Lithium and Depakote as First-Line Mood Stabilizers in Treatment of Bipolar Disorder

Jazzlyn Gallardo, D.O.
Trios Health Family Medicine PGY-1
December 2014

Bipolar Disorder

- **Mood disorder** characterized by episodes of mania, hypomania, and major depression
  - **Manic episode** – a distinct period of abnormally and persistently elevated, expansive, or irritable mood
    - Symptoms: pressured speech, motor hyperactivity, reduced need for sleep, flight of ideas, grandiosity, poor judgment, aggressiveness, and possible hostility
- **Bipolar I** – manic episodes w/periods of hypomania and depression
- **Bipolar II** – at least one hypomanic episode, at least one episode of major depression, and NO history of mania

Lithium

- **Mechanism of action**: unknown
  - Affects multiple neurotransmitter systems including norepinephrine, dopamine, serotonin, glutamate, and gamma aminobutyric acid
- Increases neurogenesis and neuroprotective factors
- Preserves or increases cortical gray matter and hippocampal volume

Lithium Preparations

- 300 mg – most commonly prescribed preparation in the U.S.
- Available as a tablet or capsule
- Also available in liquid form for patients who have difficulty swallowing pills – lithium citrate
  - 5 mL = 300 mg
- Slow-release tablets
  - May cause less nausea than conventional, immediate release forms in the beginning of treatment
  - Slightly higher incidence of diarrhea

Lithium: Pharmacokinetics

- Rapidly absorbed through the GI tract
  - Food does not alter lithium absorption
- Peak serum levels
  - 1-2 hours – standard, immediate release preparations
  - 4-5 hours – slow release preparations
- Steady state – 4-5 days after the last dose change
- Highest brain levels – within 2 hours of peak serum levels
- Excreted almost exclusively through kidneys
  - Lithium elimination half-life in young patients: 24 hours
    - Increases as renal function declines w/age

Lithium: Side Effects

- Acute
  - Nausea
  - **Tremor** – most common symptom of lithium toxicity
  - Polyuria (related to nephrogenic diabetes insipidus) and thirst
  - Weight gain
  - Loose stools
  - Cognitive impairment (including apathy, decreased creativity, and changes in verbal learning, memory, concentration)
- Long-term
  - Renal – nephrogenic diabetes insipidus
  - Thyroid – goiter, hypothyroidism, chronic autoimmune thyroiditis, and hyperthyroidism
  - Parathyroid – hypercalcemia, elevated serum parathyroid hormone, and hyperparathyroidism
  - Cardiac – dysrhythmias (rare)

Lithium: Contraindications

- Significant renal impairment
- Sodium depletion
- Dehydration
- Significant cardiovascular disease

- Psoriasis – relative contraindication

Lithium Toxicity

- Confirmed by lithium levels
- Mild toxicity: **1.5 mEq/L** (1.5 mmol/L)
- Medical emergency: **≥ 2.5 mEq/L** (2.5 mmol/L)
- Increased when lithium excretion is impaired:
  - Underlying renal insufficiency
  - Effective volume depletion
  - Elderly patients (low GFR)

Drug Interactions w/Lithium

- Increases lithium level
  - Thiazide diuretics
  - NSAIDs except aspirin
  - ACE inhibitors
  - Antibiotics – tetracyclines and metronidazole
- Decreases lithium level
  - Potassium-sparing diuretics
  - Theophylline

Prescribing Lithium

- Starting dose: **300 mg** bid or tid
  - Start with bid or tid dosing schedule to minimize side effects (especially nausea) early in treatment
  - Then consolidate the dose schedule to once daily after a number of weeks or months of treatment
- Increase by 300 – 600 mg every 1-5 days
  - Based upon response, tolerability, and BMI
- Goal: Reach therapeutic serum level
  - Generally occurs w/dose of 900 mg to 1800 mg per day

Prescribing Lithium (cont.)

- After reaching the estimated therapeutic dose range
  - **Check serum lithium concentration**
    - Should be measured 7-10 days after each dose increase
    - Levels should be drawn approx. 12 hours after the last dose (12-hour serum trough level)
      - generally collected in the morning, before the first dose of the day
  - Obtain **creatinine clearance (CrCl)** every 6-12 months
- For lithium-induced hypothyroidism, do *not* discontinue lithium → supplement w/levothyroxine

Depakote

- Also known as divalproex sodium
- Antiepileptic also used for seizures and migraine
- **Mechanism of action**: causes increased availability of gamma-aminobutyric acid (GABA) to brain neurons or may enhance the action of GABA or mimic its action at postsynaptic receptor sites
- "Ceiling" drug for bipolar disorder
  - Effective for **rapid cycling** and **mixed state**

Depakote Preparations

- Available as capsules, solution (IV and oral), syrup, and tablets
- Delayed release
- Starting dose: 500 mg qHS

Depakote: Side Effects

- Weight gain
- Nausea/Vomiting/Diarrhea
- Weakness
- Double vision
- Loss of appetite
- Hair loss
- Easy bruising
- Tremor
- Headache
- Hepatic failure and thrombocytopenia (rare)

Depakote: Contraindications/Warnings

- Hepatic disease
- Mitochondrial disorders
  - Mutations in mitochondrial DNA polymerase gamma
- Hypersensitivity reactions
- Pancreatitis
- Urea cycle disorders – hyperammonemic encephalopathy
- Pregnant women – neural tube defects and other structural abnormalities
  - E.g., craniofacial defects, cardiovascular malformations, etc.
  - Decreased IQ following *in utero* exposure

Prescribing Depakote

- Recommended initial dose: **750 mg daily** in divided doses
  - Maximum recommended dosage: 60 mg/kg/day
- Clinical response with a trough plasma concentration between 50 and 125 mcg/mL
- Maximum concentrations generally achieved within 14 days.
- No data available to support the benefits of Depakote in longer-term treatment.

Depakote: Management

- Take every day as prescribed
- If a dose is missed → take it ASAP
- If a dose is skipped, do *not* double the next dose
- Depakote and Lamictal have a pharmacokinetic interaction.
  - Depakote increases Lamictal levels in the blood.
  - Therefore, must monitor Lamictal symptoms and decrease dose (typically by 50%) as necessary.