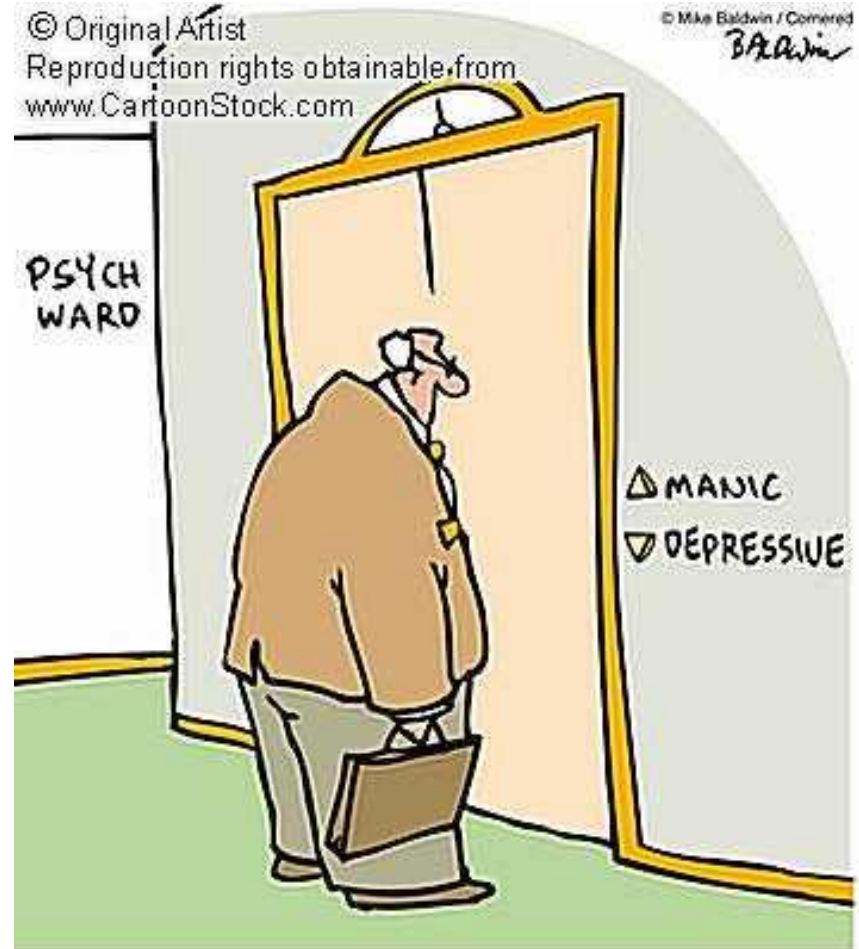


Mood stabilizers

Paz García-Portilla

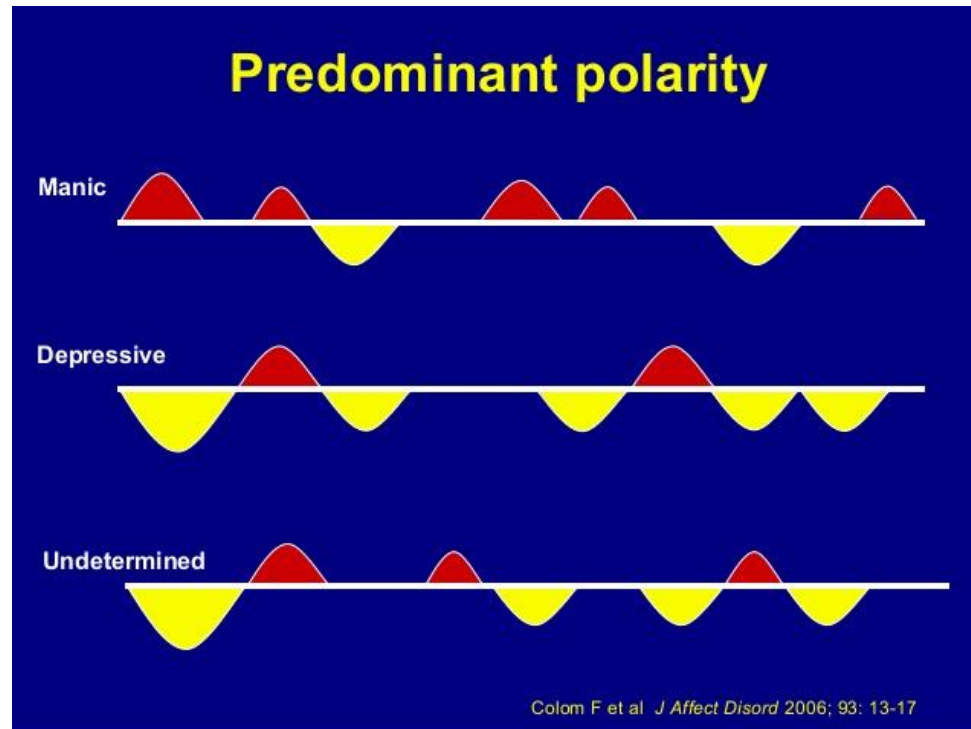


Mood stabilizers

- Approved indications
 - Maintenance treatment: to prevent relapses (new episodes) in BD
 - Acute treatment
 - Manic episodes
 - Depressive episodes
- Mood stabilizers agents
 - Lithium
 - Anticonvulsivant agents
 - Valproic acid
 - Carbamacepine
 - Oxcarbacepine
 - 2nd generation Antipsychotics
 - Quetiapine

Mood stabilizers: Maintenance treatment

