LITHIUM:
EVERYTHING OLD IS NEW AGAIN

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REGIONS HOSPITAL

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DISCLOSURES

- None

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AN UNDERUTILIZED PSYCHIATRIC TOOL

- Reduced education/training in lithium use
- Multiple alternative agents, particularly atypical antipsychotics
- Side effects and monitoring burdens
- Preferred use for euphoric mania, not for mixed/rapid cycling
- Lack of marketing, lack of incentives for research (generic)
- Direct-to-consumer marketing of atypical antipsychotics
- Portrayal in popular culture?

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20-YEAR TRENDS IN BIPOLAR MANAGEMENT IN OUTPATIENT PSYCHIATRY

- Rhee, et al. Am J Psychiatry, 2020
- Data from Natl Ambulatory Medical Care Survey 1997-2016, compared in four year time blocks
- 2nd Gen antipsychotics Rx increased from 12% in 1997-2000 to 51% in 2013-2016
- Mood stabilizers Rx decreased from 62% in 1997-2000 to 26% in 2013-2016
- Antidepressant Rx increased over time

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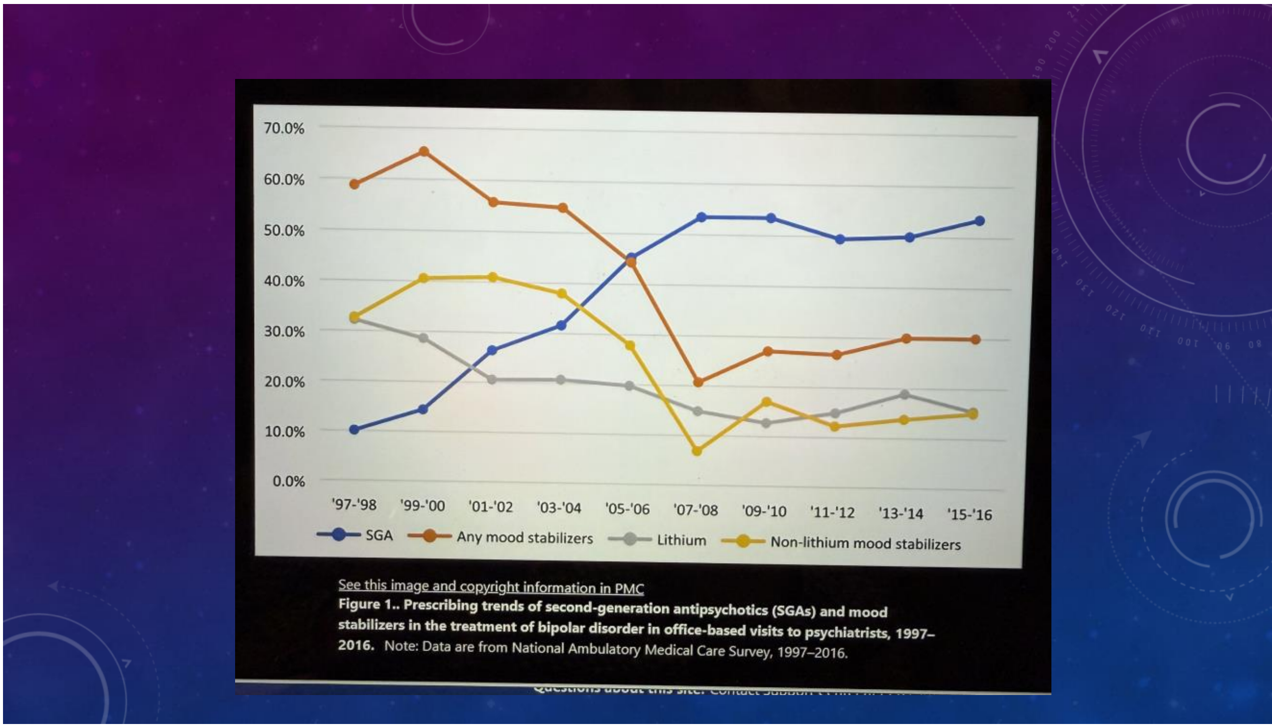

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SGA
Any mood stabilizers
Lithium
Non-lithium mood stabilizers
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Figure 1.. Prescribing trends of second-generation antipsychotics (SGAs) and mood stabilizers in the treatment of bipolar disorder in office-based visits to psychiatrists, 1997–2016. Note: Data are from National Ambulatory Medical Care Survey, 1997–2016.

