

# BIPOLAR AFFECTIVE DISORDER

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# BENEFICIAL VIDEO TO START WITH BEFORE STUDYING



# INTRODUCTION:

- Bipolar disorder (BPD) (manic-depressive illness) : is one of the most severe forms of mental illness and is characterized by **swinging moods**.
- Also known as manic depression, a mental illness that causes a person's moods to swing from **extremely happy and energized (mania) to extremely sad (depression)**.
- Chronic illness; can be **life-threatening** .



# EPIDEMIOLOGY:

- Bipolar II > in women
  - Bipolar I = men and women
- Mean age at onset: 21 years old
  - Peak intervals of 15-19yo and 20-24yo
  - Less studied in ages < 15 (*difficult to differentiate from ADHD*)
- Genetic link with first-degree relative
  - Family history is vital
  - 80-90% have biologic relative with a mood disorder



# EPIDEMIOLOGY IN SAUDI ARABIA :

- The most common psychiatric diagnoses among **inpatients** in Saudi Arabia were :
  - (1) **Schizophrenia (55.8%)**
  - (2) **Bipolar disorder (23.3%)**
  - (3) **Major depressive disorder (7.2%)**
- While the most common psychiatric diagnoses among **outpatients** were:
  - (1) **Major depressive disorder (29.3%)**
  - (2) **Schizophrenia (28.9%),**
  - (3) **Generalized anxiety disorder (15.6%)**
  - (4) **Bipolar disorder (11.5%).**

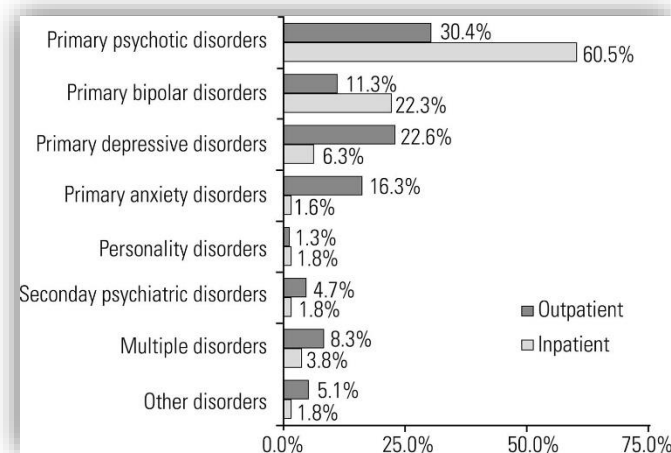
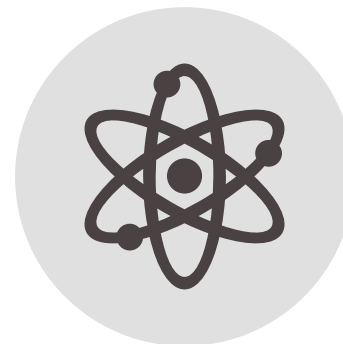


Figure 1: The prevalence of psychiatric diagnostic groups according to patient psychiatric settings in Saudi Arabia in 2017 : adopted from Patterns of psychiatric diagnoses in inpatient and outpatient psychiatric settings in Saudi Arabia .

# PATHOPHYSIOLOGY :

## Bipolar disorder is influenced by several factors:

- **Developmental**
- **Genetic**
- **Neurobiological**
- **Psychological**
- **Multiple gene loci are involved heredity**
- **Environmental**
- **Psychological stressors**
- **Immunological factors**



# DISORDER CLASSIFICATION:

## 1. Bipolar I

- A. Mood disorder with at least one manic or hypomanic episode and one major depressive disorder
- B. Characterized by manic or depressive episode followed by symptom free period

## 2. Bipolar II

- A. Recurrent Major depressive episode with hypomania
- B. Episodes usually do not require hospitalization

## 3. Cyclothymic

- A. Chronic mood disturbance at least 2years duration.
- B. Involving numerous hypomanic and depressive episodes



# DIAGNOSIS:

- A: Manic episodes are characterized by the following symptoms:

1. At least **1 week** of profound mood disturbance is present, characterized by elation, irritability, or expansiveness.
2. **Three or more** of the following symptoms are present:
  - Grandiosity
  - Diminished need for sleep
  - Excessive talking or pressured speech
  - Racing thoughts or flight of ideas
  - Clear evidence of distractibility
  - Increased level of goal-focused activity at home, at work, or sexually
  - Excessive pleasurable activities, often with painful consequences
3. The mood disturbance is sufficient to **cause impairment** at work or danger to the patient or others.
4. The mood is **not** the result of substance abuse or a medical condition.
5. If severe, may have psychotic symptoms



