MedicineToday 2013; 14(9): 18-26

PEER REVIEWED FEATURE
POINTS: 2 CPD/2 PDP

The ups and downs of bipolar disorder in general practice

JOHN W. G. TILLER MD, MB ChB, BSc, DPM, FRACP, FRANZCP, GAICD

GPs are uniquely placed to identify patients with bipolar disorder and to contribute to their management, including addressing physical health problems and encouraging a stable balanced life and sleep/wake cycle. Treatment is generally with mood stabilisers rather than antidepressants, in collaboration with a psychiatrist.

Key points

- **Patients with bipolar disorder present mostly with depression; the bipolar diagnosis is easily missed unless a history of mood elevation is sought.**
- **Although up to 15% of patients with the disorder die by suicide, the major mortality is from cardiovascular disease and cancer (linked to obesity, smoking and alcohol), with about 10 to 20 years' reduction in life span.**
- **Pharmacotherapy with mood-stabilisers is essential, with antidepressants as second-line therapy or not used at all.**
- **Electroconvulsive therapy can help both severe mania and depression.**
- **Managing concurrent physical illness, especially obesity and substance abuse, is essential. General health measures and a balanced lifestyle with a regular sleep/wake cycle improve outcomes.**
- **Most patients are best treated by GPs in conjunction with a psychiatrist.**

Patients with bipolar disorder present mostly with depression, especially treatment-resistant depression. Bipolar disorder is defined by an element of mood elevation, which may be of greater or lesser degree. This can easily be missed as it may be brief (only a few days) and may have occurred years before. The patient may not recognise that past exuberant or 'over-the-top' behaviour can indicate a bipolar diagnosis.

Treatments need to address the patient's physical status and welfare, to focus on a stable balanced life with a good sleep/wake cycle and to include a predominance of mood-stabilising rather than antidepressant pharmacotherapy. Electroconvulsive therapy (ECT) can be uniquely effective for both severe depression and mania in some patients.

DIAGNOSIS

The recognition of bipolarity through obtaining a history of mood elevation is more important than efforts to determine the subtleties of whether it is bipolar I or bipolar II disorder (see the box on page 19).[1] Taking a careful history is essential. The diagnosis can be difficult because most patients present when they are depressed and possibly despair of ever feeling 'normal', much less recall times when their mood was elevated. Diagnosis is easier if there has been an episode of florid mania that may have come to the attention of law enforcement or other authorities.

Bipolar II disorder, which involves hypomania rather than mania, almost never presents when the patient is feeling mildly elevated, and only when they are depressed. Bipolar II is not 'bipolar minor' as the disability is comparable or slightly greater than that of bipolar I disorder.

CLINICAL FEATURES

Bipolar disorder most commonly presents as a depressive episode, but almost 70% of patients

Professor Tiller is Professor Emeritus in the Department of Psychiatry, The University of Melbourne, at Albert Road Clinic, Melbourne, Vic.

RECOGNISING MOOD ELEVATION*[1]

Mood elevation is a defining element of bipolar I and II disorders. Symptoms include:

- inflated self-esteem or grandiosity
- decreased need for sleep (yet feeling rested)
- more talkative
- racing thoughts
- increased goal-directed activity
- excessive risk-taking (e.g. spending, gambling, sexual indiscretions).

Bipolar I disorder: symptoms last at least seven days, with or without psychosis.

Bipolar II disorder: symptoms last at least four days, without psychosis. Bipolar II is just as disabling as bipolar I.

* Adapted from American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed (DSM-5). Arlington, VA: APA; 2013.

show some features of mood elevation at the same time. Those with only one or two manic symptoms might be considered to have agitated depression were it not for a history of bipolar disorder.[2] About 15% have features that meet the full criteria for both mood elevation and depression simultaneously as a mixed state.

