

# Chapter 17: Bipolar Disorder

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## Introduction

Bipolar disorder is a recurrent mood disorder in which the individual usually experiences symptoms of both mania and depression. However, it is diagnosed and indeed defined based on symptoms of mania (McIntyre et al., 2020). Typically, these symptoms occur episodically and comprise elevated or expansive mood coupled with increased energy along with changes in behaviour and cognition. In addition, episodes of depression (low mood, anhedonia and diminished energy) are characteristic of bipolar disorder and episodes of illness are separated by periods of euthymia, in which patients describe their mood and overall functioning as near normal.

The illness confers a significant burden on the individual and those around them and behavioural changes can pose a considerable risk – especially when impulsive and lacking in insight. By the same token, increased energy and drive along with novel thinking can be potentially productive and even be regarded as beneficial to some extent, depending on the individual's role and the extent to which this phase

of the illness can be contained. However, the disorder also carries with it a high risk of suicide.

As such, it has been speculated from time to time that bipolar disorder may be linked to creativity, and this is especially the case in artists who also suffered from bipolar disorder. For example, Robert Schuman and Vincent Van Gogh who had manic-depressive illness (the forerunner of bipolar disorder), were highly productive during their manic episodes, but it is not clear whether having manic symptoms was a key component of their artistic talent *per se*, or whether their increased productivity was simply a consequence of having more energy and time because of a diminished need for sleep.

The story of capturing bipolar disorder extends back almost two millennia to Aretaeus of Cappadocia, a practitioner in Rome who first connected the two poles of the illness noting ‘it appears to me that melancholy is the commencement and a part of mania’ (Aydemir and Malhi, 2007). In the centuries since, many others have made observations akin to this, but it was not until the late 19<sup>th</sup> century, when Emil Kraepelin definitively segregated the psychotic disorders based upon their longitudinal course that the forerunner of today’s bipolar disorder, namely manic-depressive illness, first took shape. He observed that some psychotic patients had a progressive and deteriorating course, and he labelled this as ‘dementia praecox’ (which subsumes modern-day schizophrenia). However, other patients had a more episodic course that culminated in a more favourable outcome, and he described this manic-depressive insanity (renamed subsequently as Manic-Depressive Illness).

Maintaining Kraepelin’s longitudinal perspective and emphasising recurrence, manic-depressive illness was used for most of the 20<sup>th</sup> century. However, in the 1980’s it was supplanted by the term bipolar disorder, which was introduced in DSM-III by the American Psychiatric Association (American Psychiatric Association, 1980) to give greater prominence to ‘polarity’ (i.e. manic and depressive poles of the illness) instead of cyclicity of trajectory over time. Subsequently bipolar disorder was subdivided into bipolar I and bipolar II based on whether patients experienced episodes of mania or only hypomania. In recent years this subtyping has been challenged.

The story of the treatment of bipolar disorder has run alongside the story of its nosology and classification. The treatment of bipolar disorder was revolutionised with the discovery that lithium had clear antimanic properties and a prophylactic effect on bipolar disorder, that prevented episodes of illness. Lithium salts were known to have a beneficial effect on health in general and in particular mood symptoms since the 19<sup>th</sup> century – especially through the work of Carl Lange (Schioldann, 2009), but it was an Australian psychiatrist, John Cade, who should be

credited for the discovery its antimanic properties (Schioldann, 2013). Lithium is one of the most unique drugs in psychiatry with its specific effects on bipolar disorder. It also has neuroprotective properties as well as being the only medication with anti-suicide properties (Malhi et al., 2018a).

## Epidemiology

Bipolar Disorder affects approximately 2.5% of the population worldwide, or 1 in 40 people globally (McIntyre et al., 2020). It is a chronic, recurrent illness that usually first emerges in late adolescence and early adulthood and as such it confers a significant degree of lifelong dysfunction and disability (Yunxi et al., 2024). Unlike depression, bipolar disorder impacts men and women equally (Vöhringer and Perlis, 2016).

## Aetiology

The aetiology of bipolar disorder is similar to that of depression (see Chapter 16), in that mood disorders are on the whole a product of a combination of genetic and environmental influences. Bipolar disorder has a strong genetic underpinning and a high heritability (approximately 70%), and an estimated 10 – 15% of first-degree relatives of people with bipolar disorder are likely to have a mood disorder (Gordovez and McMahon, 2020; McIntyre et al., 2020). But while genetic factors are important, psychosocial and psychological factors play an important role in the onset and, critically, the maintenance of the disorder and as such anticipating the illness remains a considerable challenge.

## Onset

Bipolar disorder affects all ages from adolescence through to old age, with peak onset late teens and early adulthood (Mitchell et al., 2004; Vöhringer and Perlis, 2016). Although bipolar disorder is defined by the occurrence of mania (see Diagnosis below), the illness usually first presents as episodes of depression that are clinically identical to those that characterise major depression. It is only when mania manifests, that a diagnosis of bipolar disorder can be made. Thus, there is often a significant delay between illness onset and diagnosis (an average of approximately 8 years) (Keramatian et al., 2022; Fritz et al., 2017).

## Diagnosis

The diagnosis of bipolar disorder is predicated on having mania, the symptoms of which can be regarded as the polar opposites of the symptoms of

depression (Figure 17.1 below, and previous Depression chapter). A notable exception is irritability, which permeates both poles of the illness (Bell et al., 2021). The symptoms of bipolar depression are clinically indistinguishable from those of major depression, and it is this commonality that causes both diagnostic delay and treatment difficulties. It is important to note that whilst bipolar depression and major depression are clinically indistinguishable, the treatments effective in managing major depression are not equally effective in treating bipolar depression.

