

# **BIPOLAR**

## **DISORDER PMB DEFINITION GUIDELINE**

Council for Medical Schemes. Pretoria. South Africa



**Disclaimer:**

*This Bipolar Disorder Benefit Definition Guideline has been developed to prescribe the scope and level of minimum benefits beneficiaries of medical schemes are entitled to. It should be read with Regulation 15 of the PMB Regulations of the Medical Schemes Act of 1998.*

## Executive Summary

The legislation governing the provision of the Prescribed Minimum Benefits (PMBs) is contained in the Regulations enacted under the Medical Schemes Act, 1998 (Act No. 31 of 1998). It has become clear that medical scheme beneficiaries find it difficult to be fully aware of their entitlements in advance. In addition, medical schemes interpret these benefits differently, resulting in a lack of uniformity of benefit entitlements. The guideline covers the assessment, diagnosis, and management of Bipolar Disorder. It aims to define the Prescribed Minimum Benefits (PMBs) for the management of Bipolar Disorder and to make recommendations and suggestions to enhance the overall care of individuals with Bipolar Disorder. The primary objective of the PMB Definition Guideline is to *inter alia*:

- Provide clear, comprehensive descriptions of the benefits, in terms of the provisions of the PMB regulations of the Medical Schemes Act, No. 131 of 1998.
- Improve clarity in the funding decisions by medical schemes; and
- Ensure protocols and algorithms developed by medical schemes are developed on best available clinical practice guidelines.

This guideline is based on the best available evidence (*safety, efficacy, effectiveness, and economic aspects*) and clinical practice knowledge of Bipolar Disorder.

Our recommendations are put together by technical experts, healthcare professionals and the medical schemes industry. This Guideline should be read in conjunction with the supplementary information included as Annexure A to this guideline.

This PMB Definition Guideline was developed as a policy prescript in line with Section 15 (A) to (I) of the Medical Schemes Act, 131 of 1998, for the development of protocols and formularies, and should be viewed in this context.

## Acknowledgements

The Council for Medical Schemes (CMS) would like to acknowledge all stakeholders and members of the Clinical Advisory Committee (CAC) who assisted in providing technical input and development of this document, including the following general practitioners, psychiatrists, and representatives from other healthcare professionals for their insights:

Dr Eugene Allers (Psychiatrist)

Dr Mvuyiso Talatala (Psychiatrist)

Ms Carla Gerryts (Dietician)

Dr Linda Blokland (Clinical Psychologist)

Mr Winston Schoeman (Clinical Psychologist)

Mr Michael Webber (Counselling Psychologist)

Samantha Holle (Counselling Psychologist)

Ms Mareldia Achmat (Counsellor)

Ms Gerbri van Heerden (Occupational Therapist)

Ms Natasha van de Heyde (Occupational Therapist)

Ms Haneke Jonas (Occupational Therapist)

Ms Karen Coertze (Physiotherapist)

Claudia Schaft (Physiotherapist)

The individuals mentioned below from patient advocacy groups, representatives from pharmaceutical companies, and different medical schemes and administrators; were also members of the Clinical Advisory Committee set up to discuss member entitlements for Bipolar Disorder. Their contributions were immensely valuable.

Dr Lindiwe Mbekeni (Discovery Health)

Ms Cassi-Lee Rubin (Discovery Health)

Ms Cassey Chambers (South African Depression and Anxiety Group)

Dr Moresi Mahlangu (GEMS)

Dr Randal Hartnick (GEMS)  
Dr Lerato Motshudi (GEMS)  
Mr Fakir Chavoos (Pharmaceutical Task Group)  
Ms Demi-Lee Weitz (Medscheme)  
Ms Danielle Oosthuizen (Medscheme)  
Mr Fabian Bennet (Clinix Health Group)  
Ms Dina Louw (Afrocentric)  
Ms Vanessa Snow (Janssen-J&J)  
Ms Angela Riva (Jansen- J&J)  
Dr Lerato Motshudi (Akeso Clinics)  
Mr Kobus Kuhn (Financial Planning Institute)  
Mr Dewald David de Lange (Mediclinic)

Special Thanks to Dr Shamima Saloojee (Chairperson) and Dr Edith Madela-Mntla for their contribution and development of the final PMB Definitions Guideline for Bipolar Disorder.

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# **GUIDANCE FOR THE ASSESSMENT AND MANAGEMENT OF BIPOLAR DISORDER**

**This guideline provides recommendations for the:**

1. Assessment and diagnosis of Bipolar Disorder.
2. Treatment, care, and rehabilitation in Bipolar Disorder.
3. Monitoring and evaluation of patients with Bipolar Disorder and
4. Rehabilitation and re-integration of mental health care users with bipolar disorder

## **1. ASSESSMENT AND DIAGNOSIS**

### **1.1. Diagnosis**

- 1.1.1. In this guideline the term Bipolar Disorder (BD) refers to Bipolar I and Bipolar II disorder. Bipolar Disorder is used synonymously with Bipolar Mood Disorder and Bipolar Affective Disorder used in previous versions under the classification systems of mental and behavioural illnesses.
- 1.1.2. The diagnosis of BD involves the establishment of recurrent abnormal mood episodes ranging from extreme happiness, overactivity, and disinhibited behaviour to episodes of severe depression, decreased motivation, vegetative shift, and impaired cognitive functioning.
- 1.1.3. Mixed episodes refer to the occurrence of both abnormal mood states at the same time in the same individual, and a spectrum of mood states occur between the two extremes.
- 1.1.4. Evidence shows that patients with bipolar disorder who have manic/hypomanic or depressive episodes with mixed features tend to have a more severe form of bipolar disorder along with a worse course of illness and higher rates of comorbid conditions than those with non-mixed presentations.
- 1.1.5. BD is often difficult to recognise because symptoms overlap with other psychiatric disorders, psychiatric and somatic comorbidity is common, and patients may lack insight into their conditions, particularly hypomania.

