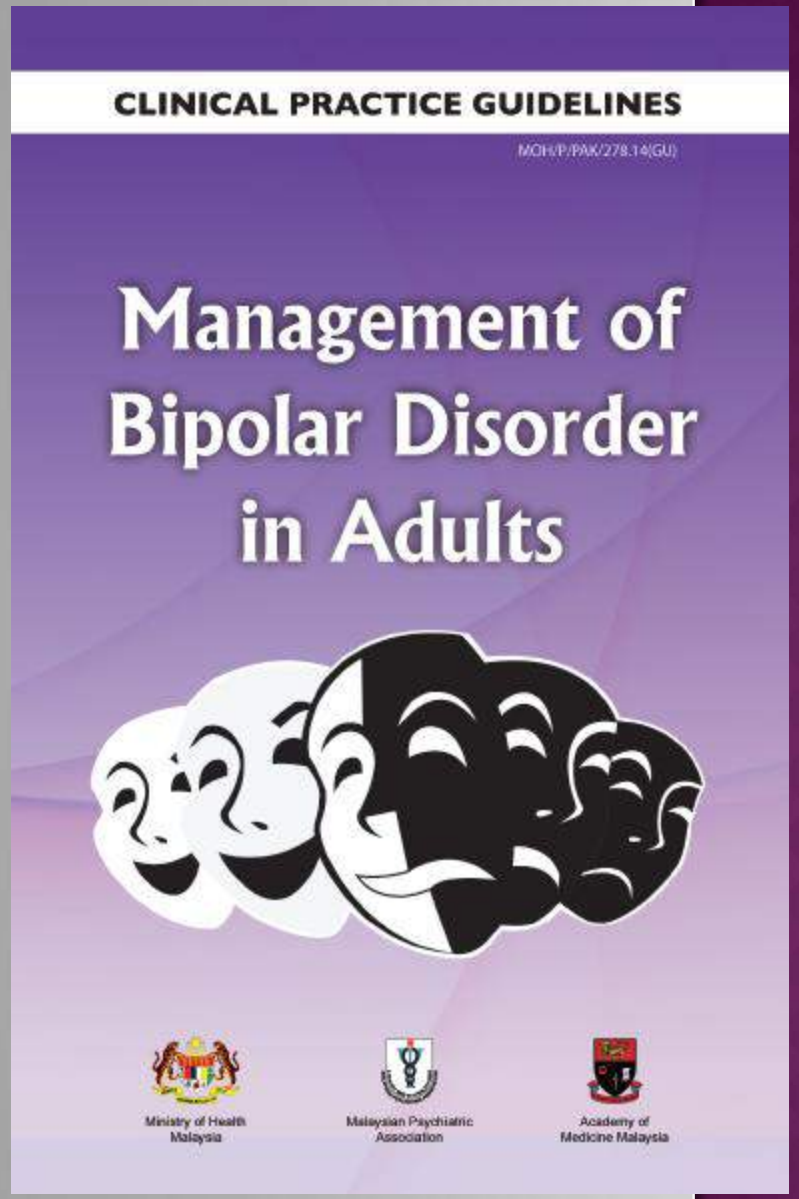


OVERVIEW

Dr. Azizul Awaluddin
Head of Department & Consultant Psychiatrist
Hospital Putrajaya

HISTORY

- Appointment by Ministry of Health
- Initiated the first meeting in July 2013
- Regular meeting (monthly discussion)
- Clinical questions
- Literature Searches > 2000 articles
- Critical Appraisal > 300 articles

DATABASE RETRIEVAL

- Guidelines International Network (G-I-N), Medline via Ovid, Pubmed and Cochrane Database of Systemic Reviews (CDSR) from 2002 until 2014
- Other references:
  - Scottish Intercollegiate Guidelines Network (2008)
  - Bipolar Affective Disorder, National Institute for Health and Clinical Excellence (2008)
  - 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.

RATIONAL OF CPG

- Challenging nature of illness (delay in diagnosis, complex clinical presentations, risk factors & co-morbidities)
- Potential impact on utilisation of mental health services (delay of treatment, recurrence, admission, substance misuse & complex psychosocial interventions)
- Varied practices &, limitation of access & facility

OBJECTIVES

- **General Objective**
  - To provide evidence-based guidelines of BD in all phases
- **Specific Objective**
  - To improve recognition & early intervention of BD
  - To promote & enhance pharmacological & psychosocial intervention in BD

TARGET POPULATION

General group

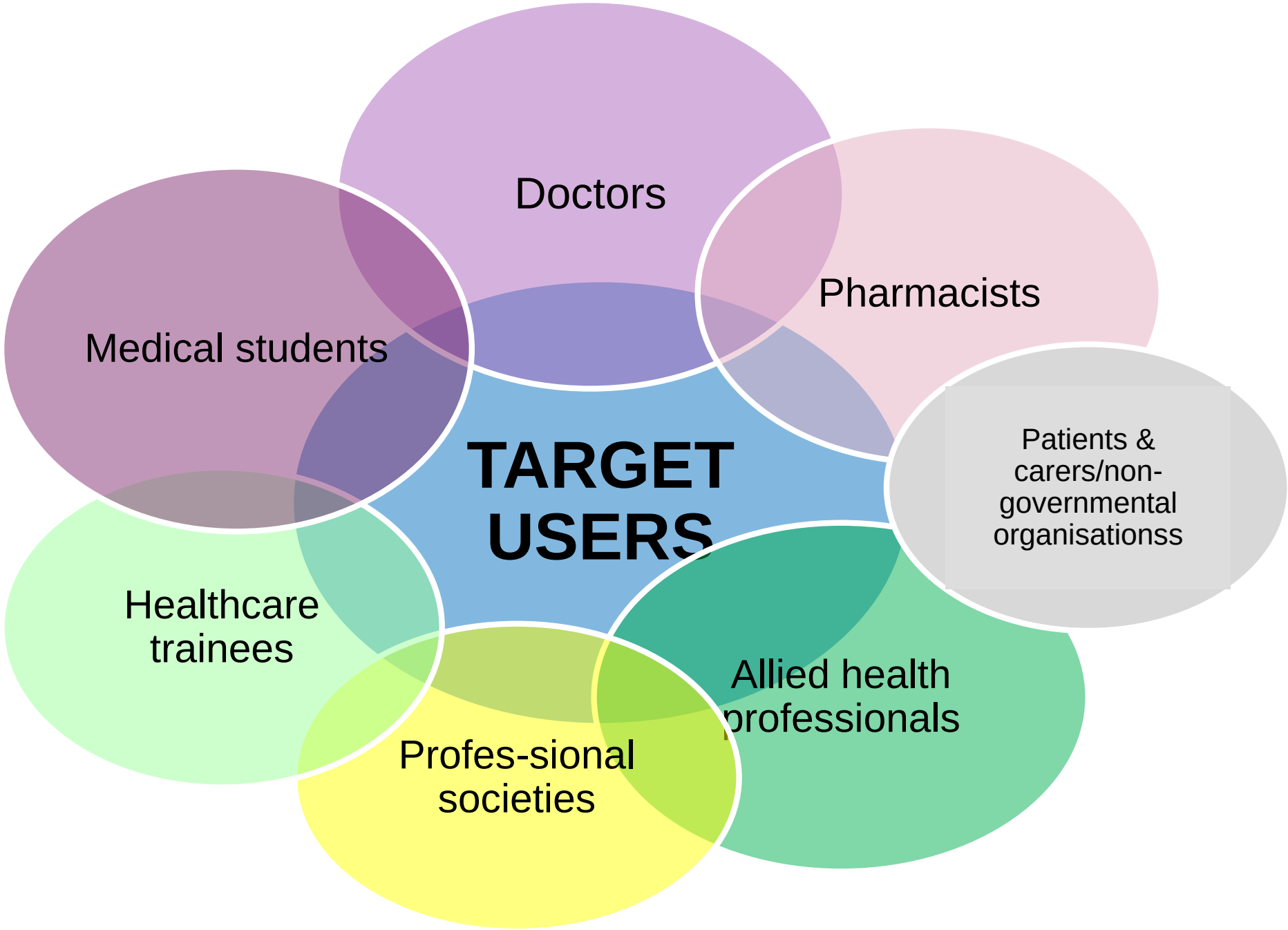
- All adults (≥18 years old) with BD

Special groups

- Elderly
- Women of child bearing age

Special considerations

- Suicide
- Substance misuse


Doctors
Pharmacists
Medical students
TARGET USERS
Patients & carers/non-governmental organisationss
Healthcare trainees
Allied health professionals
Profes-sional societies

Development Group

Chairperson:
Dr. Azizul Awaluddin
Head of Department & Consultant Psychiatrist
Hospital Putrajaya

Members (alphabetical order)

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Lecturer & Psychiatrist
Universiti Putra Malaysia

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Pusat Perubatan Universiti Kebangsaan Malaysia

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Pharmacist
Hospital Putrajaya

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Psychiatrist
Hospital Selayang

Dr. Noraini Jali
Family Medicine Specialist
Klinik Kesihatan Sg. Besar

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Psychiatrist
Hospital Kuala Lumpur

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Principal Assistant Director
Health Technology Assessment Section, MoH

Dr. Mohd. Aminuddin Mohd. Yusof
Head, CPG Unit
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Dr. Ong Lieh Yan
Psychiatrist
Hospital Bahagia Ulu Kinta

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Lecturer & Psychiatrist
Cyberjaya University College of Medical Sciences

Dr. Rahima Dahlan
Psychiatrist
Hospital Mesra Bukit Padang

Dr. Siti Hazrah Selamat Din
Psychiatrist
Hospital Permai

Dr. Zainal Fitri Zakaria
Family Medicine Specialist
Klinik Kesihatan Setapak

Dr. Zubaidah Jamil
Lecturer & Clinical Psychologist
Universiti Putra Malaysia

Review Committee

Chairperson
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Lecturer & Consultant Psychiatrist
Pusat Perubatan Universiti Kebangsaan Malaysia

Mr. Azmi Mat
Patient Advocate

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Prince Court Medical Centre

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Mental Health Unit, DCD, MoH

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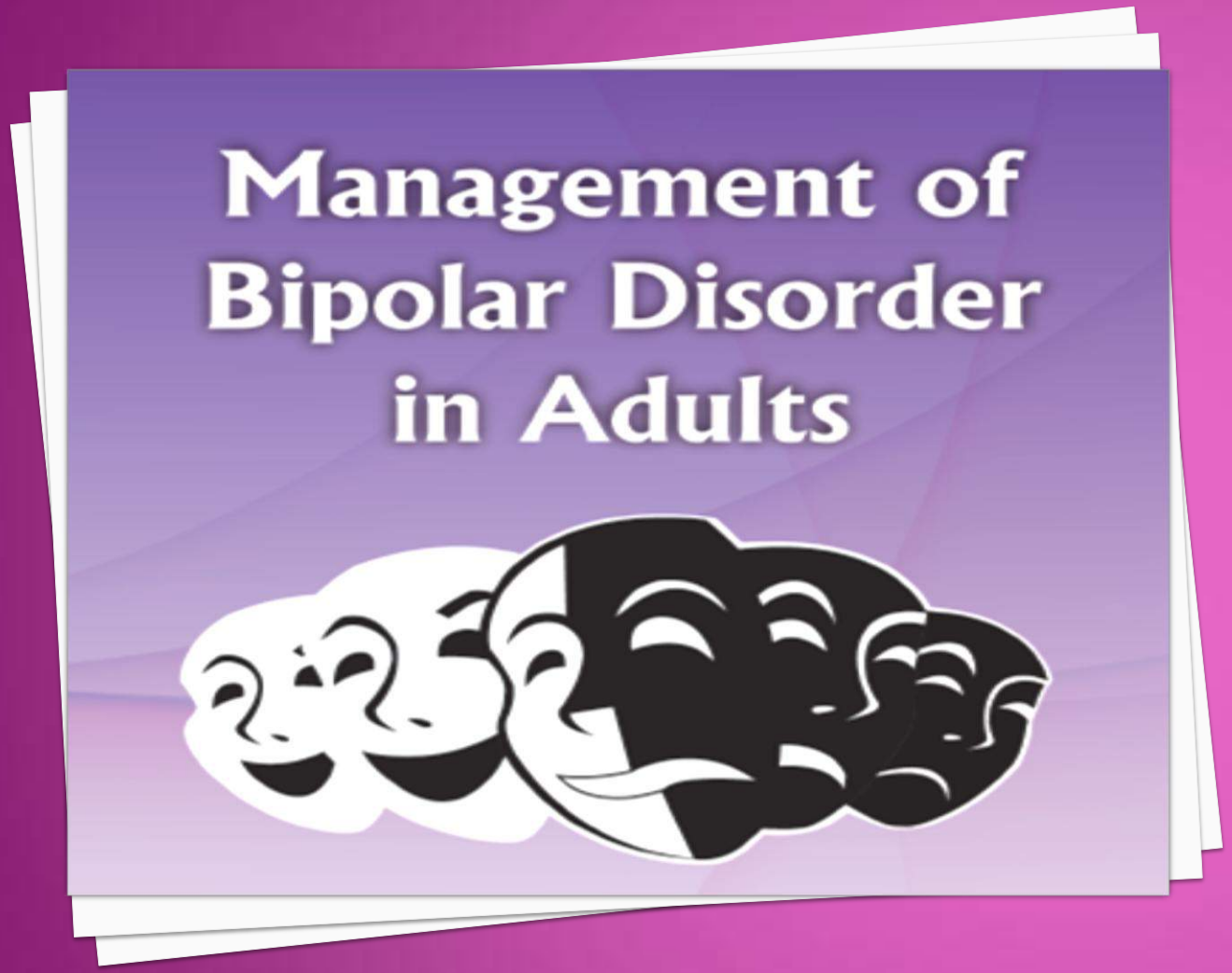
Dr. Siti Nor Aizah Ahmad
Consultant Psychiatrist
Hospital Kuala Lumpur

Dr. Wan Fadhilah Wan Ismail
Family Medicine Specialist
Klinik Kesihatan Mahmoodiah



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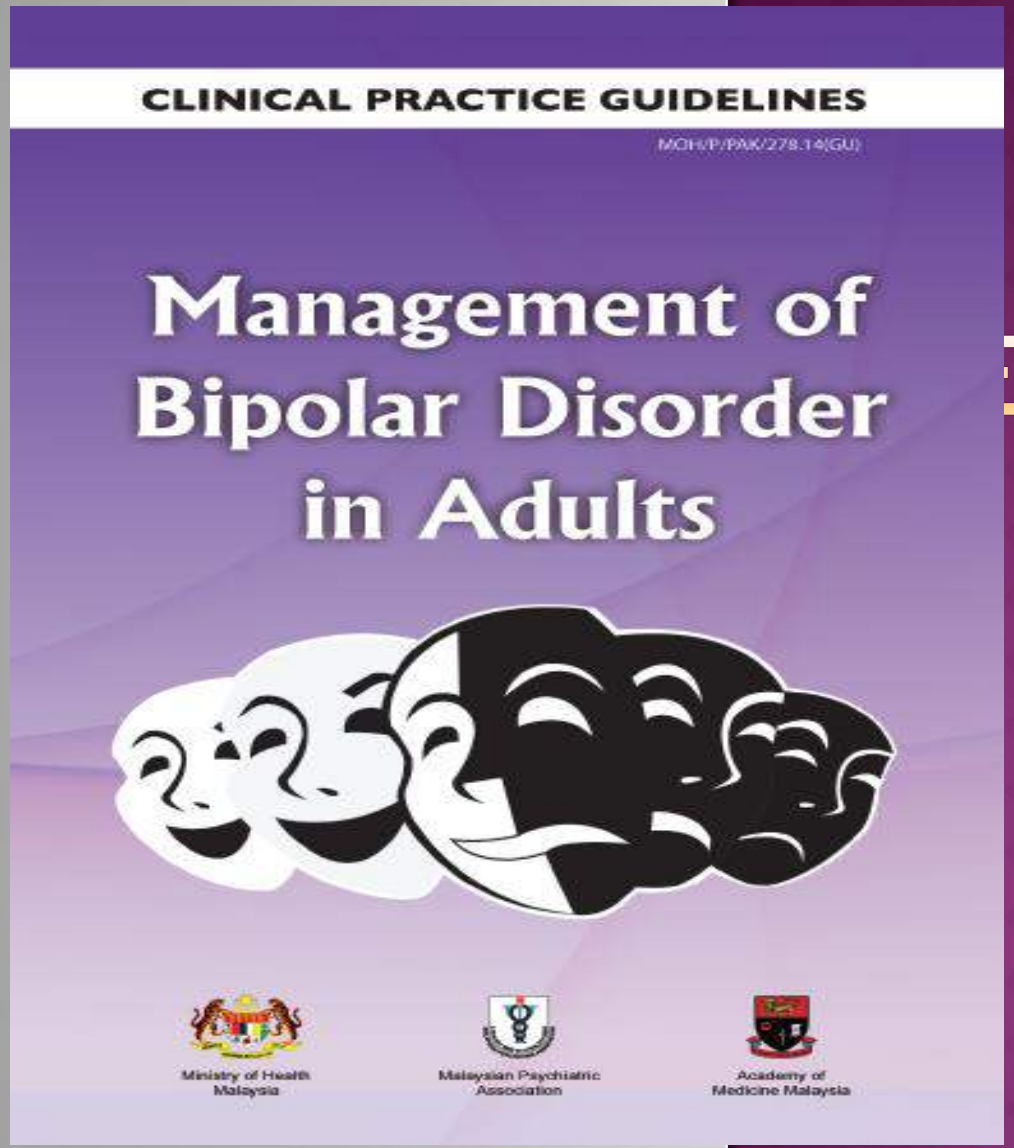


EPIDEMIOLOGY & CLINICAL PRESENTATION

Dr. Zainal Fitri Zakaria
Family Medicine Specialist, KK Setapak
&
Dr. Rafidah Bahari
Lecturer & Psychiatrist
Cyberjaya University College of Medical Sciences

LEARNING OBJECTIVES

- To describe the epidemiology of bipolar disorder (BD)
- To describe the risk factor for BD
- To identify clinical features of BD
- To know when to use screening tools for BD

INTRODUCTION

- In the World Mental Health Survey Initiative involving 11 countries, the lifetime prevalence of:[1]
  - BD I was 0.6%
  - BD II 0.4%

- However the prevalence varied between countries. For example, the USA had a lifetime prevalence of 1.0% & 1.1% for BD I & BD II respectively whereas in Japan, the lifetime prevalence was 0.1% for both BD I & BD II.[1]

1. Merikangas KR et al. Arch Gen Psychiatry. 2011 Mar;68(3):241-51

EPIDEMIOLOGY[1]

- The mean age of onset for illness is:
  - 18.2 years for BD I
  - 20.3 years for BD II
- Women are slightly more affected with prevalence rates of:
  - 1.1% for BD I
  - 1.3% for BD II
- While the rates for men are:
  - 0.8% for BD I
  - 0.9% for BD II

1. Merikangas KR et al. Arch Gen Psychiatry. 2011 Mar;68(3):241-51

RISK FACTOR

- BD risk/prevalence is inversely related to:[2]
  - age
  - educational level
  - Employment

- 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]

2. Merikangas KR et al. Arch Gen Psychiatry. 2007; 64(9):1039
3. Kieseppa T et al. American Journal of Psychiatry. 2004; 161(10):1814-1821

DIAGNOSING MENTAL ILLNESS

- In making a diagnosis of mental illnesses, 2 classification system is available in Malaysia:
  - International Classification of Diseases and Health Related Problems 10th Revision (ICD-10) for 2010.[4]
  - Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5).[5]

4. World Health Organization. International Classification of Diseases and Health Related Problems 10th Revision (Icd-10). Switzerland: WHO; 2010
5. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders 5th Edition (Dsm-5). Arlington: APA; 2013

CLINICAL FEATURES

- Diagnosis of BD require periods of mood disturbance.
- Mania or hypomania must be present before or after depressive episodes.

MOOD EPISODES

- An episode
  - a distinctive period of mood disturbance fulfilling the criteria for hypomania, mania or depression.

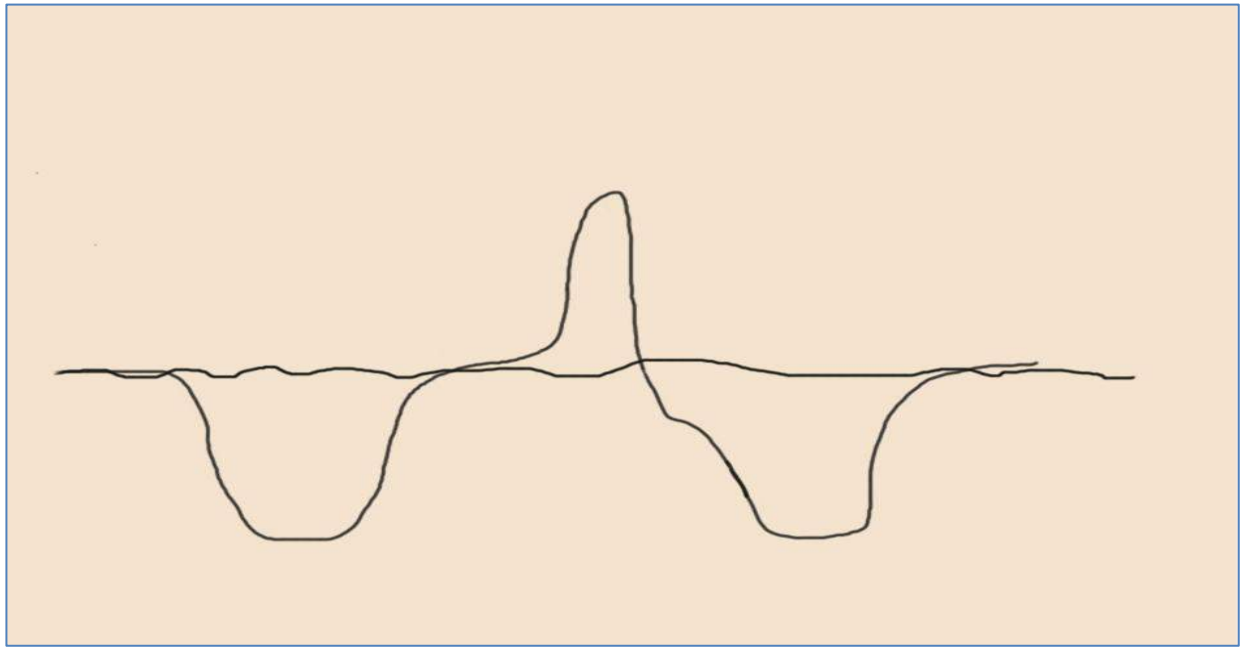
- An interval of at least 2 months free of symptoms is required to distinguish between episodes.

MOOD EPISODES IN BD

Mania

Normal

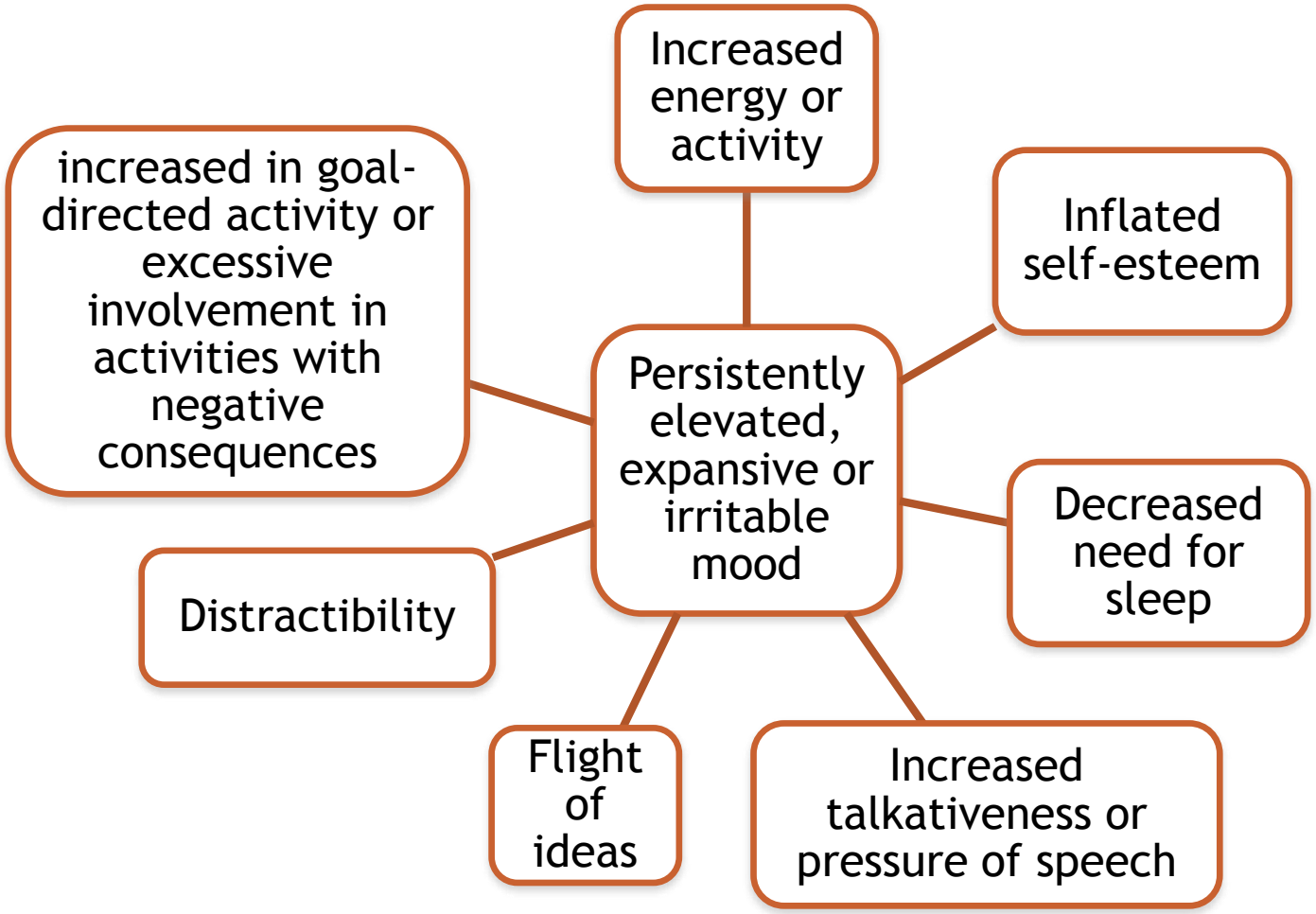
Depression



HYPOMANIA/HYPOMANIC EPISODE

ICD-10	DSM-5
F30.0 Hypomania 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.	**Hypomanic Episode** 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.

HYPOMANIC EPISODE

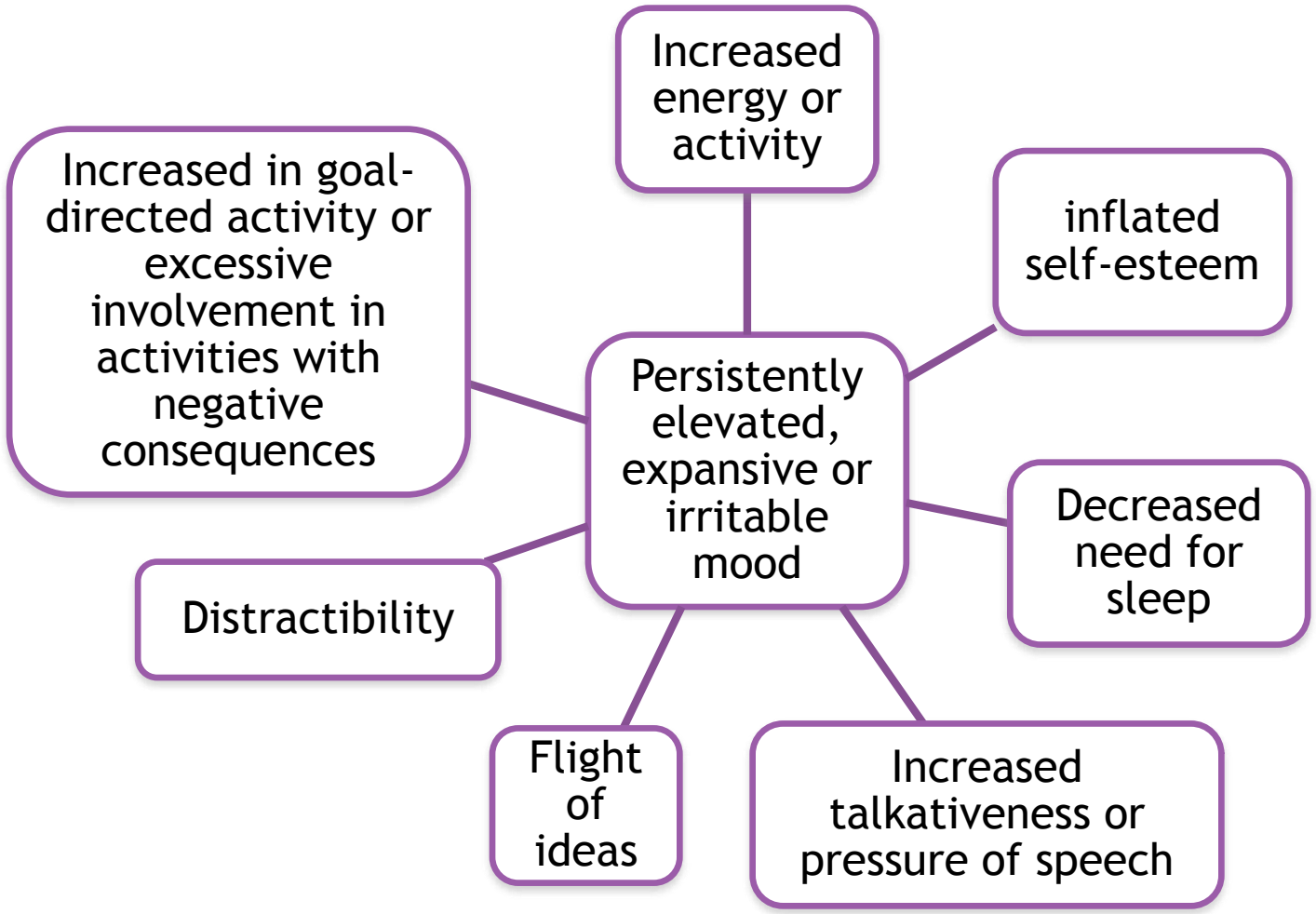


For at least 4 days

MANIA/MANIC EPISODES

ICD-10	DSM-5
F30.1 Mania without psychotic symptoms Elation, accompanied by increased energy, over-activity, pressure of speech, reduced need for sleep, inflated self-esteem, grandiose ideas and loss of social inhibitions. **F30.2 Mania with psychotic symptoms** 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.	**Manic Episode** 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.

