CLINICAL PRACTICE GUIDELINES

2024 MOH/P/PAK/555.24(GU)-e

MANAGEMENT OF BIPOLAR DISORDER

(SECOND EDITION)

MINISTRY OF HEALTH MALAYSIA

MALAYSIAN PSYCHIATRIC ASSOCIATION

ACADEMY OF MEDICINE MALAYSIA

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STATEMENT OF INTENT
This clinical practice guidelines (CPG) is meant to be a guide for clinical practice based on the best available evidence at the time of development. The guideline should not override the responsibility of the practitioners to make decisions appropriate to the circumstances of the individual. This should be done in consultation with the patients and their families or guardians, taking into account the management options available locally.

UPDATING THE CPG
These guidelines were issued in 2024 and will be reviewed in a minimum period of four years (2028) or sooner if there is a need to do so. When it is due for updating, the Chairman of the CPG or National Advisor of the related specialty will be informed about it. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed and the latest systematic review methodology used by MaHTAS will be employed. Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on the websites mentioned above.

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LEVELS OF EVIDENCE

Level	Study design
I	Properly powered and conducted randomised controlled trial; well-conducted systematic review or meta-analysis of homogeneous randomised controlled trials
II-1	Well-designed controlled trial without randomisation
II-2	Well-designed cohort or case-control analysis study
II-3	Multiple time series, with or without the intervention; results from uncontrolled studies that yield results of large magnitude
III	Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees

SOURCE: *U.S. Preventive Services Task Force. U.S. Preventive Services Task Force Procedure Manual. Rockville, MD: USPSTF; 2015.*

FORMULATION OF RECOMMENDATION

- In line with the new development in CPG methodology, the CPG Unit of MaHTAS is adapting **Grading Recommendations, Assessment, Development and Evaluation (GRADE)** in its work process. The quality of body of evidence and related effect size are carefully assessed/reviewed by the CPG DG.
- Recommendations are formulated based on **certainty of evidence** and the wording used denotes the **strength of recommendations**. This takes into account:
  - quality and level of the evidence
  - balance of benefits and harms of the options
  - patient's preference and values
  - resource implications
  - relevancy and applicability to the local target population
- The more criteria being fulfilled, the more certain is the evidence leading to strong recommendations using the word "should" being considered. Otherwise, weak recommendations use the word "may" in proposing an action to be made.
- In the CPG, a yellow box highlights important message(s) in the management while a blue box contains evidence-based recommendation(s) for the particular condition.

KEY RECOMMENDATIONS

The following recommendations are highlighted by the CPG Development Group (DG) as the key recommendations that answer the main questions addressed in the CPG and should be prioritised for implementation.

DIAGNOSIS

- Bipolar disorder 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).

TREATMENT AND MONITORING

- Antipsychotics or mood stabilisers, either as monotherapy or combination, should be used to treat acute mania or depressive episodes in bipolar disorder (BD).
- Antidepressants may be used as short-term adjunctive treatment but not as monotherapy in acute bipolar depression.
- In BD with specifiers:
  - atypical antipsychotics (AAPs) or mood stabilisers may be used as monotherapy or combination therapy in mixed features
  - AAPs may be used in anxious distress
  - combination of mood stabilisers with AAPs or another mood stabiliser is the preferred treatment of choice in rapid cycling
  - antidepressants should be avoided in mixed features and used with caution in rapid cycling
- For maintenance pharmacotherapy of BD:
  - lithium and quetiapine are the preferred first-line monotherapy while lithium plus quetiapine or aripiprazole are the preferred first-line combination therapy
  - antidepressant monotherapy should be avoided
  - aripiprazole or risperidone long-acting injectables may be considered in patients who have poor adherence to oral medications especially in preventing manic episodes
- Serum lithium level should be monitored one week upon initiation or dose change and every six months or earlier if indicated in BD.
- Electroconvulsive therapy should be considered in both bipolar manic and depressive episodes in indicated situations.
- Psychosocial interventions and psychotherapies should be offered as an adjunctive treatment for BD.

RELAPSE PREVENTION AND ADHERENCE

- Psychosocial interventions and psychotherapies should be part of strategies in relapse prevention of bipolar disorder.

SPECIAL POPULATION

- Shared decision-making in weighing the risks versus benefits of pharmacological treatment should be done in pregnant and lactating women with bipolar disorder (BD).
  - Atypical antipsychotics (AAPs) may be used in pregnancy.
  - Valproate and carbamazepine should be avoided in pregnancy given their teratogenic risks. Other mood stabilisers should be used with caution.
- For children and adolescents with BD:
  - AAPs monotherapy may be used in manic or mixed episodes
  - lurasidone and olanzapine/fluoxetine combination may be used in depressive episodes
- Patients with BD with co-morbid substance use disorder should be referred to psychiatric services.

GUIDELINES DEVELOPMENT AND OBJECTIVES

GUIDELINES DEVELOPMENT

The members of the DG for this CPG were from the Ministry of Health (MoH), Ministry of Higher Education and the private sector. There was active involvement of a multidisciplinary Review Committee (RC) during the process of the CPG development.

A systematic literature search was carried out using the following electronic databases/platforms: mainly Medline via Ovid and others e.g. Pubmed (refer to **Appendix 1** for **Example of Search Strategy**). The inclusion criteria includes everyone at risk and with bipolar disorder (BD) regardless of study design. The first search was limited to literature published in the last eight years (2014 until 2022) on humans and in English. In addition, the reference lists of all retrieved literature and guidelines were searched to further identify relevant studies. Experts in the field were also contacted for studies related to the issues addressed. All initial searches were conducted from 2 August 2022 to 17 August 2022. The literature search was repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 31 December 2023 to be included. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

References were also made to other guidelines on BD as listed below:

i. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disoder (ISBD) - Guidelines for the Management of Patients with Bipolar Disorder (2018)
ii. Ministry of Health, Malaysia - Clinical Practice Guidelines on Management of Bipolar Disorder (2014)
iii. National Institute for Health and Care Excellence (NICE) - Guideline on the Assessment and Management of Bipolar Disorder in Adults, Children and Young People in Primary and Secondary Care (2014)
iv. Royal Australian and New Zealand College of Psychiatrists (RANZCP) - The 2020 RANZCP Clinical Practice Guidelines for Mood Disorders (2020)

A total of 18 main clinical questions were developed under different sections. Members of the DG were assigned individual questions within these sections. Refer to **Appendix 2** for **Clinical Questions**. The DG members met 27 times throughout the development of these guidelines. All literature retrieved was appraised by at least two DG members using the Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in each DG meeting. All statements and

recommendations formulated after that were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. Any differences in opinion were resolved consensually. The CPG was based largely on the findings of systematic reviews/meta-analyses and clinical trials, with local practices taken into consideration.

The literatures used in these guidelines were graded using the U.S. Preventive Services Task Force Level of Evidence (2015) while the grading of recommendation was done using the principles of GRADE as much as possible (refer to the preceding page). The writing of the CPG followed strictly the requirement of Appraisal of Guidelines for Research and Evaluation (AGREE) II.

Upon completion, the draft CPG was reviewed by external reviewers. It was also posted on the MoH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG and, the Health Technology Assessment (HTA) and CPG Council, MoH Malaysia, for review and approval. Details on the CPG development by MaHTAS can be obtained from the **Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines published in 2015** (available at https://www.moh.gov.my/moh/resources/CPG_MANUAL_MAHTAS.pdf).

OBJECTIVES

The objective of the CPG is to provide evidence-based recommendations on the management of bipolar disorder in the following aspects:

- diagnosis and assessment
- treatment
- prevention
- monitoring and referral

CLINICAL QUESTIONS

Refer to **Appendix 2**.

TARGET POPULATION

Inclusion Criteria

- Persons with BD
- Special population with BD:
  - pregnant and lactating women
  - elderly
  - children and adolescents
  - persons with substance use disorder
  - persons with borderline personality disorder

Exclusion Criteria

- People with BD secondary to organic conditions

TARGET GROUP/USER

This document is intended to guide health professionals and relevant stakeholders in primary and secondary/tertiary care of both public and private sectors in the management of BD including:

i. medical doctors
ii. allied health professionals
iii. trainees and medical students
iv. patients, caregivers and their advocates
v. professional societies
vi. policy makers

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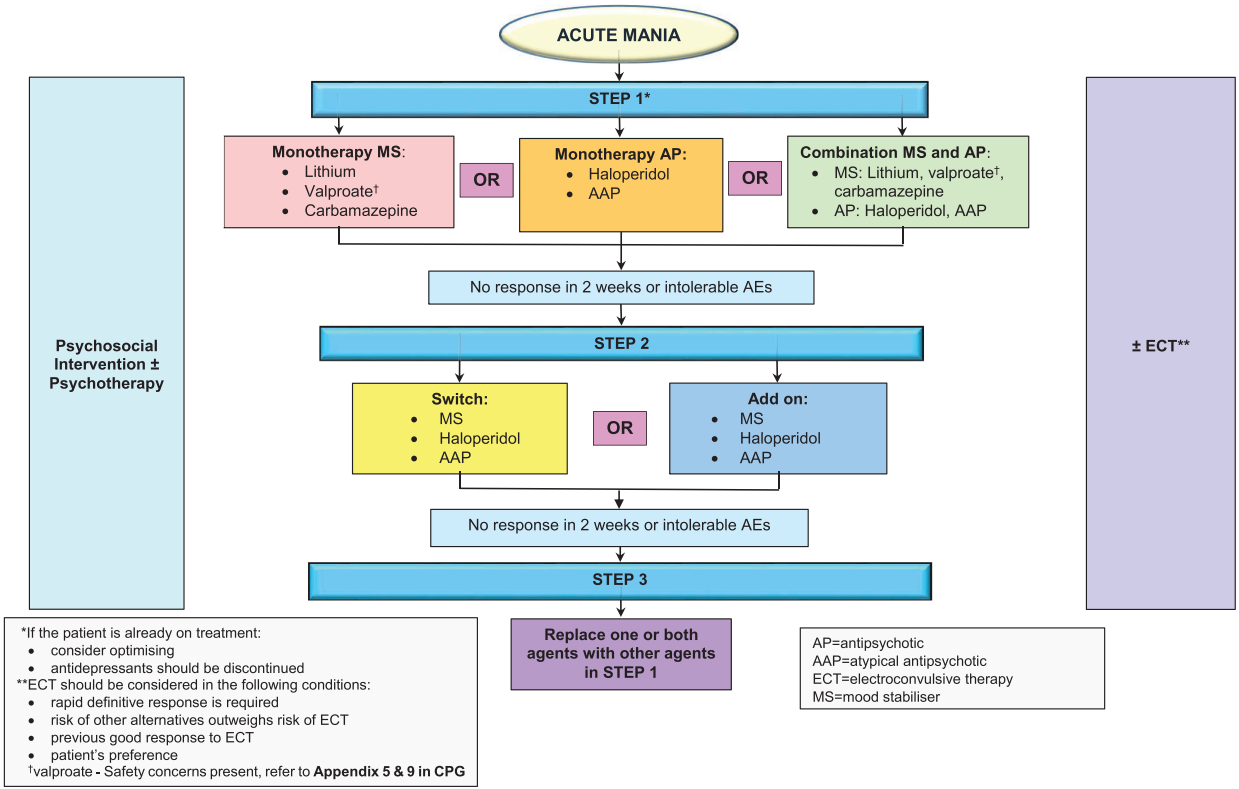
ALGORITHM 1. TREATMENT OF ACUTE MANIA



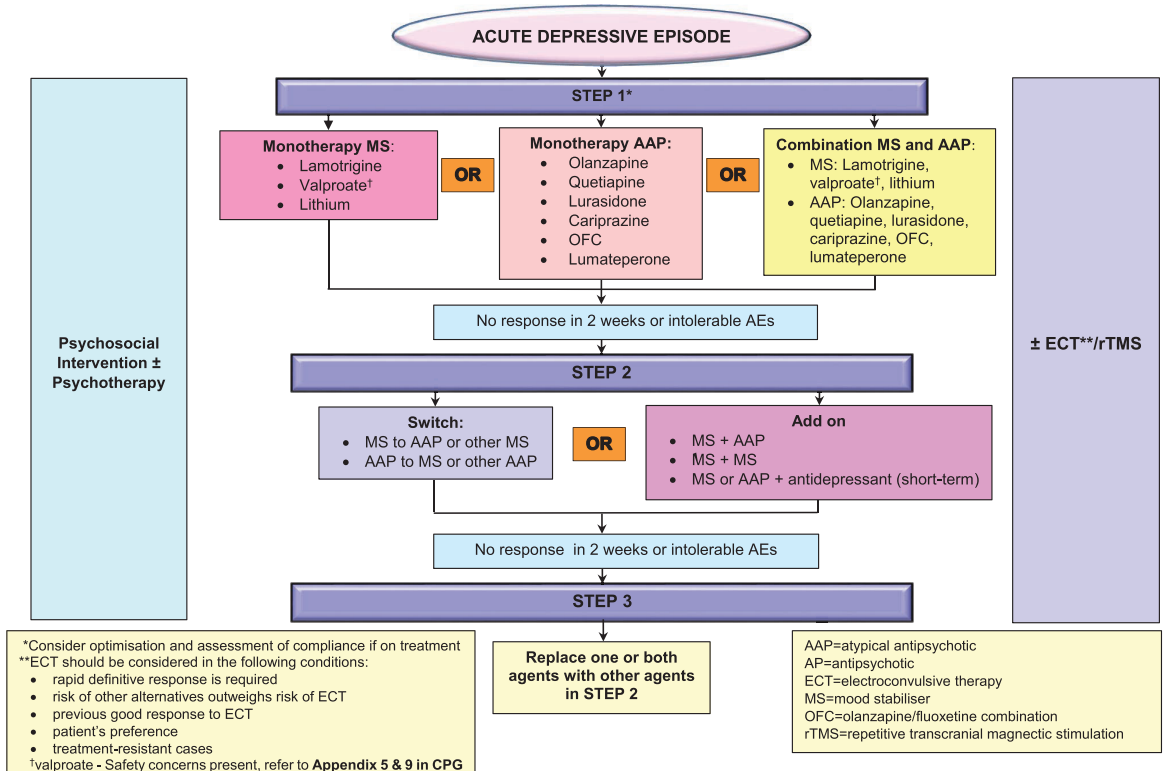
*If the patient is already on treatment:
- consider optimising
- antidepressants should be discontinued

**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

†valproate - Safety concerns present, refer to **Appendix 5 & 9 in CPG**

AP=antipsychotic
AAP=atypical antipsychotic
ECT=electroconvulsive therapy
MS=mood stabiliser

ALGORITHM 2. TREATMENT OF ACUTE DEPRESSIVE VALPROATE



1. INTRODUCTION

Bipolar disorder (BD) is a potentially life-long disabling condition presenting commonly as either bipolar I disorder (BD I) or bipolar II disorder (BD II). BD I is characterised by episodes of mania (abnormally elevated mood or irritability and related symptoms with severe functional impairment or psychotic symptoms for seven days or more). On the other hand, BD II is characterised by episodes of hypomania (abnormally elevated mood or irritability and related symptoms with decreased or increased function for four days or more) and depressive episodes.

BD is a severe mental disorder. Based on World Health Organisation (WHO) statistics in 2019, its global prevalence was estimated to be around 40 million.[1] In the Global Burden of Disease Study 2019, the prevalence of BD showed an increasing trend from 24.8 million in 1990 to 39.5 million in 2019.[2] Its prevalence in Malaysia, however, is not well-established. BD is associated with reduced functioning, cognitive impairment and decreased quality of life (QoL). It is also one of the leading causes of disability in young people and increased mortality, especially by suicide.[3]

Diagnosis of BD may be difficult given the complexity of its clinical presentation which may overlap with other psychiatric disorders and change over time. Moreover, managing BD is limited by the lack of resources including expertise and medications. Poor adherence remains a major issue that needs to be tackled in its management.

The first edition of the CPG Management of BD in Adults was published in 2014. Since then, there have been advances in the management of BD which include wider medication choices and new treatment modalities that incorporate technological advancement.

This revised edition provides updates on the evidence and related recommendations on the current management of BD, keeping in mind the acceptability of the treatment and availability of resources. It also addresses the management of children and adolescents, and looks into evidence on psychospirituality as well as complementary and alternative medicine. Previous topics on psychosocial interventions, suicide prevention and management in pregnant and lactating women are further expanded.

This CPG is aimed to be used at primary, secondary, and tertiary health care settings. It is also useful for those involved in psychiatric training. It is hoped that this CPG will be of benefit to healthcare professionals and help improve the management of patients with BD.

2. RISK FACTORS

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

Several factors increase the risk of people developing BD which include:

- offspring of maternal age group ≥40 years old (OR=1.20, 95% CI 1.10 to 1.31)[4, level II-2]
- presence of major depression with attention-deficit hyperactivity disorder (ADHD) (OR=1.50, 95% CI 1.30 to 1.72)[5, level II-2]

Apart from the above, the established risk factors for BD are:

- family history of BD[6]
- young age (<25 years old)[7]
- low educational level[6]
- low employment level[6]

Recurrence of BD means the return of symptoms e.g. mania, hypomania or depression after a period of wellness (symptom-free period). In a systematic review, factors associated with recurrence of BD were:[8, level II-2]

- early age of onset
- low socio-economic status
- family history of BD
- history of child abuse
- low maternal warmth
- co-morbid mental health disorders (anxiety disorder, ADHD and substance use disorders)
- inter-episode subsyndromal mood symptoms

3. SCREENING AND DIAGNOSIS

The diagnosis of BD relies on signs and symptoms elicited during clinical interviews with the patient and often with corroborative history from informants. Diagnostic and Statistical Manual of Mental Disorders Fifth Edition, text revision (DSM-5-TR) and International Classification of Diseases Eleventh Revision (ICD-11) classification systemfor psychiatric disorders assist in framing operational definitions i.e. making diagnoses for clinical work and research. Revisions of these classifications ensure they are at pace with the recent advancements in the field. The main changes in the new classification systems are:

- both ICD-11 and DSM-5-TR use the term bipolar disorder instead of bipolar affective disorder as in ICD-10
- ICD-11 uses subdivision of bipolar disorder type I and II, in line with DSM-5-TR
- definitions of manic and hypomanic syndromes and episodes are almost identical between ICD-11 and DSM-5-TR

Refer to **Appendix 3** for **Diagnostic Criteria of Bipolar Disorder Based on the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition, Text Revision (DSM-5-TR)** and **International Classification of Diseases Eleventh Revision (ICD-11)**.

Recommendation 1

- Bipolar Disorder should be diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition, Text Revision or International Classification of Diseases Eleventh Revision.

3.1. Screening Tools

BD commonly presents as unipolar depression on the first presentation. There is a prevalence of 17% of undiagnosed BD in primary care, amounting to over 3 in every 20 patients.[9, level II-2] This may lead to a misdiagnosis or delayed diagnosis of BD up to 10 years, which in turn may result in an increased risk of treatment-emergent mania/hypomania and suicide.[10 - 12] Screening tools for BD may assist healthcare practitioners in identifying those with underlying BD. Furthermore, identifying those who are at risk of BD allows for preventive strategies and early interventions.

The following tools are available for the screening of BD:

- Mood disorder questionnaire (MDQ)[13]
- Hypomania checklist (HCL-32)[14]
- Bipolar spectrum diagnostic scale (BSDS)[15]
- Rapid mood screener (RMS)[16]

Refer **Appendix 4** for **List of Screening Tools in Bipolar Disorder**.

In a nationwide cross-sectional study on awareness and acceptability of RMS and MDQ in BD screening among 200 healthcare practitioners (HCP) in both primary and secondary care, the findings were:[17, level III]

- only 32% of HCP used a screening tool for BD compared with 82% for MDD
- although 85% of the HCP were aware of MDQ, only 29% reported on its current use
- RMS was significantly better than MDQ in terms of accuracy, brevity, practicality and easy scoring
- HCPs were significantly more likely to use RMS than MDQ (81% vs 19%)

Bipolarity index (BI) is a tool that can increase diagnostic confidence of BD. This tool is clinician-rated. It is useful when symptoms of mania are difficult to elicit, patients deny the presence of manic symptoms or manic symptoms stem from another diagnosis. The scale has five sections; episode characteristics, age of onset, course of illness, response to treatment and family history. In a diagnostic study using BI to screen for BD in outpatient psychiatric practice, the sensitivity and specificity of BI were 0.91 and 0.90, at a cut-off point of 50, PPV of 0.88, NPV of 0.93 and AUC of 0.97.[18, level III]

It may be difficult to screen for BD in the general population. A group of researchers from the University of Melbourne introduced Bipolar at-risk (BAR) criteria which may assist in identifying those at risk of BD in the age range of 15 - 25 years. It included sub-threshold mania, depressive symptoms, cyclothymic features and genetic risk.[19, level III] Refer to **Table 1** for further description of the criteria.

Table 1: Bipolar At-Risk Criteria

Criterion	Description
Group 1: Subthreshold mania	2 - 4 consecutive days of abnormally and persistently elevated, expansive or irritable mood with at least two of the following: 1. inflated self-esteem or grandiosity 2. decreased need for sleep (e.g. feels rested after only three hours of sleep) 3. more talkative than usual or pressure to keep talking 4. flight of ideas or subjective experience that thoughts are racing 5. distractibility 6. increased goal-directed activity (socially, at work or sexually) or psychomotor agitation
Group 2: Depression and cyclothymic features	Depression defined as at least one week of depressed mood or loss of interest/pleasure with at least two of the following: 1. significant weight loss 2. insomnia or hypersomnia nearly every day 3. psychomotor retardation or agitation 4. fatigue or loss of energy 5. feelings of worthlessness or excessive/inappropriate guilt 6. diminished ability to think or concentrate 7. recurrent thoughts of death and/or recurrent suicidal ideation Cyclothymic features are defined as numerous episodes with subthreshold manic symptoms not meeting group 1 criteria and numerous episodes with depressive symptoms. e.g. sub-threshold mania as defined in group
	1 only for four hours within a 24-hour period and at least four cumulative lifetime days meeting the criteria
Group 3: Depression and genetic risk	Depression same as for group 2; genetic risk defined as first-degree relative with BD

Adapted: Bechdolf A, Nelson B, Cotton SM, et al. A preliminary evaluation of the validity of at-risk criteria for bipolar disorders in help-seeking adolescents and young adults. J Affect Disord. 2010;127(1-3):316-20

A cohort study assessed the association of BAR criteria and onset of BD over 10 to 13 years of follow-up and showed that:[20, level II-2]

- 28.6% of subjects from BAR group developed BD over a mean of 11.1 years whilst none developed BD in a clinically matched comparison group. Of these:

- 87.5% transitions were to BD II and 12.5% to BD I
- 75.0% transitions occurred in those with subthreshold mania and 25.0% in those with major depression and cyclothymic features

- Patients with suspected unipolar depression should be screened for BD.
- There is inadequate evidence to recommend a specific screening tool for BD in primary care.
- Clinical diagnostic assessment should follow any positive screening for BD.

3.2. Differential Diagnoses

Symptoms of BD can overlap with other disorders. A comprehensive current and longitudinal history, corroborative history from informants and relevant investigations are useful to rule out the differential diagnoses in BD.

Below are common differential diagnoses to be considered in BD:

a) during depressive episode -
   - major depressive disorder[6]
   - major depressive disorder with mixed episode[21, level III]
   - adjustment disorder with depressed mood[6]
   - anxiety disorders[6]
   - depressive disorder due to another medical condition[6]
   - substance-induced depressive disorder[6]
   - schizophrenia or schizoaffective disorder[6]

b) during mania or hypomania episode -
   - substance-induced bipolar disorder[6]
   - bipolar and related disorder due to another medical condition[6]
   - schizophrenia or schizoaffective disorder[6]
   - borderline personality disorder[6]
   - attention-deficit hyperactivity disorder (ADHD)[22, level III]

In a narrative review comparing the overlap and differences of ADHD and BD, the authors summarised the findings as follows:[22, level III]

- similarities - distractibility, irritability, insomnia, poor concentration, talkativeness and psychomotor agitation
- differences were as follows -

ADHD	BD
Childhood or early adolescent onset	Adolescent/adult onset
Trait-like, no change from pre-morbid state	Episodic course, change from pre-morbid state
May be excitable but not grandiose/ elated	Grandiosity/elated
Reports being unable to function	Reports high-level function, not reflecting behaviour
Chronic low self-esteem	Episodes of depression
Usually possesses insight	Tends to lack insight
Difficulty getting off to sleep	Reduced need for sleep
Complains of being unable to concentrate/focus	Subjective sense of sharpened mental abilities
Restless (fidgety, difficulty being still)	Marked overactivity and agitation

Source: Asherson, P, Young AH, Eich-Höchli D et al. Differential diagnosis, comorbidity, and treatment of attention-deficit/hyperactivity disorder in relation to bipolar disorder or borderline personality disorder in adults. Current medical research and opinion. 2014;30(8):1657-1672

3.3. Co-Morbidities

BD patients may have psychiatric and medical co-morbidities. The co-morbidities cause difficulties in treatment e.g. decision on the drugs of choice and consideration of drug interactions. It also affects the prognosis of BD in terms of aggravating the course of illness, delaying recovery, increasing risk of recurrence and suicide, and reducing QoL.

