

# Summary of guideline for the treatment of bipolar disorder

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*The past decade has witnessed an extraordinary expansion of treatments available for bipolar disorder. Ten years ago, lithium was the only approved agent for this condition. Since that time, carbamazepine, valproate and olanzapine have received regulatory approval for the acute treatment of mania. Concurrently, randomized controlled trials of various psychological interventions have been recently reported, respecting the important psychological effects of this condition. The present summary provides recommended treatment guidelines for each phase of this condition: mania, mixed episodes, depression and long-term prophylaxis. Levels of evidence for specific treatments are provided and placed in the context of overall principles of quality clinical management.*

**Key words:** bipolar disorder, lithium, mania, manic-depressive illness, mood stabilizer.

This evidence-based summary clinical practice guideline (CPG) is for specialist mental health providers of treatments for adults with bipolar disorder. They should not be equated to ‘standard care’ and recommendations made are not intended to be prescriptive but to be considered within the context of individual clinical judgement and patient preferences.

## Definitions

*Diagnostic and Statistical Manual of Mental Disorders* (DSM) diagnostic criteria for bipolar disorder apply. Because there have been no specific treatment studies in bipolar II disorder, our recommendations refer to bipolar disorder generically. All studies have either described a bipolar I sample, or have not identified separate bipolar I and II subgroups.

## Overview of bipolar disorder

There is a lack of knowledge concerning the precise pathophysiological process responsible for this strongly genetic disorder, which places considerable limitations on the development of new therapies. The illness consists of periods of mania or hypomania, depression, and ‘mixed episodes’ or ‘dysphoric mania’ (an admixture of manic and depressed symptoms). It is commonly subdivided into bipolar I disorder (at least one lifetime manic episode) and bipolar II disorder (only periods of hypomania and depression). Most patients experience multiple episodes at an average of 0.4–0.7 episodes per year, with each lasting 3–6 months.<sup>1</sup> Four episodes in a 12-month period is termed ‘rapid cycling’.

## Overview of the clinical epidemiology

Community surveys report a lifetime prevalence of bipolar disorder of up to 1.6%. It is often a recurrent and disabling illness. Full symptom resolution may occur in only 26% of patients and functional recovery may occur in 24%. A total of 10–19% of patients with bipolar disorder die by suicide. Divorce rates are double that of the general population and the rate of comorbid substance abuse is high.

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## METHOD

Our eight-person CPG team represented the disciplines of psychiatry, clinical psychology and general practice. We worked with a consumers and carers panel, who also developed a consumer CPG. We used the National Health and Medical Research Council (NHMRC) guidelines for the development of clinical guidelines. Our systematic review retrieved all English-language randomized controlled trials (RCT) and other systematic treatment reviews. We also considered the recommendations made in other international CPGs: *Practice Guideline for the Treatment of Patients With Bipolar Disorder (Revision)*;<sup>2</sup> *The Expert Consensus Guideline Series Medication Treatment of Bipolar Disorder 2000*;<sup>3</sup> and *Clinical Practice Guidelines for Bipolar Disorder From the Department of Veterans Affairs*.<sup>4</sup>

## GENERAL MANAGEMENT ISSUES

Bipolar disorder is frequently misdiagnosed as either schizophrenia or personality disorder. Patients should therefore be assessed thoroughly and the diagnosis revised as new information emerges. Although most patients are routinely treated as outpatients, hospitalization, including when to invoke mental health legislation, and monitoring of suicide risk are ongoing management considerations. It is important to closely monitor risky behaviour relating to financial matters, or that posing harm to others, such as hazardous driving. Arranging a financial power-of-attorney may be necessary for some patients. Mania leads to chaotic behaviour, so outpatient attendance is often erratic during this phase of the illness.

## CURRENT TREATMENT EVIDENCE

### Acute treatment of mania and mixed episodes

The following text accompanies Figures M1–M5.

#### *Initial clinical assessment (Figure M1)*

For acutely manic patients referral to specialist psychiatric services for community/outpatient care or hospitalization is usually necessary because of either aggression, excessive spending, or engaging in disinhibited behaviour likely to severely damage the person's reputation – with sexual indiscretions common. Insight and judgement are usually impaired early in the episode, even without the development of frank delusions. Although community or outpatient treatment is always preferable, and admission with the patient's consent occasionally possible, involuntary hospitalization under the relevant health legislation is frequently required. Hospitalization can protect the patient and the family from the damage that may result from the impaired judgement associated with the illness. The decision to hospitalize is often traumatic for both the patient and his or her family, who will need to be supported at that time. A useful clinical rule guiding decisions such as the need

for hospitalization is that the manic patient is almost always worse than he or she appears. Because of this, corroborative information on recent behaviour from family, friends or the general practitioner may be invaluable in making a complete assessment.

#### *Comprehensive clinical assessment (Figure M2)*

A full psychiatric history, mental state assessment and physical examination is necessary to confirm the diagnosis, exclude any underlying organic cause (such as a prescription drug- or substance-induced manic state), identify any physical complications (such as dehydration), and ascertain any risk to the patient or others. Because non-compliance with a mood stabilizer is a frequent cause of relapse, this should be suspected initially in all cases. If the patient is currently prescribed an antidepressant, this should be suspended immediately.

#### *Pharmacological interventions*

*Treatment of manic episode (Figure M3.1)* There are two components to the pharmacological management of acute mania. The first is the commencement of a mood stabilizer (i.e. lithium, sodium valproate, carbamazepine or olanzapine). The mood stabilizers act upon the pathologically elevated mood but have the limitation of a delay of onset of effect of approximately 1 week. The second component is the concurrent (or adjunctive) administration of an antipsychotic or benzodiazepine (or a combination of these) – essentially as a means of calming or sedating the patient with mania as an interim procedure until the mood stabilizer effect becomes apparent. There is no evidence that psychotic manic features predict response to antipsychotic agents.