- 1.1.6. Misdiagnosis of the depressive phase of BD can be problematic as traditional antidepressant medication can delay improvement of symptoms and possibly induce a switch to mania.
- 1.1.7. The diagnosis of BD must be confirmed by two mental health care practitioners, one of whom should be qualified to do physical examinations i.e., a medical practitioner (GP or psychiatrist). In primary care, one mental health care practitioner (MHCP) may make a provisional diagnosis for BD, but this must be confirmed by a general practitioner (GP) (see Table 1).
- 1.1.8. The depressive phase is the dominant phase of bipolar disorder, with patients spending approximately 75% of their time in a depressive phase.
- 1.1.9. Compared to major depressive disorders, the depressive episodes in BD are more severe, rapid in onset, frequent and respond differently to medication.
- 1.1.10. A case manager should be assigned to all mental health care users diagnosed with BD.

## **1.2 History and Examination**

1.2.1 A comprehensive multidisciplinary assessment should be conducted.

1.2.2 The assessment should include a:

- Psychiatric history.
- Medical history.
- Physical examination.
- Mental state examination.
- Past mood episodes.
- Episodes of elation, overactivity, and disinhibition.
- Episodes of despondency, lack of interest and appetite and sleep changes.
- Any other episodic and sustained changes in behaviour or symptoms between episodes and

- Comorbid mental and physical illnesses.

1.2.3 Further, the following must be conducted:

- An assessment of psychosocial and personal functioning.
- An occupational functioning or educational assessment and
- An assessment of socioeconomic status.

1.2.4 Several consultations may be required to make a final diagnosis of BD, and medical scheme benefits should cover the cost of these consultations.

1.2.5 The most used scales for assessing a manic episode include the Young Mania Rating Scale (YMRS), and those for a depressive episode include the Hamilton Depression Scale (HAM-D) and Montgomery-Asberg Depression Scale (MADRS)

### **1.3 Base-line Investigations.**

1.3.1 The following baseline investigations should be performed before initiating treatment (see Table 2)

- Anthropometry: height, weight, WC, WHP ratio.
- Blood Pressure.
- Full Blood Count with differential (FBC).
- Urea and Electrolytes (U &E).
- Thyroid Function Test (TFT.)
- Fasting Blood Glucose (FBG) or HbA1c.
- Treponema Pallidum Haemagglutination (TPHA).
- HIV with consent.
- Pregnancy Test (females of childbearing age).
- Lipogram.

- Liver Function Tests (LFT).
- Serum Calcium.
- Estimated Glomerular Filtration Rate (eGFR).
- Clotting screen (PT/PITT).
- Lithium Levels.
- Valproic Acid Levels.
- Electrocardiogram (EC)
- CT Scan if clinically indicated and
- Toxic drug screen (urine or blood) -Suspect substance use.

## **2. TREATMENT AND CARE IN PRIMARY, SECONDARY CARE OR TERTIARY CARE**

### **2.1. Primary Care**

The treatment and care of patients with BD is considered a core skill for primary care physicians, and patients with BD can be treated and cared for in an outpatient setting.

### **2.2. Referral to Secondary Care**

2.2.1. Include those patients:

- Who are at risk to themselves and/or others.
- With a poor or incomplete response to treatment.
- With non-or poor adherence to medication and
- Who require psychological intervention that is not available in primary care; they should be referred to secondary care without delay.

2.2.2. Patients must be cared for in secondary care until remission or a good response is reached. It is recommended that at least 6 follow up contacts be available to enable the positive therapeutic response.

2.2.3. The recommended maximum hospital stay is 21 days.

### **2.3. Referral back to primary care:**

2.3.1. Patients who have responded effectively to treatment and are stable, can receive maintenance treatment by the GP or any MHCP whose scope of practice incorporates care, treatment, and rehabilitation of mental health care users.

### **2.4. Referral to tertiary care:**

2.4.1. Patients who cannot be safely and effectively managed in a secondary sector facility or who require specialised intervention should be referred to a tertiary facility.

## **2.5. Pharmacological Treatment**

### **2.5.1. Prescribing Principles**

2.5.1.1. Treatment options for the management of BD include mood stabilisers, anti-depressants, antipsychotic medications, electroconvulsive therapy, adjunctive medications and psychosocial interventions depending on the phase of illness, mania/hypomania/depression/mixed-in which the patients present to the clinician.

2.5.1.2. Pharmacologic treatment of BD is divided into three categories: manic phase, depressive phase, and maintenance.

2.5.1.3. At the initiation of treatment, prescribe a dose at the lower end of the licensed dose range and slowly titrate upwards within the given dose range as per the South African Medicines Formulary of Medicines Package Insert.

2.5.1.4. Justify and record reasons for prescribed dosages outside of the recommended range.

2.5.1.5. Accurately record the rationale for continuing, changing, or stopping medication and the effects of any such changes.

### **2.5.2. Prescribing for older patients with BD**

2.5.2.1. Use medication at lower end of recommended doses.

2.5.2.2. Consider the increased risk of drug interactions.

2.5.2.3. Consider the negative impact of anticholinergic medication, or drugs with anticholinergic activity on cognitive function and mobility in older patients.

### **2.5.3. Mania/hypomania**

2.5.3.1. Pharmacological treatment is the treatment modality of choice for all phases of bipolar disorder.

2.5.3.2. The primary focus of treatment is:

- The early remission of current mood episodes to reduce the intensity of symptoms.
- To prevent the recurrence of the disorder and
- To prevent the negative consequences of the impaired judgement associated with the mania.

2.5.3.3. Add-on psychosocial interventions are essential for the prevention of relapses and recurrences and for restoring function.

2.5.3.4. The pharmacological treatment for manic and hypomanic episodes is similar.

2.5.3.5. Mood stabilisers, anticonvulsant mood stabilisers and antipsychotics alone, or in combination, are the mainstay of treatment for mania across all major international guidelines.

2.5.3.6. No algorithmic or ranking of first line medications are presented in this guideline, because of differences in inter- and intra-individual responses to a specific medication or class of medications.

2.5.3.7. Several medications alone or in combination are presented as first line options for treatment.

2.5.3.8. Selection of the appropriate treatment from the range of available medications is dependent on several factors, including:

- Intensity/severity of the illness.
- Presence of psychotic features.
- Presence of comorbid medical illnesses.
- Side effect profile of the medication.
- Cost of medication.
- Availability of medication.
- Patient preference.
- Clinicians' professional judgement.
- Family history of BD and
- Risk for suicide.