The prevalence of eating disorders in BD populations ranges from 1.9% to 33.3%.[23, level III] The prevalence of co-morbid antisocial personality disorder (ASPD) in BD ranges between 4.8% and 63%.It is higher in BD I (45.1%) than

BD II (8.2%). The most commonly abused substances in BD with ASPD are a combination of cocaine and alcohol. People with this co-morbidity have early onset of symptoms, impulsive traits, increased episodes of depression and mania, aggressive behaviour and high suicide attempts.[24, level I]

Other psychiatric co-morbidities in BD include:[25, level II-2]

- drug abuse (33.5%)
- anxiety disorder (31.8%)
- borderline personality disorder (6.9%)
- ADHD (5.2%)

Patients with BD may have medical co-morbidities as follows:[25, level II-2]

- hypertension (31.1%)
- asthma (11.7%)
- diabetes mellitus (11%)
- obesity (11%)
- hypothyroidism (11%)
- migraine (5.5%)

Another co-morbidity is human immunodeficiency virus (HIV) infection (1%).[26, level II-2]

4. TREATMENT

There are several treatment options in BD, including pharmacological interventions, psychotherapies and physical therapies. Ideally, treatment needs to be individualised and patient-centered, focusing on patient-related outcomes.

4.1. Pharmacotherapy

Pharmacological treatment is one of the main pillars in the management of BD. There is ample evidence on the effectiveness of treatment in acute mood episodes and the prevention of relapses in the maintenance phase.

Medications with mood-stabilising properties include lithium, antiepileptic agents (e.g. valproate, carbamazepine, lamotrigine), haloperidol and AAPs. Choice of medications is based on the effectiveness, safety, availability and affordability of the medication, concomitant medications, response to previous medication, family history of medication response, patient preference as well as medical and psychiatric co-morbidities. Refer to **Appendix 5** on **Recommended Adult Medication Dosages and Adverse Effects For Bipolar Disorder**.

- Response to treatment is defined as a ≥50% reduction of total score in standardised rating scales.
- Remission is an outcome of effectiveness measured by varying cut-off points in standardised scales used in clinical trials.

4.1.1. Manic episode

The manic episode in BD poses its challenges with patients potentially having agitation, impulsivity, risky behaviour, aggression and reduced insight. The goal of treatment is to rapidly achieve early remission and return to baseline levels of psychosocial functioning. Pharmacotherapy remains one of the main treatments for a manic episode.

In a large network meta-analysis on adults with acute bipolar mania:[27, level I]

- most of the anti-manic agents (aripiprazole, asenapine, carbamazepine, cariprazine, haloperidol, lithium, olanzapine, paliperidone, quetiapine, risperidone, valproate and ziprasidone) were more effective than placebo; lamotrigine was among those agents found not to be effective

- only aripiprazole, olanzapine, quetiapine, risperidone and valproate showed more acceptability (all-cause discontinuation) compared with placebo

However, there was no mention on quality assessment of the primary papers.

The above findings were supported by a more recent network meta-analysis on adults with acute bipolar mania which showed:[28, level I]

- the following pharmacological agents as monotherapy were more effective than placebo in term of response to treatment -
  - antipsychotics (APs) - haloperidol, risperidone, paliperidone, olanzapine, quetiapine, aripiprazole, cariprazine, ziprasidone
  - mood stabilisers - lithium, valproate, carbamazepine
- aripiprazole, olanzapine, quetiapine and risperidone had better acceptability (all-cause discontinuation) than placebo

The quality of most of the primary papers were moderate based on the risk of bias assessment.

In a systematic review of recently published RCTs after 2017 on adults with BD, results on acute mania/hypomania found that:[29, level I]

- olanzapine was more effective than asenapine as an adjunct to valproate in reducing Young Mania Rating Scale (YMRS) and Clinical Global Impression-Bipolar Disorder (CGI-BP) scores
- lithium was more effective than aripiprazole in reducing manic symptoms based on Manic State Rating Scale (MSRS)
- olanzapine was associated with increased waist circumference, waist-hip ratio and total cholesterol compared with asenapine
- reported AEs in aripiprazole were akathisia, mild stiffness and sedation whilst tremors were seen in lithium

The risk of bias was reported to be high in most primary papers.

In another systematic review on adults with bipolar mania, lithium was found to be:[30, level I]

- more effective than placebo in response, remission and improvement of YMRS scores
- more effective when used as a combination with either risperidone, olanzapine, quetiapine, asenapine or carbamazepine compared with lithium monotherapy
- equally effective to valproate, carbamazepine and quetiapine

There was no mention of quality assessment done on the primary papers.

A systematic review on the effectiveness and safety of brexpiprazole in BD I revealed that:[31, level I]

- brexpiprazole showed no difference in YMRS scores at 21 days compared with placebo
- akathisia was the only AE with an incidence of 5% being reported

An open-label RCT comparing the combinations of lithium with either valproate or carbamazepine in young adults (18 - 35 years old) with BD I showed that:[32, level I]

- although both groups had significant improvement in YMRS scores at eight weeks, there was NS difference between them
- AEs reported in lithium plus valproate group were fatigue, weight gain and decreased sexual desire while the lithium plus carbamazepine group had significant increased rates of diarrhoea

A post-hoc analysis of three RCTs on adults with bipolar mania comparing cariprazine vs placebo showed that the former:[33, level I]

- was more effective in reducing YMRS scores (SMD= -5.35, 95% CI -6.69 to -4.01)
- appeared to have a dose-related response in terms of extra-pyramidal symptoms (EPS), constipation and, changes in ALT and AST levels
- had a low incidence of serious AEs with NS difference between groups

Recommendation 2

- Antipsychotics or mood stabilisers, either as monotherapy* or combination**, should be used to treat acute mania in bipolar disorder.

*Monotherapy APs:

- haloperidol, risperidone, paliperidone, olanzapine, quetiapine, aripiprazole, cariprazine, ziprasidone or asenapine

Monotherapy mood stabilisers:

- lithium, valproate or carbamazepine

**Combination therapies:

- lithium with either valproate, carbamazepine, risperidone, olanzapine, quetiapine or asenapine
- valproate with olanzapine

4.1.2. Depressive episode

Depressive episodes are debilitating for patients with BD and account for much of the time spent unwell. This would include subsyndromal presentation and long-term functional impairment. Management of depressive episodes in BD proves to be a challenging task given the risk of treatment-emergent manic switch and increasing choices of treatment.

A network meta-analysis on bipolar depression comparing monotherapy vs placebo showed:[34, level I]

- response rates were higher with tranylcypromine, venlafaxine, fluoxetine, imipramine, valproate, olanzapine/fluoxetine combination (OFC), lurasidone, olanzapine, quetiapine, cariprazine and lamotrigine
- remission rates were higher with tranylcypromine, fluoxetine, venlafaxine, OFC, quetiapine, lurasidone, olanzapine, lamotrigine
- reduction in depression severity with fluoxetine, valproate, lurasidone,cariprazine, olanzapine and quetiapine
- NS difference in discontinuation rate due to AEs for all medications except aripiprazole (OR=2.25, 95% CI 1.18 to 4.30) and quetiapine (OR=1.80, 95% CI 1.26 to 2.55)

Majority (74%) of the primary papers were of low risk of bias.

A recent large network meta-analysis on adults with bipolar depression compared different pharmacological treatments with placebo and reported:[35, level I]

- based on statistically significant effectiveness and good confidence evidence, the medications that improved depressive symptoms in MADRS, HAM-D (Hamilton Depression Rating Scale), Inventory of Depressive Symptomatology (IDS) or Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR) were OFC, quetiapine, olanzapine, lurasidone, lumateperone, cariprazine and lamotrigine.
- quetiapine reduced the risk of manic switch (OR=0.49, 95% CI 0.33 to 0.75) while NS risk was seen in all other individual drugs e.g. lithium, antiepileptics, antidepressants or APs
- lumateperone (OR=2.71, 95% CI 1.29 to 5.71) and quetiapine (OR=1.99, 95% CI 1.51 to 2.63) had a higher risk of discontinuation due to AEs

Overall quality assessment showed a 94% low risk of bias.

In the third network meta-analysis on adults with bipolar depression treated with atypical antipsychotic (AAP) monotherapy vs placebo revealed:[36, level I]

- significant improvement in MADRS was seen with lurasidone, olanzapine, quetiapine and cariprazine
- NS difference in discontinuation rate due to AEs among lurasidone, cariprazine, olanzapine and ziprasidone but significantly higher risk in aripiprazole and quetiapine

According to SUCRA analyses, lurasidone, olanzapine and quetiapine ranked first for improvement in MADRS compared with placebo followed by cariprazine. Based on GRADE assessment, both direct and indirect comparisons of the above AAPs for both outcomes were of moderate to high quality.

Two meta-analyses on adults with acute bipolar depression on mood stabilisers or APs, comparison between adjunctive of mainly second-generation antidepressants and placebo showed:[37, level I; 38, level I]

- small reduction in depressive symptoms in the intervention group
- NS difference in response and remission
- NS difference in affective switch at short-term (up to 26 weeks) but a risk at long-term (52 weeks)
- NS difference in patients with at least one AE

52.6 % of included trials scored low risk on the measurement of the outcomes. Most of the 47.4% of studies that scored high risk were open-label studies.

A few guidelines recommend that antidepressants may be used as short-term adjunctive treatment but not as monotherapy in acute bipolar depression.[6, 39, 40]

In a Cochrane systematic review on glutamate receptor modulators in BD, the findings were:[41, level I]

- IV ketamine was more effective in response than placebo at 24 hours only (OR=11.61, 95% CI 1.25 to 107.74) but showed no difference with midazolam; however, there was no difference in AEs between ketamine and placebo
- no difference in response between memantine and N-acetylcysteine compared with placebo

Another systematic review of RCTs on adults with BD compared monotherapy or adjunctive AAPs vs placebo, the findings for acute depression were:[29, level I]

- cariprazine showed significant improvement in depressive symptoms in two studies and NS changes in one study
- quetiapine showed significant improvement in depressive symptoms, response rate and remission rate

The papers on cariprazine were of low risk while the ones on quetiapine had high risk of bias.

For the use of lithium, existing guidelines have recommended that it may be used in bipolar depression.[39, 40]

Recommendation 3
- Atypical antipsychotics* or mood stabilisers**, either as monotherapy or combination, should be used to treat depressive episodes in bipolar disorder.
- Antidepressants may be used as short-term adjunctive treatment but not as monotherapy in acute bipolar depression.
  - Occurrence of treatment-emergent manic switch should be monitored.

*AAPs: olanzapine, quetiapine, lurasidone, cariprazine, OFC, lumateperone
**mood stabilisers: lamotrigine, valproate, lithium

4.1.3. Bipolar disorder with specifiers

Specifiers in BD are descriptive terms on different features of the disorder. They are outlined in the International Classification of Diseases (ICD-11) and Diagnostic and Statistical Manual of Mental Health (DSM-5). Only the three most commonly studied specifiers will be addressed in this CPG.

a. Mixed features

Mixed features are present in one-third of BD in either manic or depressive episode. The presence of mixed features is associated with poorer outcomes e.g. increased time in illness, poorer response to treatment and suicidality.[42] Management of mixed features is challenging as it needs to address both mania/hypomania and depressive symptoms that occur simultaneously. Despite its common prevalence in BD, there is a paucity of RCTs on pharmacological intervention of mixed features.[43]

In a systematic review of six international clinical guidelines on the treatment of mixed states in mood disorders mainly BD among the adult population, the recommended treatments are summarised in the table below:

Phases of BD	Mania/hypomania with mixed features	Depression with mixed features
Acute episode		
First-line		
Monotherapy	Olanzapine, aripiprazole, asenapine, paliperidone,	Lurasidone, olanzapine, quetiapine, valproate
Combination therapy	Olanzapine + valproate Olanzapine + lithium Quetiapine + lithium Quetiapine + valproate Asenapine + valproate Aripiprazole + valproate	Lurasidone + valproate Lurasidone + lithium Olanzapine + valproate Olanzapine + lithium Olanzapine/fluoxetine combination (OFC) Ziprasidone + treatment as usual
Second-line	Cariprazine, ziprasidone, risperidone, clozapine, valproate, lamotrigine, carbamazepine	Aripiprazole, asenapine, carbamazepine
Maintenance		
First-line		
Monotherapy	Lithium, valproate, olanzapine, quetiapine	
Combination therapy	Quetiapine + valproate Quetiapine + lithium Aripiprazole + valproate Aripiprazole + lithium	
Second-line	Ziprasidone Risperidone + lithium Risperidone + valproate Aripiprazole + lamotrigine	

The same review recommended that antidepressants should be avoided in mixed episodes. Clozapine was an effective option in treatment-resistant patients.[43]

A systematic review on adults with BD showed that in those with mixed episodes:[30, level I]

- combination of olanzapine plus lithium or valproate was effective in acute episodes but combination of haloperidol or risperidone plus lithium or valproate was not
- combination of quetiapine plus lithium or valproate was effective in preventing relapse but the addition of aripiprazole on lithium or valproate was not
- lithium monotherapy was not effective in preventing relapse Quality assessment of primary papers however was not mentioned.

A post-hoc analysis of three RCTs on acute bipolar depression with concurrent manic symptoms compared the effectiveness of cariprazine (1.5 mg and 3 mg) vs placebo at six weeks and showed that the former had:[44, level I]

- significantly more improvement of MADRS total score, CGI-S and HAM-D scores
- significantly higher response and remission rates
- NS improvement of YMRS total score

A 6-week placebo-controlled RCT on adults with bipolar depression demonstrated that 42 mg of lumateperone, another new AAP, in those with mixed features had:[45, level I]

- significantly reduced MADRS total scores (LSMD= -4.4, 95% CI -7.26 to -1.52)
- significantly reduced CGI-S-Bipolar Version-Severity (CGI-BP-S) total scores (LSMD = -0.7, 95% CI -1.43 to -0.05)
- higher AEs of somnolence and postural dizziness but no difference in manic switch

The summary of the 2021 CANMAT guidelines for the management of BD patients with mixed presentations are as follows:[42]

- there is limited evidence for first-line treatment based on DSM-5 manic or depressive episodes with mixed features
- for DSM-IV-defined mixed episodes, asenapine and aripiprazole are first- line while olanzapine (monotherapy or combination), carbamazepine and valproate are second-line agents
- for maintenance treatment following a DSM-IV mixed episode, quetiapine (monotherapy or combination) is first-line while lithium and olanzapine are identified as second-line options

b. Anxious distress

Anxious distress is common in BD but often under-recognised by clinicians. Its symptoms include feeling keyed up or tense, feeling unusually restless, difficulty concentrating because of worry, feeling that something awful may happen and feeling that one might lose control. Prompt evaluation and treatment of its symptoms is important as it is associated with adverse outcomes including higher suicidal risk and persistence of bipolar symptoms compared with those without anxious distress.

A meta-analysis evaluating the effectiveness of pharmacotherapy vs placebo on BD patients (mostly in depressive episodes) with anxiety symptoms revealed that:[46, level I]

- pharmacotherapy (primarily AAPs - cariprazine, quetiapine, olanzapine and olanzapine-fluoxetine combination) was more effective based on improvement of scores in Generalized Anxiety Disorder-7 scale (GAD-7) or Hospital Anxiety and Depression

scale (HADS) (SMD= -0.22, 95% CI -0.34 to -0.11) and the result remained significant even after controlling depressive symptoms (SMD= -0.15, 95% CI -0.28 to -0.02)
- NS difference in all-cause discontinuation rate

A total of 32 out of 37 RCTs had moderate to strong quality based on assessment with Effective Public Health Practice Project Quality Assessment Tool.

CANMAT guidelines state that quetiapine, olanzapine-fluoxetine combination and lurasidone improve anxiety symptoms associated with bipolar depression.[40]

c. Rapid cycling

Patients who experience at least four episodes (meeting criteria for full mania, hypomania or major depression) during a 12-month period are classified in DSM-5 as "rapid cycling". The lifetime prevalence of rapid cycling is between 26% and 43% of those with BD.[47] Patients with this condition are more likely to demonstrate greater severity of illness and, higher risk at suicide attempts and functional impairment compared with non-rapid cycling patients.[48] Successful treatment of rapid cycling often requires several combinations of mood-stabilising agents.

A recent meta-analysis on mood stabilisers for treatment of rapid cycling BD showed the following:[49, level I]

- combination of lamotrigine and lithium compared to lithium monotherapy reported:
  - better improvement in Positive and Negative Syndrome Scale (PANSS) (MD= -16.67, 95% CI -22.98 to -10.36) and Brief Psychotic Rating Scale (BPRS) scores (MD= -3.07, 95% CI -5.02 to -1.12)
  - better response rate (OR=4.26, 95% CI 1.65 to 10.99)
- lithium monotherapy had NS difference in remission rate compared with any of the three combination therapies (lamotrigine, lithium and valproate)

There was no mention of AEs. The quality of primary papers was high based on the Agency for Healthcare Research and Quality (AHRQ) assessment.

In another systematic review of RCTs and meta-analysis on adults with rapid cycling BD, it was shown that:[30, level I]

- both lithium and short-term venlafaxine monotherapy had equal effectiveness in acute episodes of BD-II depression
- combination of lithium and carbamazepine was more effective in preventing relapse compared with either monotherapy
- quetiapine as an adjunct to lithium or valproate was effective and safe in the prevention of mood episodes in BD-I

There was no mention of quality assessment on the primary papers.

In the third meta-analysis on adults with rapid cycling BD:[47, level I]

- AAPs and mood stabilisers were more effective than placebo in
  - Clinical Global Impression (CGI) with Hedge's g of 0.79 (95% CI 0.71 to 0.86) for AAPs and 0.67 (95% CI 0.40 to 0.95) for mood stabilisers
  - Montgomery-Asberg Depression Rating Scale (MADRS)/ Hamilton Depression Rating Scale (HAM-D) score with Hedge's g of 0.75 (95% CI 0.56 to 0.93) for AAPs and 0.83 (95% CI 0.57 to 1.08) for mood stabilisers
- AAPs were more effective than placebo in YMRS with Hedge's g of 1.11 (95% CI 0.92 to 1.30)

There was a mixture of quality on the primary papers based on risk of bias (RoB) assessment.

Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines has no specific recommendation on the use of antidepressants in BD with rapid cycling.40 The Royal Australian and New Zealand College of Psychiatrists (RANZCP) guidelines recommend antidepressant therapy should be used cautiously in the treatment of bipolar depression when there is a history of rapid cycling.[39]

Recommendation 4

- In bipolar disorder with specifiers:
- atypical antipsychotics (AAPs) or mood stabilisers may be used as monotherapy or combination therapy in mixed features o AAPs may be used in anxious distress
- combination of mood stabilisers with AAPs or another mood stabiliser is the preferred treatment of choice in rapid cycling
- antidepressants should be avoided in mixed features and used with caution in rapid cycling

4.1.4. Maintenance phase

Maintenance phase focuses on prevention of recurrence after remission of acute mood episodes.

The duration of maintenance phase in BD is debatable. In a meta-analysis on BD I, pooled results of five RCTs showed that patients who were stable with combination therapy of mood stabilisers and AAP had lower recurrence rate at 12 months compared with those on mood stabilisers and placebo (RR=0.51, 95% CI 0.41 to 0.64 with I2 of 70.03%). There was good to moderate quality of primary papers based on risk of bias (RoB) assessment.[28, level I]

In a systematic review of five international clinical guidelines on long-term pharmacological management of BD I in adults, the recommended treatments are summarised below:[50]

Pharmacological agents	Prevention of any mood episode	Prevention of manic episode	Prevention of depressive episode
First line: Monotherapy	Lithium, valproate, lamotrigine, quetiapine, olanzapine, aripiprazole, asenapine, paliperidone, aripiprazole LAI (long-acting injectable/LAI)	Lithium, valproate, quetiapine, olanzapine, aripiprazole, asenapine, paliperidone, aripiprazole LAI	Lithium, valproate, lamotrigine, quetiapine, olanzapine, asenapine
Combination therapy	Lithium or valproate + quetiapine Lithium + aripiprazole	Lithium or valproate + quetiapine Lithium + aripiprazole	Lithium or valproate + quetiapine
Second line: Monotherapy	Carbamazepine, ziprasidone, clozapine, risperidone LAI	Carbamazepine, lamotrigine, ziprasidone, clozapine, risperidone LAI	Carbamazepine, clozapine
Combination therapy	Valproate + aripiprazole Lithium or valproate + olanzapine Lithium or valproate + ziprasidone Lithium or valproate + lurasidone Lithium or valproate + risperidone LAI Lithium + valproate	Valproate + aripiprazole Lithium or valproate + olanzapine Lithium or valproate + ziprasidone Lithium or valproate + risperidone LAI Lithium + valproate	Olanzapine fluoxetine combination Lithium or valproate + olanzapine Lithium or valproate + lurasidone Lithium or valproate + lamotrigine

The same systematic review on BD I recommended lithium or quetiapine as the best monotherapy option in the maintenance phase. For combination therapy, lithium + quetiapine or lithium + aripiprazole is the first-line treatment. It also mentioned that antidepressant monotherapy and first-generation antipsychotics (FGA) should be avoided in the maintenance phase. Clozapine may be considered in treatment-resistant BD.

A large network meta-analysis (NMA) of 41 RCTs assessed mood stabilisers or APs as monotherapy or combination therapy vs placebo in the maintenance phase of BD (mean study duration of 70.5 ± 36.6 weeks). Two categorical NMA were performed and showed the following results:[28, level I]

Studied medications	Lower risk ratio of relapse into any mood episode (from lowest to highest)	Lower risk ratio of relapse into manic/ hypomanic/ mixed episode (from lowest to highest)	Lower risk ratio of relapse into depressive episode (from lowest to highest)
First NMA (included monotherapy and combination therapy in which two drugs used were specified)	• Asenapine • Aripiprazole + valproate • Lithium + oxcarbazepine • Olanzapine • Aripiprazole LAI • Lithium + valproate • Quetiapine • Aripiprazole + lamotrigine • Aripiprazole • Lithium • Valproate • Risperidone LAI • Lamotrigine	• Asenapine • Lithium + oxcarbazepine • Aripiprazole LAI • Olanzapine, • Risperidone LAI • Lithium + valproate • Aripiprazole • Aripiprazole + lamotrigine • Lithium • Quetiapine, • Paliperidone • Valproate	• Aripiprazole + valproate • Lamotrigine + valproate • Quetiapine • Lamotrigine • Olanzapine • Lithium
Second NMA (included combination therapy of SGAs and lithium or valproate comparing with placebo and lithium or valproate)	• Quetiapine + lithium or valproate • Lurasidone + lithium or valproate • Aripiprazole + lithium or valproate • Ziprasidone + lithium or valproate	• Aripiprazole + lithium or valproate • Quetiapine + lithium or valproate	• Lurasidone + lithium or valproate • Quetiapine + lithium or valproate

- only asenapine, quetiapine, olanzapine, valproate, lithium monotherapy and combination of lurasidone or quetiapine + lithium or valproate had lower all-cause discontinuation rate
- significant AEs reported were:
  - lithium and valproate had higher risk of EPS and nausea
  - olanzapine had higher risk of somnolence
  - risperidone LAI had higher risk of hyperprolactinaemia
  - quetiapine had higher risk of dry mouth
  - lithium had higher risk of diarrhoea

Most of the RCTs assessed had low to moderate risk of bias based on Cochrane RoB.

In a meta-analysis of 11 RCTs on long-term effectiveness and safety of antidepressants in BD (treatment duration ranged up from 4.4 to 36 months), the findings were:[51, level I]

- combination of antidepressants with mood stabilisers was more effective than mood stabilisers and placebo for prophylaxis of new depressive episodes (RR=0.66, 95% CI 0.47 to 0.93; NNT=12.5), without significant increased risk of new manic/ hypomanic episodes

- compared with mood stabiliser monotherapy, antidepressant monotherapy was not superior in preventing new depressive episodes but had an increased risk of new mania/hypomania episodes (RR=2.35, 95% CI 1.42 to 3.91; NNH=4.3)

In the subgroup analysis on the prevention of depressive episodes, patients with BD II benefited significantly with antidepressants (used as combination or monotherapy) at long-term but not those with BD I. Apart from that, only second-generation antidepressants were found to be significantly effective. Three out of 11 RCTs had high risk of bias based on Cochrane RoB.

However, CANMAT states that usage of antidepressants in BD II remains controversial due to safety and effectiveness concerns.[40]

A meta-analysis on SGA LAI on BD, four RCTs found that risperidone LAI compared with oral active control (olanzapine, aripiprazole, quetiapine, ziprasidone) had:[52, level I]

- similar relapse rate for overall and manic/hypomanic episodes
- higher relapse rate of depressive episodes (RR=1.83, 95% CI 1.05 to 3.19)
- similar all-cause discontinuation rate
- comparable risk of EPS and weight gain but higher risk of hyperprolactinemia (RR=5.75, 95% CI 2.03 to 16.29)

Quality assessment based on the Jadad scores of the RCTs were 3 - 5.

CANMAT guidelines recommend that psychosocial strategies should be used to improve treatment adherence. If ineffective, LAI medications e.g. risperidone or aripiprazole LAI should be offered. They are effective in preventing relapse of any mood episode and mania.[40]

In a systematic review on BD, clozapine:[53, level I]

- was as effective as other APs (chlorpromazine, risperidone, olanzapine and quetiapine) in the improvement of Bech-Rafaelsen Mania Scale (BRMS) or YMRS scores
- when used as add-on treatment for treatment-resistant BD, was superior than the treatment as usual (lithium, valproate or APs) in all outcome measures (BPRS, CGI and BRMS) except for the HAM-D
- had common AEs of sedation, constipation and tachycardia whilst severe AEs were reduced white blood cells (5.3%) and seizures (2%)

- General principles of maintenance pharmacotherapy in BD are as follows:[50]
  - medications effective and safe in acute episodes should be continued
  - monotherapy should be preferred
  - for combination therapy, pharmacological agents with different mechanisms of action should be used and, benefits and risks should be re-evaluated every six months or earlier if indicated

Recommendation 5
- For maintenance pharmacotherapy of bipolar disorder (BD),
  - lithium and quetiapine are the preferred first-line monotherapy while lithium plus quetiapine or aripiprazole are the preferred first-line combination therapy
  - antidepressant monotherapy should be avoided
  - aripiprazole or risperidone long-acting injectables may be considered in patients who have poor adherence to oral medications especially in preventing manic episodes

4.2. Non-Pharmacological Therapy

Non-pharmacological treatment in BD includes physical therapies, psychosocial interventions and psychotherapies which are discussed further below.

