

GPs have a pivotal role in bipolar disorder

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What are the diagnostic criteria?

What are the common comorbidities?

Which patients should be referred?



BIPOLAR DISORDER IS A COMPLEX, RECURRENT, SEVERE AND POTENTIALLY LIFELONG MENTAL ILLNESS.

The peak age of onset is 15-19 years, with most cases developing before the age of 30.¹

It is characterised by episodes of mania or hypomania (with elation, overactivity, and disinhibited behaviour), as well as episodes of depression (with profound loss of interest and motivation). Patients often also experience a milder depressed mood between major affective episodes. Mixed presentations are also recognised, characterised by symptoms of the opposite polarity being present during an affective episode (e.g. pressure of speech with depressed mood).

The lifetime prevalence of bipolar I disorder (mania and depression) is estimated at 1% of the adult population, and bipolar II disorder (hypomania and depression) affects approximately 1.1%

of adults.² Bipolar disorder is associated with significant physical and psychiatric comorbidity; risk of suicide in patients with bipolar disorder is up to 20 times that of the general population.³

DIAGNOSIS

Delay in diagnosis is a major problem in bipolar disorder. Studies are retrospective, and so vulnerable to recall bias, nevertheless, a delay of ten years from onset of symptoms to diagnosis seems unexceptional.⁴

In many this delay is understandable given that up to 60% of patients initially present with depression (i.e. there is no clinical evidence of a prior manic/hypomanic episode), thereby obscuring the presence of a phasic mood disorder.⁵ Indeed, it is typical that depressive symptoms dominate the clinical picture, longitudinal studies showing time spent with depressive symptoms outnumbering that with (hypo)manic symptoms by a ratio of 3:1

in bipolar affective disorder type I and 39:1 in type II.^{6,7} All too often however, there is a history of (hypo)manic episodes, but these are missed or misdiagnosed as manifestations of borderline personality disorder or substance misuse (both of which can of course be comorbid). Reflecting this, a Welsh primary care study estimated that between 3.3% and 21.6% (depending on how conservatively findings were analysed) of patients with a diagnosis of unipolar depression had undiagnosed bipolar disorder; i.e. at least 1 in 30 patients.⁸

Unfortunately, useful screening tools for detecting bipolar disorder in primary care are not available. NICE advises that when assessing depression GPs should enquire about previous episodes of overactivity or disinhibited behaviour; if these have lasted for more than four days the patient should be referred to secondary care.⁹

Other pointers to bipolar depression »

are particularly severe or frequent episodes of depression, family history of bipolar affective disorder (see box 1, below), treatment resistance, young age, and atypical features (e.g. hypersomnia, hyperphagia or racing thoughts). Potential risk factors for bipolar disorder are listed in box 1, below.

The longitudinal perspective of primary care is ideally suited to

identifying atypical presentations of bipolar affective disorder. Obviously if mania or severe depression is suspected, or patients are a danger to themselves or others, urgent referral for specialist mental health assessment is necessary.

As outlined in box 2, below, the distinction between bipolar I and II is the duration of (hypo)manic symptoms. Bipolar II is not simply less severe bipolar

affective disorder. Although episodes of mood elevation may be less extreme, patients probably spend more time unwell than in type I and suicide attempts and completed suicide are at least as common.¹⁰

In addition to bipolar I and II, there are other bipolar spectrum presentations. Cyclothymia refers to a chronic (at least two years) mood disturbance with depression and hypomanic symptoms that does not meet the criteria for a full episode.

In a nationally representative sample of US adults diagnosed with depression, 40% of participants also had a history of subthreshold hypomanic symptoms.¹¹ Notably, these subthreshold disorders present with significant psychiatric comorbidity (nearly two thirds having a comorbid anxiety disorder, for example) and the severity of associated role impairment was similar to that of bipolar I disorder.

A diagnosis of bipolar affective disorder will generally be made by a psychiatrist. The mental health team will initiate treatment, although responsibility for monitoring of treatment often

Box 1

Risk factors for bipolar affective disorder (adapted from Rowland & Marwah¹³)

Genetic: Lifetime risk increases to about 8% if there is a parent or other first-degree relative affected. Risk generally conferred by many genes of small effect e.g. polymorphisms in genes coding for brain-derived neurotrophic factor (BDNF) and catechol-O-methyl transferase (COMT)

Childhood adversity: Associations reported with emotional abuse and neglect but difficult to establish direction of causality (e.g. consequent to parental illness rather than truly aetiological)

Stressful life events: Possible association with onset and relapse

Substance misuse: Strong association with bipolar affective disorder, though direction of causality again difficult to clarify. Association between cannabis use and relapse seems quite convincing

