The source of the following condensed material is Up-To-Date.
Bold font-definitely know; Regular font-know; *Italics font-supplemental*

Lithium

- Can be used to treat **acute mania, hypomania, bipolar depression, unipolar depression and for maintenance treatment of bipolar disorder**
- Reduced risk of suicide-long term treatment is associated with a reduced risk of suicide attempts and suicide deaths

Pharmacokinetics

- Lithium is NOT protein bound
- Brain levels are highest within 2 hours of the peak serum levels; **Steady state is achieved within 4-5 days after the last dosage change**
- **Lithium is not metabolized and is excreted almost exclusively through the kidneys**; Lithium's half –life ($t_{1/2}$) is determined primarily by renal function. The half-life ($t_{1/2}$) is about 20-24 hours in healthy young patients. Lithium's half –life increases as renal function declines with age

- Lithium levels should be drawn about **12 hours after the last dose (trough level)** and collected in the morning before the first dose of the day
    - **serum level drawn a few hours after lithium ingestion is subject to marked fluctuation** if the level is drawn one hour sooner or later, leading to unreliable information

- Serum lithium levels are closely related to renal function, salt balance, and water balance
    - Dehydration (from GI viral infections or high fever) causes higher lithium levels
    - Increasing sodium intake causes increased sodium and lithium excretion and lower lithium levels
    - Decreased sodium intake causes sodium and lithium reabsorption in the proximal tubule and an increase in serum lithium levels

Acute Lithium toxicity

- GI: Often develop nausea, vomiting, and diarrhea;
  If vomiting/diarrhea are severe, dehydration and compromised renal function can develop which can impair the patient's ability to excrete lithium (and exacerbating lithium toxicity!)
- Neurologic-sluggishness, ataxia, confusion or agitation, neuromuscular excitability (irregular coarse tremors, fasciculation, or myoclonic jerks);
    - Severe lithium toxicity may cause seizures, non-convulsive status epilepticus, and encephalopathy

Chronic Lithium toxicity

- Long term lithium use may result in a concentrating deficit in the kidneys such that dilute urine is excreted
    - Normally resulting thirst and intake of free water compensate for the fluid losses; **many patients on lithium have polyuria and polydipsia**
    - Neurologic findings
        - In contrast to acute lithium toxicity where neurologic signs develop late, chronic lithium toxicity develops gradually and often present with neurologic findings
        - Same neurologic signs as acute toxicity:
    - Severe lithium toxicity may cause seizures, non-convulsive status epilepticus, and encephalopathy
    - Renal-patients with chronic lithium therapy are **at risk for developing nephrogenic diabetes insipidus;** these patients may develop hypernatremia

- Use of lithium blood levels in identifying/treating acute/chronic lithium toxicity
    - Serum lithium concentrations often do NOT correlate with clinical signs of toxicity.
        - Patients with acute ingestion may be relatively asymptomatic despite serum concentrations above 4 mEq/L (4 mmol/L) due to slow absorption into the central nervous system. Therefore, **treatment should be based upon clinical manifestations and not solely upon drug levels**

- Lithium has a narrow therapeutic index which means the dose at which it is clinically effective is only slightly lower than the dose at which it becomes toxic

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Drug interactions with lithium

- Increases lithium level
  - Ex. Thiazide diuretics, NSAIDS (except aspirin), Angiotensin converting enzyme (ACE) inhibitors
- Decreases lithium level
  - Ex. Potassium-sparing diuretics, Theophylline

Lab test and monitoring

- Prior to beginning lithium, the following tests should be ordered:
  - Urinalysis, BUN, creatinine, TSH, calcium
  - Pregnancy test for women of child bearing age
  - ECG for patients with risk factors for coronary heart disease
- Patients on steady doses should have their levels checked every 6-12 months
  - Lithium levels should be checked 5-7 days after a dose is changed
  - Urinalysis, BUN, creatinine, TSH, Calcium should be checked every 6-12 months

Lithium acute side effects

- **GI effects** (nausea, loose stools), **polyuria** and thirst (**polydipsia**), **tremor, weight gain**
- Cognitive impairment (apathy, decreased creativity, changes in verbal learning, memory, and concentration)

