Bipolar disorder

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Bipolar (affective) disorder, originally called manic depressive illness, is one of the most challenging psychiatric disorders to manage. Although it has been associated with creativity, it has a negative impact on the lives of most patients and more than 6% die through suicide in the two decades after diagnosis.[1] Organisational change means that specialist services mostly treat acute episodes, leaving primary care with long term management. This review summarises current best practice in the diagnosis and management of bipolar disorder, signposting areas of uncertainty.

What is bipolar disorder?

Bipolar disorders are characterised by recurrent episodes of elevated mood and depression, which are accompanied by changes in activity or energy and associated with characteristic cognitive, physical, and behavioural symptoms (fig 1). The term mania is used when elevated mood is severe and sustained or associated with psychotic symptoms, leading to marked disturbance of behaviour and function. Hypomania refers to less severe elevations in mood, which may be fairly brief, with a lower level of disturbance that usually does not bring the person to medical attention; however, hypomania may progress to mania. Bipolar disorders are divided into bipolar I disorder with episodes of mania and bipolar II disorder in which only episodes of hypomania occur (fig 1). Although traditionally viewed as opposite poles, manic and depressive symptoms often co-occur, giving rise to "mixed" states.[2]

SUMMARY POINTS

- Bipolar disorder is characterised by recurrent episodes of elevated mood and depression, together with changes in activity levels
- Elevated mood is severe and sustained (mania) in bipolar I disorder and less severe (hypomania) in bipolar II disorder
- Depression is usually more common and longer lasting than elevated mood, and—together with inter-episode milder symptoms—contributes most to overall morbidity
- Other psychiatric disorders, such as anxiety disorder and alcohol and drug misuse, are common
- Risk of death from suicide and from natural causes, most often cardiovascular disease, is increased
- Treatment is with drugs and supplemental psychotherapies; for both acute episodes and maintenance, treatment is guided by whether mania or depression predominates

SOURCES AND SELECTION CRITERIA

As well as searching the Cochrane Library, we searched Medline for reviews, systematic reviews, and meta-analyses published since 2007 using the terms "bipolar disorder", "mania", and "bipolar depression". These references were used to update and supplement those obtained from recent evidence based guidelines on treating bipolar disorder, including ones from the National Institute for Health and Clinical Excellence, the British Association for Psychopharmacology, the Canadian Network for Mood and Anxiety Treatments, and the International Society for Bipolar Disorder. We also used our personal reference libraries. High quality systematic reviews, meta-analyses, and large randomised controlled trials were selected where possible and lower quality evidence and guideline recommendations when these were lacking.

In community samples, as many people experience milder episodic highs (subthreshold) as those who meet the criteria for bipolar disorder,[3] and together they form the bipolar spectrum. Cyclothymia refers to a subset of milder disorders with repeated short cycles of hypomania and mildly lowered mood occurring regularly over two or more years. There is controversy about whether these milder disorders, which can overlap with personality characteristics, should be included under the diagnosis of bipolar disorder,[4] and where to set the threshold between unipolar and bipolar disorder for those with episodes of depression and mild symptoms of hypomania.[5]

Who gets bipolar disorder?

A recent worldwide survey in 11 countries found a median age of onset of about 25 years,[3] with an overall lifetime prevalence of 0.6% for bipolar I disorder (male predominance, although an equal sex ratio has been found in other studies) and 0.4% for bipolar II disorder (female predominance). Milder subthreshold disorders had a worldwide lifetime prevalence of 1.4%. The highest values were found in the United States (1.0%, 1.1%, and 2.4% respectively.[3] Prepubertal mania is rare; typically, minor mood disturbance in adolescence progresses to episodes of depression and then to mania in adult life.[6]

What causes bipolar disorder?

