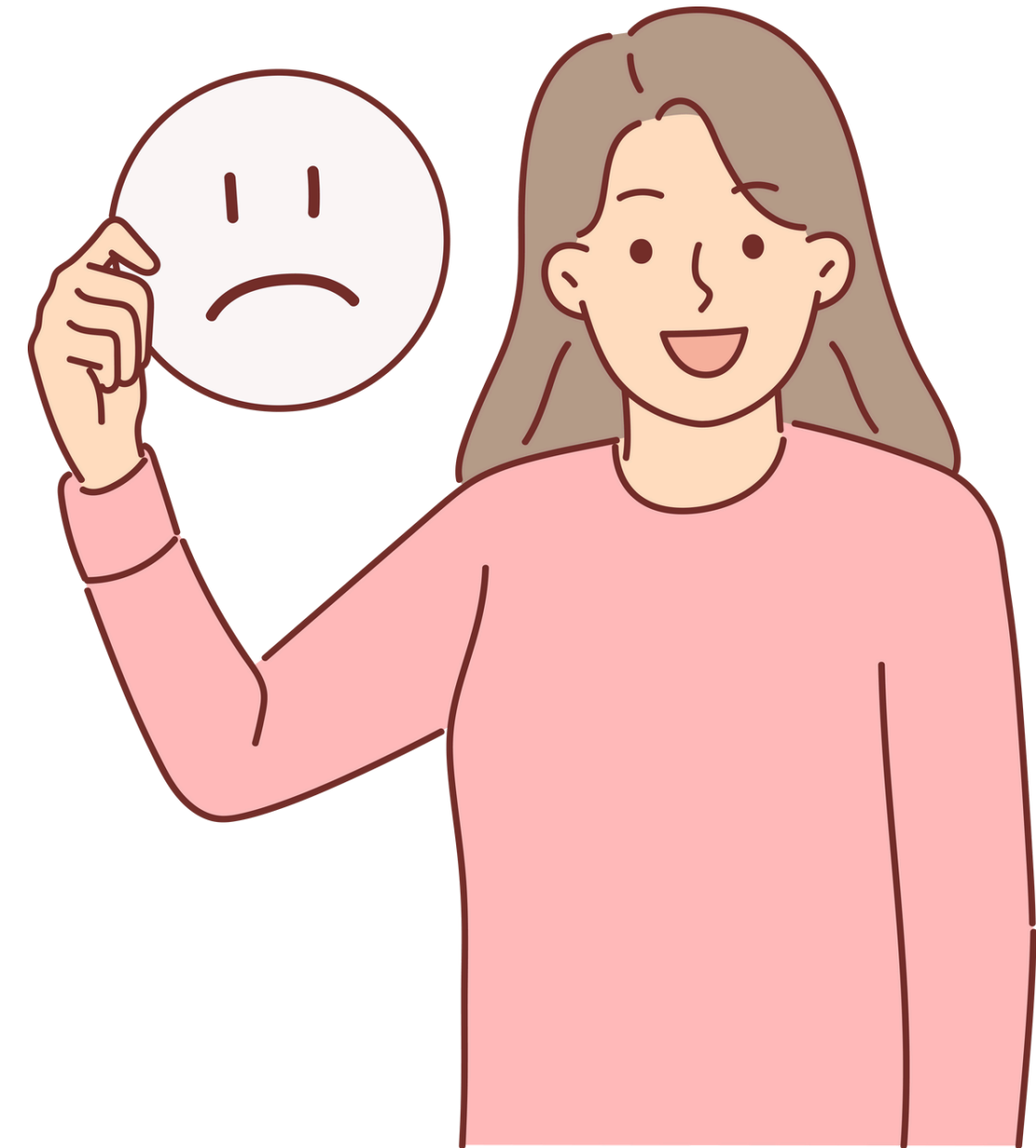


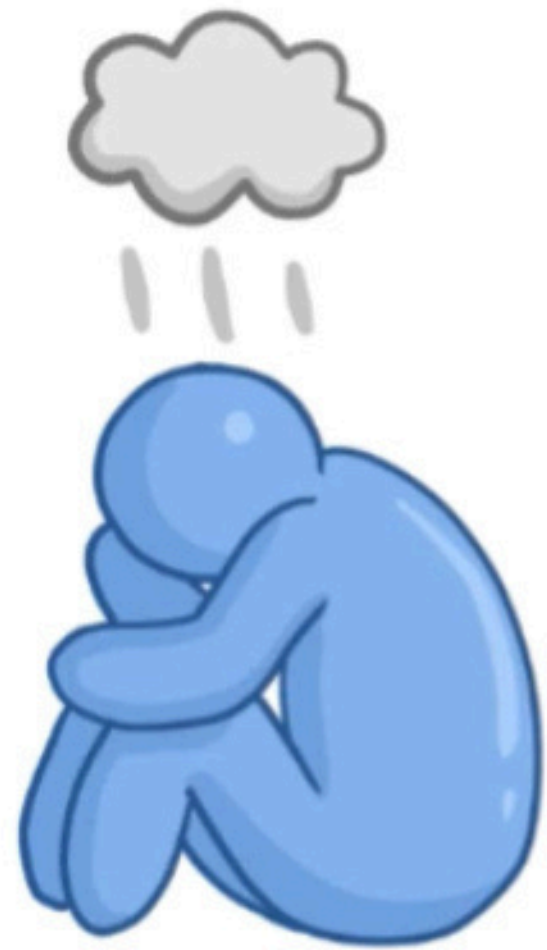
# MOOD STABILIZERS

اللهم علمنا ما ينفعنا وانفعنا بما علمتنا وزدنا علماً  
لتنفع بنا الأمة وتكف بنا الغربة .