In the past, patients who had features of both depression and mania but did not meet the stringent criteria for a mixed state – almost half the bipolar patient population – were diagnosed with 'bipolar disorder not otherwise specified'. The recently published DSM-5 classification has recognised these intermediate states by adding the specifier 'with mixed features' to the diagnosis of bipolar depression, mania or hypomania for patients who have three or more symptoms of the opposite pole (see the box on page 20 for definitions).[1]

Cycle frequency in bipolar disorder varies widely, ranging from within-day mood variations to months or years of sustained depression or episodes of mood disorder interspersed with many years of being well.

Some patients are troubled by a few symptoms of depression and a few symptoms of mood elevation without meeting the criteria for either bipolar I or bipolar II disorder. If these symptoms persist for more than two years, patients can be identified as having cyclothymic disorder. They have a 50% chance of progressing to bipolar disorder.

Bipolar disorder is not just a disorder of mood. It also significantly affects cognition, particularly executive functioning – mental sequencing, planning and organising. Additionally, patients may have poor insight into their mood at any time. As a result, they may not be good judges of how they are feeling and may be chaotic with their use of pharmacotherapy, engagement in psychological treatments or attendance at appointments. These problems should be managed. A good therapeutic relationship is fundamental in helping these processes.

Disability occurs with both poles of bipolar disorder and also intermediate states. Mania with increased activity and risk-taking can lead to sexual promiscuity, sexually transmitted infections and disruption of established relationships. Gambling and excessive or inappropriate spending can reduce a family to poverty. Alcohol and substance abuse take an added

DEFINITIONS OF PSYCHIATRIC TERMS

Bipolar I disorder: The patient meets the criteria for a current or past manic episode.

Bipolar II disorder: The patient meets the criteria for a current or past hypomanic episode and for a current or past depressive episode.

Cyclothymic disorder: For two years (or at least one year in children and adolescents), the patient has experienced numerous periods with symptoms of mood elevation and depression that do not meet criteria for a hypomanic episode or a depressive episode. These patients have up to a 50% chance of developing a bipolar disorder.

Mixed state: The patient meets the full criteria for both a manic episode and a depressive episode at the same time.

Bipolar disorder specifiers: A manic or hypomanic episode 'with mixed features' occurs when a patient meets the criteria for the relevant mood elevation and has three or more symptoms of depression. A depressive episode 'with mixed features' occurs when a patient meets the criteria for depression and has three or more symptoms of mood elevation.

Rapid cycling: Four or more episodes of mood disorder a year.

toll and may not be volunteered by the patient, so should be asked about specifically.

Depression increases the risk of suicide and can also reduce patients' ability to interact and be effective at work and in the home, leading to loss of employment, strained domestic relations and relationship breakdown. Social isolation can result from the slowness and withdrawal seen with depression. Sleep disturbance occurs with both poles of bipolar disorder.

PHYSICAL COMORBIDITY

People with bipolar disorder often have concomitant physical disorders, especially obesity, hypertension, raised levels of triglycerides and raised levels of glucose, if not diabetes. They can have a reduction in lifespan of 10 to 20 years; this reduction is greater in men (12 to 19 years) than in women (11 to 16 years).[3] Although about 15% of patients with bipolar disorder die by suicide, premature death is mostly from physical illness, particularly cardiovascular disease and cancer (linked to obesity, smoking and alcohol).

MANAGEMENT

In the management, GPs should explain to patients with suspected bipolar disorder the reasons for their diagnosis and why they are suggesting the initial interventions. It is often a relief to patients to be given a reason for symptoms that are otherwise inexplicable.

Specialist referral

Patients with bipolar disorder are best treated through a constructive collaboration between GPs and psychiatrists. When and how to refer a patient to a psychiatrist depends on location, access to services and resources, and economic and social factors, as well as the severity and acuity of the illness and its consequences.

Bipolar vulnerability is lifelong, and treatment should encompass that aspect, rather than being brief and intermittent, thereby exposing the patient to the adverse consequences of unrecognised and consequently untreated episodes of mania or depression. GPs have a role in counselling patients about the importance of managing their vulnerability to bipolar disorder with a stable lifestyle and presenting early to treat acute episodes of illness rather than waiting until they are in crisis. In addition, the importance of ongoing treatment should be explained, including maintenance therapy – even in remission – to maximise their chances of staying well.