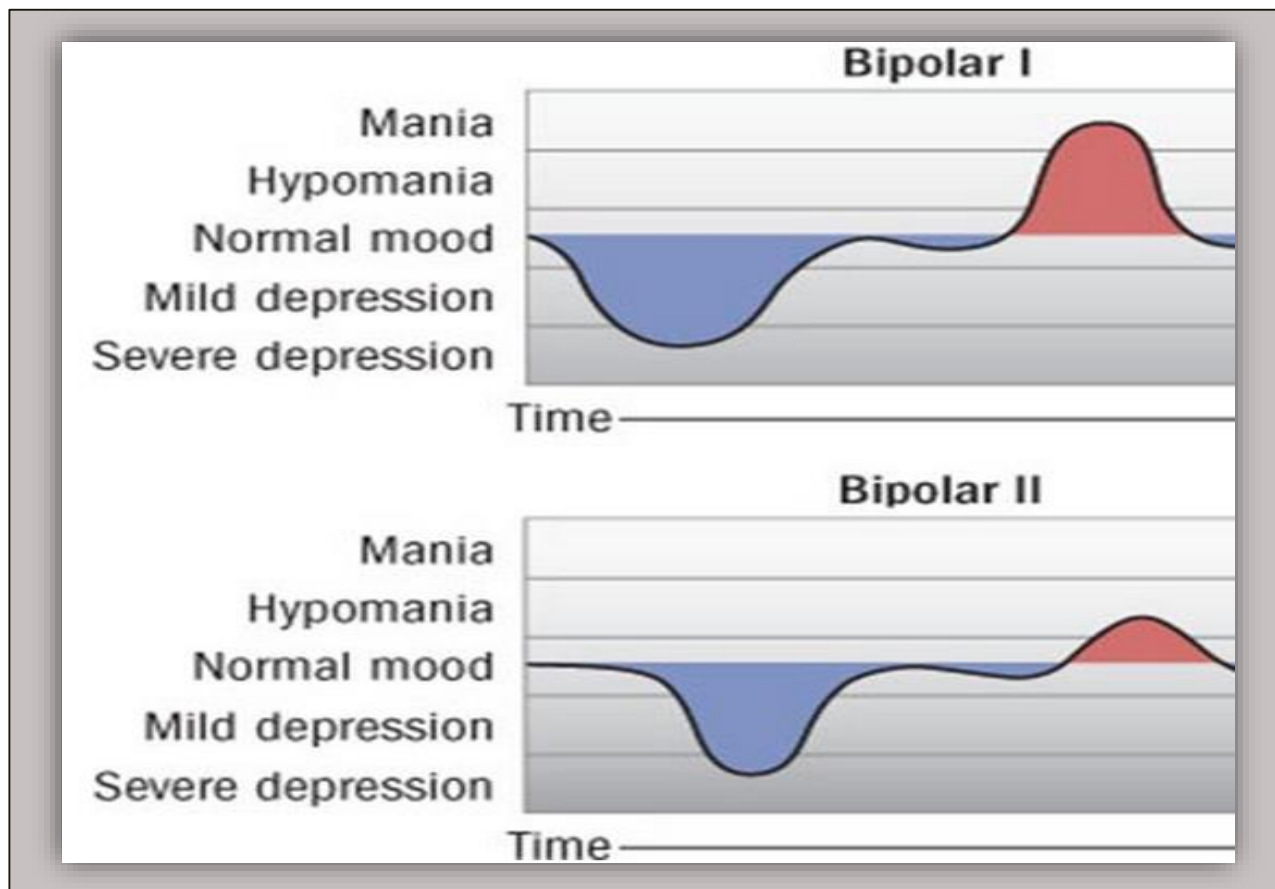


# DIAGNOSIS:

- **B: Hypomanic episodes are characterized by the following:**
  1. The patient has an elevated, expansive, or irritable mood of at **least 4 days' duration**.
  2. **Three** or more of the following symptoms are present:
    - Grandiosity or inflated self-esteem
    - Diminished need for sleep
    - Pressured speech
    - Racing thoughts or flight of ideas
    - Clear evidence of distractibility
    - Psychomotor agitation at home, at work, or sexually
    - Engaging in activities with a high potential for painful consequences
  3. The mood disturbance is **observable** to others.
  4. The mood **is not** the result of substance abuse or a medical condition.



# BIPOLAR AFFECTIVE DISORDER:



# DIAGNOSIS

## SECONDARY CAUSES OF MANIA :

# A- (MEDICAL CONDITIONS)

### CNS disorders

- brain tumor, strokes, head injuries...etc

### Infections

- Encephalitis, sepsis, HIV

### Endocrine or hormonal dysregulation

- Addison's disease, Cushing's disease, hyperthyroidism or hypothyroidism, menstrual-related or pregnancy-related or perimenopausal mood disorders

### Electrolyte or metabolic abnormalities

- (calcium or sodium fluctuations, hyperglycemia or hypoglycemia)



# DIAGNOSIS

## SECONDARY CAUSES OF MANIA :

# B- (DRUGS)

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Alcohol intoxication	Drug withdrawal (alcohol, barbiturates,	benzodiazepines, opiates)	Antidepressants (MAOIs, TCAs)
CNS stimulants (amphetamines, cocaine)	Hallucinogens (LSD, PCP)	Marijuana intoxication	NE-augmenting agents ( $\alpha$ 2- adrenergic antagonists, NE reuptake inhibitors)
Steroids	Thyroid preparations	Xanthines (caffeine, theophylline)	Nonprescription weight loss agents and decongestants (ephedra, pseudoephedrine)
Herbal products (St. John's wort)			