Ghina hlaiel

Hala mahasneh





**DEPRESSION**  
(EXTREME  
SADNESS)

# MOOD DISORDERS



SPECTRUM



**MANIA**  
(EXCESSIVE  
EXCITEMENT)

# Mood Stabilizers

1. Mood stabilizers are used to treat **acute mania** (acute treatment) & to **help prevent relapses** of manic episodes (maintenance treatment) in bipolar disorder & schizoaffective disorder .
2. Less commonly, they may be used for:
  - Augmentation of antidepressants in patients with major depression refractory to monotherapy
  - Potentiation of antipsychotics in patients with schizophrenia or schizoaffective disorder
  - Treatment of aggression and impulsivity (e.g., neurocognitive disorders, intellectual disability, personality disorders, other medical conditions)
  - Enhancement of abstinence in treatment of alcoholism

# Acute mania

- Atypical antipsychotics:  
Olanzapine, risperidone, quetiapine,  
ziprasidone, aripiprazole.
- Typical:  
haldol, chlopromazine
- Mood stabilizers:  
Lithium, valproate, carbamazepine

## Maintenance

# ~~Acute mania~~

- Lithium (gold standard)
- Valproate
- Carbamazepine
- Lamotrigine

# Mood Stabilizers include :

## 1. lithium

- the first-line mood stabilizer .
- narrow therapeutic index (warning for toxicity)
- bad S.Es

## 2. anticonvulsants

most commonly

- valproic acid,
- lamotrigine,
- and carbamazepine.

## 3. Antipsychotics

- olanzapine

# Lithium

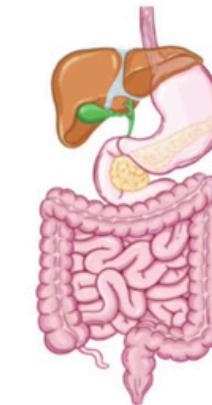
- drug of choice in acute mania
- Antimanic agent
- Inhibition of norepinephrine and dopamine release in the brain
- Increase of serotonin production in the brain
- Alteration of  $\text{Na}^+$ /  $\text{K}^+$  ion transport (brain, muscle cells)
- metabolized by the kidney
- Onset of action takes 5-7 days.

## LITHIUM

TAKEN ORALLY



RAPIDLY ABSORBED  
by GI TRACT



TRAVELS to BRAIN

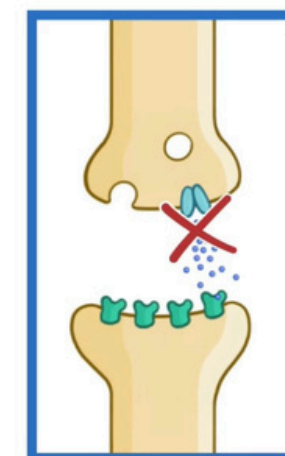


\* REGULATES RELEASE  
of NEUROTRANSMITTERS

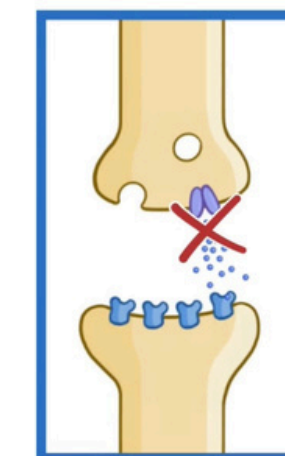
## LITHIUM

\* INHIBIT RELEASE

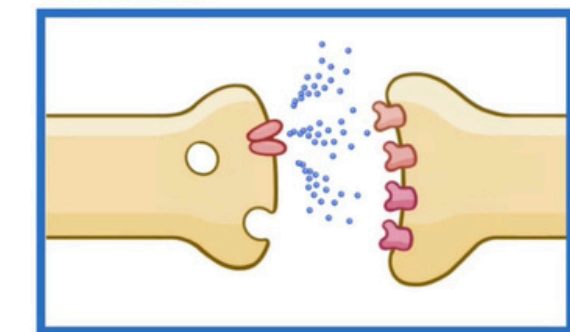
NOREPINEPHRINE



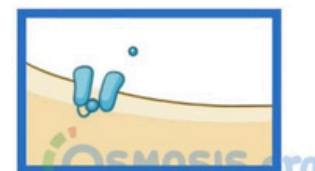
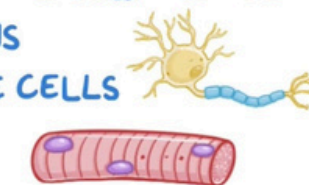
DOPAMINE



\* ↑↑ PRODUCTION  
SEROTONIN



\* ALTERS  $\text{Na}^+$ - $\text{K}^+$  ION TRANSPORT  
NEURONS  
MUSCLE CELLS






# Indications

- in acute mania
- and as prophylaxis for both manic and depressive episodes in bipolar and schizoaffective disorders.
- It is also used in cyclothymic disorder and unipolar depression.