TREATMENTS FOR BIPOLAR DISORDER

In day-to-day clinical practice, treatments for all types of bipolar disorder are broadly similar. More details of the treatment of bipolar disorder from an Australian perspective can be found in *Therapeutic Guidelines: Psychotropic version*,[4] and from an international perspective in the Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for managing patients with bipolar disorder.[5] A possible initial treatment path is outlined in the flowchart on page 22.

Psychosocial interventions

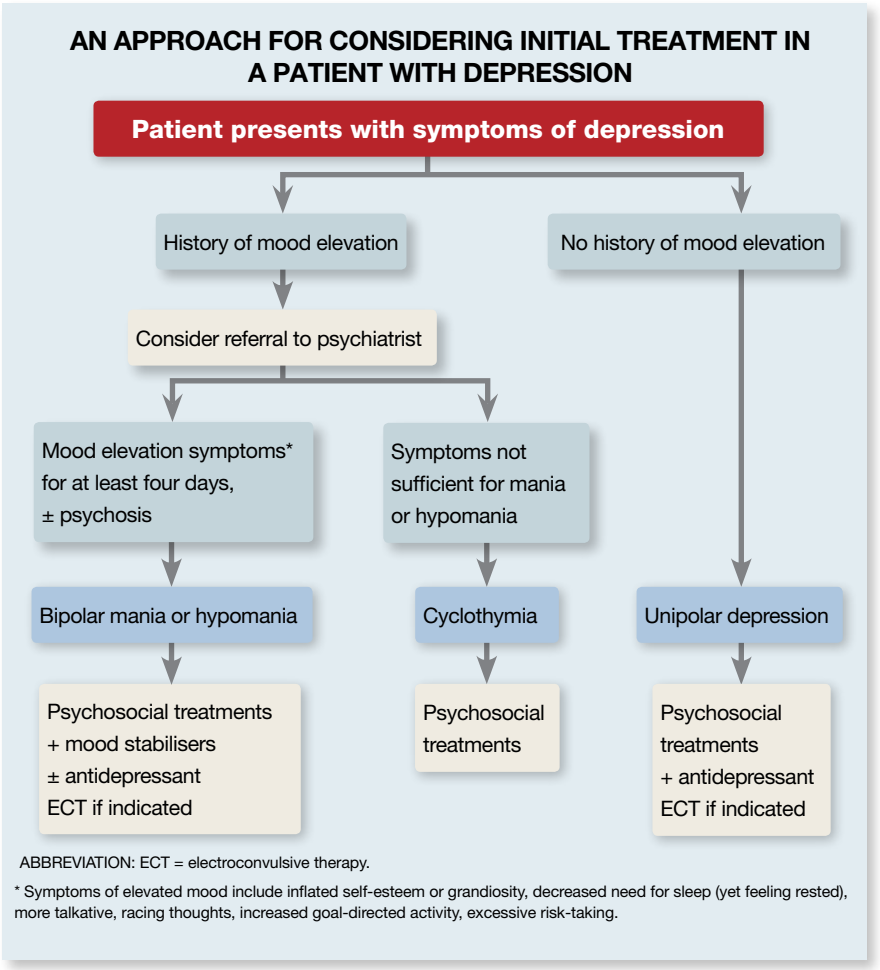
The patient should be encouraged to have a balanced lifestyle. The principles of social rhythms therapy have been shown to be helpful.[6] This therapy aims to help the patient focus on work as well as play, rest as well as exercise, and time alone as well as time with others, and to have a balanced diet and a regular stable sleep/wake cycle.

Psychoeducation that provides structured information for the family, friends, relatives and, when appropriate, workmates of the patient as well as the patient him or herself can help by providing informed, engaged, competent partners in treatment and a better chance of favourable clinical outcomes.[7]

Cognitive behaviour therapy can assist the patient with strategies to help manage their depression and reduce its severity.[8] This therapy is difficult during episodes of illness and might be easier and more effective as the patient recovers and moves towards remission. Many patients have residual symptoms that they must manage to reduce their adverse impacts.

