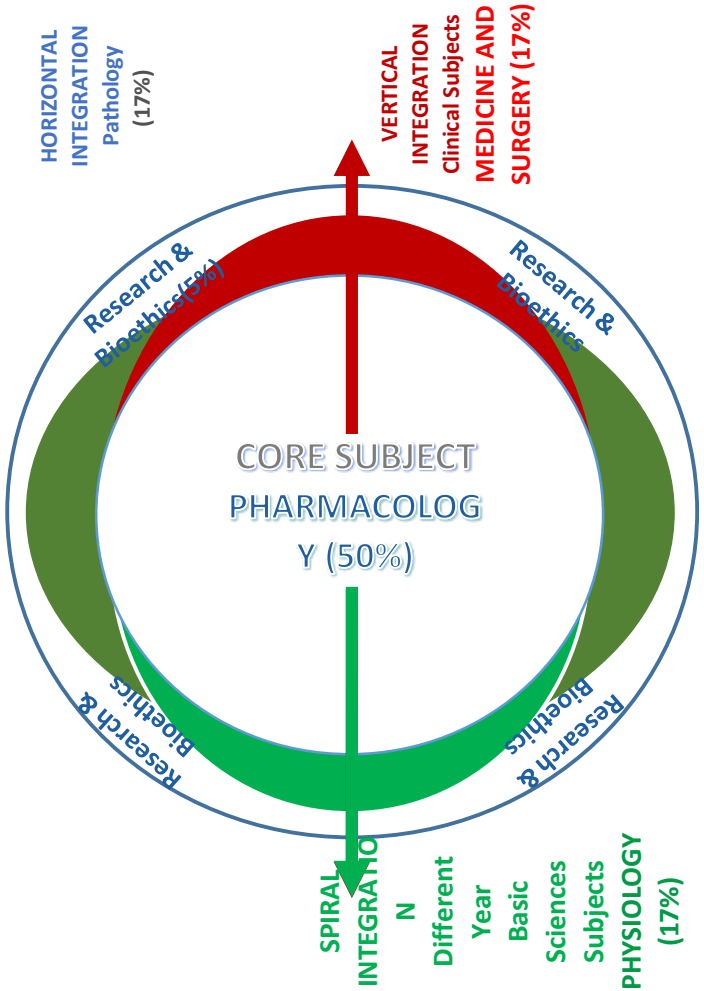

بسم الله الرحمن الرحيم

MOTTO AND VISION

- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

Prof. Umar's Clinically Oriented Integration Model
For Basic Sciences Interactive Lectures



Model 4th Year Pharmacology LGIS (18 slides)	
Core Subject –9 slides(50%)	
Horizontal Integration pathology 2 slides–(11%)	
Vertical integration (Clinical Subjects)	• (Medicine and surgery) –3 slides 17%
Spiral Integration (physiology)–(3 slides) 17%	
Research & Bioethics 1 slide(5%)	

