# Disease overview – Bipolar disorder

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## Summary

Bipolar disorder is a serious, recurrent disabling psychiatric illness characterised by episodes of mania and depression. The two major types of bipolar disorder (type I and type II), differ in the severity and duration of symptoms, and have a combined prevalence of approximately 1–2%, imposing an annual cost to the UK economy of about £2 billion. Other classifications of bipolar disorder include mixed episodes of mania and depression or rapid cycling between mania and depression. Bipolar disorder is a leading worldwide cause of disability and is associated with a particulary high risk of suicide. Other psychiatric disorders such as anxiety and substance abuse are also frequently comorbid with bipolar disorder. Misdiagnosis is common because of the variable presentation of the disorder. For example, if depressive episodes are the first symptoms manifested, patients are often mistakenly diagnosed with unipolar depression. Treatment of such patients with antidepressants, particularly in the absence of a mood stabiliser, can precipitate manic episodes. Moreover, in more chronic cases treatment with antidepressants alone may result in the development of the more serious and difficult-to-treat, rapid-cycling disorder. Thus, it is vitally important that physicians working in primary care recognise potential cases of bipolar disorder and use short screening questionnaires if bipolar disorder is suspected. Recent guidelines published by the National Institute for Health and Clinical Excellence (NICE) highlight the need for better recognition of bipolar disorder in the community allied with a reduction in suboptimal care in order to substantially improve the outcomes of affected patients.

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## Introduction

Bipolar disorder is sometimes referred to as bipolar affective disorder or manic depression. It is characterised by recurrent episodes of mania/hypomania, depression, or mixed episodes (mania and depression occurring concurrently), interspersed with periods of relatively normal mood (euthymia). The term bipolar is used to indicate the two poles, or extremes, of (hypo)mania and depression.

Bipolar disorder is characterised by recurrent episodes of mania/hypomania, depression, or mixed episodes, interspersed with episodes of relatively normal mood (euthymia).

## Classification

There are four main types of mood episode associated with bipolar disorder:

- mania – a distinct period in which there is an abnormal and persistently elevated expansive or irritable mood persisting for at least 1 week or which requires hospitalisation
- hypomania – a milder form of mania that persists for at least 4 days
- major depression – a period of depressed mood or loss of interest or pleasure in nearly all activities, persisting for at least 2 weeks
- mixed episodes – both manic and major depressive symptoms are experienced nearly every day for at least 1 week

Bipolar disorder can be subdivided into five main types.

- Bipolar I disorder consists of one or more manic or mixed episodes, and usually one or more major depressive episodes.
- Bipolar II disorder is composed of one or more major depressive episodes accompanied by at least one hypomanic episode. It generally occurs more frequently in the population than bipolar I disorder.
- Cyclothymic disorder is a milder form of bipolar disorder consisting of chronic fluctuating mood disturbances which last for at least 2 years and involve numerous periods with hypomanic symptoms and depressive symptoms that do not meet symptom or duration criteria for a major depressive episode. Many patients with cyclothymic disorder will progress to bipolar I or II disorder.
- Rapid-cycling disorder (applies to bipolar I or bipolar II disorder) arises when four or more mood episodes (mania/hypomania, mixed episodes, depression) occur in any combination or order in the preceding 12 months.
- Bipolar disorder not otherwise specified can occur when symptoms of mania and depression are experienced which do not fit into the aforementioned categories.[1]

Throughout this review the Diagnostic and Statistical Manual (DSM-IV) categories and diagnostic criteria will be used, in line with current UK guidelines, rather than the International Classification of Mental and Behavioural Disorders (ICD-10).[1–4] This is principally due to the fact that DSM-IV is more widely accepted than ICD-10 for the diagnosis of bipolar disorder, and moreover, it differentiates between bipolar I and bipolar II disorder. Furthermore, in the DSM-IV, diagnosis of hypomania more clearly differentiates between mania and hypomania by stating that hypomania should *not* cause social or occupational dysfunction. This is not the case in the ICD-10 system, which requires that hypomania causes *some* interference with personal functioning, making hypomania an almost superfluous term that describes mild mania, and which can cause confusion by encouraging the use of hypomania for overtly manic states.[3,5]

