early relapse of mania so, when discontinuing treatment, doses should be gradually tapered over at least four weeks, preferably longer if possible. For lithium discontinuation, over three months is preferable. Patients should be monitored for signs of relapse, emerging symptoms, mood and mental state while discontinuing treatment, and for up to two years after treatment has stopped.

New/upcoming treatments

Both NICE and British Association of Psychopharmacology guidance now recommend lithium be used first-line for long-term treatment of bipolar disorder, which means lithium prescribing is likely to increase.

There has been considerable interest in ketamine's potential as a treatment option in major depression, but there is only limited evidence in bipolar depression. The drawbacks to the treatment are the need for intravenous administration, the question of whether any acute benefit can be sustained and whether repeated use might be required. Ketamine's side-effect of haemorrhagic cystitis is also of concern.

How community pharmacy can help

Community pharmacy teams have an important role in ensuring medication for bipolar disorder is used effectively and safely in primary care. Medicines use reviews are one way to support patients and identify potential problems.

Important roles for community pharmacy teams are:

- Knowing the interactions of the medications used in bipolar disorder
- Knowing the signs of lithium toxicity
- Checking lithium booklets are complete and counselling on any signs of toxicity
- Counselling on the use of medication, including standby medication for mania (especially insomnia) or depressive symptoms
- Informing patients about the importance of adherence with medication
- Giving advice on side-effects and how to minimise or treat them
- Monitoring physical health and providing lifestyle advice – particularly on smoking cessation.

Physical health

All people with bipolar disorder should have an annual health check. This should include weight or BMI, and assessment of diet, nutritional status and level of physical activity; cardiovascular status, including pulse and blood pressure; metabolic status, including fasting blood glucose, glycated haemoglobin (HbA_{1c}) and blood lipid profile; liver function; and renal and thyroid function and calcium levels for people taking lithium long-term.

Summary

Bipolar disorder is a complex disorder that requires support from different health agencies. Many of the treatment strategies include medication and community pharmacy professionals have an important role to ensure medication is prescribed effectively and safely, referring the patient when needed. MURs offer an opportunity to provide support for both medicine-taking and healthy lifestyles.



Useful resources

- NICE. Bipolar disorder: The assessment and management of bipolar disorder in adults, children and young people in primary and secondary care. NICE Clinical Guideline, September 2014
- Goodwin GM *et al.* Evidence-based guidelines for treating bipolar disorder: revised third edition – recommendations from the British Association of Psychopharmacology. *Journal of Psychopharmacology* (2016), 1-59
- National patient safety alert. Safer lithium therapy. December 2009
- Drug Safety Update. MHRA. Medicines related to valproate: risk of abnormal pregnancy outcomes. 22 January 2015. gov.uk/drug-safety-update/medicines-related-to-valproate-risk-of-abnormal-pregnancy-outcomes
- Best Use of Medicines in Pregnancy (BUMPs): medicinesinpregnancy.org



Answers: learning scenario 1

- To take 400mcg daily of folic acid and continue taking sodium valproate**
INCORRECT. Folic acid supplementation may decrease the general risk of neural tube defects but the evidence does not suggest that it reduces the risk associated with *in utero* valproate exposure. Folic acid at 5mg daily should be prescribed, particularly if there is concern about an unplanned pregnancy – so your patient needs to be referred.
- To see her specialist doctor before becoming pregnant**
CORRECT. Sodium valproate can cause harmful effects to a foetus including congenital malformations (teratogenicity) and developmental delay.
- To stop taking her sodium valproate before becoming pregnant**
INCORRECT. Stopping medication would not be advisable as pregnancy does not protect against relapse of bipolar disorder and discontinuing any medication risks destabilising mood. It is important to balance possible risks of medicines to the foetus with the risk of mental illness in the mother and its effects on the health of the baby. It is also known that women are at high risk of relapse to mania or depression following childbirth.
- To change to olanzapine**
INCORRECT. Although there are other medications that have low or lower risk of teratogenic effects, this needs further discussion with her specialist doctor first. Psychotropic medication can also cause neonatal symptoms, so these also need to be considered.



Answers: learning scenario 2

- To sell some rehydration salts as loperamide is not advisable for food poisoning**
INCORRECT. Rehydration salts contain sodium. This will decrease levels of lithium which, although not as harmful as increasing levels, is still not advisable.
- To advise her that her father must continue taking the lithium as there is a risk of his bipolar relapsing, but to ensure he is well hydrated**
INCORRECT. There is a high risk of relapse if lithium is stopped abruptly but in this situation it may be the best course of action.
- To advise him to stop taking the lithium until the symptoms resolve**
INCORRECT. This may be the best course of action but medical review of the patient will be needed to ensure the kidneys have not been affected.
- To attend his GP surgery or A&E as soon as possible**
CORRECT. This could be a sign of toxicity and not food poisoning. The symptoms have been occurring for 24 hours and therefore dehydration and toxicity could have occurred. If levels are toxic, there is a higher risk of kidney failure.

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