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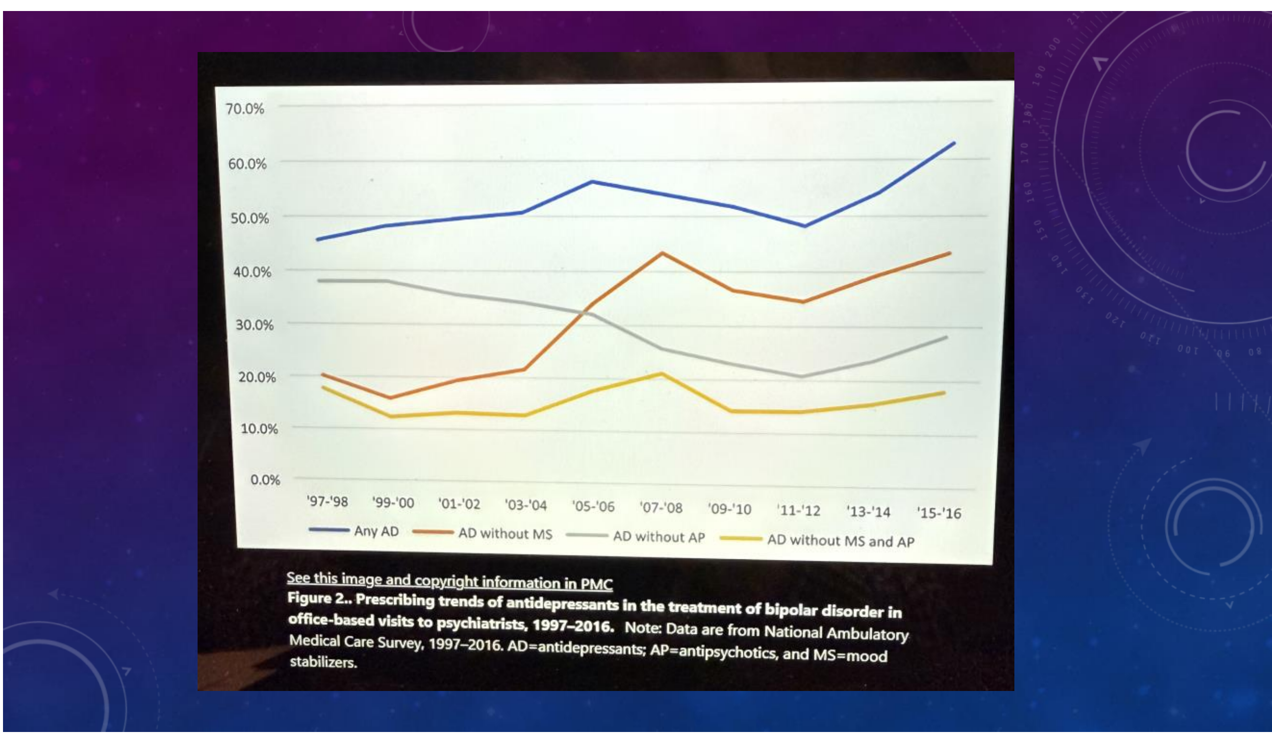

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Any AD
AD without MS
AD without AP
AD without MS and AP
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Figure 2.. Prescribing trends of antidepressants in the treatment of bipolar disorder in office-based visits to psychiatrists, 1997–2016. Note: Data are from National Ambulatory Medical Care Survey, 1997–2016. AD=antidepressants; AP=antipsychotics, and MS=mood stabilizers.

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Greek ”lithos” meaning “stone”