Bipolar I disorder has a heritability of 0.75 explained largely by common variant alleles, which partly overlap with those for schizophrenia.[7] Its phenotypic expression is a result of interacting genetic and environmental factors. Physical or sexual abuse in childhood is nearly twice as common as in healthy people and is associated with an earlier onset and more severe illness course.[8] Life events and chronic stressors are important in precipitating and perpetuating mood episodes.[9]

What makes bipolar disorder so challenging?

Comorbid psychiatric disorders, most often anxiety disorders, are common (box 1).[3] Over a third of cases, especially those with early onset disorder, also have an alcohol or drug disorder, either as a precipitant or secondary complication.

Poor insight into being ill and rejection of help are more common in acute mania than in other phases of illness. This can necessitate compulsory treatment and make collaborative management difficult, even after recovery from acute episodes.[10] Disinhibited and violent behaviour in mania may lead to risk or harm to others and involvement of the criminal justice system. By contrast, hypomania often escapes medical attention and, even if recognised, there can be a reluctance to seek treatment or prevent recurrence. The patient may view hypomania as positive and associated with increased energy and productivity.

Diagnostic criteria for bipolar disorder (based on DSM-IV)

Bipolar I disorder*: Presence, or history of, at least one manic (or mixed) episode

Bipolar II disorder*: Presence, or history of, at least one major depressive episode and at least one hypomanic episode (with no history of a manic or mixed episode)

The symptoms are not attributable to physical illness or physiological effects of a drug or other substance and are not better accounted for by another psychiatric disorder

Manic symptoms	Depressive symptoms
Elevated, expansive, or irritable mood	Depressed mood
Increased activity that is goal directed or psychomotor agitation	Markedly reduced interest in nearly all activities
Reduced need for sleep	Increased or decreased appetite or weight
Excessive involvement in pleasurable activities with likely adverse consequences	Insomnia or hypersomnia
Inflated self esteem or grandiosity	Psychomotor retardation or agitation
Increased or pressured speech	Fatigue or loss of energy
Flight of ideas or racing thoughts	Feelings of excessive worthlessness or guilt
Distractibility	Impaired concentration or indecisiveness
	Recurrent thoughts or actions of death or suicide

Manic episode: At least four manic symptoms including altered mood that persists for at least a week and causes marked functional impairment, hospital admission, or there are psychotic symptoms

Hypomanic episode: As for manic episode but less severe; symptoms persist for at least four days and functioning is noticeably altered but not enough to lead to hospital admission or to greatly impair function. There are no psychotic symptoms

Major depressive episode: Five or more persistent depressive symptoms (which must include depressed mood or diminished interest), which last for at least two weeks and occur on most days, and that cause serious distress or functional impairment

Mixed episode: Persistent mood symptoms for at least a week that meet criteria (apart from duration) for both a manic and major depressive episode, which occur at different times or rapidly alternate

Psychotic symptoms: These may occur during manic episodes in bipolar I disorder (but by definition not during hypomanic episodes) and during depressive episodes in either bipolar I or bipolar II disorder

*The World Health Organization classification ICD-10 does not distinguish between bipolar I and bipolar II disorder and requires another mood episode in addition to a single manic episode

Fig 1 | Diagnostic criteria for bipolar disorder. DSM-IV=*Diagnostic and Statistical Manual of Mental Disorders*, fourth edition; ICD-10=international classification of diseases, 10th revision

Box 1 | Differential diagnosis of bipolar disorder

Unipolar depression: Have a high index of suspicion of bipolar disorder in early onset severe depression or if there is a strong family history. Look for a history of elevated mood and remember that irritable agitation can be a presenting feature of bipolar disorder

Reaction to stress*: Check for associated symptoms suggestive of bipolar disorder when prominent fluctuating mood arises from stressful life events

Substance misuse*: Check whether mood changes came before or after an increase in drug or alcohol use because elevated mood can lead to loss of control of drug or alcohol intake

Personality disorders, traits, or cyclothymia*: Should be suspected if there is a long history of relatively mild, brief, and often rapidly varying mood fluctuation starting in adolescence, without definite episodes of mania or hypomania or long periods of stable mood

