MOOD STABILIZERS: lithium; valproic acid/divalproex (VPA); lamotrigine; carbamazepine; second generation antipsychotics

SELECTED TARGETS/PATHWAYS:

BRAIN-DERIVED NEUROTROPIC FACTOR (BDNF):
- A protein associated with promotion of neuronal growth and synaptic activity
- In animal models, lithium and VPA administration enhances BDNF activity

B-CELL LYMPHOMA (Bcl-2):
- A neuroprotective & anti-apoptotic protein
- Certain polymorphisms decrease Bcl-2 levels & increase glutamate neural toxicity
- Lithium and VPA increase the levels of Bcl-2 in key brain regions

CYCLIC ADENOSINE MONOPHOSPHATE/ PROTEIN KINASE A/ cAMP PATHWAY:
- G-protein coupled signal transduction pathways regulate the neuronal circuits modulating mood, appetite, & wakefulness
- Increased levels of stimulatory G-protein associated with this cascade are seen post-mortem in brains of patients with bipolar disorder

PROTEIN KINASE C (PKC):
- Enzyme involved with signalling pathways regulating neuronal excitability, and neuro-transmitter release
- Excessive PKC activity may lead to bipolar symptoms (altered judgment, impulsivity)
- Mood stabilizers attenuate PKC activity

GLYCOGEN SYNTHASE KINASE-3 (GSK-3):
- A pro-apoptotic peptide that opposes mechanisms responsible for neuronal plasticity, differentiation, and cytoskeletal assembly
- Inhibition of GSK-3 activity → Bcl-2 enhancement of neuroplasticity & cellular resilience
- Lithium is an inhibitor of GSK-3

CALCIUM & CALCIUM SIGNALLING:
- Crucial role in the modulation of NTs, neuron excitation & long-term neuroplastic changes
- With lithium, Ca^{2+} entry into the cell is inhibited leading to corrected NT signalling

IN SUMMARY – ACTIONS OF TARGET DRUGS: BDNF ↑, Bcl-2 ↑, GSK-3 ↓, cAMP/PKA/CREB ←→ , PKC ↓ , Ca^{2+} entry into cell ↓

LITHIUM:

DOSE:
- Adjusted to targeted serum concentrations or to effect
  - Acute mania = 0.8 – 1.2 mEq/L
  - Maintenance = 0.6 – 1.0 mEq/L
  - Full mania = 1.2 – 1.5 mEq/L
- Steady-state concentrations occur approx. 5 days of stable dosing
- 1st order kinetics (double dose = double concentration)

REGIMEN:
- When tolerated, lithium can be given as a single dose
- Structural & functional kidney changes are more prominent in pts who receive lithium in divided doses
- Once daily dosing reduces the occurrence of polyuria and may improve adherence

ONSET OF ACTION:
- Mania: relatively slow onset of action (6-10 days) compared with antipsychotics and VPA
- Depression: > 1 month may be required for max improvement

THERAPEUTIC DRUG MONITORING:

CBC & diff	Baseline and yearly
ECG	Baseline and annually
TSH	Once or twice in first 6 months, then q6-12 months
Renal Fxn	Baseline, then every 2-3 months for 6 months, then semi-annually, then annually
Serum Drug Conc.	Weekly until stable dose is achieved, then quarterly to semi-anually

ADVERSE EVENTS:
- DERM: acne, psoriasis, alopecia/hair thinning
- TOXICITY:
  - Patients with SIGNIFICANT fluid loss
  - Meds that significantly alter lithium level
- GI: nausea early in therapy; dry mouth/thirst
  - Changing to ER formulation may reduce nausea
  - Supratherapeutic lithium levels be suspected with severe NVD
- Polyuria: occurs in 30% of patients
  - Target lower serum levels (0.45 – 0.75)
  - Amiloride may be used for lithium-induced polyuria
- CKD: induced by lithium is controversial; challenging to study due to longitudinal nature of obtaining data
  - CrCl decreases modestly over years (annual loss 2mL/min)
  - ESRD related to lithium is rare (0.2% of pts on lithium for > 15 years)
- Hypothyroidism: occurs in 8-19% of patients
  - Pre-existing hypothyroidism NOT a contraindication for starting lithium

CLINICALLY SIGNIFICANT DRUG INTERACTIONS:
- NSAIDs: can increase lithium serum concentrations by 16-60%
  - Concomitant use NOT recommended
- ACEI/ARBs: increase lithium levels by 30-40%
  - Interaction is delayed; may not be seen for 3-5 weeks
- Diuretics: thiazides increase lithium levels by 25-40%
  - K^+ sparing diuretics have limited effects
- Caffeine: may decrease lithium levels

LAMOTRIGINE:

DOSE:
- Slow titration schedule to reduce the risk of SJS/TEN
  - Any break in therapy for > 5 days warrants re-titration
- Max dosage = 200 mg
  - Concomitant VPA = titration dose is reduced by 50% and max daily dose is 100 mg
  - Concomitant CBZ or phenytoin = max daily dose is 400 mg

RASH:
- Benign rash (7%); SJS/TEN (0.08%)
- Delayed hypersensitivity reaction
  - 2-8 weeks after initiation, prodromal period
- Lesions classically develop on face and upper torso
  - SJS & TEN differentiated by the extent of BSA affected
- Stop lamotrigine at first sign of rash, regardless of type and severity

VALPROIC ACID/DIVALPROEX SODIUM (Divalproex is simply enteric-coated valproic acid)

DOSE:

- Loading strategy achieves therapeutic serum concentrations more rapidly and may equate to a faster resolution of mania
- Exact levels indicative of response have not been established in bipolar disorder
  - 50 – 125 mcg/mL = reference range
- Changing from ER to non-ER formulation requires an increase in dosage (8-20% decrease in serum levels)

ADVERSE EFFECTS:

- Teratogenicity
- Rash (6%)
- Alopecia (concentration dependent risk)
  - 80-150 mcg/mL = 28% risk
  - 20-50 mcg/mL = 4% risk
- Nausea (29%)
- Transaminitis and hepatotoxicity
  - Highest risk in peds and first 6 months
- Pancreatitis
- Weight gain
- Hyperammonemia (higher doses, toxicity, concomitant topiramate)
  - Treatment: hold doses, lactulose
- Thrombocytopenia (higher doses, advanced age)
- Sedation (at higher doses)

MONITORING:

CBC with diff	Baseline, 2 weeks after initiation or dose change, then semi-annually to annually
LFTs	
Pregnancy test	In women of child-bearing age
Renal function	Baseline
Free serum conc	Consider 3-5 days after initiation or when stable dose is achieved (establish baseline relative to response, or assess ability to increase dose without concern) When altered protein binding would be expected (elderly, malnourished)
Weight, ammonia	If suspicion of hyperammonemia