2.5.3.9. Lithium is the gold standard in the treatment of the manic phase of BD.

2.5.3.10. In clinical practice, the use of lithium has declined steadily because of its narrow therapeutic index, unfavourable side effect profile, need for regular monitoring, and delay in the onset of action.

2.5.3.11. There is inconsistent evidence with regard to the superior efficacy of lithium compared to antipsychotics.

2.5.3.12. Lithium monotherapy is recommended in patients with:

- Active or moderate-high suicide risk,
- A family history of response to lithium,
- No medical comorbidity.

2.5.3.13. Lithium should not be prescribed with Angiotensin-Converting Enzyme (ACE) Inhibitors, thiazide diuretics, NSAIDS and carbamazepine because

these drug-drug interactions can precipitate lithium toxicity.2.5.3.14. In this guideline, valproate refers to valproic acid, which is responsible for the pharmacological action of all valproate preparations.

- 2.5.3.15. In clinical trials, valproate was found to be less or equally effective compared to Lithium, but more effective than placebo and with better tolerability than lithium.
- 2.5.3.16. Valproate is an effective first-line alternative to lithium in the treatment of mania.
- 2.5.3.17. Valproate is highly protein bound and should not be combined with other protein bound drugs such as aspirin because valproate can be displaced by aspirin leading to toxic levels.
- 2.5.3.18. Valproate should not be prescribed to women (and young girls who are likely to receive maintenance treatment) of childbearing age.
- 2.5.3.19. A contraindication warning is currently in place regarding the prescription of valproate to women of child -bearing age.
- 2.5.3.20 If Valproate is prescribed, liver function tests are recommended on a regular basis at the start of therapy. The recommendation is at baseline, 3 weeks later, 6 weeks later, 3 months later and 6 months later (the 36;36 principle), due to a possible risk of liver toxicity early on in treatment.
- 2.5.3.21. Patients should be advised regarding the recognition of the signs and symptoms of blood and liver disorders and to seek immediate medical help if any of these develop.
- 2.5.3.22. Second-generation antipsychotics have replaced mood stabilisers as the most prescribed medications for BD globally.
- 2.5.3.23. Antipsychotics have a faster onset of action compared to mood stabilisers.
- 2.5.3.24. Antipsychotics are effective in the treatment of mania with and without psychotic features.



- 2.5.3.25. Aripiprazole, olanzapine, quetiapine, and risperidone are superior to placebo with regards to clinical remission and improvement of psychotic symptoms in acute mania.
- 2.5.3.26. Regular metabolic monitoring must be undertaken due to the adverse metabolic side effect profile of second-generation antipsychotics.
- 2.5.3.27. Augmentation (concomitant prescription of mood stabilisers and antipsychotics) is very common in the treatment of bipolar mania in clinical practice because of the complex nature of bipolar disorder, coupled with the need for a prompt response and to prevent the harmful consequences of impulsivity and irritability.
- 2.5.3.28. Mood stabilisers combined with antipsychotics are a viable treatment option in patients who are not responsive to monotherapy.
- 2.5.3.29. Care should be taken as a combination therapy of antipsychotics and mood stabilizers may result in more frequent adverse events.

#### **2.5.4. Pharmacological Management of the Depressive Episode**

- 2.5.4.1. The treatment of bipolar depression is both more challenging and diverse and includes antidepressants, some antipsychotics, anticonvulsants, and lithium.
- 2.5.4.2. Polypharmacy is inevitable and expected in relapse prevention, given the divergent efficacy profiles of available medicines and the need to protect against both poles of the illness.
- 2.5.4.3. The following medications have proven efficacious for the depressive phase:
- Olanzapine combined with fluoxetine.
  - Quetiapine monotherapy.
  - Lamotrigine.
  - Lithium and

- Valproate.

- 2.5.4.4. Lamotrigine requires a slow titration period until a full therapeutic dose is reached or a normal blood level is reached to which the patient is responsive. Patients taking lamotrigine must be advised to contact their doctor immediately if they develop a rash when the dose of lamotrigine is increased for treatment of the allergy which can be very severe. Patients should be advised to be compliant to Lamotrigine and not skip dosages as a fluctuating blood level can also induce the allergic reaction.
- 2.5.4.5. Unopposed antidepressants are not recommended for bipolar depression. Antidepressants should be prescribed with caution as they can induce mania, a mixed state or rapid cycling.
- 2.5.4.6. Lithium has proven efficacy against suicidality and is therefore recommended in patients with severe depression and suicidal ideation.
- 2.5.4.7. Valproate combined with antidepressants is a viable option for treatment in patients who do not respond to the other medications for bipolar depression.
- 2.5.4.8. Medications or combinations of medications that have been effective during episodes of acute mania or bipolar depression should be continued in the maintenance phase.
- 2.5.4.9. Continue current treatment or switch to lithium because it is the most effective medication in preventing both depressive and manic episodes.
- 2.5.4.10. Second-generation antipsychotic (SGA) monotherapy with olanzapine, aripiprazole, risperidone, or quetiapine or combined with lithium is effective for prophylaxis.
- 2.5.4.11. Antidepressant maintenance treatment is not recommended because of the potential to induce a switch to mania, depression, mixed mood, or rapid cycling.

## 2.5.5. **Discontinuation of medication**

- 2.5.5.1. Abrupt cessation (over 2-3 days) of lithium and mood stabilisers can result in withdrawal symptoms and an increased risk of precipitating mood episodes.

- 2.5.5.2. Medications should be withdrawn gradually over 14-30 days.
- 2.5.5.3. Ongoing monitoring may be necessary several months after complete cessation to ensure stability.