Attention deficit hyperactivity disorder (ADHD)*: ADHD and bipolar disorder have similar symptoms; because ADHD is more common, bipolar disorder should not be diagnosed before adulthood unless there are clear episodes of euphoric mood

Schizophrenia or schizoaffective disorder: Prominent psychotic symptoms, especially if bizarre or not congruent with elevated or depressed mood, should raise the possibility of schizophrenia or schizoaffective disorder, particularly if the psychotic symptoms pre-date, or dominate, the mood symptoms

Medical and organic brain conditions*: Suspect an underlying organic cause in atypical or fluctuating presentations or when manic-like or depressive symptoms occur in the context of illnesses or drugs known to cause behavioural change. These include neurological conditions, cerebrovascular disease, dementia and confusional states, endocrine disorders, and after administration of steroids.

* Comorbidity with bipolar disorder must also be considered.

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Episodes of hypomania or mania nearly always have negative social, financial, and occupational consequences, which can be long lasting and, particularly with mania, devastating.

When help is sought for depression, which is more common than elevated mood,[11] previous episodes of hypomania are often not detected. Diagnosis may be delayed for many years after the first mood symptoms, which can lead to ineffective, or even harmful, treatment.[12] The "conversion rate" from depression to bipolar disorder is estimated at 1% a year,[13] and high rates of unrecognised bipolar disorder have been found in depressed patients who respond poorly to antidepressants.[14]

The disorder's variable course, ranging from isolated brief or infrequent episodes with full inter-episode recovery to severe persistent or chaotic illness, poses major challenges for management. Rapid cycling (four or more mood episodes each year) is a marker of severity and poor treatment response. Mild to moderate cognitive deficits such as impaired verbal learning, memory, and executive function can be present even when patients are euthymic and may lead to impaired functioning.[15]

Deliberate self harm—particularly associated with depressive and mixed episodes, psychosis, and substance misuse—occurs in 30-40% of patients.[16] The completed suicide rate in a recent large prospective study was 7.8% in men and 4.8% in women over a median 18 year follow-up after first psychiatric contact, higher than for depression or schizophrenia.[1] In addition, the standardised mortality ratio for natural causes of death is about 2.[17] Cardiovascular illness is the most common cause and is linked to lifestyle, obesity, and other components of the metabolic syndrome.

How is bipolar disorder diagnosed?

The key to diagnosis is the presence or history of hypomania or mania. Of note, a predominantly irritable mood may mask an underlying manic picture, and psychotic symptoms can be mistaken for schizophrenia. Take a careful history and perform a mental state examination (fig 1 and box 2), and supplement this with collateral information. Be aware that elevated mood may be denied or not reported. Hypomania may not be obvious without previous knowledge of the person and may come to medical attention only after repeated episodes, adverse consequences, or pressure from others. The overlap with other disorders (box 1) can lead to a missed diagnosis if comorbidity with bipolar disorder is not considered.

To avoid overdiagnosis, in children and adolescents the diagnosis of bipolar disorder requires the presence of mania with unequivocal euphoria (not just irritability) and an episodic course.[16 18 19]

Box 2 | Clinical assessment of bipolar disorder

Observe the patient for changes in psychomotor activity and behaviour:

- In hypomania or mania there may be obvious elation, with flamboyant gestures and dress as well as increased activity and speed of movements, with the patient having difficulty staying still. Speech may be rapid and difficult to interrupt, moving rapidly from one topic to another, with a grandiose flavour to the content. Irritability may be close to the surface or even prominent
- In depression distress may be obvious; eyes may be downcast and tears present, movements may be slow, or agitation may be present and speech similarly affected. The content of speech typically has negative themes about self, relationships with others, and the world

Take a full history of depressive and manic symptoms in current and previous episodes (including inter-episode symptoms)

Screening questions for hypomania and mania

- Do you currently (or have you in the past) experienced mood that is (was) higher than normal, or do you feel (have felt) much more irritable than usual, and that others have noticed?
- At the same time do (did) you have an increase in your energy levels so that you are (were) much more active or don't (didn't) need as much sleep?