Box 2

DSM-5 criteria for bipolar and related disorders (simplified)¹⁴

Diagnosis	Criteria
Bipolar I	● One week of abnormally elevated, expansive, or irritable mood (or less if hospitalised) plus increased activity or energy ● Three (or more) of the following seven symptoms have persisted (four if the mood is only irritable) and have been present to a significant degree: 1 Inflated self-esteem or grandiosity 2 Decreased need for sleep (e.g. feels rested after only three hours of sleep) 3 More talkative than usual or pressure to keep talking 4 Flight of ideas or subjective experience that thoughts are racing 5 Distractibility (i.e. attention too easily drawn to unimportant or irrelevant external stimuli) 6 Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation 7 Excessive involvement in pleasurable activities which have a high potential for painful consequences (e.g. engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments) ● The mood disturbance is sufficiently severe to cause marked impairment in occupational functioning or in usual social activities or relationships with others, or to necessitate hospitalisation to prevent harm to self or others, or there are psychotic features ● Symptoms are not caused by a drug of abuse, medication or a general medical condition
Bipolar II	● Four days of elevated, expansive or irritable mood plus increased activity or energy ● Three (or more) of the seven symptoms (1-7) listed above have persisted (four if the mood is only irritable) and have been present to a significant degree ● Not severe enough to cause marked impairment in social or occupational functioning, or to necessitate hospitalisation, and there are no psychotic features ● Symptoms are not caused by a drug of abuse, medication or a general medical condition ● A hypomanic episode emerging during antidepressant treatment, and persisting after this has been stopped, counts as a hypomanic episode and implies a diagnosis of bipolar II disorder
Cyclothymia	● At least two years (for children, a full year) of both hypomanic and depressive periods without ever fulfilling the criteria for an episode of mania, hypomania, or major depression

passes to primary care after a year. While many patients with bipolar affective disorder will continue to be treated by mental health services, up to 38% of bipolar patients in the UK are treated exclusively in primary care.¹² NICE guidance on when to refer back to mental health services is detailed in box 3, below.

PROGNOSIS

The risk of recurrence in bipolar affective disorder is especially high, 60% of people presenting with mania experiencing a further affective episode within two years.¹⁵ Bipolar affective disorder is a long-term condition and

must be treated accordingly. With optimal treatment patients can return to, and maintain, pre-illness levels of functioning.¹⁶

Risk of completed suicide is high. A large Danish cohort study estimated absolute risk as nearly 8% in men and 5% in women.¹⁷ It most commonly occurs in depression, with previous suicide attempts and substance misuse important risk factors.¹⁸

COMORBIDITY

Around two thirds of people with bipolar disorder also experience another mental health disorder, usually anxiety disorders, substance use disorders, or

impulse control disorders.² Bipolar disorder is associated with an increased risk of physical illness, such as ischaemic heart disease, diabetes, chronic obstructive pulmonary disease, pneumonia, and unintentional injury.¹⁹

Cardiovascular health is a particular concern, particularly given the recognised link between obesity and bipolar affective disorder and the common use of antipsychotic medications associated with metabolic syndrome. Life expectancy is reduced by at least ten years, the most common cause of premature death is cardiovascular disease (CVD).²⁰

GPs should monitor the physical health of patients with bipolar disorder when responsibility for monitoring is transferred from secondary care, and then at least annually. The health check should be comprehensive, including all the parameters recommended in box 4, below, left. The quality and outcomes framework (QOF) mental health indicators, detailed in box 5, below, left, also state that practices should produce a register of patients with bipolar disorder.

Box 3

NICE criteria for referral in bipolar disorder⁹

- Poor or partial response to treatment
- The patient's work or social functioning declines significantly
- Treatment adherence is poor
- Intolerable or medically important side effects from medication
- Comorbid alcohol or drug misuse
- The patient stops medication after a period of relatively stable mood
- A woman with bipolar disorder is pregnant or plans a pregnancy

Box 4

Assessment of physical health⁹

- Weight and BMI, diet, nutritional status and level of physical activity
- Cardiovascular status, including pulse and blood pressure
- Metabolic status, including fasting blood glucose, glycosylated haemoglobin (HbA_{1c}) and blood lipid profile (particularly important if the patient is treated with an antipsychotic)
- Liver function
- Renal and thyroid function, calcium, and three monthly lithium levels in patients taking long-term lithium
- Smoking status, with offer of assistance with smoking cessation if indicated

Box 5

QOF mental health indicators

Records

MH001 The contractor establishes and maintains a register of patients with schizophrenia, bipolar affective disorder and other psychoses and other patients on lithium therapy. **4 points**