Pharmacotherapy

As the initial presentation is often with depression, it is not surprising that antidepressants are the most commonly prescribed initial pharmacotherapy for patients with bipolar disorder. However, antidepressants are not the most desirable



treatment for most patients, and may disturb rather than improve mood. Mood-stabilising pharmacotherapy should be the mainstay of physical treatment. It may seem counterintuitive to patients with depression to be told to discontinue antidepressants, and it should be explained to them that antidepressants are destabilising their mood, rather than helping it.

Bipolar illnesses require sustained evaluation and treatment, with stability of treatment rather than frequent changing of medicines and doses. Medication may be needed long-term, and stopping medication is a major cause of relapse. Liaison with GP colleagues and psychiatrists can provide additional information and support for GPs treating patients whose clinical presentation can be extremely demanding and challenging.

Mood stabilisers

Although lithium carbonate was the first mood stabiliser to be identified and used, the anticonvulsant sodium valproate is now used much more, followed by carbamazepine. These three agents are most effective in controlling mood elevation but have modest effects in improving depression and in preventing relapse.

Lamotrigine is helpful for depression but is not effective for mania. In addition, it requires very slow dose escalation (according to the product information), and so levels can take two to three months to build to an effective therapeutic dose for some patients, although others may respond at lower doses.

Antipsychotics

Antipsychotics have been widely used for the treatment of mania with psychosis and to settle extreme agitated behaviour. In the past, this use was mostly brief, for one to two months until the psychosis remitted. There are now good data supporting a role for the newer atypical antipsychotics in managing mania and, for some of these drugs, in helping symptoms of depression. Some antipsychotics are mood stabilisers and can ameliorate both poles of the illness, while others seem effective only for mania. The best data on bipolar depression treatment are for quetiapine, with some data supporting the role of olanzapine. There are indirect data suggesting that asenapine might also help in bipolar depression.

Antipsychotics have progressed from being second- or third-line supplementary treatments for bipolar disorder to being among first-line treatments for achieving and maintaining mood stability. However, quetiapine and olanzapine have the disadvantage of significant long-term adverse effects, with appetite stimulation and consequent excessive weight gain. Clozapine, which is seldom used because of its potential adverse haematological effects, causes similar appetite stimulation and weight gain.

The atypical antipsychotics aripiprazole and ziprasidone cause less appetite stimulation but unfortunately are not effective for bipolar depression. Risperidone and paliperidone are widely used, particularly in depot formulations, to prevent manic episodes but increase the risk of prolactin elevation and extrapyramidal adverse events more than other atypical antipsychotics, especially at higher doses.

Asenapine is a new option with very modest associated weight gain. A possible advantage of this atypical antipsychotic is its activity at 5-hydroxytryptamine receptor subtypes 6 and 7 (5-HT6 and 5-HT7), which have been linked in animal models to improved cognition. This activity may have the potential over time to improve cognition, although more research is needed.

Antidepressants

Antidepressants are helpful for unipolar depression. In the early stage of bipolar disorder there may not have been an episode

of mood elevation, and at that stage antidepressants do seem efficacious for many patients. As the illness progresses, a change seems to occur. Antidepressants then may not be effective, or be may be effective only briefly, for a few weeks or months. Importantly, they can destabilise bipolar disorder when used on their own, resulting occasionally in marked mood elevation, with an increase in cycle frequency, or most commonly with a mixed state. This may well be better recognised as new diagnostic criteria allow for the diagnosis of depression with manic features as well as mania with depressive features. On balance, for most patients with established bipolar disorder, antidepressants are more likely to be ineffective and disruptive to the mood state than beneficial. If antidepressants are used for established bipolar disorder then they must be combined with a mood stabiliser.

Combination pharmacotherapy

In contrast to unipolar depression, where monotherapy is preferable, bipolar disorder is more likely to require combination therapy. This may be related to the relatively small number of approved treatments for bipolar disorder and their modest efficacy.