If the answer to both of these is yes ask about other symptoms of mania (fig 1)

Screening questions for depression

- In the past month have you often been bothered by feeling down, depressed, or hopeless?
- During the past month have you often been bothered by having little interest or pleasure in doing things?

If the answer to either of these is yes ask about other symptoms of depression (fig 1)
Ask about a family history of psychiatric disorder, especially bipolar disorder

Assess

- Triggers to episodes and current psychosocial stressors
- Effects on social, personal, and occupational functioning
- Comorbidities including substance misuse, anxiety, and physical illness
- Risk of suicide or harm to others
- Obtain a corroborative history where possible
- Consider using a self rating scale to assess previous episodes of elevated mood

Mood disorder questionnaire to screen for previous episodes of elevated mood[20]

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

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

Scoring: Likely bipolar disorder if at least 7 symptoms from section 1 are answered YES together with YES in section 2 and moderate or serious problem in section 3

Fig 2 | Mood disorder questionnaire

Self rating questionnaires, such as the mood disorder questionnaire (fig 2) or the hypomania checklist,[20 21] can help identify previous hypomanic or manic episodes with reasonable sensitivity but low specificity in general populations.

How do I distinguish between bipolar and unipolar depression?

Depression occurring in bipolar disorder cannot be reliably distinguished from unipolar depression on the basis of symptoms alone. In the absence of a history of elevated mood, a comprehensive review of studies comparing depression in the two disorders has proposed an approach based on symptom profile, family history, and illness course (box 3).[22]

How is bipolar disorder managed?

Acute treatment of episodes of illness aims to resolve symptoms and reduce immediate risk to self or others. Long term treatment aims to prevent future episodes of illness and help regain a premorbid level of functioning, improve physical health, and reduce longer term suicide risk. Patients cycling between mania or hypomania and depression are especially difficult to treat, and stabilising mood is as important as treating the acute episode.

Drugs form the mainstay of treatment for bipolar I and II disorders but their role in milder disorders is less well established (table). Specific psychotherapies are important adjuncts in reducing relapse, treating depression, and improving function (table). Other crucial elements include ensuring a strong therapeutic alliance with treating clinicians, maintaining continuity of care, and tackling comorbid disorders and risk factors for relapse, including alcohol and substance misuse and disrupted circadian rhythms.

Given the lack of evidence on how to treat comorbid psychiatric disorders (such as anxiety), usual practice is to stabilise mood and then carefully treat the specific disorder.

What drugs are effective?

Most evidence concerns the treatment of mania and bipolar depression, with less evidence on hypomania and milder mood fluctuations. Many drugs are more effective for one pole of the illness (table), so patients on "mood stabilisers" (usually referring to lithium or an anticonvulsant) may not be treated equally for both poles.

The details of effective drugs and the strength of the evidence in the table are based on recent evidence based guidelines and meta-analyses of randomised controlled trials (licensing varies by country).[18 19 23-29]

What is the role of psychotherapy?

Persistent or recurrent symptoms, functional impairment, comorbidity, and the contribution of environmental factors have stimulated interest in adjunctive psychotherapies. The current evidence based treatments, the stage of illness at which they are used, and the strength of evidence shown in the table are based on evidence based reviews and guidelines.[18 19 30-32] Definitive evidence about which treatment to choose is lacking. The treatments each have specific approaches but all deal with education about the illness, adherence to treatment, lifestyle regularity, and relapse prevention strategies.[33] Cognitive behavioural therapy helps identify and tackle harmful thought patterns and

Effective treatments for bipolar disorder[18 19 23-32]

