Bipolar disorder - Lecture 5

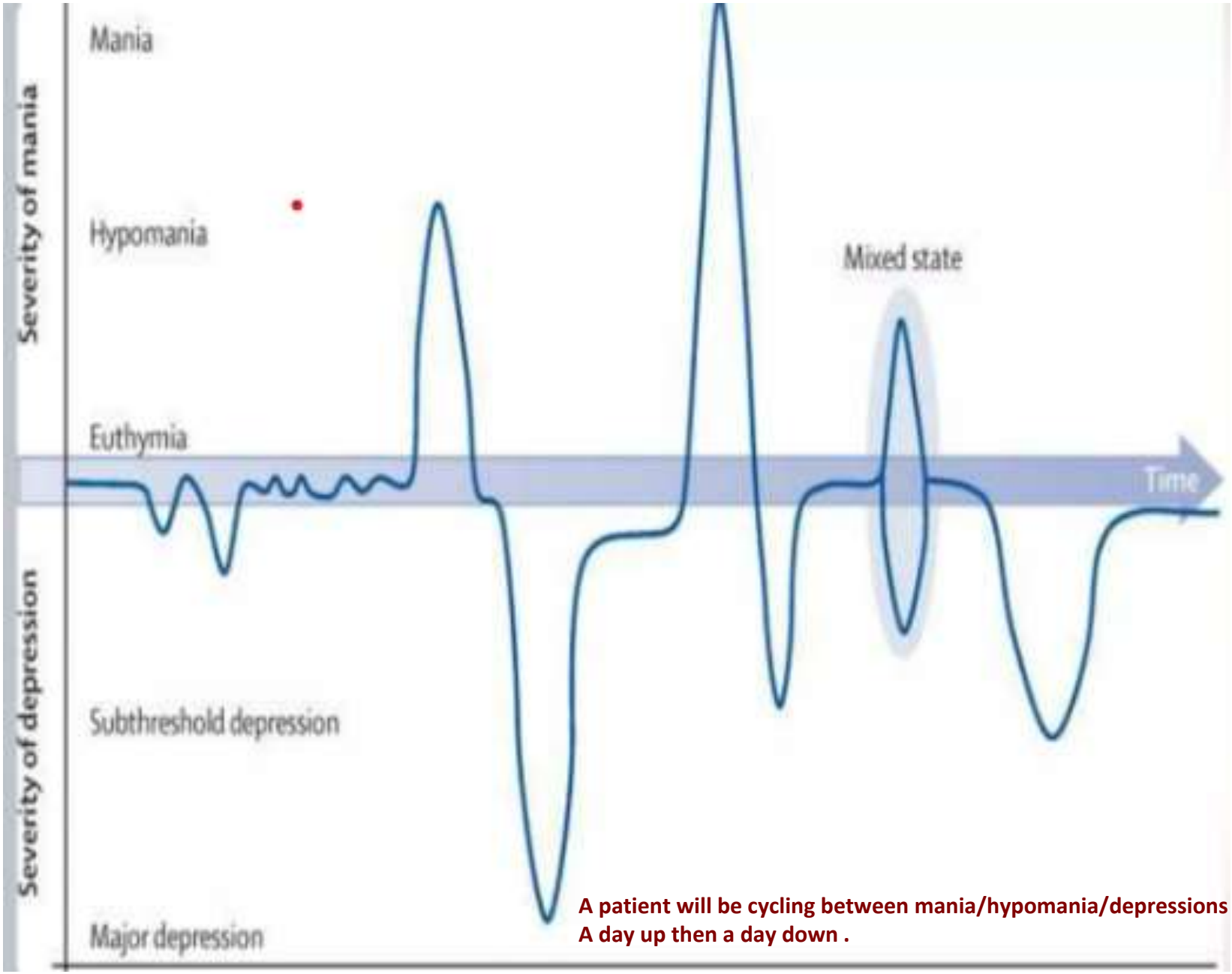
Dr Malik Zihlif

Edited by: Ahmad AlHurani

Corrected by: Roa'a Abuarab

Bipolar disorder

Bipolar is a disease in which we have a combination of issues that we already know, its **a disorder of swing** (mood swings up and down) cycling between very bad depression and very high excitement, you might think that it's similar to schizophrenia and that's true but in bipolar we don't have the hallucinations that are an important part in schizophrenia.
(Excitement in bipolar which is pure euphoric and happy phase **without having a messy mind** خربطة الأفكار).
Bipolar has multiple types, and is managed in different ways compared to schizophrenia or other types of psychosis.
-Bipolar and Schizophrenia are very close but we distinguish between them by the symptoms.