## Epidemiology

Major epidemiological studies conducted in the USA in the 1990s by the National Comorbidity Survey and the National Institute of Mental Health Epidemiologic Catchment Area Study have established the prevalence of bipolar disorder to range from 0.4 to 1.6%.[6–8] Seven studies of bipolar II disorder reported lifetime prevalence rates ranging from 0.2 to 3%, though most showed a prevalence of about 0.5%.[9] Thus, bipolar I and II disorders have a combined prevalence rate of about 1–2%, equal to or greater than that for schizophrenia, which has an approximate lifetime prevalence of 1%.[10–12] If bipolar spectrum disorders such as hypomania and cyclothymia are included in epidemiological investigations, lifetime prevalence rates of bipolar disorder increase to 3.0–6.5%.[9] The incidence of bipolar disorder appears to be approximately equally distributed in men and women, and across cultural and ethnic groups.[13] Recent NICE guidelines state that the annual incidence is approximately 7 cases per 100,000 population.[4]

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## Course and impact

Bipolar disorders are chronic conditions, characterised by an irregular course of acute episodes and high rates of comorbidity.[13] They are associated with a significant morbidity and mortality burden, including a high rate of suicide, particularly in those with bipolar II disorder.[14] The average age of onset for those with bipolar disorders is approximately 21 years. However, symptoms may appear in individuals as young as 5 years (bearing in mind that the diagnosis of bipolar disorder in children is rather controversial).[7] The onset of illness in young adults, the frequency of episodes and risk of relapse, together with rapid and unpredictable shifts in mood make bipolar disorders especially damaging, particularly in the social and occupational context.[15] Moreover, early onset bipolar disorder can be associated with a worse prognosis than onset at a later age.[16,17] Bipolar symptoms often appear for the first time in connection with life-changing events such as graduation from college and joining the workforce or the death of a close relative. In general, episode frequency increases with age, an effect that has been reported both before and after the introduction of treatments for bipolar disorder.[18,19] Rapid-cycling bipolar disorder occurs in 12–14% of patients diagnosed with bipolar disorder

Bipolar disorders are chronic conditions, characterised by an irregular course of acute episodes and high rates of comorbidity, including a high rate of suicide.

(more than four episodes of illness occurring each year) and is associated with a particularly poor outcome and treatment resistance.[19] Bipolar disorders that present later in life are usually associated with a family history of other psychiatric illnesses or other physical conditions.[4]

Suicide is a major long-term risk for patients with bipolar disorder and, in general, the depressive phase represents the period where the risk of suicide is at its highest.[3,15] This is perhaps best exemplified by data from a US study involving 2839 patients with bipolar disorder, which demonstrated that 46.3% of patients made at least one suicide attempt whilst suffering from depression compared with 13.4% whilst suffering from mania.[20] Patients with bipolar disorder are many times more likely than the general population to attempt suicide, and moreover, they are also much more likely to succeed in these attempts.[14] For example, a study of patients with predominantly bipolar I/II disorder (97%) showed that almost one-third had attempted suicide at least once.[16] Treatment with lithium is associated with a reduced risk of suicides or suicide attempts (by up to 13-fold).[21] Thus, it is essential when diagnosing and/or treating patients with bipolar disorder that the risk of suicide is assessed. Data from a variety of studies which have evaluated suicide rates in patients with depressive disorders are summarised in Table 1.[22–29] Patients with bipolar II disorder are at an especially high risk of suicide.[4,28] As illustrated in Table 1, about 17% of patients with bipolar I and 24% of patients with bipolar II disorder attempt suicide during the course of their illness.[28] About 0.4% of patients with bipolar disorder are successful in their attempt to commit suicide.[4,28]

It is essential when diagnosing and/or treating patients with bipolar disorder that the risk of suicide is assessed.

Bipolar disorder is one of the leading causes of worldwide disability. The World Health Organization (WHO) regards bipolar disorder as the fifth greatest cause of life-years lived with disability in those aged 15–44 years (Table 2).[29] In addition, it is the ninth greatest cause of disability-adjusted life years – ahead of ischaemic heart disease and cerebrovascular disease, which rank 13th and 14th, respectively.[29] A woman with an onset of bipolar disorder at 25 years of age could, on average, expect to lose 9 years of life, 12 years of normal physical health and 14 years of effective activity (such as time at work, school and child-rearing activities).[19,30]

Bipolar disorder is one of the leading causes of worldwide disability.