MANIC EPISODE

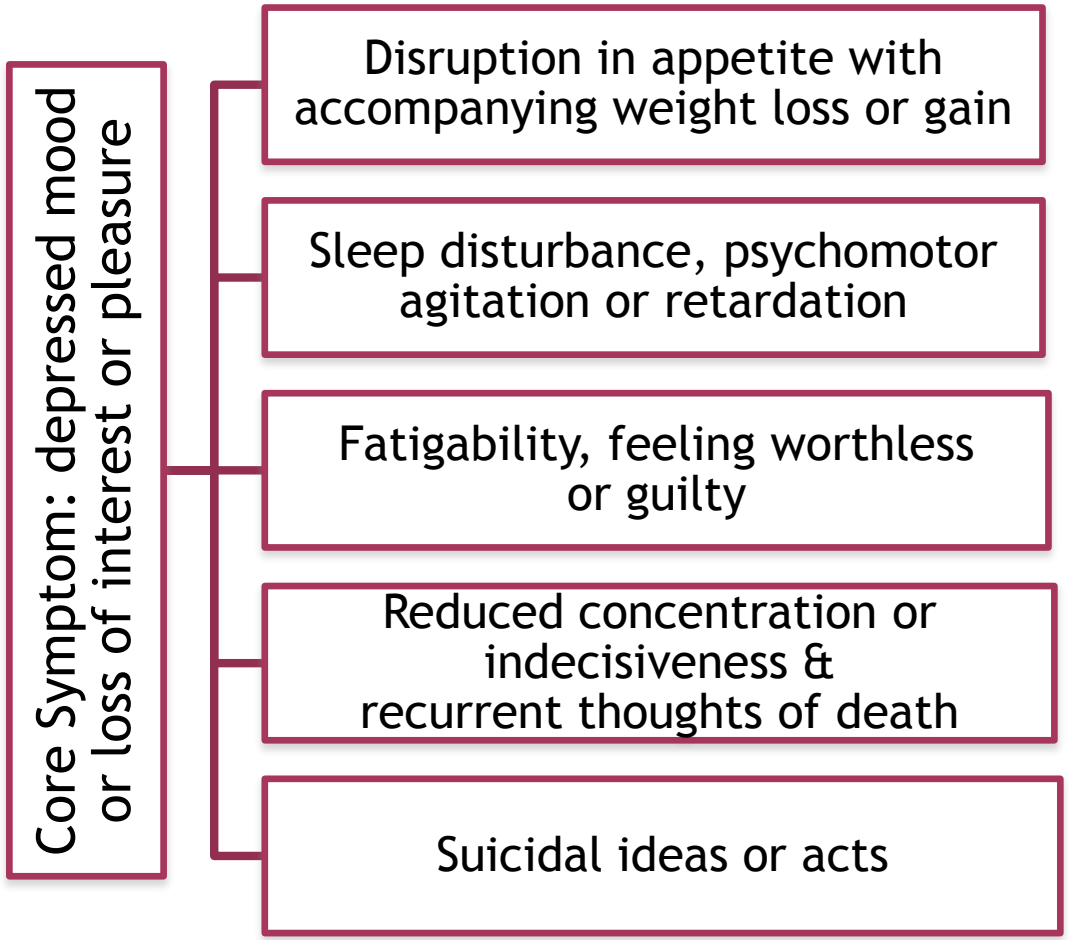


For at least 1 week

DEPRESSIVE EPISODES

ICD-10	DSM-5
F32 Depressive Episode 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.	**Major Depressive Episode** For at least two weeks, presenting with five or more of the following symptoms, of which, at least one must be depressed mood or loss of interest or pleasure. The other symptoms include disruption in appetite with accompanying weight loss or gain, sleep disturbance, psychomotor agitation or retardation, fatigability, feeling worthless or guilty, reduced concentration or indecisiveness and recurrent thoughts of death, or suicidal ideas or acts.

DEPRESSIVE EPISODE

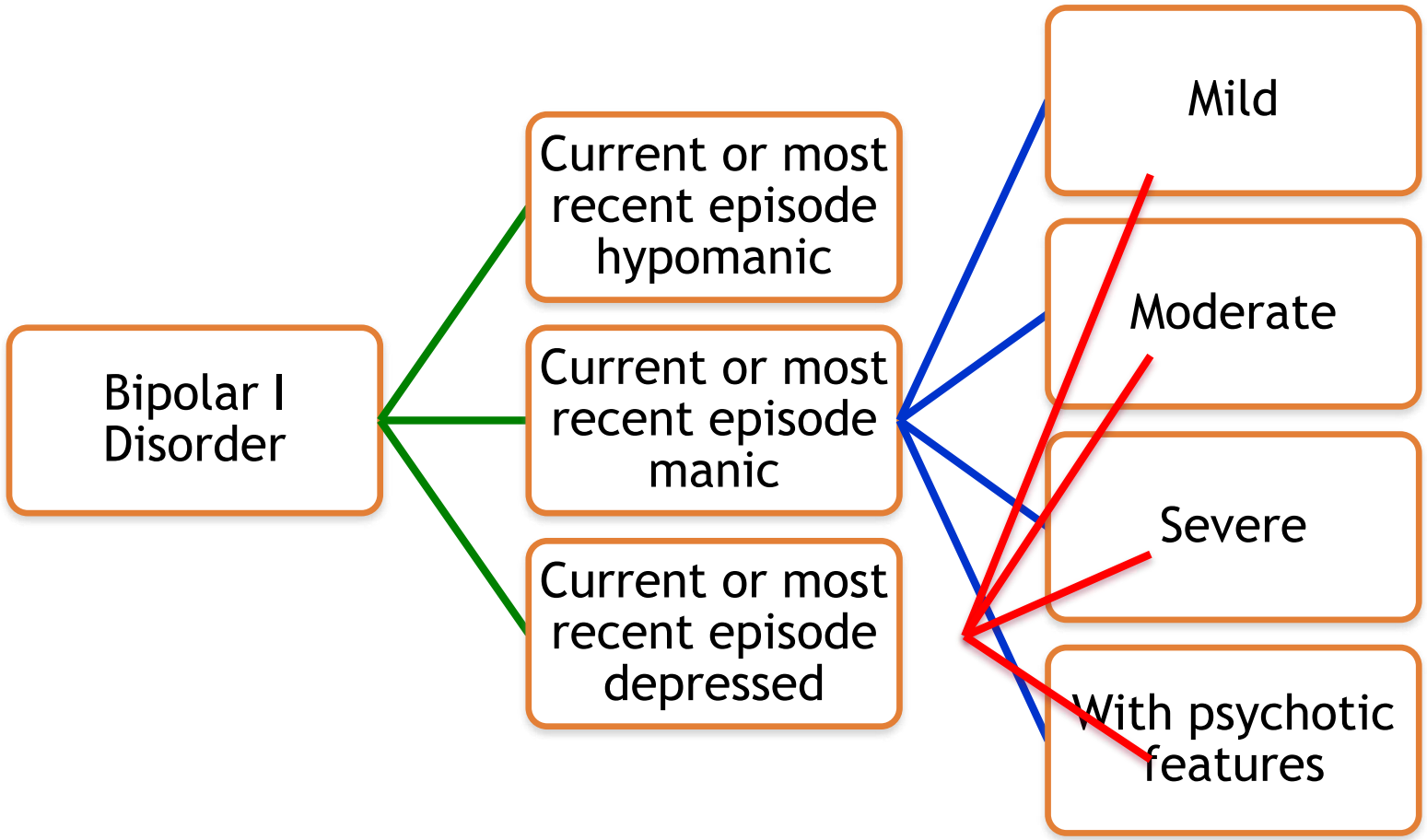


For at least 2 weeks

BIPOLAR DISORDER

ICD-10	DSM-5
F31 Bipolar Affective Disorder Having two or more episodes of mood disturbance, one of which has to be mania or hypomania and the other depression.	**Bipolar I Disorder** Having met the criteria for manic episodes at least once. **Bipolar II Disorder** Having met the criteria for hypomanic episodes at least once and major depressive episode at least once.

FURTHER CLASSIFICATION OF BIPOLAR I DISORDER



BIPOLAR II DISORDER

- Having met the criteria for hypomanic episodes at least once & major depressive episode at least once.

- Specify current or most recent episode:
  - Hypomanic
  - Depressed

MANIA OR HYPOMANIA?

- 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

RAPID CYCLING BIPOLAR DISORDER

- The rapid cycling specifier can be used for both BD I or BD II if there are presence of at least 4 manic, hypomanic or major depressive episodes in the last 12 months.

SCREENING

- The diagnosis of BD maybe difficult:
  - Its instability of presentation may delay diagnosis.
  - It is often mistaken for other psychiatric diagnoses especially major depressive disorder.[6]

- The role of primary care practitioners in detecting the disorder are very important.

- Screening tools may help detect the right patients for referral.

6. Young AH et al. Br J Psychiatry. 2011; 199(1):3-4

SCREENING TOOLS

- Tools are available for screening of BD e.g.:
  - Mood Disorder Questionnaire (MDQ)
  - Bipolar Spectrum Diagnostic Scale (BSDS)
  - Hypomania Checklist (HCL-32)

- Not enough evidence to recommend the usage of specific screening tools at primary care.
  - simple self-administered tool such as MDQ can be helpful
  - esp. in those who are diagnosed with depression
  - those with positive screening should be referred to a psychiatrist for further evaluation

DIFFERENTIAL DIAGNOSES

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

DIFFERENTIAL DIAGNOSES OF DEPRESSIVE EPISODE[7]

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

7. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders 5th Edition (Dsm-5). Arlington: APA; 2013

DIFFERENTIAL DIAGNOSES OF MANIC/HYPOMANIC EPISODE[8]

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

8. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders 5th Edition (Dsm-5). Arlington: APA; 2013

BIPOLARITY IN DEPRESSIVE ILLNESS

- BD may present first in depressive phase & difficult to differentiate from MDD.

- Risk factors for bipolarity in current major depressive episode include:[9]
  - At least 2 mood episodes in the past
  - Family history of mania
  - Occurrence of first psychiatric symptoms before the age of 30
  - Current depressive episode lasting less than 1 month
  - Mood lability with antidepressants
  - Current mixed state

9. Angst J et al. Arch Gen Psychiatry. 2011; 68(8):791-798

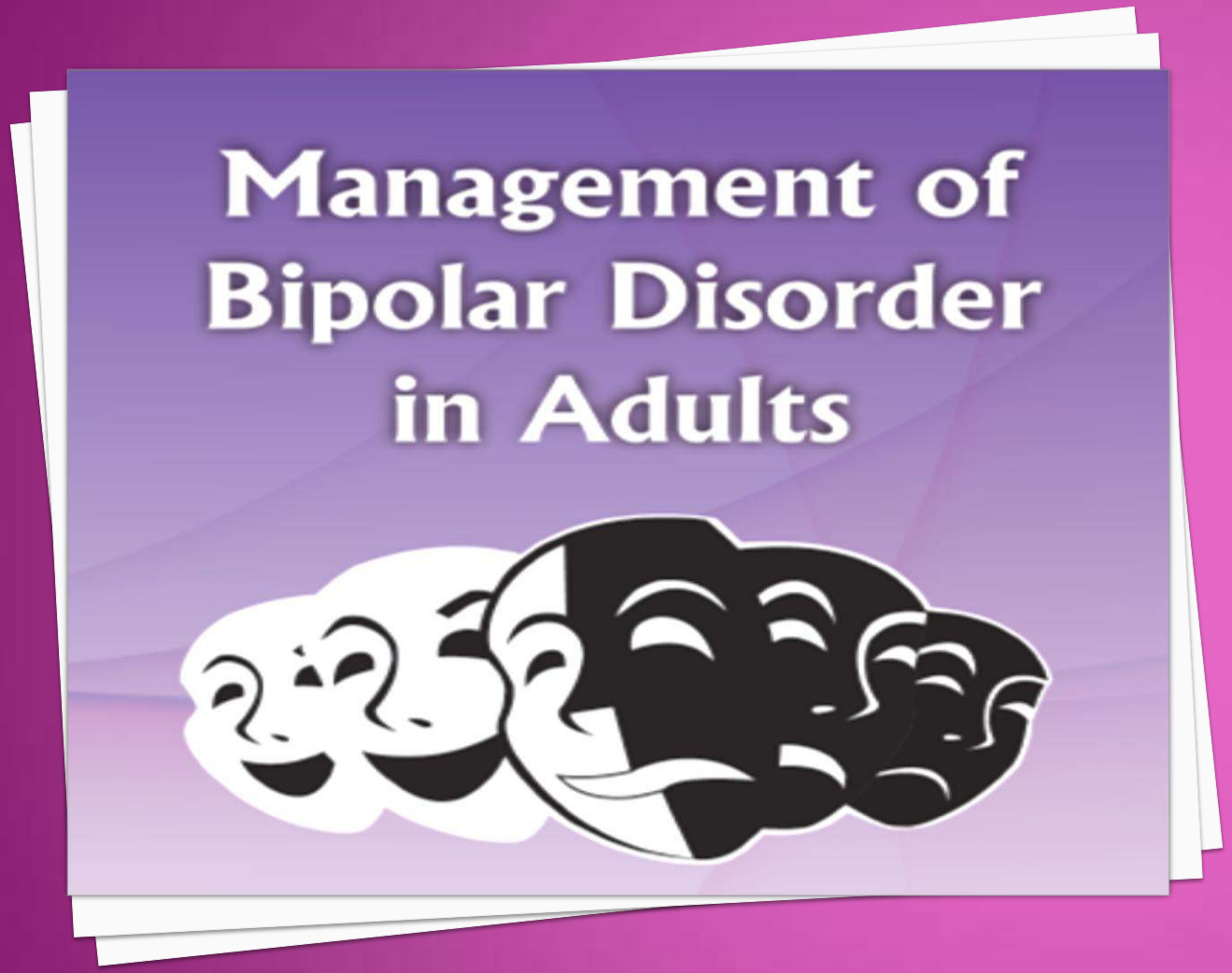
RECOMMENDATION

Recommendation 1

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

TAKE HOME MESSAGE

- Risk factors for BD include positive family history, younger age, lower educational attainment & unemployment.
- To diagnose BD, the presence of episodes of mania or hypomania is necessary along with episodes of depression.
- It is often misdiagnosed & in primary care screening tools may be helpful to identify patients for psychiatric referral.



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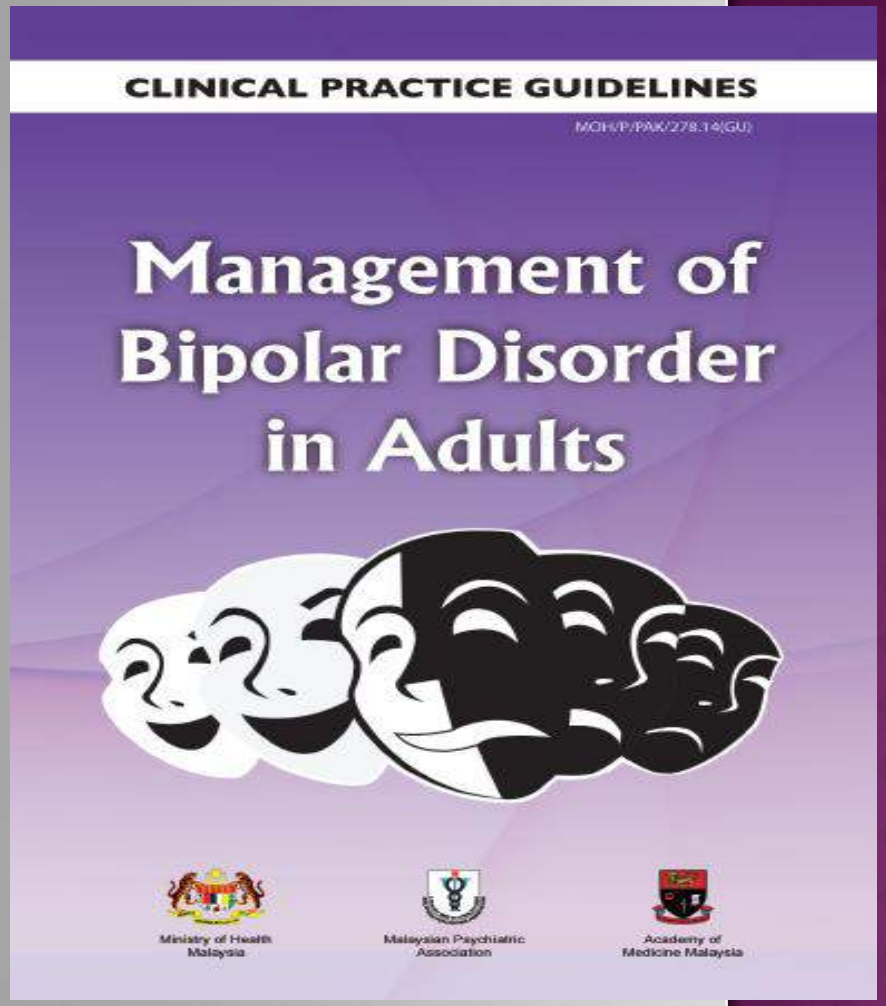


GENERAL TREATMENT & MANAGEMENT PLAN

Dr. Noraini Jali
Family Medicine Specialist
KK Sg. Besar
&
Dr. Azizul Awaluddin
Head of Department & Consultant Psychiatrist
Hospital Putrajaya

LEARNING OBJECTIVES

- To provide evidence-based guidance in all phases of BD:
  - To improve recognition & early intervention of BD
  - To promote & enhance evidence-based pharmacological & psychosocial intervention in management of BD

INTRODUCTION

- Principle of management is promoting access to services through collaboration between:
  - Patients
  - Family members &
  - Healthcare professionals
- Aims to restore the person to full health & meaningful life
- Retain confidentiality at every stage of assessment, diagnosis & treatment

INTRODUCTION - (CONT.)

- BD is a life-long illness.
- Medication is the mainstay of treatment.
- Importance of psychosocial components
- Main treatment facilities:
  - Primary care
  - Hospital
- Main treatment phases:
  - Acute
  - Maintenance

PRINCIPLES OF MANAGEMENT

- The principles of management in BD should incorporate the following:
  - Assessment & early treatment
  - Plan for psychosocial intervention
  - Dealing with treatment adherence issues
  - Addressing potential risks to self or others
  - Monitoring of clinical parameters
  - Management for special populations

INTEGRATED CARE

- NICE recommends continuity of care for people with BD at different levels of health service via the provision of certain models of intervention.[1]

- It should include:
  - Regular reviews of mental state, personal & social functioning in primary or secondary care
  - Clear guidelines for delivering & monitoring of pharmacological, psychological & 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 & agencies regarding vocational rehabilitation or other structured purposeful activities

1.NICE. The Management of Bipolar Disorder in Adults, Children and Adolescents in Primary and Secondary Care. London: 2006.

INTEGRATED CARE (CONT.)

- In Malaysia, a few service level interventions currently being carried out such as:[2]
  - community mental health team
  - assertive community treatment
  - home treatment team
  - day hospital care
  - supported employment / vocational rehabilitation

2. MOH. Clinical Practice Guidelines Management of Shizophrenia in Adults Malaysia: 2009.

INTEGRATED CARE (CONT.)

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)**

ADMISSION CRITERIA

- Based on the Malaysian Mental Health Act 2001 (Act 615) and Regulations which are:[3]
  - Risk of **harm** to self or others
  - Treatment is not suitable to be started as outpatient

3. Penyelidikan Undang-Undang Akta Kesihatan Mental 2001 (Akta 615) dan Peraturan-Peraturan & Mental Health Act 2001 (Act 615) and Regulations. 2011.

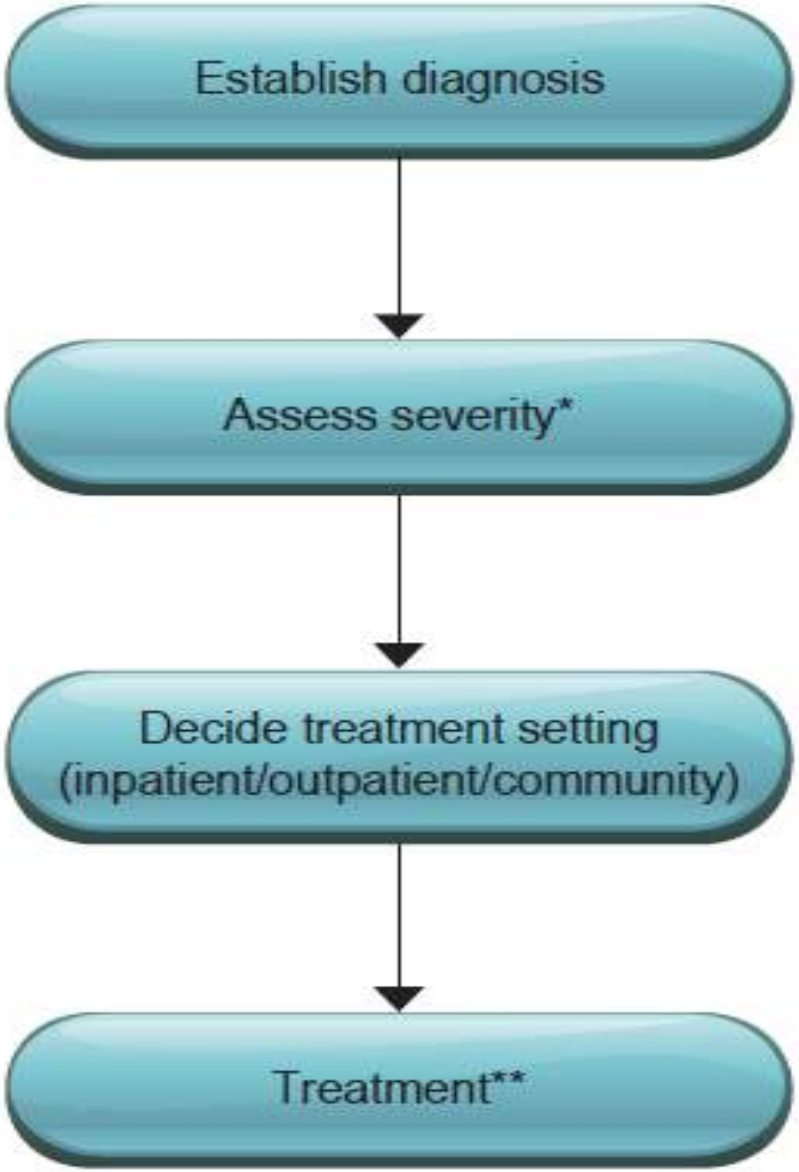
REFERRAL CRITERIA

1. **New or suspected individuals with BD**
   - Who are danger to themselves or other people
   - For assessment & plan of management

2. **People with existing BD who have either:-** [1,6]
   - Acute exacerbation of symptoms
   - Decline in functioning
   - Increase risk of harm to self or others
   - Treatment non-adherence/poor compliance
   - Poor response to treatment
   - Issues regarding stopping medication
   - Concomitant or suspected substance misuse
   - Complex presentations of mood episodes
   - Psychoeducational & psychotherapeutic needs

1.NICE. The Management of Bipolar Disorder in Adults, Children and Adolescents in Primary and Secondary Care. London: 2006.
6. Sherrod T et al. J Gerontol Nurs. 2010; 36(5):20-27.

ALGORITHM 1. GENERAL PRINCIPLES IN MANAGEMENT OF BD



GENERAL PRINCIPLES IN MANAGEMENT OF BD

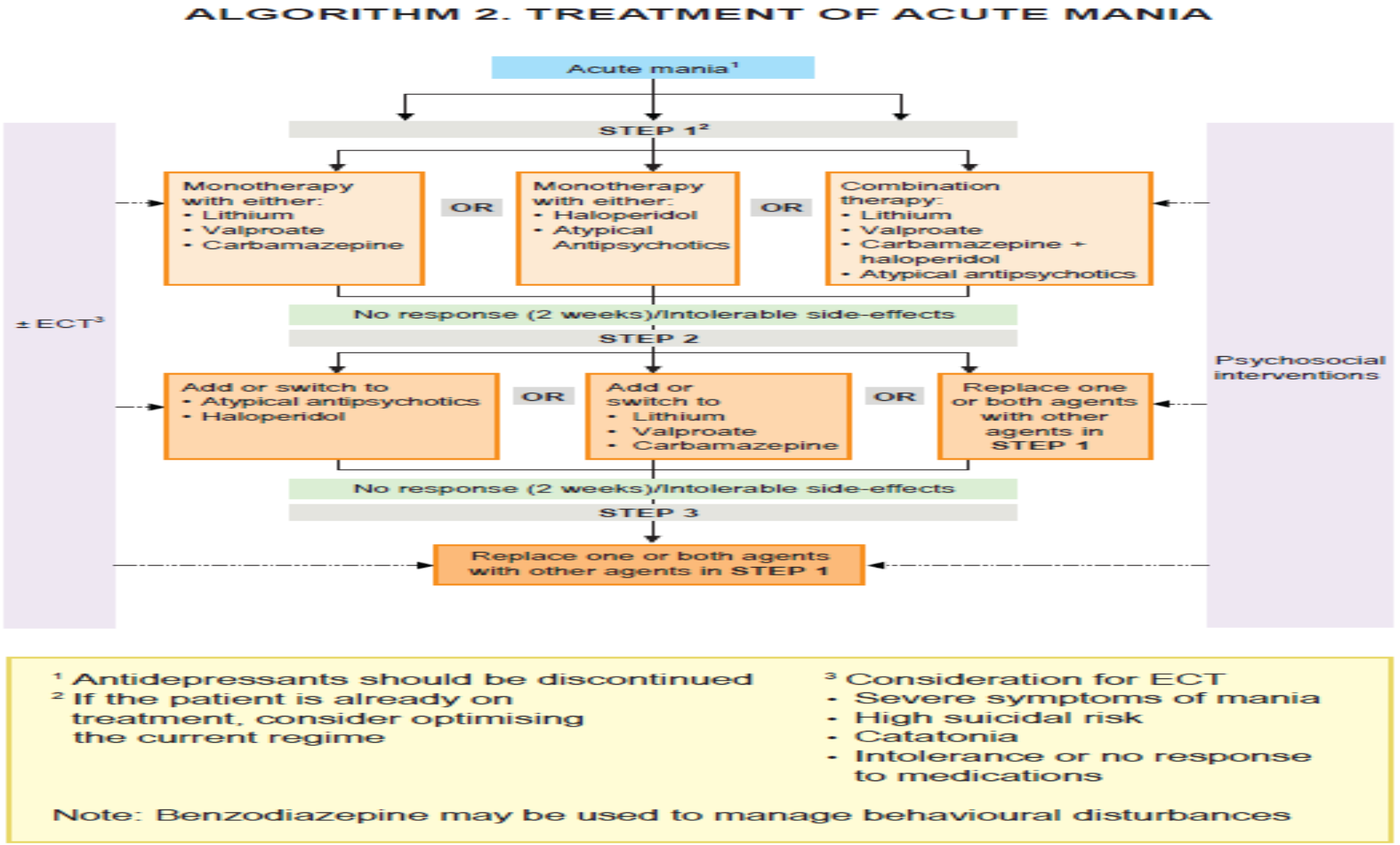
*Severity assessments include:

- Clinical symptoms, tools that can be used are -
  i. Young Mania Rating Scale (YMRS)
  ii. Hamilton Rating Scale for Depression (HAM-D)
  iii. Montgomery Asberg Depression Rating Scale (MADRS)

- Danger to self or others, family & community supports

- Availability of service provision

ALGORITHM 2. TREATMENT OF ACUTE MANIA

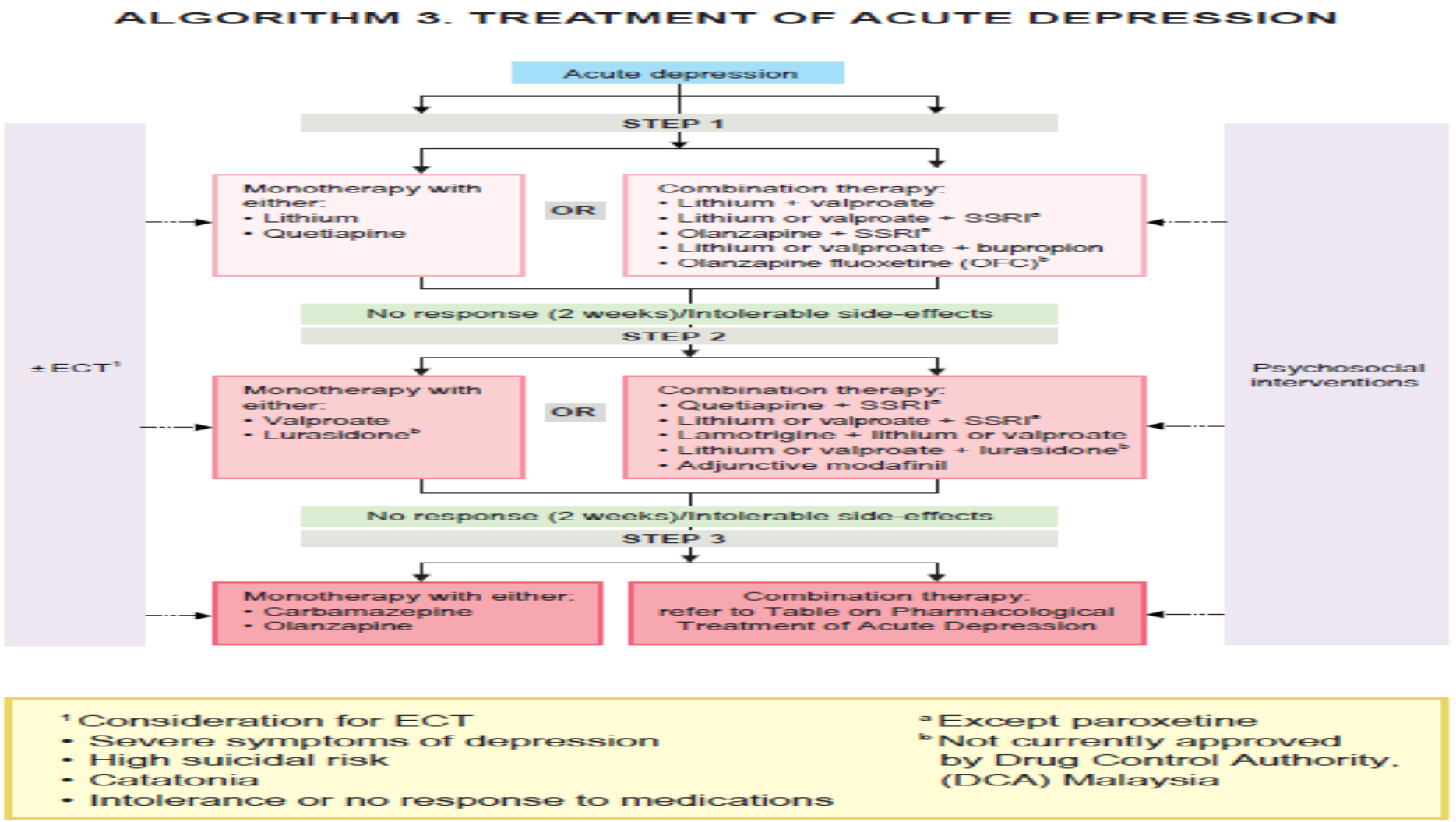


[1] Antidepressants should be discontinued
[2] If the patient is already on treatment, consider optimising the current regime

[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



MONITORING OF CLINICAL PARAMETERS

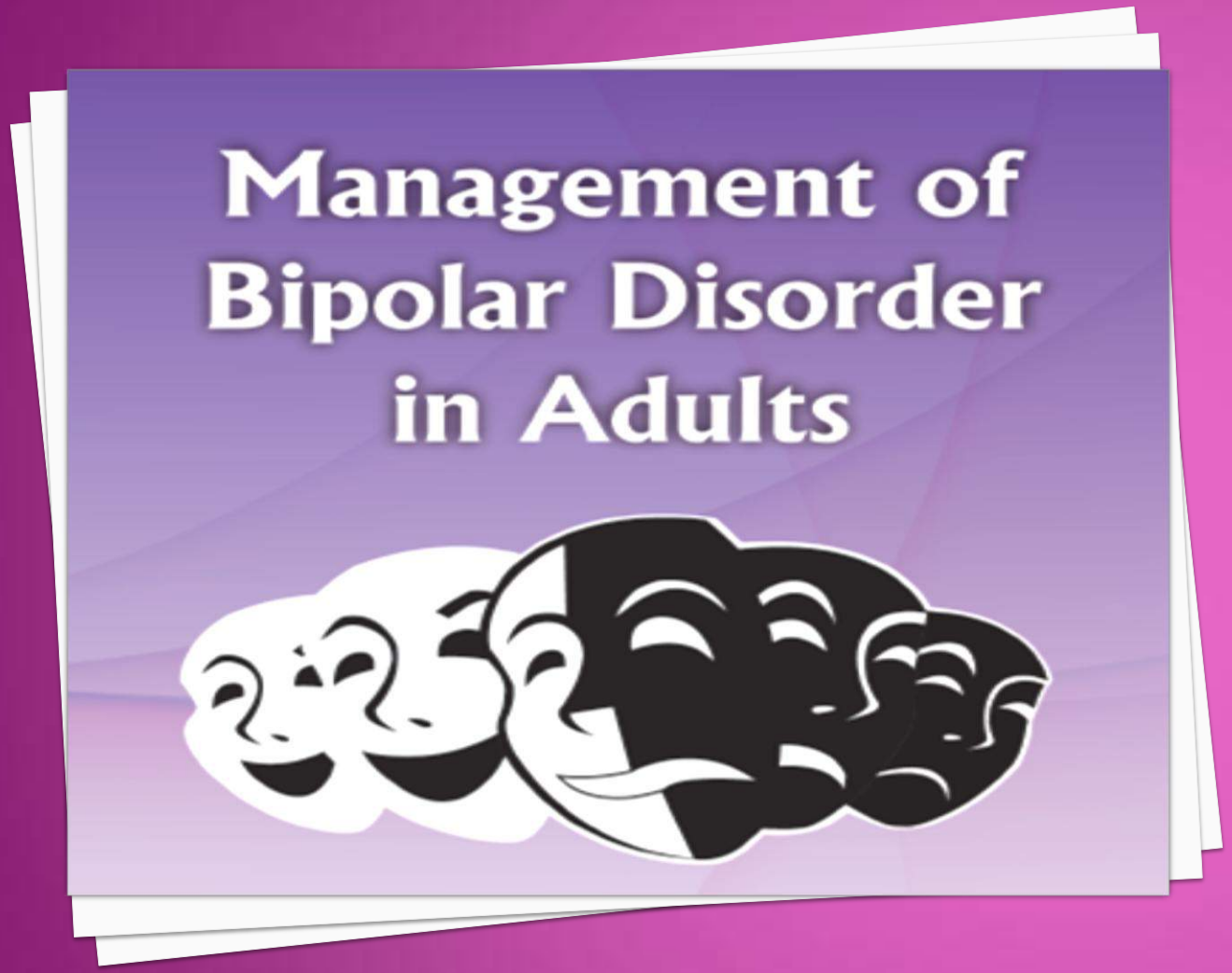
- **Physical**
  - Height
  - Weight
  - Waist circumference
  - Electrocardiogram (ECG)
- **Chemical**
  - Renal Profile
  - Liver Function Test
  - Thyroid Function Test
  - Serum Glucose
- **Therapeutic levels**
  - Lithium/Sodium valproate

