بسم الله الرحمن الرحيم

Bipolar Disorder

FINAL | Lecture 9

﴿إِنِّي تَوَكَّلْتُ عَلَى اللَّهِ رَبِّي وَرَبِّكُمْ ۚ مَا مِن دَابَّةٍ إِلَّا هُوَ آخِذٌ بِنَاصِيَتِهَا ۚ إِنَّ رَبِّي عَلَىٰ صِرَاطٍ مُّسْتَقِيمٍ﴾

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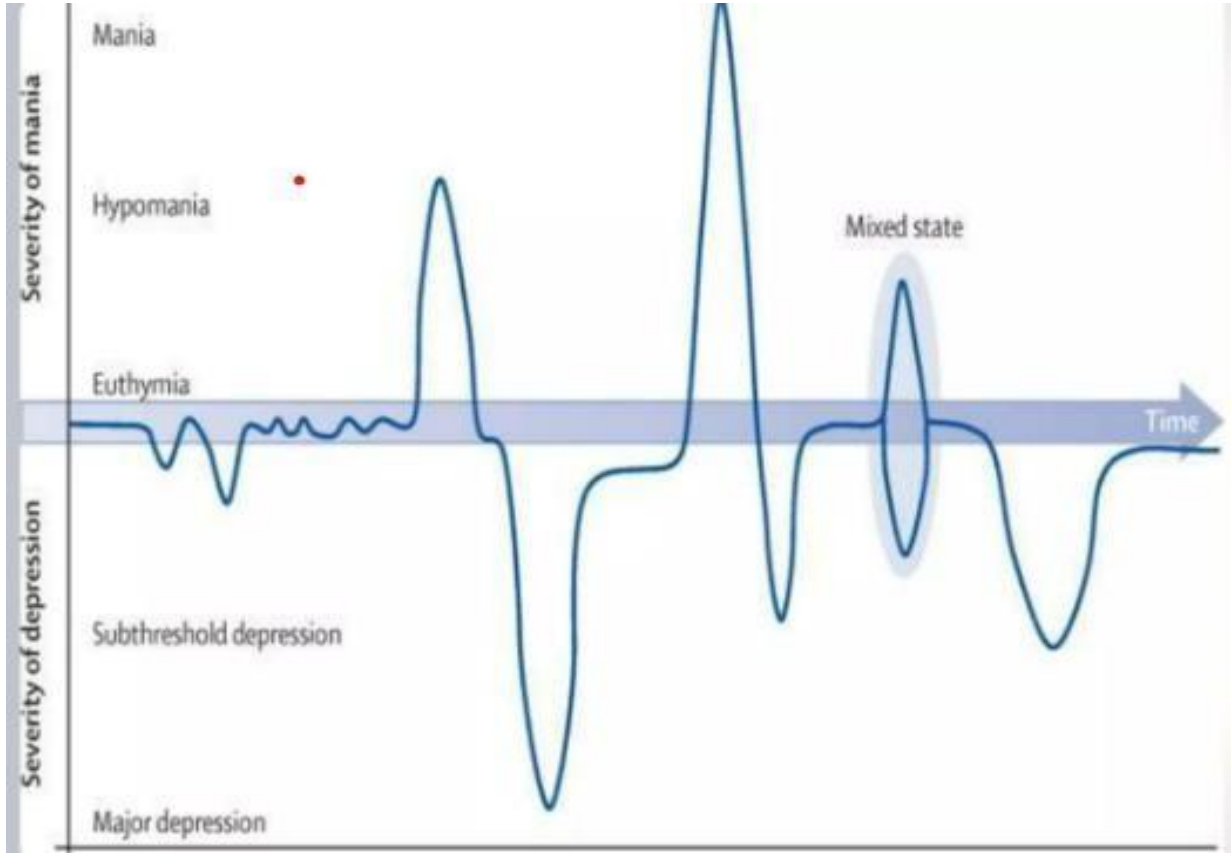
PHARMACOLOGY

Bipolar Disorder

- **Bipolar** is a situation of cyclic episodes of *mania and depression*.
- Regarding mania, in some stages 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 **subthreshold depression**.
- A particularly complex state is the **mixed** state, where symptoms of mania and depression occur **simultaneously**, so the patient can sometimes feel:

✓ ***Overstimulated:*** during mania
OR
✓ ***Understimulated:*** during depression

➢ Which makes it a **problematic situation**.



