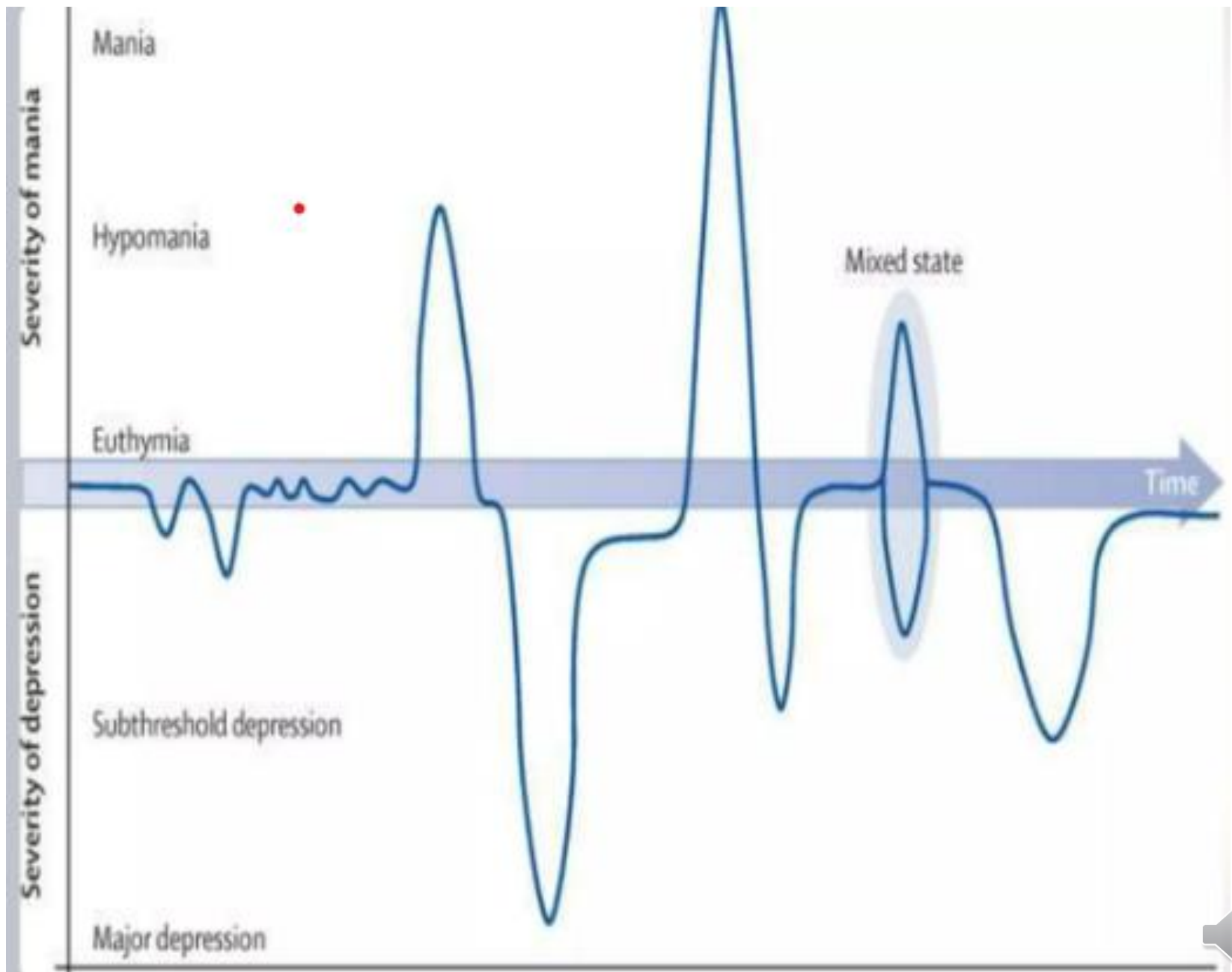


# Bipolar disorder





## Biochemical causes

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.



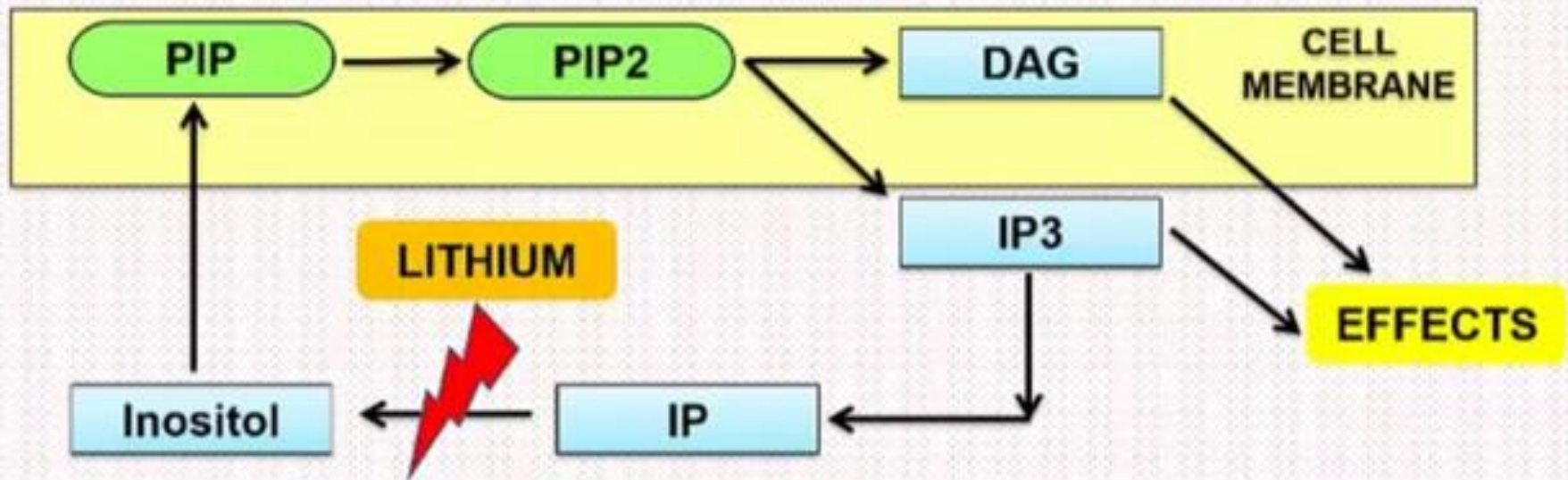
# Lithium Pharmacodynamics

- No psychotropic effect on non-Bipolars
- Affects nerve membranes, multiple receptor systems and intracellular 2<sup>nd</sup> messenger impulse transduction systems.
- 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 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**
- **Not advised to take during pregnancy, affects fetal heart development**



### **LEUCOCYTES INCREASED (LEUCOCYTOSIS)**

- ↑↑ leucocytes (12000-15000/mm<sup>3</sup>) 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<sup>+</sup>

### **EXPECTANT MOTHERS DURING PREGNANCY**

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





# 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



# 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



# 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

- 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



## 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		