4.2.1. Physical therapy

Physical therapies are increasingly common in the treatment of BD and newer strategies have been developed in recent years. In comparison to pharmacological treatment, the evidence on the effectiveness and safety of physical therapies is diverse. Despite this, the use of physical therapies would be a good complement to the management strategies and provide alternatives to treatment options.

a. Electroconvulsive therapy

In a systematic review of six international clinical guidelines on the treatment of mainly mixed states in BD among adult population, ECT was an effective option in patients with poor response to pharmacological treatment.[43]

In another systematic review of five international clinical guidelines on long-term management of BD I in adults, ECT was an effective second-line treatment option in prevention of any mood episode.[50]

In a 6-week RCT on adults with treatment-resistant bipolar depression, right unilateral electroconvulsive therapy (ECT) showed lower MADRS score (MD=6.6 points, 95% CI 2.5 to 10.6) and higher response rate (p=0.01) compared with pharmacological treatment.[54, level I] Based on the same study, there were NS differences in neurocognitive functioning between the two groups apart from worsening autobiographical memory in the ECT group.[55, level I]

Observational studies on patients treated with ECT showed:

- NS difference in number of admissions in one year between pre- and post-ECT in bipolar patients in a pre-post study on mood disorder[56, level II-3]
- increased illness-free interval and, reduced number of mood episodes and admission in non-rapid cycling BD in a 5-year pre- and post-ECT[57, level II-3]
- reduced risk for serious AEs e.g. hospitalisation due to medical events, non-suicidal death or transfer to a medical bed (HR=0.42, 95% CI 0.20 to 0.92) compared with no ECT on bipolar depression in a cohort study[58, level II-2]

RANZCP guidelines recommend the use of ECT as first-line treatment in mood disorders with severe melancholic depression, imminent risk of suicide, severe levels of distress, psychotic depression, catatonia, previous responded to ECT and patients' preference. It is also recommended as second-line in patients who fail to respond to one or more adequate course of medication. Potential AEs on cognition need to be considered before offering ECT. Adverse memory changes are short-lived and reversible; more common with bitemporal placement, higher doses, greater number of treatments and three times weekly treatment compared with twice weekly.[39]

MOH guideline on ECT recommends the use of ECT as first-line in mental disorders when rapid definitive response is required, the risk of other alternatives outweighs the risk of ECT, previous good response to ECT, and patients' preference. ECT may also be considered as second-line treatment in treatment- resistant cases, patients with severe AEs to medication and deterioration of psychiatric conditions e.g. severe or prolonged mania with persistent or life- threatening symptoms. The same guideline recommends bitemporal ECT for rapid response, bifrontal placement for those with ischaemic heart disease or cardiac arrhythmias and unilateral ECT for patients susceptible to profound confusional state.[59]

b. Repetitive transcranial magnetic stimulation

A meta-analysis on adults with bipolar depression comparing repetitive transcranial magnetic stimulation (rTMS) with sham treatment showed that the former was more effective in achieving clinical response as

measured by HAM-D or MADRS (OR=2.72, 95% CI 1.44 to 5.14). In terms of safety, there was only one case of hypomania and one case of mania. Majority of the primary papers had low RoB.[60, level I]

A systematic review on adults with BD found that:[61, level I]

- left rTMS, when compared with sham treatment, was more effective in improving working memory and processing speed but not in reducing depressive or manic symptoms while side effects were comparable between the two groups
- right rTMS, when compared with sham treatment, was more effective in reducing HAM-D scores at two weeks post-treatment but conflicting results in its effectiveness in mania
- right rTMS and left rTMS showed similar response and remission rates in depressive episodes
- bilateral rTMS was more effective than right rTMS in proportion of responders but equally effective in remission rates in depressive episodes

The RoB of the primary papers was heterogeneous.

A sham-controlled RCT on adults with BD at a clinically remitted or non-acute state found that rTMS was more effective in improving verbal learning but not in areas of processing speed, attention, working memory, visual learning, reasoning and social cognition. In fact, there was no dyscognitive effect seen across subdomains.[62, level I]

c. Deep transcranial magnetic stimulation

In the same systematic review as above, deep transcranial magnetic stimulation (TMS) was more effective than sham treatment in reducing HAM-D scores at end-point (four weeks) but not at follow-up (eight weeks). There were no AEs reported.[61, level I]

A sham-controlled RCT on adults with treatment-resistant bipolar depression found that deep TMS was more effective in improving depressive symptoms (based on HAM-D) but showed NS difference in response rate, remission rate and cognitive measures at six weeks. There were no serious AEs.[63, level I]

d. Theta burst stimulation

A systematic review on adults with BD found that theta burst stimulation (TBS) showed NS difference in response and remission rates based on MADRS score compared with sham treatment.[61, level I]

A sham-controlled RCT on adults with bipolar depression with mixed features found that TBS as an adjunct showed NS difference in effectiveness (response and remission rates based on MADRS scores) and safety.[64, level I]

e. Transcranial direct current stimulation

Transcranial direct current stimulation on adults with bipolar depression demonstrated:

- NS difference in response and remission rate compared with sham treatment in an 8-week RCT and reported AEs included increased suicidality, headaches and blurred vision[65, level I]
- It was more effective as adjunct than sham treatment in response rate (NNT=2.69, 95% CI 1.84 to 4.99) and remission (NNT=5.46, 95% CI 3.38 to 14.2) in a 6-week RCT but with higher incidences of skin redness being reported[66, level I]
- NS difference in cognitive outcomes compared with sham treatment with no dyscognitive effects reported[67, level I]

f. Bright light therapy

Adjunct bright light therapy on adults with bipolar depression showed:

- higher response rate ($p<0.01$) and improvement in HAM-D score reduction ($p<0.01$) compared with control in a 2-week RCT while reported AEs included dizziness, fatigue and sleep disturbance; no manic switch was reported[68, level I]
- higher rate of remission (OR=12.64, 95% CI 2.16 to 74.08) compared with control in a 6-week RCT with no AEs including manic switch reported[69, level I]

g. Magnetic seizure therapy

A pre-post study on adults with treatment-resistant bipolar depression showed that adjunct magnetic seizure therapy led to a reduction in HAM-D scores (Cohen's d=1.25, 95% CI 0.42 to 1.57) with a response rate of 38.5% and a remission rate of 23.1%. Serious AEs reported were hypomanic episode and hospitalisation due to fall.[70, level II-3]

h. Vagus nerve stimulation

In a 5-year cohort study involving patients with treatment-resistant bipolar depression, adjunctive vagus nerve stimulation showed significant higher cumulative percentages of response based on MADRS scores from 12 months to 60 months compared with TAU.[71, level II-2.]

There is no retrievable evidence on the comparison of physical therapies.

- The use of ECT in the maintenance phase of BD should be individualised based on a thorough risk vs benefit analysis, given the current limited robust evidence.

Recommendation 6
- Electroconvulsive therapy should be considered in both bipolar manic and depressive episodes with the following indications:
  - rapid definitive response is required
  - risk of other alternatives outweighs risk of ECT
  - previous good response to ECT
  - patient's preference
  - treatment-resistant cases
- Repetitive transcranial magnetic stimulation may be considered in the treatment of bipolar depression.

4.2.2. Psychosocial intervention

In the treatment of BD, psychosocial interventions may play a crucial role. A combination of pharmacotherapy and psychosocial intervention has been recommended in the management of BD.[39]

A meta-analysis on 11 RCTs investigated the effectiveness of psychoeducation modules compared with TAU/psychological placebo (non-specific or shared component of psychological treatment) in reducing bipolar depression in adults. There was NS difference between the intervention and comparators at post-treatment and 3 - 12 months follow-up. GRADE assessment revealed low quality of evidence.[72, level I]

In summary, established guidelines recommend psychoeducation in all phases of BD especially in the maintenance phase to patients and caregivers if appropriate.[39, 40, 73] Refer to **Appendix 6** on **Psychoeducation for Bipolar Disorder**.

In a meta-analysis of seven RCTs comparing smartphone-based interventions vs control on adults with BD, the findings were:[74, level I]
- the former (specifically phone call-based and web-based) were more effective in reducing manic (SMD= -0.19, 95% CI -0.33 to -0.04) and depressive symptoms (SMD= -0.38, 95% CI -0.61 to -0.14)
- self-monitoring using smartphone apps was effective in reducing manic symptoms (SMD=0.27, 95% CI 0.02 to 0.51) compared with baseline but NS difference for depressive symptoms

Generally, the risk of bias was low based on Cochrane RoB except for inadequate blinding of participants and personnel in two RCTs.

In another meta-analysis of five RCTs (different RCTs from the earlier meta- analysis) with more defined use of smartphone-based intervention on adults with BD, the smartphone-based interventions showed NS difference in effectiveness in reducing depressive or manic symptoms

compared with controls. Although the primary papers were of low risk of bias based on RoB2, there was considerable heterogeneity among them.[75, level I]

A 2-years cohort study examining effects of religiosity/spirituality beliefs and practices on adults with BD showed a reduction in symptoms of mania ($p<0.001$) and depression ($p=0.001$) based on YMRS and MADRS respectively. Positive religious coping predicted better QoL across physical, mental, social and environmental domains.[76, level II-2]

There is limited evidence available on psychospirituality in BD.

Supported employment is an intervention to help individuals with severe mental illness including BD to secure and maintain meaningful work. Its principles include competitive employment, rapid job search and attention to patients' preferences, among many others.[77] NICE guideline recommends that people with severe mental illness including BD who wish to find work receive supported employment services.[73] These services are available in places e.g. community mental health centres (MENTARI) or in local psychiatric services. List of available MENTARI can be accessed via https://mentari.moh.gov.my/ mentari-minds/.

4.2.3. Psychotherapy

Psychotherapy has been used as adjunctive to pharmacotherapy for BD. These include cognitive behavioural therapy (CBT), family-focused therapy (FFT), interpersonal and social rhythms therapy (IPSRT), mindfulness-based cognitive therapy (MBCT) and dialectical behaviour therapy (DBT). Different types of psychotherapies can address various aspects of the condition, helping patients cope with mood swings, manage stress and improve overall functioning.

A meta-analysis of 11 RCTs on adults with bipolar depression examined the effectiveness of psychotherapies in reducing depressive symptoms. The study found that:[72, level I]

- at post-treatment -
  - CBT was more effective in reducing depressive symptoms compared with TAU (SMD= -0.51, 95% CI -0.75 to -0.27)
  - MBCT group therapy was more effective in reducing depressive symptoms compared with TAU (SMD= -0.47, 95% CI -0.88 to -0.06) but not with waiting list
  - DBT group therapy was more effective in reducing symptoms of depression compared with waiting list (SMD= -1.18, 95% CI -2.06 to -0.30)

  - both group therapy for family therapy and IPSRT were not effective in reducing depressive symptoms compared with placebo
- at 3 - 12 months follow-up, both CBT and MBCT group therapy had NS effect on reducing symptoms of depression compared with TAU or placebo

Overall, the quality of studies was low, other than for studies examining psychoeducation vs placebo in which the quality was moderate based on GRADE.

However, in a large network meta-analysis on adjunctive psychotherapy vs TAU on adults with BD, evidence showed that CBT (individual and group) was more effective compared with TAU at 12 months follow-up in reducing depressive symptoms (SMD= -0.32, 95% CI -0.64 to -0.01). The overall quality of studies was mixed based on Cochrane RoB assessment.[78, level I]

Another meta-analysis of three RCTs on adults with BD explored the effectiveness of group CBT vs TAU/individualised therapy in reducing depressive and manic symptoms. The study revealed that group CBT was not effective in reducing depressive or manic symptoms. The overall RoB 2 of the primary studies was of some concern.[79, level I]

In a meta-analysis of five RCTs on adults with BD using IPSRT as an adjunct treatment vs control, evidence found that IPSRT was more effective in improving:[80, level I]

- depressive symptoms [Longitudinal Interval Follow-up Evaluation (LIFE)] (Hedge's g= -0.23, 95% CI -0.62 to 0.16)
- recovery rate of depression (MADRS) (Hedge's g= -0.29, 95% CI -0.55 to -0.03)
- stability of social rhythm [Social Rhythm Metrics (SRM)] (Hedge's g= -0.69, 95% CI -1.33 to -0.04)
- occupational, social and impaired functioning score (UCLA Social Attainment Scale, Social Adjustment Scale (SAS) and Longitudinal Interval Follow-Up Evaluation-Range of Impaired Functioning Tool (LIFE-RIFT) respectively] (Hedge's g= -0.34, 95% CI -0.55 to -0.14)

The overall quality of the primary papers was mixed based on RoB.

The above findings were supported by a recent RCT on adults with BD receiving IPSRT as an adjunct treatment. It showed that compared with control, IPSRT reported a significant improvement in:[81, level I]

- anxiety symptoms [Hamilton Rating Scale for Anxiety (HAM-A)]
- manic symptoms [Mania Rating Scale (MRS)]
- depressive symptoms [Inventory of Depressive Symptomatology Self- Report (IDS-SR)
- global functioning [Global Assessment of Functioning (GAF)]

- response to mood stabilisers [Retrospective Criteria of Long-term Treatment Response in Bipolar Disorder (ALDA Scale)]
- psychological functioning [Affective Morbidity Index (AMI)]

A meta-analysis on adults with BD compared MBCT vs TAU/waitlist and found NS difference in improvement of depressive and anxiety symptoms. The three related RCTs had mixed RoB.[82, level I]

The evidence on the effectiveness of Acceptance and Commitment Therapy (ACT) in managing BD is limited. A single-group clinical trial of adults with BD receiving group ACT as an adjunct treatment showed significant change in the following outcomes compared with baseline:[83, level II-3]

- decrease in anxiety symptoms [Beck Anxiety Inventory (BAI)]
- decrease in depressive symptoms [Beck Depression Inventory (BDI- II)]
- increase in QoL [The Quality of Life Inventory (QOLI)]
- increase in psychological flexibility [The Acceptance and Action Questionnaire (AAQ-2)]

In a narrative review on the management of BD based on well-established guidelines, adjunctive psychosocial interventions and psychotherapies that had been recommended in acute depression and maintenance were CBT, IPSRT, FFT ± psychoeducation.[84, level III] In the first edition of local CPG, psychosocial interventions were recommended to be incorporated into patients' care in addition to pharmacological treatment in BD.[6] The CPG DG opines that this should be maintained in the treatment of BD despite the mixed results and quality of the latest evidence.

Recommendation 7

- Psychosocial interventions and psychotherapies should be offered as an adjunctive treatment for bipolar disorder.

5. COMPLEMENTARY AND ALTERNATIVE THERAPIES

Persons with BD often self-medicate themselves with complementary and alternative medicine (CAM) despite limited evidence supporting their use.[85]

Complementary therapies mentioned in RANZCP include regular exercise being associated with improved QoL, although its benefits in BD remain less clearly defined.[39] Meanwhile, in a systematic review of nutraceuticals use in BD, there was promising, albeit conflicting evidence for omega-3 fatty acids, N-acetylcysteine and coenzyme Q10.[86]

Meanwhile, in Malaysia, among the common alternative therapies used are cannabis and kratom (ketum).[87, level III] Interactions between cannabis use (CU) and BD are complex and bidirectional whereby one may contribute to the other. The prevalence of CU is increasing globally and yet there's limited research done on the treatment options for co-morbid BD and CU.[40]

In a systematic review, a case series on patients diagnosed with BD and treated with cannabidiol (CBD) monotherapy showed no therapeutic benefits in improving manic symptoms compared with the combination of olanzapine and CBD.[88, level III]

Moreover, the CANMAT Task Force Report 2022 showed that CU in BD was associated with a worsened illness course, decreased functionality and increased mortality through suicide.[89]

- There is insufficient evidence for the use of cannabis and kratom in the treatment of BD.

6. FOLLOW-UP/MONITORING AND REFERRAL

When managing BD, exploring several key aspects to provide effective care during follow-up is crucial. Monitoring symptoms over time is essential to assess the response to treatment and the current state, whether in stable, remission or relapse. Besides that, it is important to review the compliance with medication and presence of AEs.

6.1. Parameters to be Monitored during Maintenance Phase

Parameters recommended to be monitored during the maintenance phase of BD at regular intervals are:[6]

- weight
- height
- waist circumference
- blood pressure
- electrocardiogram (ECG)
- full blood count
- fasting blood sugar
- renal function
- liver function
- lipid profile
- thyroid function
- serum calcium level
- drug serum level

- Lithium has a narrow therapeutic index and a risk of toxicity. In the first edition of the MoH CPG on BD, lithium monitoring has been recommended to be carried out at least every six months.6 Monitoring should also be done earlier in dose adjustment or suspected toxicity.

Recommendation 8

- Serum lithium level should be monitored one week upon initiation or dose change, and every six months or earlier if indicated.

Refer to **Appendix 7** on **Parameters for Monitoring during Treatment of Bipolar Disorder**

6.2. Referral Criteria

There is no direct evidence on referral criteria for BD. Existing guidelines state that BD can be managed in primary care except in the following conditions where the cases need to be referred to psychiatric services:[6, 73]

- unsure of diagnosis
- complex presentation of mood episodes
- acute exacerbation of symptoms
- 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 AEs 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 and adolescents
  - co-morbidity with alcohol or substance misuse

People with BD whose symptoms have responded effectively to treatment and remain stable may have the option to return to primary care for further management. Care plans for this group of people include the following:[73]

- latest mental state assessment and diagnosis
- detailed medication plan for review and monitoring by primary care providers
- concise and individualised recovery plan
- crisis alert plan on early warning symptoms, triggers of relapse and referral pathways

7. RELAPSE PREVENTION AND ADHERENCE

7.1. Prevention of Relapse

In BD, relapse is defined as a new mood episode occurring within 8 weeks after having achieved remission from the index episode.[90] Adjunctive psychosocial interventions and psychotherapies e.g. psychoeducation, cognitive behavioural therapy (CBT) and family therapy are useful to prevent relapse. These interventions vary in method of delivery (e.g. individual vs group format), its contents and duration of intervention.

A meta-analysis on adults with BD demonstrated that psychoeducation:[91, level I]

- was more effective than TAU in not relapsing (preventing relapse) into any episode (OR=1.98, 95% CI 1.09 to 3.58; NNT=7, 95% CI 4 to 25)
- subgroup analysis showed that group delivery was effective in not relapsing (preventing relapse) into:
  - any episode (OR=2.80, 95% CI 1.63 to 4.82; NNT=4, 95% CI 3 to 7)
  - manic episode (OR=2.07, 95% CI 1.11 to 3.85; NNT=6, 95% CI 3 to 39)
  - depressive episode (OR=2.08, 95% CI 1.05 to 4.12; NNT=6, 95% CI 3 to 77)
- subgroup analysis also showed that individual delivery was not effective in not relapsing (preventing relapse) into any mood, manic and depressive episodes

The quality of most of the primary papers was moderate based on RoB.

The above was supported by another meta-analysis of patients with BD on pharmacotherapy where the following adjuvant group interventions were more effective than TAU in the prevention of relapse:[92, level I]

- psychoeducation (RR=0.65, 95% CI 0.55 to 0.77)
- CBT (RR=0.68, 95% CI 0.50 to 0.94)

Quality assessment of primary papers however was not mentioned.

Another meta-analysis, however, on relapse prevention in a similar study population showed effectiveness in group psychoeducation (OR=0.43, 95% CI 0.28 to 0.62) but not in group CBT (OR = 0.72, 95% CI 0.19 to 2.66) when compared with control. The authors concluded that studies included in group CBT were of small size and hence might not achieve adequate statistical power to detect the differences between the groups.[79, level I] Most of the primary papers used in this meta-analysis had some concern of bias based on Cochrane RoB2.

In a large NMA on adults with BD on adjunctive psychosocial interventions, two high-quality RCTs showed carer-focused interventions e.g.

psychoeducation was more effective than TAU in relapse prevention (RR=0.61, 95% CI 0.44 to 0.86).[93, level I]

In another large NMA on patients with BD, the following adjunctive psychotherapies were more effective than TAU for relapse prevention:[78, level I]

- standard psychoeducation ≥6 group or individual sessions (OR=0.52, 95% CI 0.32 to 0.84)
- brief psychoeducation ≤3 group or individual sessions (OR=0.34, 95% CI 0.16 to 0.74)
- family or conjoint therapy (OR=0.30, 95% CI 0.17 to 0.53)
- CBT (OR=0.52, 95% CI 0.34 to 0.79)

Most of the primary papers were rated to have low to moderate risk of bias.

Meanwhile, in a small RCT on adults with BD, adjunctive mindfulness-based cognitive therapy was not effective compared with TAU in preventing the recurrence of depressive or hypo/manic episodes over a 12-month follow-up period.[94, level I]

7.2. Strategies to Improve Adherence

Adherence to treatment within patients with BD may change over time and vary between different pharmacotherapies. About half of patients with BD become non-adherent during long-term treatment.[95, level I] Non-adherence in BD is a complex phenomenon determined by a multitude of factors.

Significant risk factors for non-adherence are:[6]

- difficulties with medication routines
- negative attitudes towards drugs in general
- depressive polarity of the last acute episode
- presence of subsyndromal symptoms
- co-morbid obsessive-compulsive disorder
- current acute episode
- substance abuse/dependence
- younger age
- AEs

Enhancing adherence involves employing various approaches, which are psychological interventions, personalised adherence enhancement, technology- assisted strategies and community-based care which are discussed below.

7.2.1. Psychological interventions

The most frequently studied intervention for enhancing adherence is psychoeducation.

In a large NMA assessing non-adherence in patients with BD on pharmacotherapy, a lower risk of non-adherence was found among those who received psychoeducation alone (RR=0.27, 95% CI 0.14 to 0.53) or a combination of psychoeducation and CBT (RR=0.14, 95% CI 0.02 to 0.85) compared with TAU. The author concluded that many adjunctive psychosocial interventions lacked high-quality evidence to support their effectiveness which includes adherence.[93, level I]

A meta-analysis of 18 RCTs among adults with BD on pharmacotherapy, psychological interventions (e.g. family-focused therapy, CBT, cognitive psychoeducation therapy (CPT), psychoeducation] were more effective than control in improving medication adherence (OR=2.27, 95% CI 1.45 to 3.56).[23, level I] There was a mixture of quality of primary papers based on RoB.

In an RCT of adults with BD on mood stabilisers, multifaceted interventions that include motivational interviewing and psychoeducation were more effective than control in improving adherence at 1- and 6-month post-intervention as indicated by a higher Medication Adherence Rating Scale (MARS) score and plasma level of mood stabilisers.[96, level I]

7.2.2. Customised adherence enhancement

Customised adherence enhancement (CAE) is a module that combines the following strategies:[97, level II-3]

- psychoeducation which includes information on BD and its neurobiological facets, medication management and creation of an individualised symptom profile to detect early signs of relapse
- modified motivational enhancement therapy where the overall goal is to enhance personal motivation to increase the likelihood of medication adherence
- communication with providers where individuals are supported with discussions on the crucial aspects of treatment planning including expectations for medication response and concerns about medication AEs
- medication routines that aim to help individuals adjust their treatment plans as needed and engage in discussions with healthcare providers.

In an RCT among poorly adherent individuals with BD, CAE had significantly improved adherence at six months based on a reduction in

Tablet Routine Questionnaire (TRQ) mean score when compared with BD-specific educational program. No AEs reported.[98, level I]

7.2.3. Technology-assisted strategies

The technology-assisted strategies that are explored in adherence-related intervention studies include medication event monitoring system (MEMS), short messaging service (SMS) and android smartphone-based self-monitoring system (MONARCA System) which are described below.

In an RCT on medication adherence among poorly adherent individuals with BD, MEMS bottle caps detected worse adherence compared with self-report TRQ (66.43% vs 46.61%) with a correlation between them of 0.47 ($p<0.01$). The findings showed that both self-report and automated medication monitoring were reasonable methods of evaluating adherence, although the latter was likely to provide a more sensitive assessment on the missed drug.[99, level I]

In another RCT on treatment adherence in adults with BD I, those who received a twice-weekly mobile phone-based SMS reminder intervention for three months showed better adherence and attitude towards the medication, based on the Morisky Medication Adherence Scale and Drug Attitudes Inventory respectively, compared with TAU.[100, level I]

In two RCTs comparing MONARCA system vs control, the findings were:

- NS difference in medication adherence based on plasma concentration of medications on adults with BD I at six months. However, patients in the intervention group had significantly more depressive symptoms.[101, level I]
- NS difference in medication adherence measured by MARS on BD patients at nine months. However, the intervention group had higher depressive episodes (HR=2.89, 95% CI 1.02 to 8.23).[102, level I]

7.2.4. Community-based care

There was limited evidence on adherence interventions for BD patients conducted in the community setting.

A pre-post study of a Life Goal Program (a structured group psychotherapy programme) delivered at three community mental health centres demonstrated a significant increase in knowledge about BD among the participants with a large effect size (Cohen's d= 0.85) compared with baseline. However, there is NS difference in medication adherence as measured by MARS.[103, level II-3]

A cohort study that included patients with BD I with psychotic features revealed that ACCESS model (assertive community treatment) reported full adherence measured using an expert consensus panel criteria in the majority of BD patients (91.3%) at 24 months.[104, level II-2]

Recommendation 9
- Psychosocial interventions (e.g. psychoeducation) and psychotherapies (e.g. cognitive behavioural therapy) should be part of strategies in relapse prevention of bipolar disorder.