One of the most abundant elements in nature

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USES FOR LITHIUM

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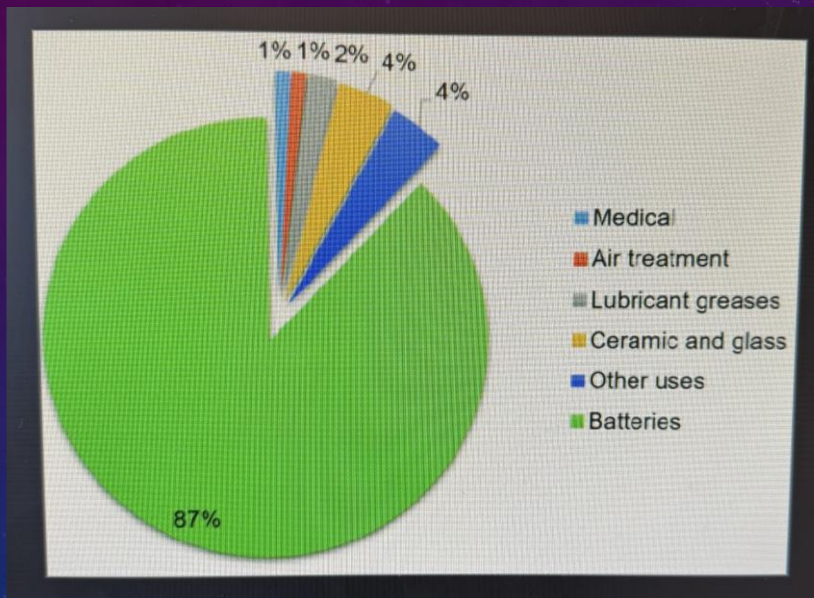

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HISTORY OF LITHIUM

FIRST DISCOVERED IN 1817 IN SWEDEN

- 1870: Dr. Silas Mitchell, neurologist: use as anticonvulsant and hypnotic
- 1871: Dr. William Hammond (Bellevue) first prescribed for mania
- Late 1800's: Lithium mineral springs for mood, gout, general health

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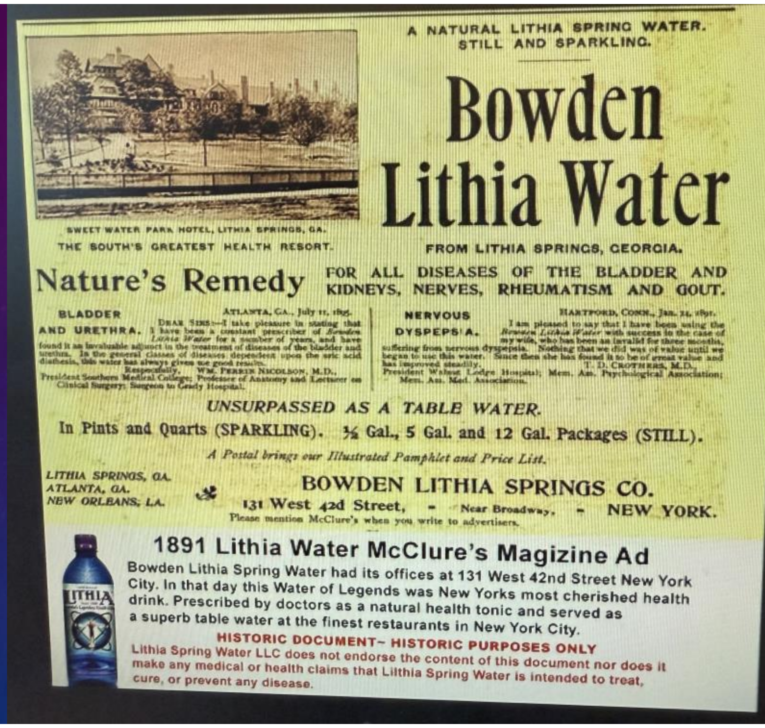

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HISTORY OF LITHIUM

1929: "Bib-Label Lithiated Lemon-Lime Soda" containing lithium citrate

1948: Lithium citrate banned from soft drinks

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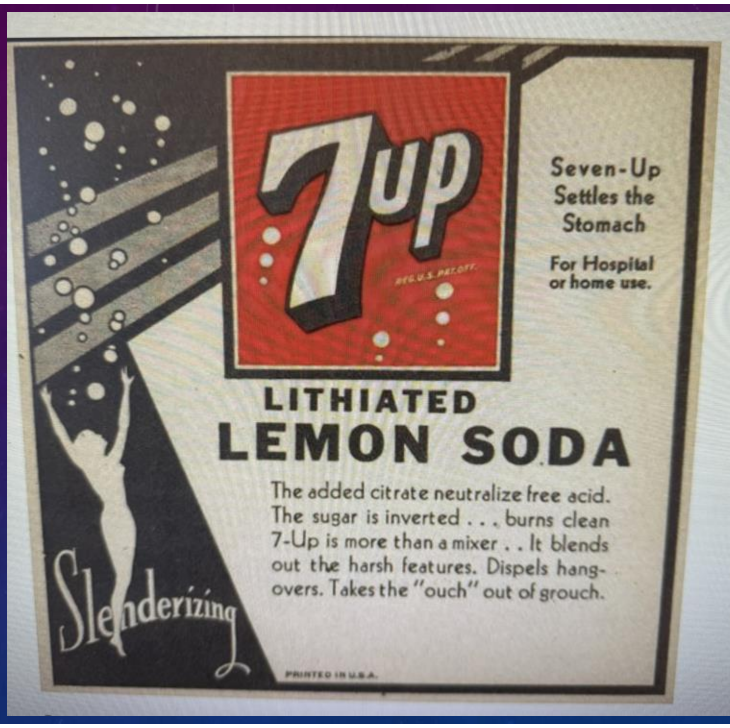
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PSYCHIATRIC USE OF LITHIUM: HISTORY