MOOD STABILIZERS

4TH YEAR MBBS

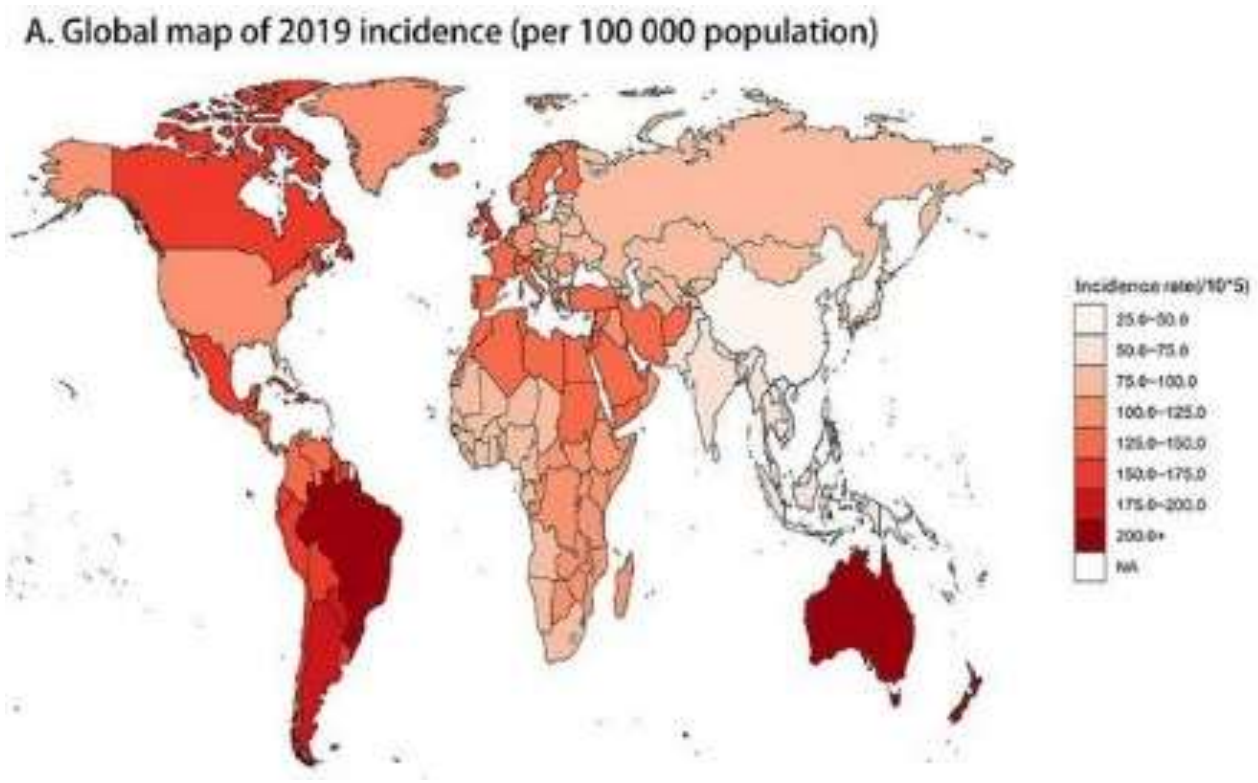
LGIS

INTRODUCTION

- Bipolar disorder is the a set of symptoms usually manic phase alternating with major depressive phase. (The sequence, number, and intensity of manic and depressive episodes are highly variable.)
- Mixed manic and depressive symptoms are also seen.
- Patients with bipolar disorder are at high risk for suicide.

EPIDEMIOLOGY

- Bipolar affective (manic-depressive) disorder occurs in 1–3% of the adult population.
- It may begin in childhood, but most cases are first diagnosed in the third and fourth decades of life.

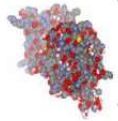


PATHOGENESIS OF BIPOLAR DISORDER

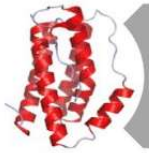
- Familial predisposition (genetically determined)
- Drugs that increase catecholamine activity tend to exacerbate mania and those that reduce activity of dopamine or norepinephrine relieve mania.
- Acetylcholine or glutamate may also be involved.
- Risk factors : inflammation, oxidative stress, neurotropic factors

Genetic Factors

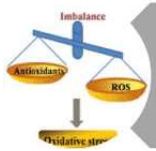
Neurotransmitter Changes



Neurotrophic Factors: ↓ BDNF



Inflammation: ↑ Cytokines



Oxidative stress: ↑ Free radicals, ↓ antioxidant defenses

MOOD STABILIZING DRUGS, & OTHER TREATMENT FOR BIPOLAR DISORDER

- LITHIUM
- ANTI PSYCHOTICS
  - Aripiprazole
  - Chlorpromazine
  - Olanzapine
  - Quetiapine
  - Risperidone
  - Ziprasidone
- ANTICONVULSANTS
  - Valproic acid
  - Carbamazepine
- OTHERS (not approved for treatment of bipolar disorder by food and drug administration)
  - Gabapentin
  - Oxcarbazepine
  - Topiramate
  - Lamotrigine (prevents recurrence)

