

CLINICAL PRACTICE GUIDELINES

MOH/P/PAK/278.14(GU)

Management of Bipolar Disorder in Adults



Ministry of Health
Malaysia



Malaysian Psychiatric
Association



Academy of
Medicine Malaysia

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<http://www.moh.gov.my>

<http://www.acadmed.org.my>

<http://www.psychiatric-malaysia.org>

STATEMENT OF INTENT

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider use his/her own clinical judgement of unique patient based on the clinical picture presented by the patient and the management options available locally.

UPDATE

These guidelines were issued in July 2014 and will be reviewed in 2018 or sooner if new evidence becomes available

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LEVELS OF EVIDENCE

Level	Study design
I	Evidence from at least one properly randomised controlled trial
II -1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE 2001

GRADES OF RECOMMENDATION

A	At least one meta-analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population
B	Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta-analysis, systematic review, or RCT
C	Evidence from expert committee reports, or opinions and / or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality

SOURCE: MODIFIED FROM THE SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK (SIGN)

Note: The grades of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

GUIDELINES DEVELOPMENT AND OBJECTIVES

GUIDELINES DEVELOPMENT

The members of the Development Group (DG) for this Clinical Practice Guidelines (CPG) were from the Ministry of Health (MoH) and Ministry of Education. There was active involvement of a multidisciplinary Review Committee (RC) during the process of the CPG development.

A literature search was carried out using the following electronic databases: Guidelines International Network (G-I-N), Medline via Ovid, Pubmed and Cochrane Database of Systemic Reviews (CDSR) (refer to **Appendix 1 for Example of Search Strategy**). The search was limited to literature published in the last ten years, 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 to identify further studies. All searches were conducted from 24 April 2012 to 30 August 2012. Literature searches were repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 28 February 2014 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 CPGs on Bipolar Disorder such as Scottish Intercollegiate Guidelines Network (2008) – Bipolar Affective Disorder, National Institute for Health and Clinical Excellence (2008) –The management of bipolar disorder in adults, children and adolescents, in primary and secondary care and Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. The CPG was evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to them being used as references.

A total of 31 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 31 times throughout the development of these guidelines. All literature retrieved were appraised by at least two DG members using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in each DG meetings. 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. This CPG is based largely on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

The literature used in these guidelines were graded using the US/ Canadian Preventive Services Task Force Level of Evidence (2001), while the grading of recommendation was modified from grades of recommendation of the Scottish Intercollegiate Guidelines Network.

On completion, the draft CPG was sent for review 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 HTA and CPG Council MoH Malaysia for review and approval.

OBJECTIVES

To provide evidence-based guidance in all phases of bipolar disorder (BD):-

- i. To improve recognition and early intervention of BD
- ii. To promote and enhance evidence-based pharmacological and psychosocial intervention in management of BD

CLINICAL QUESTIONS

Refer to **Appendix 2**

TARGET POPULATION

i. INCLUSION CRITERIA

Adults (≥ 18 years old) with a diagnosis of BD

ii. EXCLUSION CRITERIA

People with BD secondary to organic conditions are excluded. However substance/medication-induced bipolar and related disorders are addressed to a limited extent.

TARGET GROUP/USER

This document is intended to guide healthcare professionals and relevant stakeholders including:-

- | | |
|----------------------------------|--|
| i. Doctors | iv. Medical students and healthcare trainees |
| ii. Pharmacists | v. Professional societies |
| iii. Allied health professionals | vi. Patients and carers/non-governmental organisations |

HEALTHCARE SETTINGS

Outpatient, inpatient and community settings

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The draft guidelines were reviewed by a panel of experts from both public and private sectors. They were asked to comment primarily on the comprehensiveness and accuracy of the interpretation of evidence supporting the recommendations in the guidelines.

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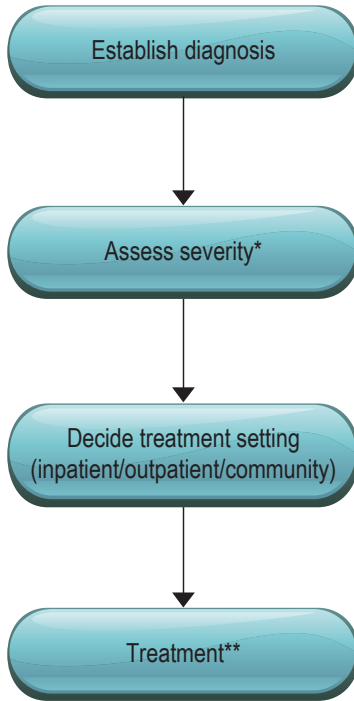
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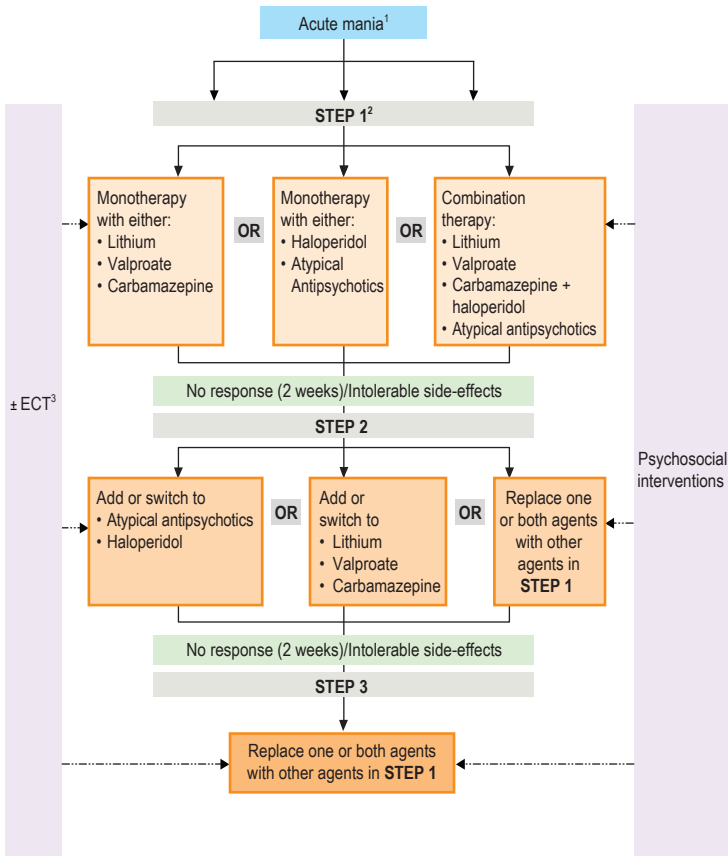
ALGORITHM 1. GENERAL PRINCIPLES IN MANAGEMENT OF BD



*Severity assessments include clinical symptoms [available tools that can be used are Young Mania Rating Scale (YMRS), Hamilton Rating Scale for Depression (HAM-D) & Montgomery Asberg Depression Rating Scale (MADRS)], danger to self or others, family & community supports and availability of service provision.

**Refer to Algorithm 2 for Treatment of Acute Mania, Algorithm 3 for Treatment of Acute Depression and Table on Recommendation on Pharmacological Treatment of Maintenance Phase in BD

ALGORITHM 2. TREATMENT OF ACUTE MANIA



¹ Antidepressants should be discontinued

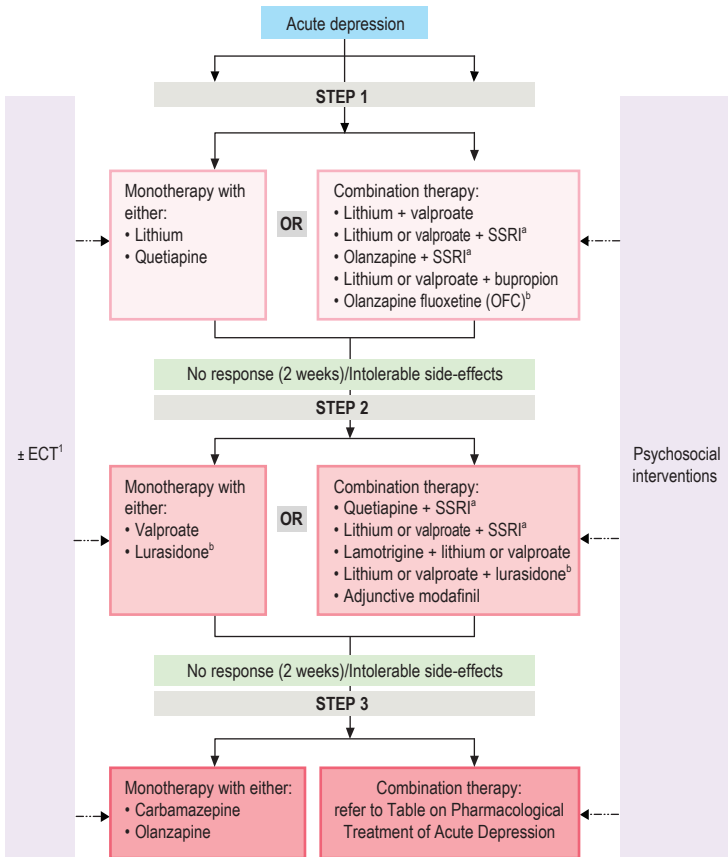
² If the patient is already on treatment, consider optimising the current regime

³ Consideration for ECT

- Severe symptoms of mania
- High suicidal risk
- Catatonia
- Intolerance or no response to medications

Note: Benzodiazepine may be used to manage behavioural disturbances

ALGORITHM 3. TREATMENT OF ACUTE DEPRESSION



¹ Consideration for ECT

- Severe symptoms of depression
- High suicidal risk
- Catatonia
- Intolerance or no response to medications

^a Except paroxetine

^b Not currently approved by Drug Control Authority, (DCA) Malaysia

1. INTRODUCTION

The management of Bipolar Disorder (BD) is challenging because the understanding of nature of the disease is still evolving. These challenges stem from variety clinical presentations, risk factors and interface with other comorbidities. This leads to the difficulties in diagnosing the condition accurately.

Despite the absence study of national prevalence, BD may potentially lead to significant impact on current utilisation of mental health services due to delay in seeking treatment, recurrent relapses or admissions, concurrent substance misuse and the need for long-term psychosocial interventions.

In Malaysia, majority of people with BD are treated in the hospitals with psychiatrists. Those patients who are stable and in full remission are sometimes being treated at the community clinics, however the continuity of treatment such as treatment compliance, blood monitoring and regular supervision is lacking due to various limitations. In view of its complex illness manifestations and unavailability of local clinical practice guidelines, patients are managed in various ways. Hence an evidence-based CPG on BD applicable to local context is timely to be developed.

This CPG is aimed to be used at primary, secondary and tertiary health care. It is also useful for those involved in psychiatric training. It focuses on the management of BD in adults with special consideration on dual diagnosis, women with child bearing age and elderly. It provides evidence-based recommendations and good practice points to be used in Malaysian health care setting.

2. EPIDEMIOLOGY AND RISK FACTORS

In the World Mental Health Survey Initiative involving 11 countries, the lifetime prevalence of BD I was 0.6% and BD II 0.4%. The prevalence varied between countries. For example, the United States of America (USA) had a lifetime prevalence of 1.0% and 1.1% for BD I and BD II respectively whereas in Japan, the lifetime prevalence was 0.1% for both BD I and BD II.^{1, level III}

The mean age of onset for illness is 18.2 years for BD I and 20.3 years for BD II. Women are slightly more affected with prevalence rates of 1.1% for BD I and 1.3% for BD II while the rates for men are 0.8% for BD I and 0.9% for BD II.^{1, level I}

BD risk/prevalence is inversely related to age, educational level and employment.^{2, level III} The high heritability of BD was demonstrated in a nationwide population-based twin sample study where the concordance rates for BD I was significantly higher in monozygotic twins at 0.43 compared to dizygotic twins at only 0.06.^{3, level III} The result of 6 robust papers in a Systematic Review (SR) showed inconsistent finding of maltreatment in childhood as a risk factor for BD.^{4, level I}

3. CLINICAL DIAGNOSIS

3.1 CLINICAL FEATURES

The diagnosis of BD is made when patients experience periods of mood disturbance. The two classification systems used in classifying mental illnesses in Malaysia, the International Classification of Diseases and Health Related Problems 10th Revision (ICD-10) for 2010 and the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) are largely similar. The illness necessitates at least an episode of hypomania or mania, which may present following or prior to depressive episodes.^{5; 6}

Table 1 below summarises the criteria for diagnosing BD, both using ICD-10 and DSM-5. Note that the DSM-5 is a recent publication and is currently used in clinical practice for diagnosing mental illness. At the time of writing, there are very few published papers utilising this classification system. Hence, for the purpose of this CPG, the papers appraised and included in this document are those that used the DSM-IV and DSM-IV-TR. Refer to the respective documents for the full criteria.