- Psychiatrist Dr. John Cade, Australia, 1947
- Postulated that mania was caused by a toxin that would be excreted in urine
- Injected urine from manic patients mixed with lithium into guinea pigs
- Noticed that the guinea pigs became calm
- 1949: Dr. Cade published his first clinical report that lithium improved mania and reduced restlessness in psychosis
- First randomized controlled trial of lithium in 1954
- FDA approved for acute mania in 1970 and prophylaxis in bipolar disorder in 1974

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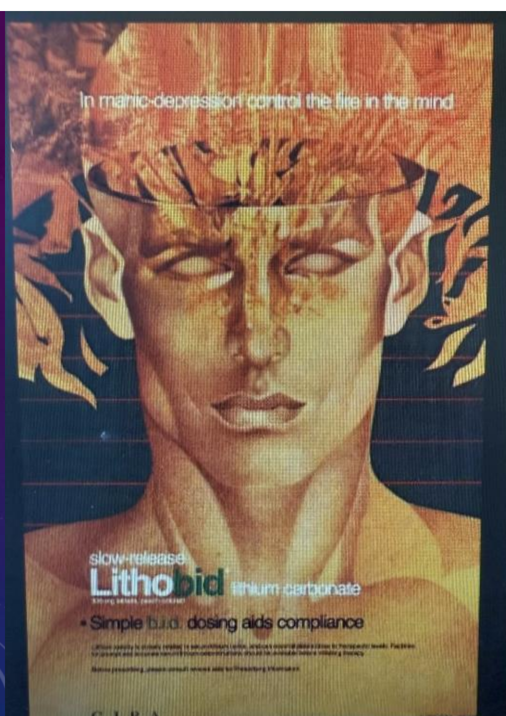

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PHARMACOKINETICS AND MECHANISM OF ACTION

Available in lithium carbonate, citrate, and slow release forms

Not protein bound, renally eliminated, narrow therapeutic index

MOA: essentially unknown. Lithium can influence ion channels and pumps, altering brain biochemistry. Inhibits GSK-3 (glycogen synthase kinase). GSK-3 has a role in neuron degeneration by impairing cellular toxin clearance

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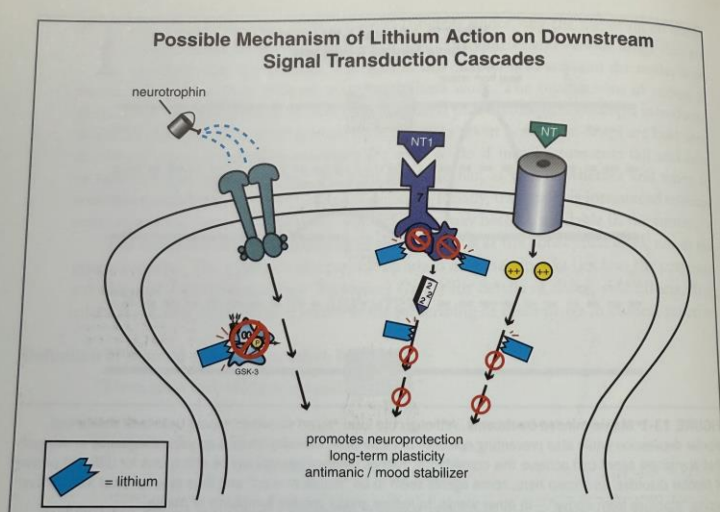

FIGURE 13-3 Lithium's mechanism of action. Although lithium is the oldest treatment for bipolar disorder, its mechanism of action is still not well understood. Several possible mechanisms exist and are shown here. Lithium may work by affecting signal transduction, perhaps through its inhibition of second messenger enzymes such as inositol monophosphatase (right), by modulation of G proteins (middle), or by interaction at various sites within downstream signal transduction cascades (left).

