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## **The 2020 Royal Australian and New Zealand College of Psychiatrists**

### **Clinical Practice Guidelines for Mood Disorders: Bipolar Disorder**

#### **Summary**

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## **Abstract**

### **Objectives:**

To provide a succinct, clinically useful summary of the management of bipolar disorder, based on the 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders (MDcpg<sup>2020</sup>).

### **Methods:**

To develop the MDcpg<sup>2020</sup>, the mood disorders committee conducted an extensive review of the available literature to develop evidence-based recommendations (EBR) based on National Health and Medical Research Council (NHMRC) guidelines. In the MDcpg2020, these recommendations sit alongside consensus-based recommendations (CBR) that were derived from extensive deliberations of the mood disorders committee, who drew on their expertise and clinical experience. Therefore, this guideline summary is an abridged version that focuses on bipolar disorder. In collaboration with international experts in the field, it synthesises the key recommendations made in relation to the diagnosis and management of bipolar disorder.

### **Results:**

The bipolar disorder summary provides a systematic approach to diagnosis, and a logical clinical framework for management. It addresses the acute phases of bipolar disorder (mania, depression and mixed states) and its longer-term management (maintenance and prophylaxis). For each phase it begins with *Actions*, which include important strategies that should be implemented from the outset wherever possible. These include for example, lifestyle changes, psychoeducation and psychological interventions. In each phase, the summary advocates the use of *Choice* medications for pharmacotherapy, which are then used in combinations along with additional *Alternatives* to manage acute symptoms or maintain mood stability and provide prophylaxis. The summary also recommends the use of ECT for each of the acute phases but not for maintenance therapy. Finally, it briefly considers bipolar disorder in children and its overlap in adults with borderline personality disorder.

### **Conclusions:**

The bipolar disorder summary provides up to date guidance regarding the management of bipolar disorder, as set out in the MDcpg<sup>2020</sup>. The recommendations are informed by evidence and clinical expertise and experience. The summary is intended for use by psychiatrists, psychologists and primary care physicians but will be of interest to anyone involved in the management of patients with bipolar disorder.

## **Introduction**

The Royal Australian and New Zealand College of Psychiatrists has published Clinical Practice Guidelines for mood disorders (MDcpg<sup>2020</sup>)<sup>1</sup>, updating earlier guidelines published

in 2015 (MDcpg<sup>2015</sup>). The objective of this paper is to provide a summary of these guidelines as they pertain to the management of bipolar disorder.

They are intended principally for psychiatrists, psychologists, and primary care physicians, but will also be useful to nursing and allied mental health staff. They may also be of interest to patients and health service administrators.

The present summary document aims to serve as a ready reference for clinicians. Readers wanting more comprehensive information are encouraged to consult the much more detailed and contextualised MDcpg<sup>2020</sup>, and other contemporary guidelines for the management of bipolar disorder.

The composition of the mood disorders committee, and the methods used to develop the full guidelines are detailed in the MDcpg<sup>2020</sup>. For the purposes of the summary, additional members with mood disorders expertise and extensive experience of international guideline development were co-opted to ensure the recommendations within the summary have relevance worldwide.

Adhering to the principles of the MDcpg<sup>2020</sup>, the present summary makes two types of recommendations that reflect the deliberations used to formulate advice. First, evidence-based recommendations (EBRs) were formulated using the Australian National Health and Medical Research Council (NHMRC) levels of evidence for treatment studies<sup>2</sup> and graded accordingly (e.g., EBR level I, II, etc). Second, where the existing evidence base for an intervention was insufficient, absent or its clinical impact and relevance uncertain, the committee members used their expertise and clinical experience to develop a consensus on the clinical usefulness, and this formed a consensus-based recommendation (CBR). It is important to note that the process involved extensive discussion and iteration of information, and that was subject to revision in light of new information and feedback from expert consultation and peer review.

## **Epidemiology**

Bipolar disorder, that features mania, affects approximately 1% of the population<sup>3</sup>. Broader conceptualisations, such as the bipolar spectrum, more than double this figure to at least 2.5%, meaning that 1 in 40 individuals worldwide may have symptoms that fit with bipolarity<sup>4</sup>. It is important to note that these descriptions (bipolar disorder, bipolar spectrum)

are not equivalents of the older term manic-depressive illness<sup>a</sup> and that episodes of illness in bipolar disorder comprise symptoms that signal exacerbations of an underlying illness process<sup>5,6</sup>.

Clinically, bipolar disorder is a recurrent illness and, following episodes of depression and mania, almost half of individuals will experience a further episode within two years if the illness is untreated<sup>7</sup>. In most individuals, the depressed phase is more common than mania, with many patients spending much of their time experiencing depression and approximately a third of episodes are likely to be an admixture of manic and depressive symptoms (mixed episodes)<sup>8</sup>. Bipolar disorder that features mania is equally common in women and men, and manifests clinically from adolescence through to old age, with peak onset in late teens and early adulthood<sup>9,10</sup>.

## Diagnosis and Classification

### Bipolar Disorder

The diagnosis of bipolar disorder is predicated on mania; the symptoms of which can be regarded as the polar opposites of the symptoms of depression (see Figure 1) - with the exception of a few non-specific symptoms that appear not to be aligned strongly with either pole<sup>4</sup>. It is important to note that some of these symptoms (e.g., increased libido, disinhibition) can only be experienced post-puberty, thus limiting the diagnosis of bipolar disorder in young children. This is partly why the diagnosis of paediatric bipolar disorder remains a source of controversy (see [later](#)).

The main classificatory systems, the Diagnostic and Statistical Manual of Mental Disorders, 5<sup>th</sup> edition (DSM-5)<sup>11</sup> and the International Classification of Diseases, 11<sup>th</sup> revision (ICD-11)<sup>12</sup> subtype bipolar disorder and differentiate between mania and milder forms<sup>13</sup>. But recently, there has been greater interest in dimensional approaches to classification, and, informed by empirical studies and clinical experience, alternative schema and cut-offs for putative bipolar syndromes have been proposed<sup>14-16</sup>.

### Mixed States

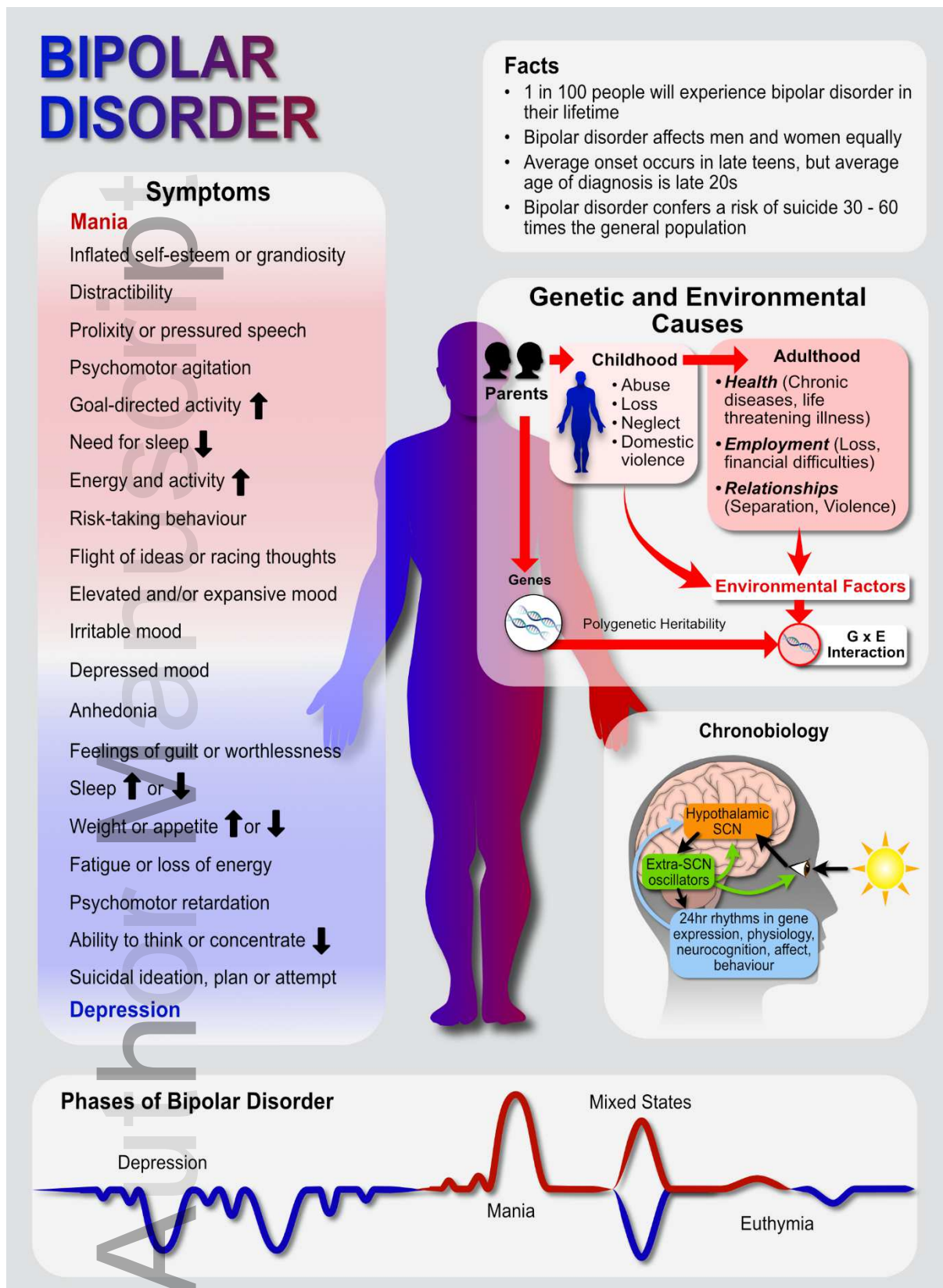
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<sup>a</sup> Emphasised recurrence

Mixed states, in which the symptoms of mania and depression co-occur, have been dealt with differently in recent iterations of the major taxonomies. DSM-IV for example, coded these presentations as mixed episodes, however DSM-5 has demoted these presentations to the status of ‘features’, in which symptoms from the opposite pole are used to specify either a major depressive, or manic, episode<sup>17</sup>. There remains concern that this may risk overdiagnosis of mixed states and, as with so many aspects of bipolar disorder, our understanding would be propelled by better biomarkers supplementing diagnosis<sup>18,19</sup>. However, the DSM-5 specifier does encourage clinicians not to default prematurely to a bipolar diagnosis and consider more carefully the nature of mixed states.