Biochemical causes

- The disease itself is not fully understood; however, it is commonly associated with alterations in **serotonin and dopamine** levels.
- There are some **biochemical causes** of the disease which include:

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.

- 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.

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.

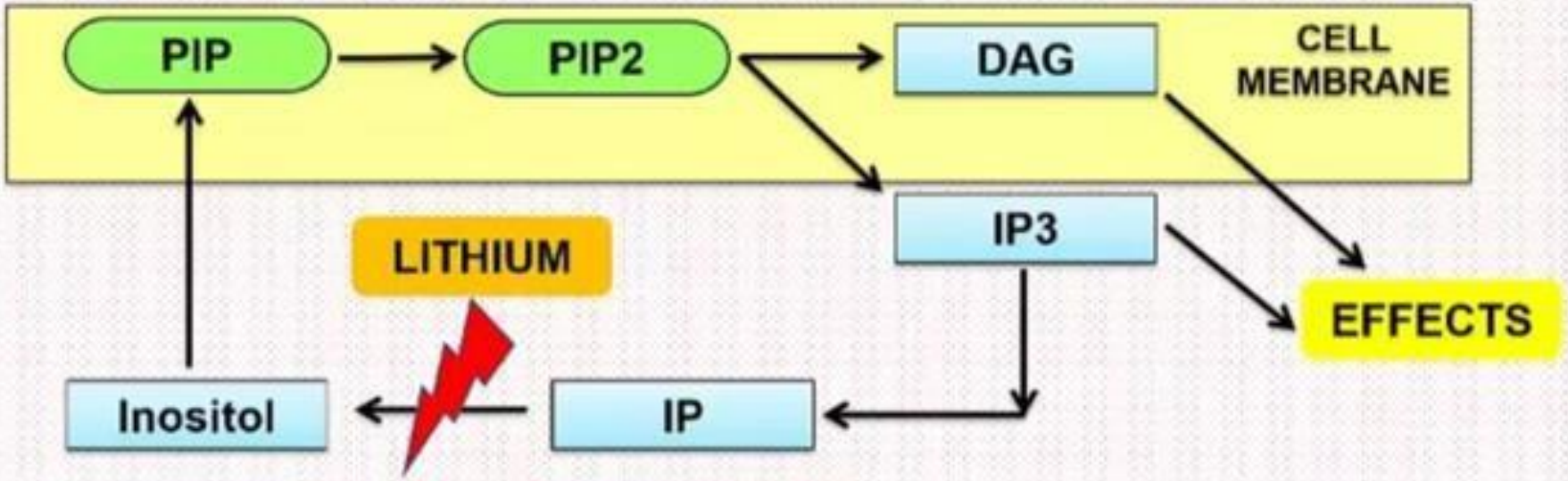
- The way in which lithium treats bipolar is **unknown**, there is an expectation that it **affects nerve membranes, multiple receptor systems and intracellular 2nd messenger impulse transduction systems.** (The patient exhibits excessive neuronal firing and excitation, which is explained by several theories. Therefore, lithium generally acts by **stabilizing the neuronal membrane**).