# Contraindications

- Pregnancy (teratogenic in 1st trimester)  
"Ebstein's anomaly", breastfeeding
  - Children < 12 years
  - Cardiac / renal / hepatic impairment
  - brain trauma, brain organ syndrome
  - NSAIDs, ACE inhibitors, diuretics  
(decrease secretion)
  - Dehydration, hyponatremia
  - Thyroid disease
- 

# Side effects

Most common lithium SEFs are **GI distress** including reduced appetite, nausea/vomiting, diarrhea

## • **NARROW THERAPEUTIC INDEX**

### Early:

- Nausea, vomiting, diarrhea, weight gain, metallic taste
- Polyurea, polydypsia (nephrogenic diabetes insipidus)
- Fine Tremor, muscle weakness, edema
- Worsening of psoriasis
- Acne
- Hair loss

### Late:

- Hypothyroidism, Goitre
- Memory impairment
- Nephro toxicity
- ECG changes : T wave flattening
- Arrhythmia
- Lithium can cause Ebstein's anomaly (20 times)



# Side effects

## MOST IMPORTANT SIDE EFFECTS

\* THIRST



\* LETHARGY



\* SLURRED SPEECH

\* MUSCLE WEAKNESS

\* SEIZURES

\* HYPERREFLEXIA

\* ATAXIA

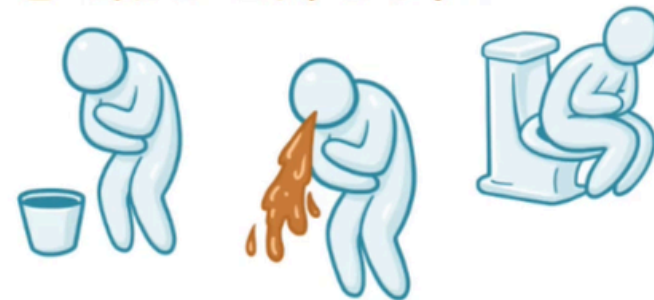


\* GASTROINTESTINAL SIDE EFFECTS

└ NAUSEA

└ VOMITING

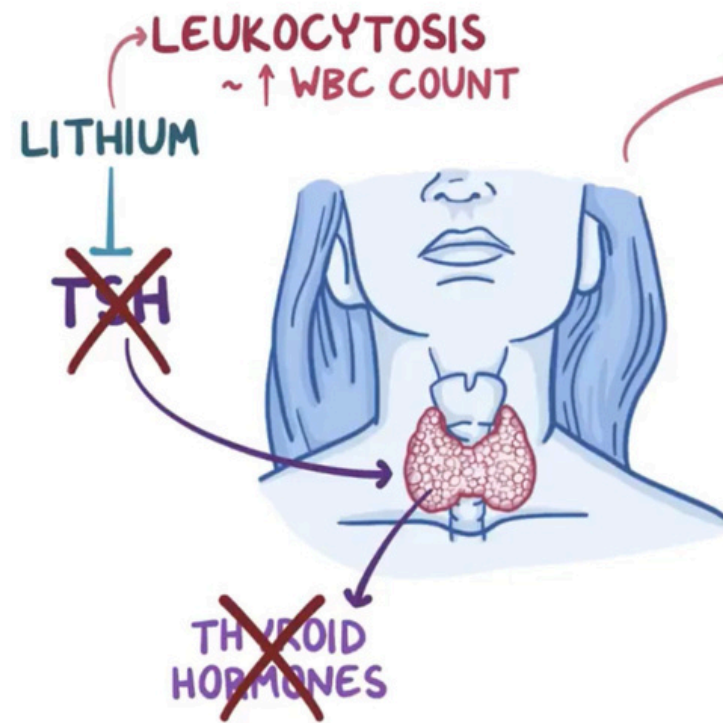
└ DIARRHEA



Toxic levels of lithium cause altered mental state, coma, delirium, coarse tremors, convulsions and death

# Side effects

## SIDE EFFECTS



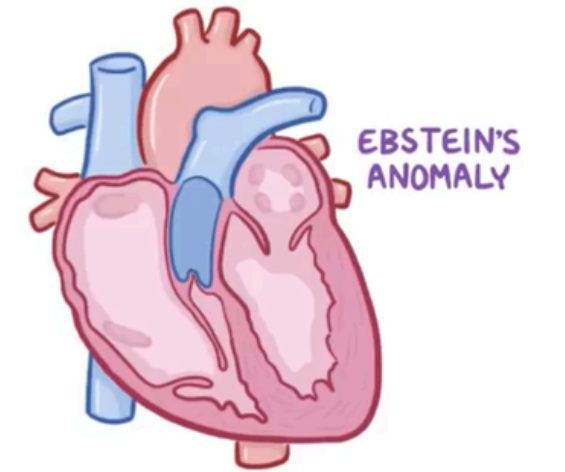
- HYPOTHYROIDISM**
- ~ WEIGHT GAIN
  - ~ COLD SENSITIVITY
  - ~ SLOWER HEART RATE
  - ~ MENTAL SLOWNESS
  - ~ CONSTIPATION
  - ↳ REACTIVE HYPERTROPHY & HYPERPLASIA