### Activity, Cognition and Emotion (ACE) Model

One way of navigating these classificatory difficulties is to revive Weygandt and Kraepelin’s perspective, in which cognition and activity were given equal weighting to mood<sup>19,20</sup>. Recent explications of this view has been championed through the ACE model<sup>20</sup>, which places greater emphasis on domains of symptoms, diminishes the central role of emotions and more readily allows for admixtures of symptoms from both ‘poles’. The architecture of the ACE model readily accommodates mixed states and therefore arguably better reflects reality (see Malhi et al., 2019<sup>19</sup> for full description and discussion).



**Figure 1. Summary of Bipolar Disorder.** The schematic shows the symptoms of bipolar disorder, extending from mania through to depression. It is important to note that many of these are mirror opposites (e.g. increased and decreased energy), while other are non-specific

(e.g. irritable mood). The symptoms of bipolar disorder manifest as episodes of depression, mania or mixed states, as shown in the graph, and these are typically separated by periods of euthymia. The figure also provides some key facts about bipolar disorder and illustrates the importance of both genetic and environmental factors in the aetiology of the illness and the key role of chronobiological mechanisms. The multitude of factors that contribute to the pathogenesis of bipolar disorder mean that it is a multifaceted illness that requires sophisticated assessment and management.

## Assessment and Formulation

The classification and diagnosis of bipolar disorder is inherently complicated, partly because of the natural history of the illness, which typically begins with depression in adolescence<sup>21</sup>. 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 symptom of bipolar disorder can easily be obscured by those induced by substance misuse, including for example stimulants and alcohol. This is important because in addition to psychosocial adversity, substance issue is associated with an earlier age of onset of bipolar disorder<sup>22</sup>.

Once a working diagnosis of bipolar disorder has been established, it is important to appraise the illness fully, and this applies to the assessment and review of the individual throughout the course of their illness. 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<sup>b</sup> and whether there is any sequence or order in

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<sup>b</sup> Predominant polarity: whether the person experiences mainly depression, mania or mixed states.

which episodes typically occur. It is also important to note triggering events to individual episodes and how the latter 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 mental state review.

It is again important to identify clearly the extent to which substances such as alcohol and other prescribed and illicit drugs precipitate episodes. If the person has an established diagnosis of bipolar disorder, and has been treated, determining their adherence to treatment is essential as episodes are often triggered by treatment cessation or withdrawal.

Occasionally, relapse or recurrence may indicate the emergence of a new illness, concurrent with bipolar disorder, and so again broader enquiry is necessary. These appraisals should occur regularly to allow for careful re-evaluation of the diagnosis, and ongoing formulation of the illness.

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. Context is important not only for defining the illness, but also for determining optimal management.

### Treatment Principles

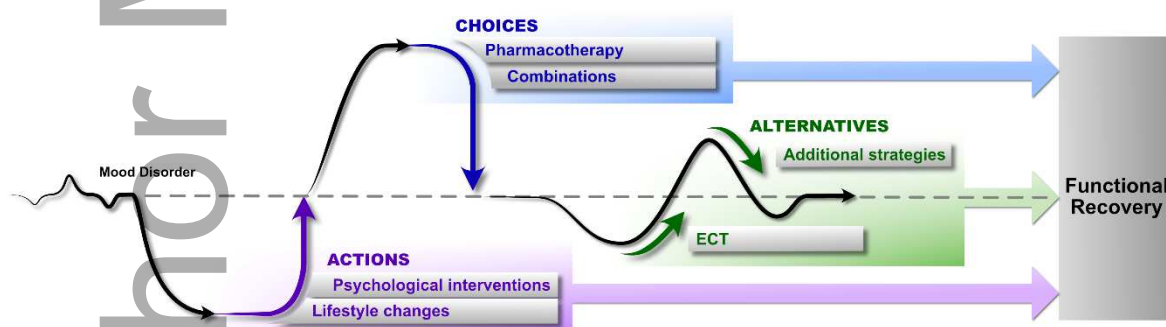
The management of bipolar disorder is more complex than that of major depression. First, bipolar disorder has additional acute episodes, namely mania and mixed presentations – that occur as well as episodes of depression. Second, the emphasis of treatment is not solely upon acute management, but also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

Therefore, to provide long-term care and ensure the successful management of bipolar disorder, it is important to establish a network of providers that functions as a

multidisciplinary team. Ideally, a psychiatrist or primary care physician should lead this team and ensure that care is properly coordinated. This is particularly important at times of acute exacerbations, for which hospitalization may be necessary, and continuity of care has to be maintained in different settings.

### Actions, Choices, Alternatives

As described in the MDcpg<sup>2020</sup> the core principles and therapeutic approach to managing bipolar disorder involves three key elements: *Actions*, *Choices* and *Alternatives*. In bipolar disorder, these are applied to each of the phases of the illness. Figure 2 shows how the *Actions* form the foundation for treatment, and as such, these are mandated. And given that these are common to all four phases of the illness, these have been addressed collectively at the outset, along with ECT, even though this is seldom used initially or early in the course of the illness. *Choices* and *Alternatives* are tailored to each phase of bipolar disorder, and hence why these are detailed separately under each phase of the illness. It is important to note, that unlike the treatment of depression where pharmacotherapy is optional, and may not be needed in some cases, in the management of bipolar disorder the use of medication is routine and usually necessary.



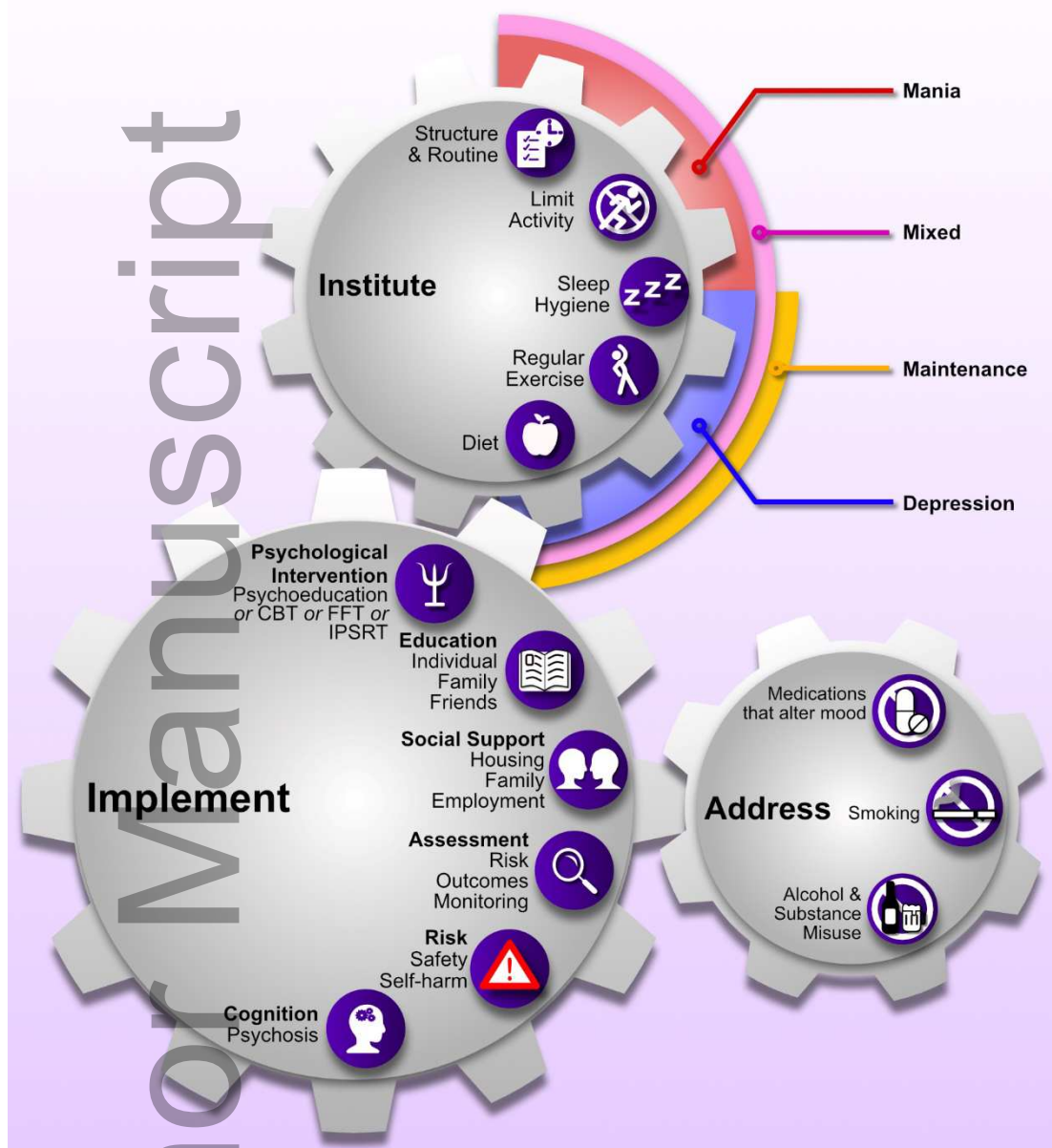
**Figure 2. The Actions, Choices, Alternatives framework for the management of mood disorders.** This framework includes 3 components. 1) *Actions* – form the foundation of management. These are considered essential and must be put in place where possible. They include lifestyle changes and psychological interventions. 2) *Choices* – involve recommended pharmacotherapeutic options that should be trialled initially followed by more complex regimens involving combinations and alternative treatment strategies. 3) *Alternatives* –

include additional strategies and physical treatments such as ECT. It is important to note that functional recovery can be achieved at any point along the process and that the aim of management is to achieve this as soon as possible.