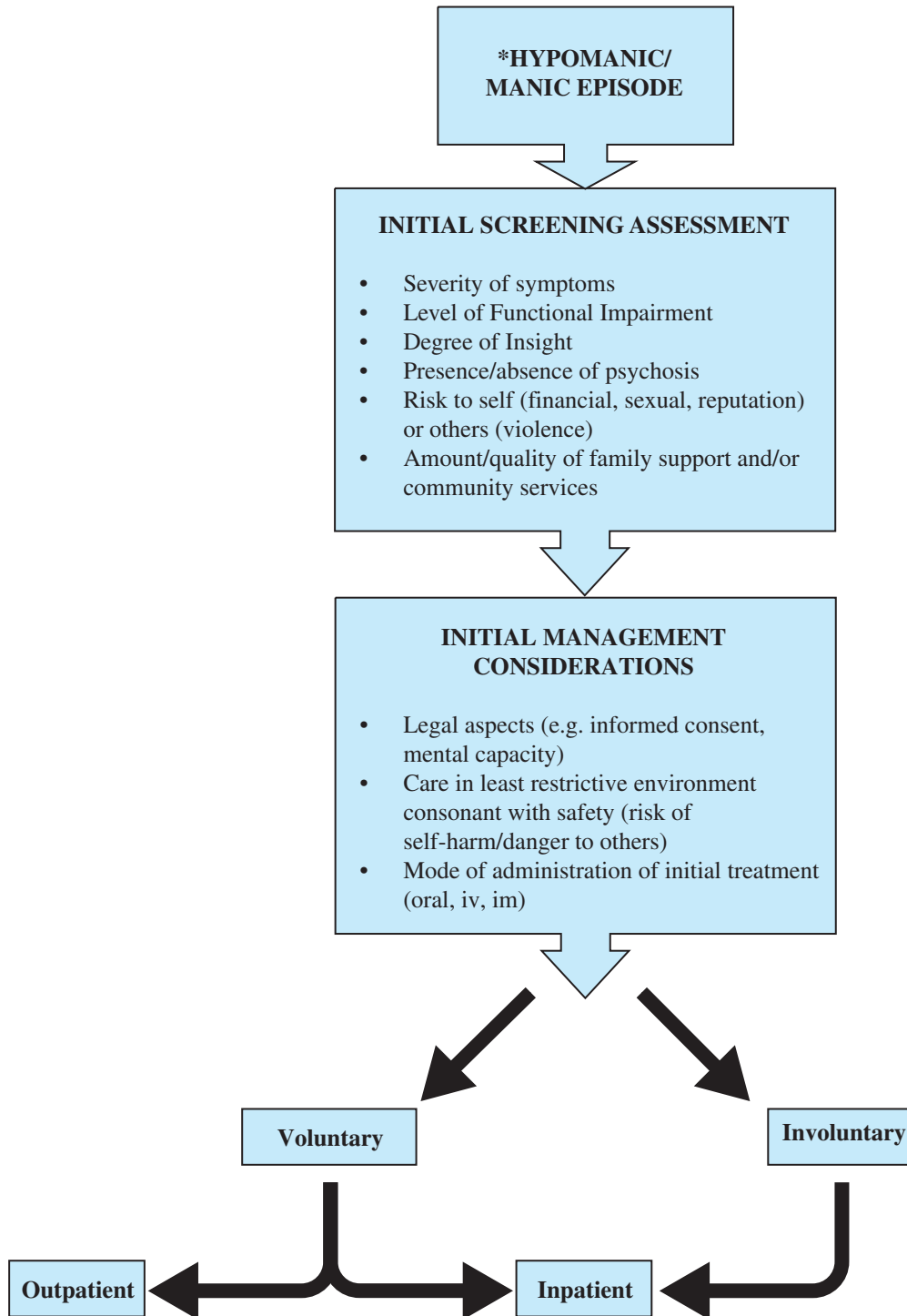
The evidence for the effectiveness of lithium compared to placebo is strong, being confirmed in several meta-analyses. Additionally, two meta-analyses have shown carbamazepine and valproate to be of similar efficacy to lithium, although there have been few methodologically sound placebo-controlled and comparative trials, particularly for carbamazepine. Olanzapine has not been included in any meta-analyses but has been demonstrated in controlled trials to be more effective than placebo and possibly valproate.

For lithium and sodium valproate, therapeutic serum concentration ranges for acute mania are reasonably well established. For carbamazepine, the plasma therapeutic range for epilepsy is a useful guide, but dosage is mainly determined by clinical responsiveness.

*Mixed episode (Figure M3.2)* The best evidence for treatment of mixed states is for valproate, although these data are based on one *post hoc* analysis of a trial of valproate and lithium in mania. The evidence for carbamazepine is weak and, although there are no specific studies of lithium, some authorities recommend its use after failure to respond to anticonvul-

# HYPOMANIC / MANIC EPISODE

## M.1. Initial Clinical Assessment



\*First presentation of mania – often non-specific psychotic episodes where clear differentiation between mania and schizophrenia is difficult. This figure works to the assumption that the diagnosis has been adequately established.