**Table 1.** Bipolar disorders and suicide risk.[22–28]

| | Lifetime prevalence of suicide (n/N [%]) | | |
|---|---|---|---|
| | Unipolar major depression | Bipolar I disorder | Bipolar II disorder |
| Dunner *et al.*[22] | 2/23 (9) | 11/29 (38) | 9/16 (56) |
| Endicott *et al.*[23] | 26/204 (13) | 30/122 (25) | 15/56 (27) |
| Coryell *et al.*[24] | 31/303 (10) | 7/29 (24) | 7/40 (18) |
| Cassano *et al.*[25] | 60/558 (11) | 9/35 (26) | 17/94 (18) |
| Vieta *et al.*[26] | – | 12/38 (32) | 6/22 (27) |
| Tondo *et al.*[27] | 24/126 (19) | 34/353 (10) | 7/25 (28) |
| **Total**[28] | **143/1214 (12)** | **103/606 (17)** | **61/253 (24)** |

**Table 2.** The leading causes of disability in 2001 in those aged 15–44 years, as estimated by the World Health Organization (WHO).[29]

| Leading causes of life years lived with disability (YLDs) | Total (%) | Leading causes of disability-adjusted life years (DALYs) | Total (%) |
|---|---|---|---|
| Unipolar depressive disorders | 16.4 | HIV/AIDS | 13.0 |
| Alcohol use disorders | 5.5 | Unipolar depressive disorders | 8.6 |
| Schizophrenia | 4.9 | Road traffic accidents | 4.9 |
| Iron-deficiency anaemia | 4.9 | Tuberculosis | 3.9 |
| **Bipolar affective disorder** | 4.7 | Alcohol use disorders | 3.0 |
| Hearing loss, adult onset | 3.8 | Self-inflicted injuries | 2.7 |
| HIV/AIDS | 2.8 | Iron-deficiency anaemia | 2.6 |
| Chronic obstructive pulmonary disease | 2.4 | Schizophrenia | 2.6 |
| Osteoarthritis | 2.3 | **Bipolar affective disorder** | 2.5 |
| Road traffic accidents | 2.3 | Violence | 2.3 |

## Aetiology and pathophysiology

Bipolar disorder is probably best viewed as a complex genetic illness with several important susceptibility genes interacting with a variety of environmental factors.

Bipolar disorder stems from a chemical imbalance in the brain that affects the way moods are experienced by the sufferer. Monozygotic twin studies have shown that if one twin has the disorder, the likelihood of the other twin also being a sufferer is over 50%.[29] However, no single candidate gene has been conclusively demonstrated to be responsible for bipolar disorder, although many genes have been implicated in its pathogenesis.[29] Thus, whilst bipolar disorder has a strongly heritable component, other (largely unknown) environmental factors also play a pivotal role. For example, bipolar disorder may be triggered by stressful life experiences. On the balance of evidence, bipolar disorder is probably best viewed as a complex genetic illness with several important susceptibility genes interacting with a variety of environmental factors to affect the susceptibility of a person developing the disorder.[29]

The pathophysiology of bipolar disorder is very poorly understood, and although there is no shortage of hypotheses to explain the disorder, there appears to be little consensus.[10] What is known from animal models and neuroimaging, electrophysiological, neurotransmitter and second messenger system studies suggest that it is a highly complex illness involving a profound alteration in brain and somatic systems.[29] The depletion of the neurotransmitters noradrenaline and/or serotonin have consistently been implicated in depressive episodes, whilst an excess of dopamine and/or depletion of gamma-amino butyric acid (GABA) may underlie manic episodes.[29] An excess of noradrenaline has also been implicated in the pathogenesis of manic episodes.[10]

## Diagnosis

There are many problems in effecting an accurate diagnosis of bipolar disorder. Patients tend not to seek help for their symptoms as many are unaware that they are ill. Moreover, when they do eventually seek medical advice they are frequently misdiagnosed, particularly if the first manifestation of the condition is depression. This is probably a consequence of the heterogeneity of bipolar disorders and the unpredictability in symptom presentation, both across the population and within individuals.[16]

Approximately three-quarters of patients with bipolar disorder are misdiagnosed, often as unipolar depression, and antidepressant therapy can precipitate manic episodes in such patients.