Table 1. Criteria for Diagnosing BD using ICD-10 and DSM-5

ICD-10	DSM-5
<p>F30.0 Hypomania</p> <p>Persistent mild elevation of mood, increased energy and activity as well as marked feelings of well-being are present accompanied by increased sociability, talkativeness, over-familiarity, increased sexual energy and decreased need for sleep or irritability. These features however, do not lead to social or occupational dysfunction and hallucinations or delusions are absent.</p>	<p>Hypomanic Episode</p> <p>Persistently elevated, expansive or irritable mood along with persistently increased energy or activity lasting at least four days accompanied by 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.</p>

<p>F30.1 Mania without psychotic symptoms</p> <p>Elation, accompanied by increased energy, over-activity, pressure of speech, reduced need for sleep, inflated self-esteem, grandiose ideas and loss of social inhibitions.</p> <p>F30.2 Mania with psychotic symptoms</p> <p>In addition to the above clinical presentation, delusions or hallucinations are present, or the patient is incomprehensible to ordinary communication due to extreme excitement, flight of ideas or excessive motor activity.</p>	<p>Manic Episode</p> <p>Persistently elevated, expansive or irritable mood along with persistently increased energy or activity lasting at least one week accompanied by 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.</p>
<p>F31 Bipolar affective disorder</p> <p>Having two or more episodes of mood disturbance, one of which has to be mania or hypomania and the other depression.</p> <p>Further classifications include:</p> <p>F31.0 Bipolar affective disorder, current episode hypomanic</p> <p>F31.1 Bipolar affective disorder, current episode manic without psychotic symptoms</p> <p>F31.2 Bipolar affective disorder, current episode manic with psychotic symptoms</p>	<p>Bipolar I Disorder</p> <p>Having met the criteria for manic episodes at least once.</p> <p>296.40 Current or most recent episode hypomanic</p> <p>Current or most recent episode manic:</p> <p>296.41 Mild</p> <p>296.42 Moderate</p> <p>296.43 Severe</p> <p>296.44 With psychotic features</p> <p>Current or most recent episode depressed:</p> <p>296.51 Mild</p> <p>296.52 Moderate</p> <p>296.53 Severe</p> <p>296.44 With psychotic features</p>

<p>F31.3 Bipolar affective disorder, current episode mild or moderate depression</p> <p>F31.4 Bipolar affective disorder, current episode severe depression without psychotic symptoms</p> <p>F31.5 Bipolar affective disorder, current episode severe depression with psychotic symptoms</p> <p>F31.6 Bipolar affective disorder, current episode mixed</p>	<p>Specify:</p> <ul style="list-style-type: none"> With anxious distress With mixed features With rapid cycling <p>296.89 Bipolar II Disorder</p> <p>Having met the criteria for hypomanic episodes at least once and major depressive episode at least once,</p> <p>Specify current or most recent episode:</p> <ul style="list-style-type: none"> Hypomanic Depressed <p>Specify:</p> <ul style="list-style-type: none"> With anxious distress With mixed features With rapid cycling
<p>F32 Depressive Episode</p> <p>The patient typically experiences a reduction in mood, energy and activity, together with reduced capacity for enjoyment, interest, concentration and fatigability. Sleep and appetite are often disturbed, and lowering of self-esteem, ideas of guilt, worthlessness as well as loss of libido are common. On examination, there may be marked psychomotor retardation, agitation and evidence of weight loss.</p> <p>F32.0 Mild depressive episode</p> <p>The presence of two or three of the above symptoms but patient is able to continue their daily activities.</p>	<p>Major Depressive Episode</p> <p>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, fatigability, feeling worthless or guilty, reduced concentration or indecisiveness and recurrent thoughts of death, or suicidal ideas or acts.</p>

<p>F32.1 Moderate depressive episode The presence of at least four of the above symptoms and patient is having difficulty continuing their daily activities.</p> <p>F32.2 Severe depressive episode without psychotic symptoms The presence of several marked depressive symptoms commonly together with suicidal ideation or act.</p> <p>F32.3 Severe depressive episode without psychotic symptoms As above, with the addition of hallucinations, delusions or stuporous state.</p>	
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An episode is defined as a distinctive period of mood disturbance fulfilling the above criteria. An interval of at least two months free of symptoms is required to distinguish between episodes.

There are many similar features between manic and hypomanic episodes 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

The **rapid cycling specifier** can be used for both BD I or BD II if there are presence of at least four manic, hypomanic or major depressive episodes in the last 12 months.

3.2 SCREENING TOOLS

Establishing the diagnosis of BD may take many years because of the instability of its presentation. BD is frequently mistaken with other psychiatric problems especially unipolar depression as they often first present with prominent depressive symptoms.^{7, level 1} Hence the role of primary care doctors in detecting BD is important because patients usually present themselves for the first time at primary care level. The

failure to diagnose BD could have serious and even fatal consequences for the patients.

There are a few tools available for screening of BD such as:-

- Mood Disorder Questionnaire (MDQ)
- Bipolar Spectrum Diagnostic Scale (BSDS)
- Hypomania Checklist (HCL-32)

These tools however have varied performance due to several factors such as setting in which it is used, cut-off value and BD subtype (refer to **Appendix 3**). Therefore the tools are not readily applied in primary care.

There is inadequate evidence to recommend the usage of specific screening tools at primary care. However a simple self-administered tool such as MDQ can be used to help the primary care doctors to suspect any case of BD especially in those who are diagnosed with depression. Those with positive screening should be referred to psychiatrist for further evaluation (refer to **Appendix 4**).

4. DIFFERENTIAL DIAGNOSIS

When considering the differential diagnoses of BD, the current presentation and the longitudinal history need to be taken into account.

During a depressive episode, the differential diagnoses include:^{5, level III}

- Depressive Disorder due to another medical condition
- Substance induced depressive disorder
- Major Depressive Disorder (MDD)
- Adjustment disorder with depressed mood
- Anxiety disorders
- Schizophrenia or schizoaffective disorder

In a manic or hypomanic phase, the conditions below need to be ruled out:^{5, level III}

- Substance induced bipolar disorder
- Bipolar and related disorder due to another medical condition for example brain injury
- Schizophrenia or schizoaffective disorder
- Borderline personality disorder

5. COMORBIDITIES

BD often co-occurs with other psychiatric illnesses. In a survey done in the USA, 92.3% of respondents with BD reported at least one lifetime comorbidities with other mental illness (OR=13.1, 95% CI 6.7 to 25.5). The commonest comorbidities was anxiety disorder (OR=6.5, 95% CI 4.7 to 9.0) followed by substance misuse disorder (OR=4.2, 95% CI 3.3 to 5.5).^{2, level III}

The lifetime prevalence of comorbid anxiety disorder is 51.2% with a prevalence rate almost doubled in BD I compared to BD II ($p < 0.01$). comorbid post-traumatic stress disorder (PTSD) is also significantly higher in people with BD I (6.4%) than those with BD II (0.9%).^{8, level III} In a study among post-partum women with BD, significant portion of them had comorbid Obsessive Compulsive Disorder (OCD) ($p = 0.036$) and PTSD ($p = 0.014$).^{9, level III}

6. BIPOLARITY IN DEPRESSIVE ILLNESS

Some BD patients may first present with a depressive phase and this may be difficult to differentiate from MDD. In a multi-centre cross-sectional study on people with current episode of Major Depressive Episode (MDE), 12.2% were diagnosed with BD I while 3.9% BD II.^{10, level III}

Risk factors for bipolarity in current episode of MDE include:-^{10, level III}

- at least two mood episodes in the past (OR=2.6, 95% CI 2.0 to 3.1)
- a family history of mania (OR=2.1, 95% CI 1.8 to 2.4)
- occurrence of first psychiatric symptoms before age 30 years (OR=1.5, 95% CI 1.3 to 1.7)
- current depressive episode lasting less than one month (OR=1.5, 95% CI 1.3 to 1.7)
- mood lability with antidepressants (OR=1.6, 95% CI 1.3 to 1.9)
- current mixed state (OR=1.3, 95% CI 1.1 to 1.6)

The number of antidepressant failures is not associated with risk of BD. Nevertheless, in those who failed at least one antidepressant treatment, the likelihood of it being bipolar depression significantly increases with the presence of the following:-^{11, level III}

- perception towards people as unfriendly (OR=2.59)
- comorbid anxiety (OR=2.99)
- diagnosis of depression within the last five years (OR=2.48)
- family history of BD (OR=2.02)
- legal problems (OR=1.74)

In a study among post-partum women referred for possible depression, 54% of them were found to have a diagnosis of BD.^{9, level III}

Studies showed that 64.1% women with BD experienced premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD) and had earlier onset of BD ($p=0.0005$) compared to those without PMS/PMDD.^{12, level III} They were also less likely to be in a recovered clinical status ($p<0.01$), had more depressive episodes in the past one year ($p<0.001$) experienced more individual PMS symptoms ($p<0.01$) and were more likely to report that PMS interfered with work or school ($p<0.001$).^{13, level III}

Recommendation 1

- Clinicians should consider the possibility of bipolar disorder in depressed people with risk factors.* **(Grade C)**

*Refer to the preceding paragraphs

7. GENERAL PRINCIPLES AND MANAGEMENT

The principle of management entails the importance of promoting access to services through collaboration between patients, family members and healthcare professionals with the aim to restore the person to full health and meaningful life. It is important to retain confidentiality at every stage of assessment, diagnosis and treatment. Such principle may encourage patients, family and carers to take part in the management throughout the illness.

BD is a life-long illness and medication is the mainstay of treatment. The types of interventions may vary during different phases of the illness. In Malaysia, the approach generally follows two main service provisions. At the primary care level, focus is on the screening for BD and referring appropriately, while the diagnosis is confirmed and appropriate pharmacological therapy is initiated at the secondary level. The treatment of the acute phase is monitored and continued to the maintenance phase accordingly. Decision on treatment setting mainly relies on assessment of symptoms severity (available tools that can be used are YMRS, HAM-D and MADRS), danger to self or others, family and community supports, and availability of service provision. Maintenance therapy of BD may be shared with the primary care. This is in tandem with the national mental health service guidelines for primary care to provide follow-up for the stable mentally-ill and psychosocial rehabilitation.

Effective management of BD utilizes a broad range of interventions. While appropriate pharmacotherapy is crucial, attention must also be given to psychosocial interventions and consequences. In view of the complexities of BD, the use of treatment algorithms is of significant value to guide clinicians to provide appropriate treatment strategies.

The principles of management in bipolar disorders should incorporate the following:-

- Assessing severity and early treatment
- Planning for psychosocial intervention
- Dealing with treatment adherence issues
- Addressing potential risks to self or others
- Monitoring parameters (refer to **Appendix 5**)
- Managing special populations

7.1 INTEGRATED CARE

BD is a long-term illness that requires a variety of care and health delivery services. There are few facilities that meet the requirements;

hence care should be shared between facilities and inter-agencies. National Institute for Health and Care Excellence (NICE) recommends continuity of care for people with BD at different levels of health service via the provision of certain models of intervention. It should include:-¹⁴

- Regular reviews of mental state, and personal and social functioning in primary or secondary care.
- Clear guidelines for delivering and monitoring of pharmacological, psychological and psychosocial interventions
- Referral to a community mental health team for relapse prevention, early intervention or crisis resolution
- Admission for patients who are at significant risk of harm
- Collaboration in partnership with other local stakeholders and agencies regarding vocational rehabilitation or other structured purposeful activities

Apart from the above, comprehensive care is particularly important especially in patients with dual diagnosis (BD with substance use disorder). These patients should be co-managed by addiction team where available.

Population-based systematic care programmes and the incorporation of specific cognitive and behavioural therapeutic strategies and effective medication regimes can significantly reduce the frequency and severity of mania or may reduce the symptoms of depression.^{15, level 1} Similarly, in psychiatric clinic, BD Programme improves long-term clinical and functional outcomes notably for manic episodes.^{16, level 1}

Management of BD entails overall improvement to include functional recovery and employment with regards to the participation of various sectors and organisational involvement. NICE 2006 documents a range of new services being created for people with severe mental illness namely the assertive community treatment, vocational rehabilitation, early intervention services, organisational developments and lithium clinics for BD. These services do not benefit people with BD alone but also for others with mental illness.