### **Diagnostic criteria for manic episode**

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).

B. During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behaviour:

1. Inflated self-esteem or grandiosity.
2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
3. More talkative than usual or pressure to keep talking.
4. Flight of ideas or subjective experience that thoughts are racing.
5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity).
7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

D. The episode is not attributable to the physiological effects of a substance or another medical condition.

The main classificatory systems, the Diagnostic and Statistical Manual of Mental Disorders, 5<sup>th</sup> edition text revision (DSM-5-TR) (American Psychiatric Association, 2022) and the International Classification of Diseases, 11<sup>th</sup> revision (ICD-11) (World Health Organization, 2019) recognise subtypes of bipolar disorder and draw a distinction between mania and milder forms. They divide bipolar disorder into two subtypes, mentioned earlier, the basis of which has been critically

contended (Angst et al., 2019; Malhi et al., 2016a). Bipolar I disorder describes patients who experience a manic episode, whereas bipolar II is used to denote those that experience manic *symptoms* but do not meet the criteria for an episode of mania. Hence, these ‘episodes’ are termed hypomania. In other words, hypomania is regarded as a less severe form of mania that typically has fewer symptoms and a shorter duration than mania.

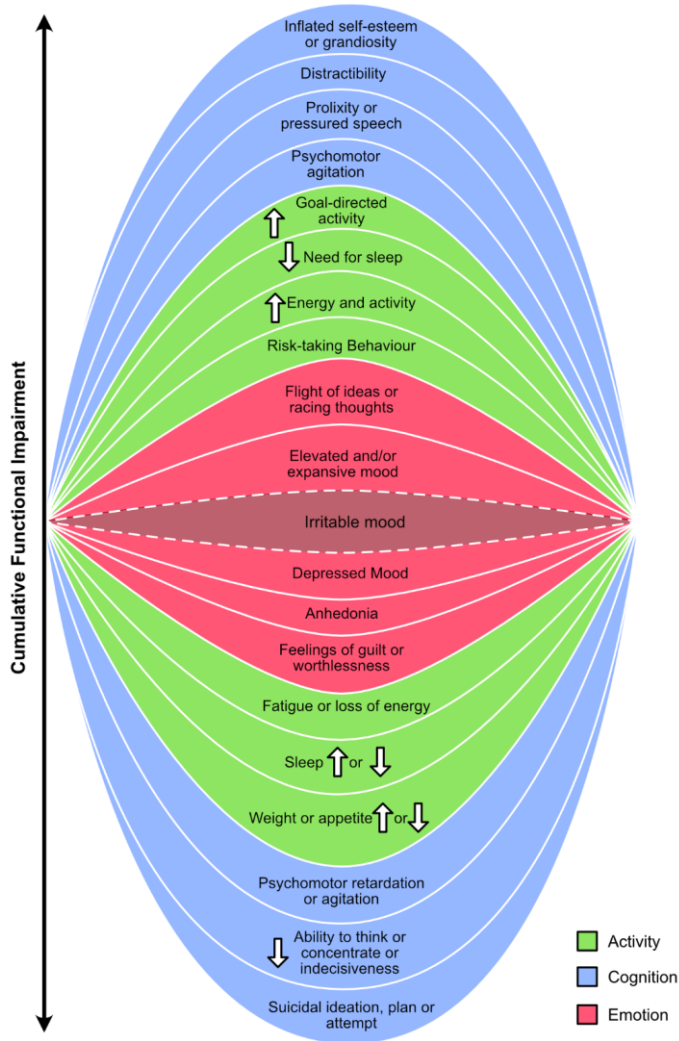
The partitioning of bipolar disorder occurred more than 40 years ago and the debate concerning the existence of a bipolar II subtype centres on the fact that no clear differences have been found between bipolar I and II with regard to symptomatology, and there are no meaningful implications for management. Hence why, in terms of treatment, the RANZCP clinical practice guidelines for mood disorders consider only bipolar disorder and do not recognise any subtypes (Malhi et al., 2021).

For the purposes of diagnosing bipolar disorder, the occurrence of manic symptoms is an essential requirement. Further, once an individual experiences these symptoms they are automatically diagnosed as having bipolar disorder even if they have previously been diagnosed as having major depression. Note, once bipolar disorder has been diagnosed subsequent episodes of depression are termed bipolar depression.

## Mixed States

The co-occurrence of symptoms from both the manic and depressive poles of mood are categorised as mixed states, or mixed mood episodes. Mixed states are very heterogeneous, firstly because they may stem from a variety of causes, and secondly because of the different symptoms of mania and depression that can be variously combined to produce a myriad of presentations. Current taxonomies do not allow for the adequate capturing of mixed mood episodes, with DSM-5-TR utilising a ‘mixed features’ specifier, that can be ‘attached’ to an episode of either depression or mania (American Psychiatric Association, 2022).

Mixed episodes (or mixed features) are perhaps best understood by ‘deconstructing’ the range of mood symptoms from both poles of the illness and recognising that there can be various combinations of symptoms related to changes in activity, cognition, and emotion, as described in the Activity, Cognition and Emotion (ACE) Model (Malhi et al., 2018b).

