Mood instability versus bipolar disorder: what to look for

Catherine Harpur, Lorna Harris and Neil Masson

It is important to differentiate between the various disorders that feature mood instability because this has significant implications for management. In this article, the authors discuss the differential diagnosis of bipolar disorder and other types of mood instability and the current recommended treatment options.

Differentiating between bipolar disorder and other types of mood instability can be challenging, particularly when the core symptoms aren’t present. Renaud et al. found that 40% of patients with borderline personality disorder had previously been incorrectly diagnosed with bipolar disorder. The implications for prognosis are significant and, given the toxicity of the medication available, treatment must be targeted and thoughtful. This article will explore the diagnostic challenges and outline current thinking about treatment.

Bipolar disorder
Prevalence and aetiology
Bipolar disorder has a lifetime prevalence of around 1 in 100. Twin studies demonstrate a heritability of over 90%, although brain development and stress can influence gene expression and the impact of the illness. A multi-gene model is proposed, causing a range of effects: abnormalities in protein breakdown, inflammation and energy metabolism causing aberrant nerve connectivity between brain centres, and alterations in noradrenaline and serotonin activity. The estimated suicide rate in bipolar disorder is 15%.

Presentation and diagnosis
The first episode of bipolar disorder is most often a depressive episode in early adulthood. However, patients might delay presenting to a clinician until they have been ill several times or until they are manic. Some patients with recurrent depression may have had a previous hypomanic episode that was overlooked and may, in fact, have bipolar disorder.

Box 1 outlines the World Health Organization ICD-10 diagnostic criteria for bipolar disorder. The diagnosis is made at clinical interview. A thorough chronological account is particularly important so that past illness episodes aren’t overlooked, and a collateral account of behaviour during episodes...
Bipolar affective disorder
More than one mood episode; two manic/hypomanic episodes or one manic/hypomanic and one depressive episode

Hypomania
Elevated/irritable mood for four days
Three of: increased activity, talkativeness, reduced concentration, reduced need for sleep, increased sexual energy, mild overspending/recklessness, over familiarity or increased sociability leading to “some interference with daily living”

Manic episode
Elated mood for one week, plus three of the symptoms listed above but also: grandiosity, racing thoughts/flight of ideas and “severe interference in daily living” +/- psychotic symptoms: voices speaking directly to them, grandiose delusions, incomprehensible thought and speech or stupor

Box 1. Summary of World Health Organization ICD-10 diagnostic criteria for bipolar disorder

is invaluable. Patients with a longer delay until treatment are likely to have poorer outcomes. In addition to discrete episodes of elation or depression, a mixed affective state exists with features of both; perhaps low mood but overactivity and reduced sleep.

Bipolar disorder has more recently been subdivided to reflect different symptom burdens, which can direct choice of treatment or focus research. The concept of predominant polarity refers to whether a patient’s mood is most often high or low. Bipolar I disorder presents with mostly manic and hypomanic states. Bipolar II disorder has mostly depressive episodes with some hypomanic episodes, and in bipolar III hypomania occurs only when triggered by antidepressants.

Mood instability
If bipolar disorder relates to severity of mood change, then mood instability relates to frequency of mood change. The 2007 Adult Psychiatric Morbidity Survey found that 13.9% of the population in England experience mood instability. The term first appeared in literature in the 1960s as a characteristic of those who would struggle if selected for polar expeditions. A recent systematic review defined mood instability as “rapid oscillations of intense affect, with a difficulty in regulating these oscillations or their behavioural consequences.” Mood instability is unpleasant and is not yet fully understood or recognised, but its high prevalence reflects its importance.

Mood instability occurs in the prodrome of bipolar disorder, and also in schizophrenia, depression, attention deficit hyperactivity disorder (ADHD) and cyclothymia. It might also be the most common symptom of bipolar disorder, inhabiting the time between discrete episodes that clinicians tend to focus on in clinician. Emotionally unstable personality disorder (EUPD) is commonly identified as a particular challenge for the interface between general practice and psychiatry. For example, how to distinguish it from bipolar disorder, and when is EUPD severe enough to warrant input from secondary care services? Patients with EUPD present frequently to GPs, not only with mood instability but with other complaints that can require significant investment of resources. The adverse impact of EUPD on the sufferer’s quality of life has been well established. Although mood instability can be a symptom of an illness or exist on its own, it is also a part of normal human experience, for example in times of grief.