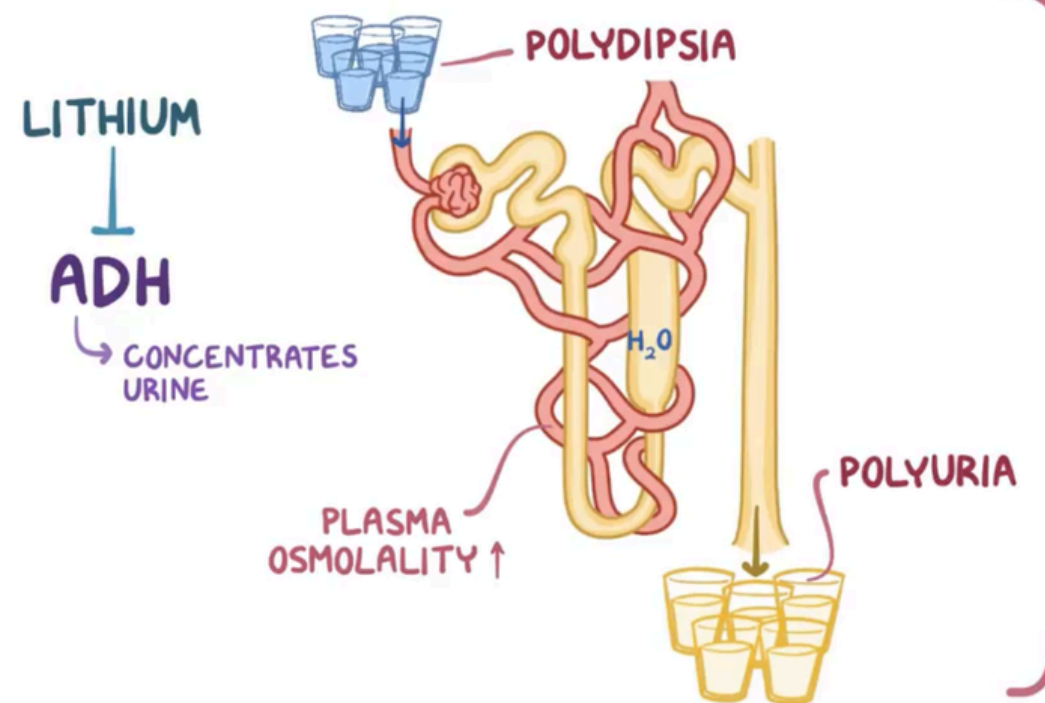
- \* NOT SAFE for PREGNANCY**
- ↳ ↑ RISK of CONGENITAL HEART DEFECTS



- \* if LEVELS ↑ to TOXIC LEVELS**
- ↳ ACUTE RENAL FAILURE
  - ↳ SEVERE NEUROLOGICAL SYMPTOMS
  - ~ ATAXIA
  - ~ CONFUSION
  - ~ DYSARTHRIA
  - ~ COMA
  - ~ DEATH



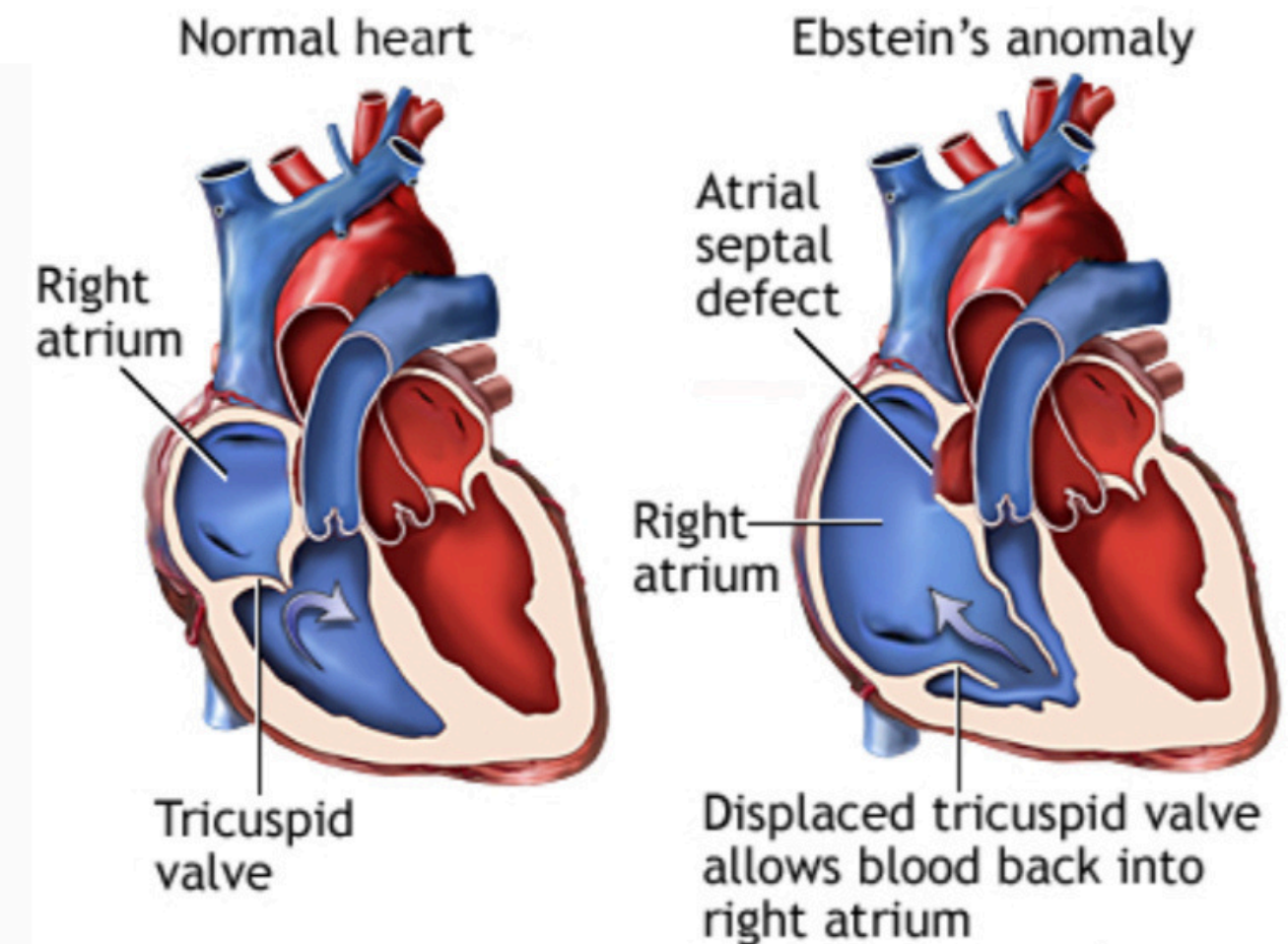
## SIDE EFFECTS



NEPHROGENIC DIABETES INSIPIDUS

# Just to remember

- **L**- leucocytes
  - **I** – Increased
  - **T** – Tremors
  - **H**- Hypothyroidism
  - **I**- Increased
  - **U**- Urine
  - **M**- should be avoided in expectant **MOTHER** as it causes Ebstein's anomaly
- Diabetes Insipidus