## M.2. Comprehensive Clinical Assessment

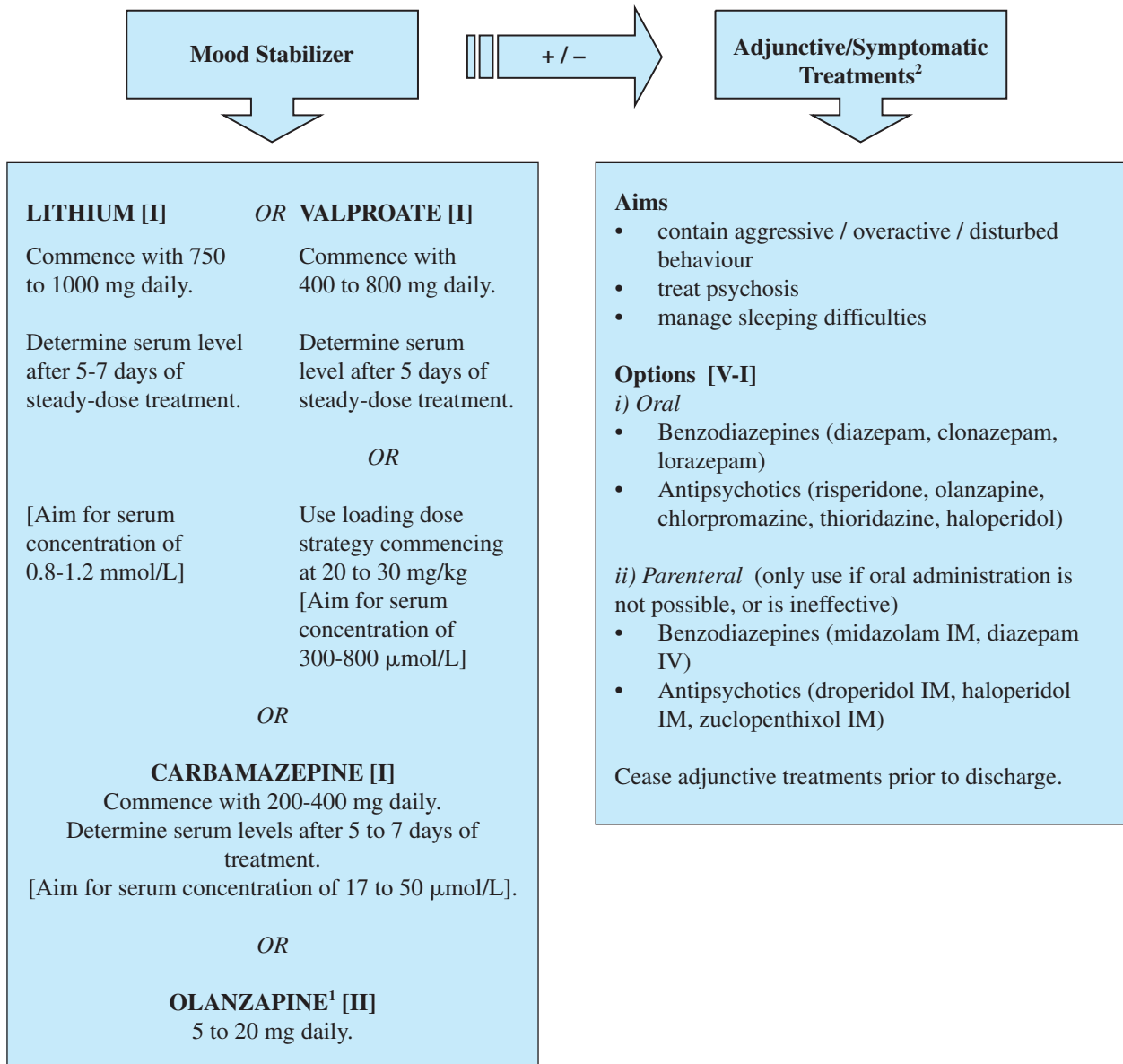
### COMPREHENSIVE CLINICAL ASSESSMENT

Clinical assessment requires patient cooperation. This may not be possible if the patient is irritable or aggressive.

- History taking and mental state assessment: includes risk assessment (potential for violence, degree of financial harm, risky sexual behaviour – exploitation; communicable diseases such as HIV, Herpes, Hepatitis-C)
- Physical examination: exclude organic causes (neurological disorder, systemic disease, substance misuse, prescription medication-induced) or physical sequelae of mania (e.g. dehydration, emaciation)
- Check compliance with mood stabilizer
- Cease any antidepressant
- Conduct routine physical investigations (urea & electrolytes, full blood count, liver function tests, thyroid function tests, therapeutic drug monitoring of mood stabilizer serum concentrations)
- Additional investigations if indicated (e.g., brain scan, cognitive/dementia screen, EEG)

### M.3. Pharmacological Interventions

#### M.3.1. Treatment of Manic Episode



#### Footnotes

1. If using olanzapine as a mood stabilizer, avoid adjunctive treatment with antipsychotic medication.
2. Adjunctive treatments may be initiated when patient is being assessed or their physical state is being corrected prior to introduction of mood stabilizer, or concurrently with mood stabilizer. May not be necessary in cases where manic episode can be contained by mood stabilizer alone.

### M.3.2. Treatment of Mixed Episode

1. Valproate [II]
2. Carbamazepine [IV]
3. Lithium [V-I]
4. Olanzapine [II]<sup>a</sup>

<sup>a</sup> Two randomized controlled studies in combined group of manic and mixed patients. No studies in pure mixed state group.

### M.4. Failure to Respond

Optimize mood stabilizer (dose/blood levels) [V-I]

OR

Switch/substitute mood stabilizer [V-I]

OR

Combine mood stabilizers [III-I]

OR

Augment mood stabilizer with risperidone or haloperidol\* [II]

Continuing failure to respond

1. Re-evaluate diagnosis – consider alternate causes (other psychoses; organic disorders)
2. Electroconvulsive Therapy [II]

\* Do not use other adjunctive antipsychotics with this combination

### M.5. Criteria for Continuation and Maintenance Treatment

#### M.5.1. First manic episode

- Continue treatment for at least six months [V-I]

#### M.5.2. Manic episode in established bipolar illness [V-I]

- Various criteria for long term treatment
  - Angst: At least two episodes of mania or depression (including current episode) in previous five years
  - NIMH Consensus development panel guidelines: Single manic episode or both hypomanic and depressed episode. Also consider past suicide attempts, psychotic episodes and functional disability associated with episodes
  - Goodwin & Jamison: Two major episodes of mania and/or depression, irrespective of frequency

sants. Olanzapine has been shown to be effective in combined samples of manic and mixed subjects.