Diagnosing and differentiating mood instability from bipolar disorder
History taken from the patient and someone close to them informs diagnosis, which is based on characterisation of the disorders in ICD-10. Rating scales can also be helpful. Table 1 provides useful rating scales to assist with differential diagnosis of bipolar disorder, EUPD and ADHD.

The clinical course of the disease through the years can be useful, but only in retrospect. Cyclothymia is often diagnosed when, through time, the severity or duration of episodes are insufficient for the diagnosis of bipolar disorder. EUPD symptoms improve with age and have higher remission rates than bipolar disorder. A National Institute of Mental Health (NIMH)-sponsored study over 16 years revealed cumulative rates of remission of 78% at eight years for EUPD. Table 2 outlines differentiating symptoms that can make the diagnosis, or its exclusion, easier.

Treatment recommendations for bipolar disorder
This guidance for adults with bipolar disorder is based on NICE and the Maudsley Prescribing Guidelines and clinical experience. The mechanism of action of medications acting as mood stabilisers is poorly understood.

Care and treatment should be patient-centred and should involve a discussion including the risks and benefits of individual drugs with special consideration to particular groups such as women of childbearing age, breastfeeding women, those with co-morbid physical conditions or adherence issues. Management can broadly be subdivided into prophylaxis and...
Mood instability

**Hypomania and mania**
If a person develops hypomania or mania in bipolar disorder, antidepressant treatment should be stopped. If the patient is not already taking an antipsychotic or mood stabiliser, NICE recommends haloperidol, olanzapine, quetiapine or risperidone, taking into account any advance statement, patient preference and clinical context. If already taking antipsychotic medication, check compliance and increase the dose if need be. Benzodiazepines are often co-prescribed, helping with agitation and sleep disturbance.\(^\text{10}\)

Figure 1 summarises the Maudsley Prescribing Guidelines for the treatment of acute mania and hypomania.\(^\text{11}\)

**Bipolar depression**
Bipolar depression differs from unipolar depression in onset, severity and treatment response. Antidepressants should not be prescribed without mood stabiliser protection due to the risk...

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Bipolar disorder</th>
<th>EUPD</th>
<th>Cyclothymia</th>
<th>ADHD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency of episodes</strong></td>
<td>Episodic (untreated mania typically lasts 3–6 months, depression 6–12 months).</td>
<td>Constant.</td>
<td>Episodic.</td>
<td>Constant.</td>
</tr>
<tr>
<td><strong>Typical trigger for episode</strong></td>
<td>Lack of sleep, stress, starting antidepressants or spontaneous.</td>
<td>Interpersonal conflict, perceived abandonment.</td>
<td>None.</td>
<td>None.</td>
</tr>
<tr>
<td><strong>Clinical course</strong></td>
<td>Chronically relapsing and remitting.</td>
<td>Worst in times of stress.</td>
<td>Little change over time.</td>
<td>Fall in those still meeting diagnostic criteria from early 20s.</td>
</tr>
<tr>
<td><strong>Psychotic features</strong></td>
<td>Mood congruent: mania – themes of grandiosity, invincibility, a higher purpose or special mission. Depression – themes of illness, poverty, persecution, death.</td>
<td>Pseudo-psychotic: Usually negative experiences of voices in internal space echoing self-image, visual illusions often of personal significance linked to trauma.</td>
<td>Absent.</td>
<td>Absent.</td>
</tr>
<tr>
<td><strong>Highly suggestive features</strong></td>
<td>Psychotic flavour to thoughts during episodes along typical themes (grandiosity, religiosity, invincibility, nihilism). Extreme behaviour: police involvement, amassing massive debt, grand purchases of homes/cars/holidays, bizarre behaviour in public. Excess energy and reduced need for sleep.</td>
<td>Poor sense of self, chronic feelings of emptiness, unclear sexual identity, self-harming. Turbulent or short-lived intense relationships. Difficulty understanding the motives or feelings of others.</td>
<td>Highs and lows never big enough to result in trouble with police/loss of work/emergency attention of doctors.</td>
<td>Consistent and pervasive symptoms of inattention and hyperactivity over time.</td>
</tr>
</tbody>
</table>