7.3. Collaborative Care Models

Collaborative care is an intervention that aims to facilitate communication and joint working relationships between health professionals (e.g. family physicians, psychiatrists, psychologists, pharmacists, nurses, etc.) in delivering integrated and comprehensive care to patients in various healthcare settings. It can be done in several ways and incorporates at least three of the following components i.e. patient self-management support, delivery system redesign, use of clinical information systems, provider decision support, health care organisation support and linkage to community resources.[105, level III] Refer to **Appendix 8** for **Collaborative Care Model Core Elements**.

In a systematic review of six RCTs comparing the effectiveness of collaborative care with TAU on adults with BD, the findings were:[106, level I]
- NS difference in 2-year relapse rate of manic/hypomanic and depressive episodes
- mixed effects on depression, mania and functionality

The RCTs assessed by the Cochrane RoB tool were of mixed quality.

A recent RCT compared collaborative care model vs TAU using telepsychiatry services in primary care over a 12-months period on adult patients. Adults with BD showed improvement in the following outcomes with NS differences between groups:[107, level I]
- mental health QoL (measured with Veterans RAND 12-Item Health Survey Mental Health Component Summary)
- depression (measured with Hopkins Symptom Checklist Depression Scale)
- anxiety (measured with GAD-7)

8. SPECIAL POPULATION

8.1. Pregnancy and Lactation

There is a high risk of relapse of BD during pregnancy or the post-partum period especially in patients not on treatment. There is, however, the issue of specific considerations to be given on the use of medications during these periods based on the new Pregnancy and Lactation Labelling Final Rule of the US Food and Drug Administration (FDA) as shown in **Appendix 9**. If medications are deemed necessary, preference should be given to monotherapy using the lowest effective dose.[40]

Given the complexity of BD management in this group of women, it is advisable to co-manage them with the obstetrics team. Risks-benefits analysis of medications on both women and the developing foetus and infant should be done with the patients using a shared decision-making approach.

The Guidelines on Pre-Pregnancy Care in MOH Specialist Hospital suggest that all women of reproductive age with BD should be referred to a pre-pregnancy care team to optimise their mental health condition before conception, pregnancy and lactation.[108]

In a large meta-analysis of six cohort studies, the use of lithium in pregnancy showed NS difference in risk of:[109, level II-2]

- diabetes in pregnancy
- pre-eclampsia
- small for gestational age
- major malformations including cardiac malformations
- foetal distress
- caesarean section
- preterm birth
- low birth weight
- post-partum hemorrhage

However, there was a small risk of neonatal admission to a special care baby unit prior to 28 days of age (OR=1.28, 95% CI 1.12 to 2.33). There was no mention on quality assessment of the primary papers.

- The use of lithium in pregnancy should be cautioned given small studies, heterogeneity of results and no report on quality assessment of primary papers in the meta-analysis mentioned above.
- However, lithium may be used on a case-to-case basis after careful consideration of risk and benefits e.g. women with high risk of relapse without lithium.

A systematic review of observational studies on the use of mood stabilisers in pregnancy showed the following outcomes:[110, level II-2]

- Lamotrigine had a favourable reproductive risk profile and was a preferred option for women of childbearing age, although an increased risk of cleft lip and palate, heart malformations and hypospadias were reported (more frequent with doses over 300 mg/day).
- Valproate and carbamazepine were classified by FDA as drugs contraindicated during pregnancy with the following adverse outcomes.
    - Valproate was considered the most teratogenic drug since it had a 1 - 5% rate of foetal abnormalities, particularly neural tube defects and especially with doses over 1,000 mg/day. Additionally, children exposed to valproate prenatally showed higher rates of low Intelligence Quotient (IQ), neurodevelopmental deficits, reduced verbal abilities, attention deficit hyperkinetic disorder and autism spectrum disorder.
    - Carbamazepine use was associated with teratogenicity e.g. neural tube defects, craniofacial abnormalities, etc.

Since 2020, the National Pharmaceutical Regulatory Agency (NPRA) has endorsed the use of the Annual Risk Acknowledgment form for valproate in women with BD in child-bearing ages (refer to **Appendix 10a** and **10b**).

There is insufficient evidence on the safety profile of APs use in BD with pregnancy. However, RANZCP guidelines state that AAPs e.g. quetiapine or olanzapine can be used in the treatment of BD with pregnancy as they are generally considered to be safe aside from a risk of gestational diabetes and having a large baby.[39]

In a systematic review of case series/reports, ECT use in first trimester of pregnancy showed no safety concerns for the mother or foetus including teratogenicity.[111, level III]

In another systematic review of mainly case series/reports on mood stabilisers and APs use in lactation, the findings were:[112, level II-2]

- carbamazepine, valproate, quetiapine, olanzapine and risperidone were relatively safe either due to their limited passage into breast milk or low infant plasma concentrations
- lamotrigine had high variability in infants' plasma concentration but no serious AEs and thus can be considered for individual cases
- lithium was a possible treatment option although there was high variability of transfer into breast milk
- other AAPs e.g. aripiprazole, paliperidone, lurasidone, ziprasidone and asenapine were not recommended due to the scarcity of data

Recommendation 10
- Shared decision-making in weighing the risks versus benefits of pharmacological treatment should be done in pregnant and lactating women with bipolar disorder.
  - Atypical antipsychotics e.g. olanzapine and quetiapine may be used in pregnancy.
  - Valproate and carbamazepine should be avoided in pregnancy given their teratogenic risks. Other mood stabilisers should be used with caution.

8.2. Elderly

Older adults make up 25% of all bipolar patients and this number is expected to increase along with the world's ever-aging population.[97] Older age bipolar disorder (OABD) includes both elderly patients whose bipolar disorder has commenced earlier in life and those who present for the first time in later life. There is sparse data on OABD, thus current guidelines recommend that first- line treatment of OABD should be similar to that for the general population with BD, whilst specifically paying attention to side effects, co-morbidities and specific risks in elderly patients.[113] In particular, careful consideration must be given to the pharmacokinetic and pharmacodynamic changes that occur in elderly patients.

A double-blind RCT comparing lithium and valproate in older patients with BD reported that:[114, level I]
- lithium was more effective than valproate based on YMRS scores at week nine (Cohen's d=0.54, 95% CI 0.17 to 0.91)
- both lithium and valproate were equally tolerated with slightly more tremor with lithium

On the other hand, a cohort study on lithium vs AAPs which included aripiprazole, quetiapine, risperidone, olanzapine and lurasidone for BD in older war veterans showed:[115, level II-2]
- all-cause discontinuation rate (lack of effectiveness, loss to follow-up and AEs) was significantly higher in lithium compared with AAPs
- NS difference in discontinuation rate due to AEs
- tremor, renal failure, toxicity and bloating/swelling were more often reported with lithium whilst extrapyramidal symptoms (EPS), sedation, restlessness and hallucinations were more with AAPs

In an RCT comparing lurasidone and placebo in older adults with bipolar I depression, the findings were:[116, level I]

- in monotherapy -
  - those on placebo who switched to lurasidone had better improvement in depressive symptoms (reduction in MADRS score)
  - no increase in mean weight or glycaemic indices and low rates of switching to hypomania or mania
- in adjunct with lithium or valproate -
  - NS difference in reduction of MADRS score
  - higher rate of akathisia and tremor were noted
- common AEs for both monotherapy and adjunctive lurasidone therapy include headache, nasopharyngitis and insomnia

8.3. Children and Adolescents

Paediatric bipolar disorder (PBD) is a diagnostic challenge as children have yet to achieve emotional, neurocognitive and physical maturity. A meta-analysis of 19 studies showed that the prevalence rate of bipolar spectrum disorders among young people below 21 years of age was 3.9% (95% CI 2.6% to 5.8%).[117, level III] Early diagnosis of BD is crucial but over-diagnosis comes with its risks of medical-related AEs and stigmatisation.

Signs and symptoms of BD may overlap with symptoms of other psychiatric disorders that may occur in young people e.g.:[40]

- ADHD
- conduct disorder
- disruptive mood dysregulation disorder
- oppositional defiant disorder
- schizophrenia
- substance use disorder
- unipolar depression

- Proper clinical assessment by a psychiatrist is important to rule out co- morbidities in children and adolescents presenting with symptoms of BD.

Family history of BD, especially if the parents developed BD early in life and the young person has a history of prominent mood lability, depression/anxiety and subsyndromal manic/hypomanic symptoms suggest a risk of developing BD.[118, level III]

The role of pharmacotherapy in paediatric mental health remains the object of debate and controversy. Careful consideration of treatment options should be given after weighing the benefits and risks.

In a meta-analysis of RCTs on the use of lithium vs active comparators/ placebo for acute mania in children with BD, it was shown that:[119, level I]

- lithium was less effective than risperidone in treating manic/mixed episodes among young people aged 6 - 15 years (SMD= 0.85, 95% CI 0.54 to 1.15) but had NS difference vs valproate or placebo
- majority of the AEs were described as mild to moderate
- high rates of psychiatric co-morbidity across all studies with the highest being ADHD

There was a potential high or unclear risk of bias in the included primary papers based on RoB.

An RCT of lithium vs quetiapine for the treatment of acute mania in young people of 10 -17 years of age with BD reported that quetiapine:[120, level I]

- showed a greater reduction in YMRS score (-11.0 vs -13.2, $p<0.001$)
- had a higher response rate (72% vs 49%, $p=0.012$)
- showed NS difference in remission rates
- had more somnolence ($p<0.001$), dizziness ($p<0.05$) and weight gain ($p=0.02$)

In an RCT in the treatment of adolescents with BD in manic or mixed episodes, compared with placebo, olanzapine:[121, level I]

- showed a greater reduction in YMRS score ($p<0.001$)
- had higher response (RR=2.19, 95% CI 1.28 to 3.74; NNT=3.80) and remission (RR=3.17, 95% CI 1.43 to 7.04; NNT=4.14) rates
- had shorter times-to-reach response ($p=0.003$) and remission ($p=0.002$) criteria
- had significantly higher common AEs with a frequency ≥5% for increased appetite, weight gain and somnolence and sedation

In a 3-week RCT on acute treatment of manic or mixed episodes in 10 - 17-year- old patients with BD I, asenapine of three different doses was significantly more effective than placebo (MDs for YMRS were -3.2, -5.3 and -6.2 for asenapine 2.5 mg, 5 mg and 10 mg bd respectively). The treatment-emergent AEs (≥5%) were somnolence, sedation, oral hypoaesthesia/paraesthesia and increased appetite.[122, level I] An open-label extension study of the same RCT demonstrated that most AEs were mild or moderate in severity at 50 weeks. The additional reported AEs (≥5%) were increased weight, headache, nausea, vomiting, fatigue and upper abdominal pain.[123, level I]

In a 30-week RCT on manic/mixed episode of 10-17-year-old patients with BD I, compared with placebo, aripiprazole:[124, level I]

- was significantly more effective (mean change from baseline for YMRS was 14.1 and 14.9 for aripiprazole with daily doses of 10 mg and 30 mg respectively); the findings were consistent in a subgroup analysis of 10

  - 12-year-old and 13 - 17-year-old study subjects with or without prior bipolar treatment
- showed greater response rates with both doses ($p<0.01$)

The commonly reported AEs were somnolence, headache and EPS.

In a recent RCT on 10 - 17-year-old patients with BD I in manic/mixed episodes, ziprasidone was more effective than placebo (MD in YMRS total score= -4.23, 95% CI -7.14 to -1.32). The common AEs were somnolence, fatigue and nausea.[125, level I]

A double-blinded RCT on 10 - 17-year-old with BD I with manic/mixed episodes showed NS difference in effectiveness and safety between valproate ER monotherapy and placebo.[126, level I]

A meta-analysis of three RCTs on quetiapine monotherapy vs placebo in children and adolescents with bipolar depression showed NS difference in the following outcomes:[127, level I]

- Children's depression rating scale revised (CDRS-R), CGI-BP-S scores, response and remission rates
- discontinuation rate due to AEs

Based on the GRADE assessment, all outcome qualities were moderate to high.

In an NMA of four RCTs on 10 - 18-year-old young persons with bipolar depression, the effectiveness and safety of AAPs (lurasidone, OFC and quetiapine) were compared with placebo. The findings were:[128, level I]

- improvement in CDRS-R with lurasidone (MD = -5.70, 95% CI -8.66 to -2.76) and OFC (MD= - 5.0, 95% CI -8.63 to -1.38) but not with quetiapine
- improvement in CGI-BP-S depression scores with lurasidone (MD= -0.40, 95% CI -0.68 to -0.12) but not with OFC
- improvement in CGI-BP-S overall scores with lurasidone (MD= -0.40, 95% CI -0.68 to -0.12) but not with OFC and quetiapine
- improvement in response rate with lurasidone (OR=2.64, 95% CI 1.67 to 4.01; NNT=5) and OFC (OR=2.64, 95% CI 1.43 to 4.50; NNT=6) but not with quetiapine
- improvement in remission rate with OFC (OR=1.93, 95% CI 1.10 to 3.17; NNT=7) but not with lurasidone and quetiapine
- discontinuation due to AEs, quetiapine had fewer discontinuation vs placebo (OR=0.32, 95% CI 0.07 to 0.83) whereas OFC had more discontinuation vs placebo (OR=3.31, 95% CI 1.08 to 8.75) and quetiapine (OR=15.08, 95% CI 2.32 to 56.84)

Based on SUCRA rankings, lurasidone had the highest rank followed by OFC and quetiapine in terms of effectiveness. For safety, quetiapine was ranked first followed by lurasidone, placebo and OFC. GRADE assessment gave mixed quality on the various outcomes.

Recommendation 11
- For children and adolescents with bipolar disorder:
  - atypical antipsychotics* monotherapy may be used in manic or mixed episodes
  - lurasidone and olanzapine/fluoxetine combination may be used in depressive episodes

*aripiprazole, asenapine, lurasidone, olanzapine, quetiapine, risperidone and ziprasidone

Refer to **Appendix 11** for **Suggested Paediatric Medications Dosing**.

8.4. People with Substance Use Disorder

Substance use disorder (SUD) is a common co-morbidity of BD. Substance use may cause, mimic, underlie or complicate mental health disorders. Empirical evidence to guide optimal management of BD and co-morbid SUD is scarce, partly because such patients are difficult to engage in clinical trials.

NICE guidelines have recommended that the use of alcohol, tobacco, prescription and non-prescription medication, and illicit drugs should be discussed with people with BD to address the negative effects of these substances.[73]

In a guidelines on the pharmacological and psychological management of adult patients with BD and co-morbid SUD, the following are recommended:[129]
- adjuvant valproate or naltrexone may improve symptoms of alcohol use disorder
- lamotrigine add-on therapy may reduce cocaine use
- varenicline may improve nicotine abstinence
- integrated group therapy may reduce substance use and BD symptoms

The strength of recommendations was weak to moderate based on GRADE.

An RCT on adjunctive psychosocial intervention for BD patients with co-morbid substance use found that Integrated Treatment Adherence Program (which combined elements of CBT and Acceptance and Commitment Therapy) significantly improved depression, mania, functioning and values-consistent living compared with those on Enhanced Assessment and Monitoring (enhanced TAU). There was also a trend for increased treatment adherence.[130, level I]

8.5. People with Borderline Personality Disorder

Borderline personality disorder (BPD) is a co-morbid of BD, each amplifying the symptoms of the other hence delaying time to remission.

NICE and CANMAT guidelines state that drug treatment should not be used specifically for symptoms or behaviour of BPD. However, AAPs and mood stabilisers are valuable in treating BPD with co-morbid BD.[40, 73] Meanwhile, the RANZCP guidelines recommend psychotherapy as the fundamental management of BPD and is of considerable importance in the management of BD.[39]

9. SUICIDE PREVENTION

Annually, WHO estimates that 703,000 people die by suicide.[131] In low- and middle-income countries, 58% of those who died by suicide and 45% of those who engaged in non-fatal suicidal behaviour had a psychiatric disorder.[132] Among those living with mental illnesses, people with BD have been associated with the highest risk of suicide.[133] In children and adolescents (<18 years of age) with BD, the prevalence of suicidal ideation was 50 - 60% and suicide attempt was 20 - 25%.[134, level II-2]

A large number of people are bereaved by suicide deaths and often require psychosocial support.[135]

While there is extensive evidence on risk formulation and management of suicidal behaviour, paucity of high-quality studies focused on individuals with BD limits the synthesis of recommendations.

9.1. Risk and Protective Factors

The risk factors for suicide in BD in adults are:[6]

- 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)

A systematic review of 14 observational studies on children and adolescents (<18 years of age) with BD showed that the risk factors for suicide attempt were:[134, level II-2]

- early illness onset
- severe illness characteristics e.g. psychosis, hospitalisation, hopelessness etc
- mixed episode
- co-morbid disorders e.g. ADHD, substance use disorder, panic disorder, oppositional defiant disorder
- past self-injurious behaviour
- past suicide ideation/suicide attempt
- past physical/sexual abuse
- parental depression
- family history of suicidality
- poor family functioning

Evidence for protective factors in suicidal behaviour in BD is limited. A small cross-sectional study on euthymic adult outpatients with BD found that personal religious activities (e.g. meditation, prayers and religious studies) and religious integration in daily living exerted a protective effect against suicide attempts.[136, level III]

9.2. Effective and Safe Intervention

Suicidal behaviour in BD has to be managed in a person-centered collaborative approach requiring both clinical and community-based strategies.[132, level III]

Specific attention is drawn to the role of lithium in preventing suicidal behaviour in BD. A systematic review of adults with BD showed:[30, level I]

- combination of olanzapine and lithium significantly reduced suicidal item score of HAM-D vs lithium alone
- lithium and valproate were equally effective in reducing suicide ideation among suicidal attempters
- no definitive evidence on anti-suicidal effect of lithium

A meta-analysis of RCTs on adults with mood disorders showed NS difference between lithium and placebo in suicide and non-fatal suicidal behaviour between the groups.[137, level I] The primary papers were of moderate quality based on RoB.

In a cohort study on patients >10 years of age with BD, ECT reduced suicide risk in depressive state (HR=0.805, 95% CI 0.514 to 0.987) but not in mania or mixed states compared with psychopharmacotherapy.[138, level II-2]

In a systematic review, a small RCT on the effectiveness of IV ketamine vs placebo in bipolar depression found that suicidal ideation scores in MADRS reduced within 40 minutes in subjects of the ketamine arm (Cohen's d=0.98, 95% CI 0.64 to 1.33) and remained significant to Day [3.139, level I]

Evidence on psychological interventions for suicidal behaviour in BD population is limited. Safety Planning is a personalised and prioritised list of coping strategies and resources to reduce suicide risk and improve help-seeking.

Components of Safety Planning include:[140, level III]

- recognising warning signs of impending suicidal crisis
- identifying and employing internal coping strategies without needing to contact another person
- utilising contacts with people as a means of distraction from suicidal thoughts and urges
- contacting family members or friends who may help to resolve a crisis and with whom suicidality can be discussed
- contacting mental health professionals or agencies
- reducing the potential use of lethal means

A meta-analysis of trials on safety planning interventions (cognitive therapy and CBT for suicide prevention) vs control (TAU or other treatment modalities) among adults with suicidal behaviour (including those with affective disorders) showed mixed results where two RCTs found significant reduction in suicidal behaviour while another two did not. The overall bias of primary papers was considered high based on RoB2.[141, level I]

10. IMPLEMENTING THE GUIDELINES

10.1. Facilitating and Limiting Factors

Existing facilitators for the application of the recommendations in the CPG include:

- wide dissemination of the CPG to healthcare providers
- training and updates on the management of BD in relevant scientific and professional meetings, seminars, conferences, etc.
- public awareness programmes on the importance of BD e.g. World Bipolar Day, World Mental Health Day, Suicide Prevention Day, etc
- peer support and psychosocial support services by non-governmental organisations and patient advocates

Existing barriers for application of the recommendations of the CPG are:

- limited awareness and knowledge among healthcare providers on BD and its management
- lack of awareness of symptoms of BD among families/carers and community
- variation in treatment practice and preferences due to limited accessibility to resources e.g. medications
- no national clinical registry for BD for planning services

10.2 Potential Resource Implications

BD is a complex mental disorder that is challenging to diagnose and treat. Those with BD need to be referred to psychiatric services for accurate diagnosis and further management. The pharmacological treatment that had been recommended by the CPG is not readily available in some healthcare facilities. The financial burden of psychotropic treatments restricts treatment options and distribution, while a scarcity of clinical psychologists limits access to essential psychosocial interventions. The available psychoeducational materials for patients fall short in effectively fostering early help-seeking tendencies and offering comprehensive management strategies.

In line with the key recommendations in this CPG, the following are proposed as clinical audit indicators for quality management of BD:

$$\text{Percentage of patients with bipolar disorder not on antidepressant monotherapy (Target of ≥80\%)} = \frac{\text{Number of patients with bipolar disorder not on antidepressant monotherapy in a period}}{\text{Number of patients with bipolar disorder in the same period}} \times 100\%$$

$$\text{Percentage of patients with bipolar disorder on lithium monitoring every six months (Target of ≥80\%)} = \frac{\text{Number of patients with bipolar disorder on lithium monitoring every six months within a period}}{\text{Total number of patients with bipolar disorder on lithium within the same period}} \times 100\%$$

Implementation strategies will be developed following the approval of the CPG by MoH which include a Quick Reference and a Training Module.

REFERENCES

1. World Health Organisation. Mental Disorders: Key Facts. Geneva: World Health Organization 2022 (Available at: https://www.who.int/news-room/fact-sheets/detail/bipolar-disorder).
2. GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatry. 2022;9(2):137-150.
3. Zhong Y, Chen Y, Su X, et al. Global, regional and national burdens of bipolar disorders in adolescents and young adults: a trend analysis from 1990 to 2019. Gen Psychiatr. 2024;37(1):e101255.
4. Polga N, Macul Ferreira de Barros P, Farhat LC, et al. Parental age and the risk of bipolar disorder in the offspring: A systematic review and meta-analysis. Acta Psychiatr Scand. 2022;145(6):568-77.
5. Chen MH, Chen YS, Hsu JW, et al. Comorbidity of ADHD and subsequent bipolar disorder among adolescents and young adults with major depression: a nationwide longitudinal study. Bipolar Disord. 2015;17(3):315-22.
6. Ministry of Health Malaysia. Management of Bipolar Disorder in Adults. Putrajaya: MoH; 2014.
7. Nowrouzi B, McIntyre RS, MacQueen G, et al. Admixture analysis of age at onset in first episode bipolar disorder. J Affect Disord. 2016;201:88-94.
8. Estrada-Prat X, Van Meter AR, Camprodon-Rosanas E, et al. Childhood factors associated with increased risk for mood episode recurrences in bipolar disorder-A systematic review. Bipolar Disord. 2019;21(6):483-502.
9. Daveney J, Panagioti M, Waheed W, et al. Unrecognized bipolar disorder in patients with depression managed in primary care: A systematic review and meta-analysis. Gen Hosp Psychiatry. 2019;58:71-6.
10. Dome P, Rihmer Z, Gonda X. Suicide Risk in Bipolar Disorder: A Brief Review. Medicina (Kaunas). 2019;55(8).
11. Fritz K, Russell AMT, Allwang C, et al. Is a delay in the diagnosis of bipolar disorder inevitable? Bipolar Disord. 2017;19(5):396-400.
12. Viktorin A, Lichtenstein P, Thase ME, et al. The risk of switch to mania in patients with bipolar disorder during treatment with an antidepressant alone and in combination with a mood stabilizer. Am J Psychiatry. 2014;171(10):1067-73.
13. Hirschfeld RM, Williams JB, Spitzer RL, et al. Development and validation of a screening instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire. Am J Psychiatry. 2000;157(11):1873-5.
14. Angst J, Adolfsson R, Benazzi F, et al. The HCL-32: towards a self-assessment tool for hypomanic symptoms in outpatients. J Affect Disord. 2005;88(2):217-33.
15. Nassir Ghaemi S, Miller CJ, Berv DA, et al. Sensitivity and specificity of a new bipolar spectrum diagnostic scale. J Affect Disord. 2005;84(2-3):273-7.
16. McIntyre RS, Patel MD, Masand PS, et al. The Rapid Mood Screener (RMS): a novel and pragmatic screener for bipolar I disorder. Curr Med Res Opin. 2021;37(1):135- 44.
17. Thase ME, Stahl SM, McIntyre RS, et al. Screening for Bipolar I Disorder and the Rapid Mood Screener: Results of a Nationwide Health Care Provider Survey. Prim Care Companion CNS Disord. 2023;25(2).
18. Aiken CB, Weisler RH, Sachs GS. The Bipolarity Index: a clinician-rated measure of diagnostic confidence. J Affect Disord. 2015;177:59-64.
19. Bechdolf A, Nelson B, Cotton SM, et al. A preliminary evaluation of the validity of at-risk criteria for bipolar disorders in help-seeking adolescents and young adults. J Affect Disord. 2010;127(1-3):316-20.