Bipolar disorder commonly goes unrecognised for 5–10 years, whilst about half of all patients undergo three or more professional evaluations before a correct diagnosis is reached.[31,32] Approximately three-quarters of patients with bipolar disorder are misdiagnosed on initial presentation to a healthcare professional.[31] Furthermore, the depressive mood episodes associated with bipolar disorders are frequently misdiagnosed as unipolar depression, and as antidepressant therapy can precipitate manic episodes in such patients, misdiagnosis can have serious consequences.[32,33] It has been estimated that approximately 37% of psychiatry clinic outpatients with a history of mania or hypomania were misdiagnosed with unipolar depression.[32] The consequence of this misdiagnosis was serious, with 23% experiencing a new or worsening rapid-cycling course (four or more mood episodes in 12 months), which was directly attributable to the use of antidepressants.[32] Other common misdiagnoses of bipolar disorder include anxiety disorder, schizophrenia, personality disorder and alcohol abuse. Although not a recommendation of the DSM-IV, it is now widely accepted that mania induced by antidepressant use should usually be regarded as evidence of bipolar disorder.[1,3]

Clearly, if psychiatrists are misdiagnosing bipolar disorder it is likely to be even more challenging to diagnose the condition correctly in the primary care setting. However, as we have seen, it is essential to avoid misdiagnosis and inappropriate prescription of antidepressant monotherapy.

Some specific signs and symptoms of bipolar disorder, which may aid in its diagnosis include:

- depression
- hyperactivity
- insomnia
- mood swings
- anxiety
- irritability
- delusion/paranoia
- low energy/fatigue
- alcohol/substance abuse
- a family history of bipolar disorder
- relationship problems.[34]

The new NICE guidelines provide clinicians with a set of criteria for specialist referral for assessment and treatment of patients with bipolar disorder in an effort to improve recognition and management of the condition in the UK.[4] These guidelines also cover diagnosis in adolescents and provide recommendations for drug treatment during the acute phase of the illness and during long-term management (see Management of Bipolar Disorder). Detailed discussion of these guidelines is beyond the scope of this review. However, for more detailed information, the reader is directed to the full guideline at *www.nice.org.uk*.

The majority of GPs tend to rely on their own personal skills and experience, and rarely use tools such as rating scales or validated questionnaires in practice. Despite this, the following screening question may be of value in reaching a diagnosis of bipolar disorder: "Have you had periods of feeling so happy or energetic that your friends told you were talking too fast or that you were too 'hyper'?" If the patient responds affirmatively, they may be suffering from mania.[35]

The following screening question may be helpful: "Have you had periods of feeling so happy or energetic that your friends told you were talking too fast or that you were too 'hyper'?"

Given the serious consequences of incorrect antidepressant prescription in bipolar disorder, a short questionnaire is an appropriate aid when determining whether to refer a patient to a psychiatrist. A screening test (the Mood Disorder Questionnaire) has been developed by Hirschfeld *et al.* that can identify 70% of patients with bipolar disorder and screens out 90% of those without bipolar disorder (Figure 1).[36] This questionnaire is appropriate for administration in primary care and positive results should indicate the need for psychiatric referral.[34] It may also improve the recognition of bipolar disorder in a psychiatric care setting.[37] Patients with suspected bipolar disorder should be urgently referred to a psychiatrist if they fulfil the following criteria:

- past or current psychotic symptoms
- at risk of suicide, or have potential to cause harm to others.
- symptoms that are severe enough to warrant hospitalisation.[34]

**Figure 1.** The Mood Disorder Questionnaire used to screen for bipolar disorder. Seven or more 'yes' answers to part 1, plus 'yes' to question 2 and 'moderate' or 'serious' answers to question 3 is classed as a positive response.[36]

| 1. Has there ever been a period of time when you were not your usual self and ... | YES | NO |
|---|---|---|
| … you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble? | ☐ | ☐ |
| … you were so irritable that you shouted at people or started ights or arguments? | ☐ | ☐ |
| … you felt much more self-confident than usual? | ☐ | ☐ |
| … you got much less sleep than usual and found you didn't really miss it? | ☐ | ☐ |
| … you were much more talkative or spoke faster than usual? | ☐ | ☐ |
| … thoughts raced through your head or you couldn't slow your mind down? | ☐ | ☐ |
| … you were so easily distracted by things around you that you had trouble concentrating or staying on track? | ☐ | ☐ |
| … you had much more energy than usual? | ☐ | ☐ |
| … you were much more active or did many more things than usual? | ☐ | ☐ |
| … you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night? | ☐ | ☐ |
| … you were much more interested in sex than usual? | ☐ | ☐ |
| … you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky? | ☐ | ☐ |
| … spending money got you or your family into trouble? | ☐ | ☐ |

2. If you checked YES to more than one of the above, have several of these ever happened during the same period of time? Please circle one response only.

YES NO

3. How much of a problem did any of these cause you – like being unable to work; having family, money or legal troubles; getting into arguments or fights? Please circle one response only.

