

# Pharmacology

Modified no.9

الكاتب: حلا صالح و لجين أحمد

المدقق: ميس قشوع و ريناس الخريسات

الدكتور: مالك زحلف

EMS

# Bipolar disorder



## Color code

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Slides



Doctor



Additional info

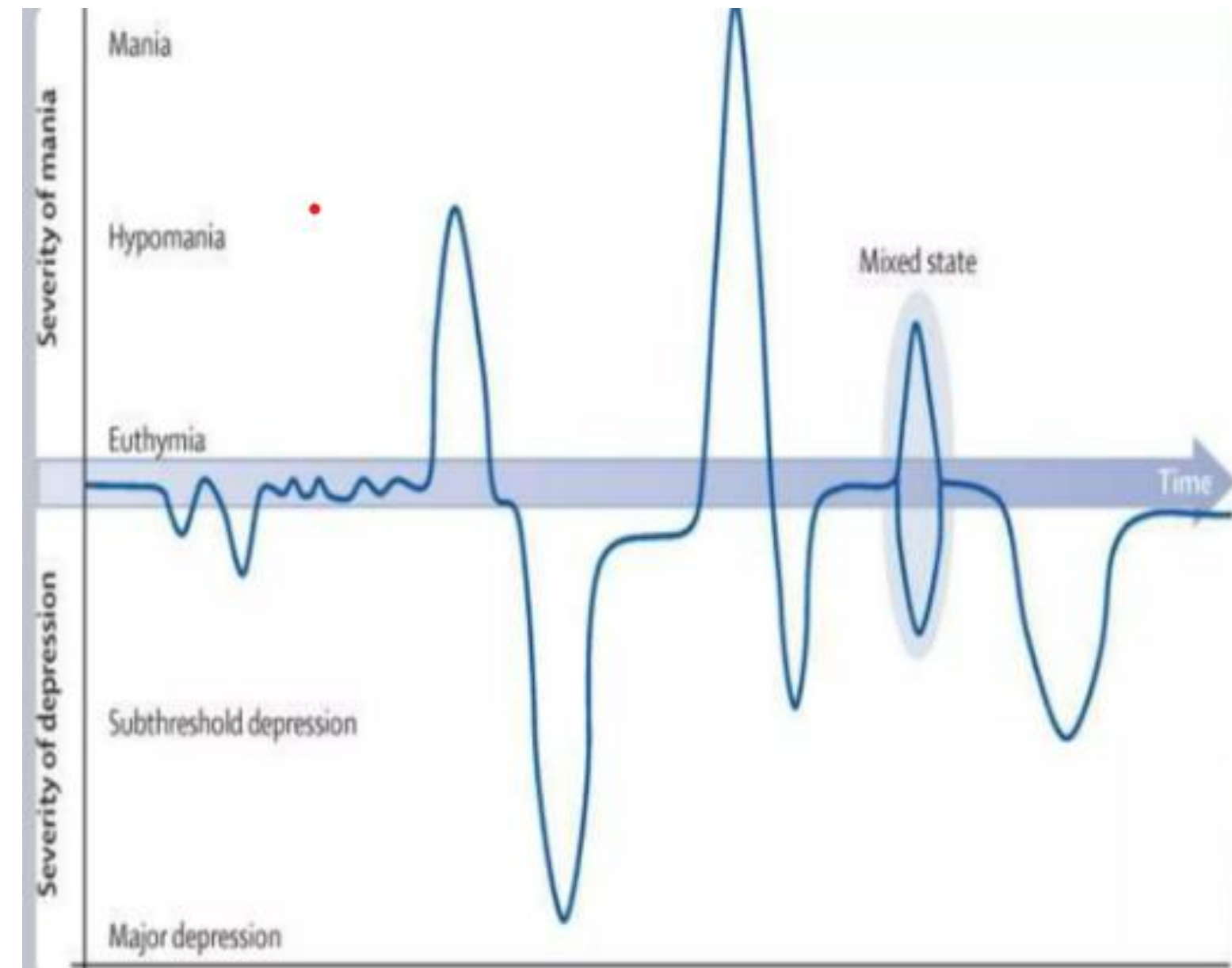


Important

❖ Flow of information in this lecture 😊

1. Discussing bipolar disease.
2. Discussing Lithium's Pharmacodynamics and pharmacokinetics of Lithium.
3. Discussing Lithium's side effects.
4. Discussing alternative treatment to bipolar disease.