### Actions

The various foundational approaches apply to all aspects of bipolar disorder, and consist of essential steps and strategies that need to be considered, both at the outset and throughout management. In bipolar disorder, the *Actions* are depicted as gears and cogs, and this is designed to underscore the cyclical and self-regulatory nature of bipolar disorder. Broadly speaking, *Actions* can be grouped into three types. First, those that can be instituted by the patient, such as lifestyle changes, in which the individual is required to maintain a healthy diet, engage in regular exercise, and ensure they maintain good sleep hygiene so as to sustain stable circadian rhythms.

## ACTIONS



**Figure 3. Actions for the management of bipolar disorder.** The *Actions* for the management of bipolar disorder need to be considered in relation 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. The latter is also key in bipolar depression, but here encouraging activity and exercise is needed rather than limiting this. Similarly, the assessment of risk is common to both acute mania and bipolar depression, but the nature of the risks is different as is the likelihood of psychosis. However, the key to long-term successful management is maintenance therapy and for this,

psychoeducation and psychological interventions are essential, along with 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 wider management approaches. As regards to the latter, psychological interventions have been included as *Actions* as they should be offered, whenever possible, to all patients. This is because, they are particularly effective if implemented from the outset and in conjunction with pharmacotherapy. When used in combination, they enhance the benefits of additional treatments and there are some psychological interventions that have been specifically tailored to treating bipolar disorder (see Psychological Interventions).

Naturally, patient insight will also be an important determinant as to which modes of treatment are appropriate at any particular phase of their illness. In mania, and especially agitated states of bipolar depression and mixed mood states, there is often the need to de-escalate disruptive or aggressive behaviour. Extremes of such behaviour coupled with diminished insight may require admission to a psychiatric facility under mental health legislation (this allows provision of care where it is deemed necessary and when the patient is unable to give consent). This is not uncommon in instances of acute mania, and a person experiencing acute manic symptoms will often need strict limit setting. However, these actions have to be considered carefully as they may be traumatic for the patient and therefore have the potential to undermine the therapeutic relationship - both with the patient and their family. Therefore, it is important to assess risk and implement measures that facilitate ongoing monitoring of clinical symptoms and assessment of outcomes.

Other *Actions* that should be implemented, or at least considered, are building or enhancing social support (e.g. through peer support) and resolving interpersonal conflict<sup>23</sup>. This is where functioning within a multidisciplinary team may allow clinicians to draw upon the services provided by allied health professionals such as social workers. Addressing other issues, such as housing and employment is clearly important, as these necessarily affect the mental health of individuals, and stressors in these domains are likely to have profound effects on mood

stability. Similarly, in instances where insight and decision-making capacity are compromised it may be necessary to provide assistance with financial management.

Finally, it may be necessary to address maladaptive habits that the individual has acquired, and this will likely require the assistance of specialists (for example, to stop smoking, alcohol and substance misuse).

### Psychological interventions

Adjunctive psychological intervention is a central component of a chronic disease management approach to bipolar disorder, and outcomes in bipolar disorder are demonstrably improved by augmenting medication with an evidence-based psychological treatment<sup>24</sup>. Concerns still remain about the quality of the evidence base for psychological interventions on their own, but there is consensus that best practice treatment of bipolar disorder involves the combination of medication and psychological treatment, and for this there is now substantive support<sup>25</sup>.

Four therapeutic approaches are considered evidence-based: Psychoeducation, Cognitive-Behavioural Therapy (CBT), Family-focused Therapy (FFT), and Interpersonal and Social Rhythm Therapy (IPSRT)<sup>26</sup>. The four recognised evidence-based treatments share a treatment approach (active collaboration, skill-development focus), and also share significant therapeutic content<sup>26</sup>. As a set, adjunctive psychological interventions have been shown to generate benefits for time to remission, time to recurrence and functional outcomes<sup>27,28</sup>, with clearest evidence for preventing relapse in the continuation phase and for stabilising symptoms in the depressive phase. Internet delivery of psychological interventions in the treatment of bipolar disorder has clear advantages with regard to reach, cost and equity, but the evidence remains nascent<sup>29</sup>.

A recent component network meta-analysis<sup>30</sup> directly compared pharmacotherapy + control with pharmacotherapy + one of the evidence-based treatments. The authors conclude that these skills-focused interventions improve relapse rates and note that findings align with the consensus that optimal bipolar disorder management involves both pharmacotherapy and psychological intervention. The component meta-analysis suggested that the strongest predictors of decreased relapse were delivery of the treatment in a family or group format and encouraging patients to monitor episode prodromes. In addition, the severity of depression was most strongly ameliorated by cognitive restructuring, and stabilising daily rhythms.

While the evidence-based psychological interventions have overlapping content, it is recommended that clinicians ‘commit’ to one of the published treatments and follow that framework using a ‘fidelity with flexibility’ approach, rather than eclectically drawing from the various approaches <sup>26</sup>.

By choosing one specific therapeutic roadmap, the clinician gains access to a particular structuring and approach to therapeutic content, roadblocks, supporting materials, professional networks and supervision. The choice of approach will in most instances follow from the core psychotherapy training which the clinician has received and as many clinicians are trained in CBT, this makes CBT an obvious first choice framework. For clinicians with a strong grounding in family approaches, FFT may be a better fit, while fewer clinicians are experts in chronobiology, so IPSRT may be a less obvious choice. Psychoeducation is typically delivered in a highly structured manualised group format, potentially requiring less clinical training to achieve adequate outcomes. In some instances, it may be necessary to abstract the basic principles of these therapies and apply them flexibly (e.g., taking into consideration the cognitive and intellectual abilities of the patient and family as well as their cultural background).

In the primary care management of bipolar disorder as a chronic condition, a key challenge is the integration of various facets of treatment. Depending on context, management may involve providing online information, self-management strategies, family support, peer-support, as well as medical and psychological intervention. At an absolute minimum, it is recommended that all cases should have a clear clinical governance structure, clear communication guidelines between those providing care and overall continuity of care throughout. Collaborative care approaches have strong evidence across a range of conditions in primary care, and have potential to be more fully elaborated for the complex dynamics of bipolar disorder <sup>31</sup>. There needs to be regular communication between the GP, treating psychiatrist, and clinical psychologist especially when there are changes in treatment or there are intercurrent illnesses.

In the MDcpg<sup>2020</sup>, adjunctive psychological intervention is now considered a foundational *Action* in the management of bipolar disorder - although it is important to note that it is not a substitute for pharmacotherapy. While this may seem at odds with the fact that pharmacotherapies are often prescribed from the outset in the management of BD, (as they are often needed), it is intended to broaden the management of BD, and actively encourage an

evidence-based biopsychosocial approach to management. Engaging the patient into care is also essential to ensure compliance with pharmacotherapy – hence the need to nuance both psychological approaches and medications.

### Choices

There are a multitude of pharmacological options for the management of bipolar disorder, across its various phases of illness. The recommendations for particular medications are based on evidence for efficacy and tolerability, and these are detailed below.

### Alternatives

Beyond the selected agents that are recommended as *Choices*, many additional pharmacological strategies can be utilised to treat various phases of bipolar disorder. These are once again detailed under the appropriate sections. In addition, ECT is an *Alternative* strategy that can be implemented and as the recommendations for administration remain the same across each phase, it is addressed collectively below.

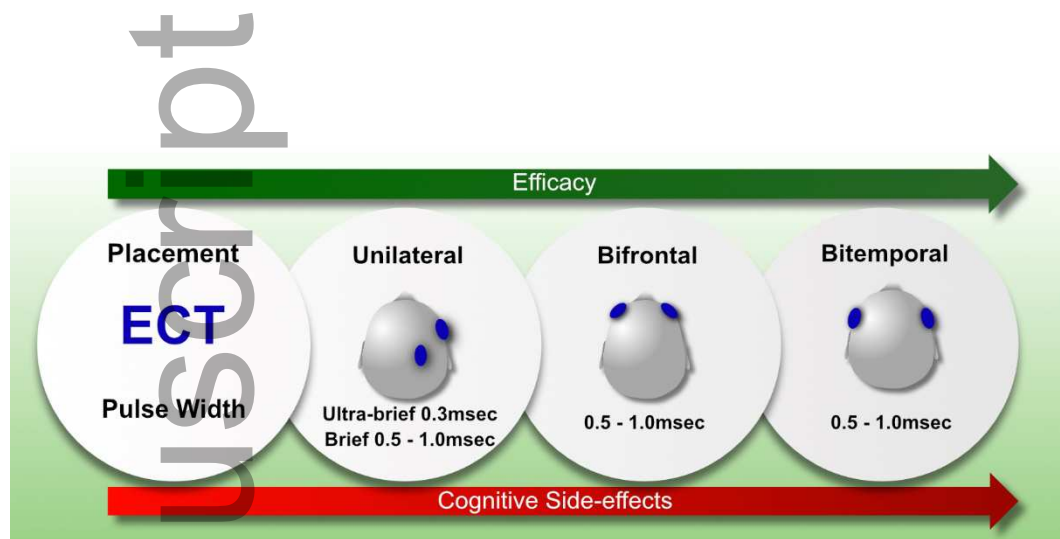
### ECT

Across all acute presentations of bipolar disorder, ECT is an important *Alternative*, with proven efficacy in mania<sup>32</sup>, bipolar depression<sup>33,34</sup> and mixed states<sup>35</sup>. The administration of ECT is no different to that done in major depression and is determined largely by placement of the electrodes and the pulse width of the current applied. This provides, with increasing efficacy, unilateral and bilateral placement, moving from bifrontal to bitemporal. In unison with this, the pulse width can also be increased from ultra-brief (0.3msec), to brief (0.5-1.0msec) (See Figure 4).

