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)

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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…

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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…

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2. **<u>Lithium</u>** (cont.)

<u>Noncompliance with Taking Lithium</u>

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 <u>baseline</u>

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