بِسْمِ اللَّهِ نَبْدَأُ



- Bipolar is a situation of cyclic episodes of mania and depression.
- In some phases, the patient has a manic attack and other times, they experience hypomania, a milder form of mania.
- On the depressive side, the patient may go through major depression or sub threshold depression.
- A particularly complex state is the mixed state, where symptoms of mania and depression occur simultaneously, so the patient can sometimes feel hyperstimulated (during mania) and at other times understimulated( during depression) making it a problematic situation.

- The disease itself is not understood, we link it the serotonin and dopamine
- There are some biochemical causes of the disease which include:

## Biochemical causes

There is some sort of hypothyroidism, so, there are changes in the hypothalamic-pituitary-adrenal axis. However, the role of hypothyroidism is not understood, but there is a link between the thyroid levels and the manic attacks.

□ Evidence is mounting of the contribution of *glutamate* to both bipolar and major depressions

□ *Hormonal imbalances* and disruptions of the hypothalamic-pituitary-adrenal axis involved in homeostasis and the stress response may also contribute to the clinical picture of bipolar disorder.

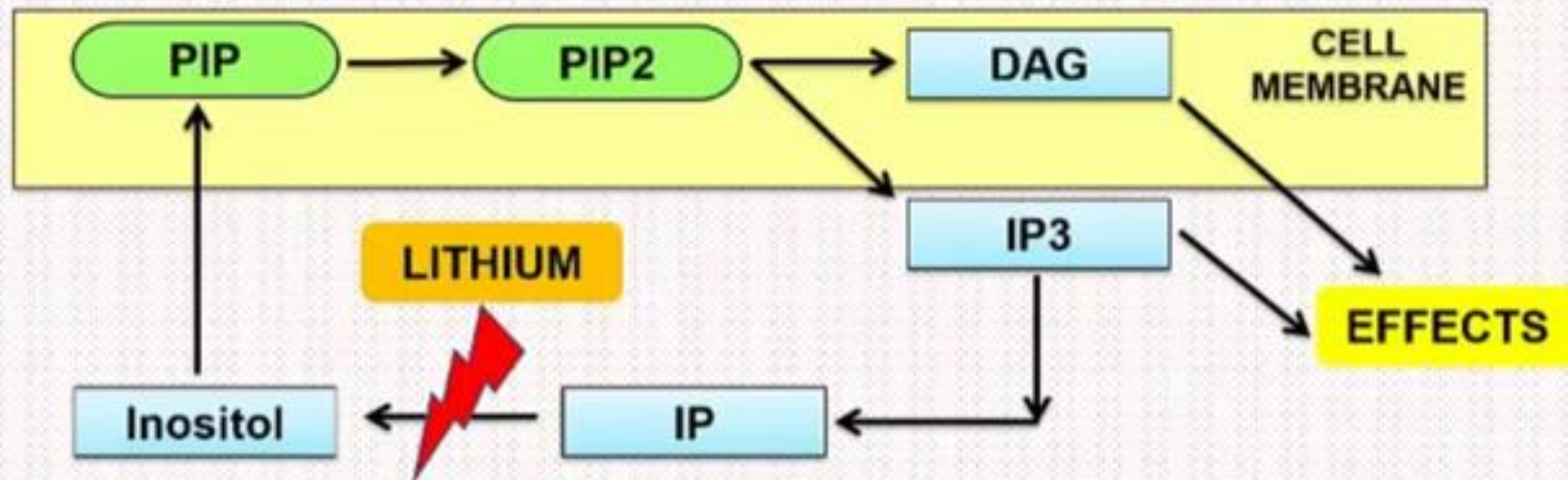
□ *catecholamine hypothesis*, which holds that an increase in epinephrine and norepinephrine causes mania and a decrease in epinephrine and norepinephrine causes depression.

# Lithium Pharmacodynamics

- For treating bipolar, we use lithium, just like sodium and potassium, it's an ion with a charge of +1.
- We use lithium for treating manic, depression, and OCD (**Obsessive-Compulsive Disorder**).
- **No psychotropic effect on non-Bipolars**, so if a person with no bipolar takes lithium by itself, it will not affect his mental health or his psychiatric situation.
- The way in which lithium treats bipolar is unknown, there is an expectation that it **affects nerve membranes, multiple receptor systems and intracellular 2<sup>nd</sup> messenger impulse transduction systems**. (The patient has too much firing - excitation has many theories- so, the lithium generally stabilizes the nerve membrane.)
- **Interacts with serotonin**
- **Potential to regulate CNS gene expression, stabilizing neurons w/ associated multiple gene expression change.**

# Lithium Pharmacodynamics

- $\text{Li}^+$  is a small monovalent cation and is handled by the kidneys similarly to  $\text{Na}^+$
- **MECHANISM** -  $\text{Li}^+$  inhibits Inositol-monophosphatase; hence, free Inositol cannot be generated from IP1. This results in decreased cell membrane phosphatidyl inositides (PIP2) - Decreased IP3 & DAG.