As the figure shows, differences in the positioning of the electrodes and the pulse width of current applied, provide increasing efficacy migrating from unilateral to bifrontal to bitemporal. However, hand-in-hand with this, there is an increasing likelihood of cognitive side-effects, which, while typically transitory, can be quite debilitating and therefore warrant careful consideration.

In the context of bipolar disorder, ECT is most likely to be used in bipolar depression, where it may in fact have a more rapid response than in major depression, and on occasion be more effective than pharmacotherapy<sup>33,34</sup>. But, as is the case with medications, ECT can induce mania. This is somewhat puzzling, given that ECT is also effective in treating mania, and

hence why it can also treat mixed states. Longer-term use of ECT in bipolar disorder may be justified in treating bipolar depression, however there is little evidence to support the use of ECT as a maintenance therapy<sup>36</sup>, or for the purposes of prophylaxis.



**Figure 4. ECT in bipolar disorder.**

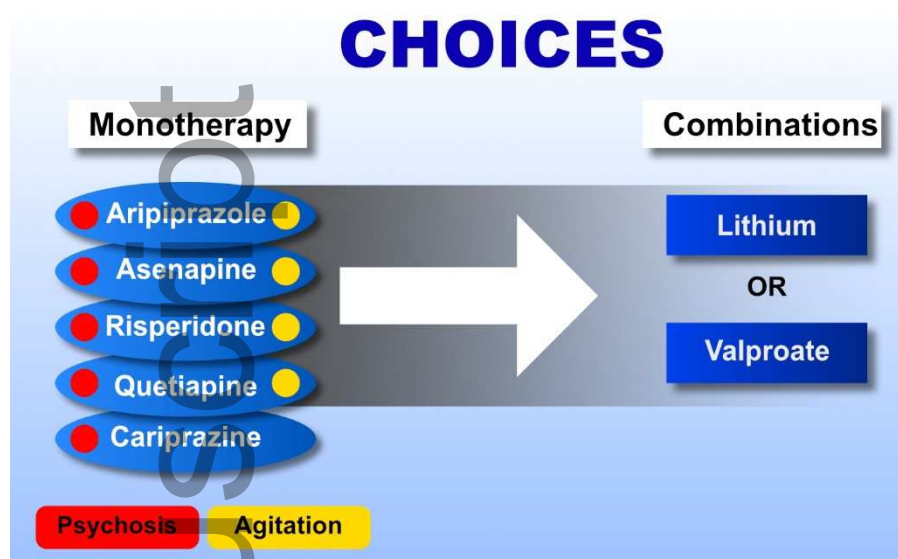
Electroconvulsive therapy is effective in treating bipolar depression, mania and mixed states. With increasing efficacy, which can be achieved by increasing the pulse-width and by shifting placement the cognitive side-effects also increase.

## Mania

### Choices

The pharmacotherapy of mania is probably the most straightforward of all the phases of bipolar disorder. The treatment of mania encompasses the management of risk and the treatment of three main components, namely acute manic symptoms, behavioural disturbance and cognitive symptoms and/or psychosis. It is important to bear this in mind, as the three components have different timescales of response to treatment. Inpatient containment and application of the mental health legislation may be required in some cases to contain risk. However, it is also important to note that some medications will invariably treat more than one syndromal component at a time, for example antipsychotic medications often quell behavioural disturbances and deal with manic, cognitive and psychotic symptoms. However, given that mania is the main target, the agents that are most effective in this regard should be

given preference with some additional consideration given to agitation and psychosis (see Figure 5).



**Figure 5. Choice treatments for the management of mania.**

The choice agents address all three components of the illness (mania, agitation, psychosis) and where possible, monotherapy and oral treatment should be given preference. In this regard, antipsychotics (with the exception of cariprazine) have the advantage of addressing psychosis and agitation in addition to countering mania. However, if monotherapy does not suffice then lithium or valproate can be added, and these can remain in place as the antipsychotic is gradually removed once the acute episode subsides. Furthermore, if combination therapy is insufficient then *Alternatives* need to be considered.

The treatment of mania often requires combinations of medications, and ideally this should include a mood stabilising agent (MSA) and second-generation antipsychotic (SGA). The medications that are useful in this regard (based on effectiveness: both efficacy and tolerability) include aripiprazole, asenapine, risperidone, quetiapine and cariprazine<sup>37</sup>. Each of these can be combined with lithium and valproate<sup>c</sup>.

In cases of refractory illness or marked agitation, various formulations of olanzapine can be used, or haloperidol may be necessary – although it is important to note that conventional

<sup>c</sup> 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

antipsychotics may be associated with post-manic depression<sup>38</sup>. In some circumstances judicious, and closely monitored, short-term use of benzodiazepines such as clonazepam may be beneficial for refractory agitation – especially where SGA akathisia is a concern (See Figure 5 Table 1). Other *Alternatives* include intramuscular options (see Figure 5 and Table 1)<sup>39-41</sup>.

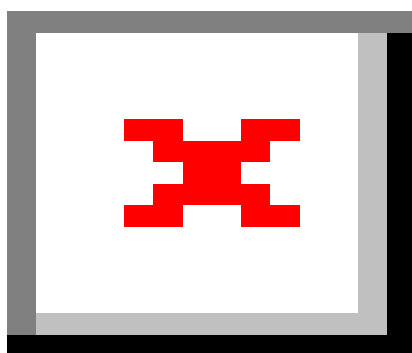
**Table 1. Agitation Pharmacotherapy**

Route of administration	Monotherapy
Oral	Asenapine**
	Risperidone*
	Quetiapine
	Haloperidol
Intramuscular	Aripiprazole
	Olanzapine***
	Haloperidol
	<b>Combinations</b>
	Haloperidol + Midazolam
	Haloperidol + Promethazine
* Also available as orally disintegrating formulation; ** Sublingual, *** Also available in wafer formulation	

### Alternatives

On occasion, *Choice* medications, even as combinations, may be insufficient, and *Alternatives* need to be considered (See Figure 6). Here again, both monotherapy and combination strategies can be employed. The monotherapies that should be considered include carbamazepine, ziprasidone, haloperidol and olanzapine, with the latter being least favoured because of its metabolic side-effects. However, sometimes olanzapine is necessary and can also be used in combination with lithium and valproate. Interestingly, the two mood stabilising agents can also be combined with each other (lithium + valproate), although the delay in onset of action of MSAs as compared to SGAs often means that either an SGA or a benzodiazepine has to be included. Hence, there are ample *Alternatives* beyond the *Choice* agents for the management of mania.

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) (see [ECT](#)). In addition to pharmacotherapy and psychological interventions, the management of risk and the contextual environment for the management of mania remains of pivotal importance – ensuring, for example, minimal stimulation and providing a place of safety where the individual can be closely monitored.



**Figure 6. Alternative treatments for the management of mania.**

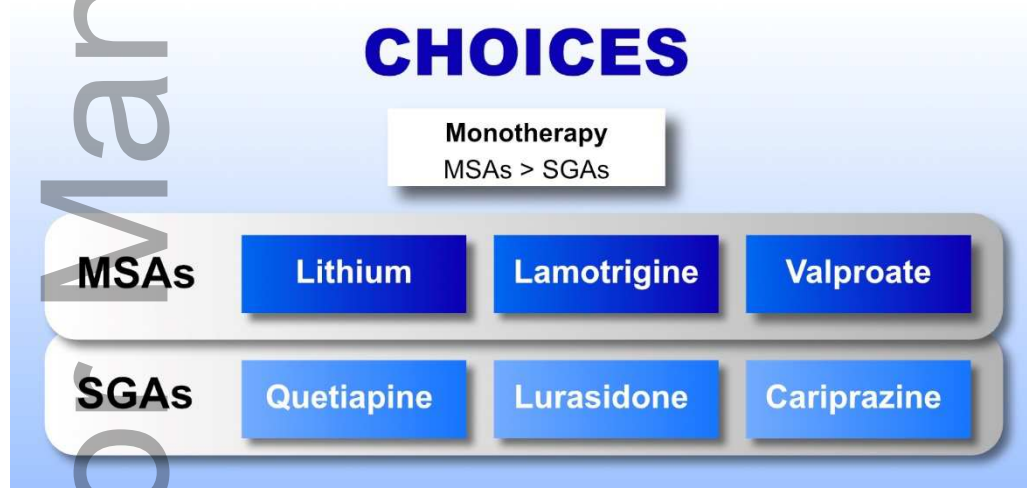
Where possible, monotherapy is preferable and options include carbamazepine, ziprasidone, haloperidol and olanzapine. Olanzapine should be used with caution because of its metabolic side-effects, but if used short term, it can be effective and can also be combined with lithium and valproate. The two mood stabilising agents can also be combined (lithium + valproate), however, because of a delay in onset of action, an SGA or a benzodiazepine often has to be included.

## **Bipolar Depression**

### Choices

Amongst the various phases of bipolar disorder, the treatment of bipolar depression is perhaps the most contentious. However, it is also the most important phase of the illness

because it confers the greatest disability. The medications best suited for treating bipolar depression belong to two broad groups: mood stabilising agents (MSAs) and second-generation antipsychotics (SGAs). With each group containing three agents that are best suited to treating bipolar depression it means that half a dozen *Choice* agents are available. This includes lithium, lamotrigine, valproate (in that order) and similarly sequenced quetiapine, lurasidone and cariprazine. Note, these are all monotherapy options and, where possible, mood stabilising agents should be given preference because they can be continued into maintenance therapy, such as lithium, and are less likely to have significant long term side effects; furthermore, lithium is the only agent that protects against suicide. Despite this, the use of lithium, is declining<sup>42</sup>. Also note, that antidepressants are not included as *Choice* agents because of insufficient evidence to support their prescription as monotherapy in the treatment of bipolar depression.