MANAGEMENT FOR SPECIAL POPULATIONS

- Substance Misuse
- Women of Reproductive Period
- Elderly

TAKE HOME MESSAGE

- Varied approach of BD consists of a broad range of interventions
- Pharmacotherapy is crucial but attention must also be given to psychosocial components & consequences
- Treatment algorithm is of great use to guide a proper & appropriate treatment strategies dealing with BD



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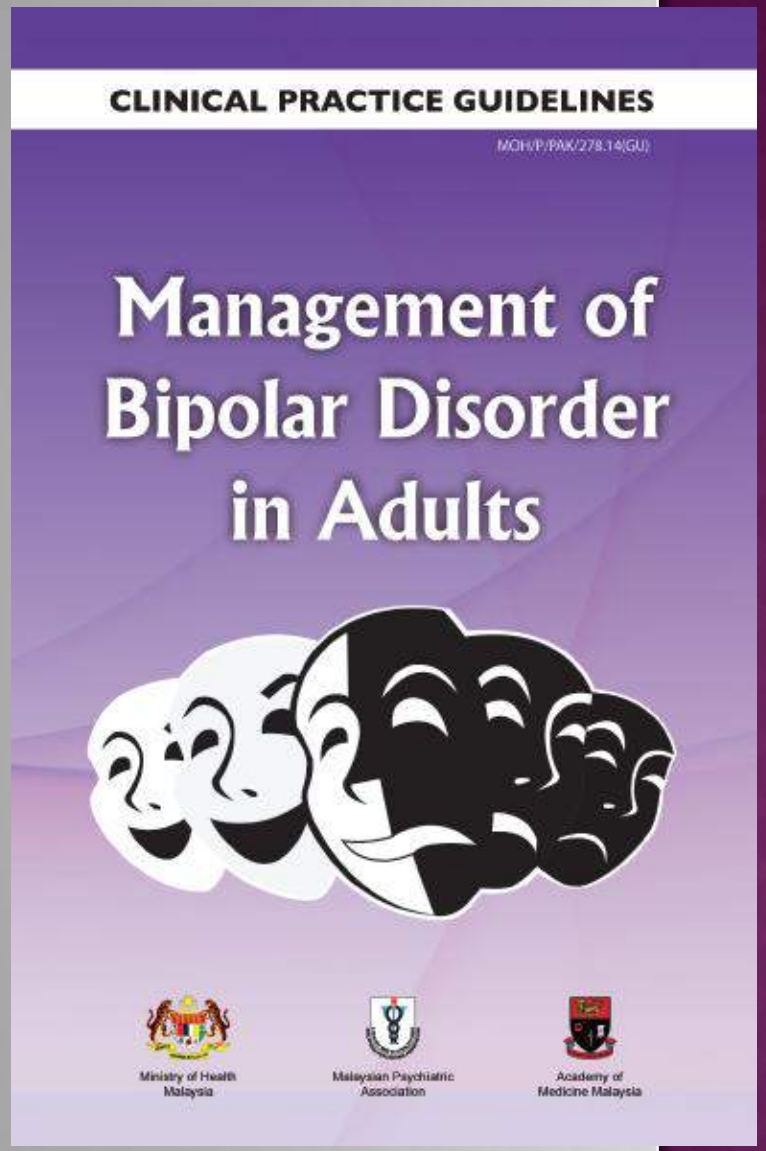


PHARMACOLOGICAL MANAGEMENT: ACUTE PHASE

Dr. Ang Jin Kiat
Lecturer & Psychiatrist
Universiti Putra Malaysia
&
Dr. Ong Lieh Yan
Psychiatrist
Hospital Bahagia Ulu Kinta

LEARNING OBJECTIVES

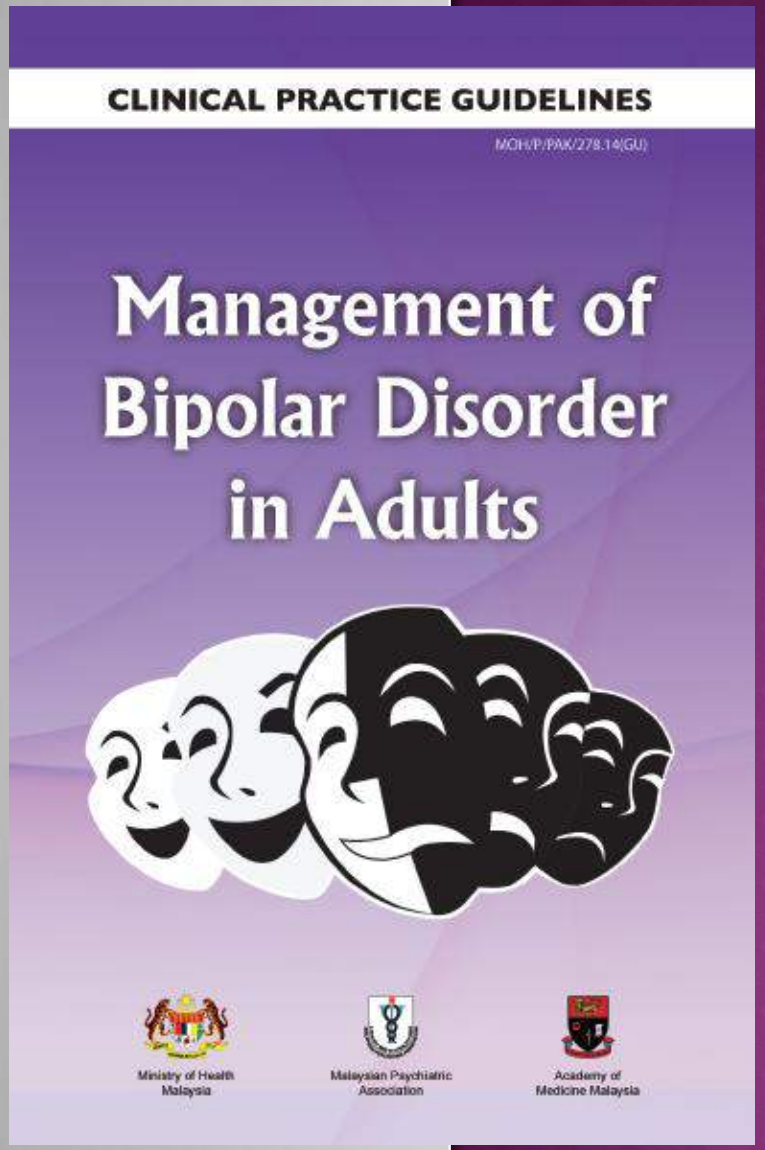
- To understand the principles of pharmacological management in the acute phase of BD.
  - Mania
  - Depression
  - Rapid cycling
  - Mixed episode

- Prescribe the appropriate pharmacological treatment in the maintenance phase.

THE PRINCIPLES OF MANAGEMENT

Should incorporate the following for acute phase:

- Assessing severity and early treatment
- Addressing potential risks to self or others
- Managing special populations


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

ACUTE PHASE

ACUTE MANIA - INTRODUCTION

- Pharmacological treatment of acute mania varies from classical mood stabilisers to atypical antipsychotics.

- Selection of medications are based on;
  - concomitant medications
  - previous medication response
  - family history of medication response
  - side effects
  - patient preferences
  - medical and psychiatric co-morbidities.

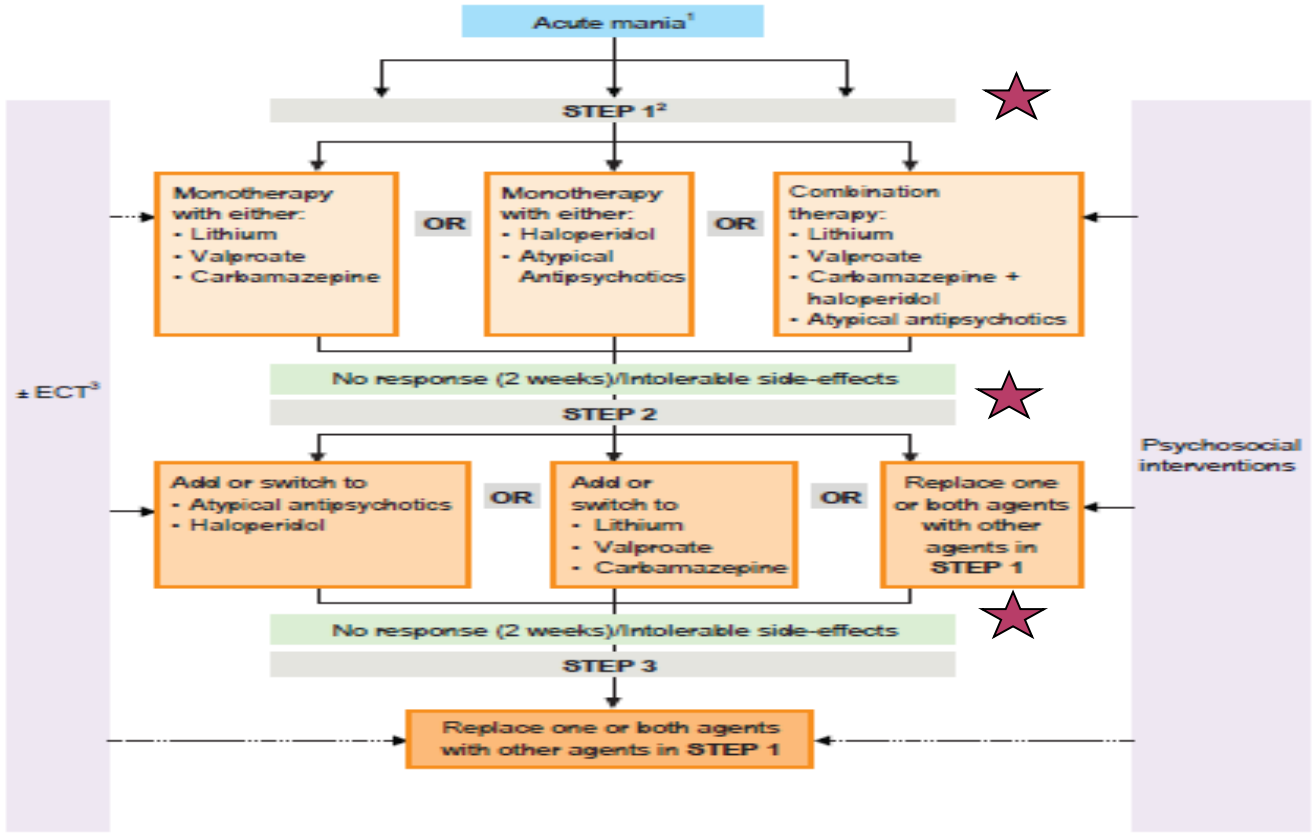
- The duration of acute treatment depends largely on clinical response and tolerability to the treatment.

ACUTE MANIA- INTRODUCTION

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

- The pharmacological treatment of acute mania consists of a variety of medication, ranging from classical mood stabilisers to atypical antipsychotics.

ACUTE PHASE MANIA

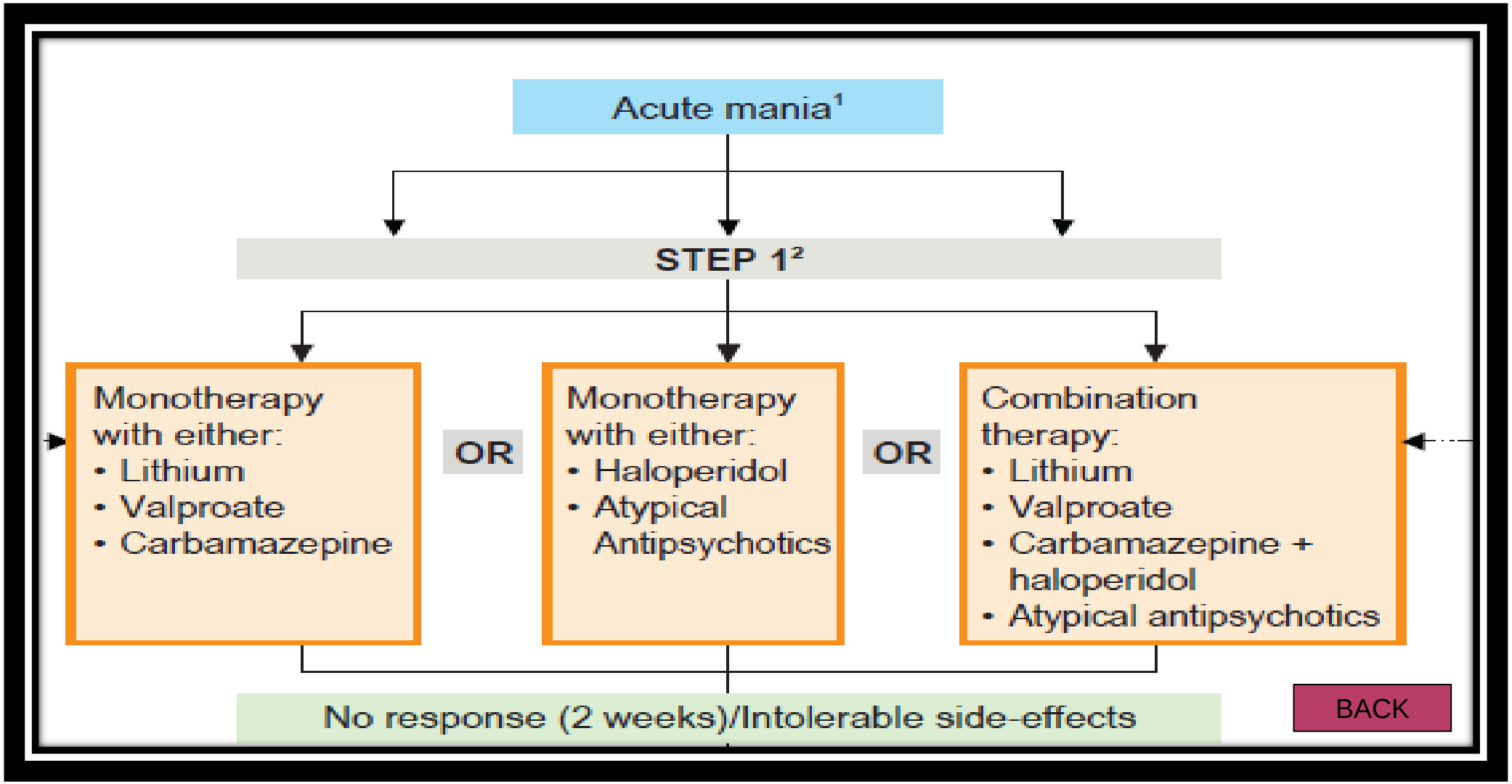


[1] Antidepressants should be discontinued
[2] If the patient is already on treatment, consider optimising the current regime

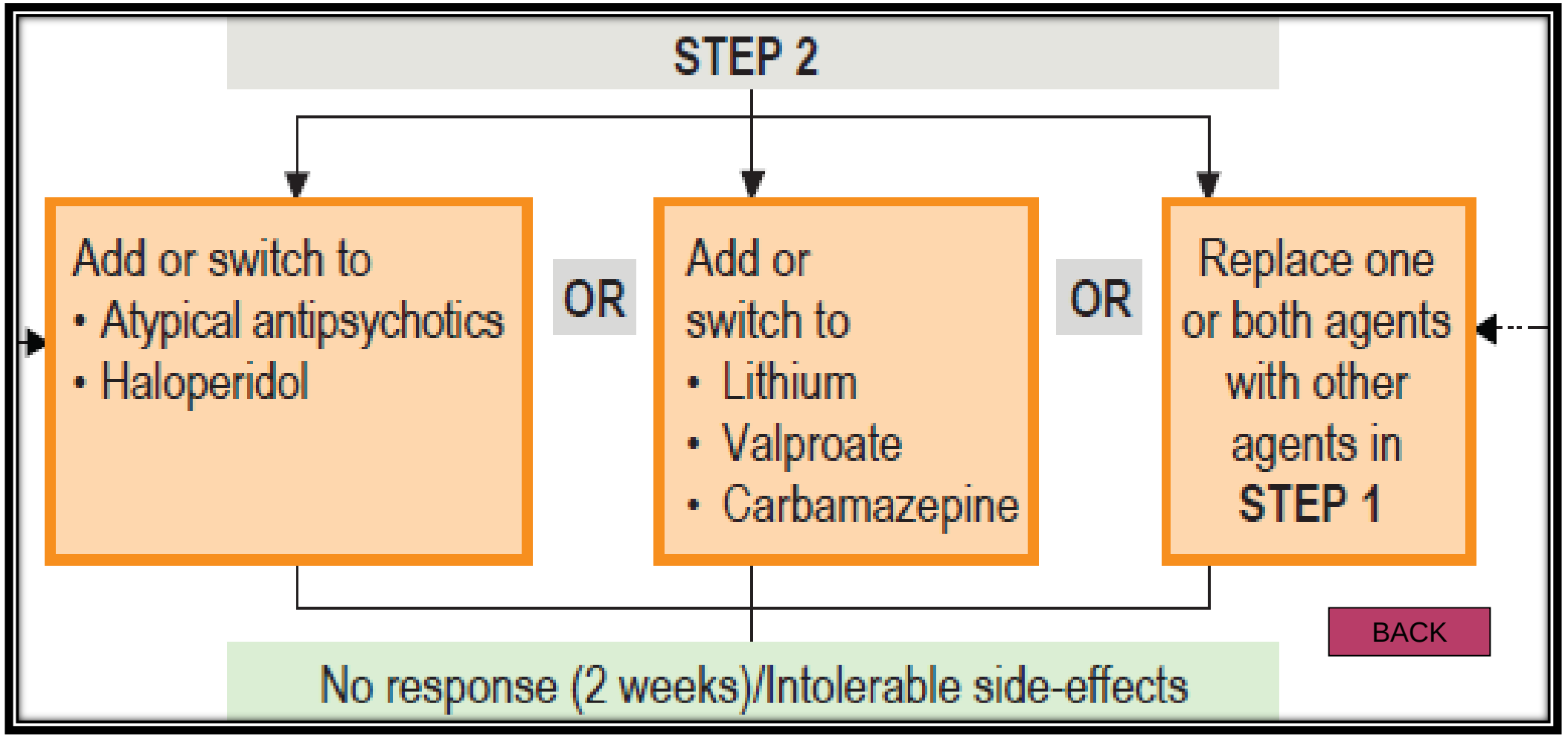
[3] Consideration for ECT
- Severe symptoms of mania
- High suicidal risk
- Catatonia
- Intolerance or no response to medications

Note: Benzodiazepine may be used to manage behavioural disturbances

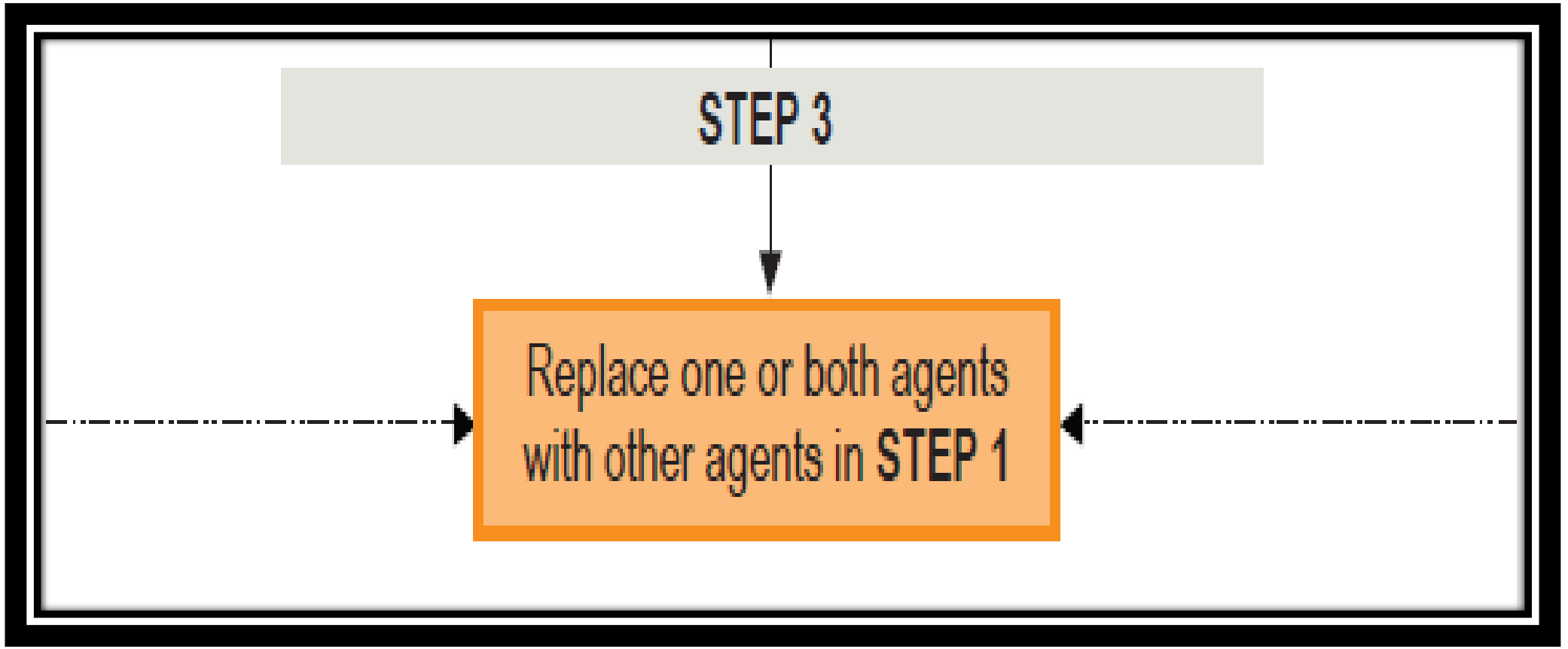
ACUTE MANIA- STEP 1



ACUTE MANIA- STEP 2



ACUTE MANIA- STEP 3



ACUTE MANIA – MOOD STABILISERS

- 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.

- Lithium, valproate and carbamazepine are equally efficacious in acute mania.[1]

1. Macritchie K, et al.Cochrane Database of Systematic Reviews 2003; (Issue 1).

ACUTE MANIA - ANTIPSYCHOTIC

- 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. [1-5]

Typical antipsychotic	Atypical antipsychotics (AAP)
• **haloperidol**	• **risperidone** • **olanzapine** • **ziprasidone** • **asenapine** • **quetiapine** • **paliperidone** • **aripiprazole**

1. Macritchie K, et al.Cochrane Database of Systematic Reviews 2003; (Issue 1).
2. Yildiz A et al. Neuropsychopharmacology. 2011; 36(2):375-389.
3. Brown R et al.Cochrane Database Syst Rev. 2013; (17):12.
4. Cipriani A et al. Cochrane Database of Systematic Reviews. 2009; (1).
5. Cipriani A et al. Cochrane Database of Systematic Review. 2006; (Issue 3).

ACUTE MANIA-NON BENEFICIAL TREATMENT

- Gabapentin, topiramate and lamotrigine are shown to be not efficacious in acute mania.[1]

1. Macritchie K, et al.Cochrane Database of Systematic Reviews 2003; (Issue 1).

ACUTE MANIA- BENZODIAZEPINE

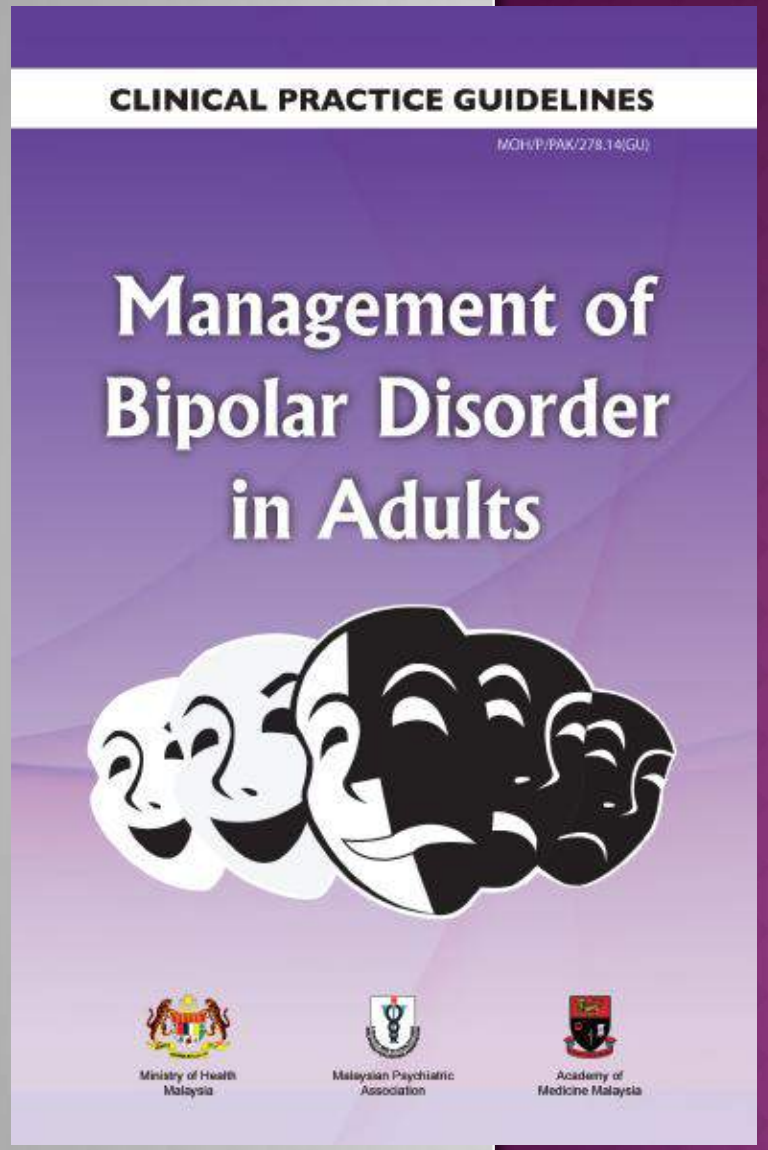
- Benzodiazepines may be used during acute mania.
- CANMAT 2005 and NICE 2006 recommend the use of benzodiazepines in combination with antimanic agents to manage behavioural disturbances.[6-7]

6. National for Collaborating Centre for Mental Health. 2006.
7. Yatham LN, et al. Bipolar Disord. 2013; 15(1):1-44.

RECOMMENDATION

Recommendation 3

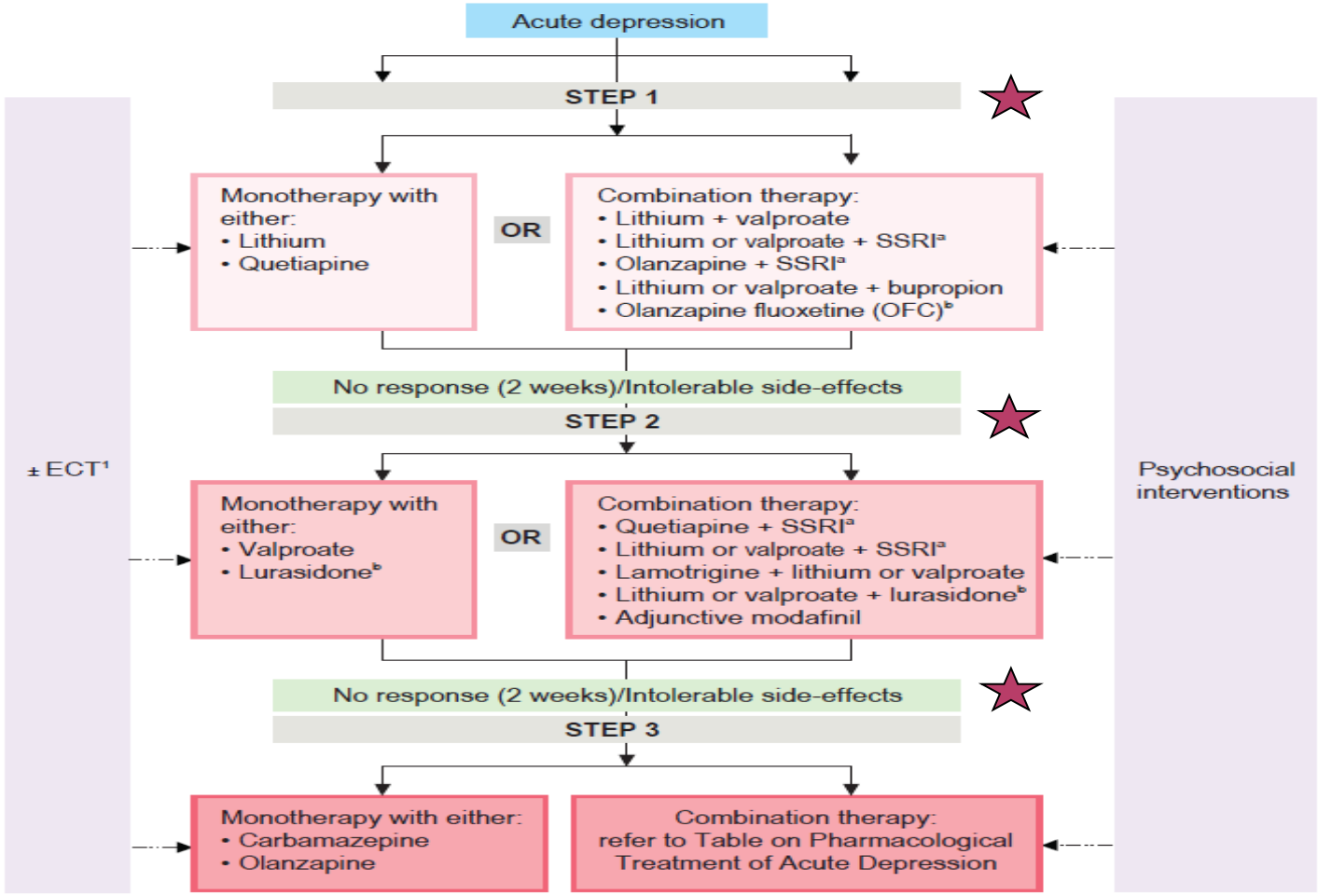
- Mood stabilisers or antipsychotics, either as monotherapy or combination, should be used to treat acute mania in bipolar disorder. **(Grade A)**