IP: Inositol monophosphate; PIP2: Phosphatidyl inositol 4,5-biphosphate;  
IP3: Inositol triphosphate; DAG: Diacylglycerol

# PHARMACOKINETICS

## SERUM LITHIUM LEVELS

Therapeutic Range  
0.6-1.2 mEq/L

>1.5 mEq/L

1.0-1.2 mEq/L

TOXICITY

ACUTE MANIA


0.6-0.8 mEq/L

MAINTENANCE  
THERAPY

**NARROW MARGIN OF SAFETY**  
Therapeutic Drug Monitoring

- Lithium has a very narrow therapeutic index which is between 0.6 mEq/L and 1.2 mEq/L.
- If the given dose was under 0.6 , it will have no activity for manic attacks, more than 1.2 is a toxic area. Toxicity is really clear after does of 1.5, so, we must keep the does under 1.5.
- **A dose of 2.5 leads to death.**

# Lithium Side Effects and Toxicity

- Relate to plasma concentration levels, so constant monitoring is key.
- Higher concentrations ( 1.0 mEq/L and up produce bothersome effects (side effects), higher than 2 mEq/L can be serious or fatal, especially 2.5.
- Symptoms can be **neurological, gastrointestinal, enlarged thyroid, rash, weight gain, memory difficulty, kidney dysfunction, cardiovascular** (all these side effects can be seen with dose between 1 and 1.5, however, the toxicity of these side effects will be really clear if the dose is more than 1.5 ).
-  Not advised to take during pregnancy, affects fetal heart development.

# The clear side effects:

## 1. Fine tremors:

- **The most common**, occurs even at the therapeutic doses.
- Tremors should be managed; **because even lithium reduces the activity of norepinephrine during the manic attack**, keeping the drug within the patient's body will produce some sort of hyper sympathetic activity which leads to clear tremors.
- It is treated by Propanol and Atenolol

## 2. Leucocytes increased (leucocytosis):


- Increase Leucocytes (12000-15000/mm<sup>3</sup>) almost always during therapy.
- Benign and reversible after treatment is stopped (**Not much of an increase of leukocytes so don't worry about**).

### 3. Hypothyroidism (decreased thyroid function):

- Benign, diffuse, nontender thyroid enlargement, reversible and nonprogressive.

- Lithium will inhibit TSH (thyroid stimulating hormone) leading to decrease T3 and T4 levels (hypothyroidism).
- Patients with depression, bipolar, psychosis, panic attacks...etc should be given **levothyroxine** in order to keep their thyroid levels within the upper limit. Leaving the thyroid within the lower limit will produce some sort of depression, lethargy, and exhaustion, so we augment whatever antidepressant the patient uses by levothyroxine.
- Although it is benign and no need for pathological or pathophysiological interventions, there are some studies which state that **hypothyroidism** is not good for those patients with depression, so you need to keep their thyroid levels high and at least at the lower limit.
- **In Jordan, when treating patients with depression or panic attack, we give them levothyroxin to improve their motivation and to reduce their depression.**

#### 4. Increased urination (polyuria and polydipsia):

- It is called **nephrogenic diabetes insipidus**.
- The patient will tolerate it after having the proper levels of water.
- Increased urination (polyuria and polydipsia): lithium inhibits ADH (antidiuretic hormone) leading to increase urination . May response to amiloride, reversible on stopping Li.
- So, we need to understand that there is an inhibition for ADH activity, increasing urination and this a problematic by itself ! Why it's problematic ? Let's know 
- Lithium is excrete through the kidney, and much of it is reabsorbed (like sodium), if urination increased it leads to lose a lot of water and sodium, when sodium is depleted, lithium will win the reabsorption competition (because it resembles the sodium) and come back to the body.