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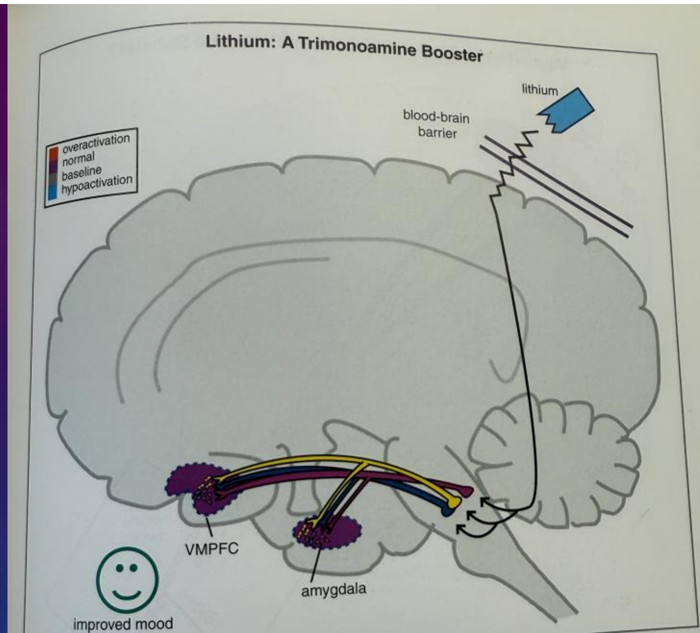

FIGURE 12-113 **Lithium in depression.** Although the mechanism of action of lithium is not clear, it does seem to boost the actions of monoamines, which may make it an efficacious augmenting agent in depression.

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SIDE EFFECTS/ADVERSE EVENTS

- GI: dyspepsia, n/v, diarrhea. Sexual dysfunction. Cardiac (conduction)
- Weight gain, hair loss, acne, sedation, cognition, coordination. Leukocytosis (benign)
- Tremor: fine tremor 4-65%, may decrease with time, propranolol may help. Severe tremor may indicate toxicity
- Thyroid: lithium may compete with iodine for uptake in thyroid gland, alter thyroglobulin, and inhibit TSH action. Hypothyroidism rate 2-4%.
- Hyperparathyroidism (rare). Check Ca++ yearly
- Kidney: renal tubular damage. Clinically significant renal morbidity is rare. Chronic renal insufficiency rate 1-5% after 10-20 years of lithium treatment. ESRD in 0.53% vs 0.2% general population. Impairment in renal concentrating ability. Diabetes insipidus (unresponsiveness of kidney to antidiuretic hormone) in 10% patients on long term lithium (treat with amiloride)
- Neurotoxicity, delirium, encephalopathy (risk with ECT)

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LITHIUM INTERACTIONS

- Pharmacokinetics of lithium tied to physiology of sodium, chloride, potassium and fluid balance
- Na+ restricted diet, thiazide diuretics, hypokalemia increase Li+ levels
- Increase Li+ levels: tetracycline, NSAIDs, ?marijuana
- Succinylcholine: prolonged muscle paralysis
- Hydroxyzine: cardiac conduction disturbances
- ACE inhibitors (lisinopril): confusion, ataxia, ECG changes
- SSRIs: increased tremor, serotonin syndrome, autonomic dysfunction
- TCAs: increased tremor
- Antipsychotics, carbamazepine: reports of neurotoxicity
- ECT: delirium, memory deficits
- Methyldopa: lithium toxicity
- Caffeine: increased clearance of lithium through kidney

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MONITORING (APA TREATMENT GUIDELINES)

- Prior to initiating: BUN, Cr, thyroid function tests, ECG (>age 40)
- First 6 months: renal labs Q2-3 months, thyroid labs “once or twice”
- After 6 months: renal and thyroid labs Q6-12 months or when clinically indicated
- Lithium levels at minimum every 6 months and whenever clinical status changes

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LITHIUM DOSING (APA GUIDELINES)

- Start in low/divided doses to minimize side effects
- Titrate upward generally to serum levels of 0.6-1.2 meq/L
- Check lithium level after dose increase. Steady state levels are reached about day 5

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MAINTENANCE TREATMENT OF BIPOLAR DISORDER: WHAT IS THE OPTIMAL LITHIUM SERUM LEVEL?