ACUTE DEPRESSION

ACUTE DEPRESSION

ALGORITHM 3. TREATMENT OF ACUTE DEPRESSION

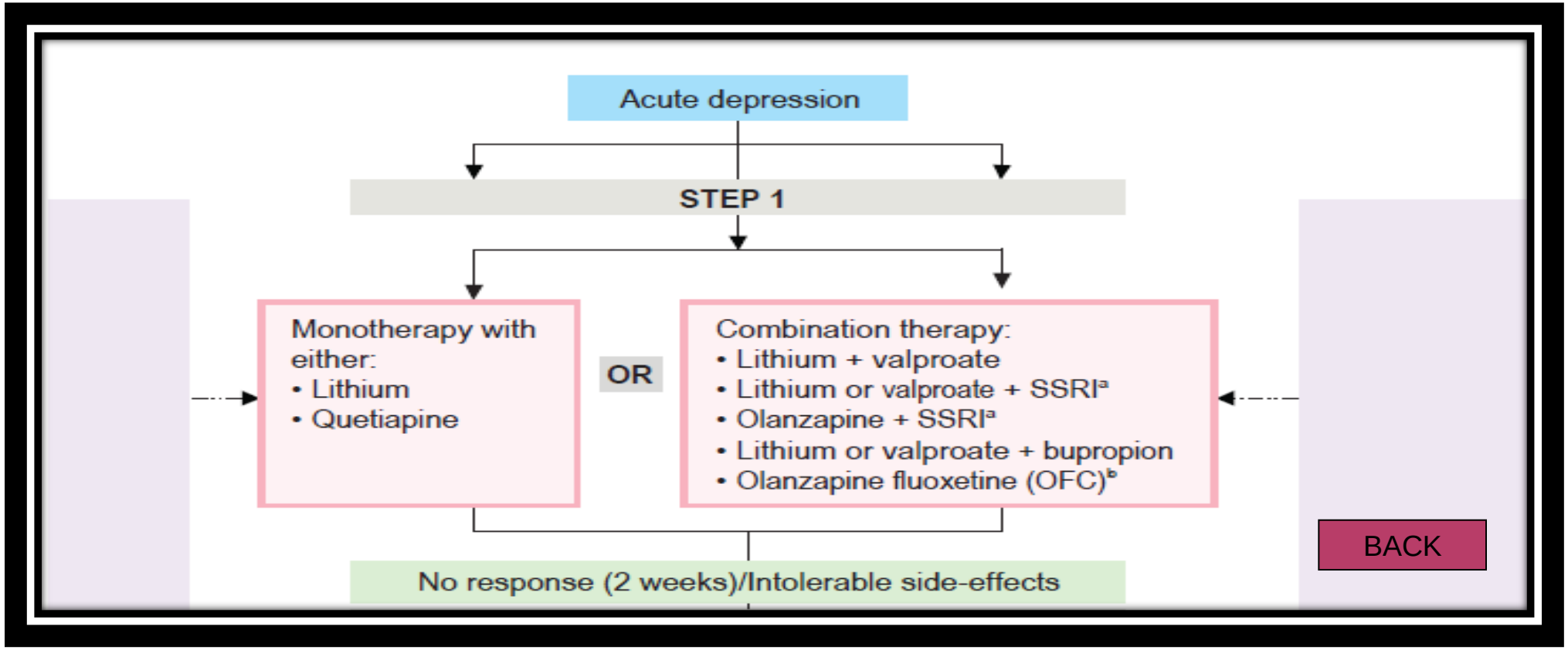


[1] Consideration for ECT
- Severe symptoms of depression
- High suicidal risk
- Catatonia
- Intolerance or no response to medications

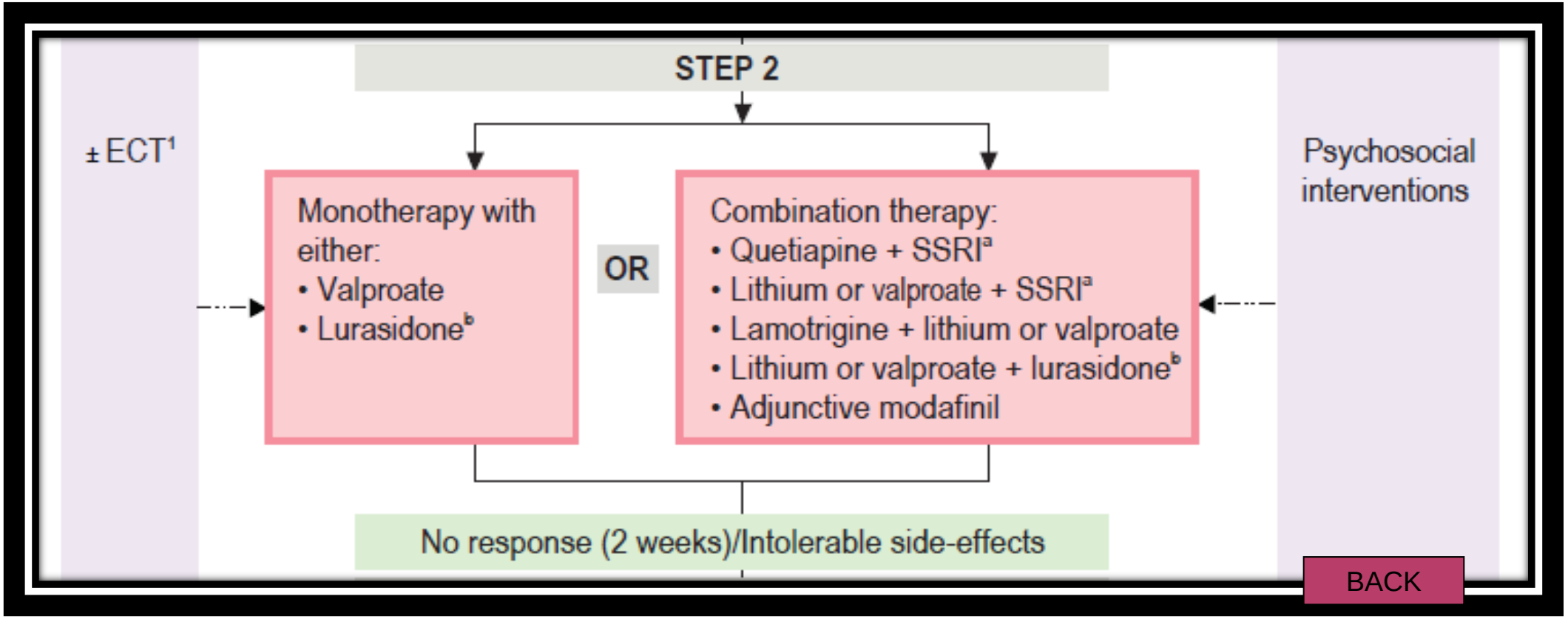
[a] Except paroxetine

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

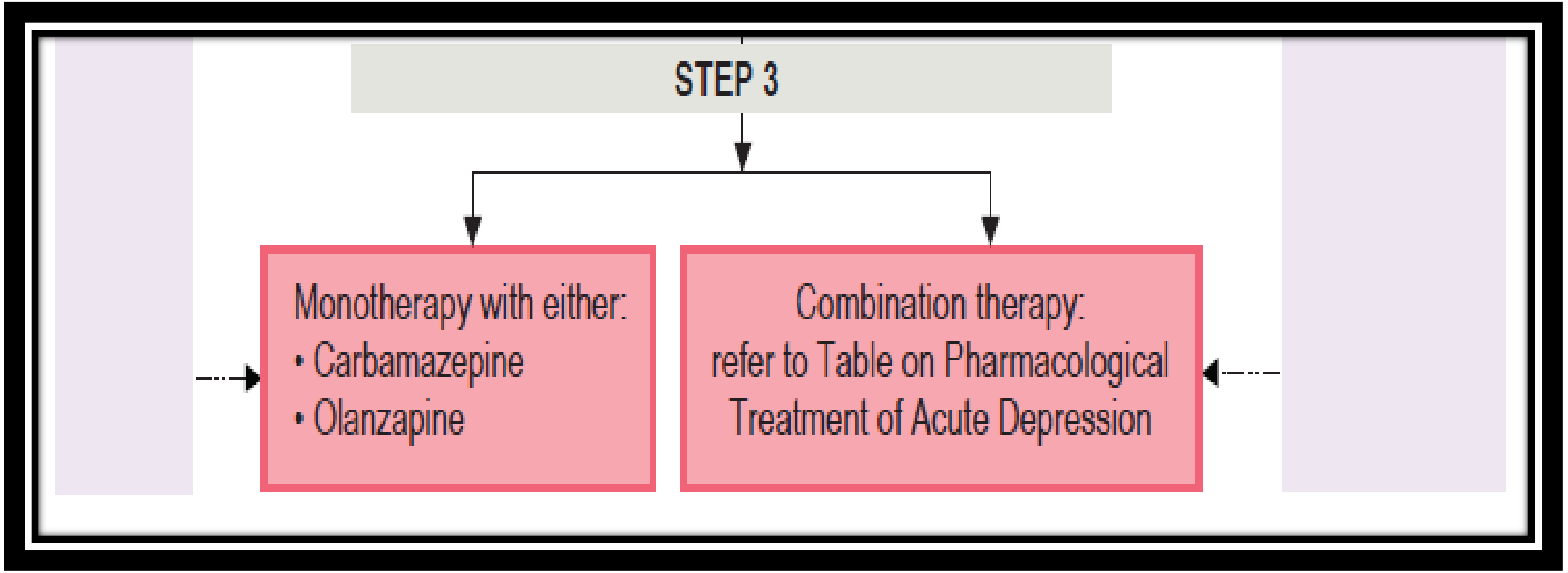
ACUTE DEPRESSION - STEP 1



ACUTE DEPRESSION - STEP 2



ACUTE DEPRESSION – STEP 3



ACUTE DEPRESSION -TREATMENT

First line	
Monotherapy	Lithium, quetiapine, extended release (XR) quetiapine
Combination therapy	Lithium or valproate + selective serotonin reuptake inhibitor (SSRI)[a], olanzapine + SSRI[a], lithium + valproate, lithium or valproate +bupropion
Second line	
Monotherapy	Valproate, lurasidone[b]
Combination therapy	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	Lithium + carbamazepine, lithium + pramipexole, lithium or valproate + venlafaxine, lithium + monoamine oxidase inhibitor (MAOI), lithium or valproate or AAP + TCA, lithium or valproate or carbamazepine + SSRI[a]+ lamotrigine, quetiapine + lamotrigine[b]

ACUTE DEPRESSION - MOOD STABILISERS

- According to CANMAT (2013), lithium and lamotrigine have been found to be effective in the treatment of acute bipolar depression.[7]

- 1 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). However, this SR included atypical antipsychotics as mood stabilisers.[8]

7. Yatham LN, et al. Bipolar Disord. 2013; 15(1):1-44.
8. Van Lieshout Rj et al. Br J Psychiatry. 2010; 196(4):266-273.

ACUTE DEPRESSION - ANTIPSYCHOTIC

- Several antipsychotics are significantly efficacious in the treatment of acute bipolar depression:-
  - Quetiapine monotherapy [9-10]
  - Quetiapine and mood stabilisers[9]
  - Olanzapine-fluoxetine combination (OFC) [10-11]

9. Chiesa A et al. Int Clin Psychopharmacol. 2012; 27(2):76-90.
10. Vieta E et al. J Clin Psychopharmacol. 2010; 30(5):579-590.
11. Tamayo JM et al. J Clin Psychopharmacol. 2009; 29(4):358-356.

ACUTE DEPRESSION - ANTIDEPRESSANTS

Efficacy

- 1 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.[12] However a recent SR did not replicate the same findings.[13]

12. Gijsman HJ et al. Am J Psychiatry. 2004; 161(9):1537-1547.
13. Sidor MM et al. J Clin Psychiatry. 2011; 72(2):156-167.

ACUTE DEPRESSION - ANTIDEPRESSANTS

Affective switching

- Antidepressants as adjunctive treatment do not significantly increase or decrease the risk of affective switch relative to placebo.[12-13]

- However among antidepressants, tricyclic antidepressants (TCA) cause more mood switching (RR=2.92, 95% CI 1.28 to 6.21)[13] while bupropion is associated with a reduced risk compared to the others (RR=0.34, 95% CI 0.13 to 0.88).[12]

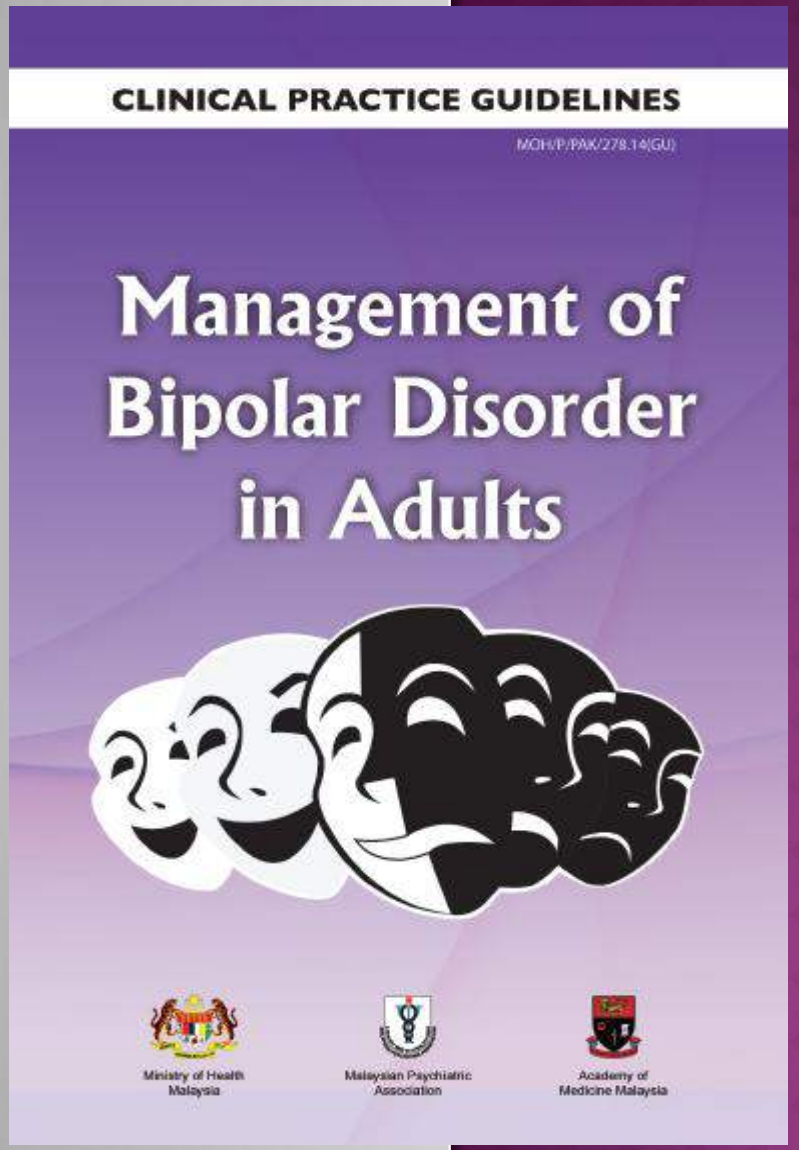
- Venlafaxine is associated with mood switch in people with BD prior history of rapid cycling compared to bupropion or sertraline.[14]

12. Gijsman HJ et al. Am J Psychiatry. 2004; 161(9):1537-1547.
13. Sidor MM et al. J Clin Psychiatry. 2011; 72(2):156-167.
14. Post RM et al. Br J Psychiatry. 2006 189:124-131.

RECOMMENDATION

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)**



RAPID CYCLING

RAPID CYCLING- INTRODUCTION

- 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.

RAPID CYCLING- MOOD STABILISERS

- A recent SR by Fountoulakis et al.,lithium and anticonvulsants were found to have comparable efficacy.

- For anticonvulsants, the comparative efficacy between monotherapy and combination therapy was found to be inconclusive.[15]

15. Fountoulakis KN, et al. J Affect Disord. 2009; 113(1-2):21-29.

RAPID CYCLING - ANTIDEPRESSANT

- The relationship between rapid cycling and the use of antidepressants is still debatable.

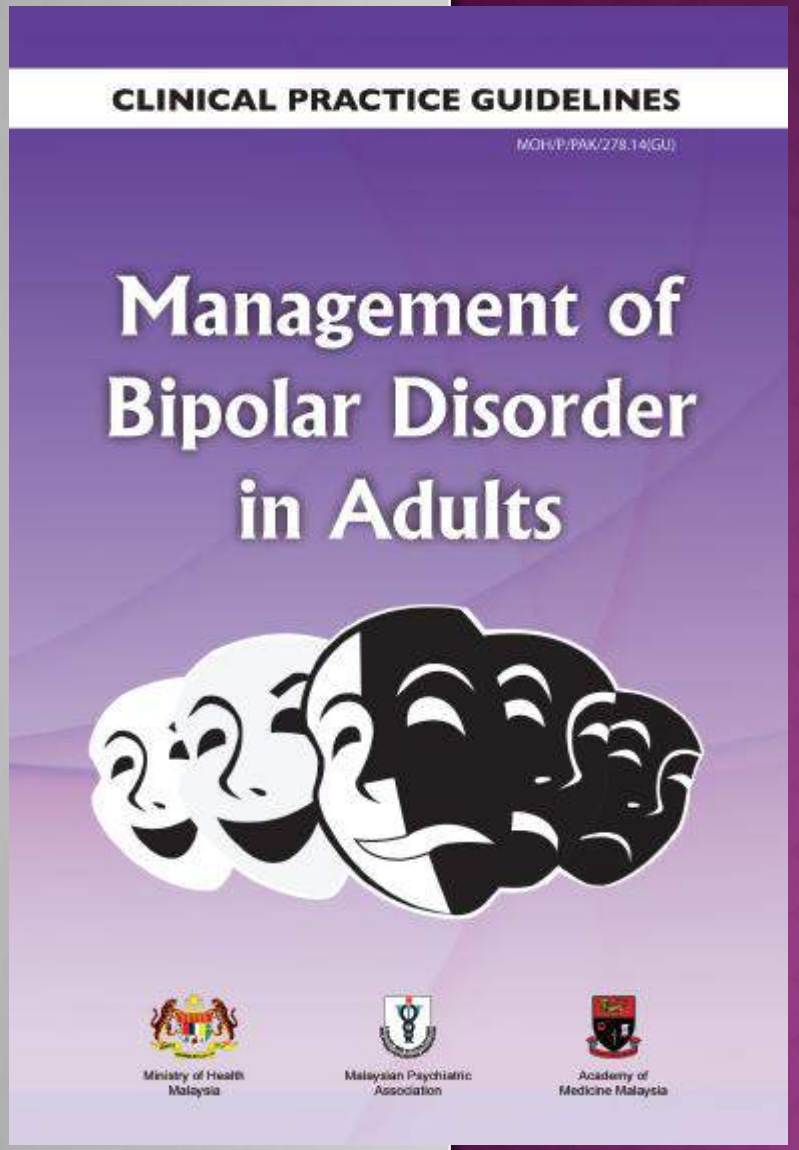
- The subjects with rapid cycling in Systematic Treatment Enhancement Program for Bipolar Disorder (STEP BD) study had three times more depressive episodes with antidepressant continuation compared to those without.[15]

15. Fountoulakis KN, et al. J Affect Disord. 2009; 113(1-2):21-29.

RECOMMENDATION

Recommendation 5

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


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

MIXED STATE

MIXED EPISODE - INTRODUCTION

- Mixed state remains one of the challenges in management of BD.

- 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]

16. APA . Diagnostic and Statistical Manual of Mental Disorders 5th Edition (Dsm-5). Arlington: APA; 2013.

MIXED EPISODE - MOOD STABILISERS

- While lithium benefits patients with mixed episodes, it may be less efficacious than valproate; however there are only few studies of such direct comparison.[17]

17. Swann AC et al. Arch Gen Psychiatry. 1997; 54(1):37-42.

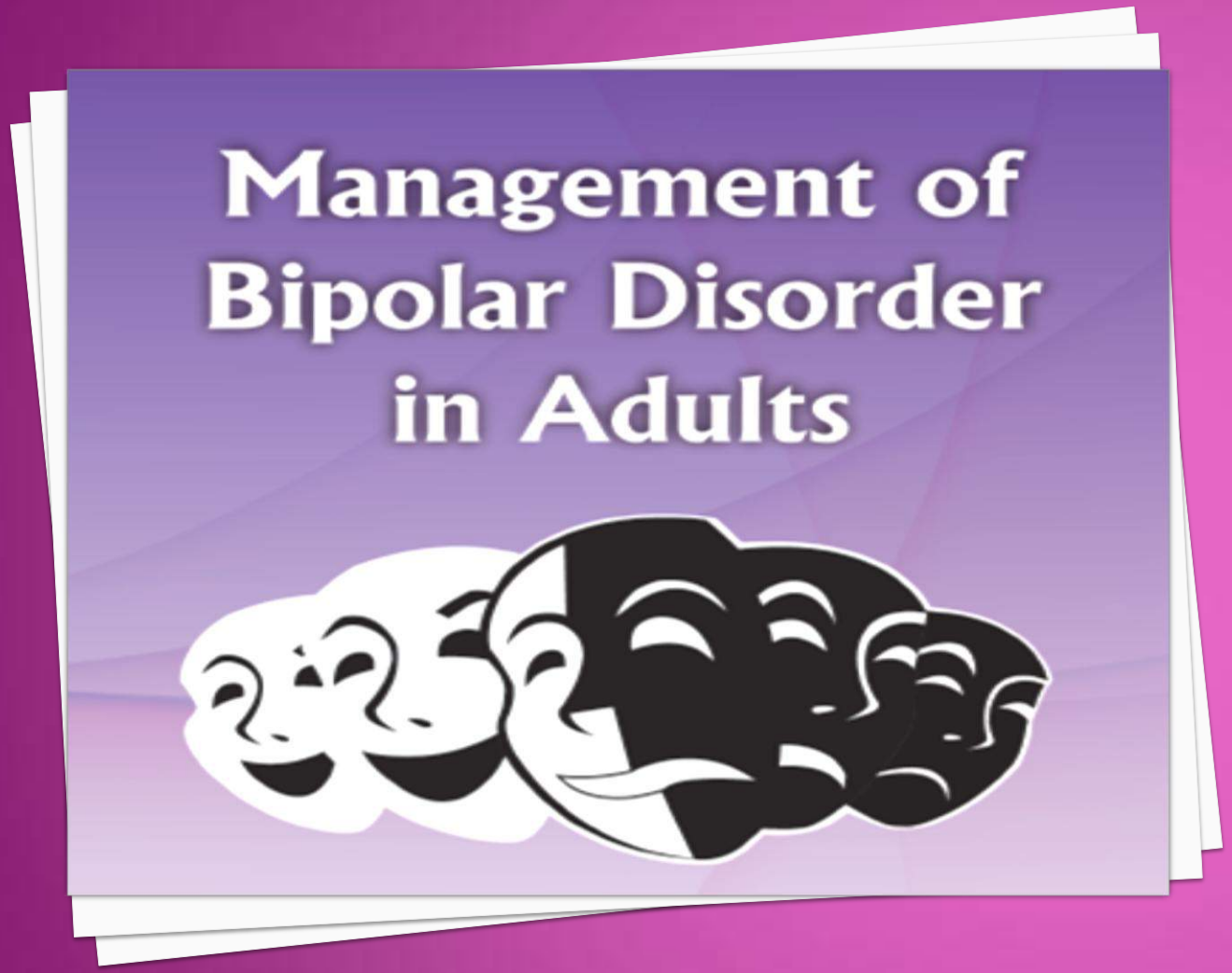
MIXED EPISODE - ANTIPSYCHOTICS

- Atypical antipsychotics have significant evidence for benefit in mixed states.[36, level I]
- Meta-analysis on the efficacy of second generation antipsychotics used in treating acute mixed states showed that aripriprazole, 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.

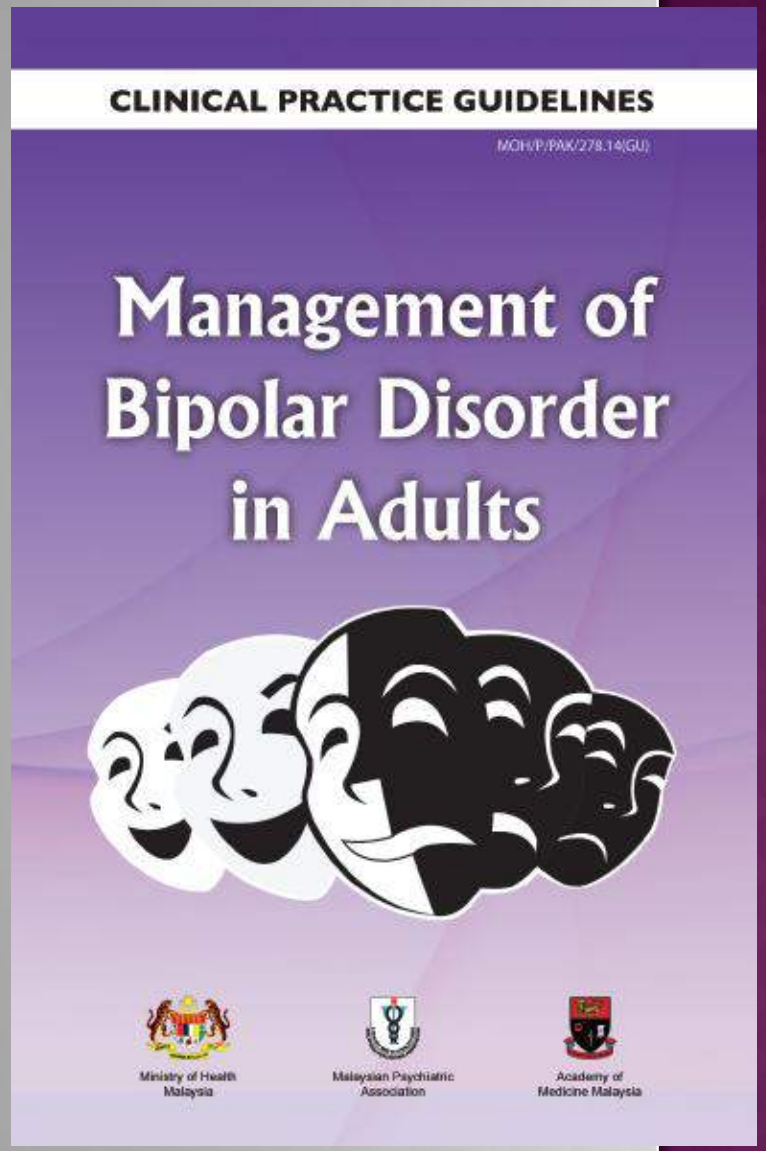
18. Muralidharan K et al. J Affect Disord. 2013; 150(2):408-414.

TAKE HOME MESSAGE

- The choice of drugs use is based on the balanced decision between the benefits and potential harms.
- Mood stabilisers or antipsychotics, either as monotherapy or combination, should be used to treat acute mania
- Lithium, quetiapine or olanzapine-fluoxetine combination be used as monotherapy in acute bipolar depression
- Antidepressants may be used as short-term adjunctive treatment in acute bipolar depression, but not as monotherapy
- The hard clinical evidence for rapid cycling and mixed state are limited



THANK YOU



PHARMACOLOGICAL MANAGEMENT: MAINTENANCE PHASE

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&
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LEARNING OBJECTIVES

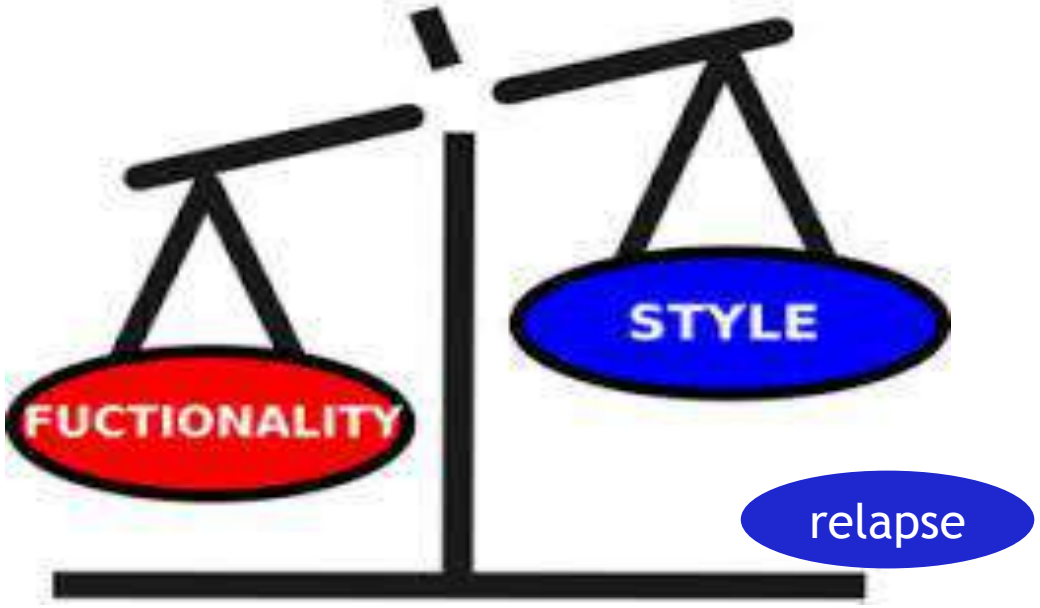
- To understand the principles of pharmacological management in the maintenance phase.
- To prescribe the appropriate pharmacological treatment in the maintenance phase.
- To look for the factors contributes to adherence
- To follow the monitoring schedule recommended for the patients who are on medications

MAINTENANCE PHASE- INTRODUCTION

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

MAINTENANCE PHASE- INTRODUCTION

- The aim is to prevent relapse and optimise functionality.



MAINTENANCE PHASE - TABLE TREATMENT

RECOMMENDATIONS ON PHARMACOLOGICAL TREATMENT OF MAINTENANCE PHASE IN BD

First line	
Monotherapy	Lithium, lamotrigine (limited efficacy in preventing mania), valproate, olanzapine, quetiapine, risperidone long acting injection (LAI), aripiprazole
Combination therapy	Adjunctive therapy with (lithium or valproate) + quetiapine/risperidone LAI/ aripiprazole/ ziprasidone
Second line	
Monotherapy	Carbamazepine, paliperidone
Combination therapy	• 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

MAINTENANCE PHASE - FIRST LINE

First line	
Monotherapy	Lithium, lamotrigine (limited efficacy in preventing mania), valproate, olanzapine, quetiapine, risperidone long acting injection (LAI), aripiprazole
Combination therapy	Adjunctive therapy with (lithium or valproate) + quetiapine/risperidone LAI/ aripiprazole/ ziprasidone

MOOD STABILISERS - LITHIUM

- Four SRs indicated that lithium is significantly more efficacious than placebo in reducing the risk of all relapse.[1-4]

- 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).[2]

1. Smith LA et al. Bipolar Disord. 2007; 9(4):394-412.
2. Geddes JR et al. Am J Psychiatry. 2004;161(2):217-222.
3. BALANCE investigators and collaborators et al. Lancet. 2010; 375 (9712):385-395.
4. Macritchie K et al. Cochrane Database of Systematic Reviews. 2001; (3).

MOOD STABILISERS - VALPROATE

- Two SRs showed that valproate was more efficacious in preventing any mood episode compared to placebo.[1,4]
- 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).[4]

1. Smith LA et al. Bipolar Disord. 2007; 9(4):394-412.
4. Macritchie K et al. Cochrane Database of Systematic Reviews. 2001; (3).

MOOD STABILISER- LAMOTRIGINE

- Lamotrigine is superior than placebo in preventing relapse due to any mood episode (RR=0.84, 95% CI 0.71 to 0.99).[1]
- However in RCT, lamotrigine was superior to placebo in delaying intervention for depressive symptoms (p=0.047) but not manic symptoms (p=0.339).[2]

1. Smith LA et al. Bipolar Disord. 2007; 9(4):394-412.
2. Calabrese JR et al. J Clin Psychiatry. 2003;64(9):1013-1024

ANTIPSYCHOTICS- OLANZAPINE

- In 2 SRs, olanzapine was significantly more efficacious than placebo in preventing relapses of any mood episode & manic[1,5] but with higher risk of weight gain.[5]

- An RCT in 1 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) & caused less insomnia (RR=0.15, 95% CI 0.07 to 0.34) compared with lithium.[5]

1. Smith LA et al. Bipolar Disord. 2007; 9(4):394-412.
5. Cipriani A et al. Cochrane Database of Systematic Reviews. 2009; (Issue 1).