Ongoing management

MH002 The percentage of patients with schizophrenia, bipolar affective disorder and other psychoses who have a comprehensive care plan documented in the record in the preceding 12 months, agreed between individuals, their family and/or carers as appropriate. **6 points**

MH003 The percentage of patients with schizophrenia, bipolar affective disorder and other psychoses who have a record of blood pressure in the preceding 12 months. **4 points**

MH006 The percentage of patients with schizophrenia, bipolar affective disorder and other psychoses who have a record of BMI in the preceding 12 months. **4 points**

TREATMENT

Although substance misuse may cloud the picture, a (hypo)manic episode should be reasonably easy to identify. Treatment will generally be initiated by, or at least in discussion with, the psychiatric team and usually involve stopping antidepressants, starting an antipsychotic and (generally when elevated mood has settled and longer term treatment can be discussed with the patient), a 'mood stabiliser'. However, as already discussed patients will more commonly present with depressive symptoms.

Recognition that this is bipolar rather than unipolar depression is crucial not only as an essential starting point for appropriate treatment and risk management, but also in avoiding contraindicated treatment. Antidepressant monotherapy can exacerbate the frequency and severity of mood symptoms as well as promote treatment resistance to appropriate medications.²¹

Treatment options in bipolar depression include quetiapine monotherapy and fluoxetine with olanzapine (see box 6, p14). Antidepressants can be used if prescribed with a mood stabiliser, but it is recommended that they are stopped within three months of remission.

Once a bipolar diagnosis is established the emphasis is on



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maintaining euthymia and preventing relapse. Lithium has best evidence and is recommended as first choice for long-term treatment by both NICE⁹ and the British Association for Psychopharmacology.²² It is also the only agent with a recognised preventive effect against suicide.²³ Valproate also has efficacy, particularly in preventing manic episodes, but cannot be prescribed in women of childbearing age. However, NICE is clear neither drug

should be initiated in primary care.⁹ Lamotrigine conversely is particularly useful in preventing depressive episodes.

The second generation antipsychotics quetiapine and olanzapine may also be used as maintenance treatments. Each of these drugs has specific monitoring requirements (see box 7, below) and it is often necessary to use a combination of treatments.

Maintenance treatment is by

definition long term. It can be difficult to persuade patients to accept treatment given both the side effects of long-term medication use and the episodic course of the illness. The suboptimal treatment of bipolar disorder in the real world is illustrated by a US survey reporting that 50% of bipolar patients were treated with antidepressant monotherapy.²⁴

Psychological therapies

Relapse can occur rapidly in bipolar affective disorder. This means it is crucial that a patient's relapse signature (the characteristic features of a developing affective episode) is outlined and shared with primary care, together with a clear management plan. This plan should ideally involve family/carers. These are the people who often identify a patient's relapse and, given that insight can be impaired during affective episodes, their account is frequently crucial in identifying dangerously unwell patients.

The floridly manic patient who 'holds it together' for the duration of an assessment, (erroneously convincing the assessor admission is not necessary), is a phenomenon psychiatric trainees soon become painfully familiar with.

Given that family involvement may raise concerns about confidentiality, it is important that consent for discussion of care with relatives is obtained when a patient is well.

The challenges of pharmacological treatment in bipolar depression have driven interest in psychological approaches. NICE recommends offering a psychological intervention that has been developed specifically for bipolar disorder or a high-intensity psychological intervention (cognitive behaviour therapy, interpersonal therapy or behavioural couples therapy) in line with the NICE recommendations on depression.⁹ However, the reality is that most GPs will find that availability of these therapies is limited.

SUBSTANCE MISUSE

Around 60% of adults with bipolar disorder experience substance use disorders at some point in their lives.²⁵ Similar to comorbid obesity, substance use disorder is thought to be associated with an aberrant reward-motivation neural network.²⁶ It is associated with delayed recovery from mood episodes, increased suicidality, functional impairment, reduced medication adherence and reduced quality of life.²⁷

PREGNANCY

The fact that many psychotropic drugs are potentially teratogenic, combined

Box 6

Medications used in bipolar affective disorder (based on NICE guidance)⁹

Phase of illness	Treatment	Notes
Mania	Olanzapine Quetiapine Risperidone Lithium	Higher metabolic risk, sedative Moderate metabolic risk, recommended for maintenance Moderate metabolic risk If already taking lithium then optimise dose and add an antipsychotic
Depression	Quetiapine Olanzapine-fluoxetine Olanzapine SSRI Lithium Lamotrigine	Can only use with mood stabiliser Combined with SSRI, olanzapine or lamotrigine Acute effects often disappointing Advise the patient to contact the doctor if a rash develops
Maintenance	Lithium Quetiapine Olanzapine Valproate Lamotrigine	Requires monitoring (generally aim for 0.6-0.8 mmol/L) Advise patients to avoid NSAIDs Cannot be used in women of childbearing age Particular efficacy in preventing bipolar depression