## **2.6. Non-pharmacological treatment**

### **2.6.1. Psychosocial Management**

- 2.6.1.1. Psychosocial management as an adjunct to pharmacotherapy has been proven to be of significant benefit during the management of the acute phase of bipolar depression and the maintenance phase of the illness.
- 2.6.1.2. Psychosocial interventions should be delivered by qualified, trained practitioners with the appropriate level of competence and duly registered to provide such services. It is recommended that such interventions are evidence-based.
- 2.6.1.3. Healthcare professionals delivering such interventions should be licensed to treat psychiatric patients through training and registration with the relevant professional bodies in South Africa. Psychosocial interventions can be classified into behavioural, cognitive, psychodynamic, humanistic, systemic, motivational, social, occupational, and environmental.
- 2.6.1.4. Psychosocial interventions such as Individual CBT, cognitive remediation therapy and programmes for family intervention for patients with Bipolar Disorder are recommended.
- 2.6.1.5. Psychosocial interventions should be delivered both on an individual basis (one-to-one) over at least 16-21 sessions, as well as on a group basis, which include social skills training, cognitive remediation, psychoeducation, and multi-family groups, synergizing the already known benefits with newer therapy models.
- 2.6.1.6. A treatment plan should be developed and followed so that patients with Bipolar Disorder can establish links between their thoughts, feelings, or actions and their current or past symptoms and/or functioning; and perceptions, beliefs, or reasoning related to target symptoms can be re-evaluated.

2.6.1.7. The role of the multi-professional team is critical in the management of patients with bipolar disorder, considering that data supports the use of psychoeducation (individual and group), Interpersonal and Social Rhythm Therapy (IPSRT), Cognitive-Behavioural Therapy (CBT) and family focused intervention, which have been shown to be associated with a reduced risk of relapse, better functioning, and better treatment adherence, leading towards full recovery.

2.6.1.8. Psychosocial management of the depressive phase of bipolar disorder

- Discuss with the individual the possible benefits and risks of psychological interventions and their preference.
- Choice of psychological interventions include cognitive behavioral therapy (CBT), interpersonal therapy(family) psychoeducation, and mindfulness-based cognitive therapy (MBCT).
- Monitor mood for signs of mania or hypomania or deterioration of depressive symptoms.

2.6.1.9. Family interventions should:

- Include the person diagnosed with Bipolar Disorder if practical.
- Include at least 10 planned sessions; and
- Take the whole family's preference for single or multi-family group intervention.

2.6.1.10. Psychoeducation may be considered both for the patient and family members in and out of hospital setting.

2.6.1.11. It is essential to discuss:

- The nature and variable course of BD.
- The role of psychological and pharmacological interventions to prevent relapse and reduce symptoms.

- The potential benefits and risks of long-term medication and psychological interventions, and the need to monitor mood and medication.
- The risk of relapse after reducing or stopping medication for an acute episode, including for women who may wish to become pregnant.
- Potential triggers for relapse, early warning signs, and self-management strategies.
- The deferment of important decisions until the individual has recovered from an episode of mania, hypomania or depression and
- The importance of maintaining relationships with carers/support systems in the short and long term.

2.6.1.12. To promote individualised therapy, clinicians should:

- Discuss treatment options with the MHCU and family if available.
- Provide the individual with information suitable for their developmental level about the purpose and likely side effects of treatment, including any monitoring that is required, and give them an opportunity to ask questions.
- Discuss the use of alcohol, tobacco, prescription and nonprescription medication and illicit drugs with the person, and their carer if appropriate. Explain the possible interaction of these substances with the therapeutic effects of the prescribed medication.
- Emphasise the importance of family support for the MHCU.

## 2.6.2. **Electro-convulsive therapy**

2.6.2.1. ECT is a safe and effective treatment for Bipolar Disorder. The clinical indications for ECT in Bipolar Disorder include:

- Treatment of severe mania that has not responded to other interventions.
  - Severe suicidality.
  - Severe psychosis and
  - Severe agitation.
- 2.6.2.2. Treatment-resistant bipolar disorder: prolonged courses of ECT without measured improvement are not recommended for people with bipolar disorder.
- 2.6.2.3. A maximum of 15 treatments per annum is recommended.
- 2.6.2.4. Longer courses may be required if progressive improvement occurs with each session.

### **3. MONITORING**

#### **3.1. Monitoring pharmacological and psychosocial therapy**

- 3.1.1 Monitoring the response to pharmacological and psychosocial therapy ensures that the effectiveness of treatment can be assessed and adjusted if needed for in- and outpatients.
- 3.1.2 It also allows MHCPs to monitor other outcomes, such as the effects on any long-term conditions and the patient's ability to continue or return to employment.
- 3.1.3 The secondary care team should maintain responsibility for monitoring the efficacy and tolerability of antipsychotic medication for at least the first 12 months or until the person's condition has stabilised, whichever is longer.
- 3.1.4 Thereafter, the responsibility for this monitoring may be transferred to primary care under shared care arrangements.
- 3.1.5 Refer to Table 2 for information on how to evaluate and monitor lithium levels in patients who are taking lithium.
- 3.1.6 More frequent monitoring for patients taking lithium will be required in

- Older patients.
- Patients taking drugs that interact with lithium.
- Patients who are at risk of impaired renal or thyroid function, raised calcium levels or other complications.
- Patients who have poor symptom control.
- Patients with poor adherence.
- Patients whose last plasma lithium level is  $\leq$  0.8 mmol per litre or higher and
- Patients with elevated urea levels and creatinine, or if Egfr falls over 2 or more tests.

3.1.7 Within the MDT, a lead professional should monitor and review access to and decisions about what psychosocial interventions to offer.

3.1.8 Psychosocial interventions should be monitored for a range of outcomes across relevant areas, including patient satisfaction and, if appropriate, family satisfaction, routinely and systematically.

## **4. REHABILITATION**

Bipolar Disorder is characterised by recurrent episodes of depression and/or mania, accompanied by inter-episodic mood symptoms that interfere with psychosocial and occupational functioning. Therefore, rehabilitation is crucial to the patient's recovery.

### **4.1. Role of Occupational Therapist**

4.1.1. Occupational therapy interventions improve and maintain performance and occupational participation for people with serious mental illness.

4.1.2. Occupational therapists work in hospital and community settings, using a combination of individual and group interventions to develop skills and build the

MHCUs' confidence in executing everyday tasks. Benefits should be available for primary, secondary, and tertiary, in- and outpatient care.

4.1.3. Interventions may include practical self-care, domestic skills, such as cooking and budgeting, work skills, leisure activities, social skills development, and carer support.