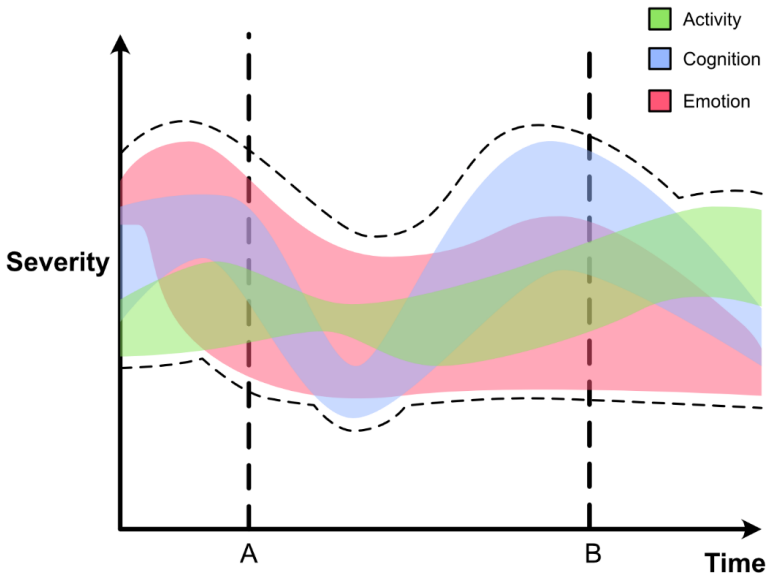


**Figure 17.1.** Symptoms of depression and mania in bipolar disorder, adapted from Malhi et al. (2021). The symptoms that may occur in an episode of either mania or depression are shown as mirror images. These symptoms have been coloured according to the ACE domains (Green = activity; Blue = cognition; Red = emotion). For further detail, see ‘ACE Model’ section below. These symptoms, produce cumulative functional impairment but are not ranked in any particular order (i.e. inflated self-esteem is not more indicative of mania than elevated and/or expansive mood). Irritability (‘irritable mood’ within DSM-5-TR) is present in both mania and depression.

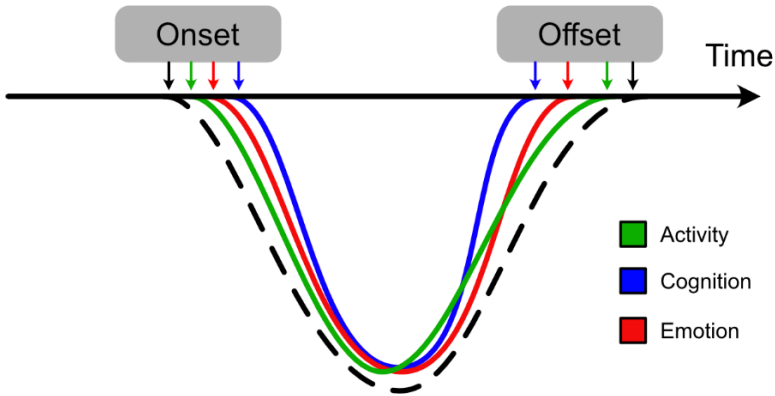
The existence of mixed states suggests that the view of bipolar disorder as a disorder of two states (mania and depression) is incomplete. Furthermore, the partitioning of mania into subtypes (I and II) that are separate categories of disorder is perhaps not the most accurate reflection of clinical reality. Consequently, in recent years, a dimensional perspective has gained ground and bipolar disorder is increasingly regarded as a spectrum with expressions of illness that span all manner of admixtures between mania and depression. This spectrum view of symptoms also accommodates expressions of major depression therefore connecting mood disorders (depressive and bipolar) and forming one set of contiguous illnesses. This dimensional view forms the basis for treatment of mood disorders.

## The ACE Model

The Activity, Cognition and Emotion (ACE) Model provides a useful framework to conceptualise the symptoms of mania and depression in bipolar disorder and the symptoms of major depression. The ACE Model categorises manic and depressive symptoms according to the 3 domains of Activity, Cognition and Emotion, allowing for a more granular appraisal of symptoms and how these change over time. It is therefore best applied longitudinally as well as cross-sectionally (see Figures 17.2 and 17.3). Importantly, the architecture of the ACE model allows mixed states to be accommodated automatically and without invalidating either depression or mania. In practice, mixed mood presentations account for approximately one-third of mood episodes in patients with bipolar disorder.



**Figure 17.2.** Change in components of ACE with time, adapted from Malhi et al. (2021). The schematic shows the three Activity (green), Cognition (blue) and Emotion (red) that vary in severity over time. The overall range of severity (peak and trough) is shown with a black dashed line. At points A and B, the total severity appears to be the same. However, it is evident that individual domains vary differentially. For example, at point A it is emotion that is most prominent, followed by cognition, but later, at point B this order is reversed, and cognition becomes the major contributor to severity. Thus, by mapping domains and individual symptoms, rather than the syndrome as a whole, the ACE model permits a more granular examination of changes over time.



**Figure 17.3.** Differential timing in onset and offset of symptoms – illustrated by ACE, adapted from Malhi et al. (2021). The black dashed line shows the overall change in symptoms with depression emerging gradually and resolving slowly. However, within this, it can be seen that changes in activity precede those of emotion and cognition and that in response to treatment or spontaneous remission, it is the cognitive symptoms that recover first followed by emotion, with activity taking the longest. This is important when monitoring the effects of treatments and also when communicating to patients what to anticipate as regards recovery. Often as initial symptoms remit, they may lead a patient to believe that they have recovered and may even prompt them to consider stopping treatment. But as is evident, some symptoms take considerably longer to remit and therefore it is important to emphasise to patients that they continue with treatment until they have regained full function.

## Course and Impact

By its very nature, bipolar disorder is a recurrent illness, in which almost one-half of all individuals who have experienced a mood episode will have a further episode of illness. In most individuals, the depressed phase is more common than mania, with many patients spending much of their time depressed. However, even though the illness is termed bipolar disorder, approximately a third of episodes are likely to be an admixture of manic and depressive symptoms (mixed episodes).