No problem Minor problem Moderate problem Serious problem

## Comorbidity

Bipolar disorder is frequently comorbid with other psychiatric disorders which can mask the diagnosis of bipolar disorder.[3] This may also contribute to a poorer treatment response and outcome.[3] Comorbidity in bipolar disorder is the rule rather than the exception, as more than 60% of bipolar patients have a comorbid diagnosis. Comorbidity is associated with a mixed affective or dysphoric state, high suicide rates, less favourable response to treatment and poorer overall outcome.[38]

Patients with bipolar disorder and with substance or alcohol misuse problems should have these issues appropriately addressed and treated, as these can make treatment more difficult, particularly as there is evidence that successful intervention can improve overall outcomes.[3,39] In addition, the use of prescribed medications such as L-dopa and corticosteroids may be associated with secondary mania.[3]

There is a particularly high comorbidity between bipolar disorder and substance (e.g. alcohol) misuse or anxiety disorders. In the National Comorbidity Survey, 93% of patients with lifetime bipolar I disorder also met the criteria for lifetime anxiety disorders, 47% for social phobia and 39% for post-traumatic stress disorder (PTSD).[6,8,40] Approximately 71% of those in the National Comorbidity Survey with a history of substance abuse disorder also suffered from lifelong bipolar I disorder.[6] In the Epidemiologic Catchment Area study, 21% of those with lifetime bipolar I or II disorders had panic disorder and the same proportion had lifetime obsessive–compulsive disorder (OCD), as compared with 0.8 and 2.6%, respectively, in the general population.[40] In practice, patients with anxiety disorders should always be assessed for comorbid mood disorders, including bipolar disorder, whilst the treatment of bipolar disorder should also take into consideration the presence of any comorbid anxiety disorders.[3]

There is a particularly high comorbidity between bipolar disorder and substance misuse or anxiety disorders.

## Management of bipolar disorder

The treatment of bipolar disorder represents a major challenge even for the most experienced clinician, with its inherent variability of symptoms, high rates of comorbid disorders and substantial risk of suicide.[41] There are numerous barriers that can hamper successful treatment of patients with bipolar disorder, and these are illustrated in Box 1. A logical treatment algorithm can be devised by subdividing the disorder according to whether a patient presents with:

- acute mania/hypomania or a mixed episode
- a depressive episode
- or after an acute episode when a previously undiagnosed or untreated patient presents to a clinician, probably for other reasons.

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Several recent attempts have been made to devise a logical treatment algorithm or treatment decision tree.[3,41] However, here we have devised a treatment algorithm based on the recommendations of the British Association for Psychopharmacology (Figure 2).[3] These recommendations deviate slightly from US guidelines in that less emphasis is placed on the use