Box 7

Monitoring requirements for drugs used in bipolar disorder. Adapted from The Maudsley Prescribing Guidelines²⁸

Drug	Baseline checks	Monitoring
Lithium	ECG if cardiac problems or ≥ 45 years U&Es (including creatinine) Calcium TFTs	● Lithium level 5-7 days after dose change then 3 monthly ● U&Es and TFTs 6 monthly ● Calcium and ECG (if indicated) yearly
Second generation antipsychotics	Weight, BP, pulse, ECG FBC, U&Es, LFTs, HbA _{1c} , lipid profile	● Weekly weight initially, then at least annually ● HbA _{1c} and cholesterol three monthly for first year then annually ● Prolactin if amenorrhea or reduced libido
Valproate	Weight, U&Es (including creatinine), FBC, LFTs	● Weight, FBC, LFTs annually
Lamotrigine	Advise to seek emergency attention if a rash develops	

key points

SELECTED BY

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Bipolar disorder is a complex, recurrent, severe and potentially lifelong mental illness. The peak age of onset is 15-19 years, with most cases developing before the age of 30. The lifetime prevalence of bipolar I disorder (mania and depression) and bipolar II disorder (hypomania and depression) is estimated to be 1.0% and 1.1% of the adult population, respectively. The risk of recurrence is high: 60% of people presenting for the first time with mania will experience a further affective episode within two years. The risk of suicide is up to 20 times higher than in the general population.

A period of ten years from onset of symptoms to diagnosis is unexceptional. Up to 60% of patients initially present with depression, without any clinical evidence of a prior manic/hypomanic episode. Once a diagnosis of bipolar disorder is made, depressive symptoms typically dominate the clinical picture. In bipolar I, the time spent with depressive symptoms outnumbers that with (hypo)manic symptoms by a ratio of 3:1; in bipolar II the ratio is 39:1.

Useful screening tools for detecting bipolar disorder in primary care are not available. NICE advises that, when assessing depression, GPs should enquire about previous episodes of overactivity or disinhibited behaviour; if these have lasted for more than four days the patient should be referred to secondary care. Other pointers to bipolar depression are: frequent or severe episodes of depression, a family history of bipolar disorder, treatment resistance, young age, and atypical features (e.g. hypersomnia, hyperphagia or racing thoughts).

The distinction between bipolar I and II is based on the duration and severity of (hypo)manic episodes. Bipolar II is not simply 'less severe' bipolar disorder: though episodes of mood elevation may be less extreme, patients probably spend more time unwell than in type I and suicide attempts and completed suicide are at least as common. In addition to these diagnoses, many more patients have subthreshold bipolar symptoms. Cyclothymia refers to a chronic mood disturbance, lasting at least two years, with depressive and hypomanic symptoms that do not meet diagnostic criteria for major depression or hypomania. In a nationally representative sample of US adults diagnosed with depression, 40% of participants also had a history of subthreshold hypomanic symptoms.

Treatment of (hypo)mania will normally be initiated by the psychiatric team and generally involves stopping antidepressants, starting an antipsychotic and, once elevated mood has settled, adding a 'mood stabiliser'. It is crucial to distinguish bipolar from unipolar depression not only as an essential starting point for appropriate treatment and risk management, but also to avoid antidepressant monotherapy, which can exacerbate the frequency and severity of mood symptoms and cause resistance to appropriate medications.

with the postpartum period being a time of extreme vulnerability to relapse, makes the management of bipolar disorder in pregnancy a specialist field.

The association of valproate with congenital and developmental abnormalities (particularly neural tube defects and autism), means it should be avoided in women of childbearing age. Lithium is safer, but an association with cardiac abnormalities is still suspected and a switch to treatment with an antipsychotic may be preferable for some women.²⁹

Pregnancies should be planned, enabling informed discussions with a psychiatrist about medication choice prior to conception, and obstetric services must be made aware of the bipolar diagnosis. The postnatal period is a high-risk time for a woman with bipolar affective disorder to develop psychosis; postpartum psychosis, classically presenting with delusions and hallucinations, mood lability and confusion occurs in around 20% of women with bipolar disorder.³⁰ It is a psychiatric emergency; onset is rapid and it puts both mother and baby at risk.

Competing interests: None

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Useful information

NHS Conditions

www.nhs.uk/conditions/bipolar-disorder/

Bipolar UK

www.bipolaruk.org.uk/

Bipolar Scotland

www.bipolarscotland.org.uk/home

Mind

www.mind.org.uk

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