- Consider the predominant polarity of the BD (~ 50% of patients)



- Take into account the family medication history if there is, and patient current and prior medication history
- Consider polytherapy if there is a partial response to monotherapy

Maintenance tx: Mood stabilizers' polarity index (PI)

- PI: A measure of the relative prophylactic efficacy of drugs used in BD maintenance treatment

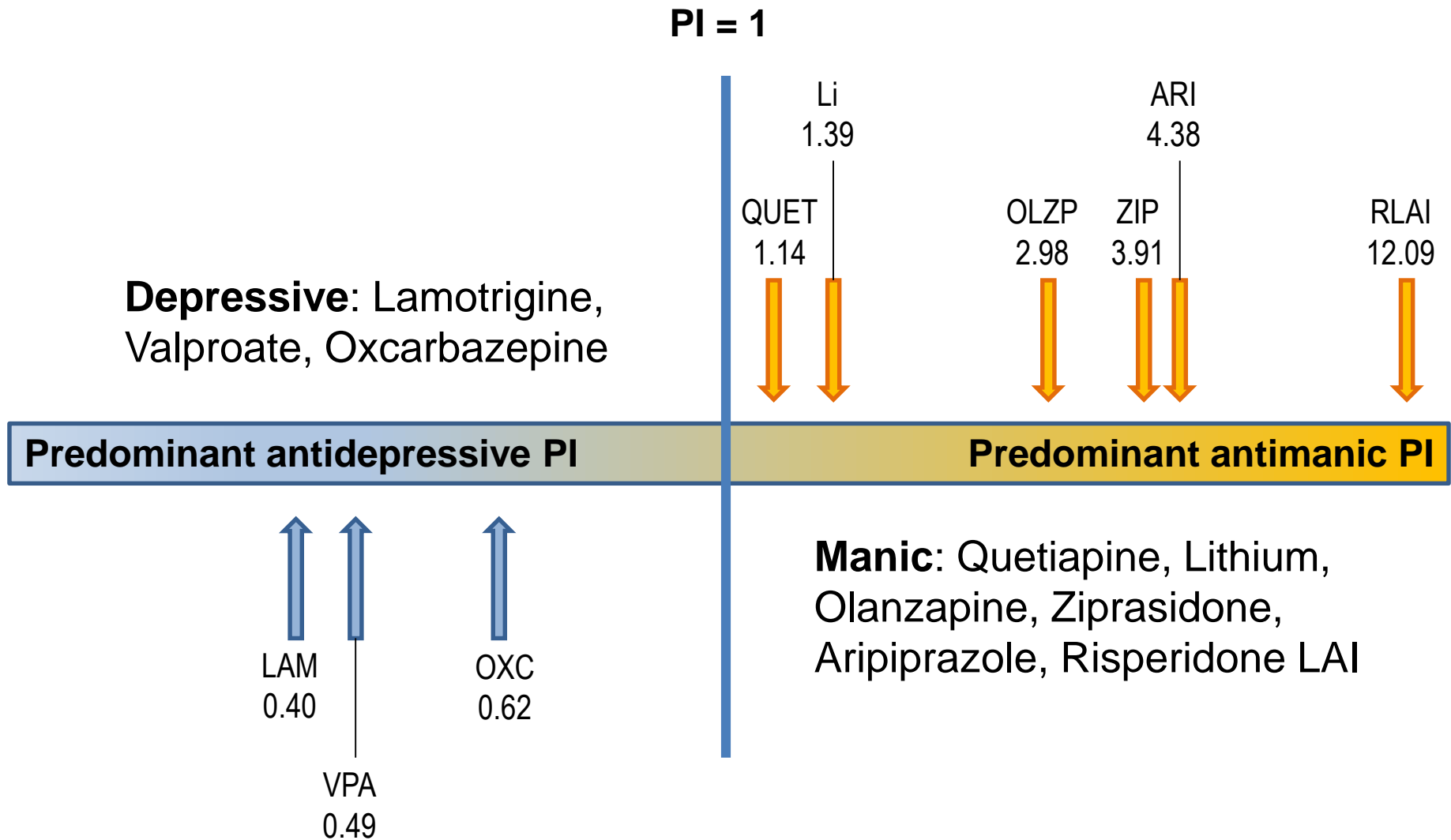
$$\text{Polarity index} = \frac{\text{NNT depression}}{\text{NNT mania}}$$