#### **Failure to respond (Figure M4)**

The timing of the decision to change treatment will depend on both clinical urgency and the degree of response. There are several options when the patient fails to respond to the initial pharmacological intervention: increase the dose and/or blood levels of the mood stabilizer; switch mood stabilizers; combine mood stabilizers; or add an adjunctive antipsychotic such as risperidone or haloperidol. The strongest evidence is for augmentation of the mood stabilizer with risperidone or haloperidol; while the next most persuasive data are for combining mood stabilizers. If the patient fails to respond to such strategies, electroconvulsive therapy (ECT) may be considered.

#### **Continuation treatment (Figure M5)**

Following remission of an initial episode of mania, the mood stabilizer should be continued for at least 6 months. Patients should be withdrawn from their benzodiazepine or antipsychotic once the acute episode has resolved. For those with a well-established history of bipolar disorder, there are a number of recommended criteria for deciding whether the patient is likely to benefit from ongoing treatment. Most of these guidelines are based on either consensus opinions or clinical wisdom, and consist of various permutations of illness frequency, severity and disability.

#### **Acute treatment of bipolar depression**

The following text accompanies Figures D1–D5.

#### **Initial Clinical Assessment (Figure D1)**

Issues similar to those described for the acute management of mania.

#### **Comprehensive clinical assessment (Figure D2)**

A full psychiatric history, mental state and physical examination should be conducted to confirm diagnosis; exclude underlying pathology; identify physical complications and gauge risk of self-harm. Non-compliance should be suspected in all cases.

#### **Pharmacological Intervention (Figure D3)**

In established bipolar disorder, depression arises: (i) in the absence of ongoing medication – de novo depression; or (ii) during ongoing treatment – breakthrough depression.

**De novo depressive episode (Figure D3.1)** The first step is to institute appropriate ‘antidepressant treatment’.

**Mood stabilizer alone (Figure D3.1.1)** Lithium is recommended as the first-line treatment unless it has been unsuccessful in the past or is poorly tolerated, in which case lamotrigine or valproate should be trialled. The administration of a mood stabilizer minimizes the risk of switching, and for patients

who are not psychotic, suicidal or hospitalized this may be sufficient. However, this antidepressant effect of mood stabilizers can take several weeks and particularly where there is a risk of self-harm, concomitant antidepressant use is advisable.

Mood stabilizer treatment should be optimized (ensuring efficacy and minimizing side-effects) by monitoring plasma levels. Lithium is the preferred choice because of its acute and preventative efficacy. However, it has a slow onset of action and it is not as effective an antidepressant as lamotrigine. Therefore, both lithium and lamotrigine should be considered as first-line options. Valproate warrants consideration in rapid cycling bipolar disorder.

**Mood stabilizer and antidepressant combined (Figure D3.1.2)** The concurrent initiation of a mood stabilizer and an antidepressant may enhance and accelerate antidepressant efficacy and diminish the likelihood of switching.

**Breakthrough depression on single mood stabilizer (Figure D3.2)** Initially optimize the dose and/or serum levels of the mood stabilizer. If this is unsuccessful consider the addition of (i) an antidepressant; or (ii) a second mood stabilizer.

**Add antidepressant (Figure D3.2.1)** Antidepressant monotherapy may induce mania/rapid cycling and should therefore be avoided. Monoamine oxidase inhibitors (MAOIs) are suited to patients with anergic bipolar depression but like tricyclic antidepressants (TCAs) they can induce mood instability. Therefore, selective serotonin reuptake inhibitors (SSRIs) and venlafaxine form the first-line choice, with MAOIs and TCAs as second-line. Newer antidepressants (mirtazapine, nefazodone or reboxetine) have not been adequately researched.

Upon remission/recovery antidepressants should be tapered so as to minimize the risk of switching while the mood stabilizer is continued.

**Add second mood stabilizer (Figure D3.2.2)** Adding a second mood stabilizer is as effective as adding an antidepressant, but it is less well tolerated.

Lithium, valproate and carbamazepine combinations are used routinely but efficacy evidence is available only for the pairing of lithium and carbamazepine. Lamotrigine is the preferred choice when considering a second mood stabilizer because of its efficacy, but its dose should be reduced in combination with valproate because of the risk of serious rash.

Therefore, overall, the addition of an antidepressant is the preferred choice but a second mood stabilizer can be trialled, especially if combination therapy is likely to continue long-term.

**Choice of antidepressant (Figure D3.3)** The SSRIs are the antidepressants of choice in the treatment of

bipolar depression because of their proven efficacy and low propensity to cause switching. Venlafaxine is a suitable alternative. The MAOIs and TCAs are of limited use long-term because of associated side-effects and the risk of switching. Nevertheless, the threshold for prescribing MAOIs should be low, especially in the presence of anergia, melancholic or atypical depressive features.

**Choice of mood stabilizer (Figure D3.4)** Mood stabilizer choice is determined by patient characteristics, clinician preferences and clinical indication. However, the evidence clearly favours lithium and lamotrigine.

#### **Failure to Respond (Figure D4)**

Initially, compliance and therapeutic optimization of ongoing treatment should be ensured. Either or both mood stabilizers and antidepressants can be substituted or yet another mood stabilizer added. By this stage lithium should have been trialled.

