QUICK REFERENCE FOR
HEALTHCARE PROVIDERS

MANAGEMENT OF BIPOLAR DISORDER

(SECOND EDITION)

MINISTRY OF HEALTH MALAYSIA

Malaysian Psychiatric Association

Academy of Medicine of Malaysia

KEY MESSAGES

1. Bipolar Disorder (BD) is a potentially life-long condition presenting commonly as either bipolar I disorder (BD I) or bipolar II disorder (BD II). BD I is characterised by episodes of mania, whilst BD II is characterised by episodes of hypomania and depressive episodes.
2. BD should be diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition, Text Revision (DSM-5-TR) or International Classification of Diseases Eleventh Revision (ICD-11).
3. Antipsychotics (APs) or mood stabilisers, either as monotherapy or combination, should be used to treat acute episodes of mania/depression & as maintenance therapy in BD; and may be used in mixed features.
4. For BD with anxious distress, atypical antipsychotics (AAPs) may be used.
5. For BD with rapid cycling, a combination of mood stabilisers with AAPs or another mood stabiliser is the preferred treatment of choice.
6. Antidepressants (AD) may be used as short-term adjunctive treatment but not as monotherapy in BD. It should be avoided in mixed episodes & used with caution in rapid cycling BD.
7. Long-acting AAP injectables may be considered in BD patients who have poor adherence to oral medications.
8. Electroconvulsive therapy should be considered in both bipolar manic & depressive episodes in indicated situations (refer to **Algorithm 1 & 2**).
9. Psychosocial interventions & psychotherapies should be offered as an adjunctive treatment for BD especially in relapse prevention.
10. Shared decision-making in weighing risks vs benefits of pharmacological treatment should be done in pregnant & lactating women with BD.

This Quick Reference provides key messages & a summary of the main recommendations in the Clinical Practice Guidelines (CPG) Management of Bipolar Disorder (Second Edition).

Details of the evidence supporting these recommendations can be found in the above CPG, available on the following websites:

Ministry of Health Malaysia: www.moh.gov.my
Academy of Medicine Malaysia: www.acadmed.org.my
Malaysian Psychiatric Association: www.psychiatry-malaysia.org

CLINICAL PRACTICE GUIDELINES SECRETARIAT
Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division, Ministry of Health Malaysia
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Federal Government Administrative Centre 62590
Putrajaya, Malaysia
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RISK FACTORS

Identifying risk factors may assist in the early detection of BD:

- family history of BD
- offspring of maternal age group ≥40 years old
- young age (<25 years old)
- presence of major depression with attention-deficit hyperactivity disorder (ADHD)
- low educational level
- low employment level

DIFFERENTIAL DIAGNOSIS

Common differential diagnoses to be considered:

a. during depressive episode -
   - major depressive disorder
   - major depressive disorder with mixed episode
   - adjustment disorder with depressed mood
   - anxiety disorder
   - depressive disorder due to another medical condition
   - substance-induced depressive disorder
   - schizophrenia or schizoaffective disorder

b. during mania or hypomania episode -
   - substance-induced bipolar disorder
   - bipolar & related disorder due to another medical condition
   - schizophrenia or schizoaffective disorder
   - borderline personality disorder
   - ADHD

CO-MORBIDITIES

Psychiatric co-morbidities include:

- drug abuse
- anxiety disorder
- borderline personality disorder
- ADHD
- anti-social personality disorder
- eating disorder