Studies have found no difference in effectiveness between lithium monotherapy and lithium combined with valproate but both were more effective than valproate.[9] The addition of an atypical antipsychotic to other mood stabilisers appears to produce better outcomes than the mood stabiliser alone. In practice, very few patients can be managed with monotherapy. Combinations such as lithium with valproate and an antipsychotic are quite common.

Occasionally patients with bipolar depression do better with an antidepressant combined with mood-stabilising therapy. Patients with bipolar II disorder may be more likely than those with bipolar I disorder to respond to this combination.

Electroconvulsive therapy

When pharmacotherapy is not adequate, ECT can be uniquely effective for some patients with bipolar disorder. ECT also provides rapid-onset treatment for patients with manic delirium. Older ECT techniques caused appreciable memory impairment in some patients, severely limiting their use as maintenance treatment. Newer techniques, such as right unilateral treatment with an ultra-brief pulse width stimulus (0.3 ms), can be efficacious with few or no cognitive adverse events for most patients when used as acute treatment, and minimal cognitive adverse events even when used as longer-term maintenance therapy.

With modern ECT, the required ECT stimulus is titrated for each patient at the start of the course to ensure subsequent doses are adequate but not excessive, in contrast to the 'one size fits all' approach used in the past. An acute course of treatment requires an average of about 10 ECT treatments to achieve recovery, but some patients may need up to 20 or more treatments.

Pharmacotherapy is most commonly used for subsequent maintenance treatment but for some patients does not result in sustained improvement. Maintenance ECT treatment is usually administered once a week after recovery, with a gradual increase in the interval between treatments until they may be as infrequent as once every six weeks. The initial aim is to see the patient well for at least 12 months before stopping maintenance ECT. Further treatment depends on the patient's clinical status. Maintenance ECT is not designed to treat an acute relapse, which requires an acute course of ECT.

Other treatments

Other treatments that have been promoted for bipolar disorder include omega-3 fatty acids, the antioxidants N-acetyl cysteine and coenzyme Q10, and anti-inflammatories. These are not approved in Australia for the management of bipolar disorder and should be seen as provisional or experimental treatments, mostly to be managed by specialists with expertise in the area.

TREATMENT OF COMORBIDITY

Concomitant physical disorders, such as obesity, hypertension, diabetes and arthritis, should be identified and treated, although treatment is most likely to be effective if the patient's mental status can be stabilised. In patients who are gaining weight, GPs should be aware of the possible contribution of pharmacotherapy to appetite stimulation and consider whether treatment changes are required.

Other comorbidities that may need treatment include substance abuse, gambling and qualities of a borderline nature, if not overt borderline personality disorder (such as an unstable sense of self, frantic efforts to avoid perceived abandonment, impulsivity and suicidal behaviour). GPs are often the best placed professionals to monitor for these problems, which can help reduce the morbidity and mortality of bipolar disorder.

TREATMENT IN PREGNANCY AND THE PUERPERIUM

Women who may become pregnant during treatment for bipolar disorder are best managed with atypical antipsychotics as mood stabilisers, because of the increased risk of congenital abnormalities in the fetus with use of lithium or mood-stabilising anticonvulsants. Because of the risk of an exacerbation of bipolar illness – either mania or depression – after parturition, medications may need to be re-introduced, doses increased or new treatments initiated at this time.

In general, it is better for a woman to have a stable mood during pregnancy, delivery and the puerperium as an episode of mental illness can compromise her life, safety and welfare as much as it could compromise the fetus. Consequently, it is sometimes necessary to use pharmacotherapy that increases the risk of fetal abnormalities. This risk should be discussed with the mother and her partner – before pregnancy if possible – and the fetus should be monitored. Termination of pregnancy should be considered and discussed with the patient if a serious fetal abnormality occurs.

ECT can be a helpful treatment for both depression and mania during pregnancy.

After 20 weeks' gestation, it should be conducted in a facility with immediate access to obstetric resources because of concerns that ECT may trigger premature labour, although this seems very uncommon.

Required pharmacotherapy may preclude some women from breastfeeding; this should be assessed from advice available at the time. Sources of such advice include the TGA (http://www.tga.gov.au), Therapeutic Guidelines (http://www.tg.org.au) and children's hospitals.