In Malaysia, there are a few service level interventions currently being carried out such as community mental health team, assertive community treatment, day hospital care, supported employment and crisis intervention and home treatment team.¹⁷

Recommendation 2

- Management of people with bipolar disorder should be collaborated between service providers at different levels of healthcare as well as care givers. **(Grade A)**

7.2 ADMISSION CRITERIA

The criteria for admission of people with BD are based on the Malaysian Mental Health Act 2001 (Act 615) and Regulations which are:-^{18, level III}

- Risk of harm to self or others
- Treatment is not suitable to be started as outpatient

7.3 REFERRAL CRITERIA

There is limited evidence on referral criteria specifically for BD. Referral of people with BD to a psychiatric service is often indicated in the following situations:-^{19, level III; 14}

- a. Newly diagnosed or undiagnosed individuals with BD
 - Assessment of danger to self or others
 - Confirmation of diagnosis and formation of management plan
- b. People with confirmed diagnosis of BD
 - Acute exacerbation of symptoms
 - Decline in functioning
 - Increased risk of harm to self or others
 - Treatment non-adherence
 - Inadequate response to treatment
 - Ambivalence about or wanting to discontinue medication
 - Concomitant or suspected substance misuse
 - Complex presentations of mood episodes
 - Psychoeducational and psychotherapeutic needs

Refer to **Algorithm 1 on General Management of BD**

8. PHARMACOLOGICAL TREATMENT

Pharmacological treatment can be divided into acute and maintenance phases. Selection of medications are based on considerations including concomitant medications, previous medication response and family history of medication response, side effects, patient preferences, as well as medical and psychiatric comorbidities.

8.1 ACUTE PHASE

The duration of acute treatment depends largely on clinical response and tolerability to the treatment.

a. Mania

The pharmacological treatment of acute mania consists of a variety of medication, ranging from classical mood stabilisers to atypical antipsychotics. Lithium is considered as the gold standard however, recent data has shown that antipsychotics are superior to mood stabilisers ($p < 0.0001$). There is no superiority over the different types of antipsychotics. The choice of drugs use is based on the balanced decision between the benefits and potential harms. Gabapentin, topiramate and lamotrigine are shown to be not efficacious in acute mania.^{20, level I} Lithium, valproate and carbamazepine are equally efficacious in acute mania.^{21, level I}

The following are efficacious medications for acute mania^{20, level I; 22, level I; 23, level I; 24, level I} and used for BD.

Mood stabilisers

- lithium
- carbamazepine
- valproate*

Typical antipsychotic

- haloperidol

Atypical antipsychotics (AAP)

- risperidone
- quetiapine
- olanzapine
- paliperidone**
- ziprasidone
- aripiprazole
- asenapine

Additionally, benzodiazepines may be used during acute mania. CANMAT 2005 and NICE 2006 recommend the use of benzodiazepines in combination with antimanic agents to manage behavioural disturbances.^{14: 26}

*The pharmacokinetics of valproate semisodium or divalproex, valproic acid and sodium valproate are similar and have no significant clinical difference.^{25, level III}

**Currently not approved by US Food and Drugs Administration for BD.

Refer to

- **Algorithm 2 on Treatment for Acute Mania**
- **Appendix 5 for Medication Dosages and Side Effects**

Recommendation 3

- Mood stabilisers or antipsychotics, either as monotherapy or combination, should be used to treat acute mania in bipolar disorder. **(Grade A)**

b. Depression

The pharmacological treatment for acute bipolar depression varies with different drugs available. According to CANMAT (2013), lithium and lamotrigine have been found to be effective in the treatment of acute bipolar depression.²⁶

In a SR of 18 Randomised Control Trials (RCTs), mood stabilisers were found to be efficacious for acute bipolar depression [NNT for clinical response=10 (95% CI 7 to 18)] and for remission NNT=8 (95% CI 5 to 14).^{27, level I} However, this SR included atypical antipsychotics as mood stabilisers.

Several antipsychotics are significantly efficacious in the treatment of acute bipolar depression:-

- Quetiapine monotherapy^{28, level I; 29, level I}
- Quetiapine and mood stabilisers^{28, level I}
- Olanzapine-fluoxetine combination (OFC)^{29, level I; 30, level I}

In a SR of 2004, antidepressants as adjuncts to mood stabilisers were efficacious in response (NNT=5, 95% CI 4 to 7) and remission (NNT=9, 95% CI 5 to 33) for short-term treatment in bipolar depression.^{31, level I} However a recent SR did not replicate the same findings.^{32, level I}

Antidepressants as adjunctive treatment do not significantly increase or decrease the risk of affective switch relative to placebo.^{31, level I; 32, level I} However among antidepressants, tricyclic antidepressants (TCA) cause more mood switching (RR=2.92, 95% CI 1.28 to 6.21)^{31, level I} while bupropion is associated with a reduced risk compared to the others (RR=0.34, 95% CI 0.13 to 0.88).^{32, level I} Venlafaxine is associated with mood switch in people with BD prior history of rapid cycling compared

to bupropion or sertraline.^{33, level I} (refer **Algorithm 3**)

The following table shows effective medications for acute depression:-

Table 2. Recommendations on Pharmacological Treatment of Acute Depression

First line	
Monotherapy	Lithium, quetiapine, extended release (XR) quetiapine
Combination therapy	<ul style="list-style-type: none"> • Lithium or valproate + selective serotonin reuptake inhibitor (SSRI)^a • Olanzapine + SSRI^a • Lithium + valproate • Lithium or valproate + bupropion • Olanzapine fluoxetine (OFC)^b
Second line	
Monotherapy	Valproate, lurasidone ^b
Combination therapy	<ul style="list-style-type: none"> • Quetiapine + SSRI^a • Lamotrigine^b + lithium or valproate • Lithium or valproate + lurasidone^b • Adjunctive modafinil
Third line	
Monotherapy	Carbamazepine, olanzapine, electroconvulsive therapy (ECT) ^c
Combination therapy	<ul style="list-style-type: none"> Lithium + carbamazepine • Lithium + pramipexole • Lithium or valproate + venlafaxine • Lithium + monoamine oxidase inhibitor (MAOI), • Lithium or valproate or AAP + Tricyclic Antidepressants (TCA) • Lithium or valproate or carbamazepine + SSRI^a + lamotrigine • Quetiapine + lamotrigine^b

^a Except paroxetine

^b Not currently approved by Drug Control Authority (DCA), Malaysia

^c Could be used as first- or second-line treatment in certain situations together with concomitant medications

Adapted from Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar Disord.* 2013 Feb;15(1):1-44.

Recommendation 4

- The following medications can be used as monotherapy in acute bipolar depression:-
 - antipsychotics (quetiapine or olanzapine-fluoxetine combination) **(Grade A)**
 - lithium **(Grade B)**
- Antidepressants may be used as short-term adjunctive treatment in acute bipolar depression. **(Grade A)**
- Antidepressants should not be used as monotherapy in acute bipolar depression. **(Grade C)**

c. Rapid Cycling

Rapid Cycling represents the most challenging subtype of BD in terms of the management due to its cyclic nature. In DSM-5 **rapid cycling is not a condition on its own but exists as a specifier** which can be used for both BD I or BD II if there are presence of at least four manic, hypomanic or major depressive episodes in the last 12 months.

In a recent SR by Fountoulakis et al., few people with rapid cycling achieved symptomatic remission ($p=0.014$) and many of them experienced episodic recurrence especially of depression ($p<0.001$). They also required more hospitalisation ($p=0.01$) and had higher rates of attempted suicide ($p=0.03$).^{34, level I}

In the same SR, lithium and anticonvulsants were found to have comparable efficacy. For anticonvulsants, the comparative efficacy between monotherapy and combination therapy was found to be inconclusive.^{34, level I}

Aripiprazole, olanzapine and quetiapine are efficacious against placebo whereas olanzapine and quetiapine have similar efficacy compared to anticonvulsants during acute episode. During the maintenance, aripiprazole is more efficacious in preventing recurrence of mood symptoms than placebo whereas quetiapine is more efficacious in preventing depressive episode but not manic or hypomanic episode in comparison to sodium valproate.^{34, level I}

The relationship between rapid cycling and the use of antidepressants is still debatable. The subjects with rapid cycling in Systematic Treatment Enhancement Program for Bipolar Disorder (STEP BD) study had three times more depressive episodes with antidepressant continuation compared to those without.^{34, level I}

There are still many gaps in the understanding of the nature of rapid cycling and the optimal treatments required. Robust evidences from well-designed RCTs are needed to arrive at any consensus on the optimal pharmacological management.

Recommendation 5

- Antidepressants should be avoided in rapid cycling bipolar disorder. (Grade B)

d. Mixed Episode

According to DSM-IV-TR, patients who are diagnosed with mixed episodes of BD will meet all criteria for an episode of mania and episode of major depression simultaneously. DSM-5 definition replaces the diagnosis of “mixed episode” with a mixed features specifier.⁵

Mixed state remains one of the challenges in management of BD. The medications that are effective in treating mixed episodes as defined by the DSM-IV-TR are likely to be equally effective in treating mixed features following the DSM-5, but new studies are needed to demonstrate it. While lithium benefits patients with mixed episodes, it may be less efficacious than valproate; however there are only few studies of such direct comparison.^{35, level I} Atypical antipsychotics have significant evidence for benefit in mixed states. Meta-analysis on the efficacy of second generation antipsychotics used in treating acute mixed states showed that aripiprazole, asenapine, olanzapine, paliperidone, risperidone and ziprasidone were better than placebo for manic symptoms whereas asenapine, quetiapine and olanzapine were more efficacious in treating depressive symptoms of mixed episodes. However the findings from more well-designed RCTs are needed to make any firm recommendation.^{36, level I}

8.2 MAINTENANCE PHASE

The maintenance phase commences after the stabilisation of acute phase. The aim is to prevent relapse and optimise functionality. There is no consensus on the duration, however long-term prophylaxis is warranted as BD is a recurrent and life-long disorder.

a. Mood Stabilisers

i. Monotherapy

- **Lithium**

Four SRs indicated that lithium is significantly more efficacious than placebo in reducing the risk of all relapse.^{37, level I; 38, level I; 39, level I; 40, level I} In subgroup analysis of one of the SR, lithium was superior in preventing manic episodes (RR= 0.62, 95% CI 0.43 to 0.88; NNT=10) but not depressive episode (RR=0.78, 95% CI 0.60 to 1.01).^{38, level I}

Lithium is more efficacious in reducing manic relapses compared to lamotrigine (RR=0.53, 95% CI 0.32 to 0.87).^{37, level I}

In a recent SR, there was no difference in efficacy between lithium and valproate in preventing any mood episodes in BD (RR=1.02, 95% CI 0.87 to 1.20).^{41, level I}

Withdrawal due to an adverse event with lithium is approximately twice as likely when compared to valproate (RR =1.81, 95% CI 1.08 to 3.03) and lamotrigine (RR=2.20, 95% CI 1.31 to 3.70).^{37, level I}

It is important to monitor serum lithium level since a rapid decrease in serum lithium level increase the risk of relapse ($p<0.05$).^{42, level I} SIGN recommends the withdrawal of lithium should be gradual to minimise the risk of relapse.⁴³ Refer to **Appendix 5** and **6** on lithium monitoring.