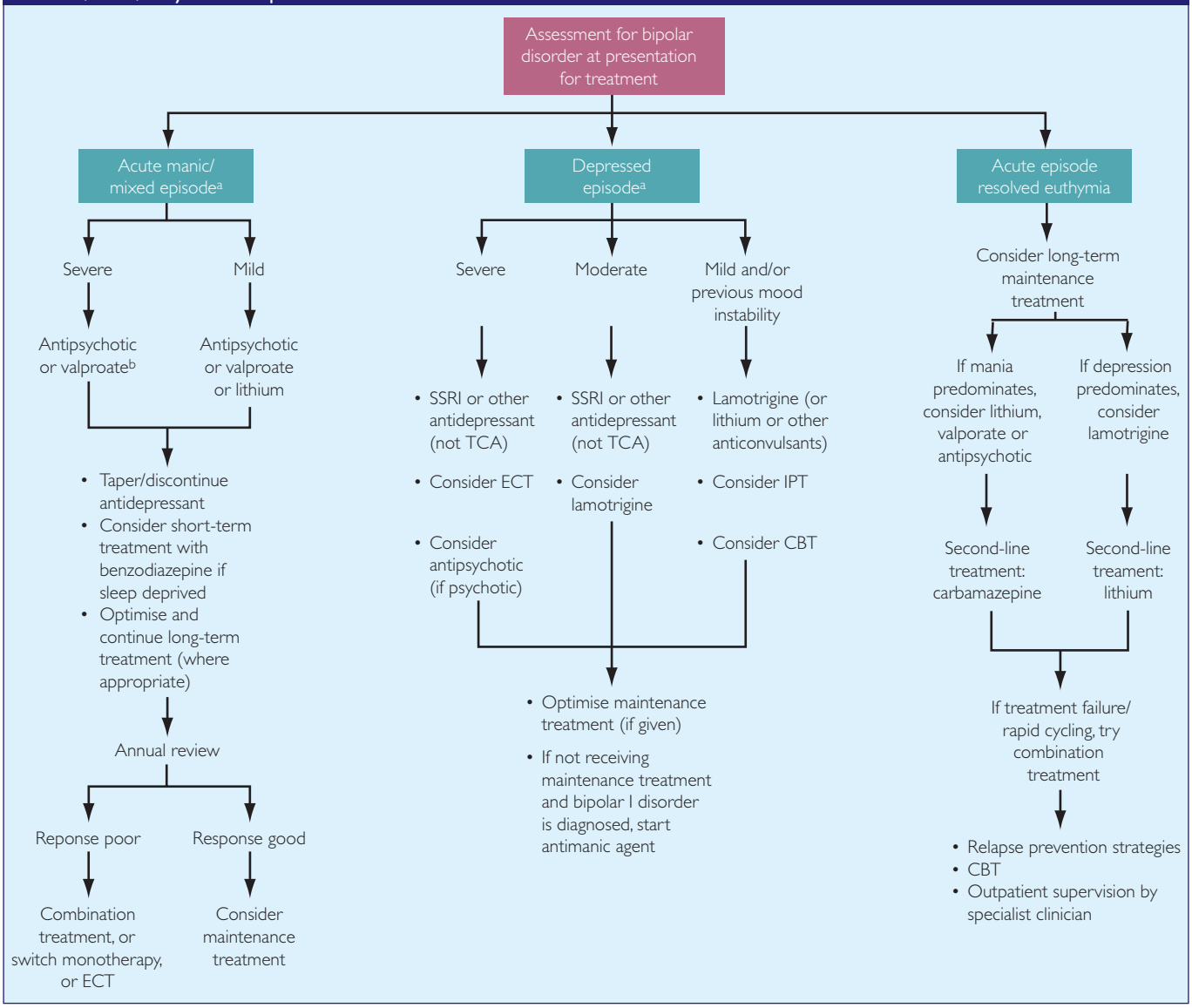
**Box 1.** Barriers to successful treatment of bipolar disorder.[3]

Undiagnosed/misdiagnosed
- Lack of patient awareness of the disorder. Patients are likely to present in primary care with other suspected disorders (e.g. depression or anxiety disorder).
- Bipolar disorder is difficult to diagnose and frequently misdiagnosed.
- Over-reliance on 'clinical experience' by GPs. A short diagnostic questionnaire is often more appropriate than a normal informal consultation.

Inappropriate treatment
- Inappropriate treatment following misdiagnosis, such as treatment with antidepressant monotherapy which can trigger mania and/or rapid cycling and worsen the prognosis.
- Bipolar disorder has a chronic, recurrent lifelong course and is difficult to treat.
- Bipolar disorder is frequently comorbid with other psychiatric disorders, which can cloud diagnosis and worsen the prognosis.
- Management of bipolar disorder is complex.

Lack of government support and guidance
- The Mental Health National Service Framework (NSF) in the UK does not specifically cater for the needs of patients with bipolar disorder (see Improving Practice).

**Figure 2.** Treatment algorithm for patients with bipolar disorder.[3]
[a]Initial treatment scheme, primarily applying to patients not already receiving maintenance treatment, though for those who are, long-term treatments should be optimised and continued as suggested in the algorithm.
[b]Valproate is not licensed in the UK for maintenance therapy. In addition it should not be prescribed routinely to women of child–bearing potential.
CBT, cognitive behavioural therapy; ECT, electroconvulsive therapy; IPT, interpersonal psychotherapy; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.




of long-term treatment with 'mood stabilisers' during acute episodes of bipolar disorder and more emphasis is placed on antipsychotics as first-line antimanic agents.[3,42]

More recently, NICE issued recommendations on the management of bipolar disorder.[4] NICE recommend various treatment options for patients with bipolar disorder and emphasise the need to involve patients and their families in treatment decisions. Other recommendations encompass the need for annual physical health checks for people with bipolar disorder, including appropriate weight management, and the need for all healthcare professionals to carefully monitor the medication taken by patients. NICE also addresses psychological approaches to management. A key priority for implementation suggested by NICE is the recommendation that lithium, olanzapine or valproate should be considered for the long-term treatment of bipolar disorder. However, valproate does not currently have a licence for maintenance treatment of bipolar disorder in the UK, and in addition should not be prescribed routinely to women of child-bearing potential due to its teratogenic potential. The choice of which drug to use as maintenance therapy should depend on various factors, including the patients' response to previous treatment. In addition, if a patient experiences

frequent relapses, switching to an alternative monotherapy or adding a second prophylactic agent (i.e. lithium, olanzapine or valproate) should be considered, though appropriate clinical monitoring is recommended.