LITHIUM

A Monovalent Cation

PHARMACOKINETICS OF LITHIUM

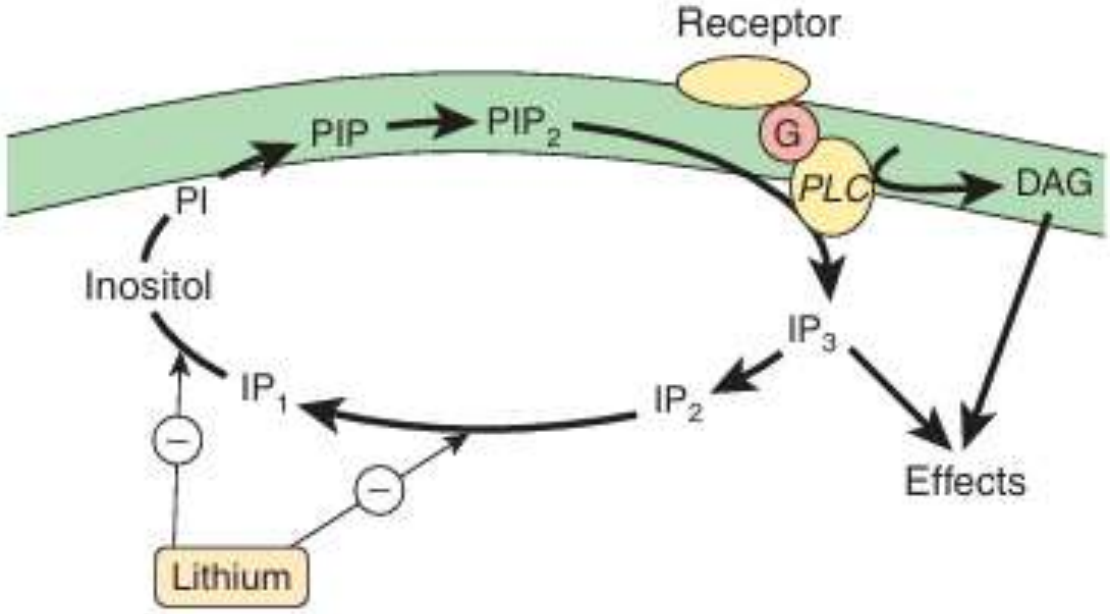
(MONOVALANT CATION)

TABLE 29–5 Pharmacokinetics of lithium.

Absorption	Virtually complete within 6–8 hours; peak plasma levels in 30 minutes to 2 hours
Distribution	In total body water; slow entry into intracellular compartment. Initial volume of distribution is 0.5 L/kg, rising to 0.7–0.9 L/kg; some sequestration in bone. No protein binding.
Metabolism	None
Excretion	Virtually entirely in urine. Lithium clearance about 20% of creatinine. Plasma half-life about 20 hours.
Target plasma concentration	0.6–1.4 mEq/L
Dosage	0.5 mEq/kg/d in divided doses

MECHANISM OF ACTION OF LITHIUM

- The schematic diagram shows the synaptic membrane of a neuron.
- Lithium, by inhibiting the recycling of inositol substrates, may cause depletion of the second-messenger source PIP 2 and therefore reduce the release of IP 3 and DAG.
- Lithium may also act by other mechanisms.