A patient will be cycling between mania/hypomania/depressions
A day up then a day down .

As always, we need to create hypotheses about why this disease happens in the first place to be able to find a suitable management mechanism.
In bipolar, we will stray away from dopamine and serotonin and focus on Glutamate, epinephrine and norepinephrine. The reason for that is that we have differences in the biochemical basis of the disorder (All of that was found accidentally after the administration of drugs during trials.

Biochemical causes

3 different hypothesis

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

In 1949 they found out that using some lithium salts (yes, the same lithium we have in batteries etc.) and found out it has mood stabling capabilities! Lithium is the only true mood stabilizer. (But at the cost of having multiple side effects)

- No psychotropic effect on non-Bipolars Doesn't increase nor decrease the psychotic activity in non-bipolars
- Affects nerve membranes, multiple receptor systems and intracellular 2nd messenger impulse transduction systems.next slide
- Interacts with serotonin has some serotonin like activity (Also check the note in the next slide
- Potential to regulate CNS gene expression, stabilizing neurons w/ associated multiple gene expression change.
- We all know that if we modify the metabolites within the body of the patient we will have multiple side effects, and another issue is that lithium is not a main component in our bodies however it's very similar to Sodium! So imagine if we're giving a patient large doses of sodium on daily basis! This will produce multiple side effects we will be talking about soon.

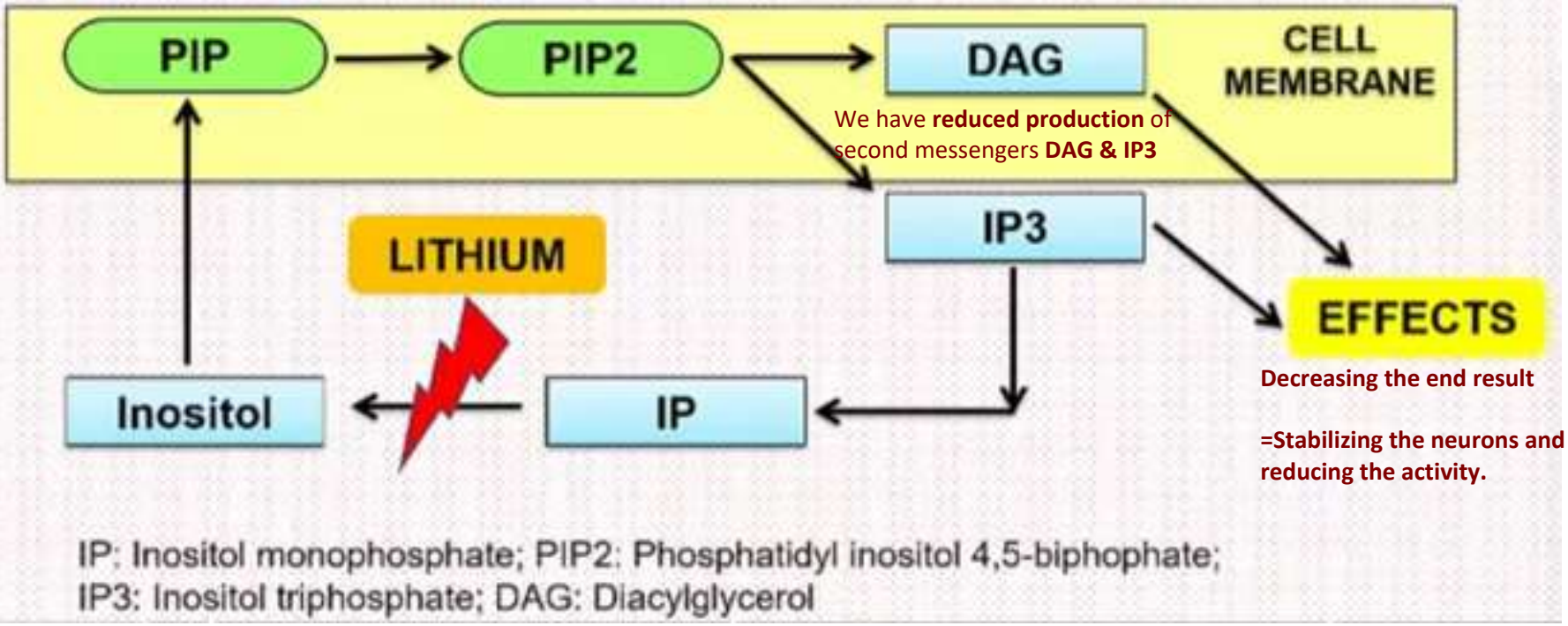
Lithium acts like its similar cation sodium with some key differences. **It induces depolarization** of the neurons **without action potential firing** (It only changes the electrical state), this makes the patient more susceptible to seizures (It doesn't cause the seizures except at very high doses).
Lithium replaces sodium in conduction while being less efficient, which will cause overall **reduction of conductivity**, which is our goal as the patient feels manic (Fired) and we want to relax and stabilize that patient. (**Overall stabilization of the brain**).