- **Valproate**

Two SRs showed that valproate was more efficacious in preventing any mood episode compared to placebo.^{37, level I; 44, level I} In subgroup analysis of the SR by Cipriani A et al., valproate was superior than placebo in preventing depressive episode (RR=0.46, 95% CI 0.24 to 0.89; NNT=13), but not manic episodes (RR=0.77, 95% CI 0.48 to 1.25).^{44, level I}

Based on available evidence, valproate caused significantly:-^{44, level I}

- more tremor (NNH=10), weight gain (NNH=4) and alopecia (NNH=10) compared to placebo
- less diarrhoea (NNH=10), less thirst (NNH=9), less enuresis (NNH=5) but more sedation (NNH=9) and infection (NNH=8) compared to lithium

- **Lamotrigine**

Lamotrigine is superior than placebo in preventing relapse due to any mood episode (RR=0.84, 95% CI 0.71 to 0.99).^{37, level I} In a multicentre RCT involving 463 subjects, lamotrigine was superior to placebo in delaying intervention for depressive symptoms ($p=0.047$) but not manic symptoms ($p=0.339$). The incidence of non-serious rashes was significantly higher in patients on lamotrigine.^{11, level I}

- **Carbamazepine**

In a SR of four RCTs, carbamazepine was similar to lithium in the rate of relapses (RR=1.18, 95% CI 0.92 to 1.51) and hospitalisations (RR=1.20, 95% CI 0.83 to 1.75), but there were fewer trial withdrawal due to adverse effects on lithium (RR=1.91, 95% CI 1.02 to 3.57).^{45, level I} Drug-drug interaction should be considered when carbamazepine is to be used for long-term.

ii. Combination Therapy

The addition of carbamazepine or oxcarbazepine to lithium improved residual depressive and manic/hypomanic symptoms from baseline to end point ($p<0.01$) in a small and short duration RCT.^{46, level I}

iii. Monotherapy vs Combination Therapy

Geddes JR et al. found that combination therapy of lithium and valproate was more efficacious to prevent any mood episodes compared to valproate monotherapy (HR=0.59, 95% CI 0.42 to 0.83; NNT=7) but not to lithium monotherapy (HR=0.82, 95% CI 0.58 to 1.17). Further analysis showed that the effect was more apparent in preventing manic relapses (HR=0.51, 95% CI 0.32 to 0.80; NNT=19).^{47, level I}

b. Antipsychotics

i. Monotherapy

In two SRs, olanzapine was significantly more efficacious than placebo in preventing relapses of any mood episode and manic^{37, level I}; ^{48, level I} but with higher risk of weight gain.^{48, level I} A RCT in one of the SR showed that olanzapine prevented more manic relapse (RR=0.59, 95% CI 0.39 to 0.89), reduced more hospital admission (RR=0.62, 95% CI 0.41 to 0.94) and caused less insomnia (RR=0.15, 95% CI 0.07 to 0.34) compared to lithium.^{48, level I} Compared to paliperidone, olanzapine is superior in delaying the recurrence of any mood symptoms (NNT=3, 95% CI 2.0 to 5.0). Paliperidone is more efficacious than placebo in

preventing relapses of any mood episodes (HR=1.43, 95% CI 1.03 to 1.98) and recurrence of mania (HR=2.06, 95% CI 1.32 to 3.22).^{49, level I}

ii. Combination Therapy

Aripiprazole combination therapy (lithium or valproate) delays any mood relapse (HR=0.54, 95% CI 0.33 to 0.89) and reduces manic relapse compared to combination of mood stabilisers and placebo (HR=0.35, 95% CI 0.15 to 0.83).^{50, level I} After controlling valproate level, combination of aripiprazole and valproate prolonged the time to depressive episode relapse compared to combination of placebo and valproate in a study on BD I ($p=0.029$).^{51, level I}

Quetiapine combined with lithium or valproate are more efficacious than placebo in delaying recurrence of any mood episode (HR=0.32, 95% CI 0.24 to 0.42), manic episode (HR=0.30, 95% CI 0.18 to 0.49) and depressive episode (HR=0.33, 95% CI 0.23 to 0.48).^{52, level I}

Olanzapine combination therapy with lithium or valproate shows no difference in terms of relapse into mood episode (RR=0.68, 95% CI 0.43 to 1.07).^{48, level I}

In one RCT, the use of adjunctive risperidone long acting injection (LAI) was significantly associated with delayed time to relapse of any mood episode compared with adjunctive placebo treatment (NNT=4, 95% CI 3.0 to 12.0) in which the RR of relapse was 2.3 fold higher with adjunctive placebo. However, the study did not specify the primary therapeutic agents used.^{53, level I}

iii. Monotherapy vs Combination Therapy

Olanzapine as monotherapy or in combination with other antipsychotics, anticonvulsants, and/or lithium has similar efficacy in achieving improvement, remission and recovery as well as preventing relapse following acute manic episode. However, the combination therapy significantly causes more tremor, akathisia, sexual dysfunction and polyuria while monotherapy is associated with more weight gain.^{54, level II-2}

c. Antidepressants

Antidepressants reduce the risk of depressive recurrences compared to mood stabiliser alone or no treatment (RR=0.73, 95% CI 0.55 to 0.97 NNT=12), however they carry higher risk of inducing mania (RR=2.37, 95% CI 1.38 to 4.05, NNH=8).^{55, level I}

The combination of antidepressant and mood stabiliser, when compared to mood stabilisers and placebo combination, is not associated with

increased efficacy or increased risk of treatment-emergent affective switch ($p=0.40$).^{56, level I}

Table 3. Recommendations on Pharmacological Treatment of Maintenance Phase in BD

First line	
Monotherapy	Lithium, lamotrigine (limited efficacy in preventing mania), valproate, olanzapine, quetiapine, risperidone LAI, aripiprazole
Combination therapy	Adjunctive therapy with (lithium or valproate)+ quetiapine/risperidone LAI/aripiprazole/ziprasidone
Second line	
Monotherapy	Carbamazepine, paliperidone
Combination therapy	<ul style="list-style-type: none"> • Lithium+valproate • Lithium+carbamazepine • Lithium or valproate + olanzapine • Lithium + risperidone • Lithium + lamotrigine • Olanzapine + fluoxetine
Third line	
Monotherapy	Asenapine
Combination therapy	Adjunctive therapy with lithium or valproate + asenapine
Not recommended:	
<ul style="list-style-type: none"> • Monotherapy with gabapentin, topiramate or antidepressants. • Adjunctive therapy with flupenthixol. 	

Adapted from Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar Disord.* 2013 Feb;15(1):1-44.

Recommendation 6

- Lithium monotherapy should be used as first-line treatment in bipolar disorder (BD). **(Grade A)**
 - Lithium monitoring should be carried out at least every six months. **(Grade C)**
 - If lithium is to be discontinued, gradual tapering is required to minimise the risk of relapse. **(Grade A)**
- Both mood stabilisers and antipsychotics should be used either alone or in combination during maintenance phase of BD. Careful consideration of risk-benefit is required when using combination therapy. **(Grade A)**

9. NON-PHARMACOLOGICAL TREATMENT

9.1 ELECTROCONVULSIVE THERAPY (ECT)

In contrast to pharmacological treatment in the management of BD, the evidence on efficacy and safety of ECT is limited. Despite this, the use of ECT is relatively common particularly in severe mania, refractory depression and refractory mania.⁴³

A recent SR by Versiani M et al., ECT showed high response rates in people with acute mania, depression and mixed with minimal effects on cognitive functions. However, the recommendation for ECT in BD remains inconclusive considering the limited quality in methodology and heterogeneity between studies.^{57, level I}

The evidence for the benefit of maintenance ECT in BD is limited but clinical experience supports its use in patients with severe symptoms who are unable to tolerate or respond poorly to other forms of maintenance treatment.

Refer to **Algorithm 2** and **Table 2**.

9.2 PSYCHOSOCIAL INTERVENTIONS

Psychosocial interventions are an integral part in the management of BD. It has been shown to enhance symptomatic outcomes and the quality of life of patients.

a. Cognitive Behavioural Therapy (CBT)

CBT is an intervention based on the principle that thoughts, feeling and behaviour are inter-related. Its aim is to train patients to identify, challenge and replace the unhelpful thoughts which are associated with undesirable mood states to more helpful ones.

CBT was found to be more efficacious when compared to Treatment As Usual (TAU) in two RCTs. In people with fewer than 12 episodes, it reduced recurrence rates of major mood episodes ($p=0.04$).^{58, level I} In people who were mildly depressed or mildly manic, it improved depression, anxiety, mania and hopelessness ($p<0.001$).^{59, level I}

A recent SR indicated that new modalities of psychological approaches, namely Cognitive Remediation, Functional Remediation and Mindfulness-based interventions showed favourable outcomes in BD. However, the quality of primary papers were not addressed in the SR.^{60, level I}

b. Interpersonal Social Rhythm Therapy (IPSRT)

IPSRT teaches patients to regulate sleep-wake patterns, work, exercise, meal times and other daily routines in addition to having therapy addressing interpersonal issues.

IPSRT in the acute phase prolongs remission compared to Intensive Clinical Management (ICM).^{61, level I}

In STEP BD programme, patients who were on regular medications combined with intensive psychosocial interventions consisting of either IPSRT, CBT or Family Focused Therapy (FFT) significantly improved their relationship functioning and life satisfaction compared to those receiving medications with brief psychoeducation following a bipolar depressive episode. Similarly, patients who received intensive psychosocial interventions as mentioned above were more likely to remain well clinically and had significantly higher year-end recovery rates and shorter times to recovery (HR=1.47, 95% CI 1.08 to 2.00) when compared to those receiving an ordinary brief psychoeducational intervention.^{62, level I}

Likewise, another SR indicated that augmentation of pharmacotherapy with either one of the psychotherapies mentioned above improved social functioning and reduced relapse prevention rates.^{63, level I}

c. Group Psychoeducation/Group-based Psychotherapy

Group psychoeducation provides understanding of the illness and its management in order to increase treatment satisfaction and adherence. It focuses on improving illness awareness, treatment compliance, early detection of prodromal symptoms or recurrences and lifestyle regularity.

ASR reported that over 5 years follow-up, patients in the psychoeducation had less recurrences ($p < 0.0001$), spent significantly less time acutely ill ($p < 0.001$) and had reduced number of hospitalisation ($p = 0.023$) when compared to the control group.^{64, level I} This is supported by a RCT showing that patients in group-based intervention had reduced rate of relapse of any type (HR=0.43, 95% CI 0.20 to 0.95) and spent less time unwell ($p = 0.02$) compared to those in control group.^{65, level I}

d. Family-oriented Interventions

This covers areas such as communication, problem solving skills and psychoeducation in order to manage stresses in the home environment leading to high levels of expressed emotion.

A Cochrane SR found a very limited role of family-oriented interventions. Family Focus Therapy was superior to Family Crisis Management in preventing relapse (NNT=4, 95% CI 2.0 to 9.0) but not improving in medication compliance and dropout rates. Other findings on the family-oriented interventions were inconclusive.^{65, level I}

e. Early Warning Signal (EWS)

EWS interventions train the patients to identify and manage early warning signs of recurrence. The main aim is to intervene early and self-manage manic and depressive symptoms.

In a Cochrane SR, EWS intervention significantly prolonged time to first recurrence of any mood episodes, manic/hypomanic and depressive episodes when compared to TAU. In addition, it improved patients' functioning and reduced hospitalisation rates.^{67, level I}

Recommendation 7

- Psychosocial interventions should be incorporated into patients' care in addition to pharmacological treatment in bipolar disorder. **(Grade A)**
- Family should be involved in the management of bipolar disorder. **(Grade A)**

10. OTHER TREATMENTS

One SR using omega-3 fatty acids as an adjunctive treatment showed positive effect for depressive (WMD in HDRS= -3.93, 95% CI -7.00 to -0.86) but not manic symptoms.^{68, level I}

BD may be effectively managed using integrative approach. Interventions such as acupuncture and dietary supplements (such as omega-3, amino acids, N-acetyl cysteine, chelated mineral and vitamin formula) have beneficial effects on physical and mental health, and quality of life when used with other medications.^{69, level I; 70, level I}

11. PREVALENCE, RISK FACTORS AND STRATEGY TO IMPROVE TREATMENT NON-ADHERENCE

Treatment adherence can be difficult to study because its definition differs across study populations and among studies within the same population. Non-adherence rates vary due to several factors including specific characteristics of the population or subpopulation, type of treatment, length of assessment period and method of measurement.^{71, level I}

Recent studies have reported 19 to 69% treatment non-adherence rates among people with BD. Significant risk factors for non-adherence are:^{71, level III; 72, level III; 73, level II-2}

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

In a SR on improvement of BD treatment adherence, several potential psychosocial interventions including cognitive-behavioural, psychoeducational and family-based interventions were suggested as effective.^{74, level I}

The use of a manualised psychosocial intervention known as customised adherence enhancement, which includes four modules on psychoeducation, modified motivational enhancement therapy, communication coaching and medication routines was found to improve treatment adherence significantly.^{75, level II-3}

Recommendation 8

- Risk factors for treatment non-adherence in bipolar disorder should be identified and addressed to improve clinical outcomes. **(Grade C)**

12. SUICIDE

The relationship between suicide and BD is important as suicide-related events contribute substantially to the disease burden. The rate of completed suicide ranges between 0.014 to 4.48 per 1,000 person-years,^{75, level II-2} which is 10 to 30 times higher than the rate in the general population. For suicide attempts, the rate ranges between 3.1% and 36.5%.^{77, level II-2; 78, level II-2; 79, level III; 80, level III; 81, level II-2}

Among all the psychiatric disorders, affective disorders including BD are associated with the highest risk of suicide.

