

# CNS

Doctor 2021



# Pharmacology Sheet (7)

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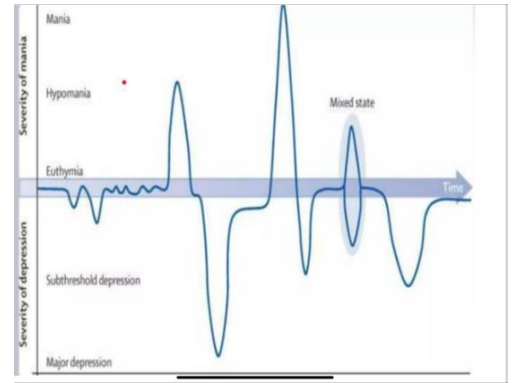
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# Bipolar

- Bipolar is a situation of manic and depression with cycles, the patient in some stages will have manic attack, sometimes hypomanic (hypomania), within these attacks the patient is over stimulated, other times the patient will be underestimated with attacks of major (deep) depression or subthreshold depression, the patient may also have a mixed attack of both manic and depression.



Briefly the patient has much of excitation within the manic attacks and little excitation in term of depression.

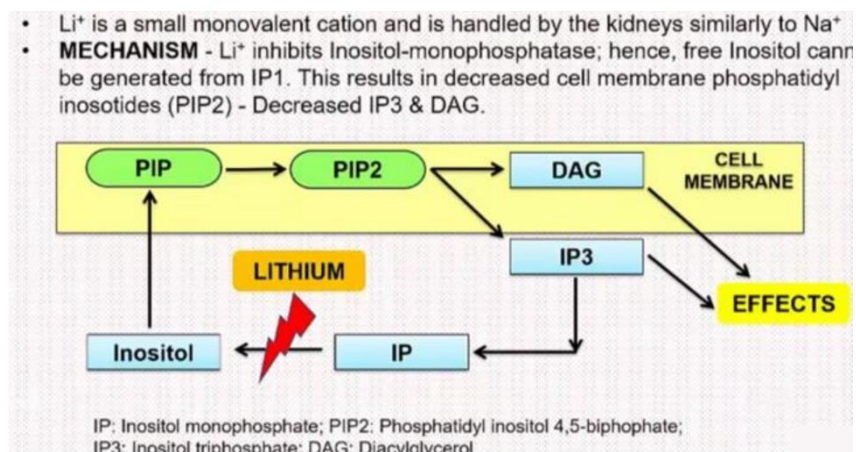
- The disease itself is not understood, we link it the serotonin and dopamine, some **biochemical causes** of the disease are:
  1. Evidence is mounting of the contribution of **glutamate** to both bipolar and major depressions.
  2. **Hormonal imbalances** and disruptions of the hypothalamic-pituitary-adrenal axis involved in homeostasis and the stress response may also contribute to the clinical picture of bipolar disorder. 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.
  3. **catecholamine hypothesis**, which holds that an increase in epinephrine and norepinephrine causes mania and a decrease in epinephrine and norepinephrine causes depression.

## Lithium:

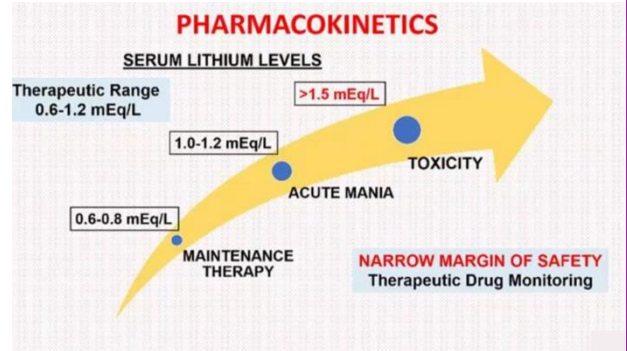
- It is an ion with charge of +1 same as the sodium and potassium ions which is using as **the main drug for treating bipolar**, it is used to treat manic, depression and sometimes with OCD.
- it has **No psychotropic effect on non-Bipolars**, meaning if the patient taken lithium by itself, it will not affect his mental health or psychiatric situation.

## Mechanism of action:

- 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 has too much firing (excitation has many theories), so, the lithium generally stabilizes the nerve membrane, works in multiple receptors and on 2<sup>nd</sup> messenger.
- It **Interacts with serotonin**.
- **Potential to regulate CNS gene expression, stabilizing neurons with associated multiple gene expression change.**



- Lithium has a very narrow therapeutic index which is between 0.6 mEq/L and 1.2 mEq/L, if the dose given 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 doses of 1.5, so, we must keep the doses under 1.5. Dose of 2.5 leads to death.