# EVALUATION AND DIAGNOSIS OF MOOD EPISODES:

Episode	Mixed episode Yes	Rapid cycling
Criteria	Criteria for both a major depressive episode and a manic episode	>4 major depressive or manic episodes (manic, mixed, or hypomanic)
Duration	Occur nearly every day for at least a 1-week period	in 12 months
Hospitalization	YES	YES



# GOALS OF TREATMENT:



To treat and reduce acute episodes of mania or depression when they occur.



To reduce the frequency of episodes.



To avoid cycling from one phase to another.



To help the patient function as effectively as possible between episodes.



# PHASES OF TREATMENT:

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Acute phase



Continuation phase



Maintenance phase



# ACUTE PHASE:

## A. Manic Phase

1. Mood stabilizer + consider benzodiazepines or antipsychotic
2. Discontinue Antidepressant

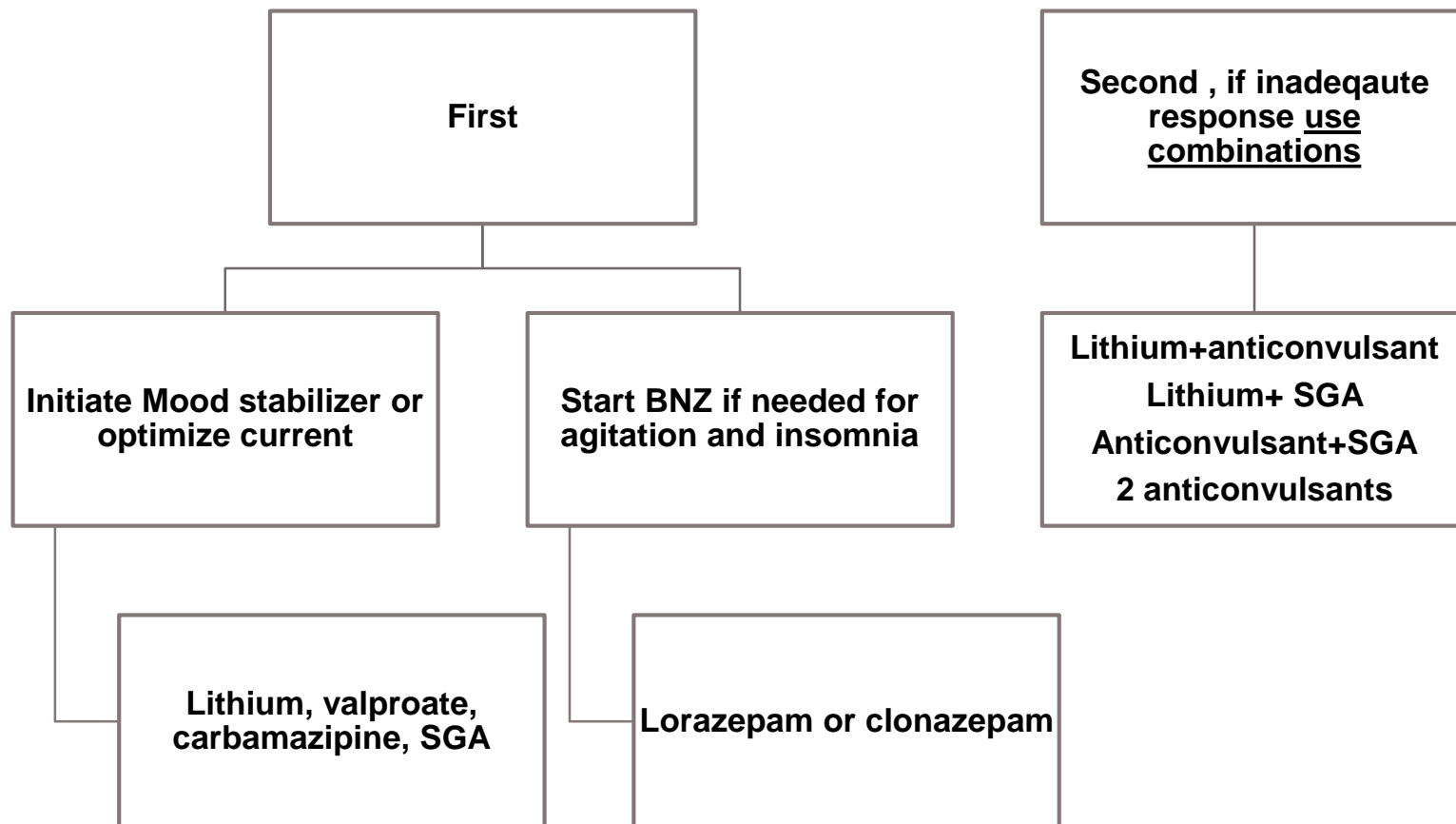