Knowledge of the risk factors for suicide in BD patients is important to assist health care providers in the detection of those at risk.

a. Risk Factors

There are many clinically relevant suicide risk factors for BD mainly those related to the acute mood episodes.^{76, level II-2; 77, level II-2; 78, level II-2; 79, level III; 80, level III; 81, level II-2} The risk factors are similar in both completed suicide and suicide attempt except for gender where suicide attempt is more frequent in women^{82, level III} while completed suicide is higher among men.^{77, level II-2} The followings are significant risk factors for suicide in BD:-

i. Sociodemographic

- Younger age^{76, level II-2; 81, level II-2}
- Male^{76, level II-2; 82, level III}
- Unemployed or disabled^{82, level III}

ii. Symptomatology

- Suicidal thought^{76, level II-2}
- Rapid mood switching^{76, level II-2; 82, level III}
- Psychotic symptoms^{76, level II-2; 83, level III}
- Depressive phase of BD^{76, level II-2; 77, level II-2; 81, level II-2; 83, level III}
- Hopelessness^{76, level II-2; 81, level II-2}
- Mixed state^{91, level II-2}

iii. Clinical characteristics

- Early onset of mood disorder^{76, level II-2; 82, level III; 84, level II-2}
- Previous suicide attempts^{76, level II-2; 77, level II-2; 81, level II-2}
- Multiple hospitalisations^{79, level III}
- Early sexual abuse^{80, level II-2; 85, level II-2}
- Stressful life events^{76, level II-2; 77, level II-2; 79, level III}
- Lack of confidant^{85, level II-2}
- Family history of suicide^{76, level II-2; 82, level III; 84, level II-2}

iv. Comorbidity

- Anxiety disorder^{76, level II-2; 82, level III}
- Cluster B personality (antisocial/borderline/histrionic/narcissistic personality disorder)^{85, level II-2; 86, level II-2}
- Substance misuse^{76, level II-2; 82, level III}

v. Treatment

- Duration of treatment (less than five years)^{77, level II-2}

b. Intervention

Several types of psychosocial interventions for suicide prevention have been proposed, including brief intervention at the emergency department, dialectical behaviour therapy and mindfulness-based cognitive therapy.^{88, level I; 89, level III} However, the evidence for the benefit of these psychosocial interventions for suicidality in BD is limited.

Two SRs in studies of suicide prevention reported only one study evaluating the use of adjunctive psychotherapy for suicidality in people with BD. Adjuvant IPSRT or ICM produced a threefold reduction of suicide rate in acute phase of treatment ($p < 0.02$) as well as a 17.5-fold reduction during maintenance phase from baseline ($p = 0.004$). There was no significant difference between IPSRT and ICM in the reduction of suicide attempts.^{90, level I; 91, level I}

Another SR reported that studies evaluating the benefit of ECT were sparse and concluded that there was no evidence for its benefit as an acute intervention for suicidality in BD.^{91, level I}

c. Prevention

In a well-conducted meta-analysis of 32 studies, lithium was effective in preventing suicide (OR=0.26, 95% CI 0.09 to 0.77) and combined suicide and deliberate self-harm including suicide attempt (OR=0.21, 95% CI 0.08 to 0.50) among people with BD.^{92, level I} Studies showed that anticonvulsants such as valproate and carbamazepine did not increase the risk of suicide^{91, level II-2} and non-lethal suicide event rate was sixteen times higher when lithium or anticonvulsants were discontinued.^{93, level II-2}

The use of antidepressants is still controversial as there is no evidence confirming the benefit of antidepressant monotherapy on reduction of or prophylaxis against suicidality in BD.^{87, level II-2; 91, level I} There is some evidence showing that antidepressants in combination with either mood stabilisers or atypical antipsychotics may reduce suicidality in BD.^{87, level II-2}

In general, non-pharmacological strategies to prevent suicide that have been suggested as useful include training primary care physicians in detection of vulnerable patients, restriction of available tools to complete suicide (such as guns, domestic gas and barbiturates) and education for family and friends of people with BD.^{94, level II-2}

Recommendation 9

- To prevent suicide in bipolar disorder:-
 - healthcare providers should be able to identify risk factors for suicide. **(Grade C)**
 - lithium should be considered as the treatment of choice. **(Grade B)**

13. SUBSTANCE MISUSE

BD and substance use disorders are highly comorbid conditions. Community based studies indicated that 60-70% of people individuals with BD met diagnostic criteria for a lifetime history of substance abuse or dependence.^{95; 96} Risk of lifetime use of illicit substances is three times greater in BD patients compared to the general population (OR=3.03, 95% CI 1.9 to 4.8).^{96, level III} Men are more likely to have comorbidity of BD and substance abuse compared to women ($p<0.001$).^{98, level III}

Although the use of excessive substance use is not associated with the course of illness ($p=0.001$), it impairs functioning of the affected individuals ($p<0.05$).^{97, level III} Effective pharmacological or psychological interventions for BD and substance use disorder are limited. A RCT showed that valproate decreased heavy drinking in people with comorbid BD and alcohol dependence ($p=0.02$).^{99, level I; 100, level I} According to Weiss RD et al., Integrated Group Therapy compared to group drug counselling reduced numbers of days using substance or drinking alcohol ($p<0.001$). Mood symptoms improved in both groups, with no significant difference between them ($p<0.1$).^{100, level I}

Recommendation 10

- All people with bipolar disorder should be assessed for substance misuse. **(Grade C)**

14. SPECIAL POPULATIONS

14.1 WOMEN OF CHILD BEARING AGE

a. Fertility Issues

Every woman of reproductive age needs to know the risks and benefits of her pharmacological treatment options including risks of untreated mood disorder in pregnancy and postpartum. Pregnancy does not appear to protect against the risk of mood episodes. Thus, medication discontinuation in pregnancy may increase risk of mood episodes. In addition, the risk of recurrence of mood symptoms and psychosis appears higher during postpartum than in pregnancy.^{101, level II-2}

Rates of menstrual disturbances are high in women with BD and in many cases, precede the diagnosis and treatment for the disorder ($p=0.04$). Those with pre-existing menstrual abnormalities are at risk of reproductive dysfunction while being treated for BD. All medications for BD may cause reproductive and hormonal abnormalities such as elevated 17 α -OH Progesterone and Luteinizing Hormone: Follicle Stimulating Hormone ratio.^{102, level III}

b. Effects of Contraception

Selection of contraceptives for women with BD should be based on patient preference and compatibility with other medications.^{103, level III}

Some medications such as carbamazepine and topiramate induce cytochrome P-450 enzymes in the liver which may increase metabolism of sex hormones and risk for contraceptive failure. Alternatively, they can use non-hormonal methods of contraception, contraceptive injections or oral contraceptives containing 50 μ g or more of the oestrogenic component. On the other hand, dose adjustments for lamotrigine may be required due to reduction in its serum concentration when an oral contraceptive is added.^{103, level III}

Considering the multiple drug interactions between hormonal contraceptives and antimanic agents, intrauterine contraception may be a favourable option.^{103, level III}

Recommendation 11

- Discussion with gynaecologist on contraceptives in view of drug interaction for bipolar disorder should be considered in treating women with the illness. **(Grade C)**

c. Preconception Counselling

Women of reproductive age with BD should be counselled that pregnancy is a time of substantial risk of relapse. The risk is 2.3 times greater after discontinuing mood stabiliser treatment. Women who discontinue the medication abruptly have a 50% risk of recurrence within two weeks compared to 22 weeks in those who gradually taper their treatment.^{104, level III} Apart from that, women with BD are significantly more likely to experience placenta abnormalities such as placenta praevia compared to non-psychiatric group.^{105, level III}

Women with BD are at high risk of relapse during the postpartum period (up to 80%) and have 10 - 20% risks of postpartum psychosis.^{104, level III} Multiple factors are associated with risk of recurrence of BD I during postpartum:-^{106, level III}

- Younger age at onset of BD ($p=0.009$)
- History of episodes during previous pregnancies ($p=0.038$)
- Complications during labour ($p=0.03$)

Therefore, relapse prevention and management strategy including contraceptive option for BD should be counselled to both patients and their partners before pregnancy.^{103, level III; 104, level III} A suggested approach to treatment of the people with BD who wishes to conceive or is pregnant is shown in **Appendix 6**.

Recommendation 12

- Preconception counselling including contraceptive option should be offered to women with bipolar disorder as well as to their partners prior to conception. **(Grade C)**

d. Treatment Considerations in Pregnancy and During Lactation

Women who on psychotropic medications and in reproductive age or plan a pregnancy should understand the risks, benefits and uncertainties of using such medications during pregnancy. If medications are needed during pregnancy, it is advisable to wait after the first trimester due to teratogenic risk. They should be selected on the basis of existing safety data, with a preference for monotherapy and at the lowest effective dose.^{107, level III} Refer to **Appendix 8**.

i. Pregnancy

Patients who discontinue mood stabilising medication after conception increase their risk of relapse into depression or mania, either which could lead to complications and untoward effects on the foetus.^{103, level III}

- **Mood Stabilisers (General)**

Discontinuing mood stabilisers presents high risks of recurrence among pregnant women diagnosed with BD ranging from 40% to 73%.^{106, level II-2; 109, level II-2} Abrupt discontinuation of the medication carries higher risk of recurrence compared to gradual discontinuation ($p < 0.0001$).^{109, level II-2}

In a study on women with epilepsy taking antiepileptic drugs, 4.2% of live births had major congenital malformation (MCM) and the risks were higher in polytherapy than monotherapy exposure ($p = 0.01$).^{110, level II-2}

Carbamazepine and sodium valproate are known to interfere with folate metabolism, therefore 5 mg of folic acid is recommended one month prior to and during pregnancy to minimise teratogenic risk.^{111, level II-2}

- **Valproate acid (VPA)**

Studies on pregnant women with epilepsy showed that VPA had more adverse outcomes including MCM compared to other antiepileptics ($p < 0.0003$). The rate of serious adverse outcomes was higher with VPA doses at or above 900 mg/day compared to lower doses.^{112, level II-2} Polytherapy regimens containing VPA have significantly more MCMs than those without (OR=2.49, 95% CI 1.31 to 4.70).^{110, level II-2} In term of monotherapy in the first trimester, VPA is associated with significantly increased risks of several congenital malformations, such as spina bifida, atrial septal defect, cleft palate and hypospadias, compared to treatment not using antiepileptic drugs or using other antiepileptic drugs.^{113, level II-2}

- **Lithium**

During pregnancy, rates of recurrence after lithium discontinuation is 52% but increased to 70% at postpartum. Risk of recurrence is less in gradual than rapid discontinuation ($p = 0.006$).^{109, level II-2}

Lithium exposure in first trimester is associated with an increased risk of cardiovascular malformation, specifically Ebstein's anomaly (0.05 - 0.1%) although the increased risk is lower than previously thought. Its exposure after first trimester is associated with an increased risk of diabetes insipidus, polyhydramnios, thyroid dysfunction and floppy baby syndrome.^{111, level II-2}

- **Lamotrigine**

Lamotrigine is protective against risk of illness recurrence in pregnancy and relatively safe in term of MCM as compared to other mood

stabilisers.^{107, level II-2} There is no evidence on major birth defects during the first trimester of lamotrigine monotherapy up to a daily dose of 400 mg ($p=0.26$)^{113, level II-2} or specific increased risk of isolated orofacial clefts relative to other malformations (OR=0.8, 95% CI 0.11 to 2.85).^{114, level II-2}

- **Carbamazepine**

As monotherapy, although the use of carbamazepine is not recommended during pregnancy, it is associated with the lowest risk of MCM in comparison to valproate, phenytoin, gabapentin, topiramate and levetiracetam.^{109, level II-2}

- **Antipsychotics**

There is limited information on the safety of atypical antipsychotics in pregnancy. Although no increase found in the risk of teratogenicity over background rate, further data is warranted.^{111, level II-2} Olanzapine, haloperidol, risperidone and quetiapine demonstrate incomplete placental passage.^{108, level II-2}

- **Antidepressants**

The newer antidepressants such as SSRI, Selective Noradrenaline Serotonin Reuptake Inhibitor (SNRI) and dual action drugs (mirtazapine and nefazodone) are not associated with increased risk in MCM (RR=1.01, 95% CI 0.57 to 1.80).^{116, level II-2} The risk of persistent pulmonary hypertension of the newborn increases in infants exposed to SSRIs in late pregnancy (NNH=351) has been noted.^{117, level I}

ii. Lactation

Maintenance of optimal maternal mental health is the primary goal in treating women who choose to breastfeed.^{103, level III} They should be educated about the possible side effects and advised to discontinue the breastfeeding if their infants develop a toxic or adverse effect while taking psychotropic medications.^{107, level III}

The importance of adequate sleep for the woman with BD cannot be overstated. This is challenging during pregnancy, postpartum period and breastfeeding. The well-established benefits of breastfeeding must be weighed against the potential risk for relapse secondary to sleep deprivation.^{103, level III}

Refer to **Appendix 7** on key issues to consider prior to administering different psychotropic medications during pregnancy and lactation.