As bipolar disorder typically emerges during adolescence and is associated with cognitive impairment (Chakrabarty et al., 2021) and brain tissue loss (Keramatian et al., 2021), it confers significant functional disability, particularly among young people aged 15-24 years (ranked third of all mental disorders) (GBD

2019 Mental Disorders Collaborators, 2022). Further, mortality studies indicate that bipolar disorder is associated with a loss of approximately 10 – 20 potential years of life. This is not solely because of suicide – indeed a significant proportion of this loss is because of the effects of the illness on the general medical health of individuals.

In addition, bipolar disorder carries the highest risk of suicide of any mental illness, (30-60 times that of the general population) and consequentially, approximately 30 – 50% of adult bipolar patients have a history of suicide attempts.

## Management of Bipolar Disorder

### Diagnosis and Formulation

The diagnosis of bipolar disorder is inherently complicated, partly because of the natural history of the illness, which typically begins with depression in adolescence (Ghaemi et al., 1999). Hence why several episodes of depression have usually occurred before mania emerges. However, as noted, the diagnosis of bipolar disorder can only be made once manic symptoms appear, and so there is often a delay in diagnosis which, in some cases, can be up to a decade. Another important diagnostic challenge is that some of the behaviours or ‘symptoms’ typical of the turmoil of adolescence, such as increased energy, not wanting to sleep, taking risks, and having heightened libidinal drive may be misconstrued as manic symptoms. The presentation can also be confounded by personality factors, especially when there is affective instability, and the symptoms of bipolar disorder can easily be obscured by those caused by substance misuse, including for example stimulants and alcohol. This is important because in addition to psychosocial adversity, substance misuse is associated with an earlier age of onset of bipolar disorder (Post et al., 2016).

A comprehensive assessment of an individual suspected of having bipolar disorder is essential. This should be repeated overtime as a longitudinal perspective is critical for accurate diagnosis and tailored management. It is important, for example, to establish if there is any specific pattern to the illness (such as seasonality), noting the duration of depression and mania, and periods of remission and recovery, so as to map the phases of illness (mania, mixed, depression), determine predominant polarity (that is, whether the person experiences mainly depression, mania or mixed states) and whether there is any sequence or order in which episodes typically occur. It is also important to note triggering events to individual episodes and how these have responded to any measures that may have been instituted. This includes identifying antidepressant-induced elevated states, which will necessitate withdrawing the medication promptly under close

supervision. It is again important to identify clearly the extent to which substances such as alcohol and other prescribed and illicit drugs precipitate episodes.

The context in which the illness arises is also important. Here, early trauma, family history, general medical health, developmental factors, life events, personality structure, current psychosocial issues and interpersonal context should be carefully assessed and reviewed. Pieced together, this information can be synthesized to provide a basis for formulating the nature of the illness, the problems that it is causing for the individual, and the factors that have likely contributed to it. Thus, understanding context is important for determining optimal management.

## Treatment Principles

The management of bipolar disorder is more complex than that of major depression. First, bipolar disorder has additional acute episodes, namely mania and mixed presentations – that occur as well as episodes of depression. Second, the emphasis of treatment is not solely upon acute management, but also on long-term maintenance and prophylaxis, and so continuity of care and the development of a robust therapeutic relationship are essential.

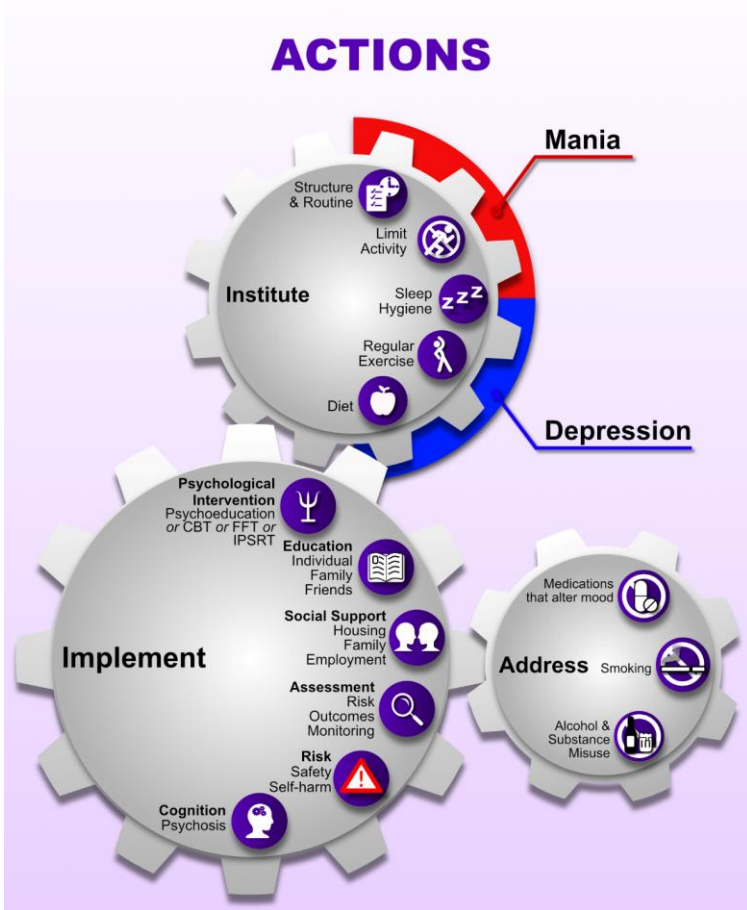
Maintenance therapy is of particular importance in the management of bipolar disorder, because of the chronic and recurrent nature of the illness, and because it is only during this phase of comparative mood stability that, in addition to sustaining wellness, preventative strategies that will avert future episodes can be implemented.