# Serotonin syndrome

## LIFE-THREATENING EFFECT of LITHIUM

↳ COMBINED w/ CERTAIN ANTIDEPRESSANT MEDICATIONS

### SEROTONIN SYNDROME

↳ ↑↑ SEROTONIN in BRAIN

- \* SKIN FLUSHING
- \* HYPERTHERMIA
- \* AGITATION
- \* MUSCLE RIGIDITY
- \* SEIZURES
- \* ALTERED MENTAL STATUS
- \* COMA



# toxicity

mild	plasma levels 1.5-2 mEq/L	<ol style="list-style-type: none"> <li>1. anorexia</li> <li>2. vomiting</li> <li>3. diarrhoea</li> <li>4. coarse tremor</li> <li>5. ataxia</li> <li>6. Dysarthria تلعثم</li> <li>7. confusion</li> <li>8. Sleepiness</li> </ol>
moderate	2-2.5  CNS	<ol style="list-style-type: none"> <li>1. impaired consciousness</li> <li>2. neurological signs:</li> <li>3. nystagmus</li> <li>4. muscle twitching</li> <li>5. hyperreflexia</li> <li>6. convulsions</li> </ol>
Severe overdosage	>2.5	<ol style="list-style-type: none"> <li>1. toxic psychosis</li> <li>2. convulsions</li> <li>3. syncope</li> <li>4. oliguria</li> <li>5. circulatory failure</li> <li>6. coma and death</li> </ol>

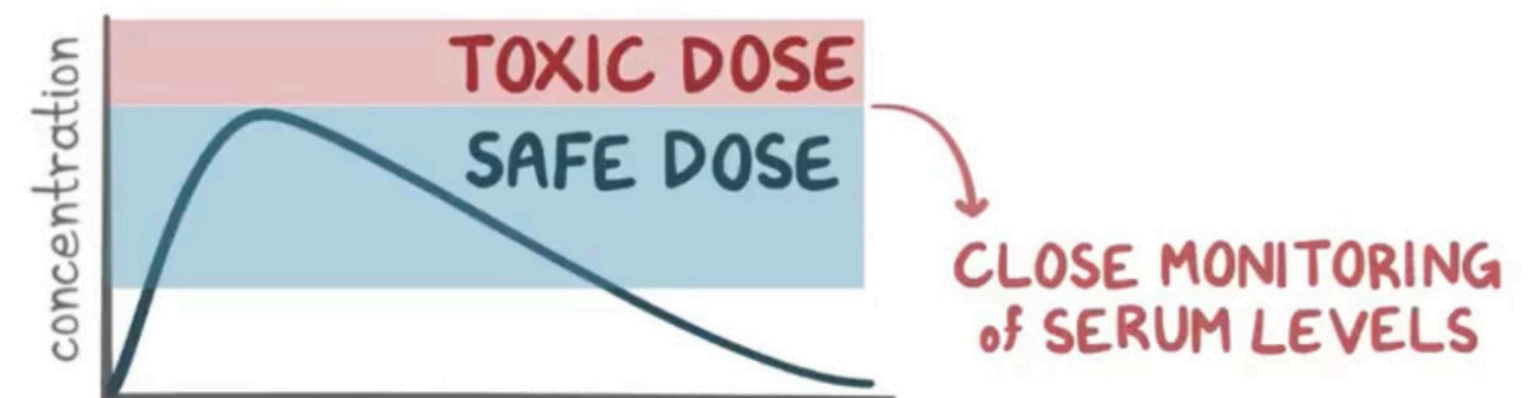
- Tremor is the most common symptoms of lithium toxicity  
ttt : propranol.

- 0.6-1.2 normal blood concentration

- Toxic: >1.5

- Potentially lethal: >2.0

## \* NARROW THERAPEUTIC WINDOW



## Management to lithium toxicity

- stop Lithium
- Hydration
- Lithium level, serum electrolytes, renal function, ECG should be obtained as soon as possible
- **Lithium level >4 -> Immediate dialysis**

## Lithium Drug Monitoring

- Blood samples taken 12 hours post dose
- Sample should be taken after 5-7 days of treatment initiation
- Therapeutic window :of **0.6 - 1.2**

**Aim for 0.8 - 1.0 during manic phase;**

**0.4 - 0.8 during maintenance phase**



## Factors that increase Li<sup>+</sup> levels:

NSAIDs

Aspirin (+/-)