Note: *We think that lithium has some serotonin activity, but this effect might be induced by stabilizing the brain as that increases serotonin activity too.*

Lithium Pharmacodynamics

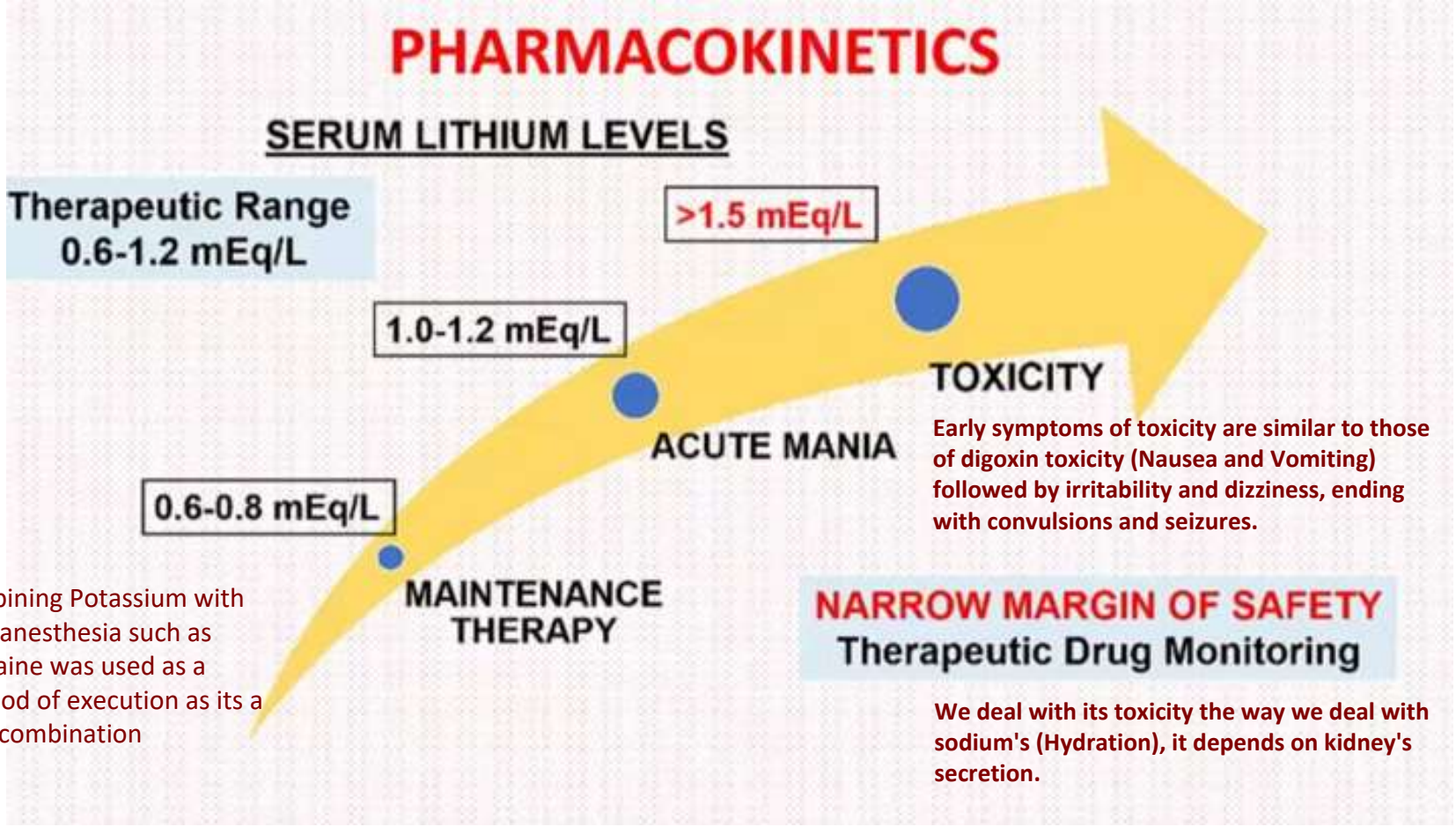
Inhibition of second messenger (**MOA**) Extra: Lithium has **multiple mechanisms of action** but this is one of many katzung talked about.