- To prevent this, patient should be hydrated (1-3 liters per day, and after days he will be tolerated with the urination); because dehydration (either caused by lithium itself, vomiting, or diarrhea) will increase lithium levels. This happens because lithium is reabsorbed in the proximal tubules, the same site where much of the sodium is reabsorbed. When sodium and water levels in the body are low, the kidneys **mistakenly reabsorb more lithium**, leading to its accumulation. Therefore, it is essential for the patient to maintain normal sodium levels to ensure lithium is properly excreted from the body.
- **If you asked about the drug that we care about Na level to be normal instead of lowering it like in the case of CVS drugs, it would be Li !!**

## **5. Contraindicated during pregnancy:**

- Foetal coitre or Ebsteins' anomaly may develop, so never ever give Li to pregnant mothers!
- **Toxicity of lithium: nephrotoxicity, neurotoxicity, neurological problems and seizures.**

# If Lithium Doesn't Work


- Some Studies say: Don't start with lithium or start with low dose of lithium with Valproic Acid (Depakote), or start with antidopaminergic drugs (antipsychotics) like Aripiprazole, Risperidone and Olanzapine.
- 40% of Bipolars are resistant to lithium or side effects hinder its effectiveness
- Therefore, we must consider alternative agents for treatment

The doctor read everything in this slide

# Valproic Acid (Depakote)

- An anti-epileptic, it is the most widely used anti-manic drug.
- Augments the post-synaptic action of GABA at its receptors (increasing synthesis and release).
- **Best for rapid-cycling and acute-mania** (if your patient has a rapid cycles (up and down) of manic and depression, Valporic acid is better choice than the lithium to start with).
- Therapeutic blood levels: 50-100 Mg/L.
- Side effects include GI upset, sedation,lethargy (most of anti epileptic drugs cause sedation and lethargy) ,tremor, metabolic liver changes and possible loss of hair.
- Can also be used for anxiety, mood, and personality disorders

### **!Important notes:**

- It may be the first drug to use, instead of lithium.
- So, it is the second choice after Li, or the first choice with low dose Li, or only to give valproic if Li doesn't work.
- We may give antipsychotics >>> continue to the next slide 

# Carbamazepine (Tegretol)

- Superior to lithium for rapid-cycling, regarded as a second-line treatment for mania.
- Correlation between therapeutic and plasma levels (estimated between 5-10 Mg/L)
- Side effects may include GI upset, sedation, ataxia and cognitive effects

# Lamotrigine

Not really much used >> new drug

- Reported effective with Bipolar, Borderline Personality, Schizoaffective, Post-Traumatic Stress Disorders
- Inhibits neuronal excitability and modifies synaptic plasticity
- Side Effects may include dizziness, tremor, headache, nausea, and rash

# Atypical Anti-psychotics

- Clozapine, Risperidone, and Olanzapine, Aripiprazole
- Risperidone seems more anti-depressant than anti-psychotic because it is strong on serotonin levels.
- Clozapine is effective, yet not readily used due to potential serious side effects
- Olanzapine is approved for short-term use in acute mania
- Aripiprazole is effective for the treatment of acute manic episodes of bipolar disorder in adults

**This table is not required**

Table FDA-approved treatments for bipolar disorder in adults				
Generic name	Mania	Mixed	Depression	Maintenance
Aripiprazole	X	X		X
Asenapine	X	X		
Carbamazepine extended-release	X	X		
Chlorpromazine	X			
Lamotrigine				X
Lithium	X			X
Olanzapine	X	X		X
Olanzapine/fluoxetine			X	
Quetiapine	X		X	
Risperidone	X	X		
Valproate	X			
Zincidone	X	X		

For mania , we usually start with either a combination of valproic acid and one of the anti-psychotics, or lithium by its own or low levels of lithium (0.4 mEq/L) with valproic acid.

- Lithium has **no antidote**, in case of toxicity we do **hemodialysis**.

## Past papers:

Which of the following drug is correctly matched with its side effect?

- A)Lithium - diabetes insipidus
- B)Olanzapine-Agranulocytosis

ANSWER : A

## AI generated questions:

- 1)Which of the following is a common adverse effect of lithium at therapeutic doses?  
A. Hypertension    B. Fine tremors    C. Hyperthyroidism    D. Hypoglycemia

ANSWER: B

- 2)Which of the following is NOT a side effect of lithium toxicity?  
A. Memory difficulty    B. Weight loss    C. Kidney dysfunction    D. Cardiovascular issues

ANSWER: B

فَبِمَا رَحْمَةٍ مِّنَ اللَّهِ لِنْتَ لَهُمْ وَلَوْ كُنْتَ فَظًّا غَلِيظَ الْقَلْبِ لَانفَضُّوا مِنْ حَوْلِكَ

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2	10 11	Hyperthyroidism	Highlighted Hypothyroidism
V2→V3			



امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!