Thiazide diuretics

Dehydration

Salt deprivation

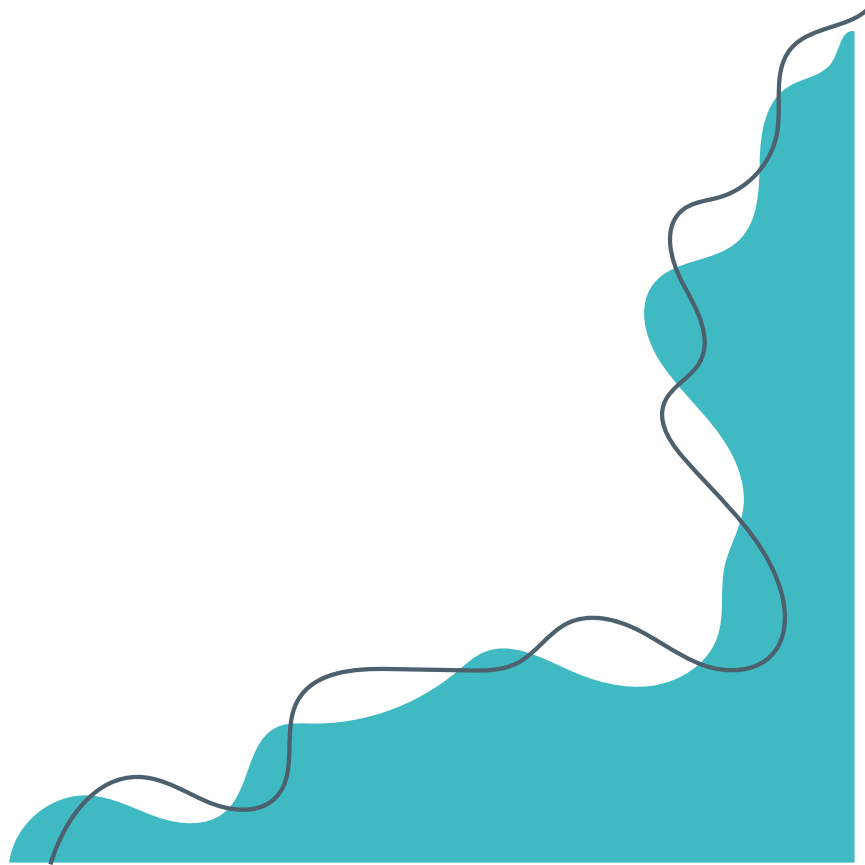
Sweating (salt loss)

Impaired renal function





Prior to initiating, patients should have :

- an ECG,
  - basic chemistries,
  - thyroid function tests,
  - a complete blood count (CBC),
  - and a pregnancy test.
- 



# anticonvulsants

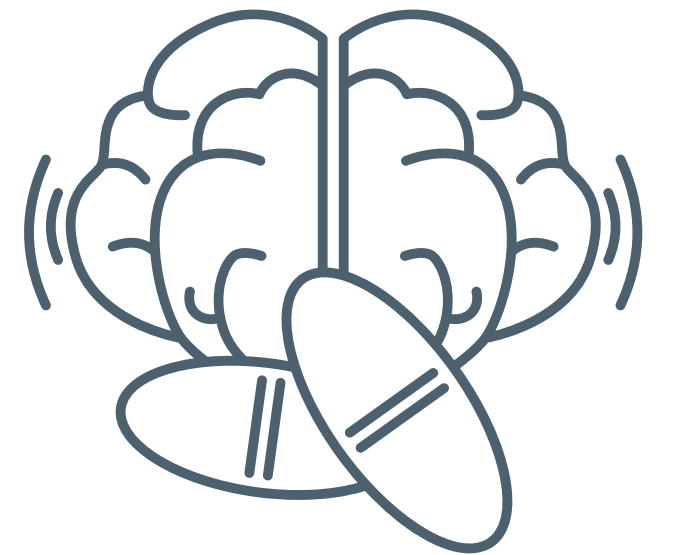
Enhance *GABA*  
inhibition

Block excitatory  
transmitters

Block neuronal Na  
channel

Block t-type ca  
channel

Mixed or unknown



# a. Valporic Acid

## Mechanism

Multiple mechanisms of action:

- blocks sodium channels
- and increases GABA concentrations in the brain.

- Valproic acid better tolerated than Lithium.

## Therapeutic uses

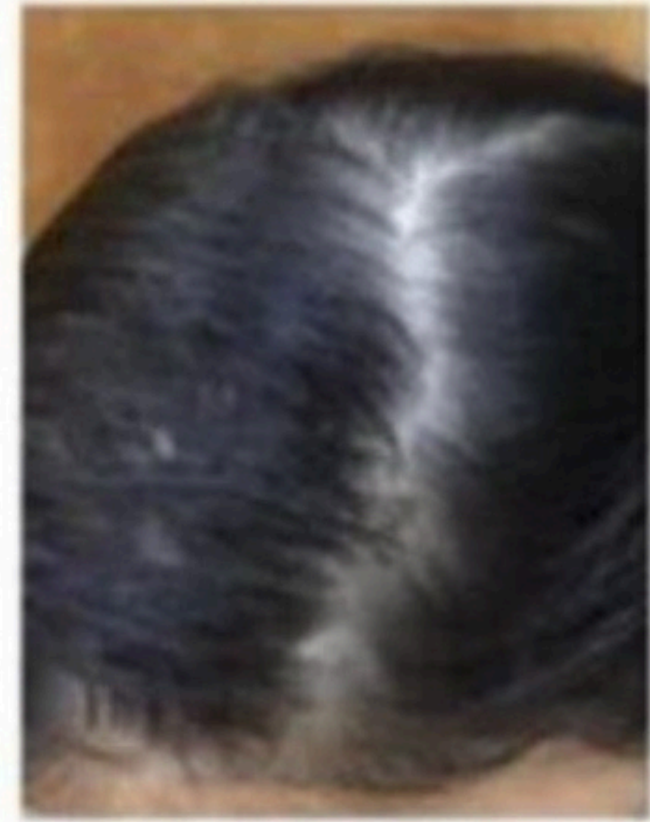
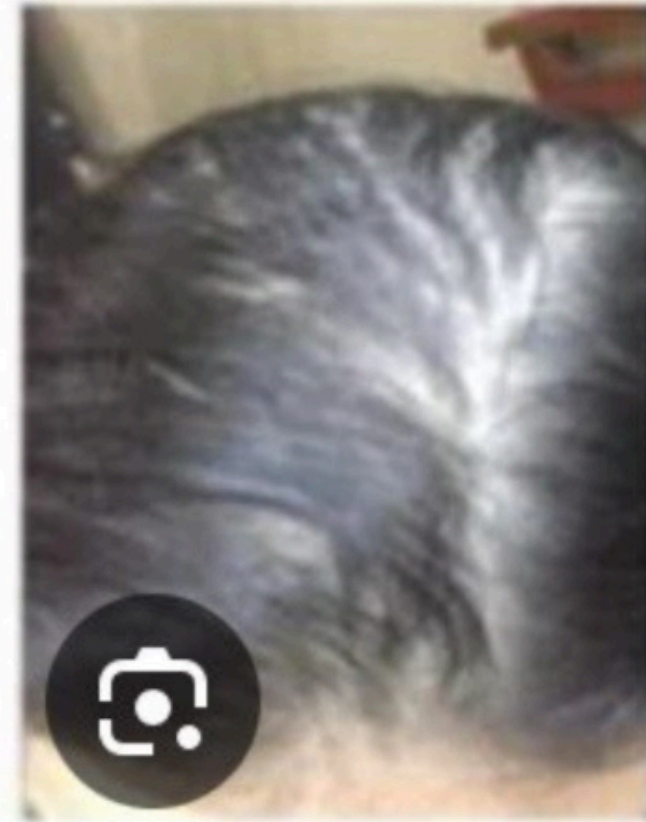
- acute mania, mania with mixed features, and rapid cycling.
- All seizures types