ANTIPSYCHOTIC-COMBINATION (LITHIUM OR VALPROATE + ARIPIPRAZOLE)

- 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).[6]

- 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).[7]

6. Marcus R et al. Bipolar Disord. 2011; 13(2):133-144.
7. Woo YS et al. Hum Psychopharmacol. 2011; 26(8):543-553.

ANTIPSYCHOTIC- COMBINATION (LITHIUM/VALPROATE + QUETIAPINE)

- 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).[8]

8. Suppes T et al. Am J Psychiatry. 2009; 166(4):476-488.

ANTIPSYCHOTIC-COMBINATION (LITHIUM/VALPROATE + RISPERIDONE LAI)

- 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 to 12) in which the RR of relapse was 2.3 fold higher with adjunctive placebo.[9]

9. Macfadden W et al. Bipolar Disord. 2009; 11(8):827-839.

MAINTENANCE PHASE - TABLE TREATMENT

RECOMMENDATIONS ON PHARMACOLOGICAL TREATMENT OF MAINTENANCE PHASE IN BD

First line	
Monotherapy	Lithium, lamotrigine (limited efficacy in preventing mania), valproate, olanzapine, quetiapine, risperidone long acting injection (LAI), aripiprazole
Combination therapy	Adjunctive therapy with (lithium or valproate) + quetiapine/risperidone LAI/ aripiprazole/ ziprasidone
Second line	
Monotherapy	Carbamazepine, paliperidone
Combination therapy	• 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

MAINTENANCE PHASE – SECOND LINE

Second line	
Monotherapy	Carbamazepine, paliperidone
Combination therapy	• Lithium + valproate • Lithium + carbamazepine • Lithium or valproate + olanzapine • Lithium + risperidone • Lithium + lamotrigine • Olanzapine + fluoxetine

MOOD STABILISER- CARBAMAZEPINE

- 1 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).[10]

- Drug-drug interaction should be considered when carbamazepine is to be used for long-term

10. Ceron-Litvoc D et al. Hum Psychopharmacol. 2009 24(1):19-28.

ANTIPSYCHOTIC- PALIPERIDONE

- 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).[11]
- Compared to paliperidone, olanzapine is superior in delaying the recurrence of any mood symptoms (NNT=3, 95% CI 2 to 5).[11]

11. Berwaerts J et al. J Affect Disord. 2012; 138(3):247-258.

MOOD STABILISER - COMBINATION (LITHIUM + VALPROATE)

- 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).[11]

12. Geddes JR et al. Lancet. 2010; 375(9712):385-395.

ANTIPSYCHOTIC- COMBINATION (LITHIUM/VALPROATE + OLANZAPINE)

- 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).[5]

- 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.[13]

- However, the combination therapy significantly causes more tremor, akathisia, sexual dysfunction and polyuria while monotherapy is associated with more weight gain.[13]

5. Cipriani A et al. Cochrane Database of Systematic Reviews. 2009; (Issue 1).
13. Gonzalez-Pinto Aet al. J Affect Disord. 2011; 131(1-3):320-329.

MAINTENANCE PHASE - TABLE TREATMENT

RECOMMENDATIONS ON PHARMACOLOGICAL TREATMENT OF MAINTENANCE PHASE IN BD

First line	
Monotherapy	Lithium, lamotrigine (limited efficacy in preventing mania), valproate, olanzapine, quetiapine, risperidone long acting injection (LAI), aripiprazole
Combination therapy	Adjunctive therapy with (lithium or valproate) + quetiapine/risperidone LAI/ aripiprazole/ ziprasidone
Second line	
Monotherapy	Carbamazepine, paliperidone
Combination therapy	• 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

MAINTENANCE PHASE - THIRD LINE

Third line	
Monotherapy	Asenapine
Combination therapy	Adjunctive therapy with lithium or valproate + asenapine

MAINTENANCE PHASE – NOT RECOMMENDED

Not recommended:

- Monotherapy with gabapentin, topiramate or antidepressants.
- Adjunctive therapy with flupenthixol.

ROLE OF 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).[14]

- 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).[15]

14. Ghaemi SN et al. Acta Psychiatr Scand. 2008; 118(5):347-356.
15. Sachs GS et al. N Engl J Med. 2007;356(17):1711-22.

RECOMMENDATION

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)**

ADHERENCE - INTRODUCTION

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.[16]

16. Montes JM et al. Patient Prefer Adherence. 2013; 7:89-94.

ADHERENCE - RISK FACTORS

Risk factors for non-adherence are:-[16-18]

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

16. Montes JM et al. Patient Prefer Adherence. 2013; 7:89-94.
17. Sajatovic M et al. Compr Psychiatry. 2009; 50(2):100-107.
18. Baldessarini RJ, et al. Hum Psychopharmacol. 2008; 23(2):95-105.

ADHERENCE-PSYCHOSOCIAL

- 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.[19]

- 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.[20]

19. Gaudiano BA et al. Behav Modif. 2008; 32(3):267-301.
20. Sajatovic M et al. Bipolar Disord. 2012; 14(3).

RECOMMENDATION

Recommendation 8

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

MONITORING SCHEDULE- INTERVAL

PARAMETERS FOR REGULAR MONITORING IN BD

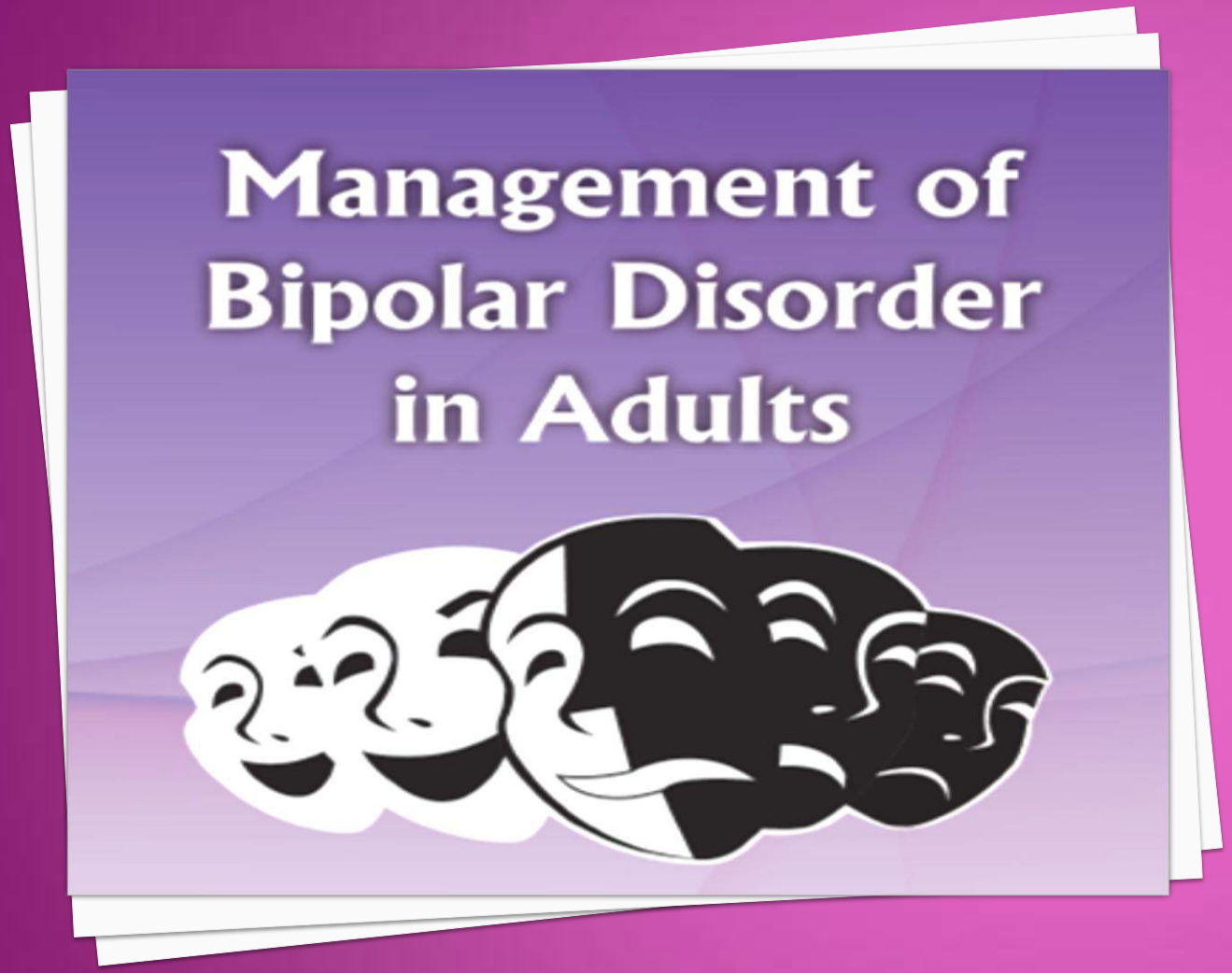
Parameter	For all patients at first visit	Antipsychotics	Lithium	Valproate	Carbamazepine
Weight, height and waist circumference	Yes	At initiation & every 3 months for first year; more often if patient gains weight rapidly	At initiation & when needed if the patient gains weight rapidly	At initiation & 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
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		

MONITORING SCHEDULE

NAME	DOSE RANGE	MAIN ADVERSE EFFECTS
MOOD STABILISERS		
Lithium	**Acute mania**: 600 – 1800 mg/day in divided doses **Maintenance dose**: 300 – 1200 mg/day in divided doses (Desired serum level : 0.6 - 1.2 mEq/L not exceeding 1.5 mEq/L) To be used with caution and correlate clinically	GI upset (in first 2 week) Polyuria & Polydipsia Metallic taste Weight gain Hypothyroidism Hyperparathyroidism Fine tremor Diabetes Insipidus
Valproate	**Acute Mania**: 600 - 2500 mg/day in divided doses Maintenance dose: 400 - 2000 mg/day in divided doses (Desired serum level 50-100 µg/mL @ 347-693 µmol/L)	GI upset Sedation Weight gain Tremor Thrombocytopenia Raised liver enzymes
Carbamazepine	**Mania/mixed episodes** 200 to 1600 mg/day in divided doses (Desired serum level 4-12 mg/L @ 17-50 µmol/L)	Steven Johnson's Syndrome Hypotension Rash GI upset Dizziness Drowsiness Fatigue

TAKE HOME MESSAGE

- The aim of maintenance phase is to prevent relapse and optimise functionality.
- 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.
- Risk factors for treatment non-adherence in bipolar disorder should be identified and addressed to improve clinical outcomes



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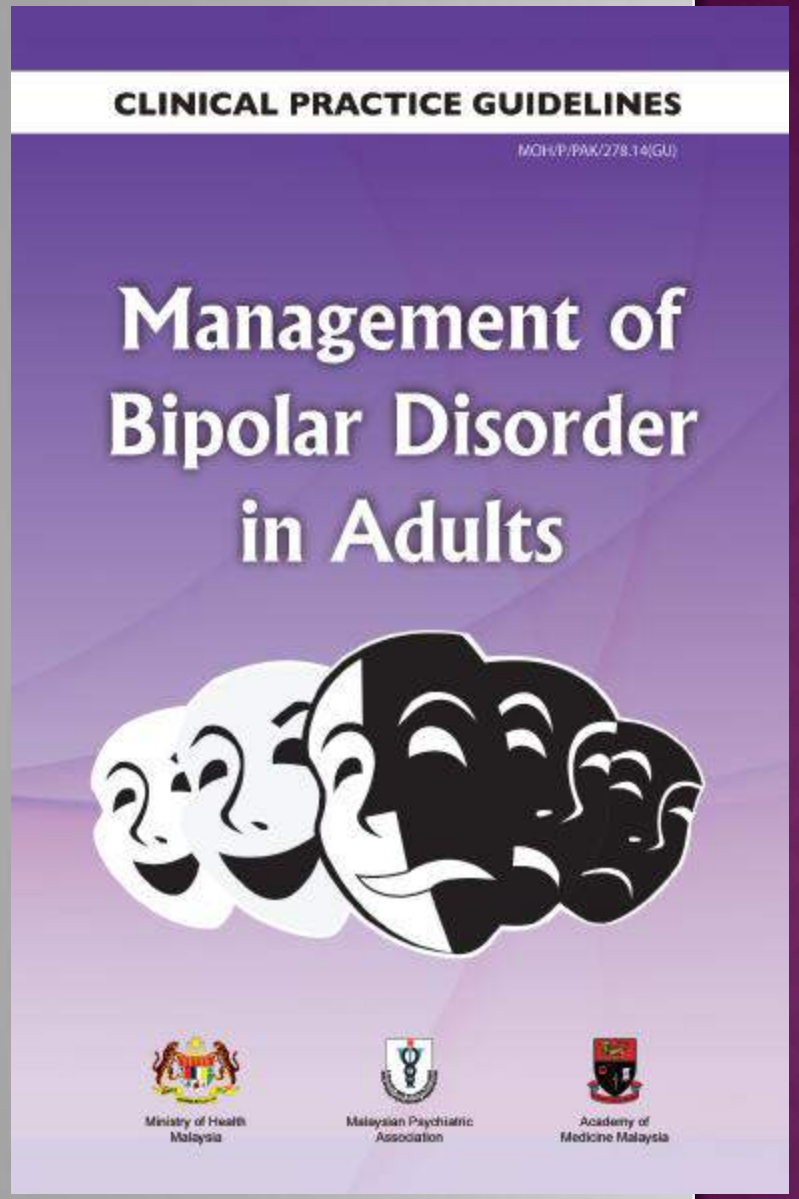


CASE DISCUSSION 1

Dr. Rafidah Bahari
Lecturer & Psychiatrist
Cyberjaya University College of Medical Sciences

HISTORY

- Mr. R, a 23-year-old Malay man, unemployed admitted to the psychiatry ward after he threatened a woman in a bakery.
- On the day of the admission, he went to seek justice for his uncle who was assaulted by a group of men. He thought he was a chosen hero and has special power.
- After failing to find them, the patient then went to the bakery where one of the men's sister works & started to feel attracted and flirt with her. However he turned abusive when she rejected.

HISTORY (CONT.)

- He then took off his clothes & hugged the woman, thus she called the police for assistance. He was brought to the hospital by force.

- Over the past ten days, the patient had the following symptoms:
  - always fight and argued with family members and strangers
  - not sleeping at night
  - went out every night clubbing
  - more talkative
  - overtly happy

HISTORY (CONT.)

- He had been diagnosed with a mental illness 5 years ago.
  - Since then, he had multiple hospital admissions due to similar symptoms.
  - He was prescribed with medications which he did not adhere to.
- He admitted taking illicit drugs occasionally.
- He had no past medical or surgical history.

MENTAL STATE EXAMINATION

- Appeared older than his age, noted tattooed arm with many bracelets and rings & was easily distracted by surrounding
- Overfamiliar & flirted openly with female doctors & nurses
- Had pressure of speech & increased volubility (volume)
- Mood predominantly irritable, at times elated
- Has delusion of being special
- No hallucinations
- Poor judgement & insight

PHYSICAL EXAMINATION

- Conscious & alert
- Vital signs normal
- Afebrile
- Good hydration status
- No puncture wounds
- No alcohol/glue smell
- No goitre/thyrotoxic signs

QUESTION 1

- List down the positive findings from the history of presenting illness.

- Which feature(s) would be the most important for you to come to a diagnosis?

ANSWER 1

- Irritable mood**
- Increased energy
- Reduced need for sleep
- Pressure of speech
- Distractibility
- Grandiose delusion
- Sexually disinhibited
- Elated mood

**most important feature

QUESTION 2

- How long had the symptoms been present for?

ANSWER 2

- Ten days

QUESTION 3

- What is his provisional diagnosis?

ANSWER 3

- Bipolar I disorder current episode manic

QUESTION 4

- Why is it mania?

ANSWER 4

- Presence of symptoms for more than one week
- Reduced social functioning, evidenced by failure to act in a socially appropriate manner
- Require hospitalisation
- Presence of grandiose delusion

QUESTION 5

- What are the differential diagnoses?

ANSWER 5

- Substance induced bipolar disorder
- Bipolar & related disorder due to another medical condition
- Schizoaffective disorder
- Personality disorder

QUESTION 6

- What investigations would you do?

ANSWER 6

- To rule out medical conditions especially
  - Thyroid function test - hyper/hypothyroidism
  - CT of the brain - space occupying lesion or head injury
- To rule out the use of substance
  - Urine drugs screen
  - Blood alcohol level
- To get further information & validate history
  - Collateral history from family & get old notes

*Screening tool maybe useful

- Questionnaires such as the Mood Disorder Questionnaire (MDQ)

FURTHER HISTORY

- Prior to the manic episode, he admited to have episodes of low mood.
  - Usually lasted for more than one month
  - Accompanying symptoms include reduced energy, fatigability, poor motivation, poor concentration & guilt
  - Sometimes, thought of killing himself

- During these episodes, he presented to primary care doctors & given short-term treatment
  - While on treatment, he experienced mood instability occasionally

QUESTION 7

- What would those episodes be classified as?

ANSWER 7

- Depressive episodes

QUESTION 8

- What could have been given to him as treatment & what would the consequences be?

ANSWER 8

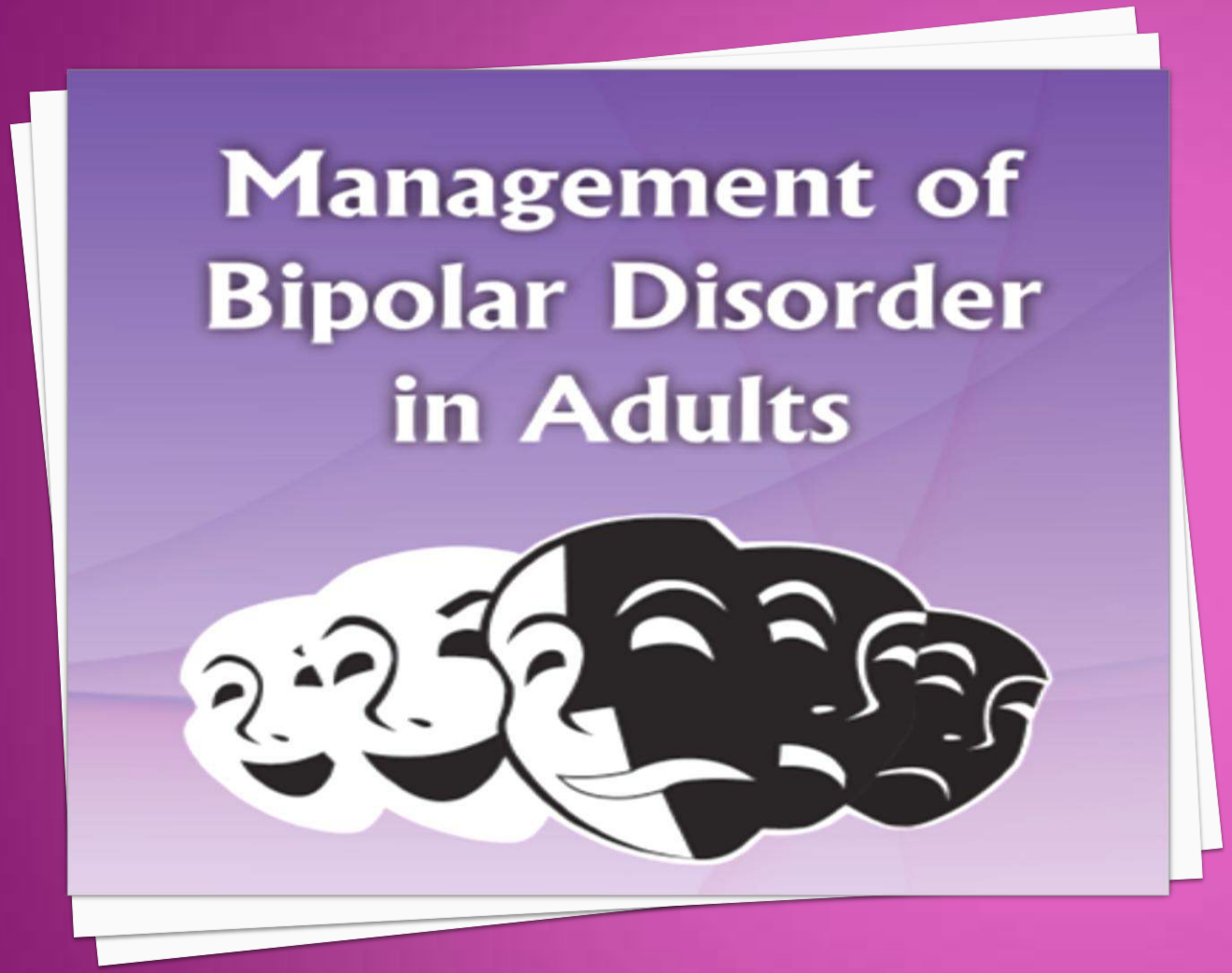
- Benzodiazepines
  - Controlled symptoms slightly
  - Patient assumed he was better, so defaulted treatment

- Antidepressants
  - Destabilise the mood disorder
  - Again patient defaulted treatment

→ Both can delay symptoms recognition &, appropriate diagnosis & treatment

TAKE HOME MESSAGE

- Patient with BD may present with mania, hypomania or depressive symptoms.
- The diagnosis of BD necessitates the presence of mania or hypomania.
- However, the most frequent initial presentation of BD is depressive episode leading to possible misdiagnosis & mistreatment.
- It is important to rule out medical causes to patient‘s presentation before diagnosing them with BD.



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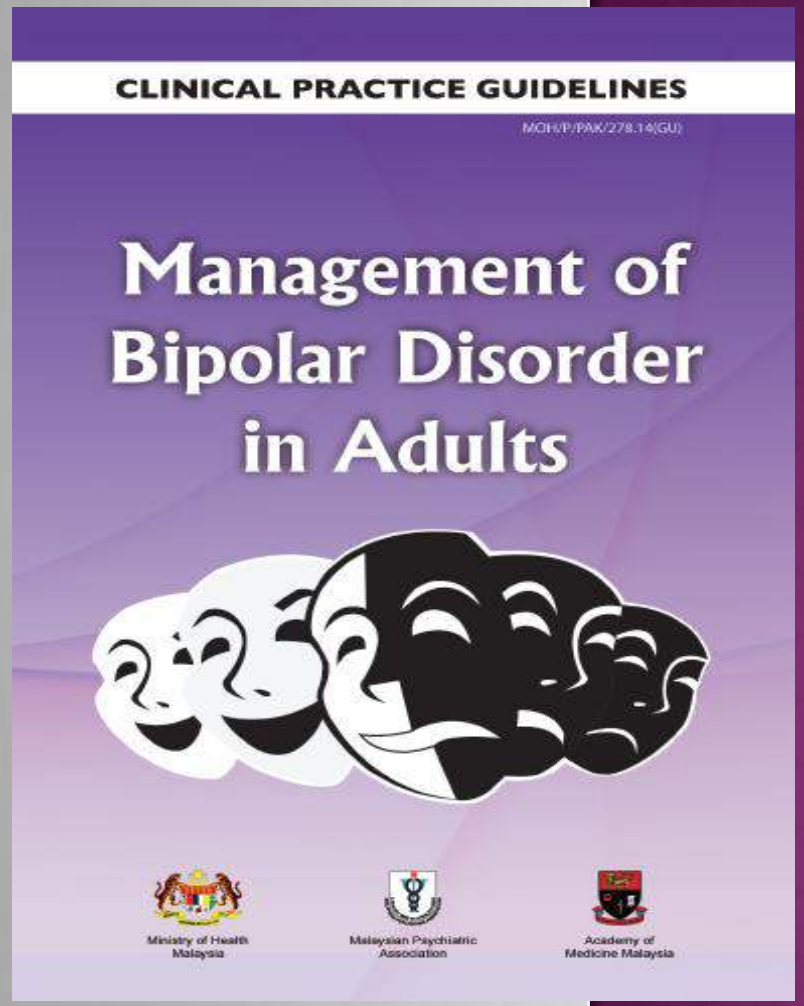
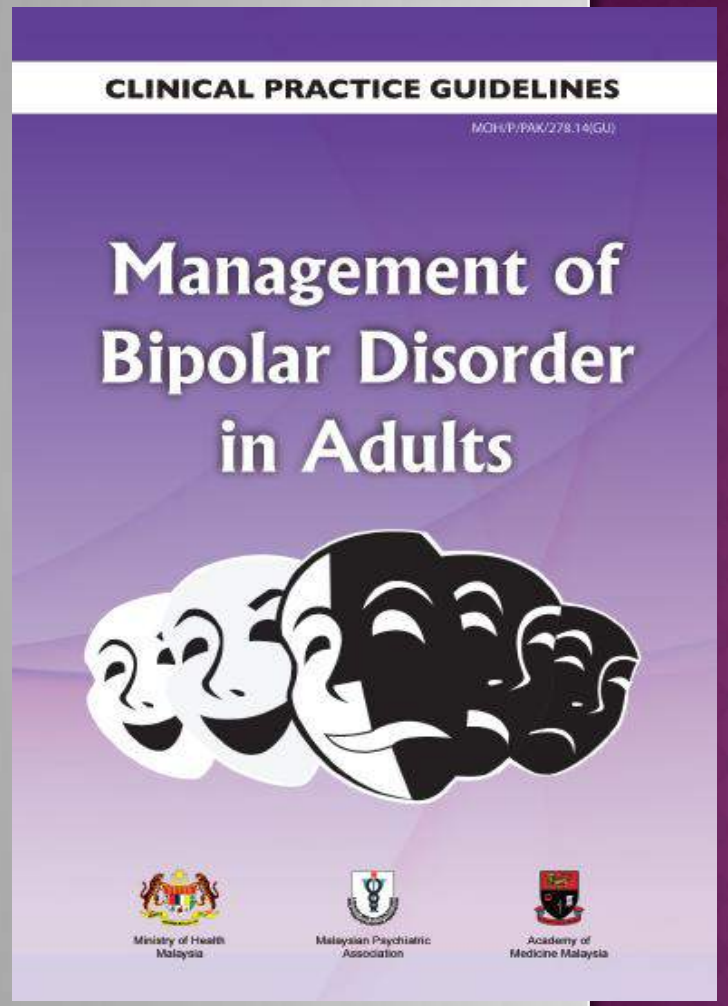


NON-PHARMACOLOGICAL MANAGEMENT

Dr. Zubaidah Jamil
Lecturer & Clinical Psychologist
Universiti Putra Malaysia

LEARNING OBJECTIVES

- To understand the role of ECT in the treatment of BD
- To understand the importance of incorporating psychological approaches in the management of BD



ELECTROCONVULSIVE THERAPY (ECT)

ELECTROCONVULSIVE THERAPY (ECT)-ACUTE

- Evidence on efficacy and safety of ECT is limited.
- However, it is commonly used to treat particularly in:[1]
  - severe mania
  - refractory depression
  - refractory mania

1. Scottish Intercollegiate Guidelines Network (SIGN). Bipolar Affective Disorder. Scotland: National Health Service; 2005.

ECT ACUTE – (CONT.)

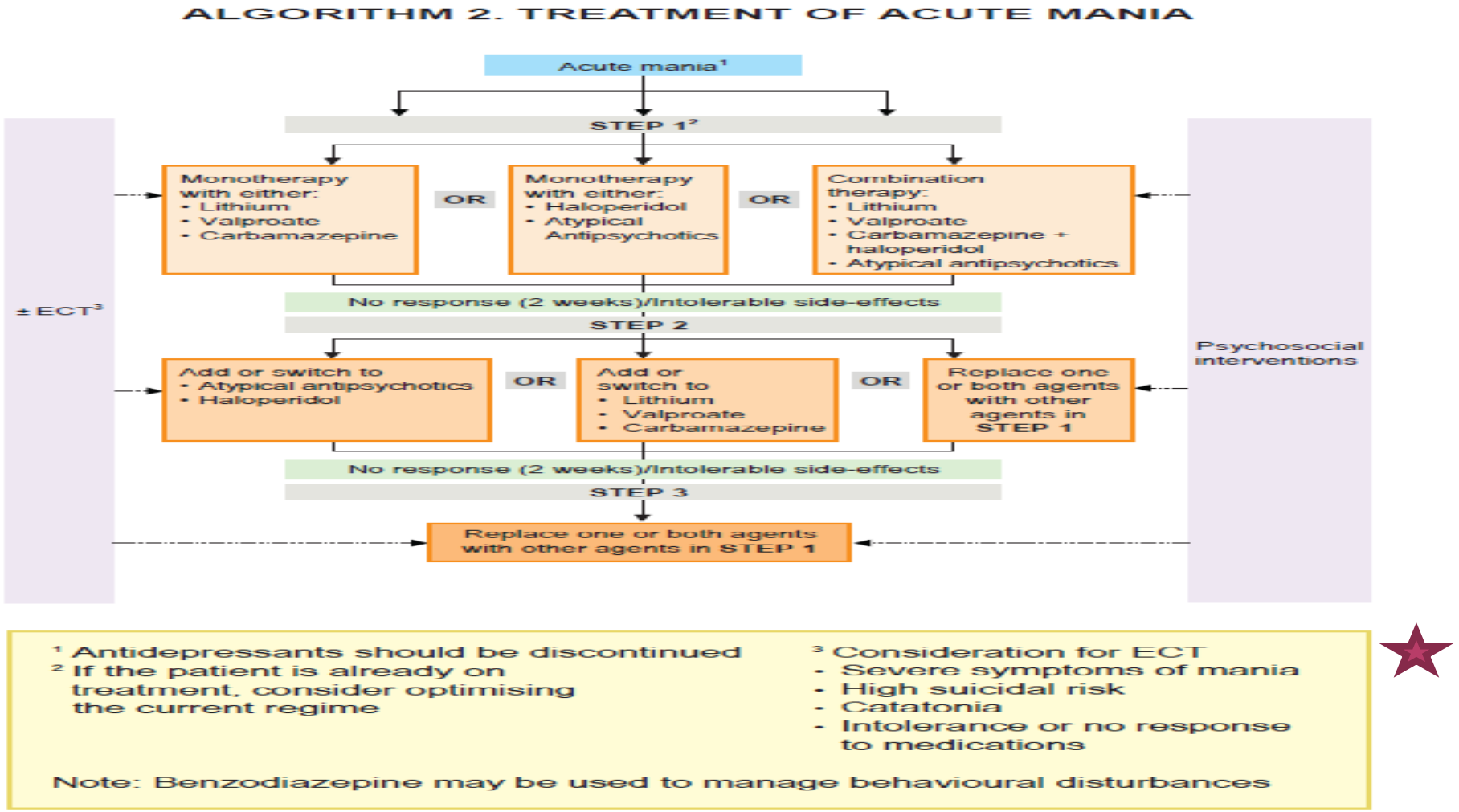
- In a SR:[2]
  - ECT showed high response rates in people with acute mania, depression and mixed with minimal effects on cognitive functions.
  - However, the recommendation for ECT in BD remains inconclusive considering the limited quality in methodology and heterogeneity between studies.

2. Versiani M et al. J ECT. 2011; 27(2):153-164.

ECT - MAINTENANCE

- 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.