PI = 1

Predominant antidepressive PI

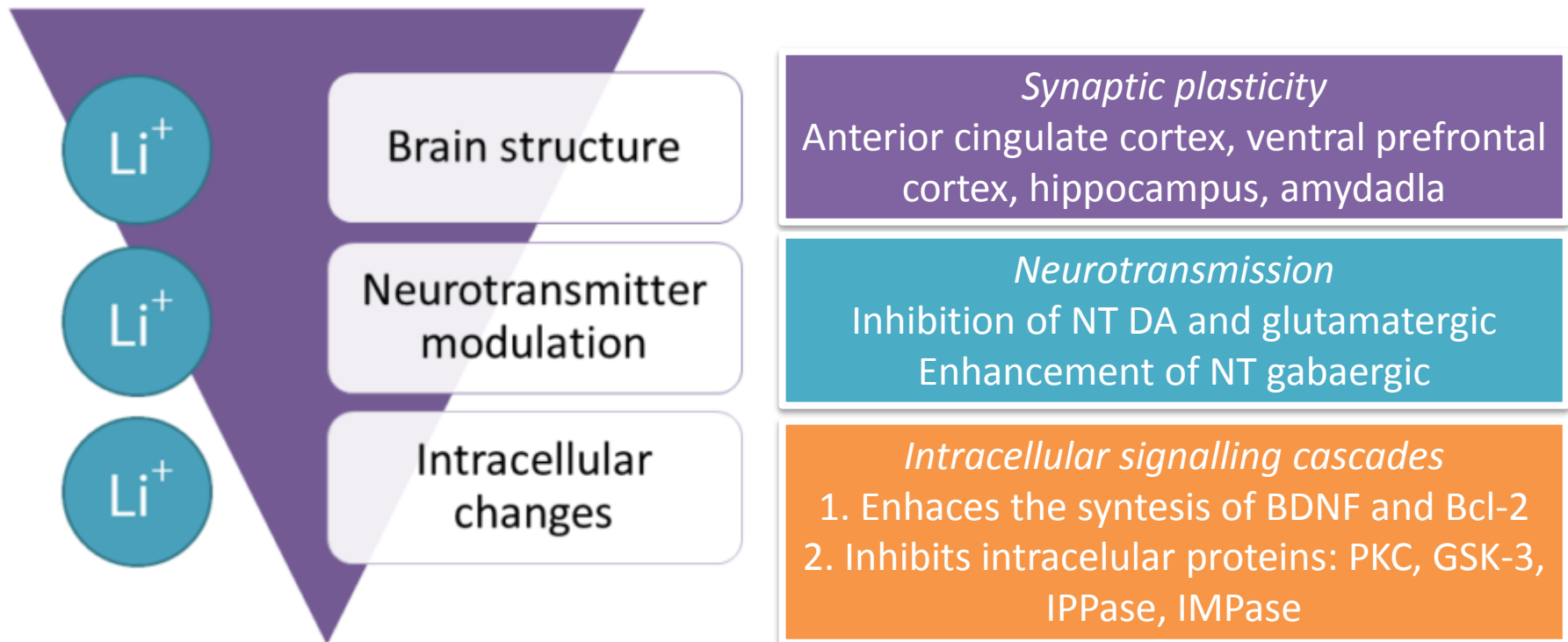
Predominant antimanic PI

Maintenance tx: Mood stabilizers' polarity index (PI)