Lithium long term side effects

- **Renal**-function is adversely effected by lithium
- **Thyroid**-function is adversely effected by lithium, most commonly **hypothyroidism**
- **Parathyroid**-may cause hypercalcemia and elevated parathyroid hormone
- Cardiac-rarely may cause cardiac dysrhythmias in patients with pre-existing cardiac disease

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Valproate (Depakote)

- Can be used to treat **acute mania, hypomania, bipolar depression, and for maintenance treatment of bipolar disorder**

Protein binding

- Is tightly protein bound
- Contraindicated in patients with a known urea cycle disorder due to an increased risk of severe hyperammonemia
- Starting dose 15 mg/kg per day; 150 lb is about 70 kg; 15 mg/kg x 70 kg = 1,050 mg; start about 1,000 mg per day

Drug-drug interactions

- Oral contraceptives may increase clearance of valproate and decrease levels during active treatment**;**
- Various anti-seizure drugs, many of which are used in treatment of bipolar disorder such as:
  Carbamazepine (Tegretol), Lamotrigine (Lamictal)

Side effects

- **GI side effects**-nausea, vomiting; Hair loss; Easy bruising, **thrombocytopenia**; **Tremor**; **Weight gain**, obesity, insulin resistance, and **metabolic syndrome**
- Polycystic ovarian syndrome (PCOS); Pancreatitis-rare

Teratogenicity: (see Teratogenicity of Bipolar Disorder Medications)

Liver related side effects

- Liver enzyme elevations: about 5-10% patients develop ALT elevations during long term valproate therapy
- **Hyperammonemia encephalopathy**
  - Lethargy, increased seizures, and rarely coma and death
  - Note: May occur without abnormalities of LFT's or elevated serum valproate levels
  - Syndrome resolves within a few days of stopping valproate
  - Mild to moderate hyperammonemia occurs in about 25-30% of patients
  - Risk factors
    - High valproate dose, high plasma concentration, concomitant use of antipsychotic drugs, concomitant use of enzyme inducing anti-seizure drugs

- Acute hepatocellular injury with jaundice
  - In some cases associated with fulminant liver failure and death
  - Risk factors: age under 2 y/o, co-existent metabolic disorders

Lab Tests and Monitoring

- Prior to beginning Valproate (Depakote), the following tests should be ordered:
  - **LFT's** (ALT, AST)
  - **Pregnancy tests** for women of child bearing age
- Patients on maintenance treatment doses should have their levels checked every 6-12 months
  - Valproate (Depakote) levels should be checked 3-5 days after a dose is changed
  - **LFT's** (ALT, AST), CBC (platelets), **weight,** should be checked every 6-12 months

Lithium vs Depakote

- Few studies available, but for patients with mixed features or greater lifetime number of episodes, valproate (Depakote) may be superior to lithium

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Teratogenicity of Bipolar Disorder Medications

Background

- Baseline incidents of major fetal malformation in general population is 2-5%
- For pregnant women with bipolar disorder, their risk of a manic episode is increased during the pregnancy and in the post-partum period
- The estimated risk of major congenital malformations appears to vary among psychotropic medications; the rank order from greatest to least teratogenic risk is:
    - **Valproic Acid (Depakote)** **Greatest teratogenic risk**
      Carbamazepine (Tegretol)
      Lithium
      Lamotrigine (Lamictal)
      Antipsychotics **Risk at same level as baseline in general population**
      Antidepressants **Least teratogenic risk**

Valproic Acid (VPA) (Depakene®); Sodium Valproate (Depakote®)

- Greatest potential for serious birth defects of all meds used for psychiatric disorders;
  1-2% for neural tube defect (this is 10-20x's general population rate)

Carbamazepine (Tegretol)

- ↑ risk (0.9%) for neural tube defects (Spina Bifida) if used during pregnancy

Lithium

- Li^+ use during pregnancy has historically resulted in concerns about congenital cardiac defects (Ebstein's anomaly) associated with 1st trimester exposure.
- Recent data suggest the risk is less than previously thought;
  The risk is between 0.05%-0.1% (1 in 2,000 to 1 in 1,000)
  General population risk 0.005% (1 in 20,000)

Lamotrigine (Lamictal)

- does not appear to increase the risk of major physical malformations beyond the baseline incidence seen in the general population

Antipsychotics

- FGA or SGA prenatal exposure does not appear to increase the risk of major physical malformations beyond the baseline incidence seen in the general population