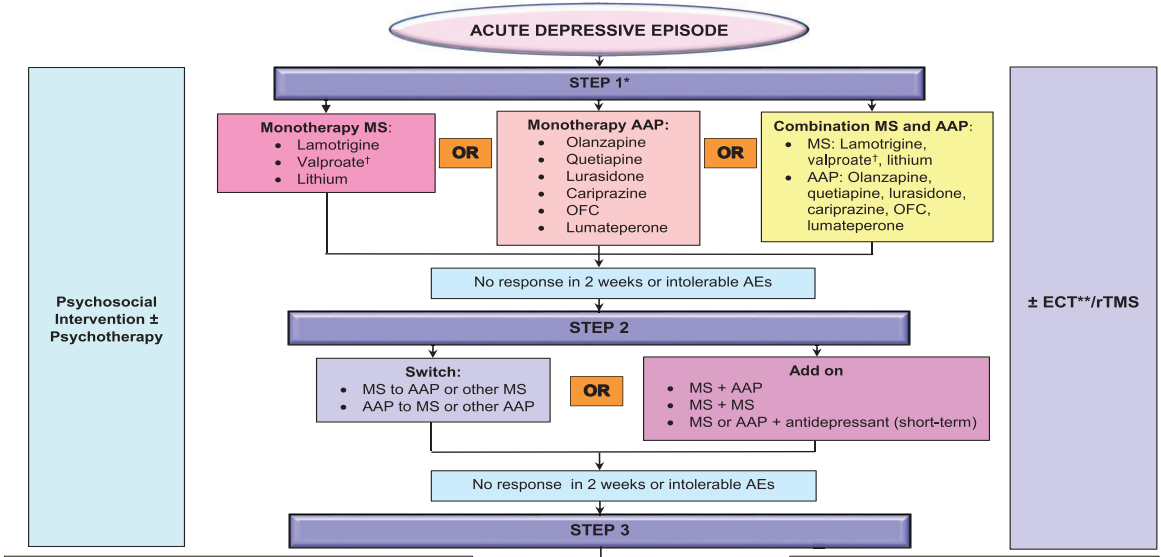
REFERRAL CRITERIA

BD can be managed in primary care EXCEPT in the following conditions:

- unsure of diagnosis
- complex presentation of mood episodes
- acute exacerbation of symptomscrisis
- increased risk of harm to self or others
- marked impairment in social or occupational functioning
- poor or partial response to treatment
- poor treatment adherence
- intolerable or medically important adverse events of medication
- psychiatric co-morbidities
- psychotherapeutic needs
- ambivalent or wanting to stop any medication after a period of relatively stable mood
- special population -
  - pregnant or planning a pregnancy
  - children & adolescents
  - co-morbidity with alcohol or substance misuse

LGORITHM 1. TREATMENT OF ACUTE MANIA

ALGORITHM 2. TREATMENT OF ACUTE DEPRESSIVE EPISODE



*Consider optimisation & assessment of compliance if on treatment
**ECT should be considered in the following conditions:
- rapid definitive response is required
- risk of other alternatives outweighs risk of ECT
- previous good response to ECT
- patient's preference
- treatment-resistant cases

†Valproate - Safety concerns present, refer to **Appendix 5 and 9 in CPG**

AAP = atypical antipsychotic
AP = antipsychotic
ECT = electroconvulsive therapy
MS = mood stabiliser
OFC = olanzapine/fluoxetine combination
rTMS = repetitive transcranial magnetic stimulation