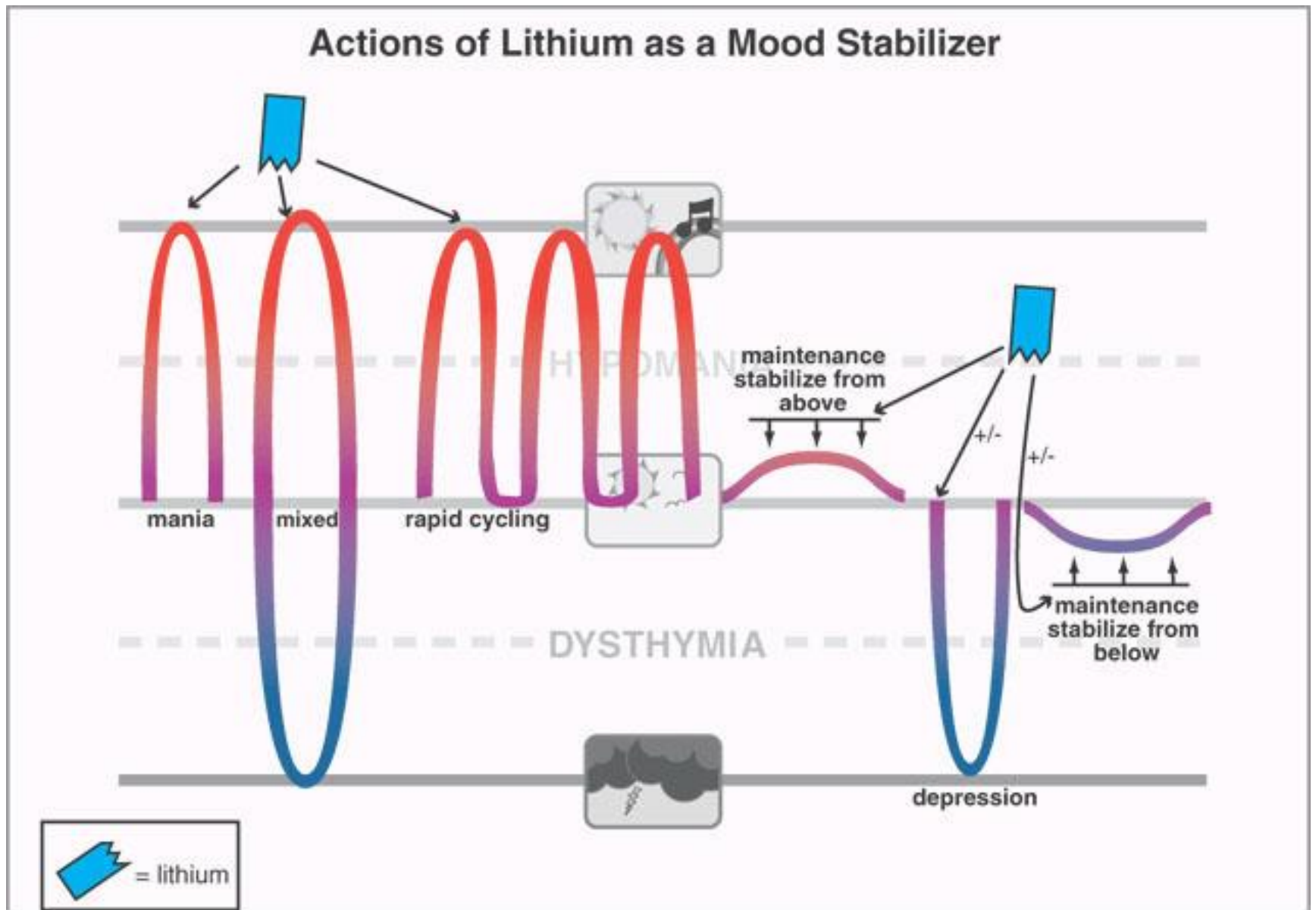


Lithium: Pharmacokinetic and mechanism of action

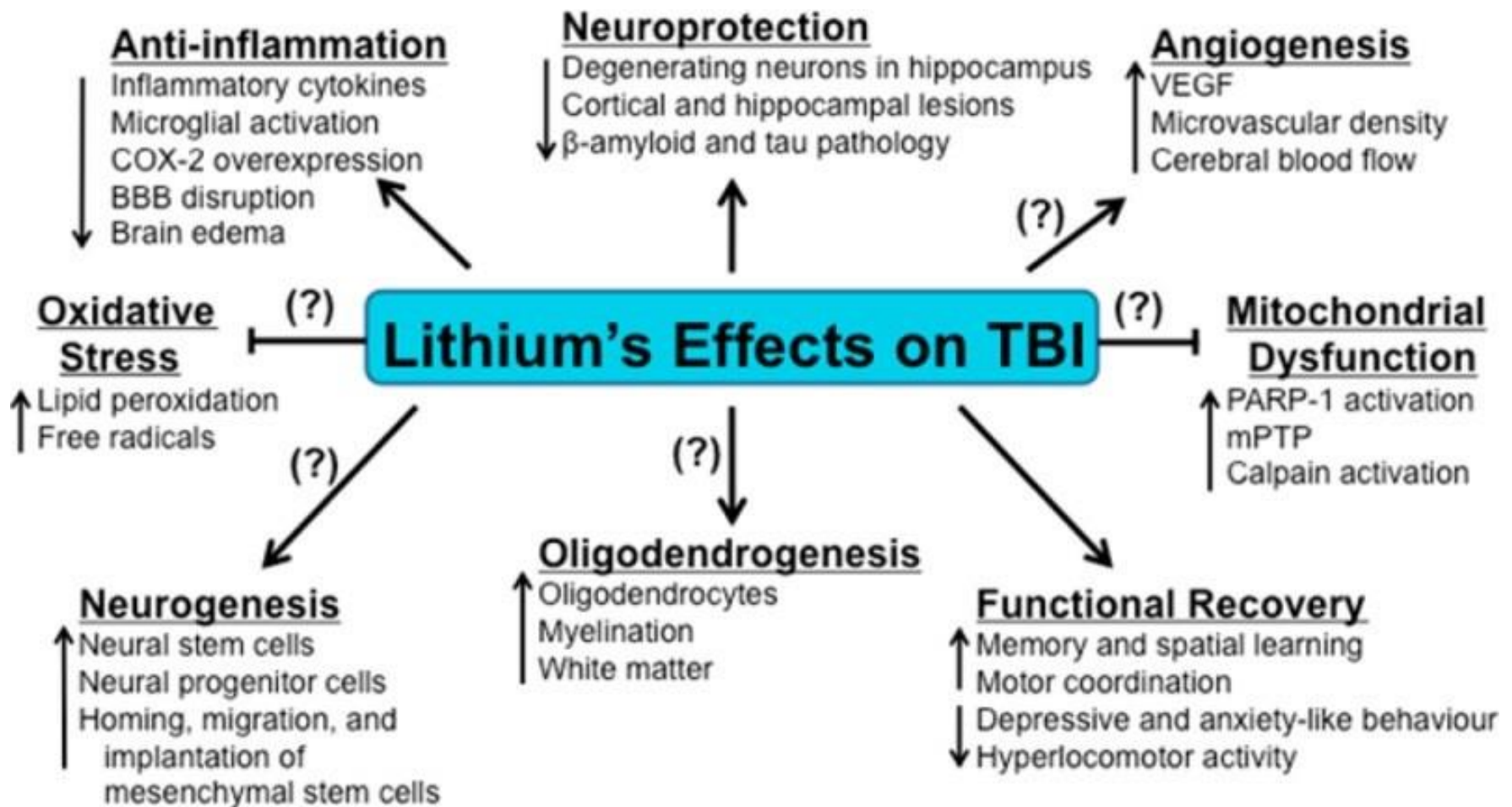
- Slow oral absorption, it does not metabolize or bind to plasma proteins, uniform distribution in body H₂O
- Multiple levels of action:



Lithium: mood stabilization



Lithium: more than mood stabilization



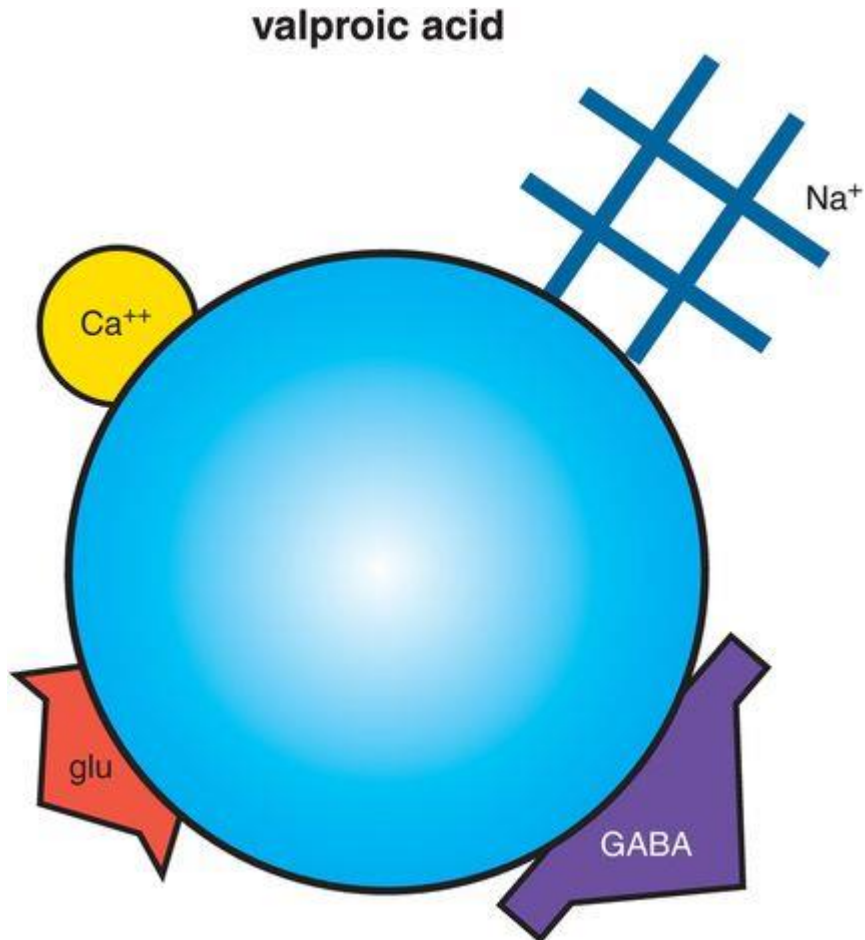
Lithium plasmatic levels and toxicity

- Lithium levels should be monitored at least every 6 months after a patient has become stable (12 hours after the patient's last dose).
- Plasmatic levels
 - Therapeutic levels: 0.6 – 1.2 mEq/L
 - Toxicity: >1.5 mEq/L
 - Concerning risk for toxicity: >2.5 mEq/L
- Clinically, the three main categories of lithium poisoning are:
 - Acute – Manifestations are predominantly gastrointestinal (GI), but progression to neuromuscular signs may occur
 - Acute-on-chronic – Both GI and neurologic manifestations may be present
 - Chronic – Manifestations are primarily neurologic

Lithium toxicity

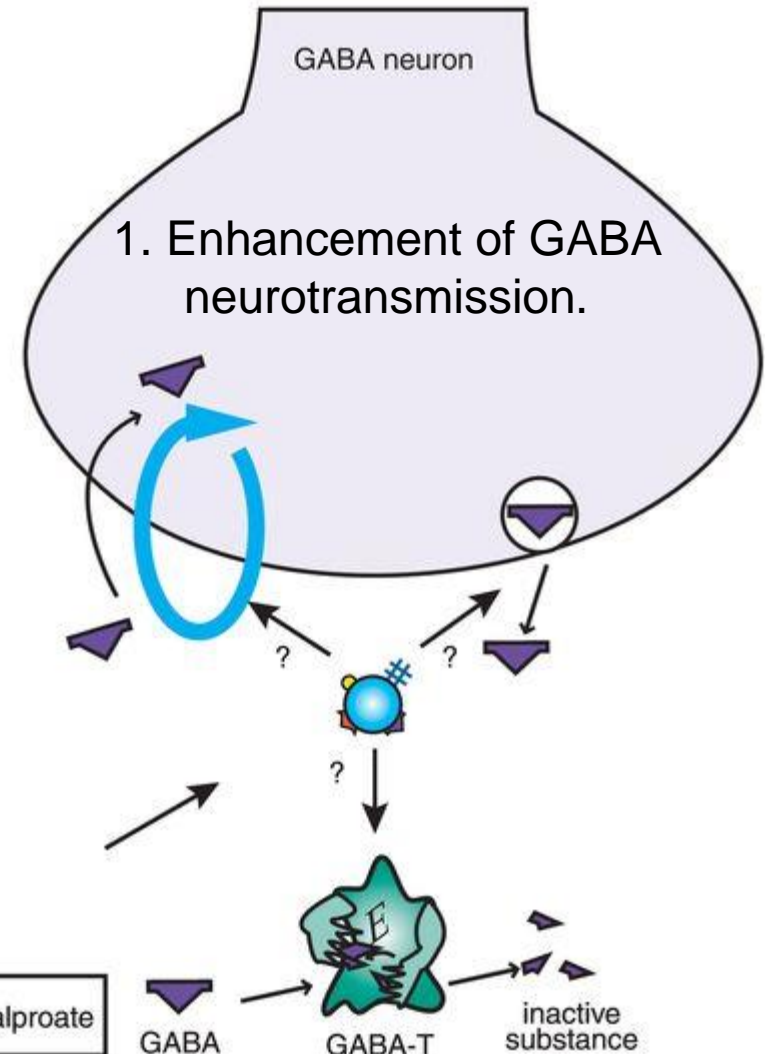
- Mild to moderate intoxication may occur at concentrations up to 2 mEq/L to 3 mEq/L
 - Lethargy, drowsiness, photophobia, coarse hand tremor, muscle weakness and myoclonic twitches, nausea, vomiting, diarrhea, ataxia, nystagmus, confusion, choreoathetosis, agitation, and ECG changes.
- Severe intoxication may occur at concentrations above 2.5 mEq/L to 3.5 mEq/L
 - Grossly impaired consciousness, increased deep tendon reflexes seizures, syncope, renal insufficiency, coma cardiovascular instability, and death.
- Lithium levels above 4 mEq/L in chronic intoxication patients may require hemodialysis
- Lithium levels above 6 mEq/L likely require hemodialysis in all patients.