- **Interacts with serotonin**

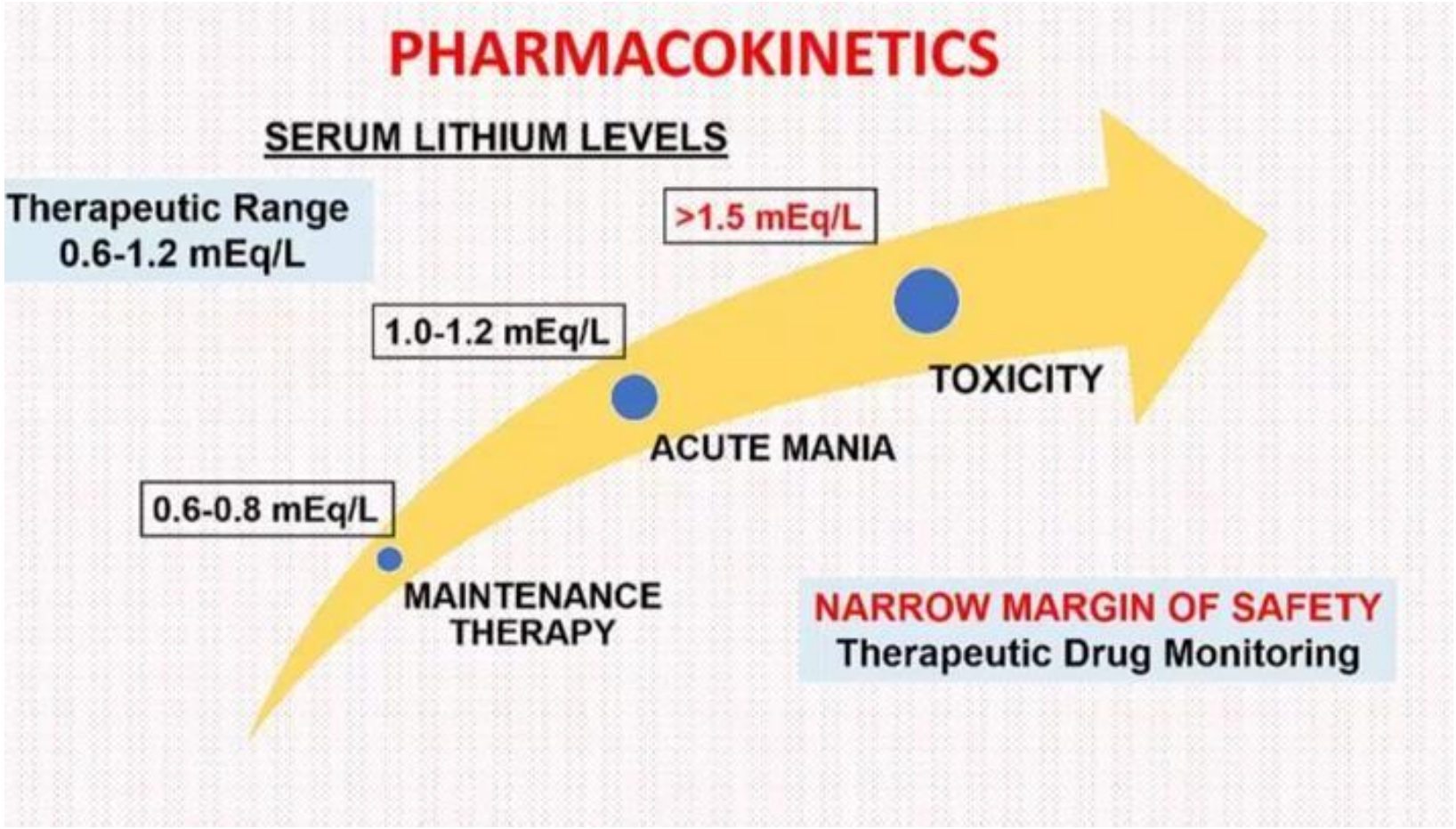
- **Potential to regulate CNS gene expression, stabilizing neurons w/ associated multiple gene expression change.**

Lithium Pharmacodynamics

- Li^+ is a small monovalent cation and is handled by the kidneys similarly to Na^+
- **MECHANISM** - Li^+ inhibits Inositol-monophosphatase; hence, free Inositol cann be generated from IP1. This results in decreased cell membrane phosphatidyl inosotides (PIP2) - Decreased IP3 & DAG.



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



- 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 dose 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 disfunction, cardiovascular** (All these side effects can be seen with dose between (1-1.5). However, the toxicity of these side effects will be really clear if the dose is **more than 1.5**).

- **<u>NOT</u> advised to take during pregnancy, affects fetal heart development**

LEUCOCYTES INCREASED (LEUCOCYTOSIS)

- ↑↑ leucocytes (12000-15000/mm^3) almost always occurs during therapy
- Benign & reverses after treatment is stopped

TREMORS (= FINE TREMORS)

- Most common adv. effect; occurs at therapeutic doses
- Treated by Propranolol or Atenolol
- Other CNS effects – athetosis, dysarthria, aphasia etc.)