**Figure 7. Choice treatments for the management of bipolar depression.** There are six *Choice* agents that should be considered when treating bipolar depression. They fall into two groups. 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).

### Alternatives

Ultimately, choice is, as always, based on efficacy and tolerability, and although the recommendations at this point are focused on the treatment of acute bipolar depression, both

maintenance and prophylaxis have to be borne in mind, and this clearly impacts choice. However, it is not uncommon for these monotherapy *Choice* treatments to be insufficient, and so after trialling a number of these medications, *Alternatives* may need to be considered, while at the same time switching from monotherapy to combinations that include couplings of two and three agents. It is important to note that in these combinations, the new group of agents is that of conventional antidepressants. Antidepressants have been the source of much controversy because they are associated with a modest risk of treatment-emergent affective switch (TEAS) and rapid cycling. However, in practice, if an atypical antipsychotic or a mood stabilising agent are already in place, the likelihood of this is significantly diminished (see Recommendation Box 1).

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. This provides various *dual* combinations, except for combining two MSAs. Note, two SGAs should *not* be combined. Similarly, by adding agents from all three groups, several combinations can be produced, including once again an MSA, an SGA and an antidepressant and, on occasion, two MSAs and an antidepressant. There is some evidence to support each of these combinations, but it is modest at best, and mainly derived either from inference across studies or clinical experience. Nevertheless, the number of medications available, and the number of combinations that are possible, means that clinically, in most cases, an effective treatment can be found.

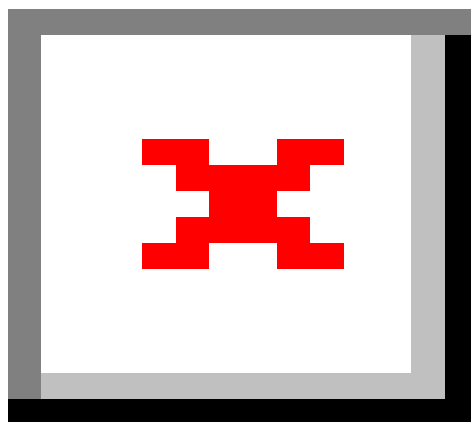
However, on occasion, further *Alternatives* may be needed, and here monotherapy options include carbamazepine and olanzapine, and adjunctive treatment includes asenapine, armodafinil (or modafinil), pramipexole and levothyroxine. ECT may also be indicated before combining antidepressants, particularly if melancholic depressive features or depressive psychosis are present (see [ECT](#)). It is important to note once again that we draw no distinction between bipolar I and bipolar II, either in relation to treatments overall, or indeed with respect to the use of antidepressants.

### Recommendation Box 1. Administration of Antidepressants in Bipolar Disorder    Grade

#### General Considerations

- |     |  |     |
|-----|--|-----|
| 1.1 | The use of antidepressants in the treatment of bipolar disorder should be overseen by a psychiatrist where possible. | CBR |
|-----|--|-----|

1.2	The clinical risks versus benefits of antidepressants in treating bipolar depression should be determined on an individual basis.	CBR
Treatment		
1.3	Adjunctive antidepressant therapy should be used cautiously in the treatment of bipolar depression when there is a history of antidepressant-induced mania, current or predominant mixed features, or a history of rapid cycling.	EBR III
1.4	Antidepressant monotherapy should be avoided in bipolar disorder	EBR III
Treatment Emergent Affective Switch (TEAS)		
1.5	Upon commencing antidepressants, patients with bipolar disorder should be closely monitored for symptoms of mania, and if these emerge then antidepressant therapy should be discontinued. Psychoeducation should be provided so that patients can identify early warning signs of mania and/or mixed symptoms.	CBR
1.6	Antidepressant therapy should be avoided in bipolar disorder patients with a history of rapid cycling and/or a high level of mood instability.	CBR
1.7	The prescription of antidepressants should consider any past history of a treatment emergent affective switch (TEAS).	CBR



**Figure 8. Alternative treatments for the management of bipolar depression.** Treatment alternatives include dyads and triads of medication combinations. MSAs are given preference and so combinations initially begin with these agents. Each of the three groups can be combined and so 5 options are possible (excluding dyads of two SGAs, and two ADs, and allowing for an MSA and SGA to be combined reciprocally).

Triads can then be formed by extending some of these dyad combinations by adding an AD where this has not already been prescribed. Note once again combinations of more than one SGA or AD are *not* advised.

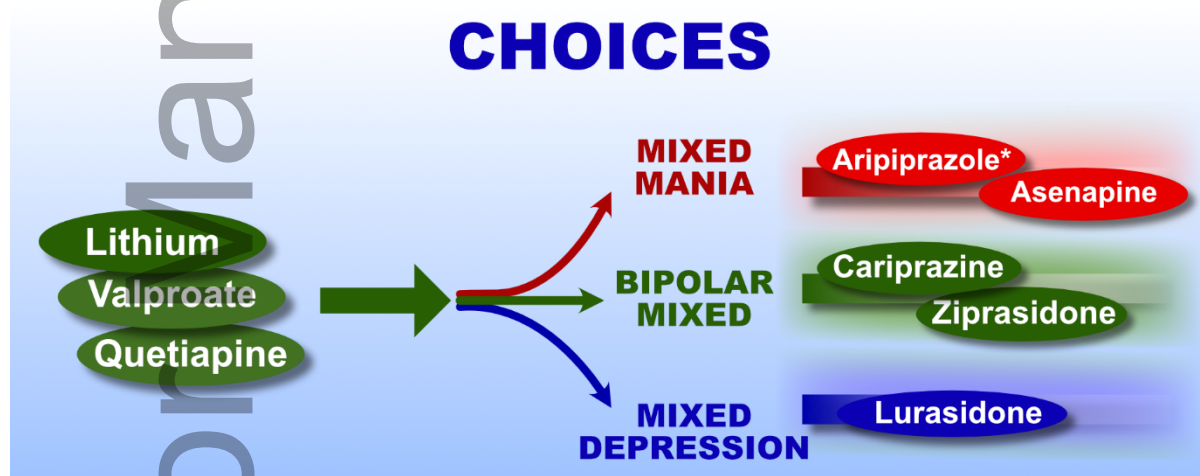
## Mixed States

### Choices

There is little or no data from large randomised controlled trials to guide clinicians on the management of patients with DSM-5 defined mixed features. Hence, the recommendations for this phase of the illness are primarily based on the efficacy of agents in each pole of the illness. Given this, the predominance of polarity becomes an important consideration in

determining *Choices*. To achieve mood stability and prevent development of contrapolar<sup>d</sup> symptoms, initially, agents that have some evidence for efficacy across both mania and depression should be considered. This then means that lithium, valproate and quetiapine monotherapy are the *Choice* agents, especially if treating a bipolar mixed state of equal polarity. However, it is important to note that none of these agents have been tested in clinical trials of patients with DSM-5 defined mixed features. Note, any one of these *Choice* agents can be substituted if necessary, with either cariprazine or ziprasidone, again as monotherapy to treat an equal-polarity mixed state. If, however these agents are unsuccessful as monotherapy, then they can be combined.

In most cases, a predominance of one pole is observed, and in the case of mixed mania, aripiprazole or asenapine can be added to one of the mood stabilising agents, and lurasidone can be added to treat mixed depression. Therefore, using these *Choice* agents, either as monotherapy or in combination, several different options are available and can be trialled.



**Figure 9. Choice treatments for the management of mixed states.** If there is no predominant polarity and both mania and depression prophylaxis is needed then lithium, valproate and quetiapine can be prescribed as monotherapy. Furthermore, these can be substituted with cariprazine or ziprasidone if necessary. If there is a predominance however, of one pole or the other, then aripiprazole can be added to treat mixed mania, and lurasidone can be added to treat mixed depression (\*aripiprazole can also be administered as a long-acting depot).

<sup>d</sup> Symptoms belonging to opposite poles.

## Alternatives

Mixed states are often difficult to treat and in cases where *Choice* medications have been unsuccessful, further combinations can be given consideration – depending on the mixed state subtype. Therefore, for a *bipolar mixed state*, carbamazepine<sup>e</sup> (see footnote) is a potential alternative, for *mixed depression* olanzapine may be effective, and for the treatment of *mixed mania* olanzapine can be combined with a mood stabiliser. Note, caution needs to be exercised when considering olanzapine because of its long-term side-effects.



**Figure 10. Alternative treatments for the management of mixed states.** Once *Choice* treatments have been exhausted *Alternatives* should be given consideration again, on the basis of polarity, if this is evident. For those with no predominance (equal polarity) carbamazepine can be trialled. For mixed depression, olanzapine can be trialled (short term) and this can also be combined with fluoxetine. Olanzapine can also be used to treat mixed mania and again it can be combined with another medication such as a MSA.

## **Maintenance**

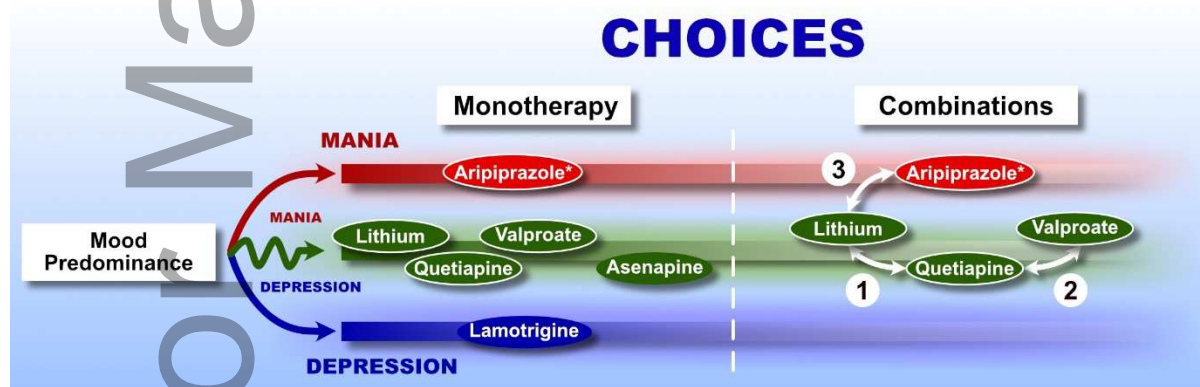
### Choices

The factors that are important in determining *Choice* emerge from assessment and formulation and the detailed appraisal of the individual's illness course and previous response to treatment. Treatment emphasis is once again tailored to predominance of mood polarity,

<sup>e</sup> If carbamazepine is utilised in patients of Asian ethnicity, it is advisable to first conduct HLA genotyping to accurately assay the risk of potential long-term side-effects.

and therefore it is important to elicit these aspects thoroughly when taking a history of the illness and its treatment.