BIPOLAR DISORDER IN CHILDREN AND ADOLESCENTS

Bipolar disorder rarely manifests during infancy and childhood, but some patients retrospectively report mood instability through their childhood. This can easily be confused with conduct disorder, impulsive behaviour and attention deficit hyperactivity disorder. Diagnosing bipolar disorder in infancy would be regarded as highly controversial.

In children with suspected bipolar disorder, psychosocial interventions are favoured rather than pharmacotherapy, along with close observation over time as childhood bipolar disorder is rare.

In adolescence, bipolar disorder should be distinguished from transient exuberance or a complication of covert substance abuse, especially of amphetamines. Adolescents with suspected bipolar disorder should be referred to a psychiatrist to confirm the diagnosis in order to avoid inappropriate treatment during this developmental phase or unwarranted delay when treatment is indicated.

RURAL PRACTICE

GPs in rural areas have needed to be more autonomous in treating patients with bipolar disorder than their urban colleagues because of restricted access to specialist services. The development of telepsychiatry and its spread from public into private practice will create opportunities for patient assessment and management not previously available.

RELAPSE

Relapse is more likely for patients who have had multiple episodes of bipolar illness and those who are partially compliant or non-compliant with treatment. Some patients may feel they have beaten the illness after a few weeks in remission and so reduce or cease medication. Others may reduce their medication so as to be stable but 'just a little high', and in doing so cause a relapse. Relapse can also occur in those who do all they can to keep well, reflecting the modest efficacy of available treatments.

CONCLUSION

GPs have an important role in the treatment of patients with bipolar disorder. They are uniquely placed to initially identify the illness and to contribute to the long-term management of patients in the community.

Psychological and social interventions are key components of treatment. Concomitant physical illnesses should be identified and treated. Pharmacotherapy should be managed, although this may often be in conjunction with a treating psychiatrist. ECT is a treatment option, especially as new ECT techniques are effective with few adverse cognitive effects. Polypharmacy is usually required, with atypical antipsychotics having an increasing role as mood stabilisers. GPs should be aware of the adverse effects profile of medications when used for long-term as well as short-term treatment. MT

REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed (DSM-5). Arlington, VA: American Psychiatric Association; 2013.
2. Goldberg JF, Perlis RH, Bowden CL, et al. Manic symptoms during depressive episodes in 1,380 patients with bipolar disorder: findings from the STEP-BD. Am J Psychiatry 2009; 166: 173-181.
3. Laursen TM, Wahlbeck K, Hällgren J, et al. Life expectancy and death by diseases of the circulatory system in patients with bipolar disorder or schizophrenia in the Nordic countries. PLoS One 2013; 8: e67133.
4. Psychotropic Expert Group. Therapeutic guidelines: psychotropic. Version 7. Melbourne: Therapeutic Guidelines Limited; 2013. [CORRECT?]
5. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disord 2013; 15: 1-44.
6. Frank E, Kupfer DJ, Ehlers CL, et al. Interpersonal and social rhythm therapy for bipolar disorder: integrating interpersonal and behaviour approaches. Behav Ther 1994; 17: 143-149.
7. Gauthier S, Wirth Y, Möbius HJ. Effects of memantine on behavioural symptoms in Alzheimer's disease patients: an analysis of the Neuropsychiatric Inventory (NPI) data of two randomised, controlled studies. Int J Geriatr Psychiatry 2005; 20: 459-464.
8. Lam DH, Hayward P, Watkins ER, Wright K, Sham P. Relapse prevention in patients with bipolar disorder: cognitive therapy outcome after 2 years. Am J Psychiatry 2005; 162: 324-329.
9. BALANCE Investigators; Geddes JR, Goodwin GM, Rendell J, et al. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. Lancet 2010; 375: 385-395.

COMPETING INTERESTS: Professor Tiller has acted as a consultant or given presentations for AstraZeneca, Eli Lilly, Lundbeck, Pfizer and Servier.