Valproate



2. Affect signalling systems like the Wnt/beta-catenin and ERK pathway.
3. Interfere with inositol and arachidonate metabolism.

Possible Sites of Action of Valproate on GABA



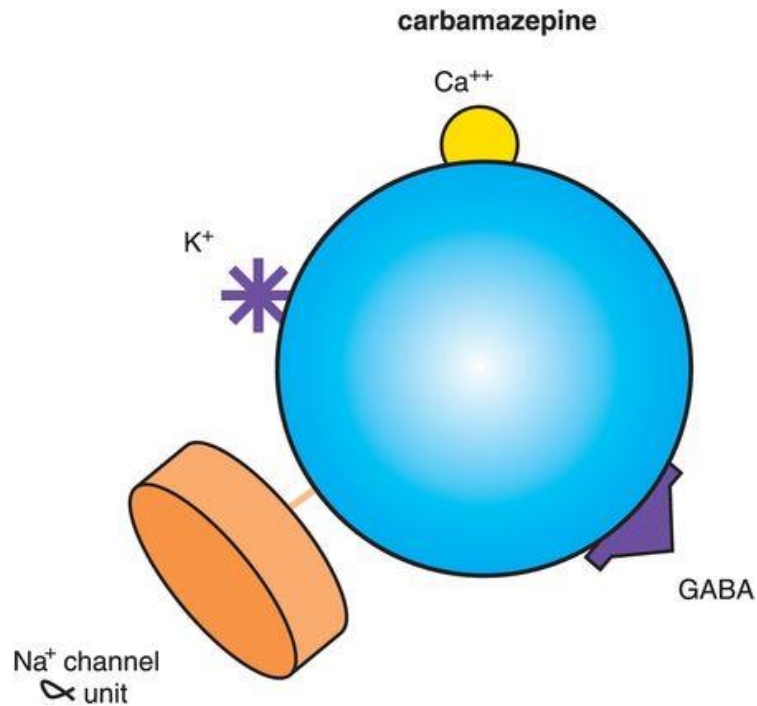
European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC)

- The key components of the valproate pregnancy prevention program include the following:
 - Assessing patients for the potential of becoming pregnant, involving the patient in evaluating her individual circumstances, and supporting informed decision making.
 - Conducting pregnancy tests before starting and during treatment as needed.
 - Counseling patients about the risks of valproate treatment and explaining the need for effective contraception throughout treatment.
 - Conducting reviews of treatment by a specialist at least annually and completing a risk acknowledgement form with patients at each review to confirm that appropriate advice has been given and understood.
 - The PRAC also recommended that the outer packaging of all valproate medicines include a visual warning about the risks in pregnancy. "In addition to boxed text, this may include a symbol/pictogram, with the details to be adapted at national level," the EMA said.