Indication	Treatment*	
	Drugs†	Adjunctive psychotherapy
Mania and mixed states	Good evidence: antipsychotics as a class, valproate, lithium, combined antipsychotics + lithium or valproate	Low stimulus environment (clinical experience)
	Suggestive evidence: carbamazepine	
	Short term benzodiazepines are clinically used for treating agitation and insomnia	
Depression	Good evidence: quetiapine	Good evidence: cognitive behavioural therapy, family focused therapy
	Suggestive evidence: olanzapine + fluoxetine‡, olanzapine, lamotrigine, lithium, valproate	
	Evidence for efficacy of antidepressants is poor	Suggestive evidence: interpersonal and social rhythm therapy
Maintenance and prevention of relapse§	Good evidence: monotherapy with lithium (mania and depression), antipsychotics as a class (mania), quetiapine (depression and mania), olanzapine (mania more than depression), lamotrigine (depression more than mania); combination therapy with antipsychotics + lithium or valproate (better than lithium or valproate alone for mania), lithium + valproate (better than valproate for overall relapse), quetiapine + lithium or valproate (better than lithium or valproate alone for mania and depression)	Good evidence: group psychoeducation (mania more than depression), family focused therapy
	Suggestive evidence: valproate (depression more than mania)	Suggestive evidence: cognitive behavioural therapy (especially less frequent relapsers), interpersonal and social rhythm therapy, cognitive remediation (cognitive impairment)
	Carbamazepine lacks an evidence base	

*Good evidence: meta-analysis and better quality randomised controlled trials against placebo unless otherwise stated; suggestive evidence: inconsistent or weak effects from meta-analysis or poorer quality randomised controlled trials against placebo.
†Inclusion of a drug in this table does not mean that the drug is licensed for the relevant indication; check approval status in your country.
‡Available as a single tablet in the United States.
§Most studies have been done in "enriched samples" where patients have responded to initial treatment with the drug(s) being investigated.

behaviours; family focused therapy aims to improve family communication patterns and strengthen problem solving and coping strategies; interpersonal and social rhythm therapy deals with problems with relationships and daily routines; psychoeducation provides information about bipolar disorder and enhances self management and early identification of relapse. We also now have evidence that cognitive remediation (behavioural training to improve cognitive performance) benefits people with bipolar disorder as well as those with schizophrenia.[32] The current challenge is how to match treatment to an individual patient's needs.

When should I refer and how should care be shared?

Box 4 shows indications for referral to specialist care; mood episodes always need specialist referral or involvement. Although some may need long term psychiatric care, many stable and well patients can be managed in primary care. Debate continues about models of psychiatric service delivery and its boundary with primary care. Whichever model is adopted, good communication and the provision of early and rapid psychiatric advice and referral are essential.[19]

How are episodes of elevated mood managed?

Mania often requires inpatient care to manage risk and allow treatment. This can require compulsory admission, and highly disturbed behaviour may need to be acutely treated with antipsychotics or benzodiazepines, or both (rapid tranquillisation). Excess stimulation must be avoided and a calm environment provided. Milder degrees of mania may be treated with intensive community support from specialist services. Mixed episodes are treated as manic episodes. Hypomania is often untreated and self limiting, but more intensive support and treatment adjustment may be needed to prevent escalation to mania in bipolar I disorder. The emphasis in bipolar II disorder is usually the management of recurrent depressive episodes.

The first step is to identify and treat any medical causes and deal with precipitants such as cessation of maintenance drugs, illicit drug use, and stressful life events. Prescribed antidepressants should be withdrawn because they may be exacerbating the elevated mood.[18 19 34] The efficacy and tolerability of any treatments for past episodes should be reviewed and current long term treatment optimised or restarted if it had been stopped.[18 19]

Antipsychotics are first line treatment for mania, particularly if severe.[18 19] A multiple treatments meta-analysis of 68 randomised controlled trials (RCTs) including both direct and indirect comparisons in the acute treatment of mania found that antipsychotics, lithium, valproate, and carbamazepine were more effective than placebo.[23] The most effective drugs were haloperidol (standardised mean difference *v* placebo −0.56, 95% confidence interval −0.69 to −0.43), risperidone (−0.50, −0.63 to −0.38), and olanzapine (−0.43, −0.54 to −0.32); all were more effective than valproate, with haloperidol also being more effective than lithium. The second generation antipsychotics risperidone, olanzapine, and quetiapine had the fewest overall dropouts.