## B. Depressed Phase

1. Mood stabilizer
2. Consider Antidepressant or thyroid hormones

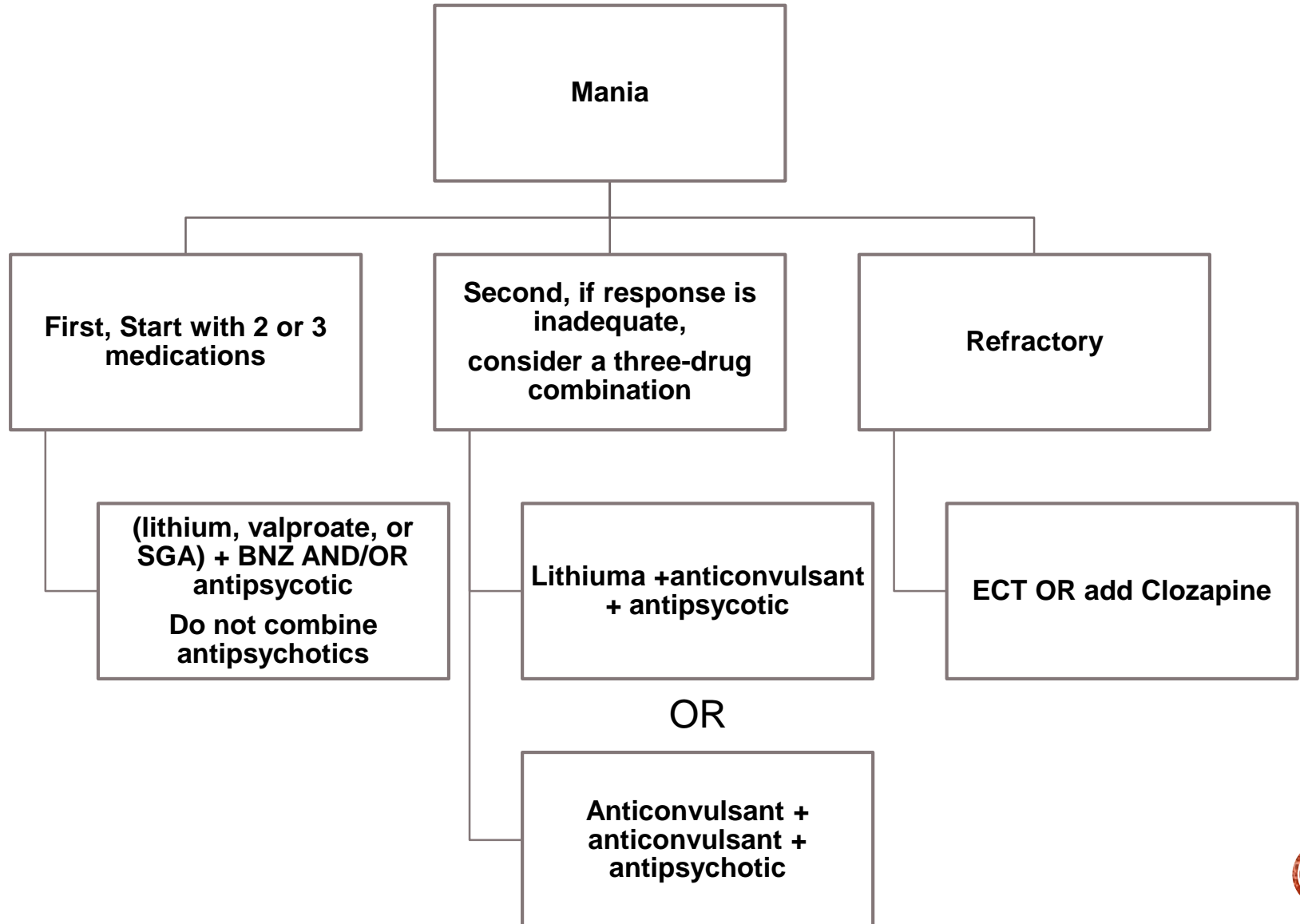




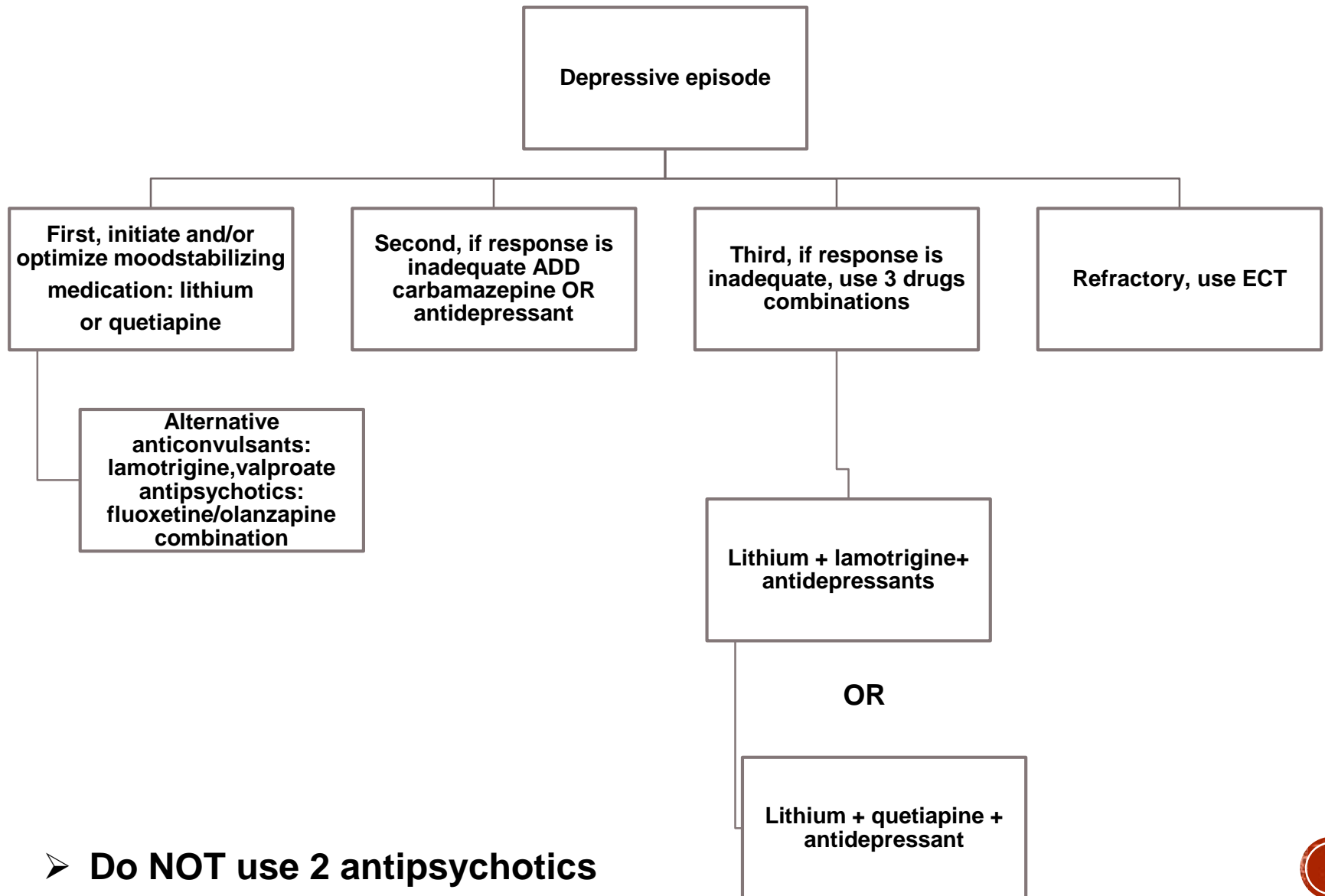
# PHARMACOLOGICAL (HYPOMANIA) :



# PHARMACOLOGICAL (MANIA) :



# PHARMACOLOGICAL (DEPRESSION):

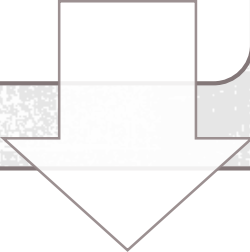


➤ **Do NOT use 2 antipsychotics**



# CONTINUATION PHASE:

6- to 12-week period when risk of relapse is relatively high



Continue mood stabilizers at same dosage effective in acute episodes



# MAINTENANCE PHASE:

1. Bipolar disorder is recurrent in over 90% of patients
2. Most patients will require maintenance (prophylactic) therapy
3. Determinants for maintenance therapy:
  - Probability of a recurrence with or without a mood stabilizer
  - Consequences of a recurrence
4. No evidence that chronic dosing causes tolerance
5. One year of maintenance therapy recommended after every manic episode
6. Long-term treatment is indicated for patients with 2 manic episodes
7. Maintenance antidepressant therapy usually not employed



# TREATMENT:



1. Mood Stabilizer



2. Anticonvulsants



3. Antipsychotics



4. Benzodiazepines



5. Antidepressants



# PHARMACOTHERAPY OPTIONS BY SUBTYPES:

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**Classical Mania:** lithium, Valproic acid, carbamazepine, Atypical Antipsychotic

**Rapid cycling:** Valproic acid only , lamotrogine, Atypical Antipsychotic

**Bipolar II:** lamotrogine, lithium?

- Depressive: Lamotrigine, lithium, quetiapine (with or without adjunctive antidepressant)



# 1. LITHIUM



Lithium is a first-line agent for acute mania, acute bipolar depression, and maintenance treatment of bipolar I and II disorders.



It may require **6 to 8 weeks** to show antidepressant efficacy.