- 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

("All drugs are toxic materials and their toxicity is determined by the dose")As lithium is an electrolyte, its one of the narrow therapeutic index drugs **so we really have to monitor the dose!** We give lithium, check the lithium concentration in the blood of the patient and according to that we do titration! either increase/decrease. We only want **0.6-0.8 Milliequivalents Per Liter, a very small concentration as maintenance therapy**, in **acute mania 1.0-1.2mEQ/L** and anything **above 1.5mEQ/L is TOXIC!** (milliequivalents are close to and even slightly less than micrograms) (Some people will have different concentrations after administering the same dose and that will cause different response and toxicity, and that's why we stay on the safe side, give a dose, check the concentration and deal accordingly. **(Drug Titration)**



Combining Potassium with local anesthesia such as lidocaine was used as a method of execution as its a fatal combination

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, higher than 2 mEq/L can be serious or fatal
- Symptoms can be neurological, gastrointestinal, enlarged thyroid, rash, weight gain, memory difficulty, kidney disfunction, cardiovascular (Adverse effects and NOT RELATED TO TOXICITY)
- Not advised to take during pregnancy, affects fetal heart development
  Teratogenic, causes ebstein's anomaly and goiter

Lithium side effects

LEUCOCYTES INCREASED (LEUCOCYTOSIS)

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

This side effect has no value therapeutically

TREMORS (= FINE TREMORS)

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

Due to its sodium like activity on membrane potential without firing of action potential (Only support sodium's movement across the membrane)

HYPOTHYROIDISM (↓↓ THYROID FUNCTION)

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

Due to second messenger inhibition that's required for thyroid to function/some books say that this effect is produced by effecting T4 to T3 conversion. (Sometimes we give T3 with lithium.)

INCREASED URINATION (Polyuria & Polydipsia)

Diabetes insipidus

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

Decreased ADH activity in a MOA similar to that of Thyroid (Second messenger inhibtion)

Next slide = more info

EXPECTANT MOTHERS DURING PREGNANCY

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

Note from previous slide:

While we have **increased urination** (Water and sodium out) **we also have lithium retention** due to its re-absorption **as its similar to sodium**, as we said lithium is dangerous to accumulate, we deal with this **by inhibiting sodium re-absorption** (To reduce lithium's re-absorption) *This will be explained in the next system but; sodium re-absorption occurs mostly on proximal tubules, and Loop of Henle and to less degree on the* ***collecting ducts and distal tubules****, some diuretics (Potassium sparing diuretics) affect* ***the latter 2*** *to prevent the re-absorption that occurs there=* ***more excretion of*** *both sodium and* ***LITHIUM*** *(****Amiloride (collecting duct)****) (We work on the late steps of re-absorption to prevent kidney's compensation)*

(Lithium build up is treated by Potassium sparing diuretics ~ Amiloride / Spironolactone**)**

Note, we don't use spironolactone as it has many side effects such as gynecomastia and other endocrine-related effects.