HYPOTHYROIDISM (↓↓ THYROID FUNCTION)

- Benign, diffuse, nontender thyroid enlargement
- Reversible and nonprogressive

INCREASED URINATION (Polyuria & Polydipsia)

- Occurs due to inhibition of ADH action
- May respond to amiloride, reversible on stopping Li^+

EXPECTANT MOTHERS DURING PREGNANCY

- Contraindicated during pregnancy
- Foetal goitre or Ebsteins' anomaly may develop

See the next slides

Lithium Side Effects and Toxicity

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 hypersympathetic activity which leads to clear **tremors**.
- It is treated by ***Propanol and Atenolol***.

2. **Leucocytes increased (leucocytosis):**

- Increase Leucocytes (12000-15000/mm^3) almost always during therapy.
- **Benign and reversible** after treatment is stopped (Not a significant ncrease of leukocytes, so don't worry about it).

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

- **Benign, diffuse, nontender** thyroid enlargement.
- **Reversible** and **nonprogressive**.

Lithium Side Effects and Toxicity

- 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 (at least at the lower normal limit).
- In Jordan, when treating patients with depression or panic attack, we give them **levothyroxin** to improve their motivation and to reduce their depression.

Lithium Side Effects and Toxicity

4. Increased urination (polyuria and polydipsia):

- This condition is known as **nephrogenic diabetes insipidus.**
- It occurs because **lithium inhibits the action of ADH (antidiuretic hormone)**, leading to **increased urine** output.
- Patients may **eventually tolerate** this effect if they maintain **adequate water** intake.
- It **may respond to amiloride and is usually reversible after stopping lithium**.

Why is this problematic?

- Lithium is **excreted** by the **kidneys** and is **reabsorbed** in a manner **similar** to **sodium**.
- **Increased urination** leads to **loss** of **water and sodium**.
- When **sodium** levels **decrease**, **lithium** is preferentially **reabsorbed** (since it mimics sodium), causing it to **accumulate in the body**.

Lithium Side Effects and Toxicity

4. Increased urination (polyuria and polydipsia):

Prevention and management:

- Patients should stay well **hydrated (about 1–3 liters/day).**
- **Dehydration** (from lithium itself, vomiting, or diarrhea) **increases lithium levels**.
- **Lithium** is reabsorbed in the **proximal tubules**, where **sodium** is also **reabsorbed**. **Low sodium or water levels** cause the **kidneys** to **reabsorb more lithium**, increasing its concentration. Therefore, **maintaining normal sodium levels** is essential for proper lithium excretion.
- Unlike many **cardiovascular** drugs where **sodium reduction** is **desired**, normal sodium levels must be maintained with **lithium therapy.**

Lithium Side Effects and Toxicity

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 suggest **alternative** approaches to initiating treatment:
  - ✓ **Avoid** starting with **lithium alone**, or begin with a **low dose of lithium** combined with **valproic acid (Depakote)**.
  - ✓ **Valproic acid** may be considered as the **first-line** treatment instead of lithium in certain cases. It can be used as a **second choice** after lithium, in combination with a **low dose of lithium**, or **alone** if lithium proves ineffective.
  - ✓ Another option is to start with **antiepileptic (Carbamazepine) or antidopaminergic drugs** (antipsychotics) such as **Aripiprazole**, **Risperidone**, or **Olanzapine**.
- 40% of Bipolars are **resistant** to lithium or **side effects** hinder its effectiveness
- Therefore, we must consider **alternative** agents for treatment

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 (In patients with rapid **cycling** (frequent **shifts** between **mania** and **depression**), **starting treatment with valproic acid is preferred over lithium**).
- Therapeutic blood levels: 50-100 Mg/L
- Side effects include GI upset, sedation, lethargy (Most antiepileptic drugs **commonly** cause **sedation** and **lethargy**), tremor, metabolic liver changes and possible loss of hair
- Can also be used for anxiety, mood, and personality disorders

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

- **Lamotrigine** is a relatively **new** drug and is **NOT** widely used yet in clinical practice.
- 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
- 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			
Ziprasidone	x	x		

- For treating mania, the usual approach is to start with either a **combination** of **valproic acid** and an **antipsychotic**, or **lithium** alone, or **low-dose lithium (0.4 mEq/L) combined with valproic acid**.
- Lithium has **NO** specific **antidote**, so in cases of toxicity, **hemodialysis** is required.

PHARMACOLOGY QUIZ

LECTURE 9

External Resources

رسالة من الفريق العلمي

Additional sources:

1. Dr Abdalrhman Froukh Lecture
2. Osmosis

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Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			