**Initial dose:** 300 mg twice daily.



**Usual dose:** 900–2,400 mg/day in two to four divided doses, with meals.



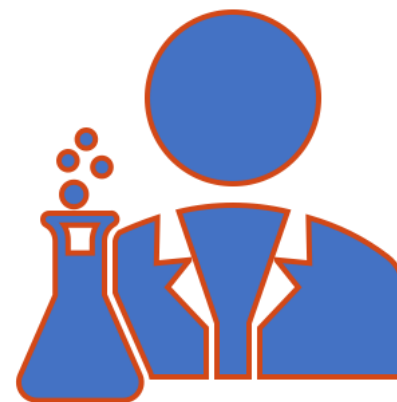


# LITHIUM:

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## Trough serum lithium concentration

- 0.6–1.2 mEq/L [mmol/L] for maintenance therapy
  - 1–1.2 mEq/L [mmol/L] for acute mood episodes
  - Sample taken 8–12 hours after the last dose
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- Lithium toxicity can occur with serum levels greater than 1.5 mEq/L (mmol/L).
  - **Elderly** may have toxic symptoms at therapeutic levels.
  - **Severe** toxic symptoms may occur with serum concentrations above 2 mEq/L (mmol/L), including vomiting, diarrhea, incontinence, incoordination, impaired cognition, arrhythmias, seizures, and kidney damage may occur.



# LITHIUM TOXICITY :

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- **Factors predisposing to lithium toxicity:**

1. Sodium restriction
2. Dehydration
3. Vomiting, diarrhea
4. Age greater than 50 years
5. Heart failure
6. Cirrhosis
7. Drug interactions that decrease lithium clearance
8. Heavy exercise, sauna baths, hot weather, and fever.



# LITHIUM LEVEL MONITORING:

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**Initially**, check serum lithium concentrations once or twice weekly.



**After a desired serum concentration** is achieved, check levels every 2 weeks.



**When stable**, check them every 3 to 6 months.



**Pregnancy:** Lithium clearance increases by 50% to 100% during pregnancy, and monitor serum levels monthly during pregnancy and weekly the month before delivery. At delivery, reduce dose to pre-pregnancy levels and maintain hydration.



# LITHIUM SIDE EFFECTS:

Side effect	Management
GI distress	adding antacids or antidiarrheals.
Fine hand tremor	- Switching to a long-acting preparation - lowering the dose, or adding propranolol, 20 mg
Lithium-induced nephrotoxicity	Lowest effective dose, once-daily dosing is used, good hydration
Transient increase in TSH, hypothyroidism.	Add levothyroxine
Nephrogenic diabetes insipidus	loop diuretics, thiazide diuretics, or triamterene. If a thiazide diuretic is used, lithium doses should be decreased by 50%



# LITHIUM DRUG INTERACTIONS:



lithium + **first-generation antipsychotics (FGA) in elderly patients** ...> neurotoxicity (eg, delirium, severe tremors and extrapyramidal symptoms).



lithium + **verapamil or diltiazem**...> **neurotoxicity** and severe bradycardia.



Lithium and ECT discontinue at least 2 days before (ECT), and resume 2 to 3 days after the last ECT treatment.



# LITHIUM MONITORING:

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**THYROID  
FUNCTION TESTS**



**RENAL FUNCTION  
TESTS (BUN, SCR,  
URINALYSIS)**



**CBC PLUS  
DIFFERENTIAL,  
ELECTROLYTES**



**PRESENCE OF  
DERMATOLOGIC  
DISORDER**



**ELECTROCARDIOG  
RAM (ECG) IF > 40  
YEARS OLD.**



**PREGNANCY TEST  
(IF FEMALE AND  
OF CHILDBEARING  
AGE, PREGNANCY  
CATEGORY D) .**



**WEIGHT**



# LITHIUM IN PREGNANCY AND LACTATION:

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When **lithium is used during pregnancy**, use the **lowest effective dose** to prevent relapse, thus lessening the risk of “floppy” infant syndrome, hypothyroidism, and nontoxic goiter in the infant. (**Ebstein's cardiac anomaly**)



**Breast-feeding** is usually discouraged for women taking lithium



# ANTICONVULSANTS :



SODIUM  
VALPROATE



CARBAMAZEPINE



LAMOTRIGINE





# ANTICONVULSANTS:

## A- VALPROATE SODIUM AND VALPROIC ACID

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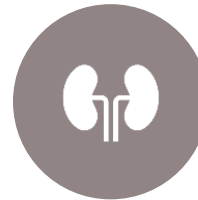
Initial Dose: 200-500 mg twice daily



Usual dose : 750–3,000 mg/day (20–60 mg/kg/day) given once daily or in divided doses.



Dose adjustment is needed in hepatic impairment.



Blood level: 50–125 mcg/ml



Measured 12 hours after the last dose.



Serum levels are most useful when assessing for compliance or toxicity.



# ANTICONVULSANTS

## A- VALPROATE SODIUM AND VALPROIC ACID

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useful for manic/mixed episodes and rapid cyclers .



Effective independent of the number of lifetime episodes.