- **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.
- Not advised to take during pregnancy, affects fetal heart development.
- The clear side effects that should be understood are:
  1. **Fine tremors: The most common, occurs even at the therapeutic doses.** tremors should be managed; because even if the norepinephrine is reduced during the manic attack, keeping the drug within the patient body will produce some sort of hyper sympathetic activity leading to clear tremors, it is treated by Propanolol and Atenolol.
  2. **Leucocytes increased (leucocytosis):** (12000-15000/mm<sup>3</sup>), benign and reversible after treatment is stopped (don't worry about).
  3. **Hypothyroidism: benign, diffuse, nontender thyroid enlargement, reversible and nonprogressive.** Lithium will inhibit TSH (thyroid stimulating hormone) leading to decreased T<sub>3</sub> and T<sub>4</sub> levels (hypothyroidism).
    - Patients with depression, bipolar, psychosis, panic attacks...etc should be given levothyroxine in order to keep 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 the antidepressant the patient use by levothyroxine.
    - -so although it is benign 2020 researches encourage giving levothyroxine. In Jordan we give it with Li.
  4. **Increased urination (polyuria and polydipsia):** lithium inhibits ADH (antidiuretic hormone) leading to increased urination. May response to amiloride, reversible on stopping Li.
    - It is called nephrogenic diabetes insipidus.
    - The patient will tolerate it after having the proper levels of water.
    - Lithium is excreted 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.
    - The patient should be hydrated (1-3 liters per day, and after days he will be tolerated with the urination); because the dehydration (ether caused by lithium itself, vomiting, or diarrhea) will increase lithium levels. He also should take sodium (keep it at a normal level) for lithium to go out of the body.
    - -Li and Na reabsorption happens in the proximal tubule, if the patient is dehydrated, Na will be excreted and Li will be reabsorbed instead, so we should keep Na at its NORMAL(NOT HIGH) LEVELS
    - -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. -never ever give Li to pregnant mothers!**

- Toxicity of lithium: nephrotoxicity, neurotoxicity, neurological problems and seizures.

## If Li doesn't work

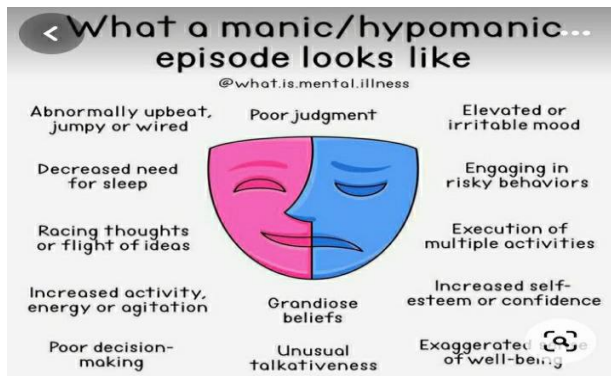
- 40% of Bipolars are resistant to lithium or side effects hinder its effectiveness, therefore, we must consider alternative agents for treatment:
  1. Valproic Acid (Depakote):
    - An anti-epileptic, it is the most widely used anti-manic drug.
    - Augments the post-synaptic action of GABA at its receptors (increasing synthesis and release).
    - Best for rapid-cycling and acute-mania (if your patient has rapid cycles( up and down)of manic and depression, valporic acid is better than the lithium to start with).
    - Can also be used for anxiety, mood, and personality disorders.
    - Therapeutic blood levels: 50-100 Mg/L.
    - Side effects include GI upset, sedation and lethargy (most of anti-epileptic drugs causes sedation and lethargy), tremor, metabolic liver changes and possible loss of hair.
    - It may be the first drug using 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.
  2. 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.  
-hence we took about these 2 drugs with Dr.Samar, the doctor wont ask about them, we just need to know that they are the choice for rapid cycles if Li doesn't work or with low dose of Li
  3. Lamotrigine: it is newer than the above,so, not much used.
    - 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, Olanzapine and 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.
- For mania we usually start with ether 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.



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			

مش مطلوب

اللهم صل على سيدنا محمد وعلى اله وصحبه وسلم



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

- A. Lithium – diabetes insipidus
- B. Olanzapine-Agranulocytosis

Answer: A