## *Pharmacotherapy of bipolar disorder*

### Lithium

Lithium has been the mainstay for treatment of bipolar disorder for several decades and is effective in the treatment and prophylaxis of mania.[15] However, lithium has a narrow therapeutic range and potential adverse events on the renal system and the thyroid gland that necessitates regular monitoring of lithium levels and renal and thyroid function. Sudden discontinuation can induce mania in up to 50% of patients, and thus short-term treatment can lead to a worse outcome than no treatment at all.[19] Lithium may also cause mild cognitive and memory impairment, tremor and weight gain. Moreover, there is evidence that the response to lithium treatment decreases with an increasing number of affective and manic episodes.[14] Patients with classic mania tend to respond better to lithium, whilst those with mixed episodes and those with rapid cycling respond less well. Due to its teratogenic properties, caution should be exercised when administering lithium to pregnant women.[43] Lithium use should be avoided during the first trimester due to an increased risk of cardiac abnormalities. If lithium is given to pregnant mothers, close monitoring of the serum lithium concentration is advised to minimise the risk of toxicity to the neonate.[43]

### Anticonvulsants

Valproate is used either as monotherapy or in combination with lithium, and is effective in the treatment and prophylaxis of mania in patients with bipolar disorder.

Valproate is used either as monotherapy or in combination with lithium, and is effective in the treatment and prophylaxis of mania in patients with bipolar disorder, though it is not indicated for prophylaxis in the UK.[3] Valproate may be more effective than lithium in terms of a longer duration of prophylaxis and less deterioration in depressive symptoms, and may be of particular benefit in patients presenting with mixed or rapid-cycling episodes of bipolar disorder.[44,45] Valproate, like lithium, is associated with an increased risk of congenital malformations in babies born to mothers treated during pregnancy and NICE caution against the routine use of valproate in women of child-bearing potential.[3,19,43] Carbamazepine is the main alternative anticonvulsant to valproate for the long-term treatment of mania, though it is associated with a large number of interactions with other medications. Again, caution is advised when administering carbamazepine during pregnancy because of the increased risk of neural tube defects and, as such, adequate folate supplements are advised (5 mg/day).[43] Lamotrigine is a particularly promising acute and prophylactic treatment for bipolar depression, though it is currently unlicensed for this indication in the UK.[3,15,19,46] However, lamotrigine is associated with an increased risk for serious rash, and the potentially fatal Stevens–Johnson syndrome. These risks are related to the starting dose of lamotrigine, speed of titration and the concomitant use of valproate.[19] Clinicians should consult the full prescribing information for relevant dosing instructions.[19]

### Antipsychotics

Atypical antipsychotics, in particular olanzapine, quetiapine and risperidone, have an expanding evidence base for their use in bipolar disorder.

Antipsychotics are commonly prescribed for the acute treatment of manic episodes and when psychotic symptoms are present in patients with bipolar disorder.[19] Atypical antipsychotics, in particular olanzapine, quetiapine and risperidone, have an emerging evidence base supporting their use in bipolar disorder.[3] Such agents are preferred over typical antipsychotics because of their more favourable adverse event profile. Antipsychotics are also useful in maintenance therapy to prevent recurrence of mood episodes in patients with bipolar disorder. Indeed, NICE specifically 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.[4]

### Antidepressants

As discussed previously, the treatment of depressive episodes in bipolar disorder is problematic as antidepressant monotherapy can induce mania and have a destabilising effect on the condition, potentially resulting in more frequent episodes of illness.[33] There is an astounding

lack of data for the treatment of bipolar depression with antidepressants in contrast to the evidence base for their use in unipolar depression. The limited evidence that is available appears to support the use of selective serotonin reuptake inhibitors (SSRIs).[3] However, for acute depressive episodes in patients with a history of mania it is recommended that SSRIs should be used with an antimanic agent (e.g. lithium, valproate or an antipsychotic). Monotherapy with SSRIs is not recommended for such patients.[3] Tricyclic antidepressants (TCAs) should be used only in treatment-resistant patients as they are associated with a greater risk of triggering mania than other antidepressants.[3] The new NICE guidelines on the management of bipolar disorder recommend that if a patient is taking an antidepressant at the onset of an acute manic episode, the antidepressant should be withdrawn.[4]