- Nolen et al, *Bipolar Disorders* 2019 review article
- Adults: 0.6-0.8 mEq/L, with option to reduce to 0.4-0.6 in case of good response but poor tolerance, or increase to 0.8-1.0 in case of insufficient response and good tolerance
- Child/adolescent: same recommendations
- Over age 65: 0.4-0.6 mEq/L

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SIX WAYS TO PROTECT THE KIDNEYS WHILE PRESCRIBING LITHIUM AIKEN, PSYCHIATRIC TIMES 2019

- Avoid toxicity
- Keep the level low (0.6-0.8 under age 60, 0.4-0.6 over age 60)
- Dose lithium once a day. Half-life is 18-24 hours.
- Watch for polyuria and polydipsia (signs of nephrogenic diabetes insipidus)
- Consider N-Acetylcysteine (antioxidant)
- Monitor kidney function frequently (3-6 months). GFR is more accurate than Cr.

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SPECIAL POPULATIONS

- FDA approved for bipolar disorder from age 7
- Pregnancy: 0.05-0.1% risk of Ebstein's anomaly (tricuspid valve defect), substantially lower than risk of neural tube defects with anticonvulsants
- Lactating: use with caution per American Academy of Pediatrics.
- Elderly: less well tolerated. Elderly are more prone to volume depletion, or to be on thiazide diuretics, NSAIDs. Lithium tremor can be worse in elderly and resemble essential tremor.

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COMPARATIVE EFFICACY IN BIPOLAR DISORDER

- Lithium superior to typical antipsychotics (multiple studies and designs (1970's)
- Atypical antipsychotic efficacy trials have used lithium as a comparator (non-inferiority approach).
- 1996 meta-analysis showed lithium, valproic acid and carbamazepine were comparable in acute mania
- 2003 (Katz, Beech) 20,000 bipolar pt database. Lithium reduce suicide risk compared to valproic acid and carbamazepine
- 2024 (Tondo) data from 13 bipolar RCTs including CBZ, QTP, VPA, ONZ, QTP, LTG(1973-2022) Rates of suicide or attempts were significantly lower with lithium
- Eppel, *J Psychiatry Reform* 2021."Long-term lithium is more effective than SGAs. For the majority of pts, side effect profile carries less risk than the use of SGAs."

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HISTORY OF SUICIDE PREVENTION WITH LITHIUM TREATMENT (TONDO, BALDESSARINI, *PHARMACEUTICALS*, 2025)

- Lifetime: 25-50% bipolar patients attempt suicide. 20X suicide mortality rate of general population
- Tondo et al (1997) review, 28 studies with 17,000 patients. Risks of attempted/completed suicides were 8.6 fold higher in non-lithium pts.
- To date, reduced suicide risk during long-term treatment with lithium in bipolar or recurrent major affective disorder has been found in 35 original studies
- Suicide risk increased 20-fold after lithium discontinuation
- Mechanism ? Direct action against aggressiveness and impulsivity.

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PSYCHIATRIC USES OF LITHIUM

- FDA approval: monotherapy for bipolar I: acute manic and mixed episodes in patients age 7 and older, maintenance treatment in patients 7 years and older
- Off-label: augmentation of antidepressants, augmentation in schizophrenia, impulsive aggression
- Borderline personality disorder: some efficacy for impulsivity, anger, self-harm

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BEYOND PSYCHIATRIC USE: LOW DOSE LITHIUM

HAMSRA ET AL, *CURRENT NEUROPHARMACOLOGY* 2023

- Review article focusing on lithium's potential benefits on aging related diseases
- Cardiovascular disease, osteoporosis, sarcopenia (muscle loss), diabetes
- Alzheimer's: mitigates AD pathogenesis in animal models, prevents cognitive decline in human studies
- Inflammation, oxidative stress

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LITHIUM AND ITS EFFECTS: DOES DOSE MATTER?

MANCHIA ET AL, *INTERNATIONAL JOURNAL OF BIPOLAR DISORDER* 2024

- Clinical and molecular effects of lithium are numerous, and seem to be dose related
- Maximal effect for mood stabilization >0.6 mEq/L
- Lower levels prevent depressive recurrences in older populations
- Neuroprotective and anti-inflammatory effects may occur with very low doses

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NEUROPROTECTIVE EFFECTS CONTINUED

- Lucini-Paioni, *J Affective Disorders*, 2021 review article
- 9 of 13 studies showed increased hippocampal volume in BD patients treated with lithium compared to those that were not
- Forlenza et al, *Br J Psychiatry 2019*. RCT of MCI patients, lithium vs placebo for 2 years then followed for 2 more years. (lithium levels 0.25-0.5). Lithium group showed stable cognition, placebo group showed cognitive and functional decline

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IS IT IN THE WATER?