As is the case for depression, the *Actions, Choices, Alternatives* framework should be used for the management of bipolar disorder. This framework provides a systematic and structured approach to the management of this complex illness.

## Actions

The *Actions* for the management of bipolar disorder need to be considered in relation to the phase of the illness being treated (see Figure 17.4 below). Broadly speaking, *Actions* can be grouped into three types. First, those that can be instituted by the patient with appropriate support, such as lifestyle changes, where it is in the individual's best interest to maintain a healthy diet, engage in regular exercise, and ensure they maintain good sleep hygiene and stable circadian rhythms. For some patients, bipolar relapses are clearly linked to a disruption of core biological circadian rhythms such as the sleep-wake cycle. For example, missing sleep because of desire (e.g., socializing) or necessity (work commitments) or as a consequence of

travel (jet lag). Hence, the development of interpersonal social rhythm therapy (IPSRT) that is aimed at stabilizing circadian rhythms.



**Figure 17.4.** Actions for the management of bipolar disorder, adapted from Malhi et al. (2020a). The *Actions* for the management of bipolar disorder should be considered according to the phase of the illness being treated. For example, in the management of acute mania, limiting activity and instituting structure and routine are important as is restoration of normal sleep patterns. Restoring sleep is also important when treating bipolar depression, but in this case encouraging activity and exercise is necessary rather than restricting this. The key to long-term successful management of bipolar disorder is maintenance therapy and for this, psychoeducation and psychological interventions are essential, alongside restoration of normal biorhythms.

In addition, there are *Actions* that also must be implemented, such as the provision of psychoeducation to the individual, their family and friends, concerning both the illness and its prognosis as well as its treatments and broader management approaches. It is important to note that psychological interventions have been included as *Actions* because they should be offered to all patients, as early as possible, as they are particularly effective if implemented from the outset, and especially in conjunction with pharmacotherapy.

Finally, it is often necessary to address negative habits that the individual has developed (e.g., smoking, alcohol and substance misuse), and this usually requires the assistance of specialists.

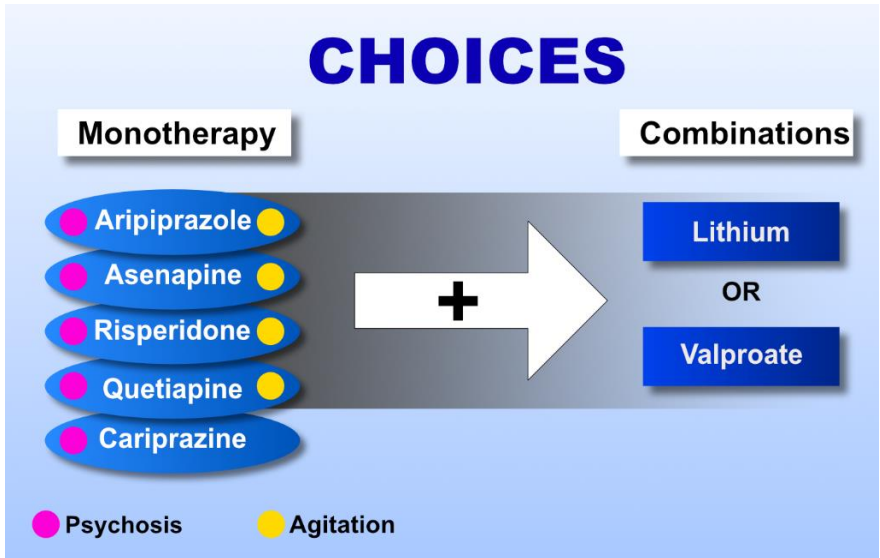
## Psychological Interventions

Adjunctive psychological intervention is central to the management of bipolar disorder (Murray, 2018; Chen et al., 2019; McIntyre et al., 2013). Four therapeutic evidence-based approaches include: Psychoeducation, Cognitive-Behavioural Therapy (CBT; see Chapter 33), Family-focused Therapy (FFT), and Interpersonal and Social Rhythm Therapy (IPSRT) (Malhi et al., 2021). These four have a common treatment approach (active collaboration, skill-development focus), and share significant therapeutic content. Psychological interventions are foundational *Actions* in the management of bipolar disorder, but unlike the management of depression, they are not a substitute for pharmacotherapy.

## Mania – Choices

The pharmacotherapy of mania encompasses the management of risk and the treatment of its three main components: acute manic symptoms, behavioural disturbance and cognitive symptoms and/or psychosis. It is important to note that the three components have different timescales of response to treatment. Hospitalisation is often required to contain risk, but in some cases, treatment can be administered as an out-patient. Most medications used to treat mania treat more than one syndromal component at a time, e.g., address agitation and psychosis as well as mania (see Figure 17.5).

The treatment of mania often requires combinations of medications, but ideally this should include a mood stabilising agent (MSA). The medications that are most commonly used are shown in Figure 17.5.