Any number of mood stabilizer pairings can be attempted in conjunction with antidepressants. However, if despite all reasonable efforts the patient remains depressed or only partially responds, it is important to re-evaluate the diagnosis and review therapy. Organic causes need to be confidently excluded. Furthermore, the impact of any comorbid medical/psychiatric conditions should be thoroughly assessed and consideration given to psychosocial factors.

Electroconvulsive therapy is arguably the most effective antidepressant therapy for bipolar depression and it should therefore be used when indicated and especially if it has been previously effective or there are psychotic symptoms.

#### **Continuation treatment (Figure D5)**

Following remission of the depressive episode it is appropriate to withdraw antidepressant treatment after 2–3 months to avoid precipitating mania and/or rapid cycling (Figure D5.1). However, in every patient it is necessary to balance the need to treat bipolar depression versus the risk of precipitating mania (Figure D5.2).

#### **Prophylaxis**

The following text accompanies Figures P1–P4. Because non-compliance is perhaps the commonest cause of relapse, it is essential for the clinician to attempt to improve compliance rates by strategies such as educating the patient about potential side-effects and minimizing these, informing patients and families about the disorders and its treatment, and supportive psychotherapy. All patients fear the potentially sudden loss of control of their behaviour and the embarrassing consequences. It is sometimes only after caring for patients over several episodes that they come to accept the diagnosis and need for treatment. Active bipolar disorder support groups operate in most States and play a very useful role in any treat-

ment programme. Written materials for patients about bipolar disorder and mood stabilizers, such as those provided by various governmental authorities or non-governmental organizations (NGO) such as SANE, can be very helpful for patient education.

An under-acknowledged issue in the long term management of bipolar disorder is that of continuity of care – a matter relevant to both the patient and clinician. Ongoing contact with the same clinician increases the likelihood of early identification of recurrences, and facilitates awareness of the ongoing impact of the illness. Unfortunately clinicians change frequently (particularly in the public health system), and the illness leads to a peripatetic lifestyle for many patients.

#### **Criteria for embarking upon long-term treatment (Figure P1)**

These have been outlined in the section titled 'Acute treatment of mania and mixed episodes'.

#### **Pharmacological interventions**

**Non-rapid cycling (Figure P2.1)** Two meta-analyses (one Cochrane and another) strongly support the evidence from randomized clinical trials of the prophylactic capacity of lithium in this disorder. While there have been randomized comparator studies (and meta-analyses) indicating that carbamazepine is of similar efficacy to lithium, there have been no prophylactic studies of either carbamazepine or valproate confirming their superiority over placebo. Recent scientific conference presentations have reported lamotrigine to be more effective than placebo in preventing episodes of bipolar depression, but these studies have yet to appear as full publications in refereed journals.

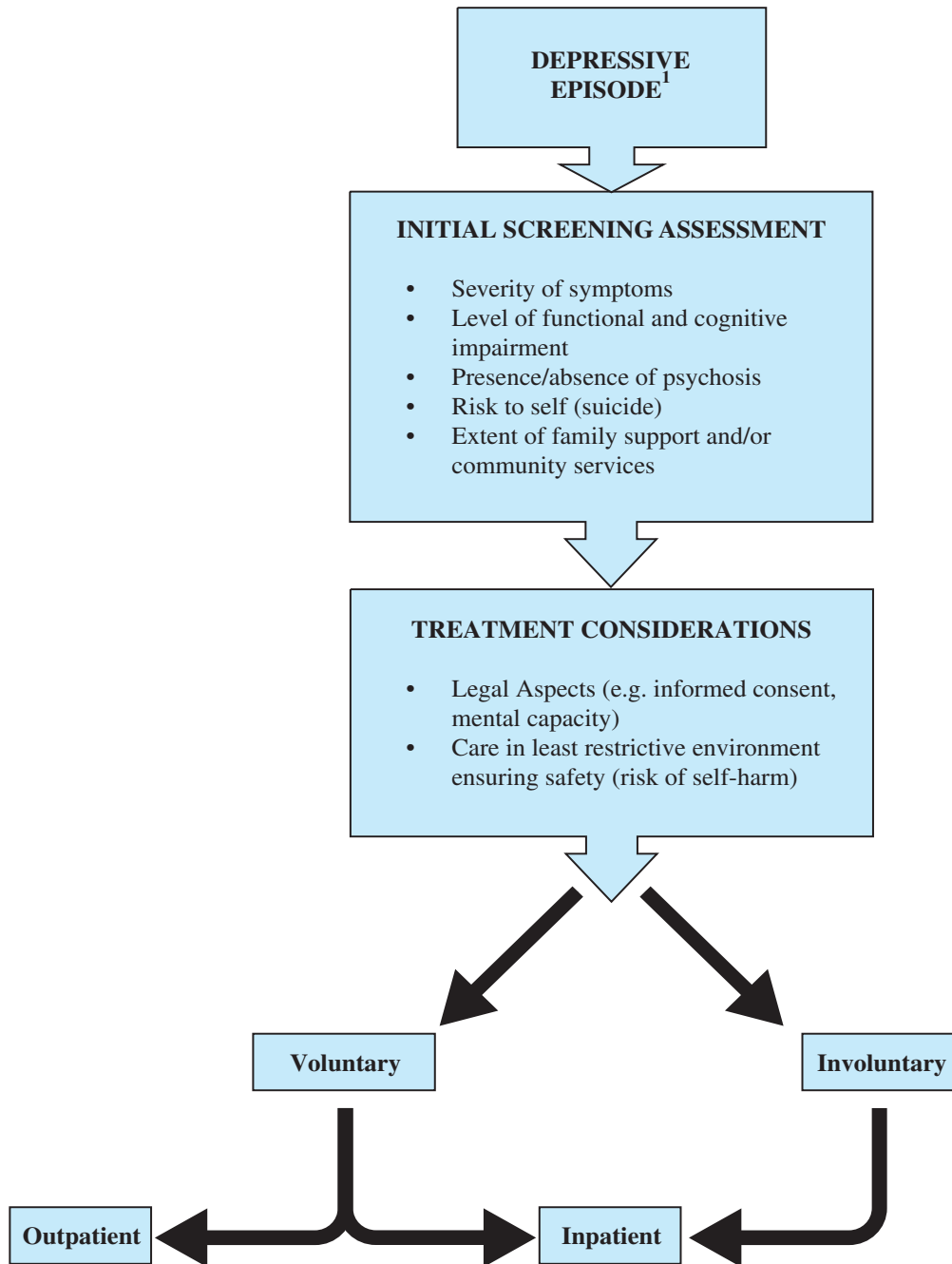
For patients on lithium, renal function (with serum creatinine and electrolytes) should be monitored every 3–6 months, and thyroid function (including thyroid-stimulating hormone (TSH)) every 6–12 months in addition to clinical assessment. Abrupt cessation of lithium leads to relapse of mania (or, less likely, depression) in many bipolar patients within the next few months. Therefore, if lithium is to be ceased, this should be undertaken slowly over at least 1–2 months.