4.1.4. Patients with Bipolar Disorder should be assisted with a return to work as this could, at times, take weeks or months and often requires a return-to-work plan.

## 4.2. **Role of Social Worker**

4.2.1. Social Work practitioners have postulated that the psychosocial functioning or dysfunction in severe mental illness was determined mainly by the interaction between the individual needs, aspirations, and functional capacities on the one side, and environmental (situations) expectations, opportunities, and resources on the other.

4.2.2. Interventions in this category may include:

- family psychoeducation and support,
- family-aided ACT, and
- case management for primary, secondary, tertiary in and outpatient care.

## 4.3. **Role of Mental Health Nurse**

4.3.1. Mental Health nurses prioritise person-centred care, therapeutic relationships, and collaboration with peer support workers to enhance treatment effectiveness.

4.3.2. Their interventions focus on improving medication adherence, providing coping support, and promoting social capabilities, ultimately improving individuals' quality of life.

4.3.3. They assist in the treatment of patients in primary, secondary and tertiary care, providing in- and outpatient care.



#### **4.4. Role of Physiotherapist**

- 4.4.1. Physical health is integral to health promotion efforts in patients with Bipolar Disorder. Therefore these patients should receive physical healthcare from primary care practitioners after being down referred from secondary care.
- 4.4.2. Encouraging healthier lifestyle choices and higher levels of habitual
- 4.4.3. physical activity is recommended.
- 4.4.4. Patients with Bipolar Disorder have a higher incidence of metabolic problems and weight gain, which can be worsened by antipsychotic medication. An exercise program must be incorporated into the management of patients with Bipolar Disorder.
- 4.4.5. A Physiotherapist serves to assess any movement disorders, level of physical activity and develops a physical therapy care plan as part of the MDT at primary, secondary level and tertiary in and outpatient care.

#### **4.5. Role of Dietician**

- 4.5.1. A dietician plays an important role in improving the physical health of patients with Bipolar Disorder for those patients on mood stabilisers or second-generation antipsychotics due to risk of metabolic problems in these patients.
- 4.5.2. They also assess the nutritional status of a patient and recommends an appropriate diet, and
- 4.5.3. Develop a care plan for primary, secondary, and tertiary inpatient and outpatient care based on the baseline assessment.

### **5. RETURN TO PRIMARY CARE**

- 5.1. For patients who have responded effectively to treatment and remain stable, consider the option to return to primary care for further management by a GP and other Mental Health Care Practitioner (MHCP)
- 5.2. Transfer arrangements for return to primary care require that a care plan is in place, which includes:

- Encouragement and support for the person to visit their GP and discuss the care plan in preparation for discharge and transfer.
- A crisis plan indicating early warning symptoms and triggers of both mania and depression relapse, and the preferred response during a relapse, including liaison and referral pathways.
- A medication plan with a date for review by the primary care provider, frequency, and nature of monitoring for effectiveness and adverse effects, and what should happen in the event of a relapse.
- A protocol for applying coping strategies and increasing doses of medication or taking additional medication for people at risk of onset of mania or for whom early warning signs and symptoms can be identified.
- An agreement between primary and secondary care providers about how to respond to an increase in risk or concern about possible risk.
- A detailed care plan should be submitted to the case Manager to coordinate optimal care for the patient both in and out-of-hospital.
- A schedule for anthropometric assessments and investigations to monitor the adverse effects of medication.
- A clear, individualised plan for social and emotional recovery goals and
- A copy of the plan for the patient and maintenance care GP.

## **6. RELAPSE AND RE-REFERRAL TO SECONDARY CARE**

6.1. When bipolar disorder is managed solely in primary care, re-refer to secondary care if any one of the following arises:

- Poor or partial response to treatment.
- Significant decline in functioning

- Treatment adherence is poor.
- Development of intolerable or medically significant side effects from medication.
- Comorbid alcohol or drug misuse is suspected.
- A woman with bipolar disorder is pregnant or planning a pregnancy.

## **7. RELAPSE AND RE-REFERRAL TO TERTIARY CARE**

7.1. Tertiary care should be considered when:

- Patients present with severe suicidality.
- Patients present with mania.
- Patients present with severe depression and
- Patients present with psychosis.

# APPENDICES

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## Appendix A

**Table 1: Assessment And Management of Patients with Bipolar Disorder at Primary and Secondary care**

## Appendix B

**Table 2: Base-Line Investigations and Monitoring**

## Appendix C

**Table 3: Pharmacological Therapy in Bipolar Disorder**

Table 1: Assessment And Management of Patients with Bipolar Disorder at Primary and Secondary care

Primary Care Level	Role	Benefit/Service
<b>Medical Practitioner</b>	<ul style="list-style-type: none"> <li>• Assessment and baseline investigations</li> <li>• Diagnosis</li> <li>• Treatment initiation</li> <li>• Monitor for 4-8 weeks.</li> <li>• Stable patients continue treatment (referral to psychiatrist when required)</li> <li>• Risk assessment and <i>referral to secondary care on an outpatient or in patient basis</i></li> </ul>	<ul style="list-style-type: none"> <li>• First consultation</li> <li>• Monitoring response and care</li> </ul>
<b>Mental Health Specialist Nurse</b>	<ul style="list-style-type: none"> <li>• Assessment and baseline investigations</li> <li>• Diagnosis</li> <li>• Treatment initiation</li> <li>• Stable patients continue treatment (referral to psychiatrist when required)</li> <li>• Risk assessment and <i>referral to secondary care on an outpatient or in patient basis</i></li> </ul>	<ul style="list-style-type: none"> <li>• First consultation</li> <li>• Monitoring response and care</li> </ul>