20. Ratheesh A, Hammond D, Watson M, et al. Bipolar At-Risk Criteria and Risk of Bipolar Disorder Over 10 or More Years. JAMA Netw Open. 2023;6(9):e2334078.
21. McIntyre RS, Berk M, Brietzke E, et al. Bipolar disorders. Lancet. 2020;396(10265):1841-56.
22. Asherson P, Young AH, Eich-Höchli D, et al. Differential diagnosis, comorbidity, and treatment of attention-deficit/hyperactivity disorder in relation to bipolar disorder or borderline personality disorder in adults. Curr Med Res Opin. 2014;30(8):1657- 72.
23. McDonald CE, Rossell SL, Phillipou A. The comorbidity of eating disorders in bipolar disorder and associated clinical correlates characterised by emotion dysregulation and impulsivity: A systematic review. J Affect Disord. 2019;259:228-43.
24. Carbone EA, de Filippis R, Caroleo M, et al. Antisocial Personality Disorder in Bipolar Disorder: A Systematic Review. Medicina (Kaunas). 2021;57(2).
25. Hossain S, Mainali P, Bhimanadham NN, et al. Medical and Psychiatric Comorbidities in Bipolar Disorder: Insights from National Inpatient Population-based Study. Cureus. 2019;11(9):e5636.
26. Yalin N, Conti I, Bagchi S, et al. Clinical characteristics and impacts of HIV infection in people with bipolar disorders. J Affect Disord. 2021;294:794-801.
27. Yildiz A, Nikodem M, Vieta E, et al. A network meta-analysis on comparative efficacy and all-cause discontinuation of antimanic treatments in acute bipolar mania. Psychol Med. 2015;45(2):299-317.
28. Kishi T, Ikuta T, Matsuda Y, et al. Mood stabilizers and/or antipsychotics for bipolar disorder in the maintenance phase: a systematic review and network meta-analysis of randomized controlled trials. Mol Psychiatry. 2021;26(8):4146-57.
29. Keramatian K, Chakrabarty T, Saraf G, et al. New Developments in the Use of Atypical Antipsychotics in the Treatment of Bipolar Disorder: a Systematic Review of Recent Randomized Controlled Trials. Curr Psychiatry Rep. 2021;23(7):39.
30. Fountoulakis KN, Tohen M, Zarate CA, Jr. Lithium treatment of Bipolar disorder in adults: A systematic review of randomized trials and meta-analyses. Eur Neuropsychopharmacol. 2022;54:100-15.
31. Vieta E, Sachs G, Chang D, et al. Two randomized, double-blind, placebo-controlled trials and one open-label, long-term trial of brexpiprazole for the acute treatment of bipolar mania. J Psychopharmacol. 2021;35(8):971-82.
32. Missio G, Moreno DH, Demetrio FN, et al. A randomized controlled trial comparing lithium plus valproic acid versus lithium plus carbamazepine in young patients with type 1 bipolar disorder: the LICAVAL study. Trials. 2019;20(1):608.
33. Earley W, Durgam S, Lu K, et al. Tolerability of cariprazine in the treatment of acute bipolar I mania: A pooled post hoc analysis of 3 phase II/III studies. J Affect Disord. 2017;215:205-12.
34. Bahji A, Ermacora D, Stephenson C, et al. Comparative efficacy and tolerability of pharmacological treatments for the treatment of acute bipolar depression: A systematic review and network meta-analysis. J Affect Disord. 2020;269:154-84.
35. Yildiz A, Siafis S, Mavridis D, et al. Comparative efficacy and tolerability of pharmacological interventions for acute bipolar depression in adults: a systematic review and network meta-analysis. Lancet Psychiatry. 2023;10(9):693-705.
36. Kadakia A, Dembek C, Heller V, et al. Efficacy and tolerability of atypical antipsychotics for acute bipolar depression: a network meta-analysis. BMC Psychiatry. 2021;21(1):249.
37. Hu Y, Zhang H, Wang H, et al. Adjunctive antidepressants for the acute treatment of bipolar depression: A systematic review and meta-analysis. Psychiatry Res. 2022;311:114468.

38. McGirr A, Vöhringer PA, Ghaemi SN, et al. Safety and efficacy of adjunctive second- generation antidepressant therapy with a mood stabiliser or an atypical antipsychotic in acute bipolar depression: a systematic review and meta-analysis of randomised placebo-controlled trials. Lancet Psychiatry. 2016;3(12):1138-46.
39. Malhi GS, Bell E, Bassett D, et al. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry. 2021;55(1):7-117.
40. Yatham LN, Kennedy SH, Parikh SV, et al. 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 Disord. 2018;20(2):97-170.
41. Dean RL, Marquardt T, Hurducas C, et al. Ketamine and other glutamate receptor modulators for depression in adults with bipolar disorder. Cochrane Database Syst Rev. 2021;10(10):CD011611.
42. Yatham LN, Chakrabarty T, Bond DJ, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) recommendations for the management of patients with bipolar disorder with mixed presentations. Bipolar Disord. 2021;23(8):767-88.
43. Verdolini N, Hidalgo-Mazzei D, Murru A, et al. Mixed states in bipolar and major depressive disorders: systematic review and quality appraisal of guidelines. Acta Psychiatr Scand. 2018;138(3):196-222.
44. McIntyre RS, Suppes T, Earley W, et al. Cariprazine efficacy in bipolar I depression with and without concurrent manic symptoms: post hoc analysis of 3 randomized, placebo-controlled studies. CNS Spectr. 2020;25(4):502-10.
45. McIntyre RS, Durgam S, Huo J, et al. The Efficacy of Lumateperone in Patients With Bipolar Depression With Mixed Features. J Clin Psychiatry. 2023;84(3).
46. Cullen C, Kappelmann N, Umer M, et al. Efficacy and acceptability of pharmacotherapy for comorbid anxiety symptoms in bipolar disorder: A systematic review and meta-analysis. Bipolar Disord. 2021;23(8):754-66.
47. Strawbridge R, Kurana S, Kerr-Gaffney J, et al. A systematic review and meta-analysis of treatments for rapid cycling bipolar disorder. Acta Psychiatr Scand. 2022;146(4):290-311.
48. Kato M, Adachi N, Kubota Y, et al. Clinical features related to rapid cycling and one-year euthymia in bipolar disorder patients: A multicenter treatment survey for bipolar disorder in psychiatric clinics (MUSUBI). J Psychiatr Res. 2020;131:228-34.
49. Zhihan G, Fengli S, Wangqiang L, et al. Lamotrigine and Lithium Combination for Treatment of Rapid Cycling Bipolar Disorder: Results From Meta-Analysis. Front Psychiatry. 2022;13:913051.
50. Verdolini N, Hidalgo-Mazzei D, Del Matto L, et al. Long-term treatment of bipolar disorder type I: A systematic and critical review of clinical guidelines with derived practice algorithms. Bipolar Disord. 2021;23(4):324-40.
51. Liu B, Zhang Y, Fang H, et al. Efficacy and safety of long-term antidepressant treatment for bipolar disorders - A meta-analysis of randomized controlled trials. J Affect Disord. 2017;223:41-8.
52. Prajapati AR, Wilson J, Song F, et al. Second-generation antipsychotic long-acting injections in bipolar disorder: Systematic review and meta-analysis. Bipolar Disord. 2018;20(8):687-96.
53. Delgado A, Velosa J, Zhang J, et al. Clozapine in bipolar disorder: A systematic review and meta-analysis. J Psychiatr Res. 2020;125:21-7.
54. Schoeyen HK, Kessler U, Andreassen OA, et al. Treatment-resistant bipolar depression: a randomized controlled trial of electroconvulsive therapy versus algorithm-based pharmacological treatment. Am J Psychiatry. 2015;172(1):41- 51.

55. Kessler U, Schoeyen HK, Andreassen OA, et al. The effect of electroconvulsive therapy on neurocognitive function in treatment-resistant bipolar disorder depression. J Clin Psychiatry. 2014;75(11):e1306-13.
56. Tor PC, Bin Abdin E. Mirror Readmission Study of the Association of Electroconvulsive Therapy With 1-Year Mood Disorder Readmissions in a Tertiary Mood Disorder Unit. J ECT. 2020;36(2):111-4.
57. Minnai GP, Salis P, Manchia M, et al. What happens to the course of bipolar disorder after electroconvulsive therapy? J Affect Disord. 2016;195:180-4.
58. Kaster TS, Vigod SN, Gomes T, et al. Risk of serious medical events in patients with depression treated with electroconvulsive therapy: a propensity score-matched, retrospective cohort study. Lancet Psychiatry. 2021;8(8):686-95.
59. Ministry of Health Malaysia. Guideline on Electroconvulsive Therapy for Ministry of Health Basis, Practicality & Policies. Putrajaya : MoH; 2021.
60. Nguyen TD, Hieronymus F, Lorentzen R, et al. The efficacy of repetitive transcranial magnetic stimulation (rTMS) for bipolar depression: A systematic review and meta- analysis. J Affect Disord. 2021;279:250-5.
61. Konstantinou G, Hui J, Ortiz A, et al. Repetitive transcranial magnetic stimulation (rTMS) in bipolar disorder: A systematic review. Bipolar Disord. 2022;24(1):10-26.
62. McIntyre RS, Lee Y, Rodrigues NB, et al. Repetitive transcranial magnetic stimulation for cognitive function in adults with bipolar disorder: A pilot study. J Affect Disord. 2021;293:73-7.
63. Matsuda Y, Kito S, Igarashi Y, et al. Efficacy and Safety of Deep Transcranial Magnetic Stimulation in Office Workers with Treatment-Resistant Depression: A Randomized, Double-Blind, Sham-Controlled Trial. Neuropsychobiology. 2020;79(3):208-13.
64. Tavares DF, Suen P, Rodrigues Dos Santos CG, et al. Treatment of mixed depression with theta-burst stimulation (TBS): results from a double-blind, randomized, sham- controlled clinical trial. Neuropsychopharmacology. 2021;46(13):2257-65.
65. Loo CK, Husain MM, McDonald WM, et al. International randomized-controlled trial of transcranial Direct Current Stimulation in depression. Brain Stimul. 2018;11(1):125-33.
66. Sampaio-Junior B, Tortella G, Borrione L, et al. Efficacy and Safety of Transcranial Direct Current Stimulation as an Add-on Treatment for Bipolar Depression: A Randomized Clinical Trial. JAMA Psychiatry. 2018;75(2):158-66.
67. Tortella G, Sampaio-Junior B, Moreno ML, et al. Cognitive outcomes of the bipolar depression electrical treatment trial (BETTER): a randomized, double-blind, sham-controlled study. Eur Arch Psychiatry Clin Neurosci. 2021;271(1):93-100.
68. Zhou TH, Dang WM, Ma YT, et al. Clinical efficacy, onset time and safety of bright light therapy in acute bipolar depression as an adjunctive therapy: A randomized controlled trial. J Affect Disord. 2018;227:90-6.
69. Sit DK, McGowan J, Wiltrout C, et al. Adjunctive Bright Light Therapy for Bipolar Depression: A Randomized Double-Blind Placebo-Controlled Trial. Am J Psychiatry. 2018;175(2):131-9.
70. Tang VM, Blumberger DM, Dimitrova J, et al. Magnetic seizure therapy is efficacious and well tolerated for treatment-resistant bipolar depression: an open-label clinical trial. J Psychiatry Neurosci. 2020;45(5):313-21.
71. Aaronson ST, Sears P, Ruvuna F, et al. A 5-Year Observational Study of Patients With Treatment-Resistant Depression Treated With Vagus Nerve Stimulation or Treatment as Usual: Comparison of Response, Remission, and Suicidality. Am J Psychiatry. 2017;174(7):640-8.

72. Yilmaz S, Huguet A, Kisely S, et al. Do psychological interventions reduce symptoms of depression for patients with bipolar I or II disorder? A meta-analysis. J Affect Disord. 2022;301:193-204.
73. National Collaborating Centre for Mental Health (UK). Bipolar Disorder: The NICE Guideline on the Assessment and Management of Bipolar Disorder in Adults, Children and Young People in Primary and Secondary Care. London: The British Psychological Society and The Royal College of Psychiatrists; 2014
74. Liu JY, Xu KK, Zhu GL, et al. Effects of smartphone-based interventions and monitoring on bipolar disorder: A systematic review and meta-analysis. World J Psychiatry. 2020;10(11):272-85.
75. Anmella G, Faurholt-Jepsen M, Hidalgo-Mazzei D, et al. Smartphone-based interventions in bipolar disorder: Systematic review and meta-analyses of efficacy. A position paper from the International Society for Bipolar Disorders (ISBD) Big Data Task Force. Bipolar Disord. 2022;24(6):580-614.
76. Stroppa A, Colugnati FA, Koenig HG, et al. Religiosity, depression, and quality of life in bipolar disorder: a two-year prospective study. Braz J Psychiatry. 2018;40(3):238-43.
77. Ministry of Health Malaysia. Guidelines on Implementation of Supported Employment Program for People with Mental Illness in MOH Facilities. Putrajaya: MoH; 2022.
78. Miklowitz DJ, Efthimiou O, Furukawa TA, et al. Adjunctive Psychotherapy for Bipolar Disorder: A Systematic Review and Component Network Meta-analysis. JAMA Psychiatry. 2021;78(2):141-50.
79. Tan MK, Chia EC, Tam WW, et al. A Meta-Analysis of Group Cognitive Behavioral Therapy and Group Psychoeducation for Treating Symptoms and Preventing Relapse in People Living with Bipolar Disorder. Healthcare (Basel). 2022;10(11).
80. Lam C, Chung MH. A meta-analysis of the effect of interpersonal and social rhythm therapy on symptom and functioning improvement in patients with bipolar disorders. Appl Res Qual Life. 2019;16:1-22.
81. Steardo L, Jr., Luciano M, Sampogna G, et al. Efficacy of the interpersonal and social rhythm therapy (IPSRT) in patients with bipolar disorder: results from a real-world, controlled trial. Ann Gen Psychiatry. 2020;19:15.
82. Xuan R, Li X, Qiao Y, et al. Mindfulness-based cognitive therapy for bipolar disorder: A systematic review and meta-analysis. Psychiatry Res. 2020;290:113116.
83. Pankowski S, Adler M, Andersson G, et al. Group acceptance and commitment therapy (ACT) for bipolar disorder and co-existing anxiety - an open pilot study. Cogn Behav Ther. 2017;46(2):114-28.
84. Murray G. Adjunctive psychosocial interventions for bipolar disorder: some psychotherapeutic context for the Canadian Network for Mood and Anxiety Treatments (CANMAT) & International Society for Bipolar Disorders (ISBD) guidelines. Bipolar Disord. 2018;20(1):25-33.
85. Sarris J, Lake J, Hoenders R. Bipolar disorder and complementary medicine: current evidence, safety issues, and clinical considerations. J Altern Complement Med. 2011;17(10):881-90.
86. Ashton MM, Kavanagh BE, Marx W, et al. A Systematic Review of Nutraceuticals for the Treatment of Bipolar Disorder. Can J Psychiatry. 2021;66(3):262-73.
87. Ismail R, Abdul Manaf MR, Hassan MR, et al. Prevalence of Drug and Substance Use among Malaysian Youth: A Nationwide Survey. Int J Environ Res Public Health. 2022;19(8).
88. Pinto JV, Saraf G, Frysch C, et al. Cannabidiol as a Treatment for Mood Disorders: A Systematic Review. Can J Psychiatry. 2020;65(4):213-27.

89. Tourjman SV, Buck G, Jutras-Aswad D, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) Task Force Report: A Systematic Review and Recommendations of Cannabis use in Bipolar Disorder and Major Depressive Disorder. Can J Psychiatry. 2023;68(5):299-311.
90. Tohen M, Frank E, Bowden CL, et al. The International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in bipolar disorders. Bipolar Disord. 2009;11(5):453-7
91. Bond K, Anderson IM. Psychoeducation for relapse prevention in bipolar disorder: a systematic review of efficacy in randomized controlled trials. Bipolar Disord. 2015;17(4):349-62.
92. Macheiner T, Skavantzos A, Pilz R, et al. A meta-analysis of adjuvant group-interventions in psychiatric care for patients with bipolar disorders. J Affect Disord. 2017;222:28-31.
93. Chatterton ML, Stockings E, Berk M, et al. Psychosocial therapies for the adjunctive treatment of bipolar disorder in adults: network meta-analysis. Br J Psychiatry. 2017;210(5):333-41.
94. Perich T, Manicavasagar V, Mitchell PB, et al. A randomized controlled trial of mindfulness-based cognitive therapy for bipolar disorder. Acta Psychiatr Scand. 2013;127(5):333-43.
95. Scott J, Colom F, Vieta E. A meta-analysis of relapse rates with adjunctive psychological therapies compared to usual psychiatric treatment for bipolar disorders. Int J Neuropsychopharmacol. 2007;10(1):123-9.
96. Pakpour AH, Modabbernia A, Lin CY, et al. Promoting medication adherence among patients with bipolar disorder: a multicenter randomized controlled trial of a multifaceted intervention. Psychol Med. 2017;47(14):2528-39.
97. Sajatovic M, Dols A, Rej S, et al. Bipolar symptoms, somatic burden, and functioning in older-age bipolar disorder: Analyses from the Global Aging & Geriatric Experiments in Bipolar Disorder Database project. Bipolar Disord. 2022;24(2):195-206.
98. Sajatovic M, Tatsuoka C, Cassidy KA, et al. A 6-Month, Prospective, Randomized Controlled Trial of Customized Adherence Enhancement Versus Bipolar-Specific Educational Control in Poorly Adherent Individuals With Bipolar Disorder. J Clin Psychiatry. 2018;79(6).
99. Sajatovic M, Levin JB, Sams J, et al. Symptom severity, self-reported adherence, and electronic pill monitoring in poorly adherent patients with bipolar disorder. Bipolar Disord. 2015;17(6):653-61.
100. Menon V, Selvakumar N, Kattimani S, et al. Therapeutic effects of mobile-based text message reminders for medication adherence in bipolar I disorder: Are they maintained after intervention cessation? J Psychiatr Res. 2018;104:163-8.
101. Faurholt-Jepsen M, Frost M, Ritz C, et al. Daily electronic self-monitoring in bipolar disorder using smartphones - the MONARCA I trial: a randomized, placebo-controlled, single-blind, parallel group trial. Psychol Med. 2015;45(13):2691-704.
102. Faurholt-Jepsen M, Frost M, Busk J, et al. Differences in mood instability in patients with bipolar disorder type I and II: a smartphone-based study. Int J Bipolar Disord. 2019;7(1):5.
103. Provencher M, Hawke L, Bélair M, et al. Dissemination of a brief psychoeducational intervention for bipolar disorder in community mental health settings. Int J Clin Psychiatry Ment Health. 2014;2:93-103.
104. Schöttle D, Schimmelmann BG, Karow A, et al. Effectiveness of integrated care including therapeutic assertive community treatment in severe schizophrenia spectrum and bipolar I disorders: the 24-month follow-up ACCESS II study. J Clin Psychiatry. 2014;75(12):1371-9.

105. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness. JAMA. 2002;288(14):1775-9.
106. Butler M, Urosevic S, Desai P, et al. Treatment for bipolar disorder in adults: a systematic review. Rockville (MD): Agency for Healthcare Research and Quality (US); 2018.
107. Cerimele JM, Blanchard BE, Johnson M, et al. Effectiveness of Collaborative Care and Colocated Specialty Care for Bipolar Disorder in Primary Care: A Secondary Analysis of a Randomized Clinical Trial. J Acad Consult Liaison Psychiatry. 2023;64(4):349-56.
108. Ministry of Health Malaysia. Guidelines on Pre-Pregnancy Care in MOH Specialist Hospital. Putrajaya : MoH; 2023.
109. Munk-Olsen T, Liu X, Viktorin A, et al. Maternal and infant outcomes associated with lithium use in pregnancy: an international collaborative meta-analysis of six cohort studies. Lancet Psychiatry. 2018;5(8):644-52.
110. Giménez A, Pacchiarotti I, Gil J, et al. Adverse outcomes during pregnancy and major congenital malformations in infants of patients with bipolar and schizoaffective disorders treated with antiepileptic drugs: A systematic review. Psychiatria Polska. 2019;53(2):223-44.
111. Calaway K, Coshal S, Jones K, et al. A Systematic Review of the Safety of Electroconvulsive Therapy Use During the First Trimester of Pregnancy. J ECT. 2016;32(4):230-5.
112. Pacchiarotti I, León-Caballero J, Murru A, et al. Mood stabilizers and antipsychotics during breastfeeding: Focus on bipolar disorder. Eur Neuropsychopharmacol. 2016;26(10):1562-78.
113. Arnold I, Dehning J, Grunze A, et al. Old Age Bipolar Disorder-Epidemiology, Aetiology and Treatment. Medicina (Kaunas). 2021;57(6).
114. Young RC, Mulsant BH, Sajatovic M, et al. GERI-BD: A Randomized Double-Blind Controlled Trial of Lithium and Divalproex in the Treatment of Mania in Older Patients With Bipolar Disorder. Focus (Am Psychiatr Publ). 2019;17(3):314-21.
115. Burton C, Mathys M, Gutierrez E. Comparison of lithium to second-generation antipsychotics for the treatment of bipolar disorder in older veterans. Psychiatry Res. 2021;303:114063.
116. Forester BP, Sajatovic M, Tsai J, et al. Safety and Effectiveness of Long-Term Treatment with Lurasidone in Older Adults with Bipolar Depression: Post-Hoc Analysis of a 6-Month, Open-Label Study. Am J Geriatr Psychiatry. 2018;26(2):150-9.
117. Van Meter A, Moreira ALR, Youngstrom E. Updated Meta-Analysis of Epidemiologic Studies of Pediatric Bipolar Disorder. J Clin Psychiatry. 2019;80(3):18r12180
118. Hafeman DM, Merranko J, Axelson D, et al. Toward the Definition of a Bipolar Prodrome: Dimensional Predictors of Bipolar Spectrum Disorders in At-Risk Youths. Am J Psychiatry. 2016;173(7):695-704.
119. Duffy A, Heffer N, Goodday SM, et al. Efficacy and tolerability of lithium for the treatment of acute mania in children with bipolar disorder: A systematic review: A report from the ISBD-IGSLi joint task force on lithium treatment. Bipolar Disord. 2018;20(7):583-93.
120. Patino LR, Klein CC, Strawn JR, et al. A Randomized, Double-Blind, Controlled Trial of Lithium Versus Quetiapine for the Treatment of Acute Mania in Youth with Early Course Bipolar Disorder. J Child Adolesc Psychopharmacol. 2021;31(7):485-93.
121. Tohen M, Kryzhanovskaya L, Carlson G, et al. Olanzapine versus placebo in the treatment of adolescents with bipolar mania. Am J Psychiatry. 2007;164(10):1547-56.

122. Findling RL, Landbloom RL, Szegedi A, et al. Asenapine for the Acute Treatment of Pediatric Manic or Mixed Episode of Bipolar I Disorder. J Am Acad Child Adolesc Psychiatry. 2015;54(12):1032-41.
123. Findling RL, Landbloom RL, Mackle M, et al. Long-term Safety of Asenapine in Pediatric Patients Diagnosed With Bipolar I Disorder: A 50-Week Open-Label, Flexible-Dose Trial. Paediatr Drugs. 2016;18(5):367-78.
124. Findling RL, Correll CU, Nyilas M, et al. Aripiprazole for the treatment of pediatric bipolar I disorder: a 30-week, randomized, placebo-controlled study. Bipolar Disord. 2013;15(2):138-49.
125. Findling RL, Atkinson S, Bachinsky M, et al. Efficacy, Safety, and Tolerability of Flexibly Dosed Ziprasidone in Children and Adolescents with Mania in Bipolar I Disorder: A Randomized Placebo-Controlled Replication Study. J Child Adolesc Psychopharmacol. 2022;32(3):143-52.
126. Wagner KD, Redden L, Kowatch RA, et al. A double-blind, randomized, placebo-controlled trial of divalproex extended-release in the treatment of bipolar disorder in children and adolescents. J Am Acad Child Adolesc Psychiatry. 2009;48(5):519-32.
127. Maneeton B, Putthisri S, Maneeton N, et al. Quetiapine monotherapy versus placebo in the treatment of children and adolescents with bipolar depression: a systematic review and meta-analysis. Neuropsychiatr Dis Treat. 2017;13:1023-32.
128. DelBello MP, Kadakia A, Heller V, et al. Systematic Review and Network Meta-analysis: Efficacy and Safety of Second-Generation Antipsychotics in Youths With Bipolar Depression. J Am Acad Child Adolesc Psychiatry. 2022;61(2):243-54.
129. González-Pinto A, Goikolea JM, Zorrilla I, et al. Clinical practice guideline on pharmacological and psychological management of adult patients with bipolar disorder and comorbid substance use. Adicciones. 2022;34(2):142-56.
130. Wenze SJ, Gaudiano BA, Weinstock LM, et al. Adjunctive psychosocial intervention following Hospital discharge for Patients with bipolar disorder and comorbid substance use: A pilot randomized controlled trial. Psychiatry Res. 2015;228(3):516- 25.
131. World Health Organization. Suicide worldwide in 2019: global health estimates. Geneva: WHO; 2021 (Available at: https://www.who.int/publications/i/item/9789240026643).
132. Knipe D, Padmanathan P, Newton-Howes G, et al. Suicide and self-harm. Lancet. 2022;399(10338):1903-16.
133. Schaffer A, Isometsä ET, Azorin JM, et al. A review of factors associated with greater likelihood of suicide attempts and suicide deaths in bipolar disorder: Part II of a report of the International Society for Bipolar Disorders Task Force on Suicide in Bipolar Disorder. Aust N Z J Psychiatry. 2015;49(11):1006-20.
134. Hauser M, Galling B, Correll CU. Suicidal ideation and suicide attempts in children and adolescents with bipolar disorder: a systematic review of prevalence and incidence rates, correlates, and targeted interventions. Bipolar Disord. 2013;15(5):507-23.
135. Cerel J, Sanford RL. It's not who you know, it's how you think you know them: suicide exposure and suicide bereavement. Psychoanal Study Child. 2018;71(1):76-96.
136. Caribé AC, Studart P, Bezerra-Filho S, et al. Is religiosity a protective factor against suicidal behavior in bipolar I outpatients? J Affect Disord. 2015;186:156-61.
137. Nabi Z, Stansfeld J, Plöderl M, et al. Effects of lithium on suicide and suicidal behaviour: a systematic review and meta-analysis of randomised trials. Epidemiol Psychiatr Sci. 2022;31:e65.