For carbamazepine and valproate, haematological and hepatic function should be monitored at least each 3–6 months after treatment has been initiated.

**Rapid cycling (Figure P2.2)** There is no convincing evidence from randomized controlled trials that any of the mood stabilizers are robustly effective in the treatment of rapid-cycling bipolar disorder. Valproate has been reported to be effective in open studies. Lamotrigine was found to have mood stabilizing properties in a double-blind placebo-controlled crossover study in a mixed group of unipolar and rapid-cycling bipolar patients, but no breakdown of thera-

# BIPOLAR DEPRESSIVE EPISODE

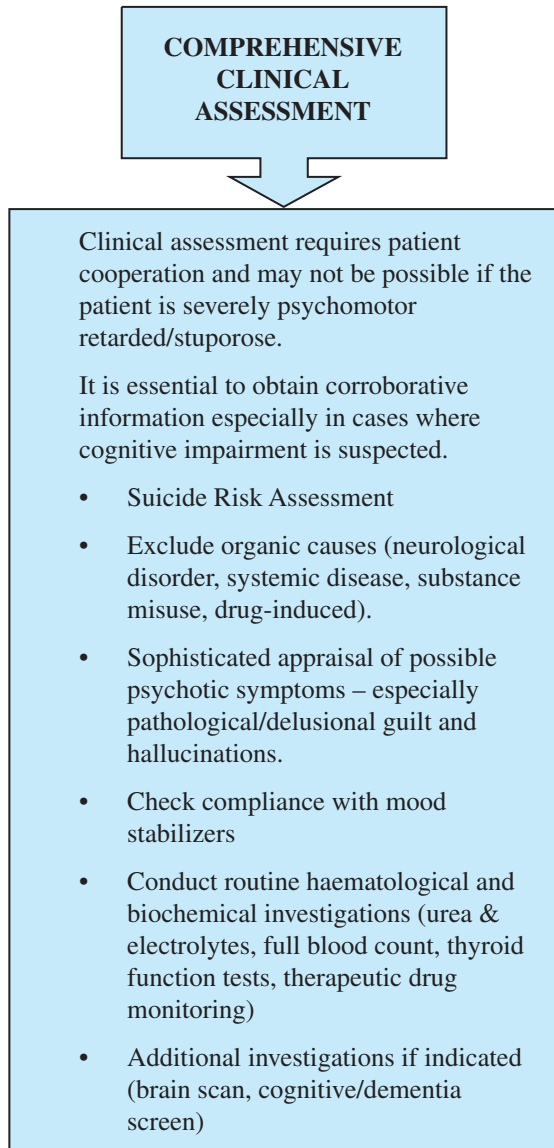
## D.1. Initial Clinical Assessment



### Footnotes

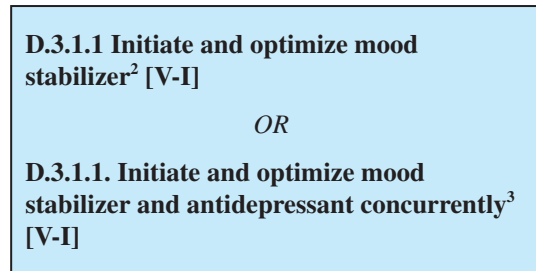
D.1. – <sup>1</sup> The differentiation of a bipolar depressive episode from a unipolar depressive episode is often difficult at first presentation. This figure works to the assumption that the diagnosis has been adequately established.