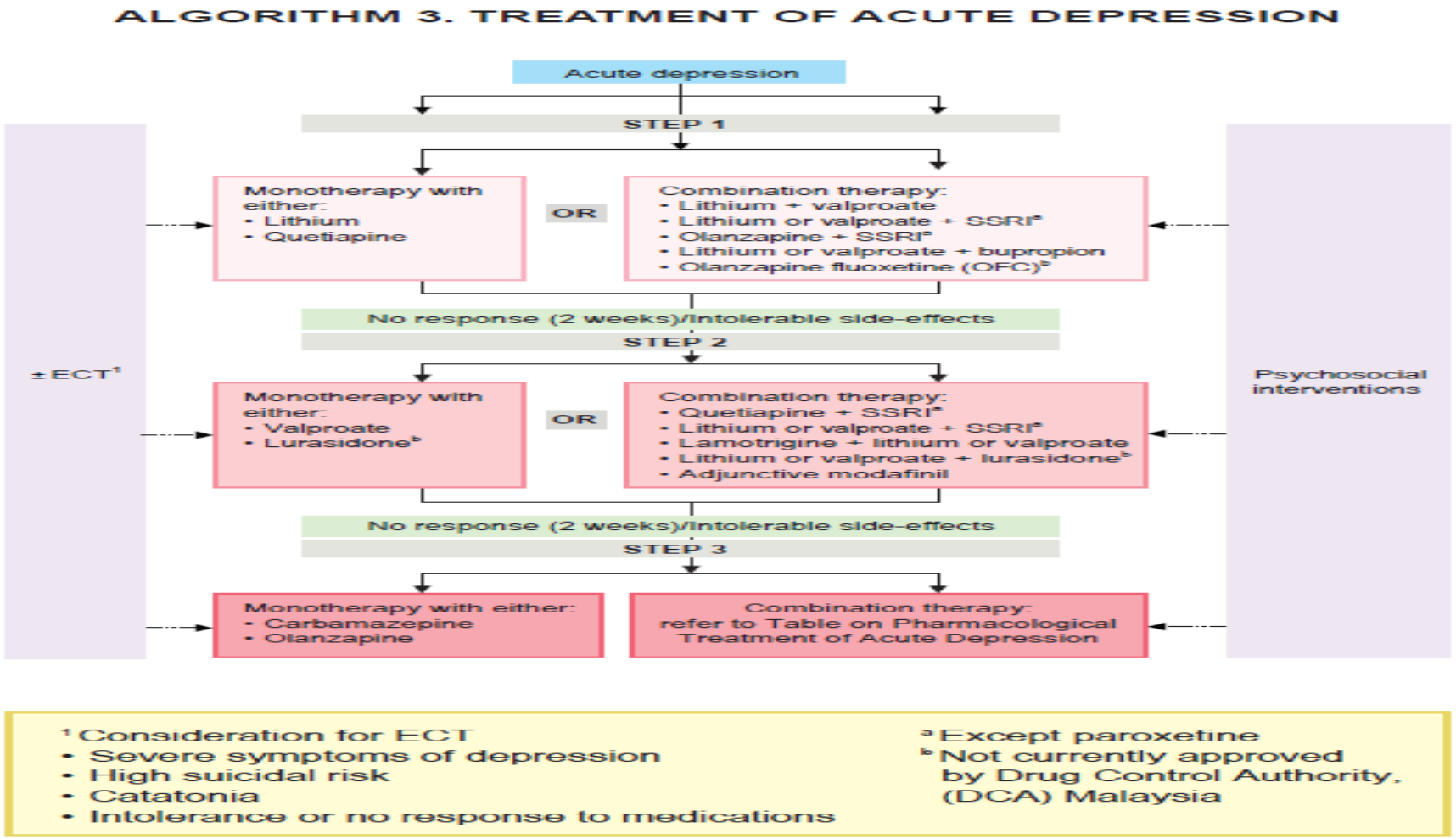
CONSIDERATIONS OF ECT- ACUTE MANIA



CONSIDERATIONS OF ECT- ACUTE MANIA

[3] Consideration for ECT
- Severe symptoms of mania
- High suicidal risk
- Catatonia
- Intolerance or no response to medications

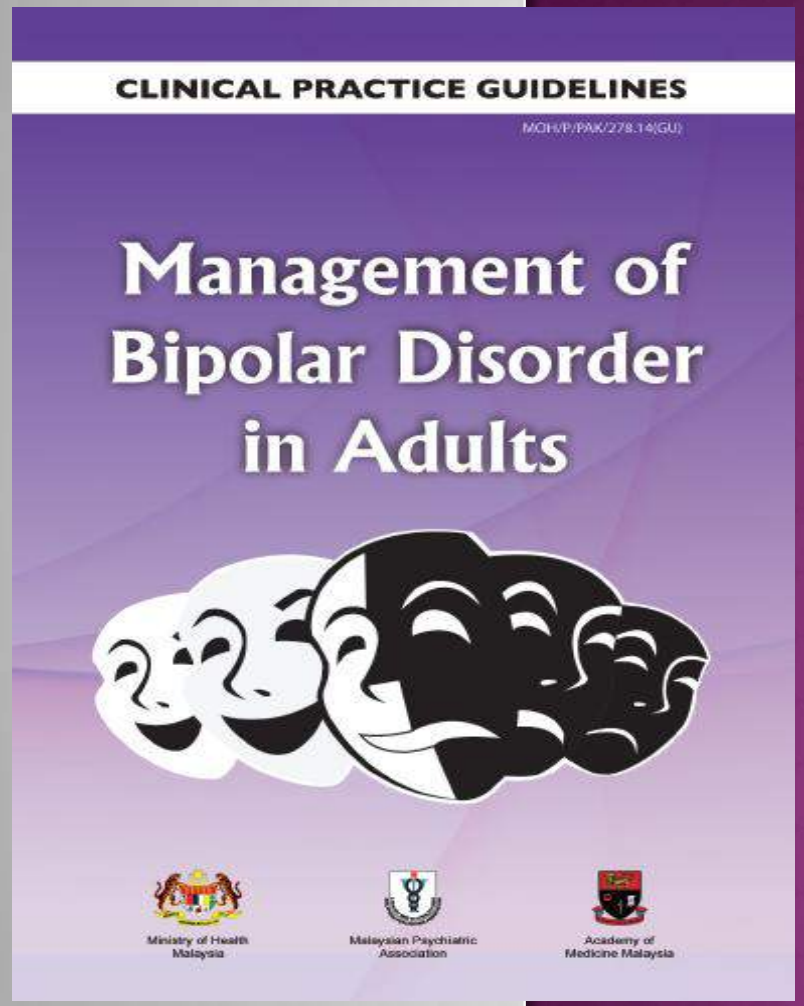
CONSIDERATIONS OF ECT- ACUTE DEPRESSION



CONSIDERATIONS OF ECT- ACUTE DEPRESSION

[1] Consideration for ECT

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



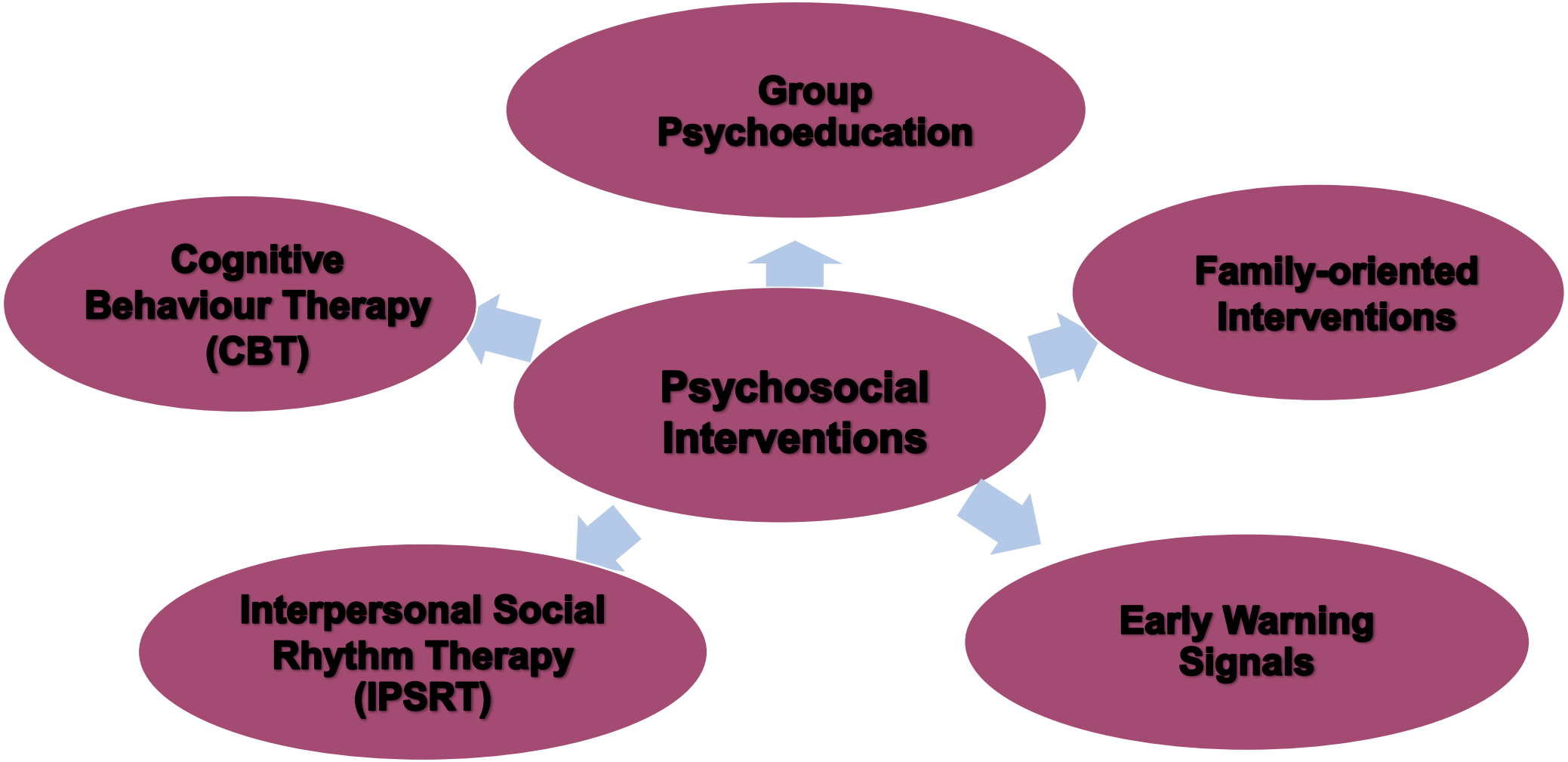
PSYCHOSOCIAL INTERVENTIONS

PSYCHOSOCIAL - INTRODUCTION

- Psychosocial interventions are important in the management of BD.

- It is to enhance:
  - symptomatic outcomes
  - quality of life of patients

PSYCHOSOCIAL - INTRODUCTION



COGNITIVE BEHAVIOURAL THERAPY (CBT) - INTRODUCTION

- CBT is an intervention based on the principle that thoughts, feeling & behaviour are inter-related.

- It aims to train patients to identify, challenge and replace the unhelpful thoughts which are associated with undesirable mood states to more helpful ones.

COGNITIVE BEHAVIOURAL THERAPY (CBT) - (CONT.)

- 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 ($p=0.04$).[3]
  - In people who were mildly depressed or mildly manic, it improved depression, anxiety, mania and hopelessness ($p<0.001$).[4]

3. Scott J et al. Br J Psychiatry. 2006; 188:313-320.
4. Costa RT et al. Rev Bras Psiquiatr. 2011; 33(2):144-149.

INTERPERSONAL SOCIAL RHYTHM THERAPY (IPSRT) - INTRODUCTION

- 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]

5. Frank E et al. Arch Gen Psychiatry. 2005; 62(9):996-1004.

INTERPERSONAL SOCIAL RHYTHM THERAPY (IPSRT) - (CONT.)

- 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 had:[6]
  - improved relationship functioning & life satisfaction
  - remained well clinically
  - higher year-end recovery rates
  - shorter times to recovery

- Augmentation of pharmacotherapy with either one of the psychotherapies mentioned above improved social functioning and reduced relapse prevention rates.[7]

6. Miklowitz DJ et al. Am J Psychiatry. 2007; 164(9):1340-1347.
7. Lam DH et al. Bipolar Disord. 2009; 11(5):474-482.

GROUP PSYCHOEDUCATION/GROUP-BASED PSYCHOTHERAPY-INTRODUCTION

- 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.

GROUP PSYCHOEDUCATION/GROUP-BASED PSYCHOTHERAPY- (CONT.)

- 1 SR reported that over 5 years follow-up, patients in the psychoeducation had less recurrences ($p<0.0001$), spent significantly less time acutely ill ($p<0.001$) & had reduced number of hospitalisation ($p=0.023$) when compared to the control group.[8]

- 1 RCT showed that patients in group-based intervention had reduced rate of relapse of any type (HR=0.43, 95% CI 0.20-0.95) & spent less time unwell ($p=0.02$) compared to those in control group.[9]

8. Colom F et al. Br J Psychiatry. 2009; 194(3):260-265.
9. Castle D et al. Br J Psychiatry. 2010 May;196(5):383-8.

FAMILY-ORIENTED INTERVENTIONS - INTRODUCTION

- This intervention covers areas such as:
  - communication,
  - problem solving skills
  - psychoeducation

- It aims to manage stresses in the home environment leading to high levels of expressed emotion.

FAMILY-ORIENTED INTERVENTIONS (CONT.)

- 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.[9]

9. Castle D et al. Br J Psychiatry. 2010 May;196(5):383-8.

EARLY WARNING SIGNAL (EWS)- INTRODUCTION

- EWS trains 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 .

EARLY WARNING SIGNAL (EWS)- (CONT.)

- 1 Cochrane SR showed that it significantly had:[10]
  - prolonged time to first recurrence of any mood episodes, manic/hypomanic and depressive episodes
  - improved patients' functioning
  - reduced hospitalisation rates

10. Morriss RK et al. Cochrane Database Syst Rev. 2007; 24(1).

OTHER PSYCHOLOGICAL MODALITIES

- 1 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 in the SR were not addressed.[4]

4. Costa RT et al. Rev Bras Psiquiatr. 2011; 33(2):144-149.

OTHER TREATMENTS

- In general, BD may be effectively managed using integrative approach.

- 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.[11-12]

11. Sarris J et al. J Altern Complement Med. 2011; 17(10):881-890.
12. Sarris J et al. Bipolar Disord. 2011; 13(5-6):454-465.

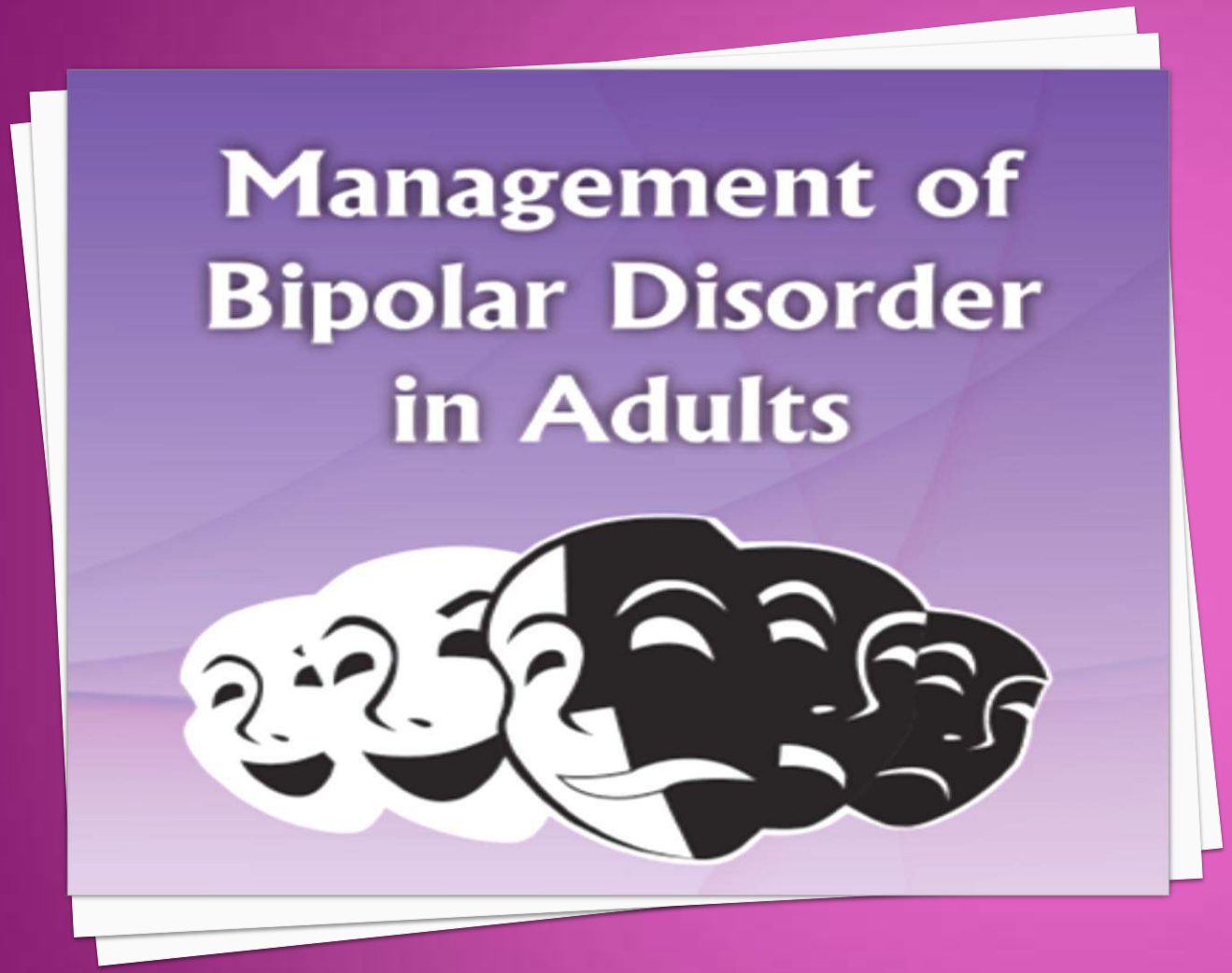
RECOMMENDATION

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)**

TAKE HOME MESSAGE

- There are psychological therapies that have been found to be effective in managing BD.
- There is a role ECT in acute and maintenance phases of BD.



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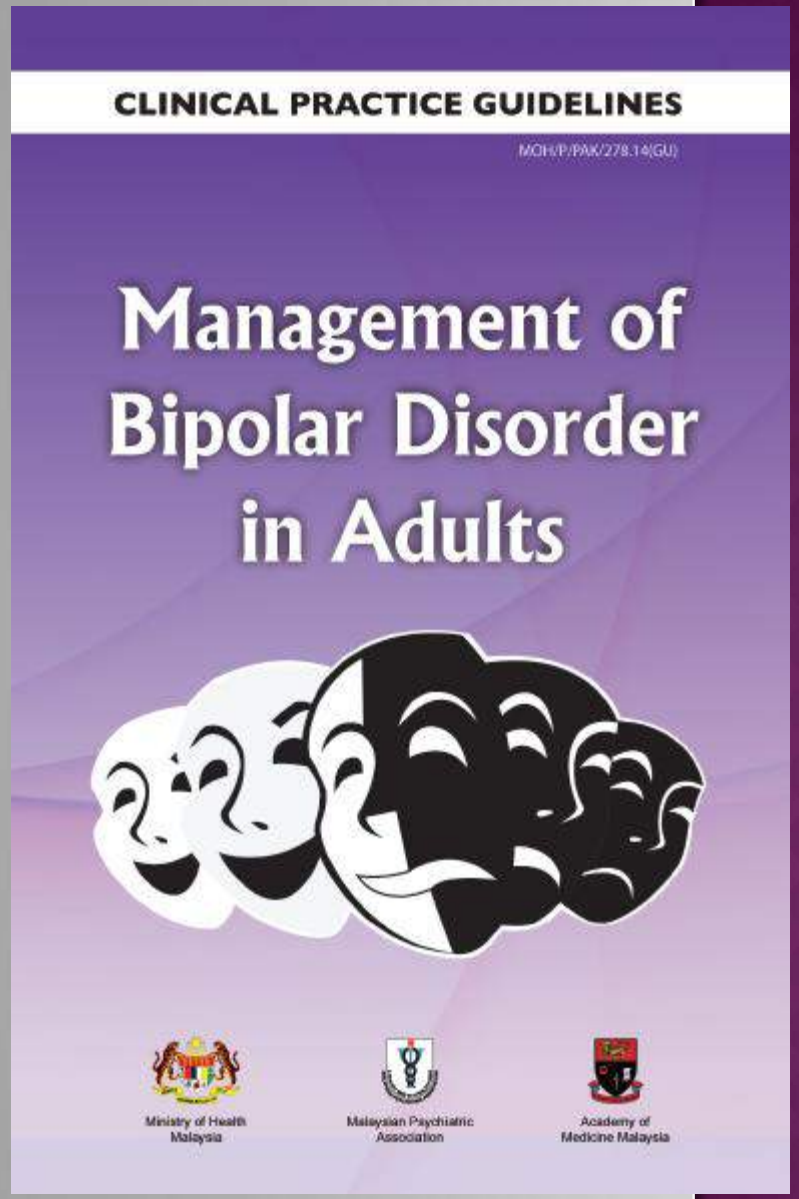


CASE DISCUSSION 2

Dr. Ang Jin Kiat
Lecturer & Psychiatrist
Universiti Putra Malaysia

HISTORY

- A 24-year-old, female, single, final year law student
- Presented with low mood for the past 6 months, which worsened in the past 1 month due to increased assignments
- Other symptoms include:
  - Diminished interest
  - Disturbed appetite
  - Lethargy
  - Poor sleep at night
  - Reduced concentration in class

HISTORY (CONT.)

- Felt that she was useless & a disgrace to her family
- Mother noticed her to be crying excessively
- Fleeting hopelessness & excessive guilt
- Had urges to cut her wrist to release her tension but resisted
- No suicidal attempt as it is prohibited by her religion
- Became very sensitive towards remarks from others, especially related to her studies

HISTORY (CONT.)

- No significant medical & surgical history

- Family history
  - The only child in the family, pampered by parents
  - Mother had post partum psychosis after her delivery, went for traditional treatment & became well after that
  - No other significant family history
  - Mensus normal flow and regular

PERSONAL HISTORY

- No complication during delivery
- Had normal developmental milestones
- Noticed to be a competitive child
- Likes to compare with others
- Strong opinionated

ACADEMIC HISTORY

- High achiever in school
- Obtained scholarship to pursue law degree in local university
- Became very anxious during the beginning of semester, needed parents to send her to university

PREMORBID PERSONALITY

- Moody person
- Said that she is a shy person but willing to fight for what she wanted in her life
- Fear of rejection

MENTAL STATE EXAMINATION

- Neatly dressed
- Cried at many occasions
- Speech was soft, mixed with sobbing, frequent pauses
- Depressed mood
- No perceptual disturbances
- Pessimistic views
- Denies suicidal ideation
- No cognitive impairment
- Judgment fair but insight fair

QUESTION 1

- State your provisional diagnosis & supporting evidence

ANSWER 1

- Major depressive disorder
  - Moderate
  - Without psychotic symptoms

- Evidenced by:
  - Low mood for the past 6 months, worsened in the past 1 month
  - Diminished interest
  - Disturbed appetite
  - Lethargy
  - Poor sleep at night
  - Reduced concentration in class

QUESTION 2

- State your differential diagnosis & supporting evidence.

ANSWER 2

- Bipolar II disorder
- Borderline personality disorder

QUESTION 3

- Outline your management?

ANSWER 3

- Investigations
  - Blood tests
  - Collaborative history
- Treatment
  - Pharmacological – SSRI
  - Psychological – CBT, IPT

HISTORY (CONT.)

- 2 weeks after treatment
  - Noticed to be more irritable and argumentative
  - Felt like scolding others especially her friends over minor issues
  - Felt that she was more vocal about her needs & dissatisfaction.
  - Felt slightly better as she was able to think about her future
  - No urge to spend unnecessarily
  - No special sense of being special

- Symptoms lasted less than a week

HISTORY (CONT.)

- Further history from mother
  - Had similar presentation before
  - Went for religious camp over the weekend
  - Slept less than usual & woke up early for morning prayers
  - Became very motivated & wanted to be the leader of her team
  - More confident than before
  - More religious
  - Asking her friends to pray more & offer their prayers
  - This episode however was brief

QUESTION 4

- State your revised diagnosis & supporting evidence.

ANSWER 4

- Bipolar II disorder current episode hypomania

QUESTION 5

- Outline your management.

ANSWER 5

- Stop antidepressant
- Start on lithium or quetiapine or combination

PROGRESS

- Became well after 4 weeks of treatment
- Completed her law degree
- Practicing in Kuala Lumpur
- Met someone in the office
- Had premarital sexual encounters
- Noticed that her menses was late
- Self-administered pregnancy test was positive

QUESTION 6

- What are the current concerns/issues?

ANSWER 6

- Use of lithium or quetiapine in pregnancy
- Early foetal exposure to medications
- Continuation of medication

QUESTION 7

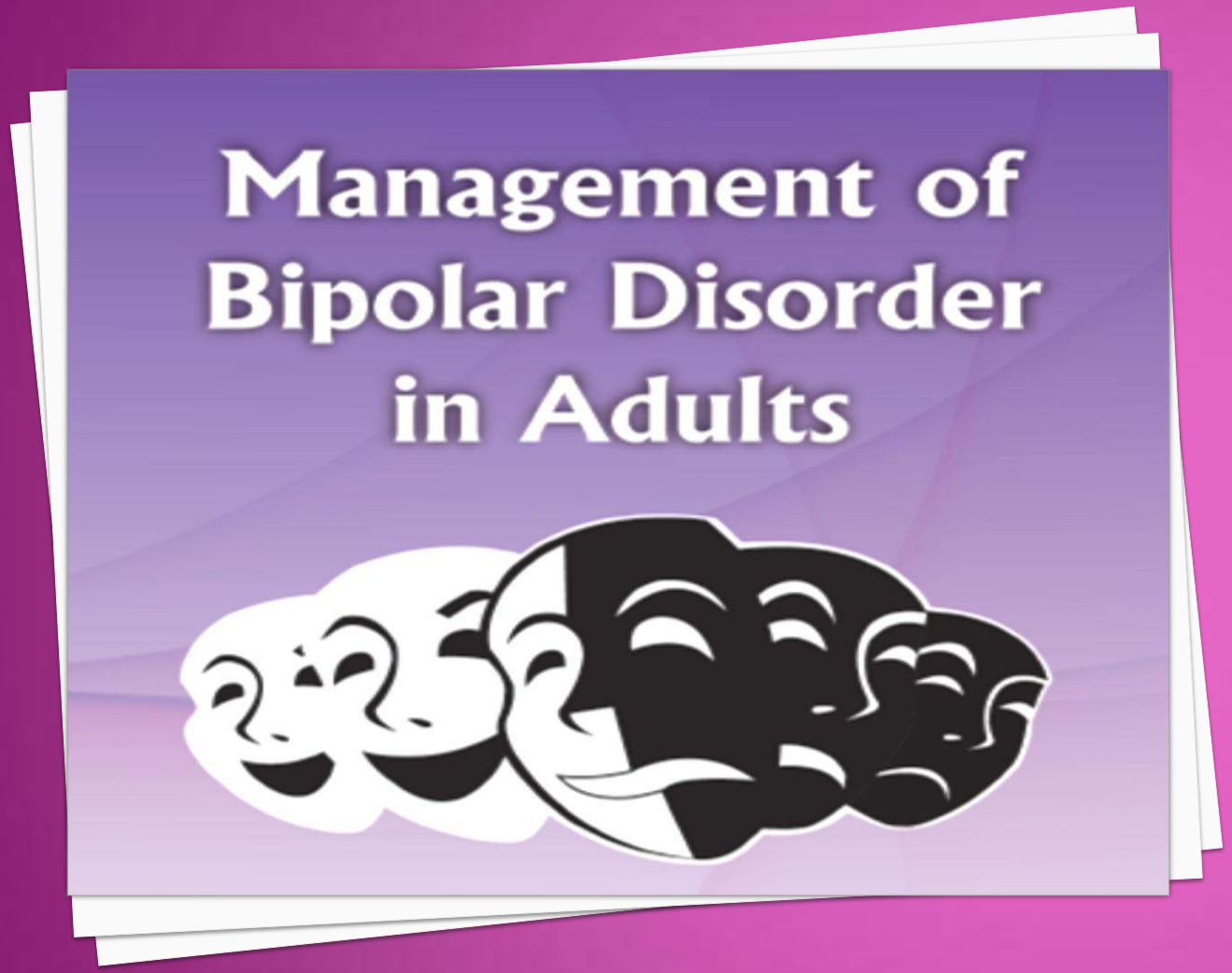
- Briefly discuss her follow up plans.

ANSWER 7

- Multi disciplinary approach
  - Refer to O&G
  - Request for detailed scan
  - Discussed about pros & cons of medications
  - Discussed about post-partum care
  - Community support
  - Family support

TAKE HOME MESSAGES

- Bipolar disorder can be misdiagnosed as major depressive disorder.
- Antidepressant-induced affective switch is sufficient to diagnose bipolar disorder.
- Antidepressant should be avoided in bipolar disorder.
- Informed-decision is the way forward.



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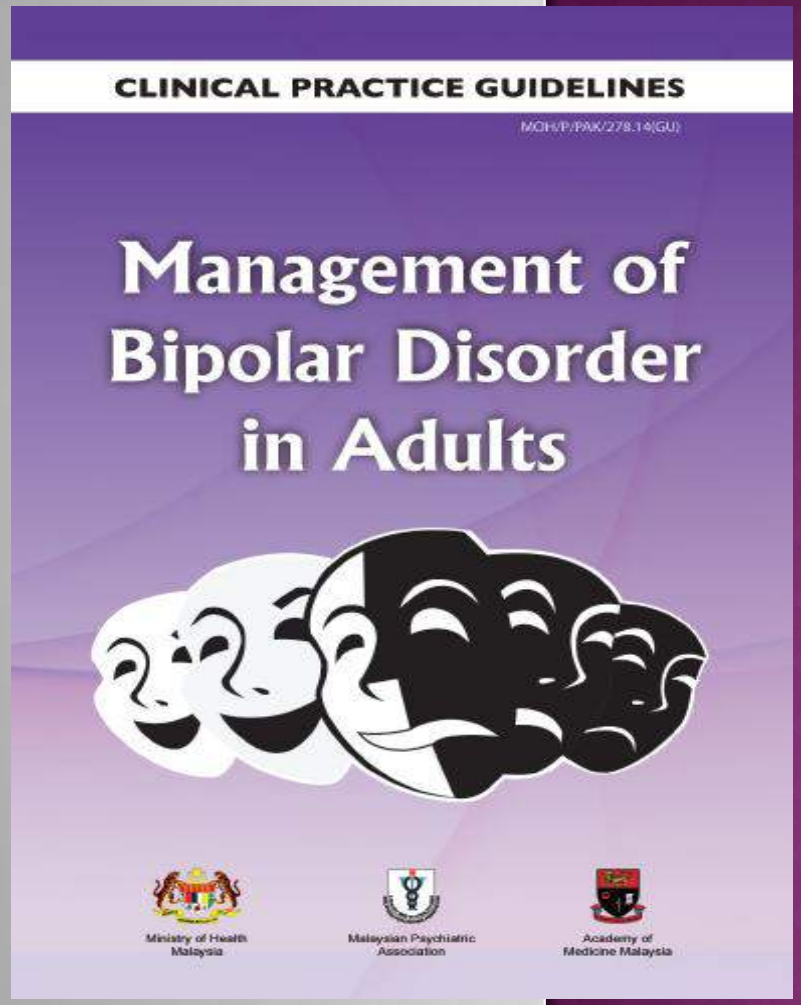
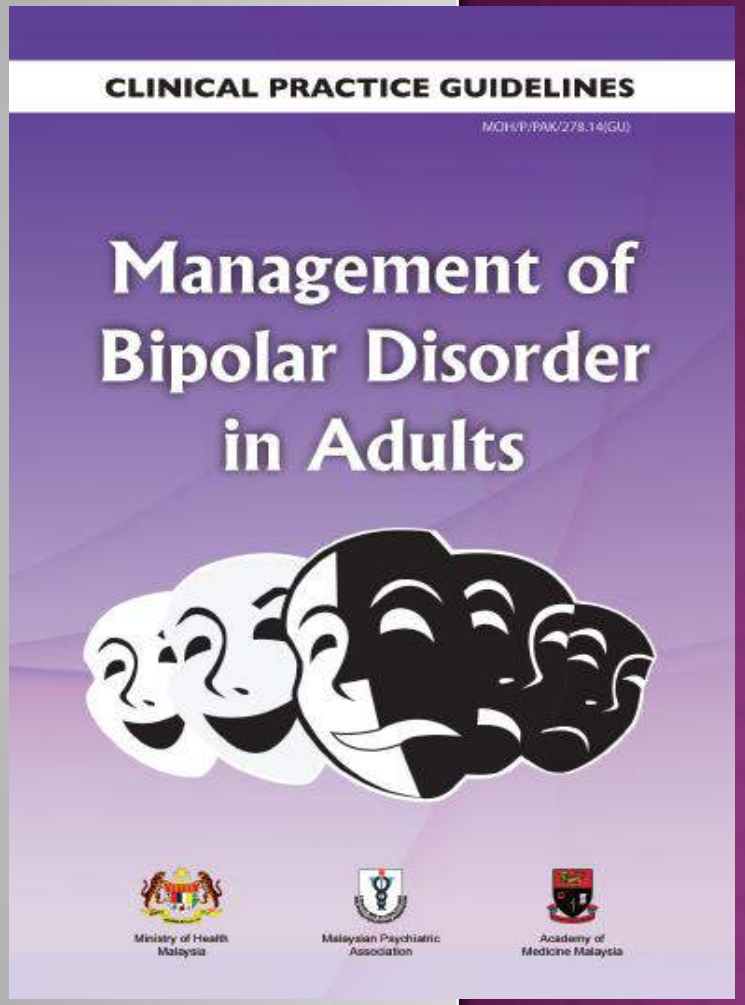


BIPOLAR DISORDER SUICIDE & SUBSTANCE MISUSE

Dr. Siti Hazrah Selamat Din
Psychiatrist
Hospital Sultanah Bahiyah
&
Dr. Norliza Chemi
Psychiatrist
Hospital Kuala Lumpur



SUICIDE IN BD

S

LEARNING OBJECTIVES

- To understand the magnitude of suicide problems in BD
- To know the risk factors for suicide in patients with BD
- To know the evidence-based treatment and prevention for suicide in BD

SUICIDES - LOCAL SCENARIO

National Health Morbidity Survey 2011

Prevalence of suicidal ideation, plan and attempt among adults was 1.7%, 0.9% and 0.5% respectively.