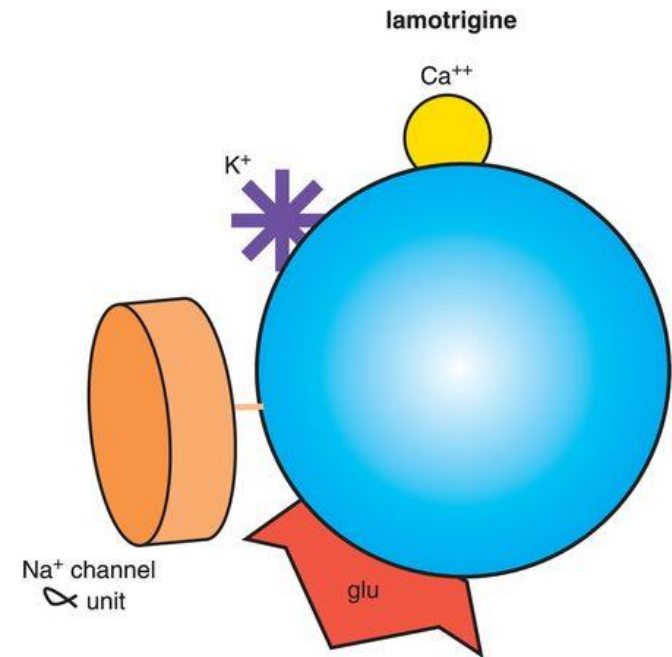


Other anticonvulsivants

Mood stabilizer



Acute depression
Maintenance stabilize from below



Mood stabilizers

Medication:	Lithium	Valproate	Carbamazepine
Starting dose (mg):	400	500	200
Typical effective dose (mg):	400–800	1000–2000	400–600
Route:	oral	oral	oral
Target blood level:	0.6–1.0 mEq/litre mania: 0.8–1.0 mEq/litre; maintenance: 0.6–0.8 mEq/litre. <i>Regular serum level monitoring is critical.</i>	Not routinely recommended	Not routinely recommended
Noteworthy side effects:	Impaired coordination, polyuria, polydipsia, cognitive problems, cardiac arrhythmias, diabetes insipidus, hypothyroidism	Caution if there is underlying hepatic disease. Hair loss and, rarely, pancreatitis are possible.	Diplopia, impaired coordination, rash, liver enzyme elevations; Rarely: Stevens-Johnson syndrome, aplastic anaemia.
Sedation:	++	++	++
Tremor:	++	++	++
Weight gain:	++	++	++
Hepatotoxicity:	-	++	+
Thrombocytopenia:	-	+	+
Leucopenia, mild asymptomatic:	-	+	+

Discontinuation of mood stabilizers

- » In a person not currently in a manic or depressed state (bipolar disorder between episodes), follow up every 3 months. Continue treatment and monitor closely for relapse.
- » Continue maintenance treatment with the mood stabilizer for at least 2 years after the last bipolar episode.
- » However, if a person has had severe episodes with psychotic symptoms or frequent relapses, **CONSULT A SPECIALIST** 🧑🏻‍⚕️ regarding the decision to discontinue maintenance treatment after 2 years.
- » When discontinuing medications, reduce gradually over a period of weeks or months.
- » If switching to another medication, begin that medication first and treat with both medications for 2 weeks before tapering off the first medication.

BD: Acute treatment

- Acute mania
 - Rapid control of agitation, impulsivity and aggression
 - If on ANTIDEPRESSANTS: REMOVE IMMEDIATELY
 - Sometimes, compulsory hospitalization and/or mechanical restriction are needed to start effective treatment
 - Choice of initial treatment is influenced by
 - Patient's current and prior medication history,
 - Need for rapid resolution of agitation and aggression,
 - Characteristics of the manic episode, and the presence of rapid cycling,
 - Patient's own willingness to accept, particular therapies and routes of administration
 - Whenever possible, oral therapy should be offered first, but, intramuscular injections are an alternative

BD: Acute treatment

- Acute mania
 - Monotherapy with Lithium, Valproate, or atypical APS
 - Drawbacks of lithium therapy
 - Narrow therapeutic index (recommended plasma level 0.8 to 1.2 mmol/L)
 - Poor tolerability, especially at higher doses
 - Risk of “rebound mania” on withdrawal
 - Lithium or Valproate + atypical APS

Antipsychotic	Level of evidence	Recommendation grade
Aripiprazole, Risperidone	A	1
Ziprasidone	A	1/2
Asenapine, Olanzapine, Quetiapine	A	2
Paliperidone	B	3
Amisulpride, Clozapine	C1	4

BD: Acute treatment

- Acute depression
 - Select the AD therapy based on
 - Severity of illness
 - Presence/absence of psychotic symptoms
 - Rapid cycling
 - If AD is required, it must be administered only to patients who are also been treated with a mood stabilizer
 - Sometimes hospitalization is needed if elevated risk of suicide

BD: Acute treatment

- Acute depression (cont.)
 - Monotherapy with Lithium, Valproate or Quetiapine
 - Combination of Lithium + Valproate, Lithium or Valproate + SSRIs, Olanzapine + SSRI (fluoxetine)
 - Mild / moderate depressive episodes may need adjunctive psychotherapy
 - Social rhythm therapy
 - Cognitive-behavioral therapy
 - Interpersonal therapy

BD II: Treatment

- Hypomania: anti-manic agents
- Depression
 - Monotherapy with Quetiapine
 - Lithium, Lamotrigine, Valproate, Lithium or Valproate + ADs
- Maintenance treatment
 - Depressive polarity (37:1): same treatment as acute depression

BD – rapid cycling: Treatment

- Main goal: To prevent new episodes
 - Treatment of substance abuse or hypothyroidism if comorbid
 - Lithium, Valproate, atypical APS or Lamotrigine
 - Avoid antidepressants
 - If patient is being treated with AD monotherapy add lithium, Valproate or Lamotrigine, and, if possible, the dose of AD should be tapered and discontinued