PHARMACOLOGICAL EFFECTS OF Li

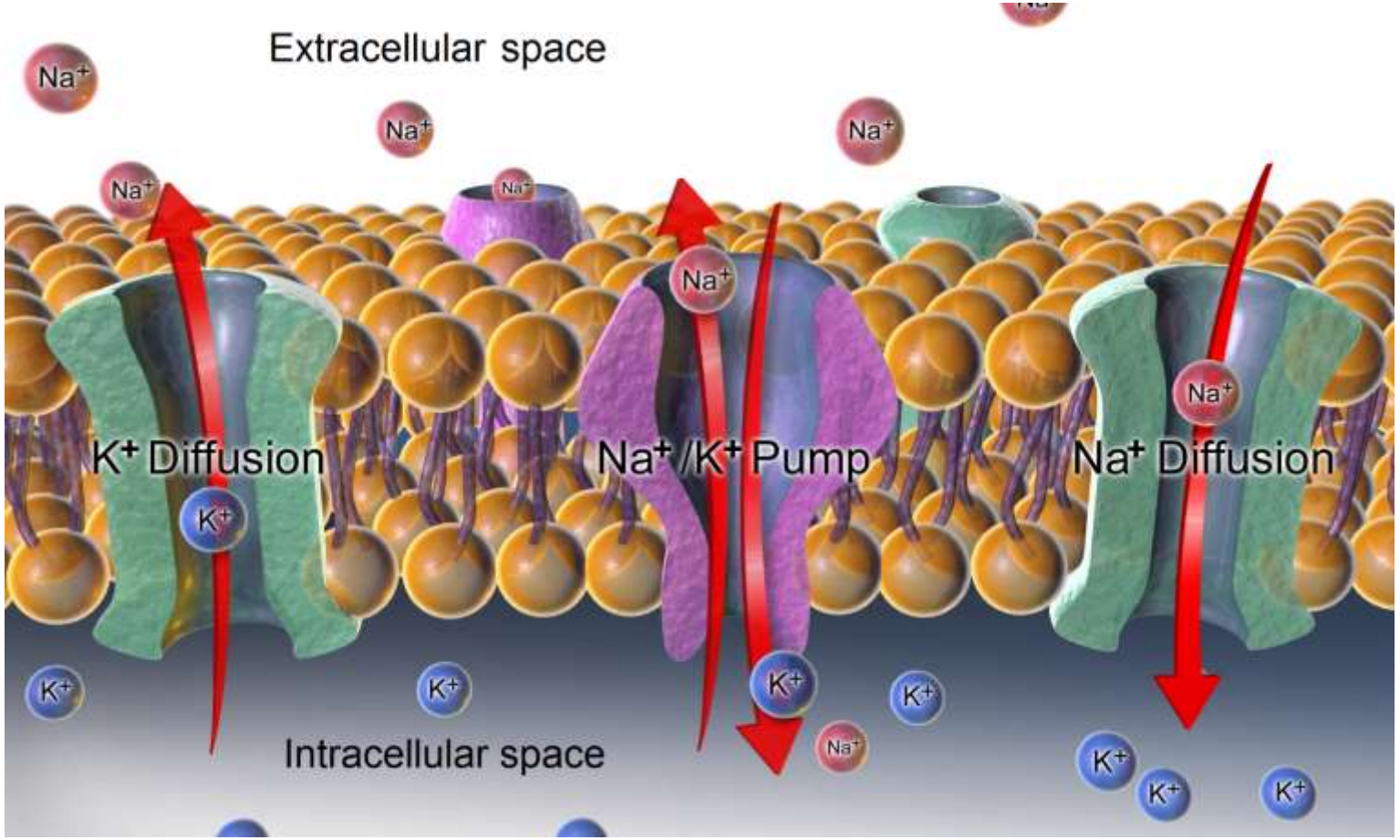
1) Effects on Electrolytes and Ion Transport

- It can substitute for sodium in generating action potentials

Na + -Na + exchange across the membrane becomes Li + -Na +

- At therapeutic concentrations (around 1 mmol/L), it does not significantly affect the Na + -Ca 2+ exchanger or the Na + /K + -ATPase pump.

SODIUM ACROSS MEMBRANES



PHARMACOLOGICAL EFFECTS OF Li

2) Effects on Second Messengers

TABLE 29–6 Enzymes affected by lithium at therapeutic concentrations.