Suicide rate on the rise in Malaysia
Tuesday June 5, 2012 (The Star)

PUTRAJAYA: The suicide rate is on the rise in Malaysia, with more than 1,000 people taking their own lives over a three-year period. Health Minister Datuk Seri Liow Tiong Lai said the ratio of suicides from 2007 to 2010 was 1.3 for every 100,000 people, but added that it could be higher.

SUICIDES IN BD - EPIDEMIOLOGY

- Rate of completed suicide ranges between 0.014 to 4.48 per 1,000 person-years[1]
  - 10 to 30 times higher than the rate in the general population
- For suicide attempts, the rate ranges between 3.1% and 36.5%.[2-6]
- Suicide attempt is more frequent in women[7] while completed suicide is higher among men.[4]

1. Sajatovic M et al. Bipolar Disord. 2012; 14(3)
2. Ruengorn C et al.Psychol Res Behav Manag. 2012; 5:37-45
3. Novick DM et al. Bipolar Disord. 2010; 12(1):1-9
4. Azorin JM et al. Compr Psychiatry. 2009; 50(2):115-120
5. Pompili M et al. NeuropsychiatrDis Treat. 2008; 4(1):247-255
6. Valtonen HM et al. Bipolar Disord. 2006 Oct;8(5 Pt 2):576-85
7. MacKinnon DF et al. Bipolar Disord. 2005; 7(5):441-448

SUICIDE IN BD – RISK FACTORS

- There are many clinically-relevant suicide risk factors for BD
- The risk factors are similar in both completed suicide and suicide attempt

SUICIDES IN BD – RISK FACTORS

Sociodemographic

- Younger age [6,8]
- Male [7-8]
- Unemployed or disabled[7]

Symptomatology

- Suicidal thought[8]
- Rapid mood switching[7-8]
- Psychotic symptoms[8-9]
- Depressive phase of BD[2, 6, 8-9]
- Hopelessness[6, 8]
- Mixed state[10]

Treatment

- Duration of treatment (less than five years)[77]

2. Ruengorn C et al.Psychol Res Behav Manag. 2012; 5:37-45
6. Valtonen HM et al. Bipolar Disord. 2006 Oct;8(5 Pt 2):576-85
8. Pompili Met al. Bipolar Disord.2013; 15(5):457-490
8. Pompili Met al. Bipolar Disord.2013; 15(5):457-490
9. Song JY et al. J Nerv Ment Dis. 2012; 200(11):978-984.
10. Saunders KE et al. Bipolar Disord. 2013; 15(5):575-583.

SUICIDES IN BD – (RISK FACTORS)

Clinical and psychosocial characteristics

- Early onset of mood disorder[8-7, 11]
- Previous suicide attempts[2, 6, 8,]
- Multiple hospitalisations[4]
- Early sexual abuse[5,12]
- Stressful life events[2, 4, 8,]
- Lack of confidante[12]
- Family history of suicide[8-7, 11]

Co-morbidity

- Anxiety disorder[7-8]
- Cluster B personality (antisocial/borderline/histrionic/narcissistic personality disorder)[12-13]
- Substance misuse[7-8]

2. Ruengorn C et al.Psychol Res Behav Manag. 2012; 5:37-45
6. Valtonen HM et al. Bipolar Disord. 2006 Oct;8(5 Pt 2):576-85
7. MacKinnon DF et al. Bipolar Disord. 2005; 7(5):441-448
8. Pompili Met al. Bipolar Disord.2013; 15(5):457-490
10. Saunders KE et al. Bipolar Disord. 2013; 15(5):575-583
11. Mann JJ et al.Am J Psychiatry. 2005; 162(9):1672-1679
12. Leverich GS et al. J Clin Psychiatry. 2003 64(5):506-515
13. Garno JL et al. J Clin Psychiatry. 2005 66(3):339-345.

SUICIDES IN BD - INTERVENTION

- Only 1 study - 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 ($p=0.004$). [14]

- No evidence for ECT benefit as an acute intervention for suicide in BD.[10]

10. Saunders KE et al. Bipolar Disord. 2013; 15(5):575-583
14. Fountoulakis KN et al. J Affect Disord. 2009 113(1-2):21-29

SUICIDES IN BD - PREVENTION

- 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).[15]

15. Cipriani A et al. Am J Psychiatry. 2005; 162(10):1805-1819.

SUICIDES IN BD - PREVENTION

- Anticonvulsants such as valproate and carbamazepine did not increase the risk of suicide.[10]
- Non-lethal suicide event rate was sixteen times higher when lithium or anticonvulsants were discontinued.[16]
- The use of antidepressants is still controversial.[17]

10. Saunders KE et al. Bipolar Disord. 2013; 15(5):575-583
16. Yerevanian BI et al. J Affect Disord. 2007; 103(1-3):5-11
17. McElroy SL et al. Bipolar Disord. 2006; 8(5 Pt 2):596-617

SUICIDES IN BD - PREVENTION

- In general, non-pharmacological strategies to prevent suicide that have been suggested as useful include:[18]
  - 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

18. Mann JJ, et al. JAMA. 2005; 294(16):2064-2074.

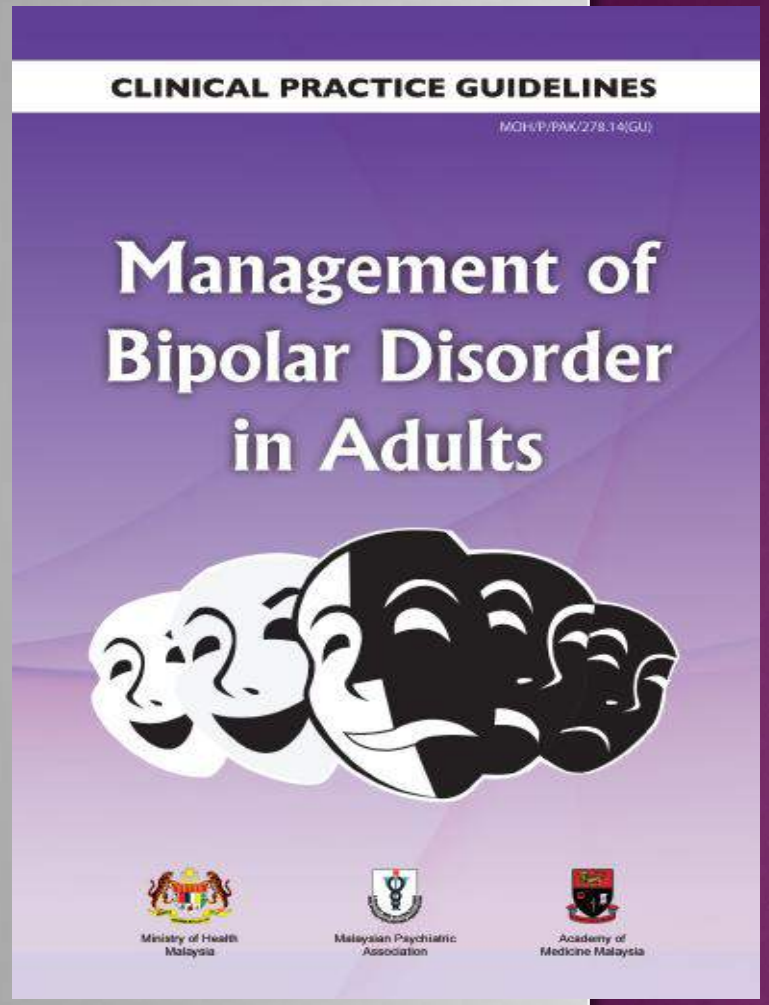
RECOMMENDATION

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)**

TAKE HOME MESSAGES

- Suicide rate is high in BD, thus it is **essential** to assess for the risk factors of suicide in BD patients
- Adjunctive psychosocial intervention significantly reduces suicide rate
- Lithium treatment prevents suicide in BD



SUBSTANCE MISUSE

LEARNING OBJECTIVES

- To understand the risk of substance misuse and its impact on people with BD
- To know the evidence-based treatment for substance misuse in BD

SUBSTANCE MISUSE- INTRODUCTION

- BD and substance use disorders are highly co-morbid conditions.
- Community based studies indicated that 60-70% of individuals with BD met diagnostic criteria for a lifetime history of substance abuse or dependence.[1,2]

1. Regier DA et al. JAMA. 1990;264:2511- 2518. Abstract
2. Kessler RC et al. Arch Gen Psychiatry. 1994;51:8-19. Abstract

SUBSTANCE MISUSE- INTRODUCTION

- Risk of lifetime use of illicit substances is three times greater in people with BD compared to the general population (OR=3.03, 95% CI 1.9 to 4.8).[2]
- Men are more likely to have co-morbidity of BD and substance abuse compared to women ($p<0.001$).[3]
- Reviews showed the use of excessive substance use is not associated with the course of BD illness ($p=0.001$).[4]
  - **However, substance misuse impairs functioning of the affected individuals ($p<0.05$).**

2. Kessler RC et al. Arch Gen Psychiatry. 1994;51:8-19. Abstract
3. Gummattira P et al. Addictive Disorders & Their Treatment 2010; 9(2):53-63
4. Lagerberg TV et al. BMC Psychiatry. 2010; 10(9)

SUBSTANCE MISUSE- TREATMENT

- Effective pharmacological or psychological interventions for BD and substance use disorder are limited.

- Only 1 RCT showed that valproate decreased heavy drinking in people with co-morbid BD and alcohol dependence (p=0.02).[5-6]

5. Salloum IM et al. Arch Gen Psychiatry. 2005; 62(1):37-45
6. Weiss RD et al. Am J Psychiatry. 2007; 164(1):100-107

SUBSTANCE MISUSE- TREATMENT PSYCHOLOGICAL

- 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 ($p<0.1$).[6]

6. Weiss RD et al. Am J Psychiatry. 2007; 164(1):100-107

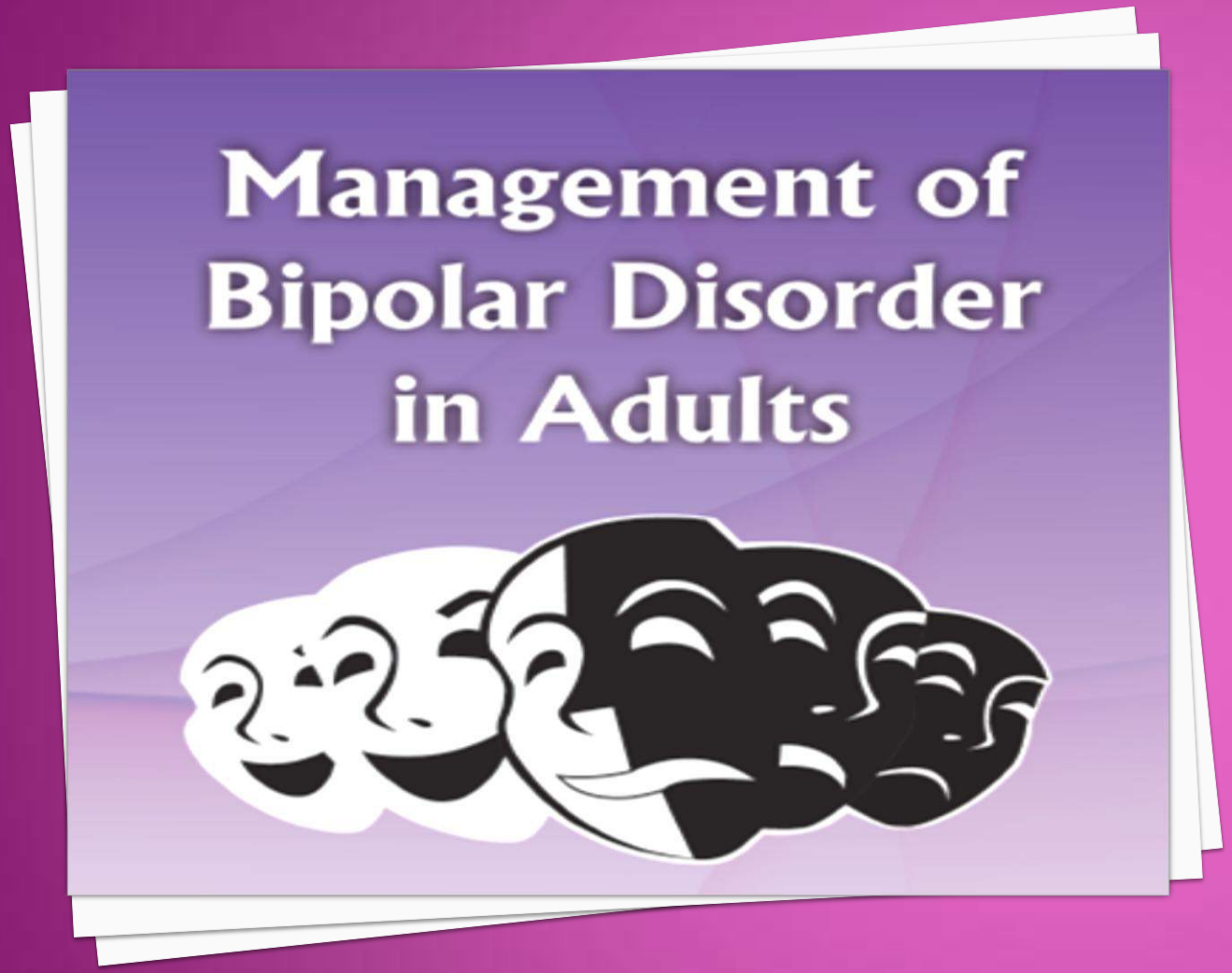
RECOMMENDATION

Recommendation 10

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

TAKE HOME MESSAGES

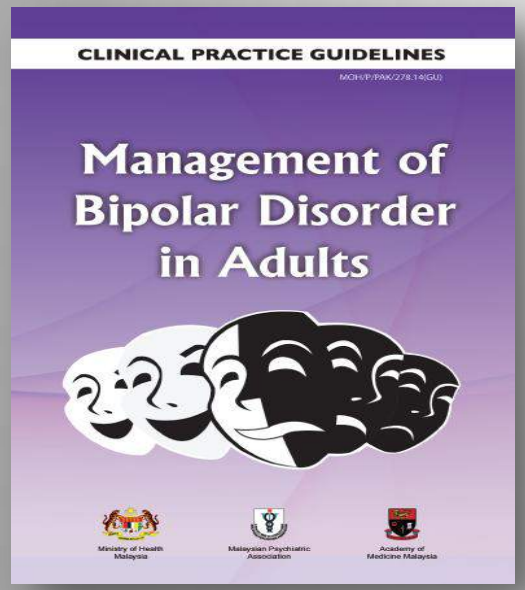
- Substance misuse is very common among persons with BD
- Evidence on the risk factors and effective treatment are limited



THANK YOU

SPECIAL POPULATION

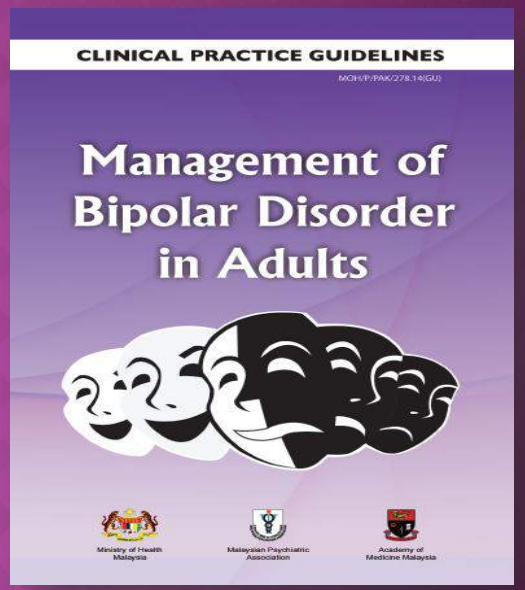
WOMEN & REPRODUCTIVE HEALTH



Dr Rahima Dahlan @ Mohd Shafie
Psychiatrist
Hospital Mesra Bukit Padang

&

Puan Nazariah Haron
Pharmacist
Hospital Putrajaya



LEARNING OBJECTIVES

- To identify the fertility issues in the treatment of women in reproductive age with BD
- To identify the effects of contraception in women with BD
- To describe the role of preconception counselling in women with BD
- To identify the effective/safe treatments in pregnant/lactating women with BD

INTRODUCTION

- Women of reproductive age need to know the risks & benefits of her pharmacological treatment options including risks of untreated mood disorder in pregnancy & postpartum.
- Pregnancy does not protect against the risk of mood episodes → medication discontinuation may increase risk of mood episodes.
- Risk of recurrence of mood symptoms & psychosis appears higher during postpartum than in pregnancy.[1]

1. Freeman MP, et al. Acta Psychiatr Scand. 2005; 112(2):88-96

WOMEN OF CHILD BEARING AGE

OUTLINE

1. Fertility Issues
2. Effects of Contraception
3. Preconception Counseling
4. Treatment Considerations in Pregnancy & during Lactation

1. FERTILITY ISSUES

- Women with pre-existing menstrual abnormalities are at risk of reproductive dysfunction while being treated for BD.

- All medications for BD may cause reproductive & hormonal abnormalities e.g.
  - elevated 17 α-OH Progestrone &
  - elevated Luteinizing Hormone:Follicle Stimulating Hormone ratio[2]

2. Rasgon NL, et al. Bipolar Disord. . 2005; 7(3):246-259

2. EFFECTS OF CONTRACEPTION

- Carbamazepine & topiramate increase metabolism of sex hormones → risk for contraceptive failure.
- Lamotrigine + oral contraceptive = reduction in lamotrigine serum concentration → dose adjustments maybe required.[3]
- Alternative: non-hormonal methods, contraceptive injections or oral contraceptives containing 50 µg or more of the oestrogenic component.

3. Ward S, et al. J Midwifery Women Health. 2007 52(1):3-13

3. PRECONCEPTION COUNSELLING-1

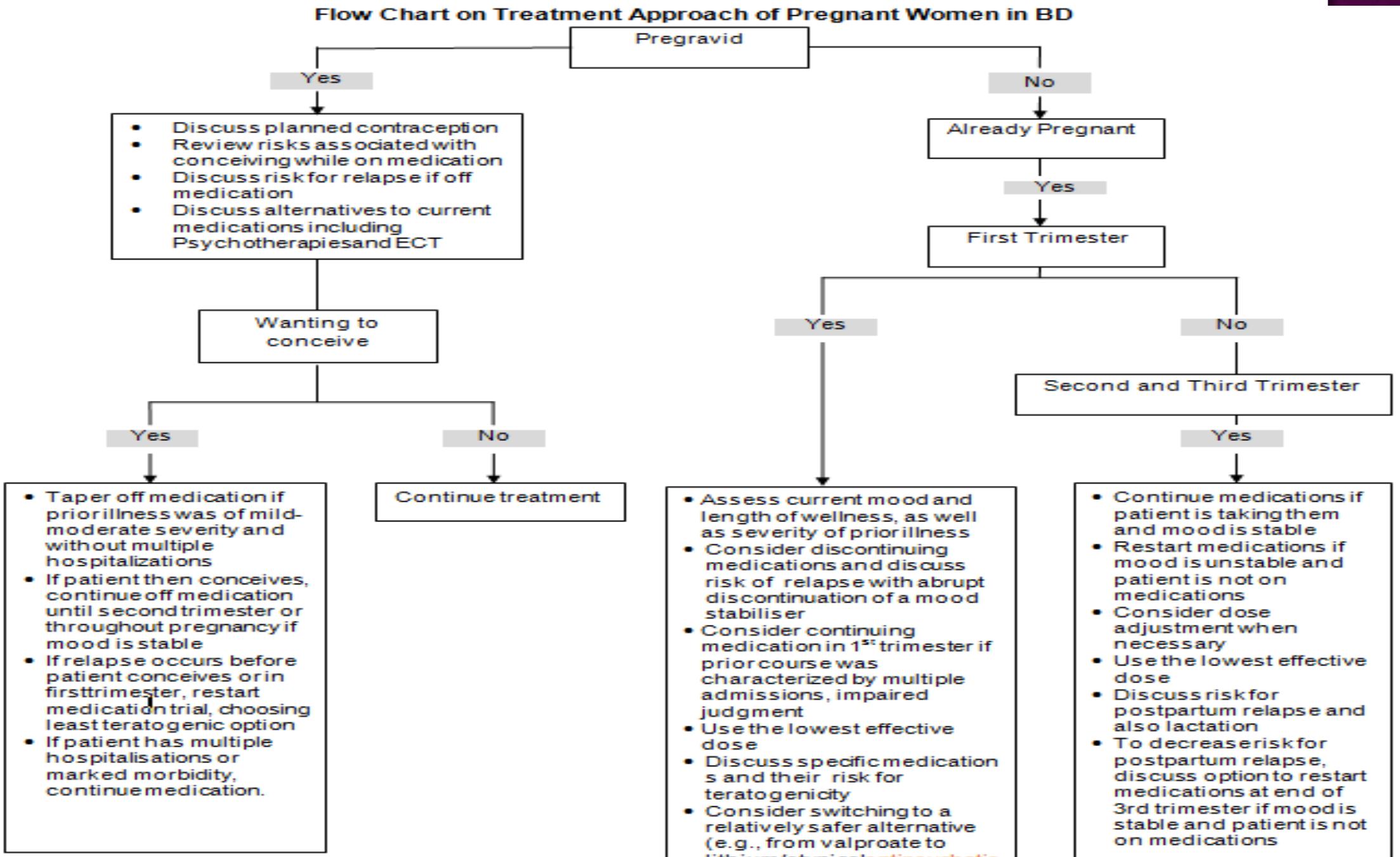
- Women of reproductive age with BD should be counselled that pregnancy is a time of substantial risk of relapse.
  - The risk is 2.3 times greater after discontinuing mood stabiliser treatment.[4]
  - Abrupt discontinuation of the medication carries higher risk of recurrence compared to gradual discontinuation ($p<0.0001$).[5]
- Women with BD are more likely to experience placenta abnormalities e.g. placenta praevia compared to non-psychiatric group.[6]

4. Frieder A, et al. Am J Obstet Gynecol. 2008; 199(6 Suppl 2):S328-332
5. Viguera AC, et al. Am J Psychiatry. 2000 157(2):179-184
6. Jablensky AV, et al. Am J Psychiatry. 2005; 162:1

3. PRECONCEPTION COUNSELLING-2

- Women with BD are at high risk of relapse during postpartum period (up to 80%) & have 10 - 20% risks of postpartum psychosis.[4]
- Risk factors for recurrence of BD I during postpartum:-[7]
  - younger age at onset of BD (p=0.009)
  - history of episodes during previous pregnancies (p=0.038)
  - complications during labour (p=0.03)
- Relapse prevention & management strategy including contraceptive option for BD should be counselled to both patients & their partners before pregnancy.[3]

3. Ward S, et al. J Midwifery Womens Health. 2007 52(1):3-13
4. Frieder A, et al. Am J Obstet Gynecol. 2008; 199(6 Suppl 2):S328-332
7. Abdel-Hay M, at al. Middle East Curr Psyhiatry. 2011; 18:45- 50



Adapted from Altshuler L, et al. Curr Psychiatry 2003;2:14 –26

4. TREATMENT CONSIDERATIONS IN PREGNANCY & LACTATION-1

i) Pregnancy

- Women who are on psychotropic medications should understand the risks, benefits & uncertainties of using such medications during pregnancy.

- If medications are needed:
  - It is advisable to wait after the first trimester due to teratogenic risk.
  - Drug selected on the basis of existing safety data, with a preference for monotherapy & at the lowest effective dose.[8]
  - Please refer to Appendix 8 for Psychotropic Medications in Pregnancy/Lactation

8. Jain AE, Lacy T. Psychotropic Drugs in Pregnancy and Lactation. J Psychiatr Pract. 2005; 11(3):177-191

“I’m on bipolar medication……”

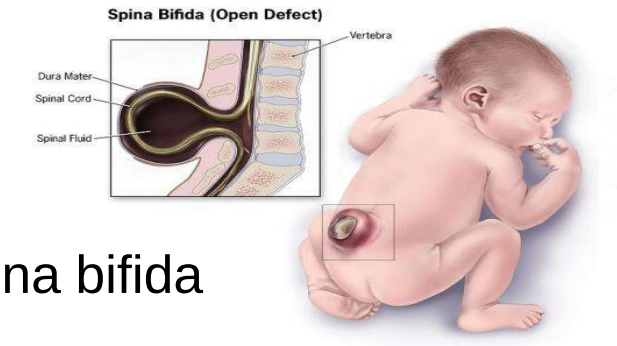
“ I just discovered I’m two months pregnant…..”

“ Is it safe…..?”

MOOD STABILISERS MAY COMPLICATE PREGNANCY..

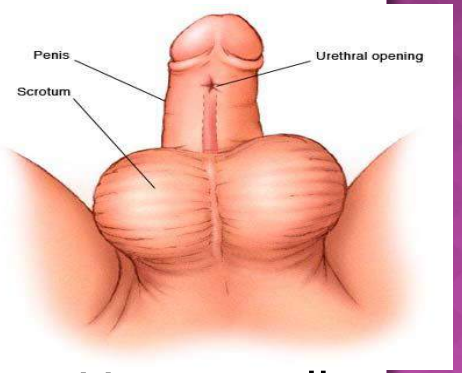
Major Congenital Malformation (MCM)

- **Valproate (VPA)**
  - Polytherapy containing VPA have more MCMs than those without (OR=2.49, 95% CI 1.31 to 4.70).[9]
  - Monotherapy in the first trimester - increased risks of several congenital malformations.[10]



Spina bifida

Cleft palate



Hypospadias

9. Morrow J, et al. J Neurol Neurosurg Psychiatry. 2006; 77(2):193-198
10. Jentink J, et al. N Engl J Med. 2010; 362(23):2185-2193

.....4. TREATMENT CONSIDERATIONS - PREGNANCY

- **Lithium**
  - i) Recurrence after lithium discontinuation:[5]
    - during pregnancy, rates of recurrence is 52% but increased to 70% at postpartum.
    - risk of recurrence is less in gradual than rapid discontinuation (p=0.006).

5. Viguera AC, et al. Am J Psychiatry. 2000 157(2):179-184

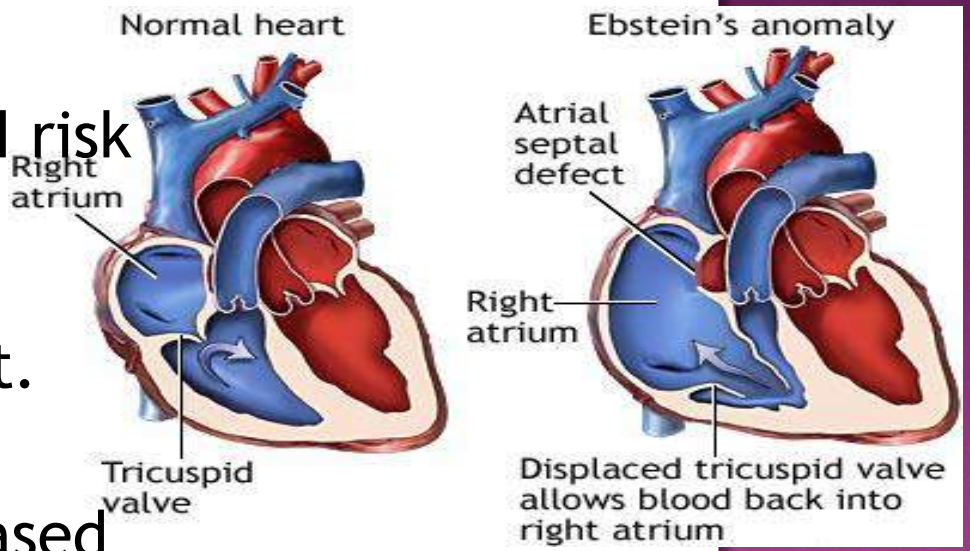
.....4. TREATMENT CONSIDERATIONS - PREGNANCY-2

ii) Lithium exposure:[11]

- **In 1st trimester** - 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.

- **After 1st trimester** - associated with an increased risk of diabetes insipidus, polyhydramnios, thyroid dysfunction & floppy baby syndrome.

Ebstein's anomaly



Floppy baby syndrome

11. Galbally M., et al. Aust N Z J Psychiatry. 2010; 44:99–108

.....4. TREATMENT CONSIDERATIONS - PREGNANCY-3

- **Lamotrigine**
  - Protective against risk of illness recurrence in pregnancy[8]
  - Relatively safe in term of MCM as compared to other mood stabilisers.[8]
  - There is no evidence on:[12]
    - ✓ major birth defects during the first trimester of lamotrigine monotherapy up to a daily dose of 400 mg (p=0.26)[10] or
    - ✓ specific increased risk of isolated orofacial clefts relative to other malformations (OR=0.8, 95% CI 0.11 to 2.85)

8. Jain AE, et al. J Psychiatr Pract. 2005; 11(3):177-191
10. Jentink J, et al. N Engl J Med. 2010; 362(23):2185-2193
12. Cunnington M, et al. Epilepsia. 2007; 48(6):1207-1210

.....4. TREATMENT CONSIDERATIONS - PREGNANCY-4

- **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 & levetiracetam.[5]

5. Viguera AC, et al. Am J Psychiatry. 2000 157(2):179-184

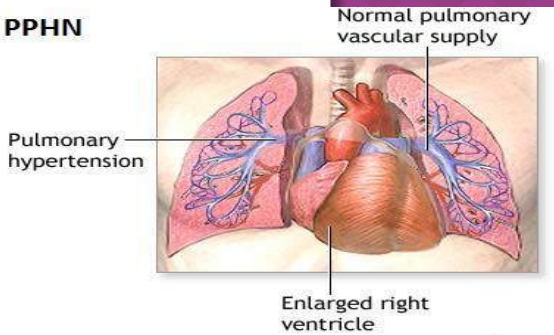
.....4. TREATMENT CONSIDERATIONS - PREGNANCY-5

- **Antipsychotic**
  - 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.[11]
  - Incomplete placental passage[13]
    - ✓ Olanzapine, haloperidol, risperidone & quetiapine

11. Galbally M., et al. Aust N Z J Psychiatry. 2010; 44:99–108
13. Newport DJ, et al. Bipolar Disord. 2008; 10(3):432-436

.....4. TREATMENT CONSIDERATIONS - PREGNANCY-6

- **Antidepressants**
  - Not associated with increased risk in MCM (RR=1.01, 95% CI 0.57 to 1.80).[14]
    - ✓ Newer antidepressants - SSRI, Selective Noradrenaline Serotonin Reuptake Inhibitor (SNRI) & dual action drugs (mirtazapine & nefazodone)
  - Persistent pulmonary hypertension of the newborn - risk increases in infants exposed to SSRIs in late pregnancy (NNH=351) has been noted.[15]



14. Einarson TR, et al. Pharmacoepidemiol Drug Saf. 2005; 14(12):823-827
15. Grigoriadis S, et al. BMJ. 2014 14:348

.....4. TREATMENT CONSIDERATIONS - PREGNANCY-7

- **Electroconvulsive therapy (ECT)**
  - NICE recommends to consider ECT if there is no response to changes in dose or drug in pregnant women with severe mania.[16]

16. National Institute for Health and Care Excellence (NICE). The Management of Bipolar Disorder in Adults, Children and Adolescent, in Primary and Secondary Care. London: NHS; 2006.

