MOOD STABILIZERS: Lithium (p.1)

1. **Introduction**

   the category of drugs known as “mood stabilizers” are used to treat pts. with bipolar mood disorder (depression + mania)

   such “mood stabilizers” actually seem to prevent/treat both depression and mania, to keep the pt. in “stable mood”, hence the name such patients are rarely treated with antidepressants, because such meds can trigger manic periods in such pts.

   “mood stabilizers” are usually either the “drug” lithium or are a small group of drugs that were developed for another purpose (to block seizures/convulsions), anticonvulsants

2. **Lithium**

   is the tradition treatment “drug” for bipolar disorder

   is clinically effective in 60-80% of pts.

   but…non-compliance is a significant problem

   28% of pts. D/C drug (usually because of SEs or do not like effect that the drug has on them, including blocking manic state)

   38% of pts. take drug but still continue to have some recurrent Sxs of the disorder (perhaps dose level is too low…?)

   23% of pts. take drug and have few/no recurrent Sxs

**Pharmacokinetics of Li**

Li is an elemental alkali metal, like Na+ or K+

is absorbed rapidly & completely after a PO dose

peak plasma levels w/i 3 hours of dosing (1- 1½ hours often)

Li crosses BBB slowly & incompletely

   concentration of Li in CNS often < plasma concentration

   note: therapeutic efficacy of Li directly correlated to plasma level of Li

   note: therapeutic window is narrow (milliEquivalents/Liter)

   too low a level --- mania recurs, relapse

   too high a level --- serious toxic SEs (even death)
MOOD STABILIZERS: Lithium (p.2)

2. Lithium (cont.)

Pharmacokinetics (cont.)
thus, initially need frequent blood tests to assess Li levels
later on, when stable levels are reached, these may be done
monthly or every 3 months, etc.

Li is not metabolized before excretion
no liver enzyme issues, drug interactions via P-450 enzymes
is excreted in urine unchanged
½ life = 18-24 hours
thus, a single dose will be slowly excreted over 1-2 weeks
when taken daily, accumulates slowly, reaching steady state in
about 2 weeks
note: there is an important relationship in the kidney between
Li+ and Na+
if pt. has normal amounts of Na+, then kidney excretes normal
amounts of Li+
if pt. is low in Na+, then kidney will excrete less Li+
if pt. is high in Na+, then kidney will excrete more Li+

Li is not plasma protein bound

Pharmacodynamics of Li
mechanism by which Li helps to stabilize mood is not known…
affects cell membranes
affects multiple RSs and likely more than one NT
affects 2nd messenger systems (G-protein, metabotropic)
may regulate gene expression in cell’s nucleus
may stabilize the glutamate system especially…
MOOD STABILIZERS: Lithium (p.3)
2. Lithium (cont.)

Side Effects & Toxicity
must closely monitor blood levels of Li
  0.5 – 0.6 mEq/L --- minimal SEs
  1.0 mEq/L --- some SEs
  >2.0 mEq/L --- toxic SEs (including fatalities)

main adverse SEs:
  GI – nausea, vomiting, diarrhea, abdominal pain
  CNS – slight tremor, lethargy, decreased concentration, dizziness,
         slurred speech, ataxia, muscle weakness, nystagmus,
         impaired memory, wt. gain
  thyroid – becomes enlarged, hypothyroid, less thyroxine
  skin – rashes & other
  kidneys – increased urine output (increased thirst, water intake)

main toxic SEs:
  fatigue, severe muscle weakness, slurred speech, increased tremors
  very enlarged thyroid ("goiter"), muscle twitches, hyper-reflexes,
  abnormal movements, seizures, psychosis, stupor

fatal SEs:
  muscle rigidity, coma, kidney failure, cardiac arrhythmias, death
  seen usually at plasma levels > 2.5 mEq/L
  there is no antidote for Li OD…
  D/C Li immediately & "push" Na+
  may take weeks to months to recover…

Li effects in Pregnancy:
can cause teratogenic effects on fetal heart
  avoid in pregnant woman, esp. during the 1st trimester
  note: bipolar post-partum woman off Li is x3 more likely to have a
        manic recurrence vs. non-post-partum woman taken off Li…
MOOD STABILIZERS: Lithium (p.4)

2. Lithium (cont.)

Noncompliance with Taking Lithium
up to 50% of pts. stop taking Li “AMA” --- increased Sxs, incl. increased risk of suicide
noncompliance is often attributed to – SEs, esp. impaired memory & impaired concentration, cognitive slowing, wt. gain, fatigue, and missing the manic “high” in mood

sometimes is a misunderstanding… “all my Sxs are gone now, I am cured and no longer need to take the drug”, etc.
bipolar pts. will need a lifelong therapy with medications
if D/C meds, risk of suicide actually increases over baseline
attempts increase x 14 (vs. never treated S)
completed suicides x 13 (vs. never treated S)

note: sometimes use Li combined with an anticonvulsant drug
helps to prevent relapse

note: bipolar pts. often have co-morbid drug abuse/use problems
55% of bipolar pts. have a Hx of drug abuse (self-medicating?)
82% w/ ETOH
30% w/ cocaine
29% w/ marijuana
21% w/ sedatives or amphetamines
13% w/ opioids