Enzyme	Enzyme Function; Action of Lithium
Inositol monophosphatase	The rate-limiting enzyme in inositol recycling; inhibited by lithium, resulting in depletion of substrate for IP_3 production (Figure 29–4)
Inositol polyphosphate 1-phosphatase	Another enzyme in inositol recycling; inhibited by lithium, resulting in depletion of substrate for IP_3 production (Figure 29–4)
Bisphosphate nucleotidase	Involved in AMP production; inhibited by lithium; may be target that results in lithium-induced nephrogenic diabetes insipidus
Fructose 1,6-biphosphatase	Involved in gluconeogenesis; inhibition by lithium of unknown relevance
Phosphoglucomutase	Involved in glycogenolysis; inhibition by lithium of unknown relevance
Glycogen synthase kinase-3	Constitutively active enzyme that appears to limit neurotrophic and neuroprotective processes; lithium inhibits

CLINICAL USES OF Li

- Bipolar effective disorder
  - Use of lithium can prevent both mania and depression
- Recurrent endogenous depression
- Schizoaffective disorder (in combination with antipsychotic drugs)
- Schizophrenia (in combination with antipsychotic drugs for treatment resistant patients)
- Unipolar depression (in combination with SSRIs or TCAs)

MONITORING the TREATMENT

- Clinicians measure serum lithium concentrations
  - For assessing the dosage required for treatment
  - For prophylactic maintenance.

- An initial determination is done 5 days after the start of treatment, 10–12 hours after the last dose.

- If the blood levels are not according to our desired value, the new dose may be calculated as

$$new\ dose = present\ dose\ * \frac{desired\ blood\ levels}{present\ blood\ levels}$$

- The serum concentration attained with the adjusted dosage can be checked after another 5 days.
- Once the desired concentration has been achieved, levels can be measured at increasing intervals.

MAINTENANCE TREATMENT

- The decision to use lithium as prophylactic treatment depends on many factors:
  - The frequency and severity of previous episodes
  - A crescendo pattern of appearance
  - The degree to which the patient is willing to follow a program of indefinite maintenance therapy.

Patients who have one or more episodes of illness per year are candidates for maintenance treatment.

❖Serum levels as low as 0.6 mEq/L are acceptable for maintenance therapy

❖Best results at 0.9 mEq/L.

DRUG INTERACTIONS

- Diuretics
  - Renal clearance of lithium is reduced about 25% (eg, thiazides)
- Nonsteroidal anti-inflammatory drugs
  - Reduced renal clearance
- All neuroleptics tested to date (except clozapine)
  - May produce more severe extrapyramidal syndromes when combined with lithium.

ADVERSE EFFECTS AND COMPLICATIONS

- Neurologic and Psychiatric Adverse Effects
  - Tremor (Propranolol and atenolol alleviate lithium-induced tremor).
  - Choreoathetosis
  - Motor hyper activity
  - Ataxia
  - Dysarthria, and aphasia
  - Psychiatric disturbances at toxic concentrations are generally marked by mental confusion and withdrawal. (temporarily stopping treatment and close monitoring of serum levels)

ADVERSE EFFECTS AND COMPLICATIONS

- Nephrogenic Diabetes Insipidus and Other Renal Adverse Effects
- Decreased Thyroid Function
- Edema
- Cardiac Adverse Effects (“sick sinus”) syndrome
- Transient acneiform eruptions
- Folliculitis
- Leucocytosis

USE DURING PREGNANCY

- Renal clearance increases during pregnancy, so dose must be adjusted after delivery
- Risk of Cardiac anomalies— especially Ebstein's anomaly

- Secreted in breast milk and may cause infant toxicity, manifested by
  - Lethargy, cyanosis, poor suck and Moro reflexes, and perhaps hepatomegaly.

OVERDOSE

- Therapeutic overdoses of lithium are more common than accidental ingestion of the drug.
- Serum levels of over 2 mEq/L must be considered as indicating likely toxicity
- Causes:
  - Diminished serum sodium
  - Use of diuretics
  - Fluctuating renal function
- Management of toxicity
  - Dialysis

BIOETHICS AND RESEARCH

BIOETHICS

- **Ethical Issues in the Diagnosis and Treatment of Bipolar Disorders** https://pmc.ncbi.nlm.nih.gov/articles/PMC6999205/

RESEARCH

- Rybakowski J. The mechanisms of lithium action–an update. Pharmacotherapy in Psychiatry and Neurology/Farmakoterapia w Psychiatrii i Neurologii. 2024;40(1):13-23.

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Thank
you