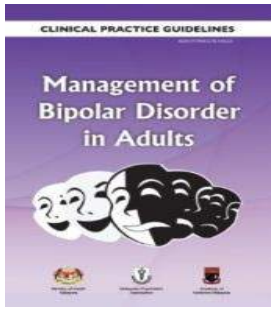
.....4. TREATMENT CONSIDERATIONS - LACTATION

ii) Lactation

- Maintenance of optimal maternal mental health - primary goal in treating women who choose to breastfeed.[3]
- Patients should be educated/advised:
  - about possible side effects &
  - to discontinue the breastfeeding if their infants develop a toxic or adverse effect while taking psychotropic medications.[8]
- The well-established benefits of breastfeeding must be weighed against the potential risk for relapse secondary to sleep deprivation.[3]

3. Ward S, et al. J Midwifery Womens Health. 2007 52(1):3-13
8. Jain AE, et al. J Psychiatr Pract. 2005; 11(3):177-191

RECOMMENDATIONS-1

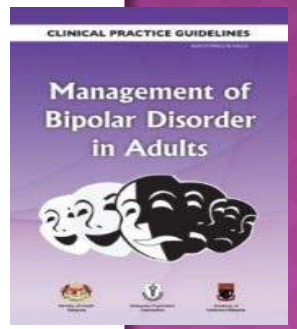


Recommendation 11

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

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)**



RECOMMENDATIONS-2

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)**

TAKE HOME MESSAGE

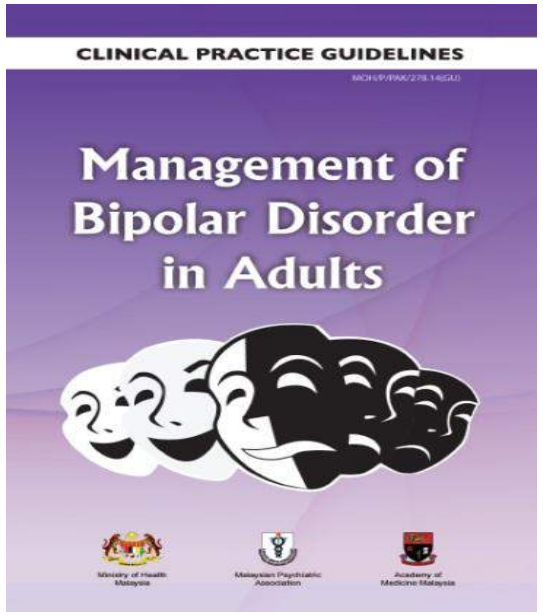
Women of reproductive age need to know the risks & benefits of pharmacological treatment options.

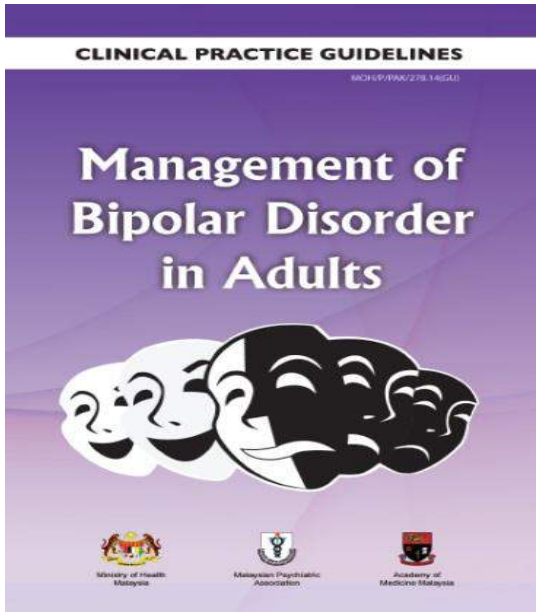
If medications are needed during pregnancy,
it is advisable to wait after the first trimester
due to teratogenic risk.

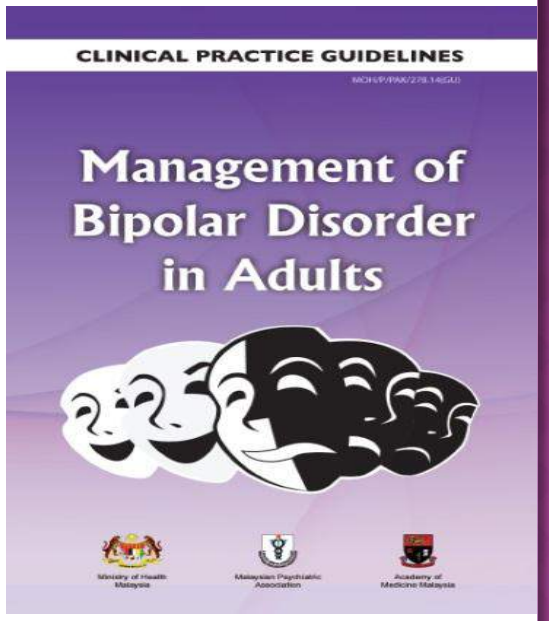
Medications should be selected on the basis of existing safety data,
with a preference for monotherapy
& at the lowest effective dose.

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

THANK YOU


CLINICAL PRACTICE GUIDELINES
Management of Bipolar Disorder in Adults


CLINICAL PRACTICE GUIDELINES
Management of Bipolar Disorder in Adults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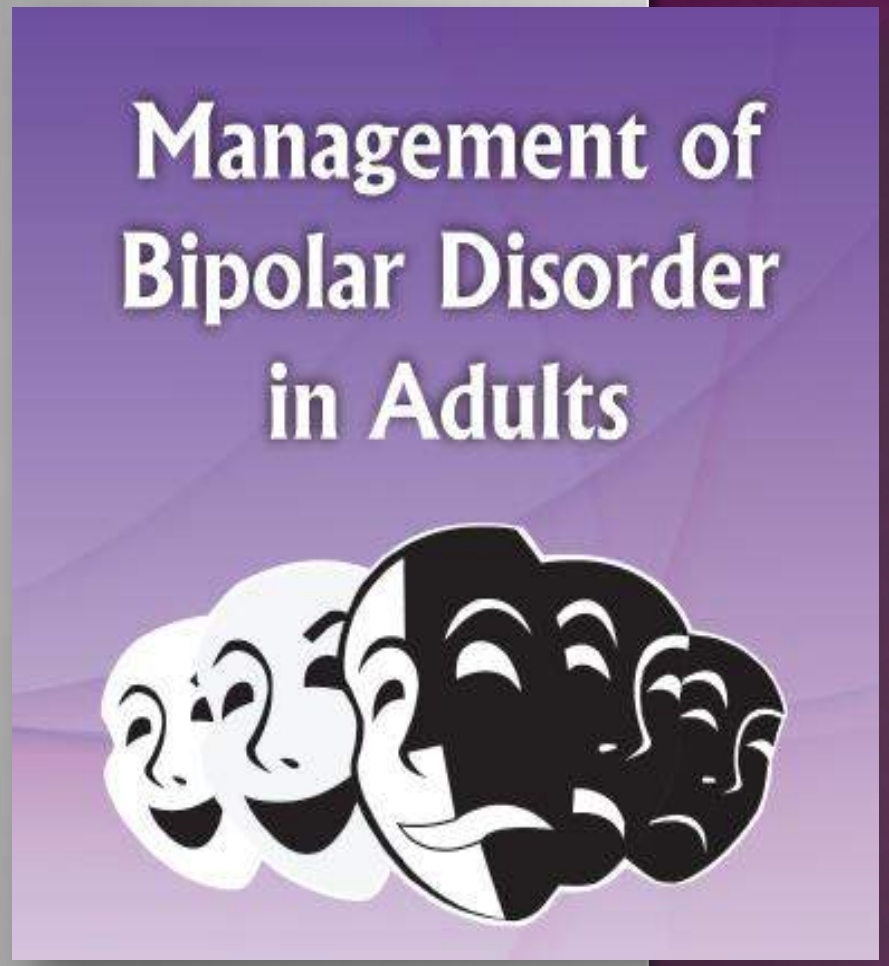

MANAGEMENT OF BIPOLAR DISORDER IN ADULTS:

ELDERLY

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KK Sg. Besar

LEARNING OBJECTIVES

- To understand the pharmacological requirements in elderly with BD
- To ascertain the role of ECT in elderly with BD

INTRODUCTION

- Psychoeducational & 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
  - medication toxicity

PHARMACOLOGICAL CONSIDERATIONS

- 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:[1]
  - Lithium
  - Valproate
  - Carbamazepine
  - Lamotrigine

  either alone or in combination with atypical antipsychotics or antidepressants are beneficial in the treatment of this group of patients[1]

1. Aziz R, et al. Am J Geriatr Pharmacother. 2006; 4(4):347-364

PHARMACOLOGICAL CONSIDERATIONS-1

- Lamotrigine & lithium are efficacious in the maintenance therapies for elderly with BD I.[2]

- Compared to placebo,[2]
  - 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)

2. Sajatovic M, et al. Am J Geriatr Psychiatry. 2005; 13(4):305-311

PHARMACOLOGICAL CONSIDERATIONS-2

- The risk of hospitalisation for lithium toxicity particularly in lithium naïve elderly increases with concomitant use of:[3]
  - 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)
- The target serum lithium level in the range between 0.4 & 0.7 mEq/L has been recommended for elderly with BD.[1]
- They require 25 - 50% lower dosage of lithium than younger patients.[1]

1. Aziz R, et al. Am J Geriatr Pharmacother. 2006; 4(4):347-364
3. Juurlink DN, et al. J Am Geriatr Soc. 2004; 52(5):794-798

ROLE OF ECT-1

- ECT is the treatment of choice for elderly with mania who:
  - are intolerant of or refractory to pharmacologic management
  - have a severe symptoms that necessitates a rapid response

ROLE OF ECT-2

- ECT is also efficacious & safe in depressed elderly patients who are poorly responsive to medication ($p<0.05$).[4]
- The mortality rate associated with ECT in elderly has been reported to be 0.01%.[1]
- Particular care may be required in the subgroup of elderly with comorbid medical illness who are at risk of cognitive deficits after ECT ($p<0.00001$).[4]

1. Aziz R, et al. Am J Geriatr Pharmacother. 2006; 4(4):347-364
4. Jain G, et al. J ECT. 2008; 24(2):122-127

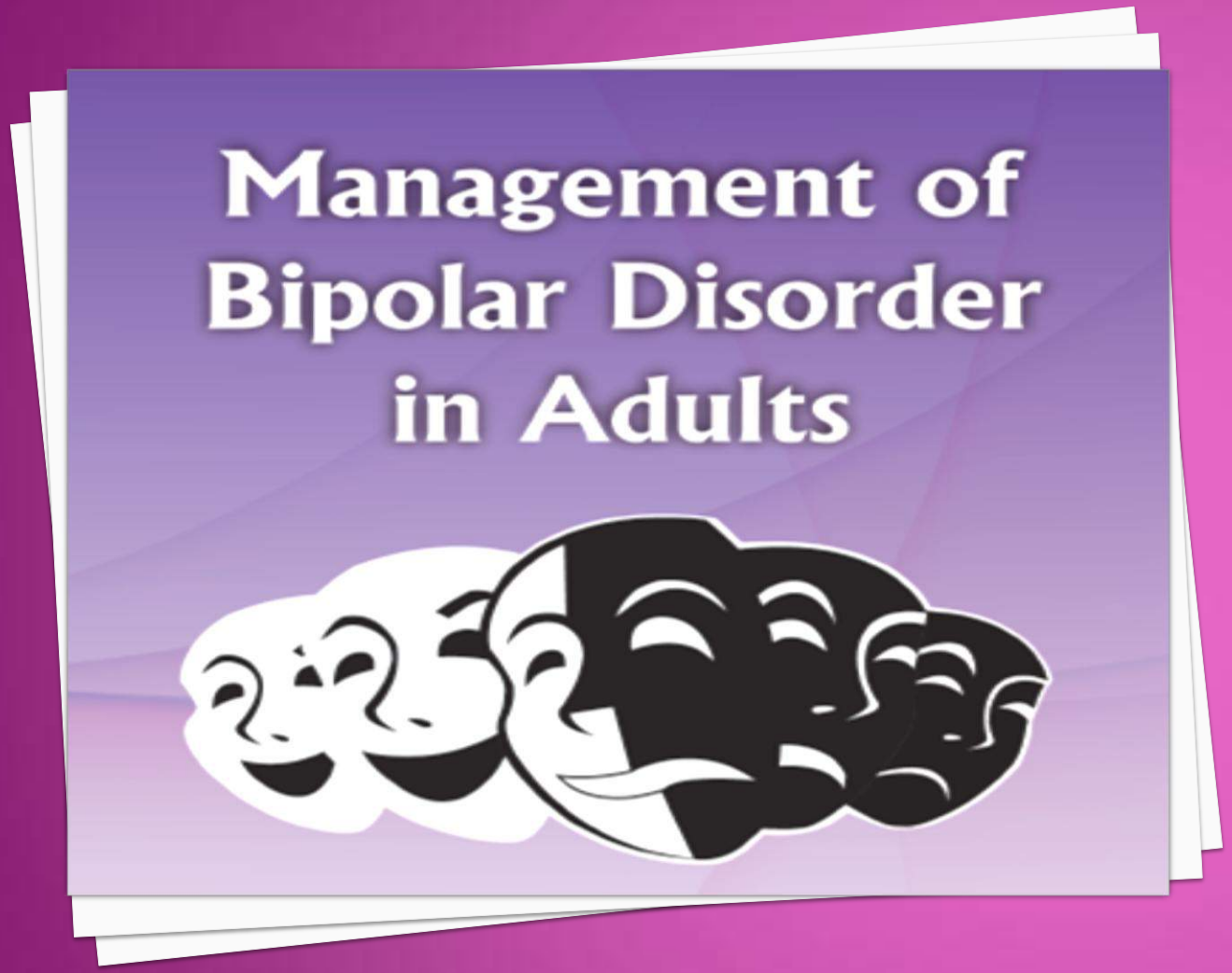
RECOMMENDATION

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)**

TAKE HOME MESSAGE

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



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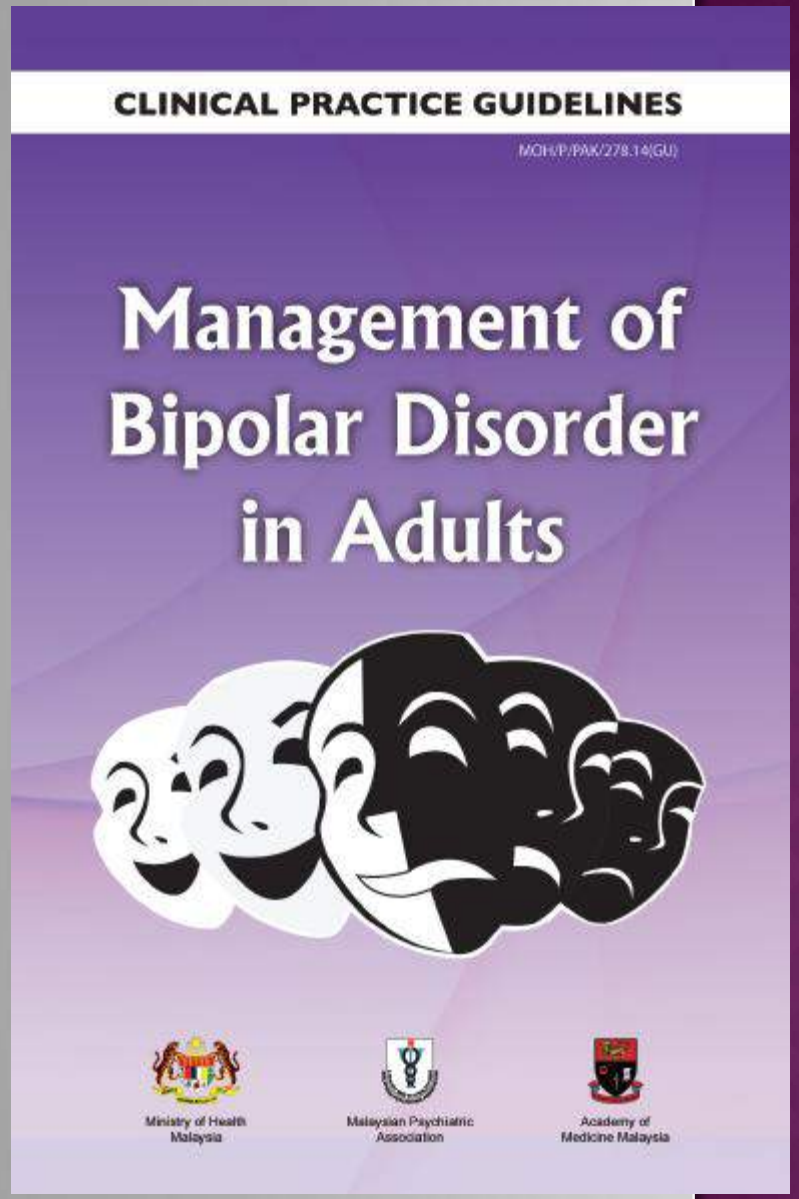

CASE DISCUSSION 3

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HISTORY

- Mr K, 30 year-old Chinese man, single, works as Software Programmer & brought by his family members to A&E after he tried to hit his father with a laptop.
- He was upset when his father refused to help him to start up a software consultation firm.
- He claimed the software that he programmed has been chosen as the winner in a competition and now worth RM 3 millions.
- He felt over the moon for the last 1 week because he claimed to be a rich man.

HISTORY (CONT.)

- He however was not able to support any of the claims with evidences & became irritable when the family members asked him to stop talking about the software unless he showed them proof supporting his claims
- Over the last 1 week also, the parents noticed that Mr. K slept only for 2-3 hours, spending most of his waking time online, blogging about his newly-developed software which he claimed could save the world energy by 50%.

HISTORY (CONT.)

- He talked almost non-stopped about the software & how he planned to get it patented.
- He believed he was chosen by God & given the power to make the day time lasts longer than 12 hours.
- He spent lots of money changing the external hard disks in order to save his discovery & intended to distribute them to the third world countries.

QUESTION 1

- List 2 clinical symptoms that he might have?

ANSWER 1

- Mania
- Psychosis (delusion of grandiosity)

FURTHER HISTORY

- He denied being controlled by external entity or being charmed. He denied hearing or seeing anything others can't hear or see.
- He denied having any panic attacks, obsessive thought or compulsive behaviour.
- He denied taking any illegal substance recently but admitted that he tried smoking cannabis few times & the last one was 6 months ago.
- No medical or surgical illness in the past
- Family history of major depressive disorder – father & paternal uncle have depression

MENTAL STATE EXAMINATION- ON THE DAY OF ADMISSION

- He enjoyed the interview as he considered himself rehearsing for his future press conference. Mood was elated, affect was congruent with his thought.
- Besides grandiose delusion, no other delusion presented, & no perceptual disturbance.
- He denied that he tried to harm his father but admitted that he was upset with his father because he did not share similar excitement.

PHYSICAL EXAMINATION

- Conscious, alert, & orientated to time, place & person
- Weight: 45 kg, height: 165 cm, waist circumference: 70 cm
- BP: 110/70 mm Hg, PR: 80/min, T: 37.6^{o}C, RR: 14
- No abnormal physical findings

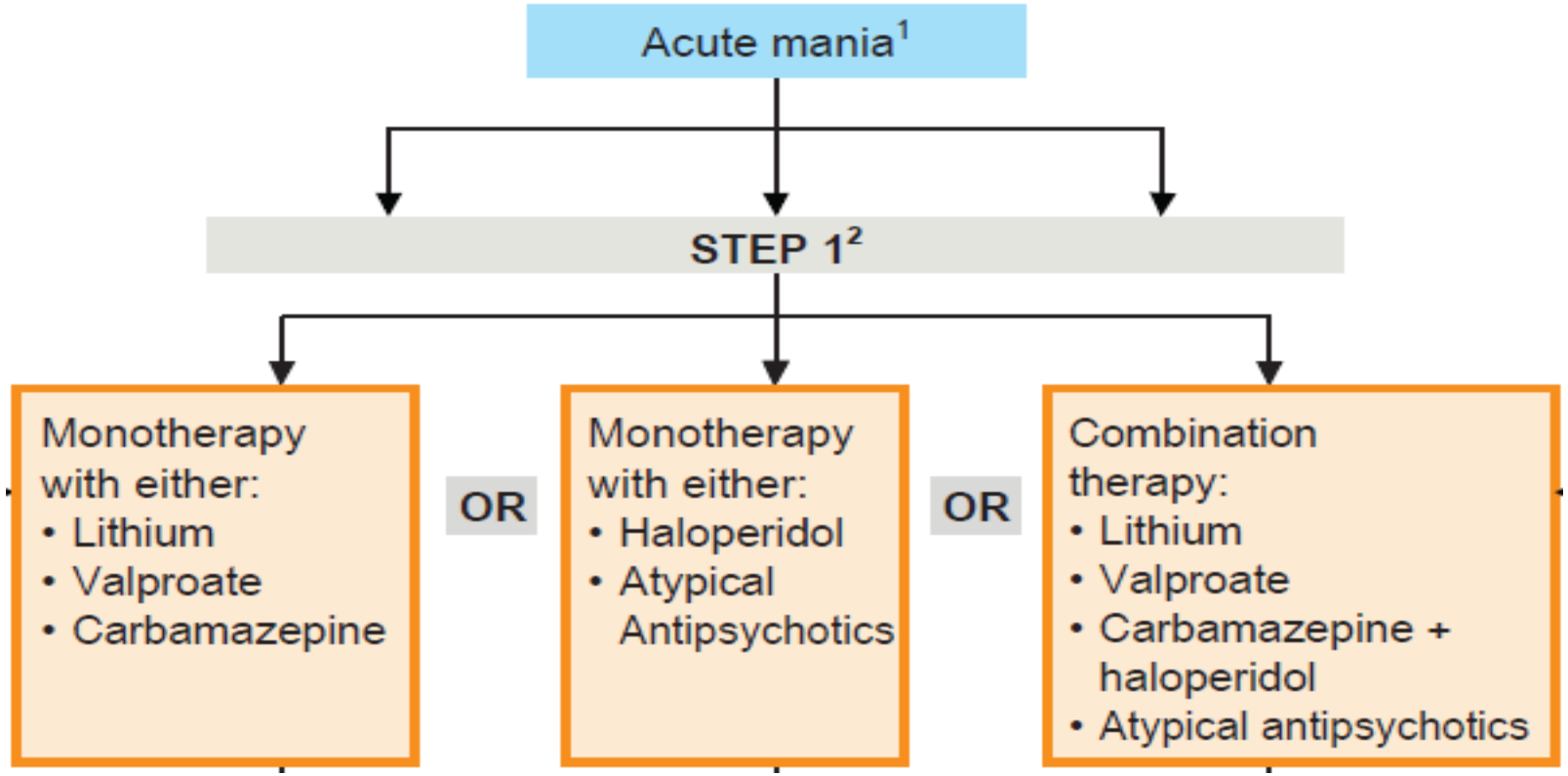
PROGRESS

- Mr. K was detained under Mental Health Acts as he refused for ward admission.
- He was physically restrained & parenteral antipsychotic IM haloperidol 10 mg was given because he started becoming more aggressive towards the nursing staffs.
- He was then transferred to psychiatric ward & diagnosed as bipolar I disorder, current episode manic.

QUESTION 2

- What medication/s would be prescribed to him?
  - A: Lithium monotherapy
  - B: Olanzapine monotherapy
  - C: Sodium valproate monotherapy
  - D: Olanzapine & lithium combination
  - E: Haloperidol & sodium valproate combination

ANSWER 2



Recommendation 3

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

ANSWER 2

Mood stabilisers	
• lithium	• carbamazepine
• valproate*	
Typical antipsychotic	
• haloperidol	
Atypical antipsychotics (AAP)	
• risperidone	• quetiapine
• olanzapine	• paliperidone**
• ziprasidone	• aripiprazole
• asenapine	

PROGRESS

- Patient responded to the combination of lithium 600 mg BD, olanzapine 15 mg OD & clonazepam 1 mg BD.
- The clonazepam was tapered down & discontinued prior to discharge.
- Patient was in full remission when he came back for his third follow-up 3 months later. The olanzapine was tapered down further & discontinued over a month
- He was maintained with lithium 600 mg BD, the lithium level was 0.8 mEq/L.

QUESTION 3

- What is the therapeutic range of lithium?

ANSWER 3

- 0.6-1.2mEq/L

QUESTION 4

- All of these are common side effects of lithium except?
  - A: tremor
  - B: diarrhoea
  - C: polyuria
  - D: polydipsia
  - E: polyphagia

ANSWER 4

- E

PROGRESS

- Patient defaulted 3 previous appointments as he felt better already & believed that he did not require to take the medication.
- His parents noticed patient started to stay up late at night, spent hours online. He became talkative again but more manageable.
- He did not show any elated mood but became slightly irritable when his parents reminded him to take medication.

QUESTION 5

- What is the current diagnosis?
  - A: Bipolar II – in hypomanic phase
  - B: Bipolar I – in hypomanic phase
  - C: Bipolar II- In manic phase
  - D: Bipolar I – in manic phase
  - E: Bipolar I - in relapse phase

ANSWER 5

- Bipolar I – currently in hypomanic phase

QUESTION 6

- What is best next plan of action?
  - A: Admit to the psychiatric ward
  - B: Check his lithium level
  - C: Educate patient on adherence
  - D: Restart olanzapine 10 mg ON
  - E: To add zolpidem 10 mg ON

ANSWER 6

- C: Educate patient on adherence

QUESTION 7

- What are the risk factors of non-adherence?

ANSWER 7

Recommendation 8

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

- Significant risk factors for non-adherence are:-
  - difficulties with medication routines
  - negative attitudes towards drugs in general
  - depressive polarity of the last acute episode
  - presence of subsyndromal symptoms
  - co-morbid obsessive-compulsive disorder
  - current acute episode
  - substance abuse/dependence
  - younger age
  - side effects

PROGRESS

- Patient refused to continue his lithium because of unpleasant taste but agreed to resume olanzapine 15 mg OD.
- The hypomanic symptoms persisted despite he took the medication regularly.
- The dose of olanzapine was increased to 20 mg OD 6 weeks later but he complained of increasing 5 kg within 1 month.

QUESTION 8

- How long should we wait before modifying the treatment regime/dose?
  - A: 1 week
  - B: 2 weeks
  - C: 4 weeks
  - D: 6 weeks
  - E: 8 weeks

ANSWER 8

- 2 weeks

QUESTION 9

- Besides weight, what other parameters are monitored regularly?
  - A: Waist circumference
  - B: Fasting sugar
  - C: Fasting lipid level
  - D: Blood Pressure
  - E: Height

ANSWER 9

- A: Waist circumference
- B: Fasting sugar
- C: Fasting lipid level
- D: Blood Pressure

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
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		

QUESTION 10

- What is the next step of action?
  - A: Change to another medication
  - B: Add another medication
  - C: Start psychosocial intervention
  - D: Give ECT
  - E: To look for co-morbidity

ANSWER 10

- A

PROGRESS

- Sodium valproate was added & patient responded well within 4 weeks. Patient has involved in more physical activities to help him managing his weight issue.

- However he was not able to go back to his previous functioning. He was worried about his work & was not able to concentrate on the task given to him.

QUESTION 11

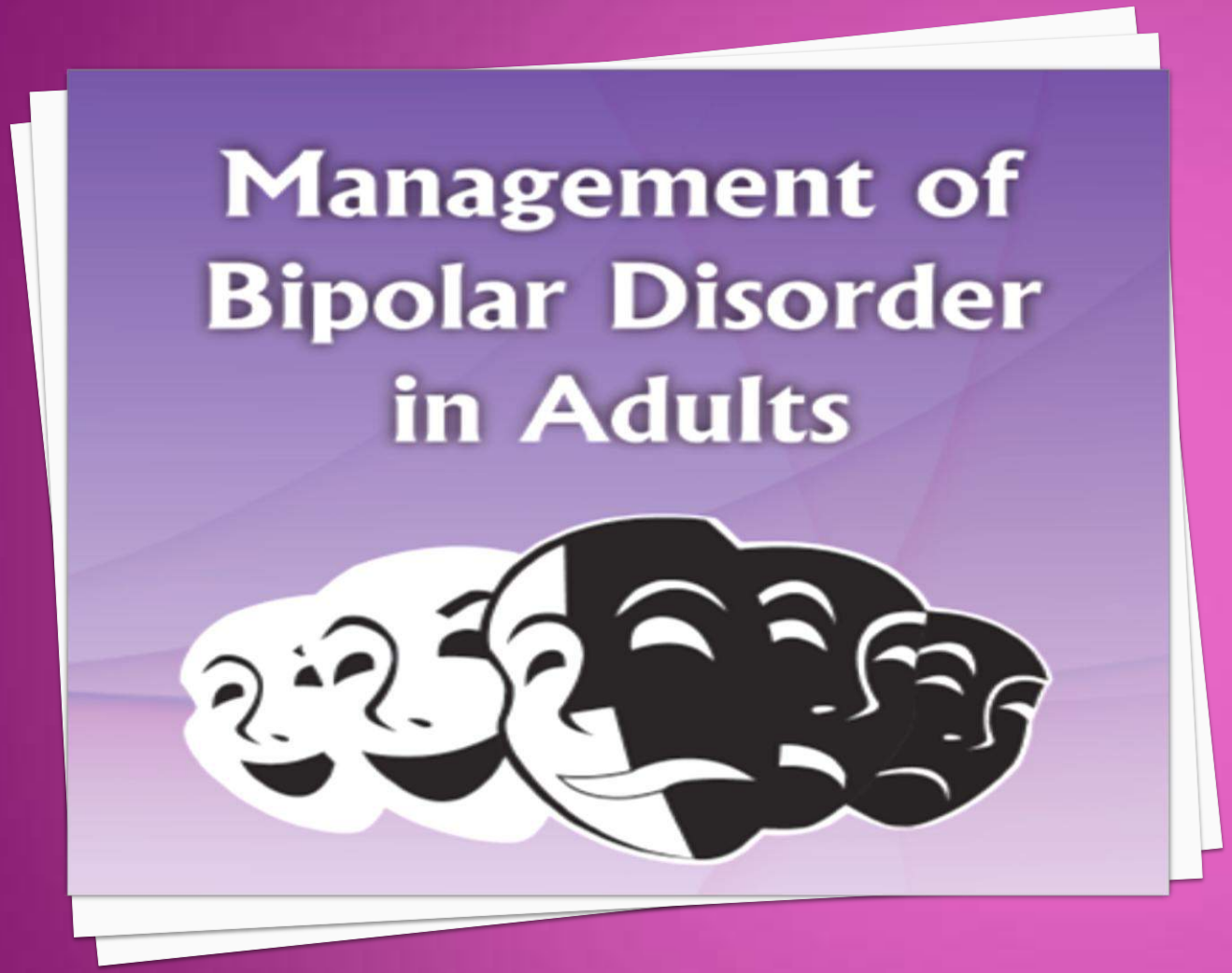
- What is the best psychosocial intervention for him?
  - A) supportive psychotherapy
  - B) cognitive behavioral therapy
  - C) psychodynamic psychotherapy
  - D) dialectical behavioral therapy
  - E) interpersonal social rhythm therapy

ANSWER 11

- E

TAKE HOME MESSAGES

- Bipolar disorder is common
- Acute mania could be treated with multiple agents be it as monotherapy or in combination
- Regular monitoring of metabolic side effects are mandatory
- Adherence to medication is important for relapse prevention



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