Table 2. Features differentiating bipolar disorder from other disorders with mood instability (emotionally unstable personality disorder [EUPD], attention deficit hyperactivity disorder [ADHD] and cyclothymia).
of switch to mania. Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) are considered to have a higher risk of precipitating mania and should be avoided. SSRIs are considered the safest antidepressants in bipolar depression, with research favouring fluoxetine.

For patients not already prescribed mood stabiliser medication, NICE recommends fluoxetine first-line combined with olanzapine, or quetiapine as monotherapy. Lamotrigine is considered a second-line treatment but it has the added benefit of providing prophylaxis against recurrence so this is a consideration for individuals prone to depressive episodes.

For patients already prescribed mood stabiliser medication, it is important to ensure adequate dosage and compliance (eg. checking serum lithium levels to ensure they are within therapeutic range), which would also provide adequate cover against a manic switch if further treatment to elevate mood was prescribed. Thereafter, NICE recommends adding fluoxetine combined with olanzapine, or adding quetiapine. If there is no response, lamotrigine should be considered as an adjunct. Maudsley Prescribing Guidelines also include valproate and lurasidone as alternative first-line agents. Lurasidone can be used as monotherapy or as an adjunct to mood stabilisers but is not licensed for bipolar depression in the UK.

**Prophylaxis**

Anticonvulsants, antipsychotics and lithium are used for prophylaxis. Lithium and valproate have the best empirical evidence. Alternatives include lamotrigine and carbamazepine. Antipsychotics are known to have mood-stabilising properties and may be considered as monotherapy or as part of combination therapy. Olanzapine, quetiapine and aripiprazole are licensed for prophylaxis in the UK.

Lithium remains the gold standard mood stabiliser and should be offered as a first-line, long-term prophylaxis for
bipolar disorder. It is known to reduce both the number and severity of relapses. Lithium is more effective at reducing manic than depressive relapses and also offers some protection against antidepressant-induced hypomania. Meta-analyses of clinical trials conclude that lithium reduces the risk of both attempted and completed suicide in patients with bipolar illness by 80%. The minimum effective plasma concentration for prophylaxis is 0.4mmol/L, with the optimal range being 0.6–0.75mmol/L. Higher plasma levels (1.0–1.2mmol/L) are sought in acute admissions for manic episodes.

Valproate should be considered as an alternative if lithium is ineffective, poorly tolerated or not suitable. It is also recommended for the treatment of acute episodes of mania and in combination with an antidepressant for the treatment of acute episodes of depression. It is especially useful in recurrent mania. However, valproate is contraindicated in pregnancy due to the risk of teratogenicity (20-fold increase in neural tube defects). The MHRA recently ruled that women and girls of childbearing potential should not be prescribed this medication unless on the Pregnancy Prevention Programme. Valproate is available in three forms (sodium valproate, valproic acid and