In maintenance therapy, it is important to know which symptoms characterise various episodes and which presentations are most likely to occur. This will make it clearer as to what needs to be targeted in terms of prophylaxis. As with other treatment phases, monotherapy is to be preferred, but again, is often not possible. The choices for monotherapy, where both depression and mania need to be prevented, include lithium, valproate, quetiapine and asenapine, with the latter two (valproate, quetiapine) having better evidence for the prevention of depression. In general, mood stabilisers are given preference when prescribing maintenance therapy, because of their better tolerability, but if there is a preponderance of mania, then aripiprazole (long-acting injectable formulation if adherence is a problem) is a suitable choice, whereas if depression predominates, then lamotrigine may be more suitable. However, in many instances, combinations are needed and therefore, lithium can be combined with quetiapine, or quetiapine can be combined with valproate, or where there is a greater likelihood of future episodes of mania, lithium can be combined with aripiprazole.

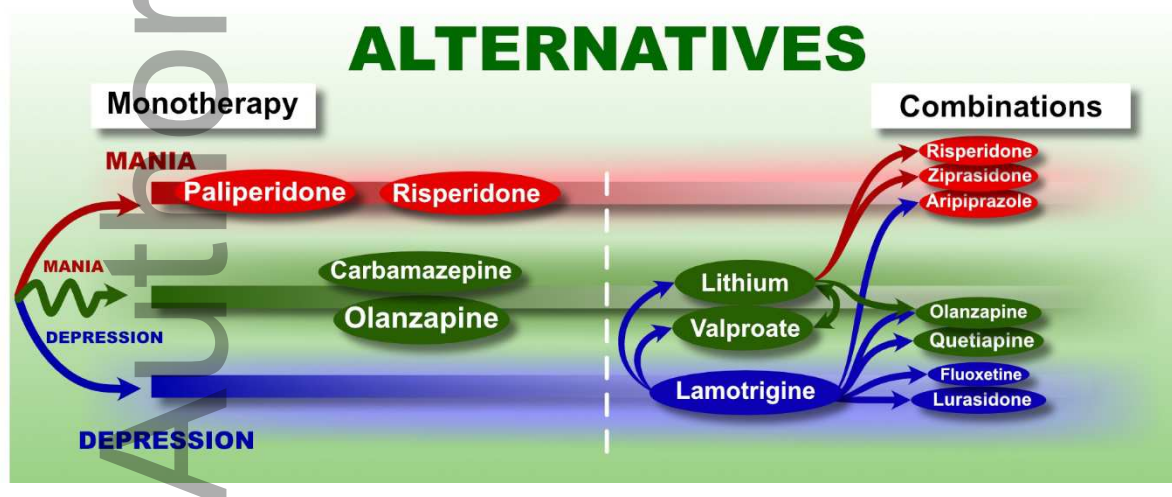


**Figure 11. Choice treatments for bipolar maintenance.** It is important to consider which symptoms have to be prevented. If both mania and depression need to be prevented then lithium, valproate, quetiapine and asenapine are suitable monotherapy choices. If the prevention of mania is a priority then aripiprazole is a suitable monotherapy choice, whereas if the prevention of depression is a priority then lamotrigine is a suitable choice as monotherapy. Note that combinations can also be used, although monotherapy is preferable, and the agents involved are the same as those recommended for monotherapy with the exception of asenapine and lamotrigine. Therefore, to prevent both mania and depression, quetiapine can be combined with lithium (1) or valproate (2) and lithium can also be

combined with aripiprazole (3) to prevent mania (\*aripiprazole can also be administered as a long-acting depot).

## Alternatives

If *Choice* agents, either as monotherapy or combinations, are unsuccessful in maintaining mood stability, then several *Alternatives* can be trialled (see Figure 12). Once again, if there is equal emphasis to be placed on both prophylaxis of mania and depression, then carbamazepine and olanzapine are options as monotherapy. Where mania is the main consideration, then paliperidone and risperidone can be trialled. However, in some instances, even these will be insufficient, and combinations may be necessary. For the purposes of combining medications, it is important to think of key, foundational medications around which the combinations are constructed. These include lithium, valproate and lamotrigine. To prevent both mania and depression, lithium can be combined with valproate, or either of these can be combined with olanzapine. Where there is a predominance of mania, lithium or valproate can be combined with risperidone or ziprasidone. Where depression is the main target in terms of prophylaxis, then lamotrigine can be combined with lurasidone, lithium or valproate, or it can be combined with quetiapine, olanzapine, or aripiprazole (increasingly recruiting an antimanic effect). Note, olanzapine should be prescribed with caution in this regard, because of its long-term metabolic side-effects.



**Figure 12. Alternative treatments for bipolar maintenance.** Determined by the symptoms of bipolar disorder that maintenance therapy aims to prevent, monotherapy alternatives include carbamazepine and olanzapine for both mania and depression. Paliperidone and

risperidone can be used where there has been shown to be a predominance of manic polarity. For combinations foundational treatments should be considered first and these include lithium, valproate and lamotrigine. These can then be combined variously as shown to prevent mania, depression or both (see text for details).

## Paediatric Bipolar Disorder

The diagnosis of paediatric bipolar disorder may apply to a young person in their mid-adolescence presenting with classic features, but it has also been applied to younger children with severe hyperactivity, impulsivity, affective dysregulation and explosive temper. The case for the latter being a variant or subtype of bipolar disorder is unproven<sup>43</sup>, and unfortunately, use of the term bipolar in this context (even in ‘bipolar spectrum’ or ‘broadband bipolar’) carries with it erroneous assumptions about aetiology, associations, treatment and prognosis. DSM-5 listed the new diagnostic category of ‘Disruptive Mood Dysregulation Disorder’ to try and stimulate more research on this segment of presentations without prematurely making a diagnosis of bipolar disorder in a young person. Where paediatric bipolar is considered, review by a psychiatrist with expertise in child and adolescent psychiatry is essential.

## Bipolar Disorder and Borderline Personality Disorder Interface

Bipolar disorder and borderline personality disorder exhibit similar clinical elements (including affective dysregulation), but significant differences also exist – including optimal management<sup>44</sup>.

In contrast to the rapid affective variability characteristic of borderline personality disorder, bipolar disorder is characterised by periods of depression, mania or mixed affective states which extend over periods ranging from days to months. Depressed mood is usually predominant, and episodes of elevated mood are essential features. Major problems with interpersonal relationships may occur but are not a prominent aspect of bipolar syndromes and tend to resolve between affective episodes<sup>45</sup>. Furthermore, in borderline personality disorder, interpersonal problems tend to continually manifest and there is a strong history of serious traumatic adverse childhood events or neglect. In bipolar disorder a history of serious adverse childhood maltreatment (trauma and/or neglect) is evident in a significant proportion of patients, but it is not a key feature in the majority.

In contrast, borderline personality disorder is characterised by a history of major difficulties with interpersonal relationships, severe affective dysregulation with frequent episodes of rage, heightened sensitivity to interpersonal interactions, prominent fear of abandonment, significant depressive symptoms but an absence of threshold manic episodes, and intensely negative self-image<sup>46</sup>. A key differentiating feature is the presence of sustained episodes of mood in bipolar disorder as opposed to fluctuating and evanescent mood in borderline personality disorder. Patients with borderline personality tend to have chronic suicidal ideations and ambivalence to life, whereas in bipolar disorders these tend to only manifest during depressed or agitated mixed phases of the illness.

The comorbid presence of borderline personality disorder with bipolar disorders, impairs the treatment response of the bipolar disorder illness<sup>47</sup>. Much more nuanced psychiatric care is needed for such patients where combined pharmacotherapy and advanced psychotherapy is essential for optimal outcomes and the use of lamotrigine may have particular benefits.

### **Conclusions**

Bipolar disorder is a serious psychiatric illness that affects individuals of all ages, from youth to old age. It is often difficult to diagnose because initially, it usually presents as depression and early symptoms of mania are easily missed. The evaluation of bipolar disorder requires careful review, ideally by those with specialist expertise. Clinical management of the illness is best considered according to its acute phases (mania, depression and mixed states), and the periods of stability in between, during which maintenance therapy and prophylactic measures should be implemented. Successful management of bipolar disorder usually requires sophisticated pharmacotherapy, both acutely and long-term, and outcomes benefit from psychological support. In most cases of bipolar disorder, using a multi-disciplinary and multi-pronged approach to management (lifestyle changes, psychological interventions, pharmacotherapy and physical treatments), the illness can be effectively treated - enabling the restoration of function and allowing individuals to pursue purposeful goals.

