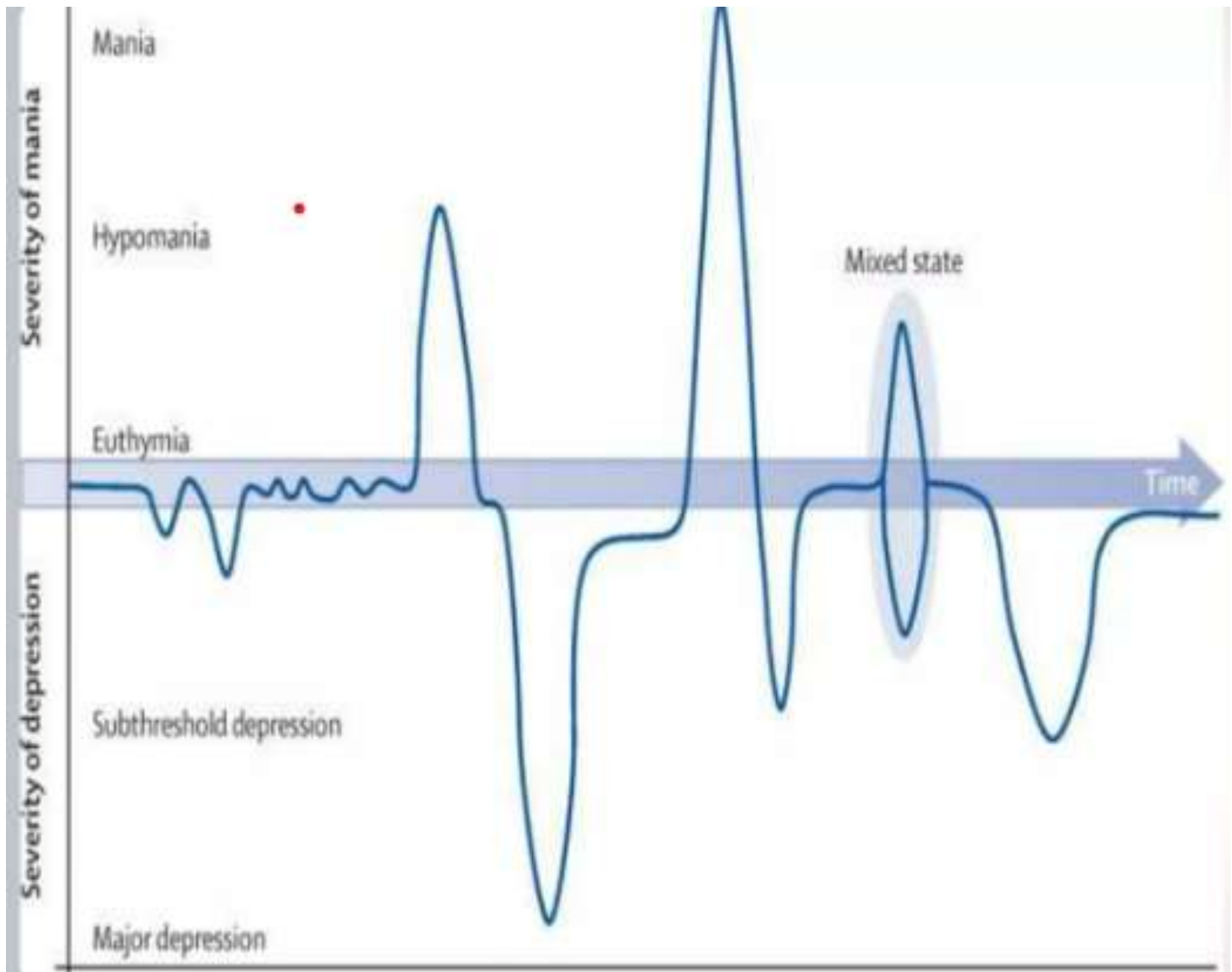


Bipolar disorder



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.