<b>Secondary Care Level</b>		
<b>Out-patient care</b>		
<b>Psychiatrist</b>	<ul style="list-style-type: none"> <li>• Assessment and investigations</li> <li>• Confirmation of MHCP diagnosis</li> <li>• Treatment review</li> <li>• <i>Refer to MDT for psychosocial intervention</i></li> </ul>	<ul style="list-style-type: none"> <li>• Monitoring response and care</li> <li>• Psychosocial therapy</li> </ul>
<b>Psychologist (Clinical/Counselling)</b>  <b>Clinical Social Worker</b>  <b>Occupational therapists</b>	<ul style="list-style-type: none"> <li>• Psychosocial interventions</li> </ul>	<ul style="list-style-type: none"> <li>• Psychosocial therapy</li> </ul>
<b>In-patient care</b>		
<b>Multidisciplinary Mental Health Team</b> <ul style="list-style-type: none"> <li>• <b>Psychiatrist</b></li> <li>• <b>MH Specialist Nurse</b></li> <li>• <b>Psychologist (Clinical/Counselling)</b></li> <li>• <b>Clinical Social Worker</b></li> <li>• <b>Occupational therapists</b></li> </ul> <b>Other healthcare professionals as part of MDT</b> <ul style="list-style-type: none"> <li>• <b>Dieticians</b></li> <li>• <b>Physiotherapist</b></li> <li>• <b>Art and music therapists</b></li> </ul>	<ul style="list-style-type: none"> <li>• Assessment and baseline investigations</li> <li>• Diagnosis</li> <li>• Pharmacological treatment</li> <li>• Development of treatment plan</li> <li>• Psychosocial intervention</li> <li>• Rehabilitation</li> <li>• Nutritional assesment and treatment</li> <li>• Physical therapy</li> <li>• Art therapy</li> </ul>	<ul style="list-style-type: none"> <li>• 21 Days in hospital (max)</li> <li>• Psychosocial therapy (in and out of hospital)</li> <li>• Services specified in the treatment plan.</li> <li>• Services specified in the treatment plan.</li> </ul>

**Table 2: Baseline investigations and monitoring**

INVESTIGATION	BASELINE	DRUG LEVELS	3 MONTHS	6 MONTHS	9 MONTHS	ANNUALLY
Anthropometry: height, weight, WC, WHP ratio	All Drugs		All	All	All	All
Blood Pressure	All Drugs		All	All	All	All
Full Blood Count with differential (FBC)	All Drugs		Valproate	Valproate	Valproate	Valproate
Urea and Electrolytes (U &E)	Drugs		Lithium, Valproate	Lithium, Valproate	Lithium, Valproate	Lithium, Valproate
Thyroid Function Test (TFT)	All Drugs			Lithium		Lithium
Fasting Blood Glucose (FBG) or HbA1c	All Drugs			SGA		SGA
Treponema Pallidum Hemagglutination (TPHA)	All Drugs					
HIV with consent	All Drugs					
Pregnancy Test (females of childbearing age)	All Drugs					
Lipogram	All Drugs			SGA		SGA
Liver Function Tests (LFT)	All Drugs		Valproate	Valproate	Valproate	Valproate
Serum Calcium	Lithium Valproate			Lithium Valproate		Lithium Valproate
Estimated Glomerular Filtration Rate (eGFR )	Lithium			Lithium		Lithium
Clotting screen (PT/PITT)	Valproate					
Lithium Levels:		Weekly, fortnightly until stable		X		X
Valproic Acid Levels		clinically indicated				
ECG	All Drugs					
CT Scan if clinically indicated	All Drugs					
Toxic drug screen (urine or blood) -Suspect substance use	All Drugs					

**Table 3: Pharmacological Therapy in Bipolar Disorder**

FIRST LINE TREATMENT							
MONOTHERAPY OR USE OF AUGMENTATION THERAPY							
MONOTHERAPY: Mood Stabilizer OR Anticonvulsant Mood Stabilizer OR Second-Generation Antipsychotic Alone							
ATC	PSYCHOTROPIC	ACUTE MANIA WITHOUT PSYCHOSIS	ACUTE MANIA WITH PSYCHOSIS	ACUTE DEPRESSION	RAPID CYCLING	MAINTENANCE	DDD
	<b>Mood Stabilizer</b>						
N05AN01	Lithium	x		x	x	x	24 mmol
	<b>Anticonvulsant Mood Stabilizer</b>						
N03AG01	Valproate	x				x	1.5 g
	<b>Second Generation Antipsychotics</b>						
N05AX08	Risperidone	x	x				5 mg
N05AH04	Quetiapine	x	x	x	x	x	0.4 g
N05AH03	Olanzapine	x	x	x	x	x	10 mg
N05AX12	Aripiprazole	x	x	x	x	x	15 mg
	<b>AUGMENTATION THERAPY: Mood stabilizer combined with Antipsychotic</b>						
	PSYCHOTROPIC	ACUTE MANIA WITHOUT PSYCHOSIS	ACUTE MANIA WITH PSYCHOSIS	ACUTE DEPRESSION	RAPID CYCLING	MAINTENANCE	
	Lithium + Antipsychotic	x	x			x	
	Valproate + Antipsychotic	x	x			x	



SECOND LINE TREATMENT - SWITCH TO A TREATMENT OPTION NOT UTILIZED IN FIRST LINE TREATMENT OR CONSIDER							
	PSYCHOTROPIC	ACUTE MANIA WITHOUT PSYCHOSIS	ACUTE MANIA WITH PSYCHOSIS	ACUTE DEPRESSION	RAPID CYCLING	MAINTENANCE	DDD
	<b>First Generation Antipsychotic</b>						
<b>N05AD01</b>	Haloperidol	x	x				8 mg
	<b>Anticonvulsant Mood Stabilizer</b>						
<b>N03AF01</b>	Carbamazepine	x					1 g
	Valproate			x			1.5g
	<b>AUGMENTATION THERAPY</b>						
	Olanzapine + Fluoxetine			x	x		
	Mood stabilizer + Antidepressant other than Olanzapine/Fluoxetine			x			
	<b>THIRD LINE TREATMENT</b>						
<b>N05AH02</b>	Clozapine	x	x				
	2 Mood Stabilizers + First line Second Generation Antipsychotic	x	x		x	x	
	2 First line Second Generation Antipsychotics + Mood stabilizer	x	x		x	x	
	ECT	x	x	x	x		