**Figure 17.5.** Choice treatments for the management of mania, adapted from Malhi et al. (2020a). Choice agents address all three components: mania, agitation, and psychosis. Where possible, monotherapy and oral treatment should be given preference. If monotherapy is insufficient then lithium or valproate can be added, and these can remain in place as the antipsychotic is gradually removed once the acute episode subsides. If combination therapy is insufficient, then *Alternatives* may need to be considered. Note that valproate is not recommended for women of childbearing age because of the high rates of teratogenicity and developmental delay among fetuses exposed to valproate

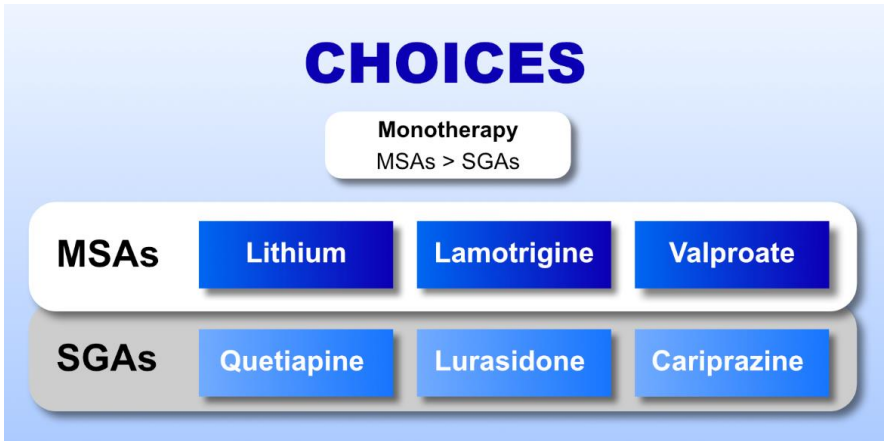
### Mania – Alternatives

On occasion, *Choice* medications, even as combinations, may be insufficient, and *Alternatives* need to be considered. Here again, both monotherapy and combination strategies can be employed.

Another *Alternative*, if all else fails, is ECT, which may be indicated from the outset if, for example, pharmacotherapy cannot be tolerated or is undesirable (e.g. pregnancy). For further detail regarding ECT, see the later ‘ECT’ section in which the recommendations for administration are addressed collectively across all phases of bipolar disorder.

## Bipolar Depression – Choices

Amongst the various phases of bipolar disorder, the treatment of bipolar depression is the most challenging. The medications used to treat bipolar depression belong to two broad groups: mood stabilising agents (MSAs) and second-generation antipsychotics (SGAs). Each group comprises three monotherapy options (see Figure 17.6). Where possible, mood stabilising agents should be given preference because they can be continued into maintenance therapy and are less likely to have significant long term side effects. Lithium for example is a good maintenance therapy and it is the only medication that protects against suicide.



**Figure 17.6.** Choice treatments for the management of bipolar depression, adapted from Malhi et al. (2020a). Mood stabilising agents (MSAs) include lithium, lamotrigine and valproate (in sequence) and these are preferable to Second generation antipsychotics (SGAs) which include quetiapine, lurasidone and cariprazine (in sequence).

## Bipolar Depression – Alternatives

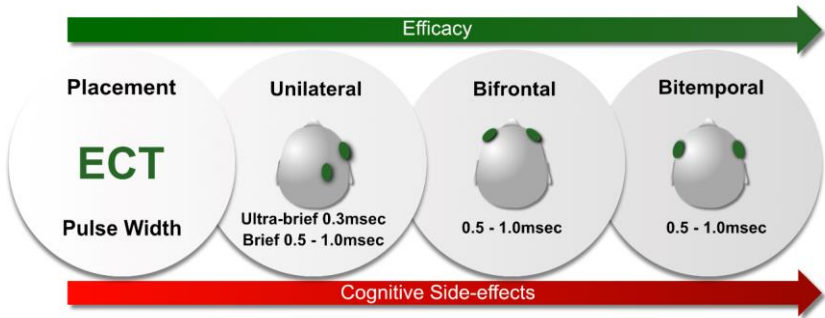
When managing bipolar depression, it is not uncommon for the above monotherapy *Choices* to be insufficient, and so *Alternatives* may need to be considered as well as combinations of medications.

The combinations of medications in the treatment of bipolar depression can be easily remembered as combinations between either an MSA and an SGA, or an agent from either of these groups, with an antidepressant (for further detail, see the RANZCP Mood Disorders Clinical Practice Guidelines 2020). It is important to note that antidepressants, when prescribed on their own, may cause mood instability in bipolar disorder and therefore should ideally only be prescribed alongside an MSA

or SGA. ECT may be indicated, particularly if there are significant melancholic depressive features or psychotic symptoms present (see ‘ECT’ section below).

## ECT

ECT (see Chapter 36) is an important *Alternative* across all acute presentations of bipolar disorder, it has proven efficacy in mania (Perugi et al., 2017), bipolar depression (Agarkar et al., 2018; Bahji et al., 2019) and mixed states (Medda et al., 2015). The effectiveness and potential side effects of ECT is determined largely by placement of the electrodes and the pulse width of the current applied (see Figure 17.7).



**Figure 17.7.** ECT in bipolar disorder, adapted from Malhi et al. (2020b).

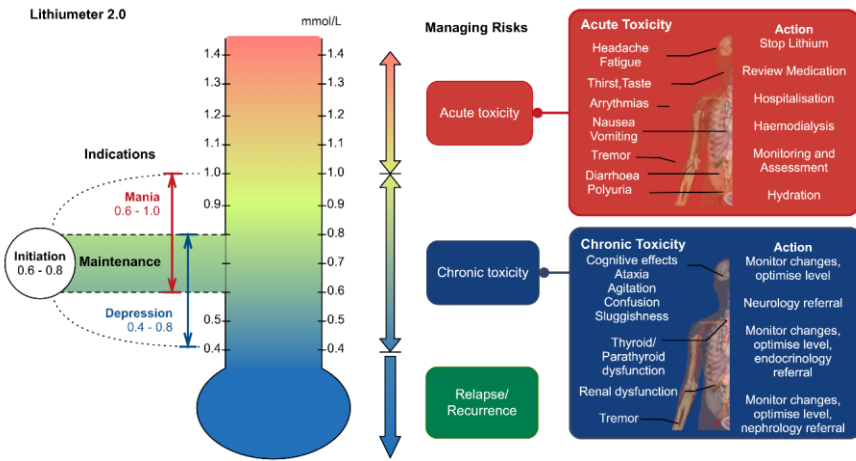
Electroconvulsive therapy is effective in treating bipolar depression, mania and mixed states. Increased efficacy can be achieved by increasing the pulse-width and by shifting placement.