NICE recommends to consider ECT if there is no response to changes in dose or drug in pregnant women with severe mania.¹¹⁸

Women with bipolar disorder who breastfeed should be informed regarding possible side effects of medications to their infants and to seek immediate medical opinion should they occur.

Recommendation 13

- Women with bipolar disorder (BD) of reproductive age who plan for pregnancy and are taking psychotropic medications should be counselled regarding the risks and benefits of using such medications. **(Grade C)**
- Abrupt discontinuation of the mood stabilisers in pregnancy and postpartum should be avoided because of risk of BD recurrence especially in the later. **(Grade C)**
- Mood stabilisers should be used with caution in BD with pregnancy in view of teratogenic risk. **(Grade C)**

14.2 ELDERLY

Psychoeducational and psychotherapeutic support as well as medication are important components in the treatment of BD among elderly. The elderly are at increased risk of developing adverse drug reaction, drug-drug interaction or medication toxicity especially when they are also treated for other diseases.

a. Pharmacological Considerations

Although there are no specific guidelines for the treatment of BD in elderly, monotherapy followed by combination therapy of the various classes of drugs may help with the resolution of symptoms. Lithium, valproate, carbamazepine and lamotrigine either alone or in combination with atypical antipsychotics or antidepressants are beneficial in the treatment of this group of patients.^{119, level II-2}

Both lamotrigine and lithium are efficacious in the maintenance therapies for elderly with BD I. Compared to placebo, lamotrigine delays time-to-intervention for depressive episodes ($p=0.011$) whereas lithium delays time-to-intervention for mania, hypomania or mixed symptoms ($p=0.034$).^{120, level I} The risk of hospitalisation for lithium toxicity particularly in lithium naïve elderly increases with concomitant use of loop diuretics (RR=5.5, 95% CI 1.9 to 16.1) or ACE inhibitors (RR=7.6, 95% CI 2.6 to 22.0).^{121, level III}

The target serum lithium level in the range between 0.4 and 0.7 mEq/L has been recommended for elderly with BD. They require 25 - 50% lower dosage of lithium than younger patients.^{119, level II-2}

Caution should be taken while prescribing medications in the elderly with bipolar disorder due to reduced metabolism and susceptibility to side effects.

b. Role of ECT

ECT is the treatment of choice for elderly with mania who are intolerant of or refractory to pharmacologic management, or who have a severe symptoms that necessitates a rapid response. The mortality rate associated with ECT in elderly has been reported to be 0.01%.^{119, level II-2} ECT is also efficacious and safe in depressed elderly patients who are poorly responsive to medication ($p < 0.05$). Particular care may be required in the subgroup of elderly with comorbid medical illness who are at risk of cognitive deficits after ECT ($p < 0.00001$).^{122, level III}

Recommendation 14

- Medications for elderly with bipolar disorder (BD) should be prescribed at the lowest effective dose. **(Grade C)**
- Electroconvulsive therapy (ECT) should be considered for elderly with BD who respond poorly to medications. **(Grade C)**
- ECT should be given with caution to the elderly with BD who has cognitive deficit. **(Grade C)**

15. IMPLEMENTING THE GUIDELINES

The management of BD should be guided by evidence-based approach in order to provide quality care to the patients. Challenges remain in establishing the diagnosis and managing complex issues in different phases of BD.

15.1 Facilitating and Limiting Factors

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

1. Wide dissemination of the CPG to healthcare providers (such as soft- and hard-copies)
2. Regular update on BD management at conferences and scientific meeting locally

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

1. Evolving understanding of the illness and its treatment
2. Insufficient resources for integrated care at different level of service delivery
3. Variation in treatment practice and preferences
4. No national registry for BD for further planning of services

15.2 Potential Resource Implications

To implement the CPG, there must be strong commitment to:-

1. Ensure widespread distribution of the CPG to healthcare providers via printed and electronic copies
2. Reinforce regular training with adequate funding of healthcare providers
3. Availability of trained multidisciplinary team at different levels of healthcare
4. Ensure availability of recommended drugs in primary care setting
5. Ensure widespread distribution of updated patient education materials

The following is proposed as **clinical audit indicator for quality management**:-

$$\frac{\text{Percentage of people with bipolar disorder on lithium monitoring every six months}}{\text{Total number of people with bipolar disorder on lithium in six months within the same period}} \times 100\%$$

Number of people with bipolar disorder on lithium monitoring every six months within a period

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APPENDIX 1

EXAMPLES OF SEARCH STRATEGY

The following MeSH terms or free text terms were used either singly or in combination, search was limit to English, human and last 10 years:-

Bipolar Disorder

1. Bipolar Disorder/
2. manic state\$.tw.
3. (manic-depressive adj1 psychos\$).tw.
4. (manic-depressive adj1 psychos\$).tw.
5. mania\$.tw.
6. (bipolar adj1 depression).tw.
7. bipolar affective psychos\$.tw.
8. (bipolar adj1 disorder\$).tw.
9. mixed state\$.tw.

Acute Treatment

1. Bipolar Disorder/
2. manic state\$.tw.
3. (manic-depressive adj1 psychos\$).tw.
4. (manic-depressive adj1 psychos\$).tw.
5. mania\$.tw.
6. (bipolar adj1 depression).tw.
7. bipolar affective psychos\$.tw.
8. (bipolar adj1 disorder\$).tw.
9. mixed state\$.tw.

Maintenance Treatment

1. Bipolar Disorder/
2. manic state\$.tw.
3. (manic-depressive adj1 psychos\$).tw.
4. (manic-depressive adj1 psychos\$).tw.
5. mania\$.tw.
6. (bipolar adj1 depression).tw.
7. bipolar affective psychos\$.tw.
8. (bipolar adj1 disorder\$).tw.
9. mixed state\$.tw.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
11. Maintenance/
12. maintenance.tw.
13. Long-Term Care/
14. (long-term adj1 care).tw.
15. long term care.tw.
16. 11 or 12 or 13 or 14 or 15
17. 10 and 16
18. Drug Therapy/
19. (therap\$ adj1 drug\$).tw.
20. pharmacotherap\$.tw.
21. 18 or 19 or 20
22. 17 and 21
23. Limit 21

Psychosocial therapy

1. Bipolar Disorder/
2. manic state\$.tw.
3. (manic-depressive adj1 psychos\$).tw.
4. (manic-depressive adj1 psychos\$).tw.
5. mania\$.tw.
6. (bipolar adj1 depression).tw.
7. bipolar affective psychos\$.tw.
8. (bipolar adj1 disorder\$).tw.
9. mixed state\$.tw.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
11. Psychotherapy, Multiple/ or Psychotherapy, Brief/ or Psychotherapy, Group/ or Psychotherapy/
12. Psychoeducation.tw.
13. Cognitive behavior#rtherap*.tw.
14. Family focus therap*.tw.
15. Family intervention*.tw.
16. 10 or 12 or 13 or 14 or 15
17. 10 and 16
18. Limit 17

APPENDIX 2

CLINICAL QUESTIONS

1. What are the criteria used in DSM-IV-TR and ICD 10 to diagnose bipolar disorder?
2. What are the effective tools in screening in bipolar disorder?
3. What are the epidemiology/risk factors of bipolar disorder?
4. What are the differential diagnoses in bipolar disorder?
5. What are the indicators of bipolarity in patients presenting with depression?
6. What are the comorbidities (including alcohol/substance misuse) with bipolar disorder?
7. What are the types of treatment offered in different levels of care (primary care/community, hospital and mental institution) in bipolar disorder?
8. What are the admission (including MHA forms and MHR) and referral criteria in bipolar disorder?
9. What are the effective/safe pharmacological (monotherapy and combination) treatments in acute phase of bipolar disorder?
10. Is ECT effective/safe in bipolar disorder?
11. What are the other effective/safe physical therapies in bipolar disorder?
12. What are the effective psychosocial interventions in bipolar disorder?
13. What are the roles of antidepressants in management of bipolar disorder?
14. What are the effective/safe pharmacological (monotherapy and combination) treatments in the maintenance phase of bipolar disorder?
15. What needs to be monitored during maintenance phase of bipolar disorder?
16. What is the prevalence and risk factors of non-adherence to treatment in bipolar patients?
17. What are the strategies available to improve adherence in bipolar disorder?
18. What are the effective/safe pharmacological (monotherapy and combination) treatments in rapid cycling bipolar disorder?
19. What are the risk factors for suicide in bipolar disorder?
20. What are the psychosocial interventions of suicide in bipolar disorder?
21. What are the strategies for suicide prevention in bipolar disorder?
22. What are the fertility issues in the treatment of women of child bearing age with bipolar disorder?
23. What are the effects of contraception in the treatment of women of child bearing age with bipolar disorder?

24. What is the role of preconception counselling in women with child bearing age with bipolar disorder?
25. What are the effective/safe treatments in pregnant/lactating women with bipolar disorder?
26. What are the drug-drug interactions in the treatment of elderly with bipolar disorder?
27. What are the effective/safe drug dosages in the treatment of elderly with bipolar disorder?
28. What is the role of ECT in the treatment of elderly with bipolar disorder?
29. What are the presentations of people with bipolar disorder who have substance misuse?
30. What are the effective/safe pharmacological (monotherapy and combination) treatments in bipolar disorder who have substance misuse?
31. What are the effective/safe psychosocial treatments in bipolar disorder who have substance misuse?

APPENDIX 3

SCREENING TOOLS FOR BD

Screening Tool	Sensitivity	Specificity	Comment
Mood Disorder Questionnaire (MDQ) ^{123, level III}	61.3%	87.5%	MDQ's performance depends upon:- <ul style="list-style-type: none"> • Setting in which it is used - sensitivity is higher in mood disorder and psychiatric outpatient sample compared to the general population (64.7% vs 25.9%). • Threshold to identify caseness - the broader definition of a case (using mild level of impairment and different cut-off point) will improve sensitivity by 30% • Subtype of BD - sensitivity is higher in detecting BD I than BD II (66.3% vs 38.6%)
Bipolar Spectrum Diagnostic Scale (BSDS) ^{124, level III}	83.3%	68.1%	<ul style="list-style-type: none"> • In patients attending community-based outpatient psychiatric clinic, the sensitivity of the BSDS is similar for BD I, BD II and BD Not Otherwise Specified (NOS)/cyclothymia. • ROC analysis indicated that cut-offs of 11 and 12 maximised the sum of sensitivity and specificity for the entire group of people with BD. The AUC is significant (0.80, 95% CI 0.76 to 0.85) • At cut-off of 11 the sensitivity is 83.3%, specificity 68.1%, PPV 21.2% and NPV 97.5% • With its high NPV, the BSDS is excellent at ruling out a diagnosis of BD
Hypomania Checklist (HCL-32) ^{125, level III}			<p>In patients attending psychiatric clinic HCL-32 showed a good accuracy:-</p> <ul style="list-style-type: none"> • cut-off 8: sensitivity 0.92, specificity 0.48; • cut-off 10: sensitivity 0.88, specificity 0.54; • cut-off 12: sensitivity 0.85, specificity 0.61 <p>The sensitivity in detecting BD II better as compared to MDQ</p> <ul style="list-style-type: none"> • cut-off 8: sensitivity 0.90, specificity 0.42; • cut-off 10: sensitivity 0.80, specificity 0.47; • cut-off 12: sensitivity 0.80, specificity 0.54

APPENDIX 4

THE MOOD DISORDERS QUESTIONNAIRE (MDQ)

The MDQ was developed by a team of psychiatrist, researchers and consumer advocates to address the need for timely and accurate evaluation of BD.