## D.2. Comprehensive Clinical Assessment

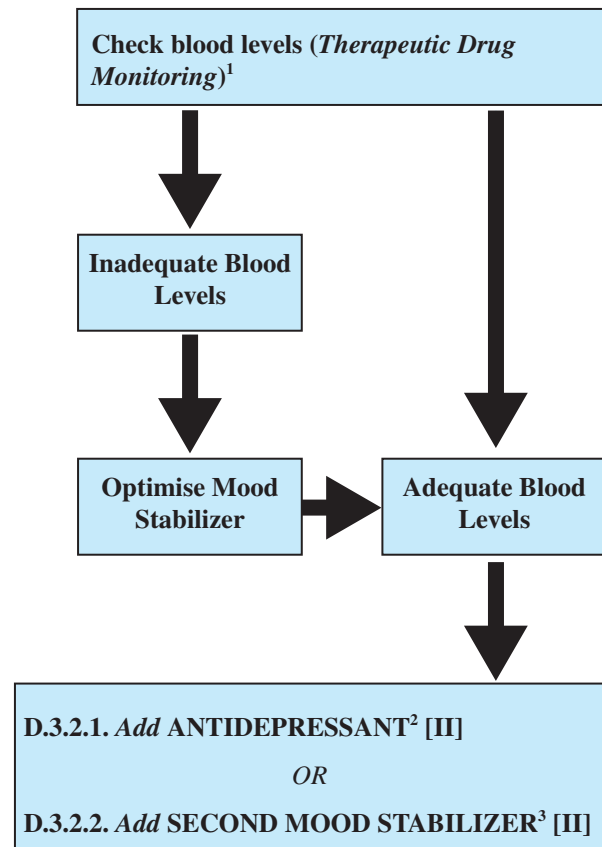


## D.3. Pharmacological Intervention

### D.3.1. *de novo* Depressive Episode<sup>1</sup>



### D.3.2. *Breakthrough* Depressive Episode on *Single Mood Stabilizer*



### Footnotes

**D.3.1.** – <sup>1</sup> Bipolar depression in the absence of any ongoing medication regardless of prior treatment.

**D.3.1.** – <sup>2</sup> American Psychiatric Association recommends the first line use of a mood stabilizer (APA Guidelines 2002). The antidepressant effects of mood stabilizer monotherapy may take up to 4 to 6 weeks to develop and is not advisable for patients that are psychotic, suicidal or hospitalized.

**D.3.1.** – <sup>3</sup> The concurrent deployment of a mood stabilizer reduces the risk of switching into mania. (Boerlin *et al.* 1998; Bottlender *et al.* 2001)

**D.3.2.** – <sup>1</sup> See comprehensive guidelines Mitchell *et al.* (2003) section 5.6.

**D.3.2.** – <sup>2</sup> The combination of an antidepressant with a mood stabilizer allows for possible enhancement and more rapid onset of antidepressant efficacy (Nemeroff *et al.* 2001; Young *et al.* 2000).

**D.3.2.** – <sup>3</sup> Data is only available for the combination of lithium and carbamazepine (Denicoff *et al.* 1997). However, lamotrigine should be the preferred choice when considering the addition of a second mood stabilizer. The dose of lamotrigine should be halved when combined with valproate (Messenheimer *et al.* 1998).

### D.3.3. Choice of Antidepressant

- **SSRIs<sup>1</sup> [II]**
- **TCAs<sup>2</sup> [II]**
- **MAOIs<sup>3</sup> [II]**
- **Venlafaxine<sup>4</sup> [III-I]**

### D.3.4. Choice of Mood Stabilizer

- **Lithium<sup>1</sup> [I]**
- **Lamotrigine<sup>2</sup> [II]**
- **Olanzapine/fluoxetine Combination<sup>3</sup>**

#### Footnotes

**D.3.3.** – <sup>1</sup> SSRIs have proven efficacy in the treatment of bipolar depression (Cohn *et al.* 1989; Nemeroff *et al.* 2001; Young *et al.* 2000).

**D.3.3.** – <sup>2</sup> The efficacy of TCAs in the acute treatment of bipolar depression is equivalent to that in major depression; however, they are of limited use long term (Prien *et al.* 1973; Prien *et al.* 1984) and are associated with a significant risk of switching (Peet 1994).

**D.3.3.** – <sup>3</sup> Conventional MAOIs, in particular tranylcypromine, have been shown to be effective in the treatment of bipolar depression in placebo-controlled and comparator studies (Himmelhoch *et al.* 1991; Frances *et al.* 1996; Himmelhoch 1982). The threshold for prescribing these antidepressants should be lower than in major depression. MAOIs may be prescribed prior to TCAs when the clinical profile includes anergia and melancholic features.

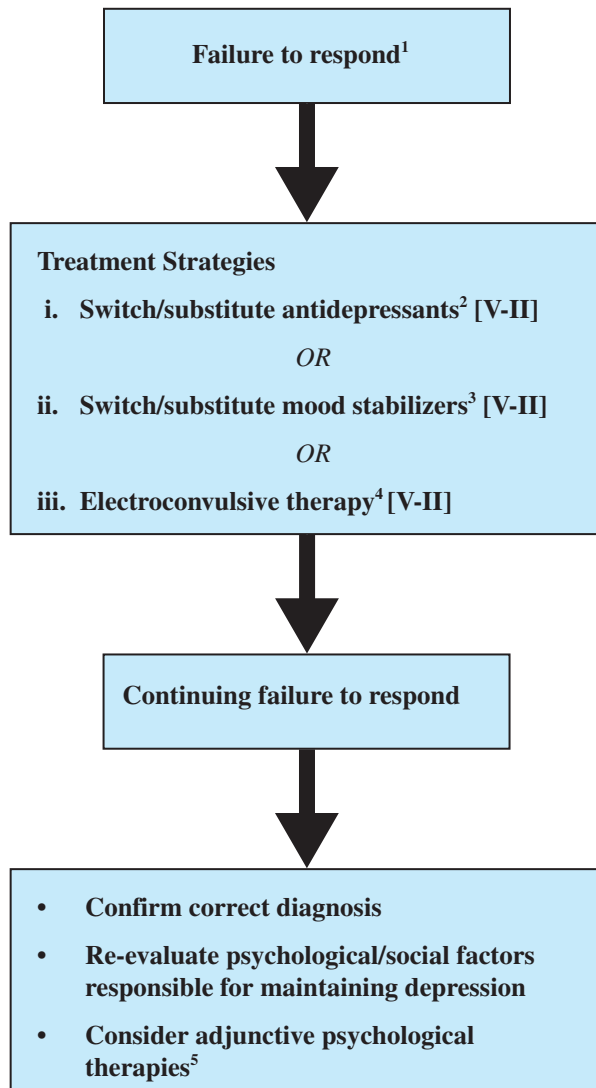
**D.3.3.** – <sup>4</sup> Has been trialled in bipolar II depression (Amsterdam and Garcia-Espana 2000).