## Lithium

In the sections above lithium has featured prominently and as such it warrants special consideration especially as it holds a unique position in the management of bipolar disorder, and it is an element about which there is often some confusion.

The properties of lithium were first definitively identified by John Cade who tested its effects on animals and himself before trialling it on his patients (Malhi, 2010; Shorter, 2009). It is the only true mood stabiliser as it not only has acute antimanic and antidepressant effects but also provides prophylaxis against both depression and mania. Further, it reduces the likelihood of suicide and is neuroprotective. Nevertheless, it is not as widely used as it should be because of its slow onset of action and the need for plasma monitoring (see Figure 17.8) (Rhee et

al., 2020). In addition, it can cause serious long term side effects involving renal and thyroid function and its acute side effects can also be troublesome.



**Figure 17.8.** Lithiummeter 2.0, adapted from Malhi et al. (2016b). The Lithiummeter demonstrates the ideal serum concentration ranges of lithium for the various stages of treating bipolar disorder. The red and blue boxes illustrate the acute and chronic toxicity effects of lithium, and the actions needed to address these.

## Conclusion

This chapter has outlined the framework for diagnosis and management of the manic and depressive phases of bipolar disorder. However, in real-world practice, bipolar disorder is a complex and heterogenous disorder, both in terms of diagnosis and treatment. In addition, its management is complicated by its chronicity, its cyclical nature, and the need for maintenance treatment. Thus, further reading regarding the management of this disorder is highly encouraged, and more detailed information regarding the nuances of treatment and the management of bipolar disorder in clinical practice can be found in the 'Further reading' list at the end of this textbook.

## Further Reading

Please note, the clinical practice guidelines and the two summary documents are freely available online.

- McIntyre, R. S., Berk, M., Brietzke, E., Goldstein, B. I., López-Jaramillo, C., Kessing, L. V., ... & Mansur, R. B. (2020). Bipolar disorders. *The Lancet*, 396(10265), 1841-1856.
- Malhi, G. S., Bell, E., Bassett, D., Boyce, P., Bryant, R., Hazell, P., ... & Murray, G. (2021). The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Australian & New Zealand Journal of Psychiatry*, 55(1), 7-117.
- Malhi, G. S., Bell, E., Boyce, P., Bassett, D., Berk, M., Bryant, R., ... & Murray, G. (2020). The 2020 Royal Australian and New Zealand College of psychiatrists clinical practice guidelines for mood disorders: Bipolar disorder summary. *Bipolar disorders*, 22(8), 805-821..
- Malhi, G. S., Irwin, L., Hamilton, A., Morris, G., Boyce, P., Mulder, R., & Porter, R. J. (2018). Modelling mood disorders: an ACE solution?. *Bipolar disorders*, 20, 4-16.
- Malhi, G. S., Bell, E., Singh, A. B., Bassett, D., Berk, M., Boyce, P., ... & Murray, G. (2020). The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders: major depression summary. *Bipolar disorders*, 22(8), 788-804.
- Malhi, G. S., Gershon, S., & Outhred, T. (2016). Lithiumeter: Version 2.0. *Bipolar disorders*, 18(8), 631-641.

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## References

- Agarkar S, Hurt SW and Young RC (2018) Speed of antidepressant response to electroconvulsive therapy in bipolar disorder vs. major depressive disorder. *Psychiatry Research* 265: 355-359.
- American Psychiatric Association (1980) *Diagnostic and statistical manual of mental disorders*. Washington, D.C: American Psychiatric Association.
- American Psychiatric Association (2022) *Diagnostic and statistical manual of mental disorders : DSM-5-TR*. Washington, DC: American Psychiatric Association Publishing.
- Angst J, Rössler W, Ajdacic-Gross V, et al. (2019) Differences between unipolar mania and bipolar-I disorder: Evidence from nine epidemiological studies. *Bipolar Disorders* 21(5): 437-448.
- Aydemir O and Malhi GS (2007) Aretaeus of Cappadocia. *Acta Neuropsychiatrica* 19(1): 62-63.
- Bahji A, Hawken ER, Sepehry AA, et al. (2019) ECT beyond unipolar major depression: systematic review and meta-analysis of electroconvulsive therapy in bipolar depression. *Acta Psychiatrica Scandinavica* 139(3): 214-226.
- Bell E, Boyce P, Porter RJ, et al. (2021) Irritability in Mood Disorders: Neurobiological Underpinnings and Implications for Pharmacological Intervention. *CNS Drugs* 35(6): 619-641.
- Chakrabarty T, Torres IJ, Su WW, et al. (2021) Cognitive subgroups in first episode bipolar I disorder: Relation to clinical and brain volumetric variables. *Acta Psychiatrica Scandinavica* 143(2): 151-161.
- Chen M, Fitzgerald HM, Madera JJ, et al. (2019) Functional outcome assessment in bipolar disorder: A systematic literature review. *Bipolar Disorders* 21(3): 194-214.
- Fritz K, Russell AMT, Allwang C, et al. (2017) Is a delay in the diagnosis of bipolar disorder inevitable? *Bipolar Disorders* 19(5): 396-400.
- GBD 2019 Mental Disorders Collaborators (2022) Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2013;2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet Psychiatry* 9(2): 137-150.
- Ghaemi SN, Sachs GS, M. Chiou A, et al. (1999) Is bipolar disorder still underdiagnosed? Are antidepressants overutilized? *Journal of Affective Disorders* 52(1): 135-144.
- Gordovez FJA and McMahon FJ (2020) The genetics of bipolar disorder. *Molecular psychiatry* 25(3): 544-559.
- Keramatian K, Chakrabarty T, Saraf G, et al. (2021) Grey matter abnormalities in first-episode mania: A systematic review and meta-analysis of voxel-based morphometry studies. *Bipolar Disorders* 23(3): 228-240.