138. Liang CS, Chung CH, Ho PS, et al. Superior anti-suicidal effects of electroconvulsive therapy in unipolar disorder and bipolar depression. Bipolar Disord. 2018;20(6):539- 46.
139. Joseph B, Parsaik AK, Ahmed AT, et al. A Systematic Review on the Efficacy of Intravenous Racemic Ketamine for Bipolar Depression. J Clin Psychopharmacol. 2021;41(1):71-5.
140. Stanley B, Brown GK, Karlin B, et al. Safety plan treatment manual to reduce suicide risk: Veteran version. Washington, DC: United States Department of Veterans Affairs; 2008.
141. Nuij C, van Ballegooijen W, de Beurs D, et al. Safety planning-type interventions for suicide prevention: meta-analysis. Br J Psychiatry. 2021;219(2):419-26.
142. Kishi T, Ikuta T, Matsuda Y, et.al. Pharmacological treatment for bipolar mania: a systematic review and network meta-analysis of double-blind randomized controlled trials. Mol Psychiatry. 2022;27(2):1136-1144.
143. Yatham LN, Kennedy SH, Parikh SV, et.al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) guidelines for the management of patients with bipolar disorder. Bipolar Disord. 2018;20(2):97-170.

Appendix 1

EXAMPLE OF SEARCH STRATEGY

Clinical Question: What are the safe and effective pharmacotherapy in the management of manic episode in BD?

1. BIPOLAR DISORDER/
2. (bipolar adj2 affective psychos#s).tw.
3. (bipolar adj1 (depressi* or disorder*)).tw.
4. (bipolar adj2 mood disorder*).tw.
5. (manic adj1 (depressi* or disorder*)).tw.
6. (manic depressi* adj2 psychos#s).tw.
7. (manic-depressi* adj1 psychos#s).tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. MANIA/
10. (manic adj1 (state* or episode*)).tw.
11. hypomani*.tw.
12. (hypomanic adj1 (episode* or state*)).tw.
13. mania*.tw.
14. 9 or 10 or 11 or 12 or 13
15. DRUG THERAPY/
16. (drug adj1 therap*).tw.
17. pharmacotherap*.tw.
18. mood stabilizer*.tw.
19. ANTIPSYCHOTIC/
20. (antipsychotic* adj1 (agent* or drug* or effect* or medication* or therap*)). tw.
21. antipsychotic*.tw.
22. (neuroleptic adj1 (agent* or drug* or medication* or therap*)).tw.
23. neuroleptic*.tw.
24. (major adj1 tranquili*).tw.
25. (major tranquili#ing adj2 (agent* or medication* or therap*)).tw.
26. ANTIMANIC AGENTS/
27. (antimanic adj1 (agent* or drug* or effect* or medication* or therap*)).tw.
28. antimanic*.tw.
29. ANTIDEPRESSANTS/
30. (antidepress* adj1 (agent* or drug*or medication* or therap*)).tw.
31. antidepressant*.tw.
32. thymoanaleptic*.tw.
33. thymoleptic*.tw.
34. PSYCHOTROPIC DRUGS/

35 (psychotropic* adj1 (drug* or agent* or medication* or therap*)).tw.
36. psychotropic*.tw.
37. (psychoactive adj1 (agent* or drug* or medication* or therap*)).tw.
38. psychopharmaceutical*.tw.
39. (psychopharmaceutical adj1 (agent* or drug* or medication* or therap*)). tw.
40. ANTICONVULSANTS/
41. (anticonvuls* adj1 (agent* or drug* or medication* or therap*)).tw.
42. (antiepileptic* adj1 (agent* or drug* or medication* or therap*)).tw.
43. antiepileptic*.tw.
44. anticonvulsant*.tw.
45. BENZODIAZEPINES/
46. benzodiazepine*.tw.
47. (benzodiazepine adj1 compound*).tw.
48. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
49. 8 and 14 and 48
50. limit 49 to (english language and humans and “all adult (19 plus years)” and last 9 years)

Appendix 2

CLINICAL QUESTIONS

1. What are the risk and protective factors for bipolar disorder?
2. What are the accurate screening and diagnostic tools in bipolar disorder?
3. What are the differential diagnoses in bipolar disorder?
4. What are the indicators of bipolarity in patients with depression?
5. What are the co-morbidities in bipolar disorder?
6. What are the effective and safe pharmacotherapy in the management of
   - manic episode in bipolar disorder?
   - depressive episode in bipolar disorder?
   - bipolar disorder with specifiers (mixed features, anxious distress and rapid cycling)?
   - maintenance phase of bipolar disorder?
7. What are the effective and safe physical therapies in bipolar disorder?
8. What are the effective and safe psychosocial interventions in bipolar disorder?
9. What are the effective and safe psychotherapies in bipolar disorder?
10. What are the effective and safe complementary and alternative therapies in bipolar disorder?
11. What are the parameters to be monitored during the maintenance phase of bipolar disorder?
12. What are the referral criteria for patients with bipolar disorder?
13. What are the effective and safe strategies in the prevention of bipolar disorder?
14. What are the effective strategies to improve adherence in bipolar disorder?
15. How effective are Collaborative Care Models in the management of bipolar disorder?
16. What are the effective and safe treatments in the following special population with bipolar disorder?
    - pregnancy and lactation
    - elderly
    - children and adolescents
    - people with addictions (behavioural and substance)
    - borderline personality disorder
17. What are the risk and protective factors for suicide in bipolar disorder?
18. What are the effective and safe interventions in suicide prevention in bipolar disorder?

Appendix 3

DIAGNOSTIC CRITERIA OF BIPOLAR DISORDER BASED ON DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS FIFTH EDITION, TEXT REVISION (DSM-5-TR) AND INTERNATIONAL CLASSIFICATION OF DISEASES ELEVENTH REVISION (ICD-11)

ICD-11	DSM-5-TR
Hypomanic Episode A persistent mood state lasting for at least several days characterised by persistent elevation of mood or increased irritability as well as increased activity or a subjective experience of increased energy, accompanied by other characteristic symptoms e.g.: • increased talkativeness • rapid or racing thoughts • increased self-esteem • decreased need for sleep • distractibility • impulsive or reckless behaviour	**Hypomanic Episode** Abnormally and persistently elevated, expansive or irritable mood along AND persistently increased energy or activity lasting at least four days accompanied by three or four (if mood is only irritable): • inflated self-esteem or grandiosity • decreased need for sleep • increased talkativeness or pressure of speech • flight of ideas • distractibility • increased in goal-directed activity • excessive involvement in activities with negative consequences
Manic Episode An extreme mood state lasting at least one week unless shortened by a treatment intervention characterised by euphoria, irritability or expansiveness and by increased activity or a subjective experience of increased energy, accompanied by other characteristic symptoms e.g.: • rapid or pressured speech • flight of ideas • increased self-esteem or grandiosity • decreased need for sleep • distractibility • impulsive or reckless behaviour • rapid changes among different mood states (i.e. mood lability)	**Manic Episode** Abnormally and persistently elevated, expansive or irritable mood along AND persistently increased energy or activity lasting at least one week accompanied by three or four (if mood is only irritable): • inflated self-esteem or grandiosity • decreased need for sleep • increased talkativeness or pressure of speech • flight of ideas • distractibility • increased in goal-directed activity or excessive involvement in activities with negative consequences
At least one manic episode is not better explained by schizoaffective disorder and is not superimposed on schizophrenia or other psychotic disorders.	

<table>
<tr><th>ICD-11</th><th>DSM-5-TR</th></tr>
<tr><td colspan="2">A manic/hypomanic episode during antidepressant treatment is accepted as evidence of BD.
The symptoms in hypomania represent a change from the individual's typical mood, energy level and behaviour but are not severe enough to cause marked impairment in functioning.
There are similarities between mania and hypomania symptoms; however the diagnosis of manic episode necessitates that the disturbance is severe enough:
• causing impairment in social or occupational functioning or
• requiring hospitalisation or
• with psychotic features</td></tr>
<tr><td>Depressive Episode

A period of depressed mood or diminished interest in activities occurring most of the day, nearly every day during a period lasting at least two weeks accompanied by other symptoms e.g.:
• changes in appetite or sleep
• psychomotor agitation or retardation
• fatigue
• worthlessness or excessive or inappropriate guilt feelings or hopelessness
• difficulty concentrating
• suicidality</td><td>Major Depressive Episode

For at least two weeks, presenting with five or more of the following symptoms, of which, at least one must be depressed mood or loss of interest or pleasure. The other symptoms include:
• disruption in appetite with accompanying weight loss or gain
• sleep disturbance
• psychomotor agitation or retardation
• fatiguability
• feeling worthless or guilty
• reduced concentration or indecisiveness
• recurrent thoughts of death or suicidal ideas or acts</td></tr>
<tr><td>6A60 Bipolar Type I Disorder

An episodic mood disorder defined by the occurrence of one or more manic or mixed episodes.
• 6460.0 Bipolar type I disorder, current episode manic without psychotic symptoms
• 6460.1 Bipolar type I disorder, current episode manic with psychotic symptoms
• 6A60.2 Bipolar type I disorder, current episode hypomanic
• 6460.3 Bipolar type I disorder, current episode depressive, mild
• 6460.4 Bipolar type I disorder, current episode depressive, moderate without psychotic symptoms</td><td>Bipolar I Disorder

Having met the criteria for at least one manic episode.
• Current or most recent episode manic:
○ F31.11 Mild
○ F31.12 Moderate
○ F31.13 Severe
○ F31.2 With psychotic features
○ F31.73 In partial remission
○ F31.74 In full remission
• Current or most recent episode depressed:
○ F31.31 Mild
○ F31.32 Moderate
○ F31.4 Severe
○ F31.5 With psychotic features
○ F31.75 In partial remission
○ F31.76 In full remission</td></tr>
</table>

ICD-11	DSM-5-TR
• 6460.5 Bipolar type I disorder, current episode depressive, moderate with psychotic symptoms • 6460.6 Bipolar type I disorder, current episode depressive, severe without psychotic symptoms • 6460.7 Bipolar type I disorder, current episode depressive, severe with psychotic symptoms **6A61 Bipolar Type II Disorder** An episodic mood disorder is defined by the occurrence of one or more hypomanic episodes and at least one depressive episode. Refer to ICD-11 for more coding.	**F31.81 Bipolar II Disorder** Having met the criteria for hypomanic episodes at least once and major depressive episode at least once, Specify current or most recent episode: Hypomanic Depressed Current or most recent episode hypomanic F31.0 Not in remission F31.71 In partial remission F31.72 in full remission **Specifiers (both BD I and II)**: With anxious distress With mixed features With rapid cycling With melancholic features With atypical features With mood-congruent psychotic features With mood-incongruent psychotic features With catatonia With peripartum onset With seasonal pattern Refer to DSM-5-TR for more coding.
6A62 Cyclothymia A persistent instability of mood over a period of at least two years, involving numerous periods of hypomanic and depressive symptoms that are present during more of the time than not, but not sufficient to meet the full criteria for an episode.	**F34.0 Cyclothymic disorder** At least two years (for children, a full year) of both hypomanic and depressive symptoms without ever fulfilling the criteria for an episode of mania, hypomania or major depressive disorder. Specify With anxious distress
Mixed Episode A mixed episode is characterised by the presence of several prominent manic and several prominent depressive symptoms consistent with those observed in manic episodes and depressive episodes, which either occur simultaneously or alternate very rapidly.	**Mixed features** **Manic or hypomanic episode, with mixed features** Full criteria are met for a manic or hypomanic episode, and at least three depressive symptoms are present.

ICD-11	DSM-5-TR
	Depressive episode, with mixed features Full criteria are met for a depressive episode, and at least three manic/ hypomanic symptoms are present.
Rapid cycling High frequency of mood episodes (at least four) over the past 12 months	**Rapid cycling** At least four mood episodes in the previous 12 months that met the criteria for manic, hypomanic or major depressive episodes.

An interval of at least two months free of symptoms is required to distinguish between episodes.

Source:

1. ICD-11 International Classification of Diseases 11th Revision. The global standard for diagnostic health information (Available at: https://icd.who.int/).
2. American Psychiatric Association. Bipolar and Related Disorders. In Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision. Washington DC: APA; 2022.

Appendix 4

LIST OF SCREENING TOOLS IN BIPOLAR DISORDER

Screening tool	No. of items	Rater	Cut-off points	Sensitivity	Specificity	Comments
Mood disorder questionnaire (MDQ)	17	Self-rated	7 (range 3 - 7)	80%	70%	Screens for lifetime history of (hypo) mania. There was no evidence of a difference in diagnostic accuracy between Asian and non-Asian studies for both the MDQ and HCL-32.[1]
Hypomania checklist (HCL-32)	32	Self-rated	14 (range 7 - 18)	82%	57%	Screens for lifetime history of hypomania. More significantly accurate than MDQ to detect BD II in mental healthcare centre.[2]
Bipolar spectrum diagnostic scale (BSDS)	19	Self-rated	13	69%	86%	Uses 19 sentences describing manifestations of bipolar disorder.[3]
Rapid mood screener (RMS)	6	Self-rated	4	88%	80%	Validated for BD I only.
Rapid mood screener (RMS)	6	Self-rated	4	88%	80%	Validated for BD I only. RMS is significantly better than MDQ in the following:[4] 1. sensitivity/ specificity 2. brevity 3. practicality 4. easy scoring
Bipolarity index (BI)	5	Clinician-rated	50	91%	90%	High score suggests likelihood of a true bipolar diagnosis. Score 50: BD Score 40 - 50: at risk of conversion to BD, thus careful monitoring.[5] Only 1 study done in unselected clinical patients.

Reference:

1. Wang YY, Xu DD, Liu R, et al. Comparison of the screening ability between the 32-item Hypomania Checklist (HCL-32) and the Mood Disorder Questionnaire (MDQ) for bipolar disorder: A meta-analysis and systematic review. Psychiatry Res. 2019;273:461-466.
2. Carvalho AF, Takwoingi Y, Sales PM, et al. Screening for bipolar spectrum disorders: A comprehensive meta-analysis of accuracy studies. J Affect Disord. 2015;172:337-46.
3. Ghaemi SN, Miller CJ, Berv DA, et al. Sensitivity and specificity of a new bipolar spectrum diagnostic scale. Journal of affective disorders. 2005;84(2- 3):273-7.
4. McIntyre RS, Patel MD, Masand PS, et al. The Rapid Mood Screener (RMS): a novel and pragmatic screener for bipolar I disorder. Current Medical Research and Opinion. 2021;37(1):135-44.
5. Aiken CB, Weisler RH, Sachs GS. The Bipolarity Index: a clinician-rated measure of diagnostic confidence. J Affect Disord. 2015;177:59-64.

RECOMMENDED ADULT MEDICATION DOSAGES AND ADVERSE EFFECTS FOR BIPOLAR DISORDER

MEDICATION	DOSING GUIDE	RENAL DOSE	HEPATIC DOSE	COMMON/SIGNIFICANT ADVERSE EFFECTS	REMARKS
MOOD STABILISERS					
Lithium	**Acute mania, acute episodes with mixed features, acute hypomania, acute bipolar depression** *Oral* - Initial: 600 - 900 mg/day in 2 - 3 divided doses. Titrate in increment of 300 - 600 mg to usual therapeutic dose range of 900 - 1800 mg/day in divided doses. (Max dose: 1.8 g/day in 1 to 3 divided doses)	**CrCl <30 mL/min** Use not recommended	No dosage adjustment provided in the manufacturer's labelling	**Cardiac**: cardiac arrhythmia, T-wave inversion, oedema, hypotension **CNS:** drowsiness, abnormal EEG, confusion, memory impairment, tremor **Dermatologic:** acne, exacerbation psoriasis **GI:** dyspepsia, nausea, vomiting, abdominal pain, diarrhoea, dysgeusia **Renal:** changes in eGFR **Endocrine and metabolic:** polydipsia and polyuria, weight gain, hyperparathyroidism, hypercalcemia, hypothyroidism, diabetes insipidus **Others**: sexual dysfunction **Lithium toxicity:** tremor, tinnitus, seizure, ataxia	• **Therapeutic Drug Monitoring (TDM)** ○ Steady state: 4 - 5 days ○ Sampling time: before next morning dose OR 12 hours from last evening dose ○ Therapeutic range: Indication: Plasma trough concentration (mmol/L) Acute mania: 0.8 - 1.2 Maintenance: 0.8 - 1.0 • May be taken with meals to avoid GI upset • Caution use during periods of dehydration e.g. acute gastroenteritis, fasting and intense exercise • Drug interaction with SGLT2 inhibitor: Reduced serum lithium concentration. Monitor serum lithium concentration more frequently during treatment with an SGLT2 inhibitor, particularly following initiation or dose changes.

MEDICATION	DOSING GUIDE	RENAL DOSE	HEPATIC DOSE	COMMON/SIGNIFICANT ADVERSE EFFECTS	REMARKS
Valproate	**Acute manic or acute episodes with mixed features, depressive episodes** *Oral* - IR: 600 mg daily and increase by 200 mg/day at 3-day interval until control is achieved. ER: 1000mg daily (in once or twice daily regimen) Usual dose range : 1000 to 2000 mg/day (i.e 20 - 30 mg/kg/day) (Max dose: 2500mg/day or 60 mg/kg/day)	**CrCl <10 mL/min:** No specific dosage adjustment necessary. However, free valproate clearance may be reduced up to ~30%.	**Severe impairment**: Use is contraindicated	**CNS:** dizziness, drowsiness, **Hematologic:** thrombocytopenia, decreased platelet aggregation **Liver:** hepatotoxicity/hepatic failure, hyperammonaemia, hepatic encephalopathy **Dermatologic:** SJS, TEN, DRESS **GI:** abdominal pain, diarrhoea, nausea, vomiting, pancreatitis **Psychiatric:** suicidal Ideation	• **TDM:** ○ Therapeutic range: 50 - 125 mg/L ○ Steady state: 2 - 4 days ○ Sampling time: 30 minutes OR just before next dose ○ Therapeutic serum levels generally occur with total daily doses of 1.5 - 2.5 g • Valproate administration may also impair fertility in men. Fertility dysfunctions are in some cases reversible at least 3 months after treatment discontinuation, however, the reversibility of male infertility was unknown. Offspring of men on valproate have an increased risk of learning or behavioural problems • Valproate is highly albumin-bound (~90%). Cautious use of valproate in patients with hypoalbuminaemia as free valproate levels are elevated.
Lamotrigine	**Acute bipolar depression** *Oral* - **Patients not taking any interacting medications:** Week 1 and 2: 25 mg once daily Week 3 and 4: 50 mg/day in 1 - 2 divided doses Week 5: 100 mg/day in 1 - 2 divided doses Week 6 and maintenance: 200 mg/day in 1 - 2 divided doses (up to 400 mg/day)	**CrCl <30 mL/min:** Titrate with caution as some pharmacokinetics parameters (e.g. half life) may vary considerably	**Moderate to severe impairment WITHOUT ascites**: Decrease doses by ~25% **Moderate to severe impairment WITH ascites:** Decrease doses by ~50%	**Hematologic:** agranulocytosis, neutropaenia, pancytopenia, pure red cell aplasia, aplastic anaemia **Dermatologic:** skin rash, SJS, TENS, DRESS **GI:** nausea, vomiting, diarrhoea **Ophthalmic:** blurred vision, diplopia **CNS:** ataxia, dizziness, drowsiness, headache, tremor, aseptic meningitis	• Periodically reassess needed for continued use after 16 weeks • **Restarting therapy:** If lamotrigine has been discontinued for >5 half-lives (half-life varies depending on concomitant antiepileptics), reinitiate with initial dosage. The greater the interval of time since previous dosage, the greater the consideration should be given to restarting with initial dosing recommendations.

MEDICATION	DOSING GUIDE	RENAL DOSE	HEPATIC DOSE	COMMON/SIGNIFICANT ADVERSE EFFECTS	REMARKS
	Patients taking valproate Week 1 and 2: 25 mg every other day Week 3 and 4: 25 mg once daily Week 5: 50 mg/day in 1 - 2 divided doses Week 6 and maintenance: 100 mg/day in 1 - 2 divided doses **Patients taking drug(s) that induce lamotriginine metabolism but not taking valproate** Week 1 and 2: 50 mg/day in 1 - 2 divided doses Week 3 and 4: 100 mg/day in 1 - 2 divided doses Week 5: 200 mg/day in 1 - 2 divided doses Week 6 and maintenance: 300 mg/day in 1 - 2 divided doses				
Carbamazepine	**Bipolar I disorder, acute manic or mixed episodes, depressive episodes** *Oral -* IR: 200 mg twice daily; may increase in increment of 200 mg/day every 1 to 4 days. ER: To be given in twice daily regimen Usual dose range: 400 -1600 mg/day in 2 to 3 divided doses (Max dose: 1.6 g/day)	No dosage adjustment necessary	No dosage adjustment provided in the manufacturer's labelling. Use with caution and consider dose reduction as it is metabolised primarily in the liver.	**Hematologic:** Aplastic anaemia, leukopenia, neutropenia, thrombocytopenia **Cardiac:** sinus tachycardia **Liver:** Hepatotoxicity/hepatic failure, increased serum transaminases **Dermatologic:** maculopapular rash, SJS, TEN, DRESS, AGEP **Electrolytes:** hyponatraemia, SIADH **CNS:** ataxia, dizziness, drowsiness	• **TDM** ○ **Steady state**: Initiation: 2 - 3 weeks Dose adjustment: 2 - 5 days ○ **Sampling time:** 0 - 30 min before dose; after steady state achieved ○ **Therapeutic range**: 4 - 12 µg/ml

MEDICATION	DOSING GUIDE	RENAL DOSE	HEPATIC DOSE	COMMON/SIGNIFICANT ADVERSE EFFECTS	REMARKS
				GI: Nausea, vomiting, constipation, xerostomia **ENT:** tinnitus	
ANTIPSYCHOTICS					
Aripiprazole	**Acute mania or episodes with mixed features, acute hypomania and maintenance treatment** *Oral* - 10 - 15 mg once daily; increase dose in 5 - 10mg/day increment at intervals of ≥1 week (Max dose: 30 mg/day) *LAI* - 400 mg once monthly	No dosage adjustment necessary	No dosage adjustment necessary	**Endocrine and metabolic:** weight gain, hypertriglyceridaemia, hypercholesterolaemia, hyperglycaemia **CNS:** drowsiness, extrapyramidal reaction, headache, insomnia **Hematologic:** neutropenia	For long acting injectable, consider reduce the dose to 300mg once monthly if there are adverse reactions with dose of 400mg once monthly
Asenapine	**Acute mania or episodes with mixed features** *Oral* - 5 - 10 mg twice daily (Max dose: 10 mg twice daily)	No dosage adjustment necessary	**Child-Pugh class C**: Use is contraindicated	**CNS:** drowsiness, insomnia, akathisia, extrapyramidal reaction, headache, dizziness **Endocrine and metabolic:** weight gain, hypertriglyceridemia, hypercholesterolemia, hyperglycaemia, **GI**: oral hypoesthesia	
Cariprazine	**Acute mania and acute episodes with mixed features** *Oral* - Initial: 1.5 mg once daily; titrate in increment of 1.5 or 3 mg. Recommended dosing range: 3 - 6 mg once daily (Max dose: 6 mg/day) **Bipolar major depression** *Oral* -	**CrCl <30 mL/min** Use not recommended	**Child-Pugh class C**: Use not recommended	**GI:** nausea, vomiting, constipation **CNS:** akathisia, dizziness, extrapyramidal reaction, insomnia, somnolence, headache **Endocrine and metabolic**: hyperglycaemia, weight gain	

MEDICATION	DOSING GUIDE	RENAL DOSE	HEPATIC DOSE	COMMON/SIGNIFICANT ADVERSE EFFECTS	REMARKS
	Initial 1.5 mg once daily; increase to 3 mg on day 15. (Max dose: 3 mg/day)				
Clozapine	**Maintenance/treatment resistant** *Oral* - Initial: 25 mg daily; titrate in increments of 25 mg at intervals >1 day (Max dose: 550 mg/day in divided doses)	No dosage adjustment provided in the manufacturer's labelling	Dose reduction may be necessary with significant impairment	**Cardiac:** hypotension, syncope, tachycardia **Endocrine metabolic**: sweating, increased weight, hyperglycaemia **GI**: constipation, excessive salivation, nausea, xerostomia **CNS:** dizziness, headache, somnolence **Ophthalmic**: visual disturbance **Other**: fever	
Haloperidol	**Acute mania, episodes with mixed features and acute hypomania** *Oral* - 2 - 15 mg/day **or** 0.2 mg/kg/day (up to 15 mg/day), in 1 or 2 divided dose. Titrate in increment of <5 mg every 2 days (Max dose: 30 mg/day)	No dosage adjustment necessary	No dosage adjustment provided in the manufacturer's labelling. Concentrations may increase in patients with hepatic impairment as it is metabolised primarily in liver and protein binding may decrease.	**Cardiac**: hypotension **GI**: constipation, xerostomia **CNS**: akathisia, extrapyramidal reaction, somnolence **Ophthalmic**: blurred vision	May worsen depressive symptoms
Lumateperone	**Depressive episodes** *Oral* - 42 mg once daily	No dosage adjustment necessary	**Child-Pugh class B and C**: Max: 21 mg once daily	**GI**: nausea, xerostomia **CNS:** dizziness, somnolence, extrapyramidal reaction	Currently not registered with NPRA
Lurasidone	**Depressive episodes** *Oral* - Initial, 20 mg once daily. Titrate in increment of 20 mg every >2 days. (Max dose: 120 mg once daily)	**CrCl <50 mL/min**: Max: 80 mg/day	**Child-Pugh class B**: Max: 80 mg/day **Child-Pugh class C**: Max: 40 mg/day	**Endocrine and metabolic:** dyslipidaemia, hyperglycaemia, weight gain **GI**: diarrhoea, nausea, vomiting	Take with meals (>350 calories) for adequate absorption