## Addverse effect

- CNS : NDA ( nystagmus , diplopia , ataxia )
- Liver : **Microsomal enzyme inhibition**
- Blood : neutropenia
- Teratogenic : craniofacial anomalies and neural tube deficit
- Alopecia
- Pancreatitis
- Fulminant hepatic toxicity
  - weight gain

# Hemorrhagic Pancreatitis

Gross pathology of acute hemorrhagic pancreatitis. Hemorrhagic fat necrosis and a pseudocyst filled with blood are seen on cross section.



Formulation of Sodium Valproate...

# b. Carbamazepine

## Mechanism

- Acts by blocking sodium channels and inhibiting action potentials.

## Therapeutic uses

- mania with mixed features and rapid cycling
- bipolar disorder

## Adverse effects

1. CNS : NDA ( nystagmus , diplopia , ataxia )
2. Liver : Microsomal enzyme induction
3. Blood : Leukopenia, aplastic anemia, thrombocytopenia, and Agranulocytosis
4. Teratogenic : craniofacial anomalies cleft palate ) and neural tube deficit
5. Increase ADH secretion >> hyponatremia and edema
6. Significant drug interactions with many medications metabolized by the cytochrome P450 pathway
7. Toxicity: Confusion, stupor, motor restlessness, tremor, twitching, and vomiting.

# C. lamotrigine

## Mechanism

- work on sodium channels that modulate glutamate and aspartate.

## Therapeutic uses

- Efficacy for **bipolar depression**,
- little efficacy for acute mania or prevention of mania.

## Adverse effects

- dizziness, sedation, headaches, and ataxia.
- Most serious side effect is Stevens Johnson syndrome (life-threatening rash involving skin and mucous membranes) in 0.1%. This is most likely in the first 2 to 8 weeks, but is minimized by starting with low doses and increasing slowly.
- Valproate will ↑ lamotrigine levels, and lamotrigine will ↓ valproate levels.

# Stevens- Johnson syndrome

(life-threatening rash involving skin and mucous membranes) in 0.1%. This is most likely in the first 2-8 weeks, but is minimized by starting with low doses and increasing slowly.



## Other anticonvulsants

### 1-Oxcarbazepine (Trileptal)

- As effective in mood disorders as carbamazepine, but better tolerated
- Less risk of rash and hepatic toxicity
- Monitor sodium levels for hyponatremia

### 2-Gabapentin (Neurontin)

- Often used adjunctively to help with anxiety, sleep, neuropathic pain
- Little efficacy in bipolar disorder

### 3-Pregabalin (Lyrica)

- Used in GAD (second-line) and fibromyalgia
- Little efficacy in bipolar disorder


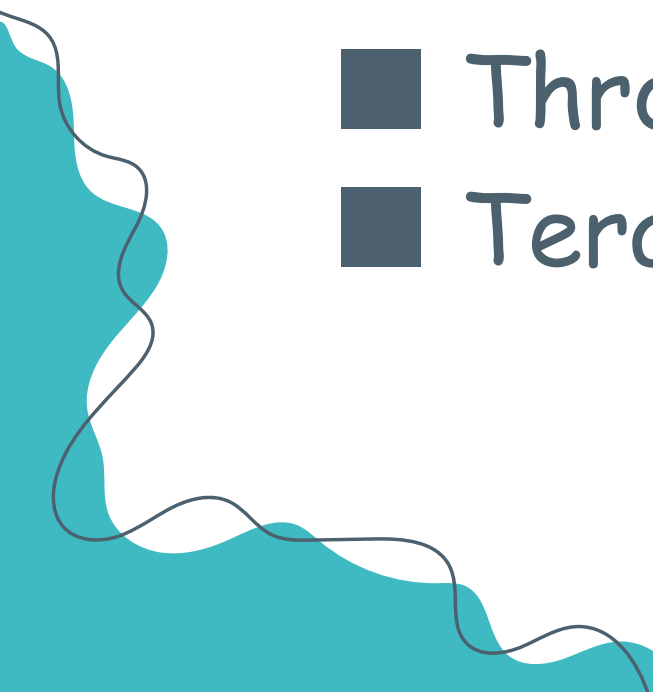
### 4-Tiagabine (Gabitril): Questionable benefit in treating anxiety