### Benzodiazepines

Short-term treatment with benzodiazepines, such as clonazepam or lorazepam, may be beneficial to promote sleep in patients who are agitated and overactive during acute manic or mixed episodes.[3]

## *Non-pharmacological treatment of bipolar disorder*

### Electroconvulsive therapy (ECT)

Despite generally good results, ECT is significantly underutilised in the management of bipolar mood disorder.[47] ECT should be considered for patients experiencing an acute manic episode and who are either severely ill or whose mania is treatment resistant, or in those patients with severe mania occurring during pregnancy.[3] During a depressive episode, ECT may also be useful in patients at high risk of suicide, or in those with psychosis, severe depression during pregnancy or life-threatening inanition.[3] Maintenance ECT should be considered in patients who respond well to ECT during acute episodes of bipolar disorder and who respond poorly to oral agents.[3] Clinicians should consider stopping or reducing lithium or benzodiazepines before giving ECT.[4]

Despite generally good results, ECT is significantly underutilised in the management of bipolar mood disorder.

### Psychotherapy

As the research into psychological interventions in bipolar disorder has been relatively sparse, drug treatments remain the mainstay of management.[19] However, there is increasing evidence for the use of psychosocial interventions such as cognitive behavioural therapy (CBT) as an adjunct to medication for patients with bipolar disorder, and it may be particularly beneficial for long-term treatment.[48] CBT can increase patient compliance with drug regimens and reduce the risk of relapse, especially in those suffering from frequent relapses despite long-term pharmacotherapy.[3,49] Family therapy may be useful for patients from families with high levels of expressed emotion and user groups can provide helpful support and information about the disorder and its treatment.[3,50] Interpersonal therapy or CBT should also be considered during the treatment of acute depressive episodes of bipolar disorder, though the benefits are less certain than during long-term treatment.[3]

## Socioeconomic impact

The economic impact of bipolar disorder upon UK society is estimated at £2 billion (at 1999/2000 prices) with nearly 300,000 people suffering with the disorder.[51] Approximately 10% of this cost (£199 million) was attributed to resources utilised by the National Health Service, of which hospital admissions accounted for 35%. Four per cent (£86 million) of the total cost was attributed to non-healthcare resource use whilst the remaining 86% (£1,770 million) comprised indirect costs. A large proportion (£1,510 million) of indirect costs relate to the higher rate of unemployment (46%) amongst patients with bipolar disorder relative to the general population.[51] Other indirect costs include absenteeism from work and the cost to society of excess suicide rates (640 cases per year) associated with the condition.[51] Thus, bipolar disorder has an important socioeconomic impact in the UK, despite its status as a neglected and often overlooked disorder.

The economic impact of bipolar disorder upon UK society is estimated at £2 billion.

## Key points

- Bipolar disorder is characterised by recurrent episodes of mania or hypomania, depression or mixed episodes of both states.
- The cause of bipolar disorder is largely unknown. Although it is known to have a strong genetic component, lifestyle, stressors and environmental factors also play a pivotal role in its pathogenesis.
- Bipolar I and II disorders have a combined overall lifetime prevalence of 1–2%, whilst bipolar spectrum disorders have a prevalence of 3.0–6.5%.
- Bipolar disorder is difficult to diagnose and its management can be challenging. This situation is, in part, due to the high degree of comorbidity with other conditions such as anxiety disorders and substance abuse.
- Lithium treatment has been in use for many years and can be very effective in treating bipolar disorder, though it has a narrow therapeutic range and its use requires regular monitoring, particularly with regard to renal and thyroid function. Discontinuation of lithium may also induce mania and patients' response to treatment appears to decrease with increasing numbers of affective and manic episodes.
- Anticonvulsants such as valproate – though only indicated for acute mania in the UK – are becoming increasingly used in the management of bipolar disorder.
- Atypical antipsychotics such as olanzapine, quetiapine and risperidone are also being used more frequently to manage bipolar disorder, particularly when treating the manic phase of the condition.
- Antidepressants, particularly SSRIs, are an important component in the management of depressive episodes in bipolar disorder. However, antidepressants should be used in combination with a 'mood stabiliser', as otherwise they are liable to induce manic episodes.
- The early age of onset, chronic recurrent course and high risk of suicide associated with bipolar disorder imposes a major socioeconomic impact, with estimated costs to the UK economy of over £2 billion in 1999/2000.

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Figure 1 is adapted from Hirschfeld *et al.*, 2000.[36]
Figure 2 is adapted from Goodwin *et al.*, 2003.[3]