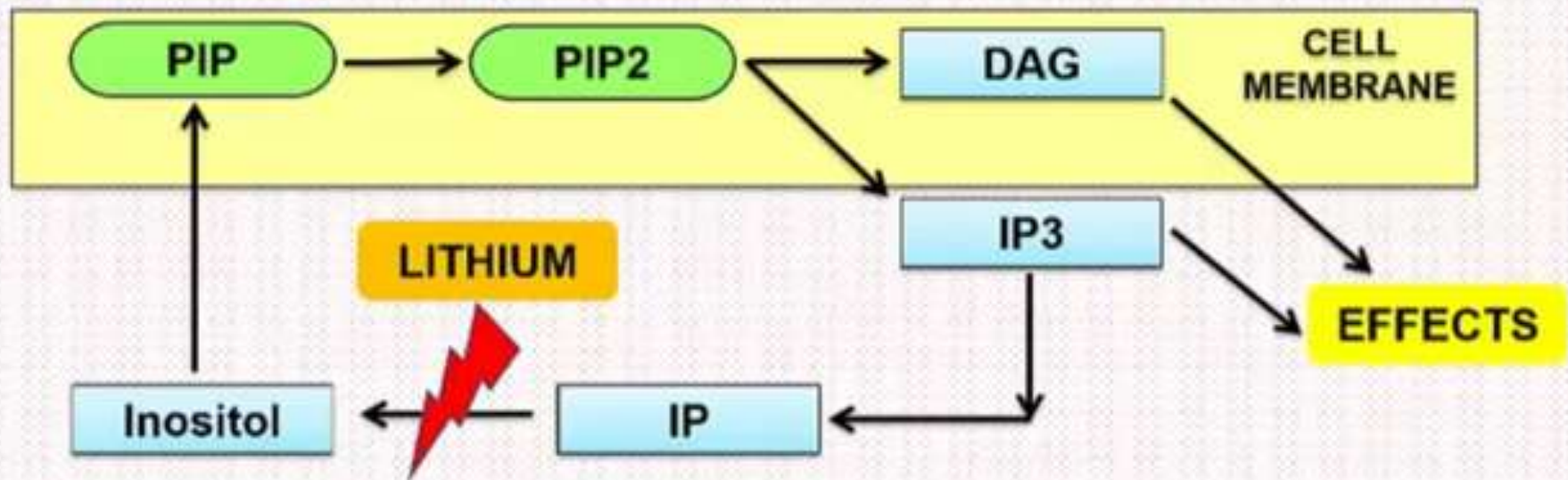
catecholamine hypothesis, which holds that an increase in epinephrine and norepinephrine causes mania and a decrease in epinephrine and norepinephrine causes depression.

Lithium Pharmacodynamics

- No psychotropic effect on non-Bipolars
- Affects nerve membranes, multiple receptor systems and intracellular 2nd messenger impulse transduction systems.
- 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 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

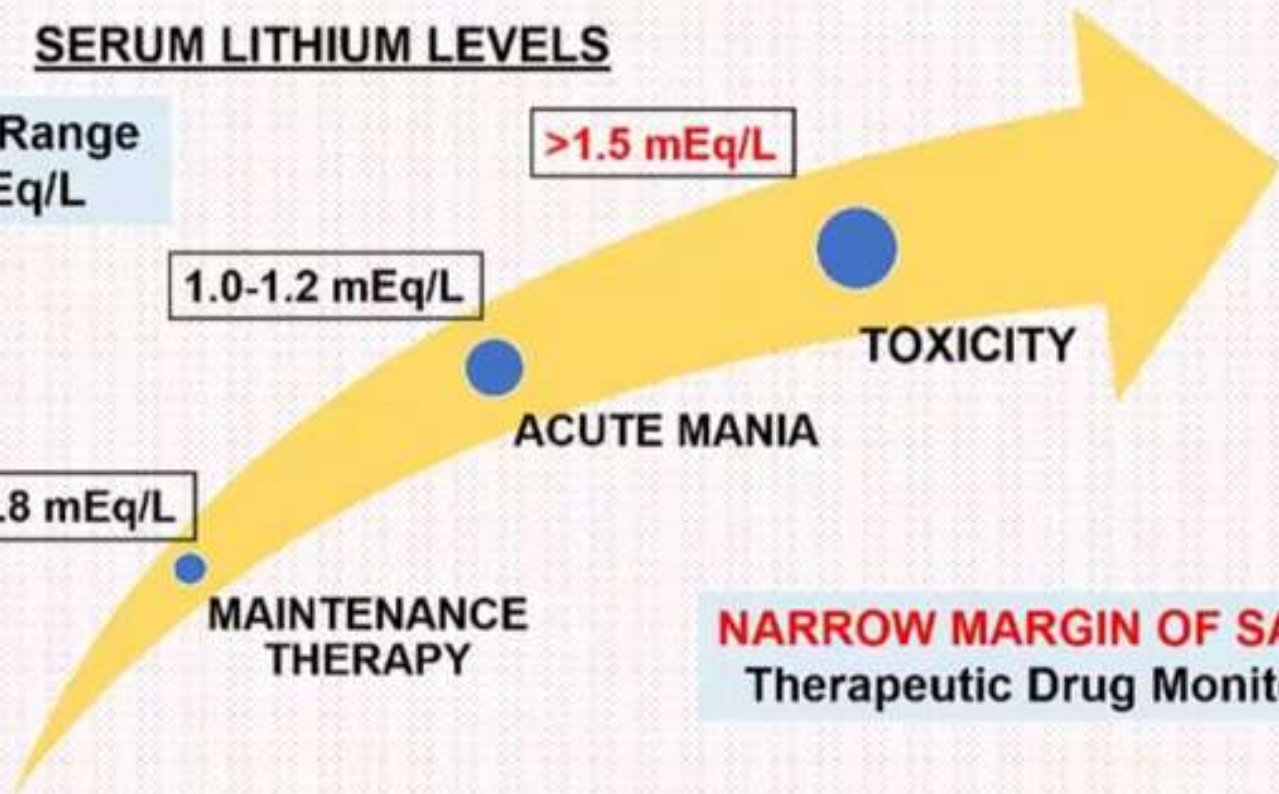
0.6-0.8 mEq/L

TOXICITY

ACUTE MANIA

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 dysfunction, cardiovascular**
- **Not advised to take during pregnancy, affects fetal heart development**

LEUCOCYTES INCREASED (LEUCOCYTOSIS)

- ↑↑ leucocytes (12000-15000/mm³) 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

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		