Box 3 | Distinguishing between bipolar I depression and unipolar depression*

Clinical suspicion increases with the number of features present for both types of depression

Greater likelihood of bipolar I depression

Atypical depressive features (hypersomnia, increased appetite, feeling of "leaden paralysis"—feeling that the body or limbs are extremely heavy and difficult to move)
Mood lability
Psychotic features or pathological guilt
Psychomotor retardation
Early onset of depression (<25 years)
Multiple episodes of depression
Family history of bipolar disorder

Greater likelihood of unipolar depression

Reduced sleep or initial insomnia
Loss of appetite or weight (or both)
Normal or increased activity levels
Somatic (bodily) problems
Later onset of depression (>25 years)
Longer duration of depressive episode (>6 months)
No family history of bipolar disorder

*Based on a comprehensive review of studies comparing the clinical features of depression in the two disorders[22]

Box 4 | Referral to specialist care

During acute episodes of illness refer all patients with known or suspected bipolar disorder to specialist care (or if currently under a specialist team ensure access to care) to:

- Treat the acute episode
- Assess and manage risk
- Confirm the diagnosis (if necessary)
- Establish or review the longer term management plan

Patients with an established diagnosis of bipolar disorder should remain under specialist care if they:

- Have difficulty engaging with services or adhering to treatment
- Have frequent relapses, poorly controlled illness, or persistent symptoms
- Have severe psychiatric comorbidity, including anxiety disorders or alcohol or drug misuse
- Require management of suicide risk or risk to others

Stable patients with bipolar disorder not currently under specialist care should be referred if they:

- Are considering getting pregnant or if they are pregnant
- Have side effects or complications from treatment that may require a change in drugs
- Are considering altering or stopping treatment
- Require access to specific psychotherapies

If monotherapy with an antipsychotic, valproate, or lithium is insufficiently effective they can be combined. A meta-analysis of eight RCTs found combination therapy with an antipsychotic and lithium or valproate more effective than valproate or lithium alone,[24] and one RCT found that a valproate-antipsychotic combination was more effective than an antipsychotic alone.[35] Benzodiazepines may be needed short term for the management of agitation and insomnia, but they lack intrinsic antimanic properties.

How is depression managed in people with bipolar disorder?

As for mania, identify and remove any precipitants and establish the treatment history. Choice of drugs (table) is informed by the drug history and the need to avoid a switch to elevated mood. For patients on long term treatments with mild depression, guidelines recommend optimising their dose and monitoring mood initially.[18 19] There are a limited number of evidence based treatments for bipolar depression (table).

A meta-analysis of 19 RCTs in bipolar depression found the best evidence of efficacy against placebo for quetiapine (five trials). Olanzapine and combined olanzapine and fluoxetine were each effective in single trials and lamotrigine was effective but with a small effect size (five trials).[25] A recent meta-analysis of 15 RCTs found no significant benefit for antidepressants over placebo in the treatment of bipolar depression.[26] Guidelines recommend that antidepressants should always be combined with an antimanic drug to reduce the risk of destabilising mood. Selective serotonin reuptake inhibitors are the drugs of choice,[18 19] because they are least likely to cause a switch to mania.[34] Unless the history shows benefit from continuing antidepressant drugs, guidelines recommend considering withdrawal after the resolution of depressive symptoms.[18 19]

Consider effective psychological treatments (table) alongside drugs, especially if depression is prolonged or recurrent or mild symptoms persist.

How should maintenance or prophylactic treatment be approached?