<table>
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<tr>
<th>Medication</th>
<th>Type</th>
<th>Dosage</th>
<th>Side-effects</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>Mood stabiliser</td>
<td>Starting dosage 200–400mg daily; Usual dosage 400–1000mg daily but depends on plasma level</td>
<td>Toxicity (levels &gt;1.5mmol/L): anorexia, nausea, diarrhoea, muscle weakness, drowsiness, ataxia, coarse tremor, muscle twitching, confusion, disorientation, seizures, coma</td>
<td>NSAIDs, ACE inhibitors, diuretics</td>
</tr>
<tr>
<td>Valproate</td>
<td>Mood stabiliser</td>
<td>Usual dosage 400–1000mg daily</td>
<td>Deranged LFTs, thrombocytopenia, leucopenia, pancreatitis</td>
<td>Aspirin, anticonvulsants, warfarin, antibiotics</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Mood stabiliser</td>
<td>400–1000mg daily</td>
<td>Erythematous rash, hyponatraemia, agranulocytosis, thrombocytopenia SIADH</td>
<td>Oral contraceptives, warfarin, corticosteroids</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Mood stabiliser</td>
<td>25mg for 14 days; Then 50mg for 2 weeks; Then increasing by 50–100mg every 2 weeks to a usual dosage of 100–200mg daily</td>
<td>Stevens-Johnson syndrome, bone marrow suppression, seizures</td>
<td>Oral contraceptives, valproate, carbamazepine, phenytoin</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Antipsychotic (first-generation)</td>
<td>5–20mg daily</td>
<td>QTc prolongation, NMS, VTE</td>
<td>Tricyclic antidepressants, anticholinergics, sedative medications</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Antipsychotic (second-generation)</td>
<td>10–20mg daily</td>
<td>Diabetes, NMS, VTE</td>
<td>Sedative medications</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Antipsychotic (second-generation)</td>
<td>300–600mg daily</td>
<td>NMS, VTE</td>
<td>Sedative medications, phenytoin, carbamazepine, lamotrigine</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Antipsychotic (second-generation)</td>
<td>4–6mg daily</td>
<td>NMS, VTE, priapism</td>
<td>Carbamazepine, sedative medications</td>
</tr>
</tbody>
</table>

LFTs = liver function tests; SIADH = syndrome of inappropriate antidiuretic hormone secretion; NMS = neuroleptic malignant syndrome; VTE = venous thromboembolism

Table 3. Properties of the use of most common medications used in bipolar disorder
valproate semisodium); in the UK, sodium valproate is widely used. Only valproate semisodium is licensed for bipolar disorder but despite this, the use of sodium valproate is common in clinical practice.

Carbamazepine is generally considered to be less effective than lithium and is considered a third-line agent for prophylaxis. It is often poorly tolerated and generally used less in clinical practice but is still licensed for maintenance treatment in patients who have not responded to lithium. It should be avoided in women of childbearing potential due to the risk of teratogenicity.

Lamotrigine is effective in bipolar depression and as prophylaxis against further episodes of depression. The evidence for use in mania is less strong and so generally the use of lamotrigine is reserved for bipolar depression. It is useful as an adjunct to lithium or an alternative to it in pregnancy. Due to the risk of Stevens-Johnson syndrome, the dose must be titrated gradually.

**Rapid cycling**
Rapid cycling bipolar disorder is harder to treat. The research for this subgroup is limited and NICE suggests that the treatment approach is similar to non-rapid cycling. However, in clinical practice valproate is generally found to be most effective and can be combined with lithium if necessary. Adjunctive treatment with antipsychotics should also be considered (best evidence for quetiapine, olanzapine and aripiprazole).

**Prescribing considerations**
Table 3 details additional information on prescribing for some of the medications more commonly used in the treatment of bipolar disorder. Included are only the more severe side-effects and important interactions; the lists are not exhaustive.

**Pregnancy**
All women of childbearing age should be counselled about contraception while on treatment for bipolar disorder and should be referred for specialist pre-conception counselling within secondary care. Specialist advice should be sought immediately during pregnancy for all women with a history of bipolar disorder.

**Physical health monitoring**
For the majority of patients, core management will lie within secondary care. However, often the physical health monitoring of patients prescribed medication for bipolar disorder is carried out within primary care. Table 4 summarises recommended