### 5-Topiramate (Topamax)

- May be helpful with impulse control disorders
- Beneficial side effect is **weight loss**
- Can cause hypochloremic, metabolic acidosis, as well as kidney stones
- The most limiting side effect is **cognitive slowing**




# Side Effects

- GI symptoms
  - Weight gain
  - Sedation
  - Alopecia
  - Pancreatitis
  - Hepatotoxicity or benign aminotransferase elevations
  - ↑ ammonia
  - Thrombocytopenia
  - Teratogenic effects during pregnancy (neural tube defects)
- 
- 





# Guidelines

- Start antiepileptic drugs ( AEDS ) following a second epileptic seizure .
  - Therapy should be started with ONE drug ( monotherapy ) : → if failed , SUBSTITUTE with another drug . if failed , use combination of 2 drugs .
  - Combination of valproic acid + lamotrigine → Stevens - Johnson's syndrome
  - Stopping of AEDS can be considered if seizure free for > 2 years , with AEDs being stopped over 2- 3 month
- 

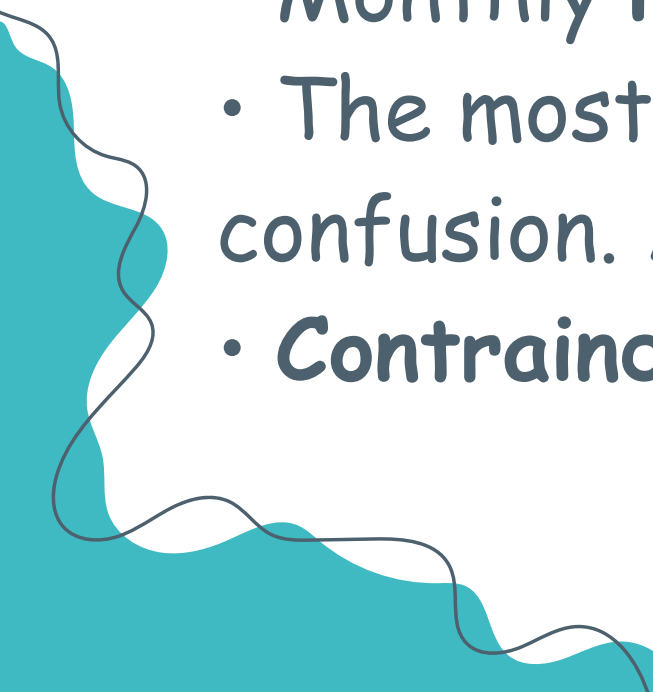
# AEDS and pregnancy

- Around 1-2 % of newborns born to non - epileptic mothers have congenital defects .  
This rises to 3-4 % if the mother takes antiepileptic medication .
- The risks of **uncontrolled epilepsy during pregnancy** generally outweigh the risks of medication to the fetus , so her drug should be continued .
- Pregnant should be advised to take **folic acid 5 mg / day** well before pregnancy to minimize the risk of neural tube defects .
- Best drugs in pregnancy : **lamotrigine - levetiracetam**
- **Breast feeding** is acceptable with nearly ALL anti - epileptic drugs



# ELECTROCONVULSIVE THERAPY (ECT)



- ECT is the **most effective** treatment for major depressive disorder
  - A **generalized tonic-clonic seizure** is then induced using **unilateral or bilateral electrodes**
  - It is often used in patients who **cannot tolerate** medications or who have failed other treatments
  - premedicated with **atropine**, and then given general anesthesia and muscle relaxants.
  - typically a course of **8-12 sessions** given three times weekly.
  - **Monthly maintenance ECT** is often used to **prevent relapse of symptoms**.
  - The most common side effects are muscle soreness, headaches, amnesia, seizure and confusion. And heart problems in long term but its rare .
  - **Contraindicated** if there is space occupying intracranial lesion ( increase icp)
- 

**TABLE 3. PSYCHIATRIC USES OF ANTIPILEPTIC DRUGS**

Carbamazepine	Agitation, bipolar disorder, impulsivity
Clonazepam	Anxiety
Diazepam	Alcohol withdrawal, anxiety
Gabapentin	Anxiety
Lamotrigine	Bipolar disorder, refractory depression
Lorazepam	Agitation, alcohol withdrawal, anxiety
Oxcarbazepine	Aggression, bipolar disorder, impulsivity
Pregabalin	Anxiety
Topiramate	Alcohol withdrawal, binge eating
Valproic acid	Bipolar disorder



Mood stabilizer	Lithium	Valproic acid	Carbamazepine
Main use	First medical therapy for bipolar disorders	as Lithium in mania prophylaxis	1 <sup>st</sup> line for acute mania & mania prophylaxis
Note	Only medication to reduce suicide rate	not as lithium effective in depression prophylaxis	Indicated for rapid cyclers and mixed patients
SEFs	<b>Tremor, Confusion, Seizure , Nausea, vomiting , diarrhea, Hypothyroidism</b> Hyperparathyroidism hypercalcemia Polyuria & polydipsia bradycardia Mild leukocytosis	Thrombocytopenia Nausea, vomiting, weight gain, Transaminitis, Sedation, tremor, hair loss and Increased risk of neural tube defect	<b>Rash, Nausea, vomiting, diarrhea, transaminitis</b> ,Sedation, dizziness, ataxia, confusion ,AV conduction delays ,Aplastic anemia ,agranulocytosis Water retention
Before use it	baseline creatinine, TSH, CBC and pregnancy test	LFTs, CBC and pregnancy test	LFTs, CBC and EKG
Steady state achieved after	5 days	4-5 days	5 days
Target	blood level between 0.6-1.2	between 50-125	4-12mcg/ml



**THANK YOU**