If Lithium Doesn't Work

- 40% of Bipolars are resistant to lithium or side effects hinder its effectiveness
- Therefore, we must consider alternative agents for treatment
- We'll try to treat them with any CNS-Depressing agent we already talked about. All of the drugs in the upcoming slides are ones that we already know.
- 1) If lithium didn't improve the patient
  2) If lithium didn't give ENOUGH improvement
  3) We use these agents in "Bridging" as lithium takes 5-7 days until the onset of activity (reaching the therapeutic level) we bridge lithium on valproic acid or other anti psychotics).

As manic attacks are similar to convulsions, we can try anti-epileptic agents, **best** drug of those being the **valproic acid** (As it has **multiple mechanisms of action**) next to that, ***lamotrigine****, (equally effective) but as it causes steven johnson syndrome in 1/1000* we delay its use. Then carbamazepine, why not phenytoin? because it ONLY works on sodium stabilization (No multiple mechanisms of actions)

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**
- **Therapeutic blood levels: 50-100 Mg/L**
- **Side effects include GI upset, sedation, lethargy,tremor, metabolic liver changes and possible loss of hair**
- **Can also be used for anxiety, mood, and personality disorders**

Sedation is the **major side effect of antiepileptics except** lamotrigine

In manic treatment, the more mechanisms of action a drug has the better the effect, this was proved by using mono-activity drugs. (Other anti convulsants don't have the activity we need, they have no effect in treatment of manic)

Carbamazepine (Tegretol)

- Superior to lithium for rapid-cycling (Acute cycling) regarded as a second-line treatment for mania.

- Correlation between therapeutic and plasma levels (estimated between 5-10 Mg/L) (Monitoring is needed)
- Side effects may include GI upset, **sedation**, ataxia and cognitive effects

Lamotrigine

- Reported effective with Bipolar, Borderline Personality, Schizoaffective, Post-Traumatic Stress Disorders

- Inhibits neuronal excitability and modifies synaptic plasticity
- Side Effects may include dizziness (But not sedation), **TREMOR**, headache, nausea, and rash -Steven Johnson syndrome
- New studies say that this is the best drug with the least recurrence due to its effects on serotonin

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

Table FDA-approved treatments for bipolar disorder in adults

Generic name	Mania	Mixed	Depression	Maintenance
Arlpiprazole	X	X		X
Asenaplne forget about this	X	X		
Carbamazepine extended-release	X	X		
Chlorpromazine Typical anti-psychotic	X			
Lamotrigine				X
Lithium	X			X
Olanzapine Causes diabetes	X	X		X
Olanzapine/fluoxetine	Even tho we said don't give antidepressants as they increase glutamate causing excitement, and they have side effect of causing mania, but not if they're combined with other agents like Olanzapine		X	Olanzapine is a D2 blocker, preventing the excitatory effect of fluoxetine.
Quetiapine	X		X	5-HT2A/C blockers, serotonin activity -> depression dopamine blocking -> prevention of excitation
Risperidone	X	X		
Valproate	X			
Ziprasidone	X	X		

This whole table is not for memorization, just make sure you understand each drug and its effects

All of those can be used for **acute attacks of mania!** Except for **Lamotrigine** (Less activity) but its used for maintenance because it has a special feature that is improving depression and low relapse

After learning about all of these drugs, and how they have huge side effects lists and high recurrence rates, a take home message is that

-psychiatry is all about managing side effects, we need more great doctors just like you guys are to help improve this very important and rapidly growing section of public-wellbeing.

-Adherence is one of the major issues in this regard too

And medicine as an art lies here.

You'll figure it out, you always do