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Ongoing monitoring</th>
<th>Additional monitoring</th>
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<tbody>
<tr>
<td><strong>Lithium</strong></td>
<td>U&amp;Es, estimated glomerular filtration rate, thyroid function tests, calcium, full blood count, weight or BMI ECG if cardiovascular disease or risk factors</td>
<td>6-monthly: U&amp;Es, eGFR, calcium, TFTs Annually: glucose, lipids Weight or BMI, FBC (if indicated)</td>
</tr>
<tr>
<td><strong>Valproate</strong></td>
<td>FBC, LFTs, weight or BMI</td>
<td>6-monthly: FBC and LFTs for first year Thereafter annually: FBC, LFTs, glucose, lipids, weight or BMI</td>
</tr>
<tr>
<td><strong>Carbamazepine</strong></td>
<td>U&amp;Es, FBC, LFTs</td>
<td>6-monthly: U&amp;Es, FBC LFTs periodically if indicated Annually: glucose, lipids, weight or BMI</td>
</tr>
<tr>
<td><strong>Lamotrigine</strong></td>
<td>FBC, U&amp;Es, LFTs</td>
<td>Annually: Glucose, lipids, weight or BMI</td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td>FBC, U&amp;Es, LFTs, TFTs, glucose, lipids, ECG, weight or BMI</td>
<td>FBC, U&amp;Es, LFTs, TFTs, glucose, lipids, ECG, weight or BMI</td>
</tr>
</tbody>
</table>

U&Es = urea and electrolytes; eGFR = estimated glomerular filtration rate; TFTs = thyroid function tests; FBC = full blood count; LFTs = liver function tests; BMI = body mass index

*Older people/ if taking any concomitant drugs that interact with lithium/ if at risk of impaired renal or thyroid function, raised calcium or other complications/ poor compliance/ poor symptom control/ if last serum lithium level was 0.8mmol/L or higher

Table 4. Baseline and ongoing monitoring required for patients on mood stabilisers
physical health monitoring required for patients on mood stabilisers.

Psychological interventions
A number of psychological interventions can be used in bipolar disorder. Treatment generally entails psychoeducation to help with acquisition of insight, recognition of symptoms, regulation of sleep and mood, and maintaining compliance with medication. NICE suggests that cognitive behavioural therapy, interpersonal therapy or behavioural couples therapy should be offered in bipolar depression. This can be delivered in primary or secondary care depending on local provision and available services.

Treating mood instability
While there are clear guidelines and licensed medications for treating bipolar disorder, the decision to treat mood instability that is not part of bipolar disorder is more ambiguous and varied.

EUPD
Opinion on whether to use medication to treat mood instability as part of EUPD is divided. NICE guidance only recommends short-term use of sedatives, such as sedative antihistamines, in a crisis situation or medication for co-morbid disorders, but not for the intrinsic symptoms of EUPD such as mood instability.14 There is no licensed treatment for EUPD and the decision to use medication is idiosyncratic. In severe cases, clinicians do often consider an empirical trial of medication for symptomatic relief, including mood stabilisers and antipsychotics, where the potential benefits outweigh the potential risks, for example escalation in self-harm or risk-taking behaviour. When considering initiation of any drug treatment, clinicians must take into account prescribing risks, including iatrogenic effects such as metabolic syndrome, teratogenicity, overdose risk, alcohol and illicit drug use.

Cyclothymia
The mild lows and emotional highs of cyclothymia mean it often goes unrecognised and untreated. However, in cases where the symptoms cause significant impairment then medication can be considered. Although there are no licensed treatments for cyclothymia, the treatment approach is the same as that for bipolar disorder, described above.

ADHD
The mood instability associated with ADHD does respond to drug treatments for the disorder itself. These include stimulants (such as methylphenidate) and non-stimulants (such as atomoxetine). In contrast, there is no clear evidence base for using mood stabilisers or antipsychotics for mood instability in this patient group.

Mood instability alone
In the absence of associated symptoms, an identified cause or significant functional impairment, mood instability alone would rarely be treated with medication as the evidence base is limited.

Conclusion
Mood instability is a common symptom in the general population and is associated with several mental disorders, namely bipolar disorder, EUPD, cyclothymia and ADHD. Differentiation between the underlying causes has important implications for managing causative factors, explaining prognosis and arranging appropriate non-pharmacological and pharmacological treatments.

References

Declaration of interests
Dr Neil Masson received research funds from Cingulate Therapeutics in 2017.

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