Effective acutely in patients with comorbid conditions (eg, substance abuse, anxiety disorders, general medical disorders, migraine).



In maintenance treatment, a positive response to divalproex during mania predicts a positive prophylactic response.



# VALPROATE SODIUM SIDE EFFECTS:

The most frequent dose-related side effects of valproate are:

GI complaints

Fine tremor

sedation.

Other side effects are ataxia, lethargy, alopecia, pruritus, prolonged bleeding, transient increases in liver enzymes, weight gain, hyperammonemia and polycystic ovarian syndrome **PCOS**



### Boxed warnings for valproic acid

- i. Hepatic failure, especially in children younger than 2 years. Risk is lower for adults, but liver function test monitoring is warranted.
- ii. Life-threatening pancreatitis has been reported in children and adults. The patient should be counseled to seek medical attention for abdominal pain, nausea, vomiting, or loss of appetite. Valproic acid should be discontinued if the patient develops pancreatitis.
- iii. Teratogenic effects, especially neural tube defects, have been related to the use of valproic acid during pregnancy. The benefits of use versus the risk to the fetus should be evaluated. The woman should be counseled to talk with providers if a pregnancy is planned ahead of time to optimize treatment of bipolar disorder and switch medications, if possible.
- iv. Although rare, blood dyscrasias may occur, including leukopenia.

# MONITORING

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- Monitor platelets and liver function during first 3–6 months if evidence of increased bruising or bleeding.
- Monitor closely if patients exhibit hematologic or hepatic abnormalities or in patients receiving drugs that affect coagulation, such as aspirin or warfarin.
- Discontinue if platelets are  $<100,000/\text{mm}^3/\text{L}$  OR if prolonged bleeding time.
- **Pregnancy** : **NOT RECOMMENDED** during first trimester due to risk of neural tube defects.



# ANTICONVULSANTS

## B- CARBAMAZEPINE

Commonly used for acute and maintenance therapy.

Use in combination in treatment resistant patients.

**Initial dose:** 200 mg twice daily

**Usual dose:** 200–1,800 mg/day in two to four divided doses.

Dose adjustment is needed in hepatic impairment.

Serum samples are drawn 10 to 12 hours after the dose and at **least 4 to 7 days after dosage initiation or change.**

Maintain levels between 6 and 10 mcg/mL (25–42

µmol/L.



# CARBAMAZEPINE MONITORING

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CBC and platelets at baseline, and that subsequent monitoring be individualized by the clinician.



Monitor more closely if patient exhibits hematologic or hepatic SE.



Serum electrolyte levels should be monitored in the elderly or those at risk for hyponatremia.



# CARBAMAZEPINE DRUG INTERACTIONS



Carbamazepine induces the hepatic metabolism of some medications (OC), dosage adjustments may be required.



Certain medications that inhibit CYP3A4 (eg, **cimetidine, diltiazem, erythromycin, fluoxetine, ketoconazole, nefazodone, and verapamil**) may cause carbamazepine toxicity.



**Carbamazepine + valproate**, reduce the carbamazepine dose, as its free levels can be increased.



**Do NOT combine clozapine and carbamazepine** because of possible additive bone marrow suppression.





# ANTICONVULSANTS

## C- LAMOTRIGINE

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- Effective for **maintenance treatment** of bipolar I and II disorder in adults.
- Has both antidepressant and mood-stabilizing effects.
- It may have augmenting properties.
- **low rate of switching** patients to mania.
- It seems most effective for prevention of bipolar depression.



# ANTICONVULSANTS

## C- LAMOTRIGINE



**Initial Dose** 25 mg Daily



**Usual Dose** 50–400 mg/day in divided doses. Dosage should be slowly increased



Lamotrigine should be administered at 25 mg/day for the first 2 weeks, then 50 mg/day for weeks 3 and 4. After that, 50 mg can be added per week as clinically indicated???