**D.3.4.** – <sup>1</sup> Several placebo-controlled, double blind studies demonstrate the efficacy of lithium in the treatment of bipolar depression. However, it is less effective in those with rapid cycling (Swann *et al.* 1997). It may also protect against suicide (Baldessarini *et al.* 1999).

**D.3.4.** – <sup>2</sup> Lamotrigine is an effective antidepressant in bipolar depression (Calabrese 1999; Frye 2000).

**D.3.4.** – <sup>3</sup> Promising emerging evidence (Tohen *et al.* 2002) [Abstract].

#### D.4. Failure to Respond



#### D.5. Continuation Treatment

**D.5.1.** – Withdraw antidepressant treatment after 2 to 3 months to avoid precipitating mania / rapid cycling. [V-II]

**D.5.2.** – Maintenance treatment with antidepressants. Have a role in the treatment of patients with recurrent depressive episodes if administered in conjunction with a mood stabilizer. Need to balance the need to treat episodes of depression versus the risk of precipitating mania / rapid cycling. [V-II]

#### Footnotes

D.4. – <sup>1</sup> Failure to respond to a mood stabilizer or a combination of a mood stabilizer and an antidepressant.

D.4. – <sup>2</sup> No evidence for the treatment of bipolar depression. Switch between classes of antidepressants when reason is because of a lack of efficacy and within class when because of side effects/intolerance.

D.4. – <sup>3</sup> Administration of mood stabilizers may overlap. See D.3.2. – <sup>3</sup>.

D.4. – <sup>4</sup> The initiation of ECT should not be delayed especially if previously effective or in the presence of psychotic symptoms (Sackeim and Rush 1995).

## PROPHYLAXIS OF BIPOLAR DISORDER

### P.1. Criteria for embarking upon long term treatment

- P.1. Manic episode in established bipolar illness [V-I]**
- Various criteria for long term treatment
    - Angst: At least two episodes of mania or depression (including current episode) in previous five years
    - NIMH Consensus development panel guidelines: Single manic episode or both hypomanic and depressed episode. Also consider past suicide attempts, psychotic episodes and functional disability associated with episodes
    - Goodwin & Jamison: Two major episodes of mania and/or depression, irrespective of frequency

### P.2. Pharmacological interventions

#### P.2.1 Non-rapid Cycling

- LITHIUM [I]**  
(Aim for serum concentration of 0.6 to 0.8 mmol/L)
- OR*
- VALPROATE [III-II]**  
(Usual dose range 1000 to 2500 mg; serum concentration 350-700  $\mu$ .mol/L)
- OR*
- CARBAMAZEPINE [II]**  
(Usual dose range 600 to 1200 mg; serum concentration 17 to 50  $\mu$ .mol/L)
- OR*
- LAMOTRIGINE [II]<sup>a</sup>**  
(Usual dose range 50 to 300 mg; serum concentration not useful)

<sup>a</sup> Not yet published as full refereed article – currently conference abstracts only.

#### P.2.2. Rapid Cycling

- VALPROATE [IV]**  
(Usual dose range 1000 to 2500 mg; serum concentration 350-700  $\mu$ .mol/L)
- OR*
- LAMOTRIGINE [IV]**  
(Usual dose range 50 to 300 mg; serum concentration not useful)
- OR*
- CARBAMAZEPINE [IV]**  
(Usual dose range 600 to 1200 mg; serum concentration 17 to 50  $\mu$ .mol/L)
- OR*
- LITHIUM [V-I]**  
(Aim for serum concentration of 0.6 to 0.8 mmol/L)

#### P.3. Psychological interventions

- **PSYCHOEDUCATION**
    - Individual [II]
    - Family-focused therapy (FFT) [II]
- OR*
- **COGNITIVE BEHAVIOURAL THERAPY [II]**
- OR*
- **INTERPERSONAL AND SOCIAL RHYTHM THERAPY (IPSRT) [V-I]**

Note: For all psychotherapies, main therapeutic effect is observed in prevention of depressive episodes

## P.4. Failure to Respond

### P.4.1 – NON-RAPID CYCLING

- Exclude non-compliance
- Treat any comorbid substance misuse
- Trial alternative mood stabilizer *alone* or in *combination* with current mood stabilizer (strongest evidence is for lithium + valproate) [III-I]

### P.4.2 – RAPID CYCLING

- Exclude non-compliance
- Treat any comorbid substance misuse
- Exclude antidepressant-induced affective instability
- Exclude subclinical hypothyroidism
- Trial alternative mood stabilizer *alone* or in *combination* with current mood stabilizer (strongest evidence is for lithium + valproate) [IV]

peutic response by diagnostic subgroup was provided. There have been no specific studies of lithium in this population.

### **Psychological interventions (Figure P3)**

Long-term issues with bipolar disorder include: difficulty in acceptance of illness and the impact of this condition on self-concept and self-esteem; dealing with stigma; and the resultant effects on treatment adherence. There have been randomized controlled trials of psychoeducational therapies (both individual and family: family focused therapy (FFT)) that have demonstrated the capacity of those therapies to prevent relapse (particularly of depression). Similar efficacy has been demonstrated for cognitive behavioural therapy. Interpersonal and social rhythm therapy (IPSRT) has been recommended, but the outcome of controlled trials has yet to be reported.

### **Failure to respond**

**Non-rapid cycling (Figure P4.1)** There is some evidence that adding a second mood stabilizer (particularly using the combination of lithium and valproate) enhances prophylactic capacity.

**Rapid cycling (Figure P4.2)** Initially potential causes of rapid-cycling bipolar disorder should be excluded and managed (i.e. comorbid substance abuse, anti-depressant medications, and (subclinical) hypothyroidism).

### **ACKNOWLEDGEMENTS**

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