RECOMMENDED ADULT MEDICATION DOSAGES FOR BIPOLAR DISORDER

MEDICATION	USUAL DOSE RANGE	RENAL IMPAIRMENT DOSE			HEPATIC IMPAIRMENT DOSE		
		CrCl 60 - 89 ml/min	CrCl 30 - 59 ml/min	CrCl <30 ml/min	Mild	Moderate	Severe
MOOD STABILISERS							
Lithium	***PO***: 900 - 1800 mg/day in divided doses. (Max dose: 1.8 g/day in 1 to 3 divided doses)	No dose adjustment	Initiate at lower dose	Avoid	No dose adjustment		
Valproate	***PO***: 1000 to 2000 mg/day (i.e. 20 - 30 mg/kg/day) (Max dose: 2500 mg/day or 60 mg/kg/day)	No dose adjustment		**<10:** Caution*	No dose adjustment		Avoid
Lamotrigine	***PO***: 100 - 400 mg/day in divided doses	No dose adjustment		Caution use	No dose adjustment	**WITHOUT ascites**: ↓ dose by ~25% **WITH ascites:** ↓ dose by ~50%	
Carbamazepine	***PO***: 400 - 1600 mg/day in 2 to 3 divided doses (Max dose: 1.6 g/day)	No dose adjustment			Use with caution & consider dose reduction as it is metabolised primarily in the liver		
ANTIPSYCHOTICS							
Aripiprazole	***PO***: 10 - 15 mg once daily (Max: 30 mg/day) ***LAI***: 400 mg once monthly	No dose adjustment			No dose adjustment		
Asenapine	***PO***: 5 - 10 mg twice daily (Max dose: 10 mg twice daily)	No dose adjustment			No dose adjustment		Avoid
Cariprazine	***PO***: 3 - 6 mg once daily (Max: 6 mg/day)	No dose adjustment		Avoid	No dose adjustment		Avoid
Haloperidol	***PO***: 3 - 15 mg/day (Max: 30 mg/day)	No dose adjustment			Caution use		
Lumateperone	***PO***: 42 mg once daily (Max: 42mg/day)	No dose adjustment			No dose adjustment	Max: 21 mg once daily	
Lurasidone	***PO***: 20 - 60 mg once daily (Max: 120 mg/day)	No dose adjustment	**<50:** Max: 80 mg/day		No dose adjustment	Max: 80 mg/day	Max: 40 mg/day
Olanzapine	***PO***: 5 - 20 mg once daily (Max: 20 mg/day)	No dose adjustment necessary			Caution use		
Paliperidone	***PO***: 6 mg once daily (Max: 12 mg/day)	**50 - <80:** Initial: 3 mg OD Max: 6 mg OD	**10 - <50:** Initial: 1.5 mg OD Max: 3 mg OD	**<10:** Avoid	No dose adjustment		Not information
Quetiapine	***PO:*** 50 - 400 mg once daily (Max: 800 mg/day)	No dose adjustment necessary			Initial: 25 mg once daily		Avoid
Risperidone	***PO:*** 2- 3 mg/day (Max: 8 mg/day) ***LAI:*** 25 mg every 2 weeks (Max: 50 mg every 2 weeks)	No adjust-ment	**30 - 60:** 50 - 75% of usual dose	**10 - 30:** 50% of usual dose	**<10:** Avoid	No dose adjustment		0.5 mg twice daily
Ziprasidone	***PO***: 40 - 80 mg twice daily (Max: 80 mg BD)	No dosage adjustment necessary			Caution use		
ANTIDEPRESSANT							
Fluoxetine (to be used in combination)	***PO:*** 20 - 50 mg/day (Max: 75 mg/day)	No dosage adjustment necessary			Use lower dose (up to 50% reduction) & less frequent interval in patients with cirrhosis & chronic liver disease		

CrCl = creatinine clearance, PO = orally, LAI = long acting injectables
*Note: Refer to the main CPG for important notations & dose for specific bipolar episodes.