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# BIPOLAR DISORDER

## Symptoms

### Mania

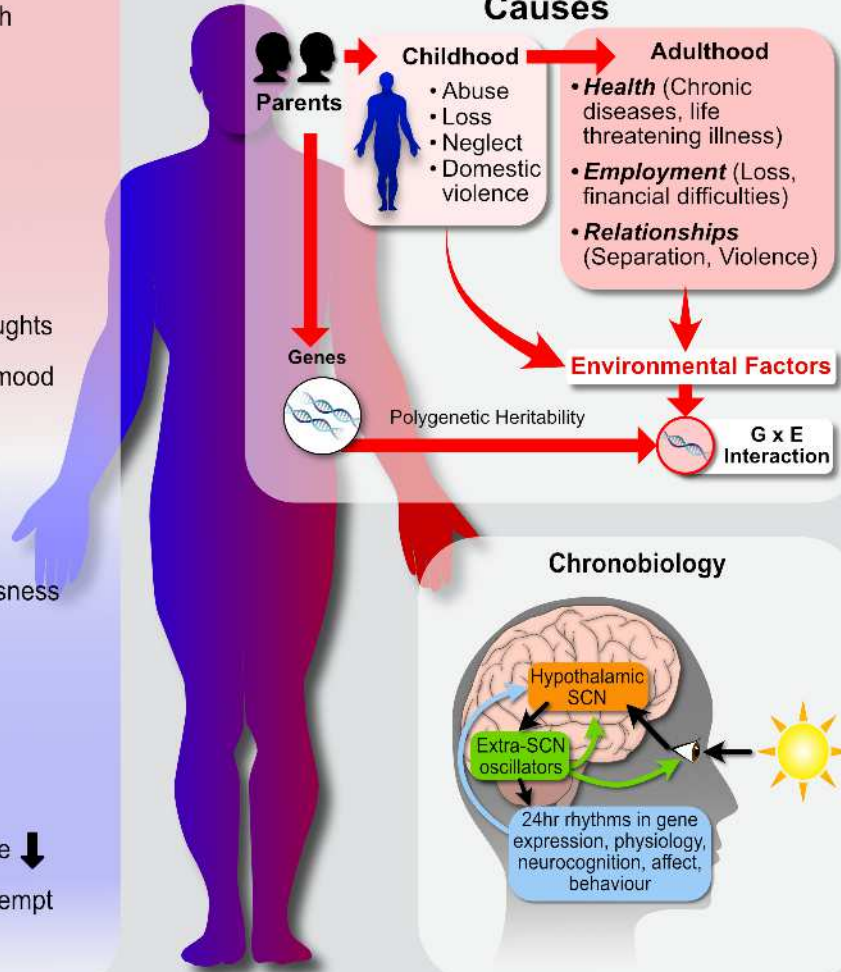
- Inflated self-esteem or grandiosity
- Distractibility
- Prolixity or pressured speech
- Psychomotor agitation
- Goal-directed activity ↑
- Need for sleep ↓
- Energy and activity ↑
- Risk-taking behaviour
- Flight of ideas or racing thoughts
- Elevated and/or expansive mood
- Irritable mood
- Depressed mood
- Anhedonia
- Feelings of guilt or worthlessness
- Sleep ↑ or ↓
- Weight or appetite ↑ or ↓
- Fatigue or loss of energy
- Psychomotor retardation
- Ability to think or concentrate ↓
- Suicidal ideation, plan or attempt

### Depression

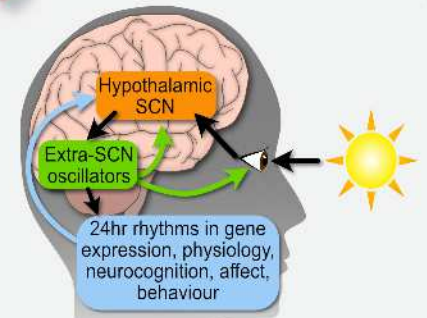
## Facts

- 1 in 100 people will experience bipolar disorder in their lifetime
- Bipolar disorder affects men and women equally
- Average onset occurs in late teens, but average age of diagnosis is late 20s
- Bipolar disorder confers a risk of suicide 30 - 60 times the general population