MEDICATION	DOSING GUIDE	RENAL DOSE	HEPATIC DOSE	COMMON/SIGNIFICANT ADVERSE EFFECTS	REMARKS
				CNS: akathisia, extrapyramidal reaction, parkinsonism, somnolence **Psychiatric**: anxiety	
Olanzapine	**Acute mixed or manic episodes** *Oral* - Initial: 10 - 15 mg once daily, titrate in increment of 5 mg at intervals of ≥1 day (Max dose: 20 mg/day) **Acute depressive episode** *Oral* - Initial: 5 mg once daily; titrate in increment of 5 mg every 1 - 7 days (Max dose: monotherapy = 20 mg/day; combination = 15 mg/day)	No dosage adjustment necessary	**When used in combination with fluoxetine:** Initial: 2.5 - 5 mg daily	**Cardiac**: orthostatic hypotension, peripheral oedema **Endocrine and metabolic**: hypercholesterolaemia, hyperglycaemia, hyperprolactinaemia, increased appetite, hypertriglycerides, weight gain **GI:** constipation, xerostomia **CNS**: akathisia, asthenia, dizziness, tremor, dystonia	• Take at bedtime to help reduce daytime sedation • Only oral formulations registered with NPRA
Paliperidone	**Acute manic and mixed episodes** *Oral* - Initial, 6 mg once daily; titrate in increment of 3 mg/day every ≥5 days (Max dose: 12 mg/day)	**CrCl 50 - <80 mL/min:** Initial: 3 mg OD Max: 6 mg OD **CrCl 10 - <50 mL/min:** Initial: 1.5 mg OD Max:3 mg OD **CrCl <10 mL/min:** Not recommended	No adjustment provided in the manufacturer's labelling.	**Cardiac:** tachycardia, prolonged QT interval **Endocrine and metabolic**: weight gain, hyperprolactinaemia, **GI:** constipation, indigestion **CNS:** akathisia, dyskinesia, dystonia, extrapyramidal reaction, parkinsonism somnolence, tremor **Psychiatric:** anxiety	
Quetiapine	**Acute mania, acute episodes with mixed features and acute hypomania** *IR* -	No dosage adjustment necessary	**Child-Pugh class A and B:** Initial: 25 mg once daily; may increase by	**Cardiac**: orthostatic hypotension	

MEDICATION	DOSING GUIDE	RENAL DOSE	HEPATIC DOSE	COMMON/SIGNIFICANT ADVERSE EFFECTS	REMARKS
	100 - 200 mg once daily at bedtime or in 2 divided doses; titrate in increment of <200 mg/day *ER* - 300 mg once daily on Day 1, increase to 600 mg once daily on Day 2, then adjust accordingly (Max dose: 800 mg/day) **Acute depressive episode** *IR, ER* - 50 mg once daily at bedtime; increase to 100 mg once daily on Day 2. Further increase by 50 - 100 mg/day to reach usual target dose of 300 mg OD by Day 4 - 7. (Max dose: 300 mg/day)		25 - 50 mg/day based on response and tolerability until effective dose achieved, dividing total daily dose into 1 - 3 divided doses **Child-Pugh class C**: Avoid use	**Endocrine and metabolic**: hypercholesterolemia, hpertriglycerides, weight gain **GI**: xerostomia **CNS**: asthenia, dizziness, extrapyramidal reaction, headache, insomnia, somnolence **Psychiatric**: agitation	
Risperidone	**Acute mania, acute episodes with mixed features and acute hypomania** *Oral* - 1 - 3 mg/day in 1 or 2 divided doses, increase 1 mg/day at interval >24 hours (Max dose: 8 mg/day) *LAI* - 25 mg every 2 weeks; may increase dose in increment of 12.5 mg no sooner than every 4 weeks	**CrCl 30 - 60 mL/min:** Administer 50 - 75% of usual indication-specific dose **CrCl 10 - 30 mL/min:** Administer 50% of usual indication-specific dose **CrCl <10 mL/min:** Consider alternative agent. If necessary, administer 25% of	**Child-Pugh class C**: 0.5 mg twice daily; titration in increment of no more than 0.5 mg twice daily. Increase to dosages above 1.5 mg twice a day occurring at interval of at least 1 week.	**Endocrine and metabolic:** weight gain, hyperprolactinaemia **GI:** constipation, excessive salivation, indigestion, nausea, abdominal pain, vomiting, xerostomia **CNS:** akathisia, dizziness, dystonia, sedation, parkinsonism, tremor **Ophthalmic:** blurred vision **Psychiatric:** anxiety	Risperdal CONSTA is discontinued in Malaysia effective 31.07.2024

MEDICATION	DOSING GUIDE	RENAL DOSE	HEPATIC DOSE	COMMON/SIGNIFICANT ADVERSE EFFECTS	REMARKS
	(Max dose: 50 mg every 2 weeks)	usual indication-specific dose			
Ziprasidone	**Acute mania, acute episodes with mixed features and acute hypomania** *Oral -* Initial: 40 mg twice daily; increase to 60 or 80 mg twice daily. If indicated, maximum recommended dose may be reached as early as Day 2 of treatment. (Max dose: 80 mg twice daily)	No dosage adjustment is necessary	No dosage adjustment provided in the manufacturer's labelling. Use with caution as it undergoes extensive hepatic metabolism and systemic exposure may be increased.	**Endocrine and metabolic**: weight gain **GI**: constipation, indigestion, nausea **CNS**: akathisia, dizziness, extrapyramidal reaction, headache, somnolence, tremor **Cardiac:** prolong QTc interval	• Oral dose needs to be taken with a meal (≥500 calories) to be adequately absorbed • Only oral forms are registered under NPRA
SELECTIVE SEROTONIN REUPTAKE INHIBITOR (SSRI)					
Fluoxetine	**Acute depressive episode** *Oral -* Initial: 20 mg once daily in the evening with another AAP (e.g. olanzapine) or mood stabilisers; titrate in increment of 10 - 20 mg every 1 - 7 days (Usual dose range: 20 - 50 mg/day)	No dosage adjustment necessary	Use lower dose (up to 50%) reduction and less frequent interval in patients with cirrhosis and chronic liver disease	**GI:** diarrhoea, indigestion, loss of appetite, nausea, xerostomia **CNS**: asthenia, dizziness, insomnia, somnolence, tremor **Psychiatric**: anxiety, suicidal ideation **Respiratory**: pharyngitis, rhinitis **Other**: influenza-like illness	

Source:

1. Individual product information leaflet.
2. Clinical Drug Information, Inc. Wolters Kluwer. UpToDate® [Mobile application software].
3. Micromedex® Solution [Mobile application software].
4. MOH Clinical Pharmacy Working Committee. Clinical Pharmacokinetics Pharmacy Handbook. 2nd ed. Petaling Jaya: Pharmacy Practice & Development Division, MOH; 2019.
5. PDSB. Quest3+ Product Search Sistem Pendaftaran Produk & Perlesenan (Available at: https://quest3plus.bpfk.gov.my/pmo2/index.php).
6. Medicines and Healthcare Products Regulatory Agency (MHRA), UK:(Available at: https://www.gov.uk/drug-safety-update/valproate-re-analysis- of-study-on-risks-in-children-of-men-taking-valproate).

.7. National Health Service (NHS).Sodium Valproate: Medicine to treat epilepsy and BD (Available at: https://www.nhs.uk/medicines/sodium-valproate/).

Appendix 6

PSYCHOEDUCATION FOR BIPOLAR DISORDER

Duration	90 minutes per session
Total number of sessions	21 sessions, weekly
Methods of delivery	Individual or group (8 to 12 participants per group)

Major components

a. Information on illness features
b. Importance of treatment compliance
c. Early detection of prodromal signs of recurrence
d. Management of mood symptoms or co-morbid conditions
e. Lifestyle regularity

List of sessions and its description

1. Introduction
2. What is bipolar illness?
3. Causal and triggering factors
4. Symptoms (I): mania and hypomania
5. Symptoms (II): depression and mixed episodes
6. Course and outcome
7. Treatment (I): mood stabilisers
8. Treatment (II): antimanic agents
9. Treatment (III): antidepressants
10. Serum levels: lithium, carbamazepine and valproate
11. Pregnancy and genetic counselling
12. Psychopharmacology vs alternative therapies
13. Risk associated with treatment withdrawal
14. Alcohol and street drugs: risks in bipolar illness
15. Early detection of manic and hypomanic episodes
16. Early detection of depressive and mixed episodes
17. What to do when a new phase is detected?
18. Regularity
19. Stress management techniques
20. Problem-solving techniques
21. Final sessions

Source: Colom F, Vieta E, Martínez-Arán A, et al. A Randomized Trial on the Efficacy of Group Psychoeducation in the Prophylaxis of Recurrences in Bipolar Patients Whose Disease Is in Remission. Arch Gen Psychiatry. 2003;60(4):402-407.

Appendix 7

PARAMETERS FOR MONITORING DURING TREATMENT OF BIPOLAR DISEASE

Relevant physical examination and laboratory investigations should be performed before initiation of pharmacological treatment and at regular interval thereafter

Parameter	For all patients at first visit	Anti-psychotics	Lithium	Valproate	Carbamazepine
Weight (include waist size and BMI, if possible) *closer monitoring if rapid weight gain	Yes	Monthly for the first 3 months and annually thereafter*	Every 6 months and annually thereafter*	Every 3 months for the first year and annually thereafter*	Every 6 months and annually thereafter*
Blood pressure	Yes	At every visit			
Fasting blood sugar	Yes	Every 3 - 6 months and annually thereafter	Annually		
Electrocardiogram	Yes	If relevant abnormalities are detected, recheck after each dose increase		If clinically indicated	If relevant abnormalities are detected, recheck after each dose increase
Full blood count	Yes	Annually	If clinically indicated	Every 3 months for the first year and annually thereafter	Monthly for the first 3 months and annually thereafter
Thyroid function	Yes	Annually	Every 6 months, more often if indicated	NA	
Renal function	Yes	Annually	Every 6 months, more often if indicated	Annually	Every 6 months
Liver function	Yes	Annually		Every 3 months for the first year and annually thereafter	Monthly for the first 3 months and annually thereafter

Parameter	For all patients at first visit	Anti-psychotics	Lithium	Valproate	Carbamazepine
Lipid profile	Yes	Every 3 months for the first year and annually thereafter	Annually		
Drug serum level	NA		1 week after initiation and 1 week after every dose change until the level is stable, then every 3 - 6 months	Every 6 months only if there is ineffectiveness, poor adherence, or toxicity	
Serum calcium level	Yes for Lithium initiation	Annually	Every 6 months	NA	

Adapted from:

1. Ministry of Health. Clinical Practice Guidelines on Management of Bipolar Disorder. Putrajaya: MoH; 2014
2. Taylor DM, Gaughran F, Pillinger T. Maudsley Practice Guidelines for Physical Health Conditions in Psychiatry. London: Wiley Blackwell; 2020
3. Clinical Drug Information, Inc. Wolters Kluwer. UpToDate® [Mobile application software].
4. Micromedex® Solution [Mobile application software]

Appendix 8

COLLABORATIVE CARE MODEL CORE ELEMENTS

Element	Focus	Example
Patient self-management support	Coaching, problem-solving, or skills-focused psychotherapy or psychoeducation targeting ability to self-manage symptoms and participate more effectively in clinical care and decision-making.	Behavioural change strategies or coaching, illness-specific psychoeducation, shared decision-making interventions, cognitive-behavioural or problem-solving therapies.
Clinical information systems use	Facilitation of information flow from relevant clinical sources to treating clinicians for optimal management of individuals, panels or populations.	Case registries, reminder systems, provision of timely clinical information (e.g. laboratory and study results) regarding individuals in treatment and/or feedback to providers.
Delivery system redesign	Redefinition of work roles for physicians and support staff to facilitate anticipatory or preventive rather than reactive care; allocation of staff to implement other CCM elements e.g. self-management support and information flow.	Licensed clinical staff or health educators to provide psychoeducation, ensure provision of appropriately timed clinical information for specific cases, or review of panel or population data for anticipatory and preventive management needs.
Provider decision support	Facilitated provision of expert-level input to generalist clinicians managing cases without need for specialty consultation separated in time and space from clinical needs.	On-site or facilitated expert consultation or provision of simplified clinical practice guidelines supported by local clinician champions.
Community resource linkage	Support for clinical and non-clinical needs from resources outside the health care organisation proper.	Referral to peer support groups, exercise programmes, housing resources, home care programmes.
Health care organisation support	Organisation-level leadership and tangible resources to support CCM goals and practices.	Provision of adequate clinical staff for CCM training and implementation; support from key non-clinical services e.g. informatics; championship by organisation leadership, optimally with a commitment to sustainability after the research phase of the intervention ends.

Adapted:

1. Bauer MS, McBride L, Williford WO, et al. Collaborative care for bipolar disorder: part I. Intervention and implementation in a randomized effectiveness trial. Psychiatr Serv. 2006;57(7):927-36
2. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness. JAMA. 2002;288(14):1775-9

SUMMARY OF MEDICATIONS FOR BIPOLAR DISORDER WITH PREGNANCY AND LACTATION

MEDICATION		PREGNANCY	LACTATION
ANTIPSYCHOTICS	Aripiprazole*	• **HUMAN DATA SUGGEST LOW RISK.** • Aripiprazole crosses placenta. • Due to limited data, avoid use in pregnancy. However, if the mother's condition requires treatment with aripiprazole, the lowest effective dose, avoiding the first trimester if possible, should be used.	• **NOT RECOMMENDED DURING LACTATION**. • An alternate drug may be preferred, especially while nursing a newborn or preterm infant due to limited information available. • Aripiprazole can lower serum prolactin in a dose-related manner. Cases of lactation cessation have occurred, but cases of gynecomastia and galactorrhea have also been reported. • Weight loss and poor weight gain have been reported in breastfed infants whose mothers were taking aripiprazole. • ****Relative Infant Dose (RID)**: 0.7 - 8.3%.
	Asenapine*	• **NO HUMAN DATA - ANIMAL DATA SUGGEST MODERATE RISK.** • There are no adequate data from the use of asenapine in pregnant women. However, maternal and embryo-foetal toxic effects were found in animal studies. • Should not be used during pregnancy unless clearly necessary and only if the potential benefit outweighs potential risk to the foetus.	• Manufacturer's labelling recommends that women receiving asenapine should not breastfeed. • If asenapine is required by the mother, it is not a reason to discontinue breastfeeding. However, **an alternate drug may be preferred**, especially while nursing a newborn or preterm infant.
	Cariprazine*	• **NO HUMAN DATA - ANIMAL DATA SUGGEST MODERATE RISK.** • Absence of human pregnancy data prevents a better assessment of the embryo-foetal risk.	• No information is available on the use of cariprazine during lactation. An alternate drug may be preferred until more data become available.
	Clozapine*	• **COMPATIBLE - MATERNAL BENEFIT >> EMBRYO-FOETAL RISK**. • Clozapine crosses placenta and can be detected in foetal blood and amniotic fluid. • Other agents are preferred for use in pregnancy; however, if indicated, may be used in women who cannot be switched to recommended APs.	• **NOT RECOMMENDED DURING LACTATION**. • Due to limited information with clozapine during breastfeeding, and sedation and adverse haematologic effects have been reported in breastfed infants, other agents are preferred. • Monitoring: ○ Monitor infant for excessive sedation and periodic monitoring of the infant's white blood cell count is advisable.
	Haloperidol*	• **LIMITED HUMAN DATA - ANIMAL DATA SUGGEST MODERATE RISK** • Neonatal tardive dyskinesia may be an uncommon complication of exposure throughout gestation.	• **POSSIBLE TO USE CAUTIOUSLY DURING LACTATION.** • Limited information indicates that maternal doses of haloperidol up to 10 mg daily produce low levels in milk and usually do not affect the breastfed infant. Very limited long-term follow-up data indicate no

MEDICATION		PREGNANCY	LACTATION
ANTIPSYCHOTICS		• Avoid first trimester exposure if possible. • **Preferred drug if first generation APs is needed in pregnant patients. However, minimum effective dose should be used to reduce risk of AEs.**	adverse developmental effects when haloperidol is used alone. However, use with other APs occasionally might negatively affect the infant. • Monitoring: ○ Monitor infant for drowsiness and developmental milestones, especially if other APs are used concurrently.
	Lumateperone*	• Insufficient data to establish any drug-associated risk for birth defects, miscarriage, maternal or foetal outcomes.	• No information is available on clinical use of lumateperone during breastfeeding. • However, amounts of lumateperone and its metabolites in breastmilk appear to be low and would not be expected to cause any AEs in breastfed infants. • If lumateperone is required by the mother, it is not a reason to discontinue breastfeeding
	Lurasidone*	• **LIMITED HUMAN DATA - POTENTIAL RISK IN THIRD TRIMESTER.**	• Lurasidone is >99% bound to plasma proteins, so it is unlikely that it would be excreted into milk in sufficient amounts to affect a breastfed infant. • Due to limited information, **an alternate drug may be preferred**, especially while nursing a newborn or preterm infant.
	Olanzapine*	• **COMPATIBLE - MATERNAL BENEFIT >> EMBRYO-FOETAL RISK.** • Olanzapine crosses placenta. • No established olanzapine-associated risk of major birth defects, miscarriage or adverse maternal or foetal outcomes following maternal use. • Pharmacokinetics properties of olanzapine are not significantly altered by pregnancy. However, serum levels may change (even at a stable dose, possibly due to decreased CYP1A2 activity during second and third trimester. • **Potential for excessive maternal weight gain and development of gestational diabetes**.	• **ACCEPTABLE DURING LACTATION.** • **First-line of AAPs during breastfeeding**. • Maternal doses of olanzapine up to 20 mg daily produce low levels in milk and undetectable levels in the serum of breastfed infants. • ****RID**: 0.3 - 4%. • Monitoring: ○ Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalisation. ○ Monitor infant for drowsiness, irritability, poor feeding, extrapyramidal symptoms and developmental milestones, especially if other APs are used concurrently.
	Paliperidone*	• **LIMITED HUMAN DATA - ANIMAL DATA SUGGEST LOW RISK.** • Information specific to paliperidone in pregnancy is limited. However, if the mother requires its use, the benefits probably outweigh foetal risk.	• **POSSIBLE TO USE CAUTIOUSLY DURING LACTATION.** • Due to little long-term follow-up data, other agents may be preferred, especially while nursing a newborn or preterm infant. • Monitoring: ○ Monitor breastfed infants for drowsiness, adequate growth and weight gain, jitteriness, tremors and abnormal movements.

MEDICATION		PREGNANCY	LACTATION
ANTIPSYCHOTICS	Quetiapine*	• **COMPATIBLE - MATERNAL BENEFIT >> EMBRYO-FOETAL RISK.** • Quetiapine crosses placenta. • If treatment with AAPs is needed in a woman planning a pregnancy, use of quetiapine may be considered.	• **POSSIBLE TO USE DURING LACTATION.** • **First- or second-choice agent during breastfeeding.** • Limited long-term follow-up of infants exposed to quetiapine indicates that infants generally developed normally. • Cases of galactorrhoea and milk ejection have been reported rarely. • ****RID**: 0.02 - 0.1%. • Monitoring: ○ Monitor infant for drowsiness and developmental milestones, especially if other APs are used concurrently.
	Risperidone*	• **COMPATIBLE - MATERNAL BENEFIT >> EMBRYO-FOETAL RISK.** • Risperidone and its metabolite cross placenta. • Risperidone can increase serum prolactin levels which may decrease fertility in females on risperidone.	• **POSSIBLE TO USE CAUTIOUSLY DURING LACTATION.** • **Second line of AAPs during breastfeeding** due to limited data available and higher excretion into milk relative to other agents. Other agents may be preferred, especially while nursing a newborn or preterm infant • Sedation, failure to thrive, jitteriness, tremors, abnormal muscle movements and respiratory depression have been reported in infants exposed to risperidone in milk. • Monitoring: ○ Monitor infant for drowsiness, weight gain, tremors, abnormal respiratory rate, abnormal muscle movements and developmental milestones, especially if other APs are used concurrently. • ****RID**: 2.3% - 4.7%.
	Ziprasidone*	• **LIMITED HUMAN DATA - ANIMAL DATA SUGGEST RISK.** • Safest course is to avoid ziprasidone in pregnancy due to limited human data. • However, if a woman requires treatment in pregnancy, medication should not be withheld. Instead, an informed consent on the unknown risk to her embryo-foetal should be obtained.	• **POSSIBLE TO USE CAUTIOUSLY DURING LACTATION.** • Due to limited data, **other APs may be preferred**, especially while nursing a newborn or preterm infant. • Monitoring: ○ Breastfed infants should be monitored for excess sedation, irritability, poor feeding and EPS e.g. tremors and abnormal muscle movements.

MEDICATION		PREGNANCY	LACTATION
MOOD STABILISERS	Carbamazepine	• **NOT RECOMMENDED FOR TREATMENT OF BIPOLAR DISORDER**. • Carbamazepine and its active metabolite cross the placenta; concentrations are variable. • May be associated with teratogenic effects, including spina bifida, craniofacial defects, cardiovascular malformations and developmental delays. Risk of congenital malformations increases with higher doses. • Foetal carbamazepine syndrome has been proposed consisting of minor craniofacial defects, fingernail hypoplasia and developmental delay.	• **POSSIBLE AND COMPATIBLE TO USE IN LACTATION.** • Breastfeeding during carbamazepine monotherapy does not appear to adversely affect infant growth or development. • Carbamazepine and its active metabolite have relatively high levels in breastmilk and breastfed infants have serum levels that are sometimes measurable, but usually well below the therapeutic range. • Most infants have no adverse reactions, but sedation, poor sucking, withdrawal reactions and cases of hepatic dysfunction have been reported. • Monitoring: ○ Monitor infant for jaundice, drowsiness, adequate weight gain and developmental milestones, especially in younger, exclusively breastfed infants and when using combinations of anticonvulsant or psychotropic drugs. ○ Measuring infant serum carbamazepine levels is not recommended; however breastfeeding should be discontinued if AEs are observed.
	Lamotrigine	• **COMPATIBLE - MATERNAL BENEFIT >> EMBRYO-FOETAL RISK**. • Crosses the human placenta and can be measured in the plasma of exposed newborns. • Significant risk for oral clefts following first trimester exposure. • Increased risk of malformations may be associated with larger doses. • Clearance of lamotrigine increases by >50% starting early in pregnancy and reverts to the non-pregnant state quickly after delivery. Pregnant women may require dose adjustments in order to maintain clinical response. • Monitoring: ○ Where facilities are available, baseline serum concentrations should be measured once or twice prior to pregnancy. Monitoring can then be continued up to monthly during pregnancy and every second day during the first week post-partum.	• **POSSIBLE TO USE IN LACTATION.** • Lamotrigine monotherapy does not appear to adversely affect growth or development in most infants. • However, neonates and young infants are at risk for high serum levels because maternal serum and milk levels can rise to high levels postpartum if lamotrigine dosage has been increased during pregnancy but not reduced after delivery to the pre-pregnancy dosage. • If an infant rash occurs, breastfeeding should be discontinued until the cause can be established. • Breastfeeding should be discontinued in infants with lamotrigine toxicity. • Monitoring: ○ Breastfed infants should be carefully monitored for side effects e.g. apnoea, rash, drowsiness or poor sucking, including measurement of serum levels to rule out toxicity if there is a concern.