- Keramatian K, Pinto JV, Schaffer A, et al. (2022) Clinical and demographic factors associated with delayed diagnosis of bipolar disorder: Data from Health Outcomes and Patient Evaluations in Bipolar Disorder (HOPE-BD) study. *Journal of Affective Disorders* 296: 506-513.
- Malhi GS (2010) History of the Introduction of Lithium into Medicine and Psychiatry. *Acta Neuropsychiatrica* 22(3): 161.
- Malhi GS, Bell E, Bassett D, et al. (2021) The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Australian & New Zealand Journal of Psychiatry* 55(1): 7-117.
- Malhi GS, Bell E, Boyce P, et al. (2020a) The 2020 Royal Australian and New Zealand College of psychiatrists clinical practice guidelines for mood disorders: Bipolar disorder summary. *Bipolar Disorders* 22(8): 805-821.
- Malhi GS, Bell E, Singh AB, et al. (2020b) The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders: Major depression summary. *Bipolar Disorders* 22(8): 788-804.
- Malhi GS, Byrow Y, Boyce P, et al. (2016a) Why the hype about subtype? Bipolar I, bipolar II-it's simply bipolar, through and through! *Australian and New Zealand Journal of Psychiatry* 50(4): 303-306.
- Malhi GS, Das P, Outhred T, et al. (2018a) Understanding suicide: Focusing on its mechanisms through a lithium lens. *Journal of Affective Disorders* 241: 338-347.
- Malhi GS, Gershon S and Outhred T (2016b) Lithiummeter: Version 2.0. *Bipolar Disorders* 18(8): 631-641.
- Malhi GS, Irwin L, Hamilton A, et al. (2018b) Modelling mood disorders: An ACE solution? *Bipolar Disorders* 20: 4-16.
- McIntyre RS, Berk M, Brietzke E, et al. (2020) Bipolar disorders. *The Lancet* 396(10265): 1841-1856.
- McIntyre RS, Cha DS, Soczynska JK, et al. (2013) Cognitive deficits and functional outcomes in major depressive disorder: Determinants, substrates, and treatment interventions. *Depression and Anxiety* 30(6): 515-527.
- Medda P, Toni C, Mariani MG, et al. (2015) Electroconvulsive therapy in 197 patients with a severe, drug-resistant bipolar mixed state: treatment outcome and predictors of response. *The Journal of clinical psychiatry* 76(9): 1168-1173.
- Mitchell PB, Slade T and Andrews G (2004) Twelve-month prevalence and disability of DSM-IV bipolar disorder in an Australian general population survey. *Psychological medicine* 34(5): 777-785.
- Murray G (2018) Adjunctive psychosocial interventions for bipolar disorder: Some psychotherapeutic context for the Canadian Network for Mood and Anxiety Treatments (CANMAT) & International Society for Bipolar Disorders (ISBD) guidelines. *Bipolar Disorders* 20(5): 494-495.

- Perugi G, Medda P, Toni C, et al. (2017) The Role of Electroconvulsive Therapy (ECT) in Bipolar Disorder: Effectiveness in 522 Patients with Bipolar Depression, Mixed-state, Mania and Catatonic Features. *Current neuropsychopharmacology* 15(3): 359-371.
- Post RM, Altshuler LL, Kupka R, et al. (2016) Age of onset of bipolar disorder: Combined effect of childhood adversity and familial loading of psychiatric disorders. *Journal of psychiatric research* 81: 63-70.
- Rhee TG, Olfson M, Nierenberg AA, et al. (2020) 20-Year Trends in the Pharmacologic Treatment of Bipolar Disorder by Psychiatrists in Outpatient Care Settings. *American Journal of Psychiatry* 177(8): 706-715.
- Schioldann J (2009) Introduction pages. *History of the Introduction of Lithium into Medicine and Psychiatry: Birth of Modern Psychopharmacology 1949*. Adelaide: Adelaide Academic Press and Brascoe Publishing, pp.xix-xxv.
- Schioldann J (2013) From guinea pigs to manic patients: Cade's 'story of lithium'. *Australian & New Zealand Journal of Psychiatry* 47(5): 484-486.
- Shorter E (2009) The history of lithium therapy. *Bipolar Disorders* 11(s2): 4-9.
- Vöhringer PA and Perlis RH (2016) Discriminating Between Bipolar Disorder and Major Depressive Disorder. *Psychiatric Clinics* 39(1): 1-10.
- World Health Organization (2019) *International statistical classification of diseases and related health problems (11th Revision)*. Geneva: World Health Organisation.
- Yunxi Z, Yifan C, Xiaoying S, et al. (2024) Global, regional and national burdens of bipolar disorders in adolescents and young adults: a trend analysis from 1990 to 2019. *General Psychiatry* 37(1): e101255.