## References

- Beardsley, S.J. et al. (2021) 'Valproate use in women aged 15–44 years: an observational study in general practice', *BJGP Open*, 5(2), p. BJGPO.2020.0104. Available at: <https://doi.org/10.3399/BJGPO.2020.0104>.
- Chatterton, M.L. et al. (2017) 'Psychosocial therapies for the adjunctive treatment of bipolar disorder in adults: Network meta-analysis', *British Journal of Psychiatry*, 210(5), pp. 333–341. Available at: <https://doi.org/10.1192/bjp.bp.116.195321>.
- Cipriani, A. et al. (2013) 'Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis', *BMJ*, 346(jun27 4), pp. f3646–f3646. Available at: <https://doi.org/10.1136/bmj.f3646>.
- Crapanzano, C. et al. (2022) 'Lithium and Valproate in Bipolar Disorder: From International Evidence-based Guidelines to Clinical Predictors', *Clinical Psychopharmacology and Neuroscience*, 20(3), pp. 403–414. Available at: <https://doi.org/10.9758/cpn.2022.20.3.403>.
- Demissie, M. et al. (2018) 'Psychological interventions for bipolar disorder in low- and middle-income countries: systematic review', *BJPsych Open*, 4(5), pp. 375–384. Available at: <https://doi.org/10.1192/bjo.2018.46>.
- Docrat, S. et al. (2019) 'Mental health system costs, resources and constraints in South Africa: a national survey', *Health Policy and Planning*, 34(9), pp. 706–719. Available at: <https://doi.org/10.1093/heapol/czz085>.
- Drancourt, N. et al. (2013) 'Duration of untreated bipolar disorder: missed opportunities on the long road to optimal treatment', *Acta Psychiatrica Scandinavica*, 127(2), pp. 136–144. Available at: <https://doi.org/10.1111/j.1600-0447.2012.01917.x>.
- Fountoulakis, K.N., Tohen, M. and Zarate, C.A. (2022) 'Lithium treatment of Bipolar disorder in adults: A systematic review of randomized trials and meta-analyses', *European Neuropsychopharmacology*, 54, pp. 100–115. Available at: <https://doi.org/10.1016/j.euroneuro.2021.10.003>.
- Geoffroy, P.A. et al. (2012) 'Combination Therapy for Manic Phases: A Critical Review of a Common Practice', *CNS Neuroscience & Therapeutics*, 18(12), pp. 957–964. Available at: <https://doi.org/10.1111/cns.12017>.
- Gitlin, M.J. (2018) 'Antidepressants in bipolar depression: an enduring controversy', *International Journal of Bipolar Disorders*, 6(1), p. 25. Available at: <https://doi.org/10.1186/s40345-018-0133-9>.
- Goes, F.S. (2023) 'Diagnosis and management of bipolar disorders', *BMJ (Clinical research ed.)*, 381, p. e073591. Available at: <https://doi.org/10.1136/bmj-2022-073591>.
- Gomes, F.A. et al. (2023) 'Does the Ranking Matter? A Retrospective Cohort Study Investigating the Impact of the 2018 CANMAT and ISBD Guidelines for the Management of Patients with Bipolar Disorder Treatment Recommendations for Acute Mania on Rehospitalization Rates', *The Canadian Journal of Psychiatry*, 68(8), pp. 605–612. Available at: <https://doi.org/10.1177/07067437231156235>.
- Jauhar, S. and Young, A.H. (2019) 'Controversies in bipolar disorder; role of second-generation antipsychotic for maintenance therapy', *International Journal of Bipolar Disorders*, 7(1), p. 10. Available at: <https://doi.org/10.1186/s40345-019-0145-0>.

- Jeong, J.-H. et al. (2023) 'Korean Medication Algorithm Project for Bipolar Disorder 2022: Comparisons with Other Treatment Guidelines', *Clinical Psychopharmacology and Neuroscience*, 21(1), pp. 32–48. Available at: <https://doi.org/10.9758/cpn.2023.21.1.32>.
- Karanti, A. et al. (2016) 'Changes in mood stabilizer prescription patterns in bipolar disorder', *Journal of Affective Disorders*, 195, pp. 50–56. Available at: <https://doi.org/10.1016/j.jad.2016.01.043>.
- Ketter, T.A. (2010) 'Strategies for Monitoring Outcomes in Patients With Bipolar Disorder', *The Primary Care Companion to The Journal of Clinical Psychiatry*, pp. 10–16. Available at: <https://doi.org/10.4088/PCC.9064su1c.02>.
- Kishi, T. et al. (2022) 'Pharmacological treatment for bipolar mania: a systematic review and network meta-analysis of double-blind randomized controlled trials', *Molecular Psychiatry*, 27(2), pp. 1136–1144. Available at: <https://doi.org/10.1038/s41380-021-01334-4>.
- Köhler-Forsberg, O. et al. (2023) 'Lithium plus antipsychotics or anticonvulsants for bipolar disorder: Comparing clinical response and metabolic changes', *The Australian and New Zealand Journal of Psychiatry*, 57(1), pp. 93–103. Available at: <https://doi.org/10.1177/00048674221077619>.
- Krishnan, K.R.R. (2005) 'Psychiatric and Medical Comorbidities of Bipolar Disorder', *Psychosomatic Medicine*, 67(1), pp. 1–8. Available at: <https://doi.org/10.1097/01.psy.0000151489.36347.18>.
- Lin, S.-K. et al. (2022) 'Prescription Patterns for Bipolar Disorder in Asian Countries: Findings from Research on Asian Prescription Pattern-Bipolar Disorder', *Clinical Psychopharmacology and Neuroscience*, 20(1), pp. 61–69. Available at: <https://doi.org/10.9758/cpn.2022.20.1.61>.
- Walsh, J. Treatment of the bipolar client: Clinical social work contributions. *Clin Soc Work J* 17, 367–381 (1989). <https://doi.org/10.1007/BF00756562>
- Malhi, G.S. et al. (2007) 'Neuropsychological deficits and functional impairment in bipolar depression, hypomania and euthymia', *Bipolar Disorders*, 9(1–2), pp. 114–125. Available at: <https://doi.org/10.1111/j.1399-5618.2007.00324.x>.
- Miklowitz, D.J. et al. (2021) 'Adjunctive Psychotherapy for Bipolar Disorder: A Systematic Review and Component Network Meta-analysis', *JAMA Psychiatry*, 78(2), p. 141. Available at: <https://doi.org/10.1001/jamapsychiatry.2020.2993>.
- Ng, F. et al. (2009) 'The International Society for Bipolar Disorders (ISBD) consensus guidelines for the safety monitoring of bipolar disorder treatments', *Bipolar Disorders*, 11(6), pp. 559–595. Available at: <https://doi.org/10.1111/j.1399-5618.2009.00737.x>.
- Nierenberg, A.A. et al. (2023a) 'Diagnosis and Treatment of Bipolar Disorder: A Review', *JAMA*, 330(14), p. 1370. Available at: <https://doi.org/10.1001/jama.2023.18588>.
- Nierenberg, A.A. et al. (2023b) 'Diagnosis and Treatment of Bipolar Disorder: A Review', *JAMA*, 330(14), p. 1370. Available at: <https://doi.org/10.1001/jama.2023.18588>.
- Petersen, I. et al. (2019) 'Risk correlates for physical-mental multimorbidities in South Africa: a cross-sectional study', *Epidemiology and Psychiatric Sciences*, 28(4), pp. 418–426. Available at: <https://doi.org/10.1017/S2045796017000737>.
- Pfennig, A. et al. (2013) 'The Diagnosis and Treatment of Bipolar Disorder', *Deutsches Ärzteblatt international* [Preprint]. Available at: <https://doi.org/10.3238/arztebl.2013.0092>.