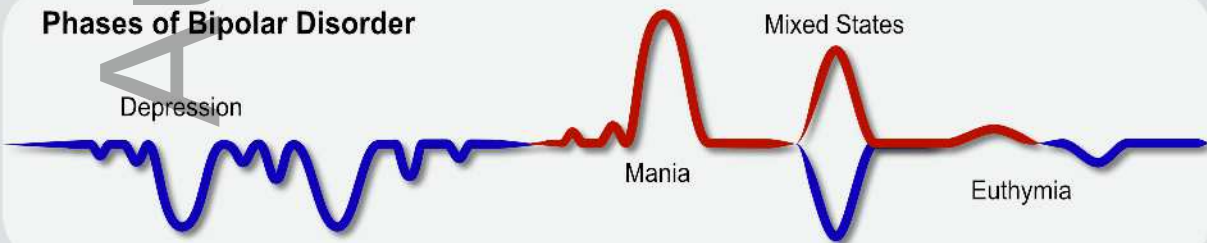
## Genetic and Environmental Causes



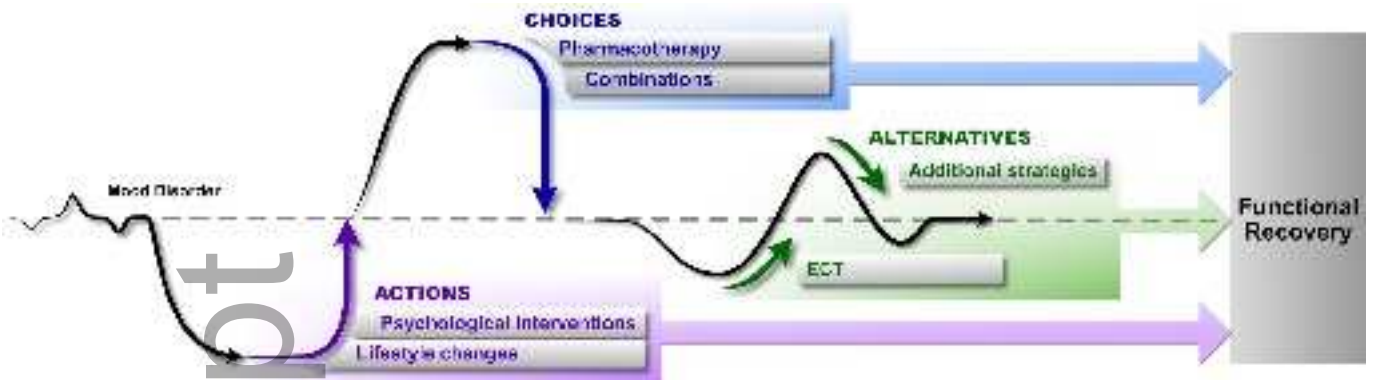
## Chronobiology



## Phases of Bipolar Disorder

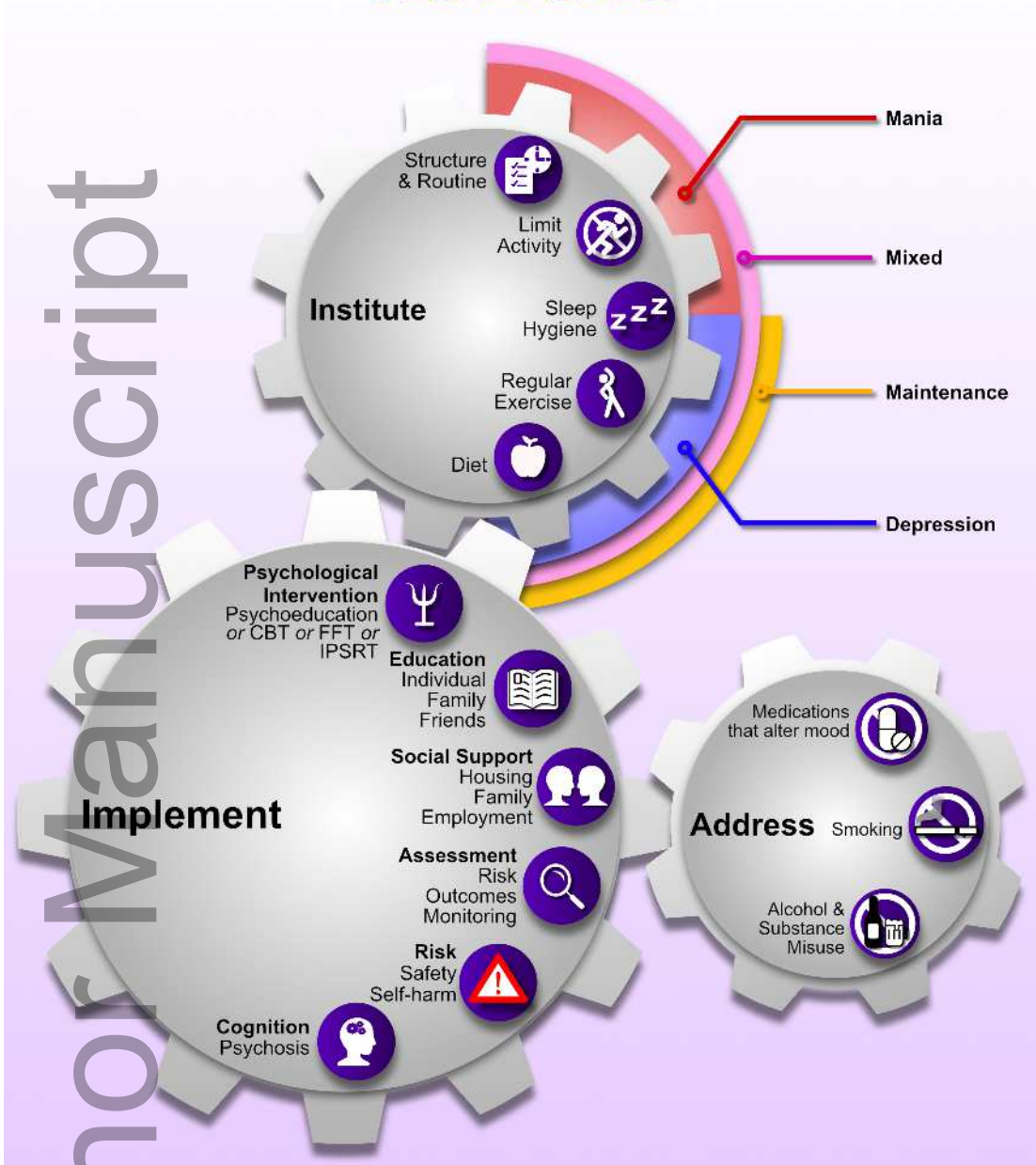


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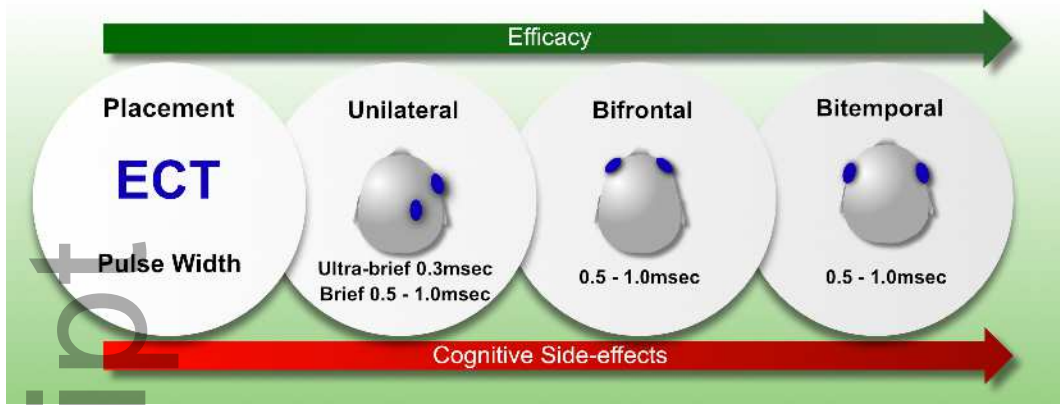


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# ACTIONS



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# CHOICES

## Monotherapy

- Aripiprazole ●
- Asenapine ●
- Risperidone ●
- Quetiapine ●
- Cariprazine ●

## Combinations

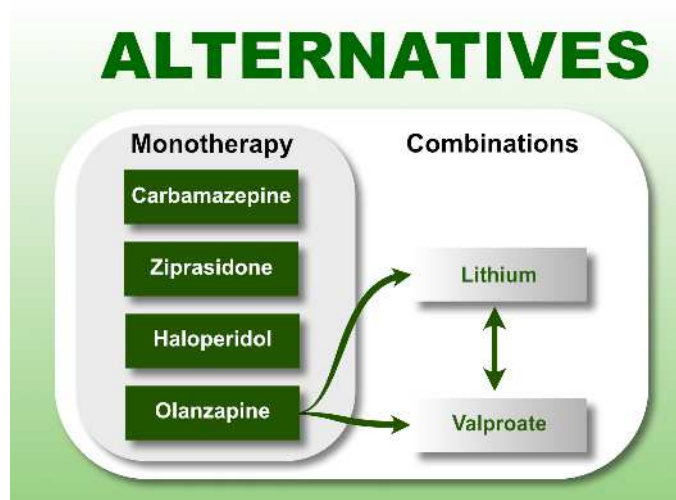
- Lithium
- OR
- Valproate



Psychosis Agitation

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# CHOICES

Monotherapy  
MSAs > SGAs

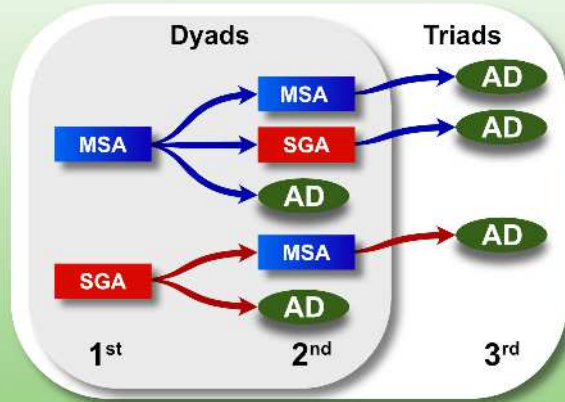
MSAs	Lithium	Lamotrigine	Valproate
SGAs	Quetiapine	Lurasidone	Cariprazine

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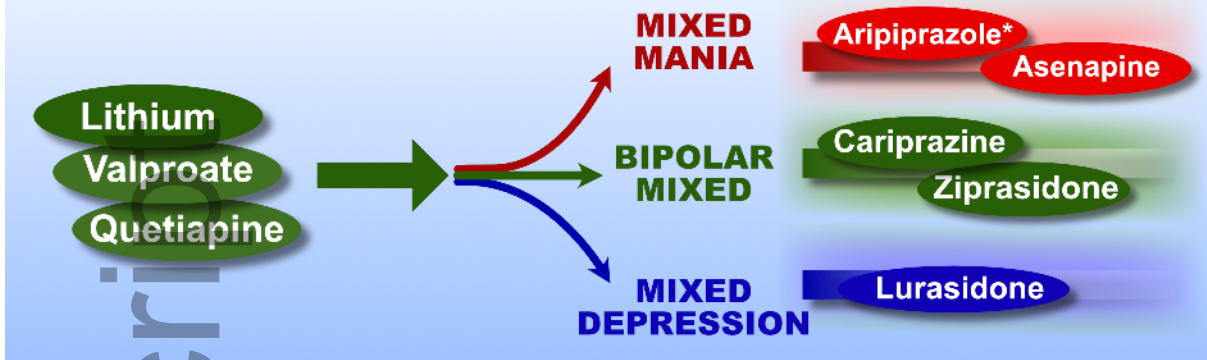
# ALTERNATIVES

## Combinations



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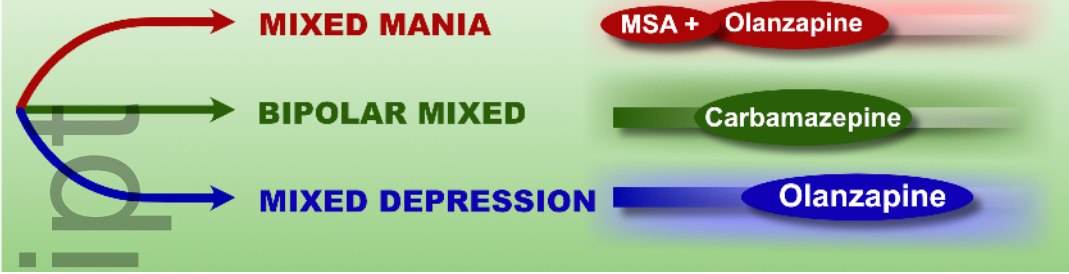
# CHOICES



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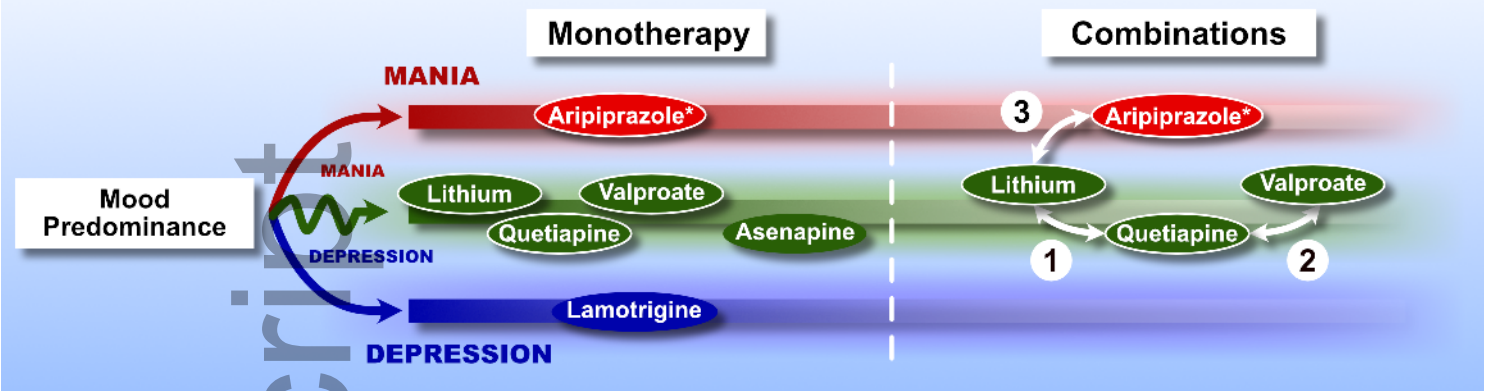
# ALTERNATIVES



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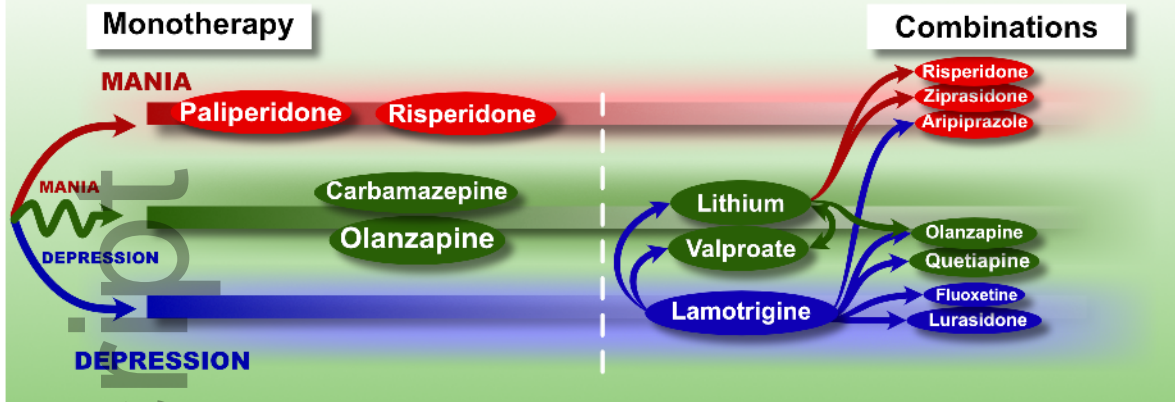
# CHOICES



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# ALTERNATIVES



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