Clinical Utility

- The MDQ is a brief self-report instrument that takes about 5 minutes to complete.
- The instrument is designed for screening purpose only and it is not to be used as a diagnostic tool.
- A positive screen should be followed by a comprehensive evaluation

Scoring

In order to screen positive for possible BD, all three of the following criteria must be met:

- **“YES”** to 7 or more of the 13 items in Question 1 **AND**
- **“YES”** to Question number 2 **AND**
- **“Moderate Problem”** or **“Serious Problem”** to Question 3

		YES	NO
1.	Has there ever been a period of time when you were not your usual self and...	<input type="checkbox"/>	<input type="checkbox"/>
	...you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?	<input type="checkbox"/>	<input type="checkbox"/>
	...you were so irritable that you shouted at people or started fights or arguments?	<input type="checkbox"/>	<input type="checkbox"/>
	...you felt much more self-confident than usual?	<input type="checkbox"/>	<input type="checkbox"/>
	...you got much less sleep than usual and found you didn't really miss it?	<input type="checkbox"/>	<input type="checkbox"/>
	...you were much more talkative or spoke much faster than usual?	<input type="checkbox"/>	<input type="checkbox"/>
	...thoughts raced through your head or you couldn't slow your mind down?	<input type="checkbox"/>	<input type="checkbox"/>

	...you were so easily distracted by things around you that you had trouble concentrating or staying on track?	<input type="checkbox"/>	<input type="checkbox"/>
	...you had much more energy than usual?	<input type="checkbox"/>	<input type="checkbox"/>
	...you were much more active or did many more things than usual?	<input type="checkbox"/>	<input type="checkbox"/>
	...you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?	<input type="checkbox"/>	<input type="checkbox"/>
	...you were much more interested in sex than usual?	<input type="checkbox"/>	<input type="checkbox"/>
	...you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?	<input type="checkbox"/>	<input type="checkbox"/>
	...spending money got you or your family into trouble?	<input type="checkbox"/>	<input type="checkbox"/>
2.	If you checked YES to more than one of the above, have several of these ever happened during the same period of time?	<input type="checkbox"/>	<input type="checkbox"/>
3.	How much of a problem did any of these cause you – like being unable to work; having family, money or legal troubles; getting into arguments or fights? <i>Please circle one response only.</i> No Problem Minor Problem Moderate Problem Serious Problem		
4.	Have any of your blood relatives (i.e. children, siblings, parents, grandparents, aunts, uncles) had manic-depressive illness or bipolar disorder?	<input type="checkbox"/>	<input type="checkbox"/>
5.	Has a health professional ever told you that you have manic depressive illness or bipolar disorder?	<input type="checkbox"/>	<input type="checkbox"/>

Source: 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;157:1873-1875.

APPENDIX 5

PARAMETERS FOR REGULAR MONITORING IN BD

Relevant physical examination and baseline laboratory investigations should be performed prior to initiation in pharmacological treatment and at regular interval thereafter.

Parameter	For all patients at first visit	Antipsychotics	Lithium	Valproate	Carbamazepine
Weight, height and waist circumference	Yes	At initiation & every 3 months for first year; more often if patient gains weight rapidly	At initiation & when needed if the patient gains weight rapidly	At initiation & at 6 months if patient gains weight rapidly	
Blood pressure	Yes	At every visit			
Fasting blood sugar	Yes	At initiation & at 3 months (1 month for olanzapine); more often if levels are elevated			
ECG	If indicated by history or clinical picture	At initiation if there are risk factors for or existing cardiovascular disease	At initiation if there are risk factors for or existing cardiovascular disease		
Full blood count	Yes		Only if clinically indicated	At initiation & 6 months	
Thyroid function	Yes		At initiation & every 6 months, more often if levels are deteriorated		
Renal function	Yes		At initiation & every 6 months; more often if there is deterioration or patients on other medications such as Anticholinesterase inhibitors, diuretics or Non steroidal anti-inflammatory drugs		Urea & electrolytes every 6 months

Parameter	For all patients at first visit	Antipsychotics	Lithium	Valproate	Carbamazepine
Liver function	Yes	At initiation & when necessary		At initiation & 6 months	
Lipid profile	Yes	At initiation & at least yearly; more often if levels are elevated			
Drug serum level			1 week after initiation & 1 week after every dose change until level stable, then every 3 to 6 months	Every 6 months Only if there is ineffectiveness, poor adherence or toxicity	
Serum calcium level			At initiation & yearly		

APPENDIX 6

SUGGESTED DRUGS DOSAGES AND ADVERSE EFFECTS IN BD

NAME	DOSE RANGE	MAIN ADVERSE EFFECTS
MOOD STABILISERS		
Lithium	<p>Acute mania: 600 – 1800 mg/day in divided doses</p> <p>Maintenance dose: 300 – 1200 mg/day in divided doses</p> <p>(Desired serum level : 0.6 - 1.2 mEq/L not exceeding 1.5 mEq/L) To be used with caution and correlate clinically</p>	<p>GI upset (in first 2 week)</p> <p>Polyuria & Polydipsia</p> <p>Metallic taste</p> <p>Weight gain</p> <p>Hypothyroidism</p> <p>Hyperparathyroidism</p> <p>Fine tremor</p> <p>Diabetes Insipidus</p>
Valproate	<p>Acute Mania: 600 - 2500 mg/day in divided doses</p> <p>Maintenance dose: 400 - 2000 mg/day in divided doses</p> <p>(Desired serum level 50-100 µg/mL @ 347-693 µmol/L)</p>	<p>GI upset</p> <p>Sedation</p> <p>Weight gain</p> <p>Tremor</p> <p>Thrombocytopenia</p> <p>Raised liver enzymes</p>
Carbamazepine	<p>Mania/mixed episodes</p> <p>200 to 1600 mg/day in divided doses (Desired serum level 4-12 mg/L @ 17-50 µmol/L)</p>	<p>Steven Johnson's Syndrome</p> <p>Hypotension</p> <p>Rash</p> <p>GI upset</p> <p>Dizziness</p> <p>Drowsiness</p> <p>Fatigue</p>
Lamotrigine	<p>Bipolar I Disorder:</p> <p>Maintenance dose: 100 – 400 mg/day in divided doses</p> <p>a) For patients not taking enzyme inducing drugs or valproate: Initial dose: 25 mg/day Maintenance dose: 200 mg/day</p> <p>b) For patients with valproate regimen : Initial dose: 25 mg/day EOD Maintenance dose: 100 mg/day</p> <p>c) For patients with enzyme inducing antiepileptic drug regimen (e.g. carbamazepine) without valproate: Initial dose: 50 mg/day Maintenance dose: 400 mg/day in divided doses</p>	<p>Skin rash</p> <p>Headache</p> <p>Insomnia</p> <p>GI upset</p> <p>Steven Johnson's Syndrome</p> <p>Diplopia, Blurred vision</p> <p>Precaution: Patients on lamotrigine who develop skin rash should be promptly evaluated and the drug to be withdrawn immediately unless the rash is clearly not drug-related. Rechallenge is not recommended unless the potential benefit clearly outweighs the risk.</p>

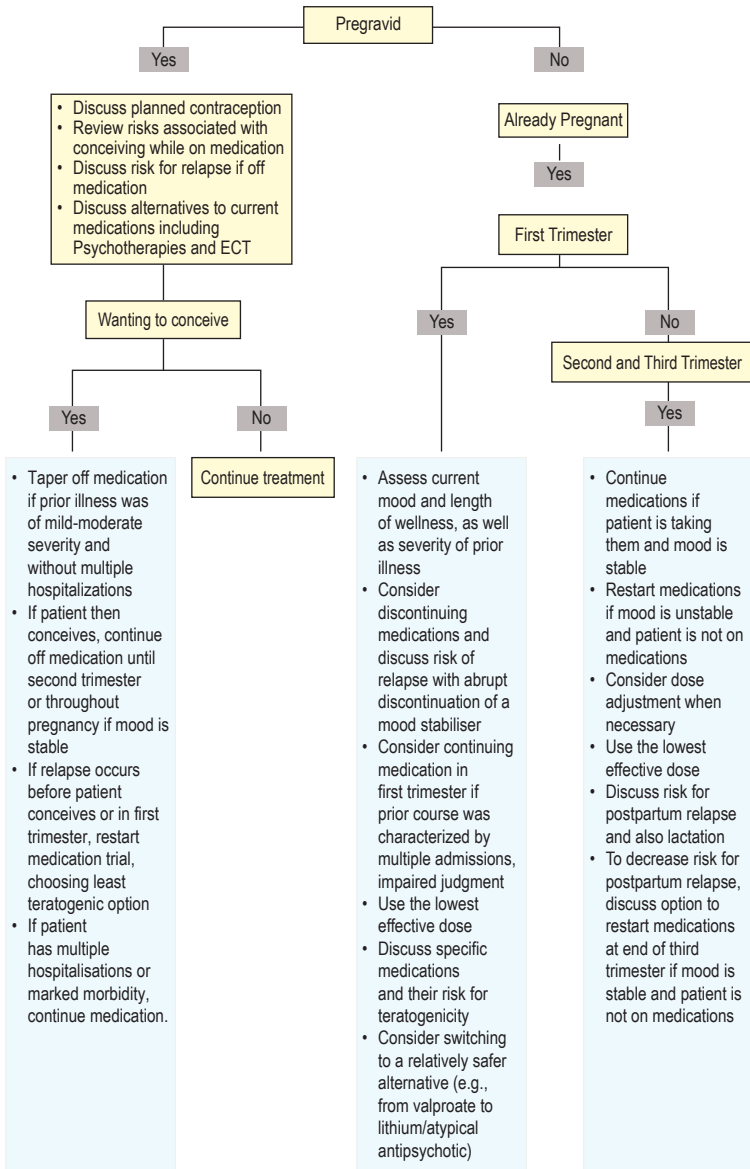
NAME	DOSE RANGE	MAIN ADVERSE EFFECTS
ANTIPSYCHOTICS		
Quetiapine	<p>Acute depression: 50 - 300 mg/day in divided doses</p> <p>Acute mania: 300 - 800 mg/day in divided doses</p> <p>Maintenance (monotherapy or adjunctive therapy) 400 - 800 mg/day in divided doses</p>	<p>Orthostatic hypotension</p> <p>Somnolence</p> <p>Weight gain</p> <p>Dizziness</p> <p>Dyslipidemia</p> <p>Extrapyramidal symptoms (EPS)</p> <p>Hyperglycemia</p>
Olanzapine	<p>Acute mania/mixed episodes:</p> <p>Monotherapy: 10 - 20 mg/day</p> <p>Maintenance therapy: 5 - 20 mg/day</p>	<p>Weight gain</p> <p>Dyslipidaemia</p> <p>Somnolence</p> <p>Dizziness</p> <p>Hyperglycemia</p> <p>EPS</p>
Paliperidone	Oral: 6 - 12 mg/day	<p>Tachycardia</p> <p>Somnolence</p> <p>EPS</p> <p>Headache</p> <p>Tremor</p>
Risperidone	<p>Bipolar I Disorder 2 - 6 mg/day in divided doses</p>	<p>Weight gain</p> <p>EPS</p> <p>Hyperprolactinaemia</p> <p>Postural hypotension</p> <p>Dyslipidaemia</p>
Risperidone LAI	25 - 50 mg every 2 weeks	
Aripiprazole	<p>Bipolar I Disorder Monotherapy 15 - 30 mg/day</p> <p>Adjunct to lithium/valproate: 10 - 15 mg/day</p>	<p>Agitation</p> <p>Akathisia</p> <p>Headache</p> <p>Insomnia</p> <p>Anxiety</p>
Ziprasidone hydrochloride	<p>Acute mania/mixed episodes: 40 - 80 mg/day after meal in divided doses</p>	<p>QT Prolongation</p> <p>Akathisia</p> <p>EPS</p> <p>Somnolence</p>
Asenapine	<p>Acute mania/mixed episodes:</p> <p>Monotherapy: 20 mg/day sublingually in divided doses</p> <p>As adjunctive with lithium or valproate: 10 - 20 mg/day sublingually in divided doses</p>	<p>Bitter taste</p> <p>Oral hypoesthesia</p> <p>Akathisia</p> <p>Drowsiness</p> <p>Dizziness</p> <p>EPS</p> <p>Somnolence</p>
Haloperidol	3 - 30 mg/day	<p>EPS</p> <p>Hypotension</p> <p>Constipation</p> <p>Akathisia</p> <p>Cardiac abnormalitie</p>

Lurasidone	20 - 120 mg/day	EPS GI upset Akathisia Somnolence
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NAME	DOSE RANGE	MAIN ADVERSE EFFECTS
Selective Serotonin Reuptake Inhibitors (SSRIs)		
Escitalopram	10 - 20 mg/day	GI upset Headache Sexual dysfunction
Sertraline	50 - 200 mg/day	
Fluoxetine	20 - 40 mg /day	GI upset Dry mouth Sweating Dizziness Fatigue
Fluvoxamine	50 mg - 300mg/day	Anorexia Insomnia Somnolence Headache
Monoamine Oxidase Inhibitor (MAOI)		
Moclobemide	150 - 300 mg/day in divided doses	Nausea Somnolence Dizziness Headache Insomnia
Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs)		
Venlafaxine	37.5 - 225 mg/day	Headache Hypertension Palpitations GI upset Sweating Sexual dysfunction Caution: risk of mood switch
Others		
Bupropion	150 - 400 mg/day in divided doses	Headache Insomnia Seizure Rash Constipation Nausea
Modafinil	100 - 400 mg/day in divided doses	Headache Insomnia Anxiety GI upset

APPENDIX 7

FLOW CHART ON TREATMENT APPROACH OF PREGNANT WOMEN IN BD



Adapted from Altshuler L, Richards M, Yonkers K. Treating bipolar disorder during pregnancy. *Curr Psychiatry* 2003;2:14 –26.