It is crucial that patients are engaged and enabled to make informed choices. This requires an understanding of the disorder and treatment that is tailored to individual circumstances. Patients should be enabled to identify triggers for relapse, understand the role of drugs for prevention and treatment of exacerbation, and identify functional and symptomatic goals. Stigma remains a major problem for many.

It is often difficult for patients to accept the need for long term treatment. A large study that assessed adherence by prescription collection found that only 54% of patients were fully adherent to maintenance drugs and 21% were non-adherent.[36] Overall benefit is unclear after an initial episode when the course of illness is uncertain and side effects of drugs (including weight gain) need to be balanced against the detrimental effect of further episodes.[18] The National Institute for Health and Clinical Excellence (NICE) recommends considering long term treatment in bipolar I disorder after two acute episodes, or a single manic episode with severe consequences, and in bipolar II disorder if there are frequent relapses, functional impairment, or suicide risk.[19]

Choice of drug(s) for maintenance or prophylaxis (table) is informed by the predominant pattern of relapse. A meta-analysis of 20 RCTs of maintenance treatment,[27] and a subsequent large RCT with lithium and quetiapine,[37] found that lithium and antipsychotic monotherapy and combined antipsychotics and lithium or valproate were effective against manic relapse. Quetiapine as monotherapy or combined with lithium and valproate was effective against depressive relapse.

In a pooled analysis of two placebo controlled RCTs, lamotrigine was effective against depressive—and to a lesser degree manic—relapse.[28] A recent open label RCT found that valproate monotherapy was less effective than lithium or combined lithium-valproate in preventing emergent mood episodes.[29] Meta-analytical evidence also shows that lithium reduces suicide when used in maintenance treatment of mood disorders.[38] Such treatment has a low therapeutic index, however, and requires regular monitoring of serum lithium concentration every three months and renal and thyroid function six monthly.[19 39] Rapid withdrawal can trigger relapse, so lithium should be stopped over several months.[40] For many patients polypharmacy is unavoidable but associated with problems with tolerability and adherence; it therefore needs to be planned rather than drugs just accumulating over time. If long term treatment is stopped, it must be done gradually over months and under specialist supervision. Close follow-up is needed to detect early signs of relapse.

Offer all patients who need long term treatment psychoeducation (see above). Other psychological treatments are indicated for inter-episodic and comorbid symptoms such as anxiety; repeated relapse; or persisting social, functional, or cognitive impairment (table).

What are the implications of bipolar disorder for women of childbearing age?

Women of childbearing age with bipolar disorder should be referred for specialist preconception advice if they are considering pregnancy and managed jointly between psychiatric and obstetric services if they are pregnant. A large retrospective study found that 23% of women

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

National Institute for Health and Clinical Excellence (www.nice.org.uk/cg38)—Clinical guideline 38 on the management of bipolar disorder. This guideline is about to be updated but sets UK standards

British Association for Psychopharmacology (www.bap.org.uk/pdfs/Bipolar_guidelines.pdf)—Up to date UK evidence based guidelines for treating bipolar disorder

British Association for Psychopharmacology (www.bap.org.uk/onlinecpd.php)—Subscription based modules on the drug treatment of psychiatric disorders including bipolar disorder, delivered by UK experts in the field

International Society of Bipolar Disorders (www.isbd.org/)—Forum for professional collaboration and education on bipolar disorders

Resources for patients

NHS Choices (www.nhs.uk/Conditions/Bipolar-disorder/)—An introduction to symptoms, diagnosis, and treatment for bipolar disorder with links to UK resources

Bipolar UK (www.bipolaruk.org.uk)—Self help organisation for people with bipolar disorder, their families, and carers; provides a range of self help groups and self management courses

Bipolar Scotland (www.bipolarscotland.org.uk/)—Self help organisation providing services and support in Scotland

National Institutes of Mental Health (www.nimh.nih.gov/health/publications/bipolar-disorder/complete-index.shtml)—A detailed downloadable booklet on bipolar disorder

Royal College of Psychiatrists (www.rcpsych.ac.uk/mentalhealthinfo/problems/bipolardisorder.aspx)—Information on a wide range of aspects related to bipolar disorder and the experience of patients.