MEDICATION		PREGNANCY	LACTATION
			○ Monitoring of infant's platelet count, liver function and serum concentrations before and after increases in maternal lamotrigine dosage might also be advisable. • ****RID**: 5 - 31%.
	Lithium	• **HUMAN DATA SUGGEST RISK.** • Foetal echocardiography between 16 and 20 weeks gestation should be considered in a woman with first-trimester lithium exposure because of the potential increased risk of cardiac malformations. • Incidence of AEs may be associated with higher maternal doses. • Due to pregnancy-induced physiologic changes, maternal serum concentrations should be monitored and dosage adjusted during pregnancy. • Discontinuing lithium 24 - 48 hours before Caesarean section delivery or at the onset of spontaneous labour and resuming the pre-pregnancy lithium dose immediately after delivery should minimise the infant's serum lithium concentration at birth. • Use of drug near term may produce severe toxicity in the newborn which is usually reversible.	• **POSSIBLE TO USE CAUTIOUSLY IN LACTATION.** • Lithium excretion into breastmilk and concentrations in infant serum are highly variable; most sources do not consider it an absolute contraindication in healthy full-term infants, especially in infants >2 months of age and during lithium monotherapy. • Long-term effects of lithium on infants are not certain; however, limited data indicate no obvious problems in growth and development. • Lithium in milk can adversely affect the infant acutely when its elimination is impaired (dehydration/newborn/premature infants). Infants who are preterm, dehydrated or have an infection should receive hydration and be assessed for lithium toxicity. • As maternal lithium requirements and dosage may be increased during pregnancy, maternal serum levels should be monitored frequently postpartum and dosage reduced as necessary to avoid excessive infant exposure via breastmilk. • If infant's serum lithium level is elevated, reducing the percentage of breastfeeding can decrease it. • ****RID**: 0 - 30%. • Monitoring: ○ Monitor infant for lethargy, growth and feeding problems. ○ Monitor infant serum lithium, serum creatinine, BUN and TSH if clinical concerns arise.
	Valproate	• **CONTRAINDICATED and an alternative treatment should be decided on, with appropriate specialist consultation, for women planning pregnancy.** • High teratogenic potential and children exposed in-utero to valproate have a high risk congenital malformations and neurodevelopmental disorders.	• **POSSIBLE TO USE IN LACTATION.** • Valproate levels in breastmilk are low and infant's serum levels range from undetectable to low. Breastfeeding during valproate monotherapy does not appear to adversely affect infant growth or development. • Combination therapy with sedating anticonvulsants or psychotropics

MEDICATION		PREGNANCY	LACTATION
	Valproate	**CONTRAINDICATED and an alternative treatment should be decided on, with appropriate specialist consultation, for women planning pregnancy.** High teratogenic potential and children exposed in-utero to valproate have a high risk congenital malformations and neurodevelopmental disorders. **Pregnancy test** Treatment must not be initiated in women of child bearing potential without a negative pregnancy test to rule out unintended use in pregnancy. **Contraception** Patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. **Pregnancy Planning** Treatment with valproate should be discontinued prior to conception and before contraception is discontinued. If needed, alternative treatment options should be considered. **In case of pregnancy** Refer to a specialist to re-evaluate treatment with valproate and consider alternative options.	• **POSSIBLE TO USE IN LACTATION.** • Valproate levels in breastmilk are low and infant's serum levels range from undetectable to low. Breastfeeding during valproate monotherapy does not appear to adversely affect infant growth or development. • Combination therapy with sedating anticonvulsants or psychotropics may result in infant's sedation or withdrawal reactions. • Monitoring: ○ Breastfed infants should be monitored for jaundice. ○ Breastfed infants should be monitored for jaundice unusual bruising or bleeding and other signs of liver damage during maternal therapy.

* Risk of EPS and/or withdrawal symptoms in newborns if APs is used in the third trimester.

** In general, 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%.[4,5]

Source:

1. Briggs GG, Towers CV, Forinash AB. Briggs Drugs in Pregnancy and Lactation 14th ed. Wolters Kluwer; 2022.
2. Drugs and Lactation Database (Lactmed) (Available at: https://www.ncbi.nlm.nih.gov/books/NBK501922/).
3. Uguz F. A New Safety Scoring System for the Use of Psychotropic Drugs During Lactation. Am J Ther. 2021;28(1):e118-e126.
4. Larsen ER, Damkier P, Pedersen LH, et.al. Use of psychotropic drugs during pregnancy and breastfeeding. Acta Psychiatr Scand Suppl. 2015;(445): 1-28.
5. Clinical Drug Information, Inc. Wolters Kluwer. UpToDate® [Mobile application software].

Appendix 10a

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ANNUAL RISK ACKNOWLEDGEMENT FORM
PART A. TO BE COMPLETED AND SIGNED BY THE PRESCRIBER

Patient's name *:* _____
MRN/IC No. *:* _____
Address *:* _____

For girls and women of childbearing age treated with Sodium Valproate < Product Name >. Please read, complete and sign this form during a visit with the prescriber: at treatment initiation, during annual visit and when the woman plans pregnancy or is pregnant.

Name of patient or care-giver: _____
I confirm the above-named patient needs sodium valproate because:
- □ this patient does not respond adequately to other treatments, or
- □ this patient does not tolerate other treatments,
- □ that this patient is stable on.....dose and she is reluctant to change to other,
- □ other reasons .....(to specify)

I have discussed the following information with the above-named patient or caregiver:
- □ The overall risk to fetus and children whose mothers are exposed to sodium valproate during pregnancy are :
  - approximately 10% chance of birth defects and
  - up to 30% to 40%, chance of a wide range of early developmental problems that can lead to learning difficulties.
- □ Sodium valproate should not be used in pregnancy (except in rare situations such as epileptic patients that are resistant or intolerant to other treatments)
- □ The need for regular (at least annually) review and the need to continue sodium valproate treatment by the prescriber
- □ The need for a negative pregnancy test at treatment initiation and as required there-after (if child-bearing age)
- □ The need for an effective contraception without interruption during the entire duration of sodium valproate (if childbearing age).
- □ To need to arrange an appointment with her doctor as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception, and before contraception is discontinued.
- □ The need to contact her doctor immediately for an urgent review of the treatment in case of suspected or inadvertent pregnancy
- □ In case of pregnancy, I confirm that this patient:
  - receives the lowest possible effective dose of sodium valproate to minimise the possible harmful effect on the unborn
  - is informed about the possibilities of pregnancy support or counselling and appropriate monitoring of her baby if she is pregnant

Name of Prescriber :_____Signature _____Date_____

Part A and B shall be completed. All boxes shall be ticked, and the form signed by the prescriber. This is to make sure that all the risks and information related to the use of sodium valproate during pregnancy have been understood.
Part A - to be kept by the prescriber

ANNUAL RISK ACKNOWLEDGEMENT FORM
PART B. TO BE COMPLETED BY THE PRESCRIBER AND SIGNED BY THE PATIENT OR CAREGIVER

Patient's name *: _____*
MRN/IC No. *: _____*
Address *: _____*

For girls and women of childbearing age treated with Sodium Valproate < Product Name >. Please read, complete and sign this form during a visit with the prescriber: at treatment initiation, during annual visit and when the woman plans pregnancy or is pregnant.

I discussed the following with my doctor and understand

- □ Why I need sodium valproate rather than other medicine.
- □ I have decided to continue with the treatment after being advised of the risk.
- □ That I should visit the prescriber regularly (at least annually) to review whether sodium valproate treatment remains the best option for me.
- □ The overall risk to fetus and children whose mothers took sodium valproate during pregnancy are:
  - an approximately 10% chance of birth defects
  - up to 30 to 40 % chance of a wide range of early developmental problems that can lead to significant learning difficulties
- □ Why I need a negative pregnancy test at testament initiation and if needed thereafter (if *childbearing age*).
- □ That I must use effective contraception without interruption during the entire duration of treatment with sodium valproate (*if childbearing age*).
- □ We discussed the possibilities of effective contraception or we planned a consultation with a professional who is experienced in advising on effective contraception.
- □ The need for regular (at least annually) review and the need to continue sodium valproate treatment by the prescriber.
- □ The need to consult my doctor as soon as I am planning to become pregnant to ensure timely discussion and switching to alternative treatment options prior to conception, and before conception is discontinued.
- □ That I should request an **urgent** appointment if I think I am pregnant.

In case of a pregnancy I have discussed the following with my doctor and understand:

- the possibilities of pregnancy support or counseling
- the need to appropriate monitoring of my baby if I am pregnant.

Name of Patient/Caregiver:_____Signature _____Date_____
Name of Prescriber : _____Signature _____Date_____

Part B shall be completed. All boxes shall be ticked, and the form signed by the prescriber and the patient. This is to make sure that all the risks and information related to the use of sodium valproate during pregnancy have been understood.
Part B - to be given to the patient
- a copy kept by the prescriber

Appendix 10b

BORANG PENGAKUAN RISIKO TAHUNAN
BAHAGIAN A: UNTUK DILENGKAPKAN DAN DITANDATANGANI OLEH PEGAWAI PERUBATAN

Nama Pesakit **:** _____
MRN/No. Kad pengenalan **:** _____
Alamat **:** _____

Untuk kanak-kanak perempuan dan wanita yang dalam lingkungan umur boleh melahirkan anak dan dirawat dengan ***Sodium Valproate***. Sila baca, lengkapkan dan tandatangan borang ini sebelum memulakan rawatan,semasa rawatan tahunan dan apabila wanita tersebut bercadang untuk mengandung atau sedang mengandung.

Nama pesakit atau penjaga: _____ saya mengesahkan bahawa penama di atas memerlukan rawatan sodium valproate kerana

- □ pesakit tidak respon dengan secukupnya terhadap rawatan ubat yang lain, Atau
- □ pesakit tidak serasi dengan rawatan yang lain, Atau
- □ pesakit telah stabil dengan ..... dos dan enggan untuk menukar ubat yang lain, Atau
- □ sebab-sebab lain ..... (jelaskan)

Saya telah berbincang mengenai maklumat dengan pesakit atau penjaga:

- □ Risiko keseluruhan terhadap janin dan kanak-kanak di mana ibunya terdedah kepada sodium valproate semasa mengandung adalah lebih kurang 10% risiko untuk mendapat kecacatan kelahiran manakala risiko sebanyak 30% ke 40% untuk mendapat masalah perkembangan awal yang boleh menyebabkan masalah pembelajaran.
- □ Sodium valproate tidak sepatutnya diberikan kepada ibu mengandung kecuali dalam situasi tertentu seperti pesakit epilepsi yang sukar dirawat dengan ubatan lain.
- □ Keperluan untuk pemantauan secara berkala (sekurangnya setiap tahun) dan keperluan untuk melihat samada rawatan sodium valproate perlu diteruskan.
- □ Keperluan untuk memastikan ujian kehamilan adalah negatif sebelum dan selepas rawatan dimulakan.
- □ Keperluan untuk mengambil langkah kontraseptif yang berterusan sepanjang rawatan sodium valproate diberikan.
- □ Untuk memastikan pesakit dibawah pemantaun doktor obstetrik jika merancang untuk hamil dan berbincang untuk rawatan alternatif serta pilihan ubatan psikiatri yang lain sebelum mengandung atau sebelum perancang kehamilan dihentikan.
- □ Pesakit perlu memberitahu doktor dan berjumpa untuk temujanji susulan secepat mungkin sekiranya didapati atau disyaki hamil.
- □ Untuk kes pesakit yang sudah hamil. Saya sahkan pesakit yang hamil ini:
  - Hanya menerima dos efektif yang minimum untuk mengurangkan risiko kecacatan janin.
  - Telah dimaklumkan tentang sokongan kaunseling dan pemantauan rapi terhadap kandungan sepanjang semasa proses kehamilan.

Nama Penerima :_____Tarikh tandatangan :_____

Bahagian A dan B hendaklah dilengkapkan. Kesemua kotak hendaklah ditanda dan borang perlu ditandatangan oleh pegawai perubatan. Ini untuk memastikan semua risiko dan maklumat tentang penggunaan sodium valproate semasa mengandung telah difahami.
Bahagian A - untuk simpanan pegawai perubatan.

BORANG PENGAKUAN RISIKO TAHUNAN
BAHAGIAN B: UNTUK DILENGKAPKAN OLEH PEGAWAI PERUBATAN DAN DITANDATANGANI OLEH PESAKIT ATAU PENJAGA

Nama Pesakit **: _____**
MRN/No. Kad pengenalan **: _____**
Alamat **: _____**

Untuk kanak-kanak perempuan dan wanita yang dalam lingkungan umur melahirkan anak dan dirawat dengan ***Sodium Valproate*** .Sila baca, lengkapkan dan tandatangan borang ini sebelum memulakan rawatan,semasa rawatan tahunan dan apabila wanita tersebut bercadang untuk mengandung atau sedang mengandung.

Saya telah berbincang dengan pegawai perubatan mengenai maklumat berikut:

- □ Keperluan untuk saya mengambil sodium valproate berbanding ubatan lain.
- □ Saya telah memutuskan untuk meneruskan rawatan dengan sodium valproate selepas dimaklumkan mengenai risiko.
- □ Saya akan hadir untuk temujanji secara berkala (sekurangnya setahun sekali) untuk memantau samada rawatan sodium valproate kekal sebagai pilihan terbaik untuk rawatan saya.
- □ Risiko keseluruhan terhadap janin dan kanak-kanak di mana ibunya terdedah kepada sodium valproate semasa mengandung adalah lebih kurang 10% risiko untuk mendapat kecacatan kelahiran manakala risiko sebanyak 30% ke 40% untuk mendapat masalah perkembangan awal yang boleh menyebabkan masalah pembelajaran.
- □ Kenapa saya perlu pastikan ujian kehamilan sebelum dan selepas memulakan rawatan (untuk wanita dalam lingkungan umur melahirkan anak).
- □ Saya perlu menggunakan kaedah kontraseptif yang efektif tanpa gangguan sepanjang rawatan saya dengan sodium valproate (untuk wanita dalam lingkungan umur melahirkan anak).
- □ Kami telah berbincang mengenai kebarangkalian kontraseptif yang efektif atau kami akan mendapatkan konsultasi dengan pegawai kesihatan yang arif dengan kontraseptif.
- □ Saya perlu pemantauan secara berkala (sekurangnya setiap tahun) dan keperluan untuk melihat samada rawatan sodium valproate perlu diteruskan.
- □ Saya perlu memastikan saya dibawah pemantaun doktor obstetrik jika merancang untuk hamil dan berbincang untuk rawatan alternatif serta pilihan ubatan psikiatri yang lain sebelum mengandung atau sebelum perancang kehamilan dihentikan.
- □ Saya perlu mendapatkan temujanji serta merta jika didapati saya mengandung.
- □ Sekiranya saya mengandung, saya akan berbincang dengan pegawai perubatan mengenai:
  - Kebarangkalian untuk mendapatkan sokongan dan kaunseling semasa mengandung
  - Keperluan untuk mendapatkan pemantauan bayi saya sekiranya saya mengandung

Nama Pesakit/Penjaga: _____Tarikh tandatangan: _____
Nama Penerima: _____Tandatangan: _____Tarikh: _____

Bahagian B hendaklah dilengkapkan: semua kotak perlu ditanda dan borang perlu ditandatangani oleh pegawai perubatan dan pesakit. Ini untuk memastikan semua risiko dan maklumat tentang penggunaan sodium valproate semasa mengandung telah difahami.
Bahagian B - untuk simpanan pesakit, satu salinan untuk simpanan pegawai perubatan.

SUGGESTED PAEDIATRIC MEDICATIONS DOSING

MEDICATION	DOSING GUIDE	RENAL	HEPATIC	REMARKS
ATYPICAL ANTIPSYCHOTICS				
Aripiprazole	**Acute mania or episodes with mixed features** **10 to 17 years old:** *Oral* D1: 2 mg once daily for 2 days; D3: 5 mg once daily for 2 days; D5: 10 mg once daily; may titrate subsequent dose in increment of 5 mg/day) (Usual target dose: 10 mg once daily) (Max dose: 30 mg daily)	No dosage adjusment necessary.	No dosage adjusment necessary.	• Only strength 5 mg, 10 mg and 15 mg are registered with NPRA. • Commonly seen ADR in paediatric populations: somnolence, extrapyramidal reaction, fatigue, nausea, akathisia, blurred vision, salivary hypersecretion, dizziness.
Asenapine	**Acute mania or episodes with mixed features** **10 to 17 years old:** *Sublingual* D1: 2.5 mg twice daily; D4: May increase to 5 mg twice daily; D7: May increase to 10 mg twice daily (Max dose: 10 mg twice daily)	No dosage adjusment necessary.	**Severe hepatic impairment (Child-Pugh Class C):** Use is contraindicated.	• Only strength 5 mg and 10 mg are registered with NPRA. • Commonly seen ADR in paediatric populations: somnolence, dizziness, dysgeusia, oral paraesthesia, nausea, increased appetite, fatigue, increased weight.
Lurasidone	**Bipolar disorder (depressive episodes)** **10 to 17 years old** *Oral* 20 mg once daily; may titrate after 1 week based on response although dose titration is not required (Usual target dose: 20 mg - 40 mg once daily) (Max dose: 80 mg/day)	**CrCl <50 mL/minute:** Reduce initial dose. Do not exceed an initial dose of 20 mg daily (Max dose: 80 mg/day).	**Moderate impairment:** Reduce initial dose. Do not exceed an initial dose of 20 mg daily (Max dose: 80 mg/day)	• Take with a meal (>350 calories) for adequate absorption. • Commonly seen ADR in paediatric populations: nausea, weight gain, insomnia.

MEDICATION	DOSING GUIDE	RENAL	HEPATIC	REMARKS
			Severe impairment: Reduce initial dose. Do not exceed an initial dose of 20 mg daily (Max dose: 40 mg/day)	
Olanzapine	**Acute mania or episodes with mixed features** **13 to 17 years old** *Oral* Initial: 2.5 - 5 mg once daily Dose titration: Increment/decrement of 2.5 or 5 mg at weekly interval (Usual target dose: 10 mg/day) (Max dose: 20 mg/day) **Depressive episodes (in combination with fluoxetine)** **10 to 17 years old** *Oral* Initial: 2.5 mg of oral olanzapine and 20 mg of oral fluoxetine once daily (Max dose: 12 mg olanzapine/50 mg fluoxetine)	No dosage adjustment is necessary as not removed by dialysis.	Use with caution. Dosage adjustment may be necessary; however, no specific recommendations exist.	• Only strength 5 mg and 10 mg are registered with NPRA. • Commonly seen ADR in paediatric populations: sedation,weight gain, increased appetite, headache, fatigue, dizziness, dry mouth, abdominal pain. • Fixed dose OFC capsule is not available in Malaysian market.
Quetiapine	**Mania or episodes with mixed features** **10 to 17 years old** *Oral, immediate release (IR)* D1: 25 mg twice daily D2: 50 mg twice daily D3: 100 mg twice daily D4: 150 mg twice daily D5: 200 mg twice daily Dose titration: Increment of ≤100 mg/day based on clinical response and tolerability (Usual dosage range: 200 - 300 mg twice daily)	No dosage adjustment is necessary.	*Immediate release* 25 mg once daily; titrate by 25 - 50 mg/day to effective dose based on individual clinical response and tolerability. *Extended release* 50 mg once daily; titrate by 50 mg once	• Commonly seen ADR in paediatric populations: somnolence, dizziness, fatigue, increased appetite, nausea, vomiting, dry mouth, tachycardia, weight gain. • Switching from IR to ER: May convert at the equivalent total daily dose and administer once daily; individual dosage adjustments may be necessary.

MEDICATION	DOSING GUIDE	RENAL	HEPATIC	REMARKS
	(Max dose: 600 mg/day) **Total daily doses may also be divided into 3 doses per day *Oral, extended release (ER)* D1: 50 mg once daily D2: 100 mg once daily D3: 200 mg once daily D4: 300 mg oce daily D5: 400 mg once daily (Usual dosage range: 400 - 600 mg once daily) (Max dose: 600 mg/day)		daily to effective dose based on individual clinical response and tolerability.	
Risperidone	**Mania** **10 to 17 years old** *Oral* Initial: 0.5 mg once daily Titrate in increment of 0.5 - 1 mg/day at intervals >24 hours Usual target dose: 1 - 2.5 mg/day **Doses >2.5mg/day do not confer additional benefit and are associated with increased adverse events.	No pediatric-specific dosage recommendations. Based on experience in adult patients, dosing adjustments suggested.	No pediatric-specific dosage recommendations. Based on experience in adult patients, dosing adjustments suggested.	• No specific FDA/ NPRA approved dose in children/adolescent population for use of risperidone LAI in bipolar disorder.* • In patients with persistent somnolence, administering half the daily dose twice daily may be beneficial. • Well accepted for treatment of behavioural symptoms in children and adolescents, but may have more sedation and weight gain in paediatric populations than in adult populations. • Other commonly seen side effects in paediatric population include cough, nasal congestion, nasopharyngitis, fatigue.

MEDICATION	DOSING GUIDE	RENAL	HEPATIC	REMARKS
Ziprasidone				• No specific FDA/ NPRA approved dose in children/adolescent population for use of ziprasidone in bipolar disorder*.
ANTIDEPRESSANT				
Fluoxetine	**Depressive episodes (in combination with olanzapine)** *Oral* **≥10 years old and adolescents** 20 mg orally once daily in the evening in combination with olanzapine 2.5 mg; titrate to clinical effect and tolerability (Max: 50 mg/day)	**≥7 years old and adolescents:** Adjusment not routinely needed *With chronic administration, additional accumulation of fluoxetine or norfluoxetine may occur in patients with severely impaired renal function.	**≥7 years old and adolescents:** Lower doses or less frequent administration are recommended. *Elimination half-life of fluoxetine is prolonged in patients with hepatic impairment.	• Fixed dose OFC capsule is not available in Malaysian market.
MOOD STABILISERS				
Lithium	**Acute mania or episodes with mixed features** *Oral* **≥7 years old, weight <30 kg**: Initial: 300 mg twice daily; Dose titration: Increment of 300 mg/weekly **7 years old, weight >30 kg** Initial: 300 mg 3 times daily; Dose titration: Increment of 300 mg every 3 days	**CrCl 30 - 89 ml/min:** Initiate therapy with low dose. **CrCl <30 ml/min**: Avoid use.	No dosage adjustments provided in the manufacturer's labeling.	• Commonly seen ADR in paediatric populations: nausea/vomiting, polyuria, thyroid abnormalities, tremor, thirst/polydipsia, dizziness, rash/dermatitis, ataxia/gait disturbance, reduced appetite, blurry vision. • Only immediate release lithium carbonate formulation is registered with NPRA.

MEDICATION	DOSING GUIDE		RENAL	HEPATIC	REMARKS
	Usual Dose Range:				• Prior to treatment initiation: ensure prompt and accurate serum lithium levels can be determined since toxicity can occur at doses closes to therapeutic levels.
		>7 years old, wt <30 kg	**>7 years old, weight >30 kg**		
	Acute therapy dose range	600 - 1500 mg in divided daily dose	1200 - 1800 mg in divided daily dose		

* At the time of writing, there is no specific FDA/NPRA approval dose for use in children/adolescent population

Source:

1. Clinical Drug Information, Inc. Wolters Kluwer. UpToDate® [Mobile application software]
2. Micromedex® Solution [Mobile application software]
3. Invidual product information leaflet
4. Stahl SM. Stahl's essential psychopharmacology: Prescriber's guide. Cambridge University Press; 2014
5. Quest3+ Product Search Sistem Pendaftaran Produk & Perlesenan (Available at: https://quest3plus.bpfk.gov.my/pmo2/index.php)

LIST OF ABBREVIATIONS

AD	anti-depressant
ADHD	attention-deficit hyperactive disorder
AE(s)	adverse event(s)
AP	antipsychotic
AAP	atypical antipsychotic
ACT	Acceptance and Commitment Therapy
ALT	alanine aminotransferase
ASPD	antisocial personality disorder
AST	aspartate aminotransferase
BAI	Beck Anxiety Inventory
BD	bipolar disorder
BD I	bipolar I disorder
BD II	bipolar II disorder
BI	bipolarity index
BSDS	Bipolar spectrum diagnostic scale
BPD	Borderline personality disorder
BPRS	Brief Psychotic Rating Scale
BW	birth weight
CAE	customised adherence enhancement
CAM	complementary and alternative medicine
CANMAT	Canadian Network for Mood and Anxiety Treatments
CBD	cannabidiol
CBT	cognitive behavioural therapy
CGI-BP	Clinical Global Impression-bipolar disorder
CGI-BP-S	CGI-S-Bipolar Version-Severity
CU	cannabis use
DBT	dialectical behaviour therapy
DSM-5-TR	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition, text revision
ECG	electrocardiogram
ECT	electroconvulsive therapy
EPA	eicosapentaenoic acid
EPS	extra-pyramidal symptoms
ER	extended release
FDA	Food and Drug Administration
FFT	family-focused therapy
FGA	first generation antipsychotic
GAD-7	Generalized Anxiety Disorder-7 Scale

GRADE	Grading of Recommendations, Assessments, Development and Evaluations
HADS	Hospital Anxiety and Depression Scale
HCL-32	Hypomania checklist
HCP	healthcare practitioner
ICD-11	International Classification of Diseases Eleventh Revision
IDS	Inventory of Depressive Symptomatology (IDS)
IPSRT	Interpersonal and Social Rhythm Therapy (IPSRT)
MSRS	Manic State Rating Scale
MARS	Medication Adherence Rating Scale
MDQ	Mood disorder questionaire
NMA	network meta-analysis
HAM-D	Hamilton Depression Rating Scale
HR	hazard ratio
IDS	Inventory of Depressive Symptomatology
IQ	Intelligence Quotient
IR	immediate release
LAI	long-acting injectable
Li	lithium
LSMD	least squares mean difference
MA	meta-analysis
MADRS	Montgomery-Asberg Depression Rating Scale
MBCT	mindfulness-based cognitive therapy
MDQ	Mood disorder questionnaire
MEMS	medication event monitoring system
mg	milligramme
MSRS	Manic State Rating Scale
NMA	network meta-analysis
NOS	Newcastle-Ottawa Scale
NPRA	National Pharmaceutical Regulatory Agency
NS	non-significant
OFC	olanzapine/fluoxetine combination
QoL	quality of life
QIDS-SR	Quick Inventory of Depressive Symptomatology Self-Report
OR	odds ratio
PANSS	Positive and Negative Syndrome Scale
RANZCP	Royal Australian and New Zealand College of Psychiatrist
RCT(s)	randomised controlled trial(s)
RID	Relative Infant Dose
RMS	Rapid mood screener

RoB	risk of bias
rTMS	repetitive transcranial magnetic stimulation
SGA	second generation antipsychotic
SMD	standard mean difference
SMS	short messaging service
SR	systematic review
SUCRA	Surface Under the Cumulative Ranking Curve
SUD	substance use disorder
TAU	treatment as usual
TBS	theta burst stimulation
TRQ	Tablet Routine Questionnaire
WHO	World Health Organisation
YMRS	Young Mania Rating Scale

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