Popiolek, K. et al. (2019) 'Electroconvulsive therapy in bipolar depression – effectiveness and prognostic factors', *Acta Psychiatrica Scandinavica*, 140(3), pp. 196–204. Available at: <https://doi.org/10.1111/acps.13075>.

Qureshi, M.M. and Young, A.H. (2021) 'Hamlet's augury: how to manage discontinuation of mood stabilizers in bipolar disorder', *Therapeutic Advances in Psychopharmacology*, 11, p. 204512532110006. Available at: <https://doi.org/10.1177/20451253211000612>.

Rhee, T.G. 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), pp. 706–715. Available at: <https://doi.org/10.1176/appi.ajp.2020.19091000>.

Samara, M.T., Levine, S.Z. and Leucht, S. (2023) 'Linkage of Young Mania Rating Scale to Clinical Global Impression Scale to Enhance Utility in Clinical Practice and Research Trials', *Pharmacopsychiatry*, 56(01), pp. 18–24. Available at: <https://doi.org/10.1055/a-1841-6672>.

Smith, L.A. et al. (2007) 'Acute bipolar mania: a systematic review and meta-analysis of co-therapy vs. monotherapy', *Acta Psychiatrica Scandinavica*, 115(1), pp. 12–20. Available at: <https://doi.org/10.1111/j.1600-0447.2006.00912.x>.

Smith, L.A. et al. (2010) 'Valproate for the treatment of acute bipolar depression: Systematic review and meta-analysis', *Journal of Affective Disorders*, 122(1–2), pp. 1–9. Available at: <https://doi.org/10.1016/j.jad.2009.10.033>.

Tajika, A. et al. (2022) 'Mood Stabilizers and Antipsychotics for Acute Mania: Systematic Review and Meta-Analysis of Augmentation Therapy vs Monotherapy From the Perspective of Time to the Onset of Treatment Effects', *International Journal of Neuropsychopharmacology*, 25(10), pp. 839–852. Available at: <https://doi.org/10.1093/ijnp/pyac050>.

Thase, M. (2008) 'Selecting appropriate treatments for maintenance therapy for bipolar disorder.', *Journal of Clinical Psychiatry*, 69.

Tohen, M. and Grundy, S. (1999) 'Management of acute mania', *The Journal of Clinical Psychiatry*, 60 Suppl 5, pp. 31–34; discussion 35–36.

Yatham, L.N. et al. (2018) 'Canadian Network for Mood and Anxiety Treatments ( CANMAT ) and International Society for Bipolar Disorders ( ISBD ) 2018 guidelines for the management of patients with bipolar disorder', *Bipolar Disorders*, 20(2), pp. 97–170. Available at: <https://doi.org/10.1111/bdi.12609>.

Yildiz, A. et al. (2023) 'Comparative efficacy and tolerability of pharmacological interventions for acute bipolar depression in adults: a systematic review and network meta-analysis', *The Lancet Psychiatry*, 10(9), pp. 693–705. Available at: [https://doi.org/10.1016/S2215-0366\(23\)00199-2](https://doi.org/10.1016/S2215-0366(23)00199-2).

What is primary care mental health?: WHO and Wonca Working Party on Mental Health. *Ment Health Fam Med*. 2008 Mar;5(1):9-13. PMID: 22477841; PMCID: PMC2777553.

Huang H, Nissen N, Lim CT, Gören JL, Spottswood M, Huang H. Treating Bipolar Disorder in Primary Care: Diagnosis, Pharmacology, and Management. *Int J Gen Med*. 2022 Nov 23;15:8299-8314. doi: 10.2147/IJGM.S386875. PMID: 36447648; PMCID: PMC9701507.

Culpepper L. The role of primary care clinicians in diagnosing and treating bipolar disorder. *Prim Care Companion J Clin Psychiatry*. 2010;12(Suppl 1):4-9. doi: 10.4088/PCC.9064su1c.01. PMID: 20628500; PMCID: PMC2902189.

Fortney JC, Bauer AM, Cerimele JM, et al. Comparison of teleintegrated care and telereferral care for treating complex psychiatric disorders in primary care: a pragmatic randomized comparative effectiveness trial. *JAMA Psychiatry*. 2021;78(11):1189. doi: 10.1001/jamapsychiatry.2021.2318 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

Çakmak S, Süt H, Öztürk S, Tamam L, Bal U. The Effects of Occupational Therapy and Psychosocial Interventions on Interpersonal Functioning and Personal and Social Performance Levels of Corresponding Patients. *Noro Psikiyatrs Ars*. 2016 Sep;53(3):234-240. doi: 10.5152/npa.2015.10130. Epub 2016 Sep 1. PMID: 28373800; PMCID: PMC5378204.