- Blumi et al, *Journal of Psychiatric Research* 2013. "Lithium in the public water supply and suicide mortality in Texas" suggests higher levels of lithium in water supply offered protective effect against suicide deaths
- Schrauzer et al, *Biological Trace Element Research* 1990. "Lithium in drinking water and the incidences of crimes, suicides, and arrests related to drug addictions" Data from 27 Texas counties 1978-1987, showed violence and suicides were lower in areas with higher lithium levels in drinking water
- Tondo, *Pharmaceuticals* 2025: reviewed 42 studies of Li+ in drinking water and local rates of suicide and violent behaviors. 48% found an inverse correlation

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REFERENCES

- Schatzberg and Nemeroff, Textbook of Psychopharmacology
- Stahl's Essential Psychopharmacology
- Bernstein, Handbook of Drug Therapy in Psychiatry
- Bhalla et al, 50 Studies Every Psychiatrist Should Know

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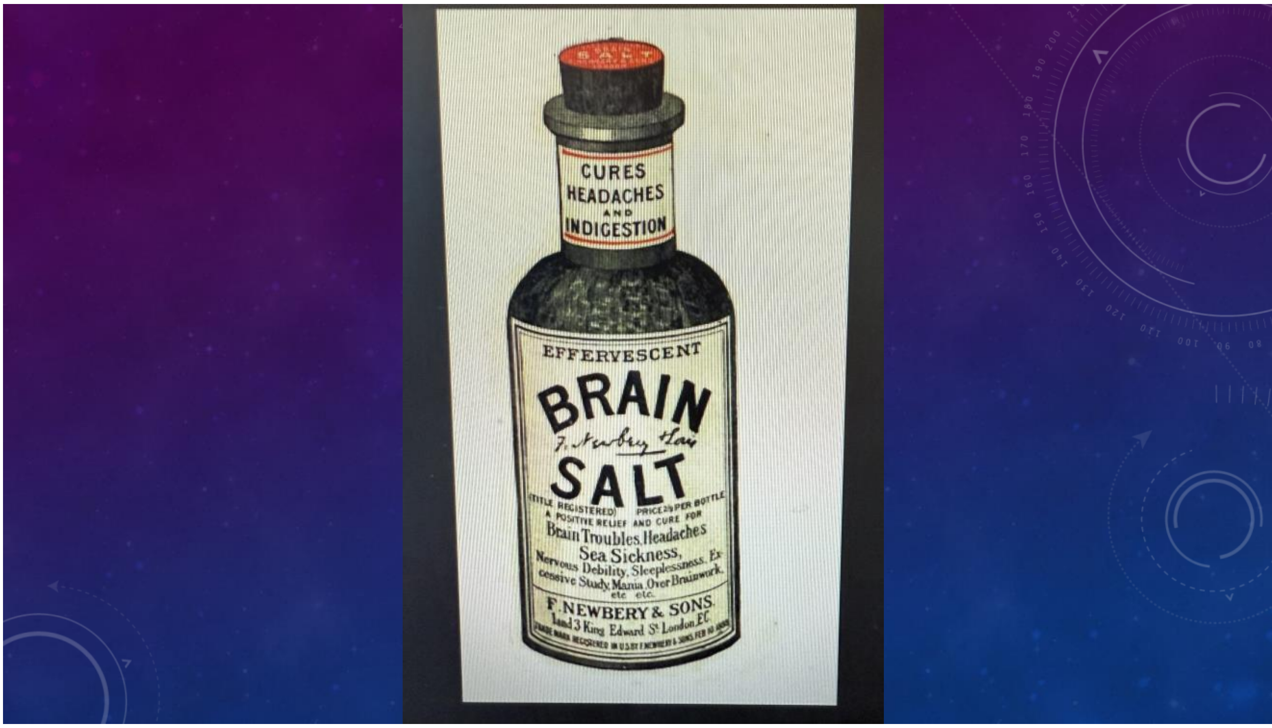
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