ADVERSE EFFECTS & USE OF MEDICATIONS IN PREGNANCY & LACTATION

MEDICATION	COMMON/SIGNIFICANT ADVERSE EFFECTS	PREGNANCY	LACTATION
Mood stabilisers			
Lithium	Polyuria, polydipsia, weight gain, hyperparathyroidism, hypothyroidism, fatigue, acne, dysgeusia, diabetes insipidus, fine tremor, gastrointestinal (GI) upset	Human data suggest risk	• Relative infant dose (RID): 12.2% • Possible to use cautiously
Valproate	Raised liver enzymes, GI upset, fatigue, drowsiness, weight gain, thrombocytopaenia, skin reaction (Stevens-Johnson Syndrome/SJS, Toxic Epidermal Necrolysis Syndrome/ TENS, Drug Reaction with Eosinophilia & Systemic Symptoms Syndrome)	Contraindicated	• Possible to use in lactation
Lamotrigine	Serious skin rashes (SJS, TENS), blood dyscrasias, aseptic meningitis, GI upset, dizziness, blurred vision, diplopia, headache	Compatible	• RID: 5 - 31% • Possible to use in lactation
Carbamazepine	Serious skin rashes (SJS, TENS), blood dyscrasias, hepatoxicity, hyponatraemia, dizziness, drowsiness, GI upset, nystagmus, tinnitus	Not recommended for BD	• Possible & compatible
Antipsychotics			
Aripiprazole	Weight gain, dyslipidaemia, hyperglycaemia, drowsiness, extrapyramidal symptoms (EPS), headache, insomnia, neutropaenia	Human data suggest low risk	• RID: 0.7 - 8.3% • Not recommended during lactation
Asenapine	Drowsiness, insomnia, akathisia, EPS, headache, dizziness, weight gain, hypertriglyceridaemia, hypercholesterolaemia, hyperglycaemia, oral hypoesthesia	No human data - animal data suggest moderate risk	• Not recommended during lactation
Cariprazine	GI upset, akathisia, dizziness, EPS, insomnia, somnolence, headache, hyperglycaemia, weight gain	No human data - animal data suggest moderate risk	• No information available
Haloperidol	Hypotension, constipation, xerostomia, akathisia, EPS, somnolence, blurred vision	Limited human data - animal data suggest moderate risk	• Possible to use cautiously
Lumateperone	Nausea, xerostomia, dizziness, somnolence, EPS	Limited human data	• No information available
Lurasidone	Dyslipidaemia, hyperglycaemia, weight gain, GI upset, akathisia, EPS, parkinsonism, somnolence	Limited human data - risk in third trimester	• No information available
Olanzapine	Orthostatic hypotension, hypercholesterolaemia, hyperglycaemia, hyperprolactinaemia, weight gain, akathisia, EPS, anticholinergic effects	Compatible	• RID: 0.3 - 4% • Acceptable during lactation • First-line of AAPs for lactation
Paliperidone	Tachycardia, weight gain, hyperprolactinaemia, akathisia, dyskinesia, dystonia, EPS, somnolence, tremor	Limited human data - animal data suggest low risk	• Possible to use cautiously
Quetiapine	Orthostatic hypotension, dyslipidaemia, weight gain, anticholinergic effects, asthenia, EPS, somnolence	Compatible	• RID: 0.02 - 0.1% • Possible to use during lactation • First/second choice for lactation
Risperidone	Weight gain, hyperprolactinaemia, dyslipidaemia, EPS, excessive salivation, GI upset, akathisia, dizziness, sedation, blurred vision, anxiety	Compatible	• RID: 2.3% - 4.7% • Possible to use cautiously • Second-line of AAPs for lactation
Ziprasidone	Weight gain, GI upset, akathisia, dizziness, EPS, headache, somnolence, tremor, prolonged QTc interval	Limited human data - animal data suggest risk	• Possible to use cautiously
Selective Serotonin Reuptake Inhibitor			
Fluoxetine	GI upset, xerostomia, dizziness, insomnia, somnolence, tremor, anxiety	Human data suggest risk in third trimester	• RID: 3% - 12% • Possible to use during lactation

RID <10% is considered compatible with breastfeeding. However, worth noting that some sources recommend that for psychotropic agents, breastfeeding is considered acceptable if RID is <5%

*Note: Refer to main CPG for important notation.

SUICIDE PREVENTION

Identifying risk factors for suicide in BD is important.

Risk factors:

- sociodemographic
  - younger age
  - male
  - unemployed
  - disabled
- symptomatology
  - suicidal ideation
  - rapid cycling
  - psychotic symptoms
  - depressive phase
  - hopelessness
  - mixed state
- clinical characteristics
  - early onset of mood disorder
  - previous suicide attempts
  - multiple hospitalisations
  - early sexual abuse
  - stressful life events
  - lack of confidant
  - family history of suicide
- co-morbidity
  - anxiety disorder
  - Cluster B personality (antisocial/borderline/histrionic/narcissistic personality disorder)
  - substance misuse
- treatment
  - duration of treatment (<5 years)

Personalised, collaborative management of suicidal behaviour in BD including emerging treatment options e.g. safety planning is advocated.

Components of Safety Planning

✓ Recognising warning signs of impending suicidal crisis
✓ Identifying & employing internal coping strategies without needing to contact another person
✓ Utilising contacts with people as a means of distraction from suicidal thoughts & urges
✓ Contacting family members or friends who may help to resolve a crisis & with whom suicidality can be discussed
✓ Contacting mental health professionals or agencies
✓ Reducing the potential use of lethal means