APPENDIX 8

PSYCHOTROPIC MEDICATIONS IN PREGNANCY/LACTATION

Medication Pregnancy/	FDA Use-in-pregnancy Risk Category	Teratogenic Risk	Lactation Information	AAP breast-feeding Rating Scale	Neuro-developmental	Neonatal Toxicity and Syndromes	Guidelines
SSRIs		No teratogenic risk Most prospective studies have not shown significant adverse effects with SSRIs that have half-lives longer than paroxetine	Best studied class in lactation			Late exposure to SSRIs (fluoxetine, fluvoxamine, paroxetine, sertraline) shows increase in premature delivery, lower birth weight (mean 175 gm), and lower APGAR scores	Well studied as a class Not associated with teratogenic effects
Fluoxetine	C	One of best studied medications in pregnancy Second most fetal medication exposure (umbilical cord) of SSRIs 3rd trimester administration has higher frequency of admission of neonates to special care nurseries	Highest proportion in breast milk (compared with nortriptyline, paroxetine, and sertraline)	U	No neurobehavioral effects (N = 40) in gestational-exposed children aged 15–71 months	Feeding difficulties/jitteriness	

<p>Sertraline</p>	<p>C</p>	<p>One of lowest for fetal medication exposure (umbilical cord concentration) of SSRIs</p>	<p>Undetectable levels in infants Most favorable for breast-feeding</p>	<p>U</p>			
<p>Citalopram</p>	<p>C</p>	<p>Highest fetal medication exposure (umbilical cord concentration) of SSRIs</p>		<p>NA</p>			
<p>Tricyclics</p>		<p>Not associated with teratogenic effects</p>	<p>Widely used during lactation</p>		<p>No neurodevelopmental differences compared with controls</p>	<p>Jitteriness, irritability Anticholinergic side effects (functional bowel obstruction/ urinary retention)</p>	<p>Secondary TCAs recommended because they have fewest anticholinergic effects Need to monitor levels closely, particularly during third trimester May need to increase up to 1.6 times preconception level for therapeutic effect</p>

Nortriptyline	D	Less anticholinergic, less orthostatic hypotension potential (due to being secondary tricyclic)	Undetectable levels in infants Most favorable for breast-feeding	NA		Seizures	Not recommended
Clomipramine	C			U		Respiratory depression (case report)	Not recommended
MAOIs	C	Not recommended during pregnancy Studies indicate teratogenic potential	Not recommended	NA		Potential for hypertensive crises	Not recommended
Bupropion	B	No increase in major malformations (N=136)	No adverse effect (N=1)	U			Recent study indicates safety with regards to teratogenesis
Other Antidepressants							Recent study indicates safety with regards to teratogenesis
Venlafaxine	C	No teratogenic risk (N = 150)	Mean infant dose 7.6% of maternal weight adjusted dose (N=3)	NA			Not recommended
Mirtazapine	C	Limited data	Case report (N=1): no adverse effects	NA			Limited data

Duloxetine	C	No data		NA			Monotherapy over polytherapy
Mood Stabilisers							
Lithium	D	<p>Teratogenic effects first trimester</p> <p>Risk of Ebstein's anomaly 20–40 times higher than in the general population, which is 1/20,000</p> <p>Umbilical cord levels equal to maternal blood levels⁶⁷</p>	Discouraged during lactation	<p>Use with caution</p>	<p>No overt neurobehavioral differences from controls (N = 60) in 5 year follow-up of children gestationally exposed to lithium</p>	<p>Floppy baby syndrome</p> <p>Fetal cardiac arrhythmias, hypoglycemia, nephrogenic diabetes insipidus</p> <p>Reversible thyroid changes</p> <p>Polyhydramnios, large for gestational age infants</p> <p>Flaccidity</p> <p>Lethargy</p> <p>Poor sucking reflex (case reports)</p>	<p>Try to avoid first trimester use if possible</p> <p>Use lowest possible dose in divided doses</p> <p>Last month of pregnancy, monitor lithium levels weekly (one month prior to delivery) 2–3 days prior to delivery, either decrease dose by 25% or discontinue lithium</p> <p>Fetal echocardiogram and ultrasound at 16–18 weeks gestation for cardiac abnormalities</p> <p>Neonatal echocardiogram</p>

<p>Valproate</p>	<p>D</p>	<p>Teratogenic effects: Neural tube defect 1%–2% (10–20 times higher than in general population) Craniofacial, limb, cardiovascular, genitourinary malformations Teratogenic effect increases with anticonvulsant polypharmacy and in valproate doses >1000 mg/day⁷ Fetal concentrations 145%–219% higher than maternal levels at birth</p>	<p>Compatible with breast-feeding</p>	<p>Compatible</p>	<p>Developmental delay and mental retardation reported</p>	<p>Low birth weight Fetal valproate syndrome Hepatotoxicity, coagulopathies, neonatal hypoglycemia</p>	<p>Monotherapy (vs. polypharmacy) recommended Final month of pregnancy may require increase in dose Folate supplementation recommended</p>
<p>Carbamazepine</p>	<p>C</p>	<p>Teratogenic risk (but less frequent and severe compared with valproate) Neural tube defects, cleft palate, cardiovascular, and urinary tract abnormalities Fetal serum levels 50%–80% of maternal levels Teratogenic effect increased when combined with valproate</p>	<p>Compatible with breast-feeding</p>	<p>Compatible</p>	<p>Neurobehavioral studies found no significant differences compared with controls (N=36 mother-child dyads)</p>	<p>Fetal carbamazepine syndrome Transient hepatotoxicity and fetal vitamin K deficiency Reductions in birth weight (250 gm) Decreased mean head circumference</p>	<p>Obtain maternal alpha fetoprotein levels Fetal echocardiogram and ultrasound at 16–18 weeks gestation Folate supplementation (4–5 mg/day) Vitamin K supplementation (20 mg/day) Neonate IM dose vitamin K (1 mg)</p>

Antipsychotics 2nd-generation (atypical) agents	C	No major malformations (N=23) 2 cases of gestational diabetes	5/21 breast-fed infants with adverse effects	NA			
			No major malformations (N=151)				
Risperidone	C		No adverse effects (N=4)	NA		No adverse effects (N=2)	
Quetiapine	C	Animal studies: delayed skeletal ossification, pup death and decreased fetal weight	Infants expected to ingest 0.43% of maternal dose (N=1)	U		No adverse effect (N=1)	
Ziprasidone	C	Animal studies: developmental delays, possible teratogenic effects, increase in stillbirths		U			Not recommended until more data collected
Aripiprazole	C	Animal studies: delayed skeletal ossification, decreased fetal weight		NA			Not recommended until more data collected

Conventional agents			Milk: plasma ratio<1 (acceptable in breast-feeding)			Extrapyramidal side effects, increased muscle tone, rooting, tendon reflex, (persisting for several months) Jaundice, intestinal obstruction	
High Potency	C	No teratogenic effects		U	No consistent findings	Theoretical risk of Neuroleptic Malignant Syndrome	
Low Potency	C	Increased risk for nonspecific teratogenic effects		U		Theoretical risk of Neuroleptic Malignant Syndrome	
Benzodiazepines Alprazolam Lorazepam Clonazepam Diazepam	D D C D	Initial studies indicated increase in oral clefts, later studies failed to show this, data inconclusive Pooled meta-analyses indicate 7/10,000 risk of oral cleft from 1st trimester BZD exposure (general pop 6/10,000) Most studies involved diazepam and alprazolam. No clear data on clonazepam.	Not recommended	U U NA U	Inconsistent data	Floppy infant syndrome Restlessness, hypertonia, hyperreflexia, tremulousness, apnea, diarrhea, vomiting (until 3 months of age)	Detailed ultrasound at 18–20 weeks gestation for evaluation of oral cleft

*See Appendix 9, AAP: American Academy of Pediatrics; U: unknown but may be of concern; NA: not available

Adopted from Jain AE, Lacy T. Psychotropic drugs in pregnancy and lactation. J Psychiatr Pract. 2005 May;11(3):177-91

APPENDIX 9

U.S. FOOD AND DRUG ADMINISTRATION (FDA) USE-IN-PREGNANCY RATINGS

A	<p>Controlled studies show no risk. Adequate, well-controlled studies in pregnant women who have failed to demonstrate a risk to the fetus in any trimester of pregnancy</p>
B	<p>No evidence of risk in humans. Adequate, well-controlled studies in pregnant women who have not shown increased risk of fetal abnormalities despite adverse findings in animals, or, in the absence of adequate human studies, animal studies show no fetal risk. The chance of fetal harm is remote, but remains a possibility.</p>
C	<p>Risk cannot be ruled out. Adequate, well controlled human studies are lacking, and animal studies have a shown a risk to the fetus or are lacking as well. There is a chance of fetal harm if the drug is administered during pregnancy, but the potential benefits may outweigh the potential risk.</p>
D	<p>Positive evidence of risk. Studies in humans, or investigational or post-marketing data, have demonstrated fetal risk. Nevertheless, potential benefits from the use of the drug may outweigh the potential risk. For example, the drug may be acceptable if needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective.</p>
X	<p>Contraindicated in pregnancy. Studies in animals or humans, or investigational or post-marketing reports, have demonstrated positive evidence of fetal abnormalities or risk which clearly outweighs any possible benefit to the patient.</p>

LIST OF ABBREVIATIONS

AAP	Atypical Antipsychotics
AUC	Area Under Curve
BD	Bipolar Disorder
BSDS	Bipolar Spectrum Diagnostic Scale
CBT	Cognitive Behavioural Therapy
CI	Confidence Interval
CPG(s)	Clinical Practice Guidelines
DG	Development Group
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5th Edition
ECT	Electroconvulsive Therapy
EPS	Extrapyramidal symptoms
EWS	Early Warning Signal
FFT	Family Focus Therapy
HAM-D	Hamilton Rating Scale for Depression
HCL-32	Hypomania Checklist 32
ICD-10	International Classification of Diseases and Health Related Problems 10 th Revision
ICM	Intensive Case Management
LAI	Long Acting Injection
IPSRT	Interpersonal Social Rhythm Therapy
MADRS	Montgomery Asberg Depression Rating Scale
MAOI	Monoamine Oxidase Inhibitor
MCM	Major Congenital Malformation
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MDQ	Mood Disorder Questionnaire
NNH	Number Need To Harm
NNT	Number Need To Treat
NOS	Not Otherwise Specific
NPV	Negative Predictive Value
OCD	Obsessive Compulsive Disorder
OFC	Olanzapine-Fluoxetine combination
PPV	Positive Predictive Value
PTSD	Post-Traumatic Stress Disorder
RCT	Randomised Control Trial
PMDD	Premenstrual Dysphoric Disorder
PMS	Premenstrual Syndrome
ROC	Receiver Operating Curve
RR	Relative Risk
SNRI	Selective Noradrenaline Serotonin Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
SR	Systematic Review
STEP BD	Systematic Treatment Enhancement Program for Bipolar Disorder
TAU	Treatment As Usual
TCA	Tricyclic Antidepressants
USA	United States of America
VPA	Valproate Acid
WMD	Weighted Mean Difference
YMRS	Young Mania Rating Scale

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