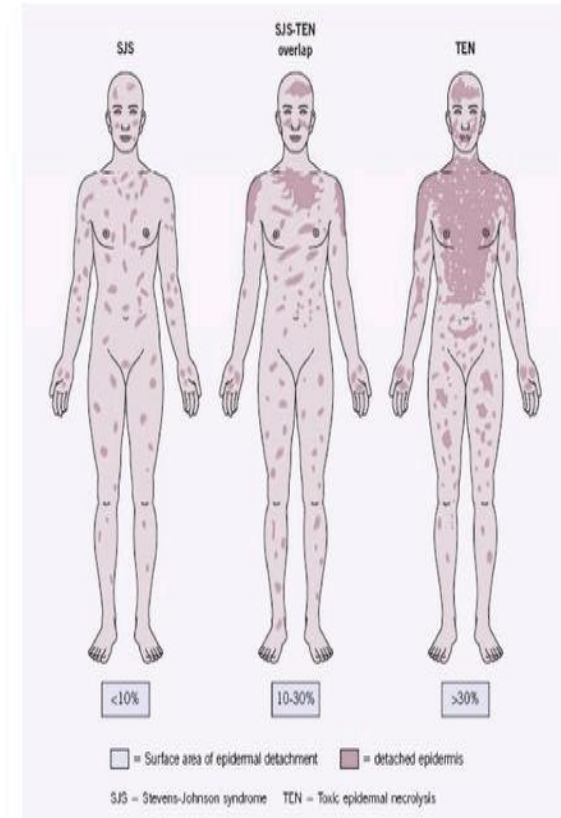
# ANTICONVULSANTS

## C- LAMOTRIGINE

- **Side effects:** headache, nausea, ataxia, diplopia, drowsiness, tremor, maculopapular rash and pruritus.
- Most rashes resolve with continued therapy, some progress to life-threatening Stevens–Johnson syndrome.

### The incidence of rash is greatest with:

1. Concomitant administration of **valproate**
2. **Rapid dose escalation of lamotrigine**
3. **High initial doses**



Pictorial representation of SJS, SJS-TEN overlap and TEN showing the surface of epidermal detachment (Adapted from Fig 21.9 Bologna and Bastuji-Garin S. et al. Arch Derm 129: 92, 1993)



Black box warning for Stevens-Johnson syndrome: can be minimized or eliminated with slow-dose titration:

- i. If monotherapy: 25 mg orally daily for 14 days, 50 mg/day for 14 days, and 100 mg/day for 1 week; then 200 mg/day
- ii. If in combination with valproic acid: 25 mg orally every other day for 14 days, 25 mg/day for 14 days, and 50 mg/day for 1 week; then 100 mg/day
- iii. If in combination with carbamazepine (or enzyme inducer): 50 mg orally daily for 14 days, 100 mg/day for 14 days, and 200 mg/day for 1 week; then 400 mg/day

# ANTIPSYCHOTICS:

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FGA.....> Haloperidol

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SGA.....> aripiprazole, asenapine, olanzapine, quetiapine, risperidone, and ziprasidone.

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**Effective as monotherapy or ADD ON therapy in ACUTE MANIA**

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Maintainance, weigh risks versus benefits, Because of long-term side effects (eg, obesity, type 2 diabetes, hyperlipidemia, hyperprolactinemia, cardiac disease, and tardive dyskinesia).



# ANTIPSYCHOTICS



**Haloperidol decanoate**, long-acting injection is a monotherapy option for maintenance therapy of bipolar disorder with noncompliance or treatment resistance.



**Quetiapine** and the combination of **fluoxetine/olanzapine** are effective for acute bipolar depression.



**Clozapin** is indicated in Acute manic refractory patients as monotherapy , Monitor WBC, Risk of agranulocytosis.



# ANTIPSYCHOTICS

Antipsychotic	Dose	Use	Side effects
<b>Aripiprazole</b>	10–30 mg/day once daily		Weight gain, insomnia
<b>Olanzapine</b>	5–20 mg/day once daily		Weight gain, inc choles, inc TG, inc BG, somnolance, insomnia
<b>Olanzapine /fluoxetinec</b>	6–12 mg olanzapine and 25–50 mg fluoxetine Daily.	effective <u>for acute bipolar depression.</u>	
<b>Quitapine</b>	50–800 mg/day in divided doses or once daily.	effective <u>for acute bipolar depression.</u>	Weight gain, inc choles, inc TG, somnolance, EPS
<b>Risperidone</b>	0.5–6 mg/day once daily or in divided doses		Parkinsonism, weight gain, somnolance, insomnia

# BENZODIAZEPINES

- High-potency benzodiazepines (eg, **clonazepam and lorazepam**) **are commonly** used alternatives to (or adjuncts to) antipsychotics for acute mania, agitation, anxiety, panic, and insomnia or in those who cannot take mood stabilizers.
- **Intramuscular (IM) lorazepam may be used for acute agitation.**
- **A relative contraindication for long-term benzodiazepines is a history of drug or alcohol abuse or dependency.**





# ANTIDEPRESSANTS

## A. Indications

- 1. Patients who cannot wait for 4- to 6-week delay before response to mood stabilizer
- 2. Patients who have a history of response to previous treatment with antidepressants
- 3. Patients who have not responded to mood stabilizers or psychotherapy in the past

## B. Limit antidepressants to management of acute episodes

- 1. Antidepressants may accelerate the course of bipolar disorder and induce rapid cycling
- 2. Antidepressants may induce a switch to mania (especially tricyclic antidepressants)
- 3. Simultaneously use mood stabilizer

## C. Maintain on antidepressant for 3–6 months, then slowly taper

## D. Choice of antidepressant

- 1. Bupropion may be less likely than tricyclic antidepressants to induce switch
- 2. Others: SSRIs, venlafaxine, nefazodone, mirtazapine
- 3. If atypical features: use SSRIs or monoamine oxidase inhibitors (MAOIs)
- 4. Avoid tricyclic antidepressants
- 5. Consider carbamazepine, lamotrigine



# QUESTIONS?

Thank you!