TIPS FOR NON-SPECIALISTS

Always check for a past (and family) history of elevated mood and increased energy or activity levels in patients presenting with depression

Never treat patients with bipolar disorder with antidepressant drugs alone; an effective antimanic agent must also be prescribed

In patients who respond poorly to treatment use non-judgmental questioning to assess the contribution of treatment non-adherence or drug and alcohol misuse

In patients prescribed lithium, check serum lithium concentrations every three months and renal and thyroid function six monthly. Ensure that patients know the signs of lithium toxicity and the drugs that should be avoided (such as non-steroidal anti-inflammatory drugs) because they can interact with lithium

Do not prescribe valproate to pregnant women and prescribe this drug to those of child bearing potential only if no effective alternative is available. A full discussion of the risks and effective use of contraception are required

Refer women who want to get pregnant for specialist preconception counselling because of the risks to both mother and fetus

Decide the duration of, and changes to, treatment in consultation with a specialist. Never stop long term drugs without specialist advice and support. Closely monitor for relapse if treatment is altered or stopped

Be aware of the high risk of suicide and the potential for rapid escalation of mania; ensure that early and rapid specialist help is available if needed

Include people with a diagnosis of bipolar disorder on a severe mental illness case register and monitor and treat physical health problems (such as obesity and other components of the metabolic syndrome)

with bipolar disorder relapsed during pregnancy. This figure was even higher (52%) in the postpartum period, with most relapses being depressive.[41] Risk is increased if mood stabilisers are stopped during pregnancy—two prospective studies reported that 85-100% of women relapsed compared with 30-37% if mood stabilisers were continued.[41] Lithium and anticonvulsants are associated with an increased risk of teratogenicity. The risk is greatest with valproate, which also causes later neurodevelopmental delay in children exposed prenatally.[19] Current guidance is that valproate is contraindicated in women of childbearing age and, if used, effective contraception is needed.[19] Valproate is contraindicated in pregnancy, and other anticonvulsants are contraindicated in the first trimester; lithium should be used only under obstetric supervision and, if possible, avoided during the first trimester. Antipsychotics are the antimanic treatment of choice during pregnancy, and cognitive therapy is preferred over antidepressants for depression.[19] After delivery, consider reinstating or starting drugs to prevent relapse. Breastfeeding is contraindicated for women on lithium, lamotrigine, and clozapine.[19]

What are the options when treatments don't seem to help?

For poor response to treatment review the diagnosis and attempt to identify and deal with any co-occurring disorders, drug or alcohol misuse, and non-adherence with treatment, which is reported in nearly half of patients with bipolar disorder.[36]

Next, increase the dose of current drugs within licensed limits and tolerability, then switch or add an alternative evidence based drug. Consider adjunctive psychotherapy and tackle environmental factors where possible. A meta-analysis of six cohort studies found that electroconvulsive therapy was as effective for bipolar depression as for unipolar depression,[42] making it an option for severe bipolar depression and when other treatments have failed; it is also an option for treatment resistant mania.[19] Clozapine can be considered for treatment resistant mania and rapid cycling, although evidence is limited.[18]

Consider referral to a tertiary treatment centre for difficult or complex cases.[19]

What is the outlook for patients with bipolar disorder?

Most patients recover from their first episode but about 80% relapse within five to seven years. Most have three or more episodes over 20 years,[13] with the risk of relapse persisting into old age. In longitudinal follow-up studies patients experience moderate to severe impairment for 26-32% of the time. The course of illness and function are worse in patients with severe episodes, an early onset, and cognitive deficits.[43] Treatment is more effective earlier in the course of illness, emphasising the need for early initiation of long term treatment. Nevertheless, many patients have a good outcome and can live a full life, although they need to remain aware of, and manage, the risks and triggers associated with relapse.

References are in the version on bmj.com.

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