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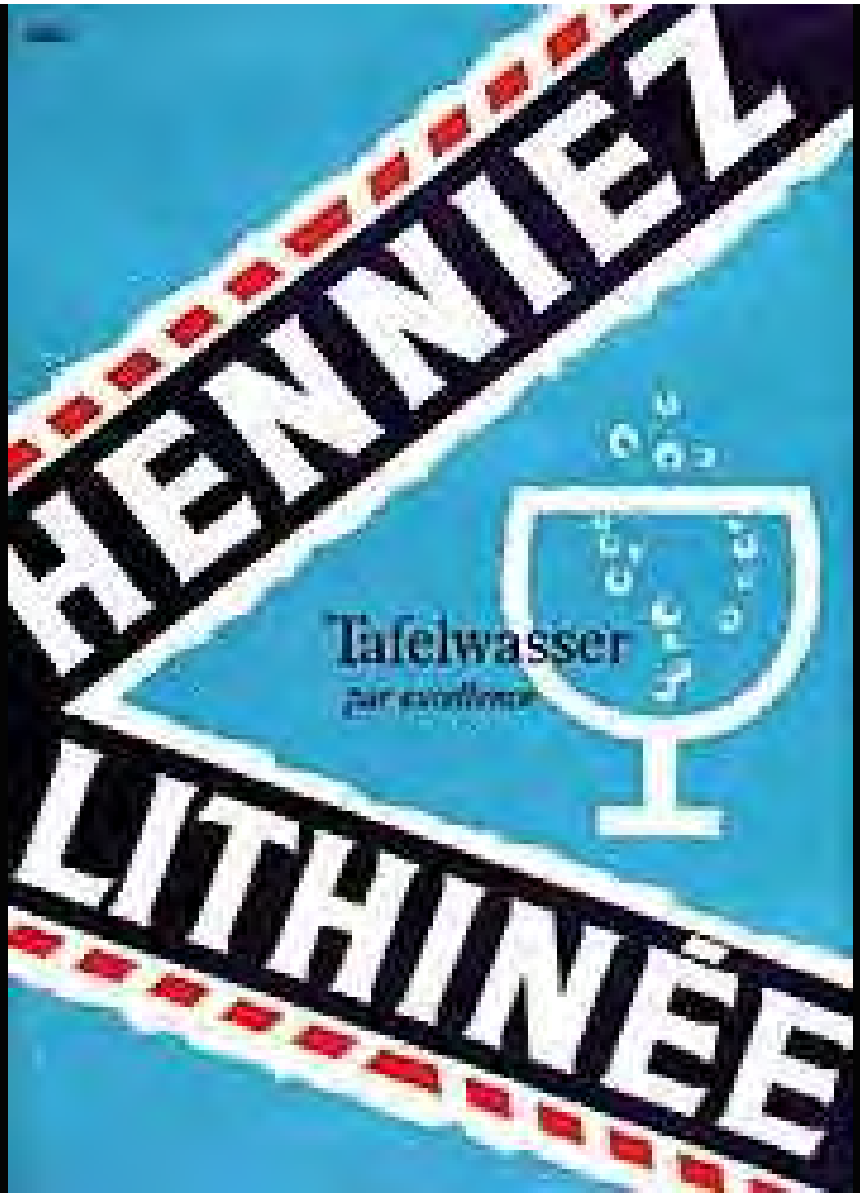
Ospedale Luigi Sacco
Sistema Socio Sanitario Regione Lombardia
ASST Fatebenefratelli Sacco

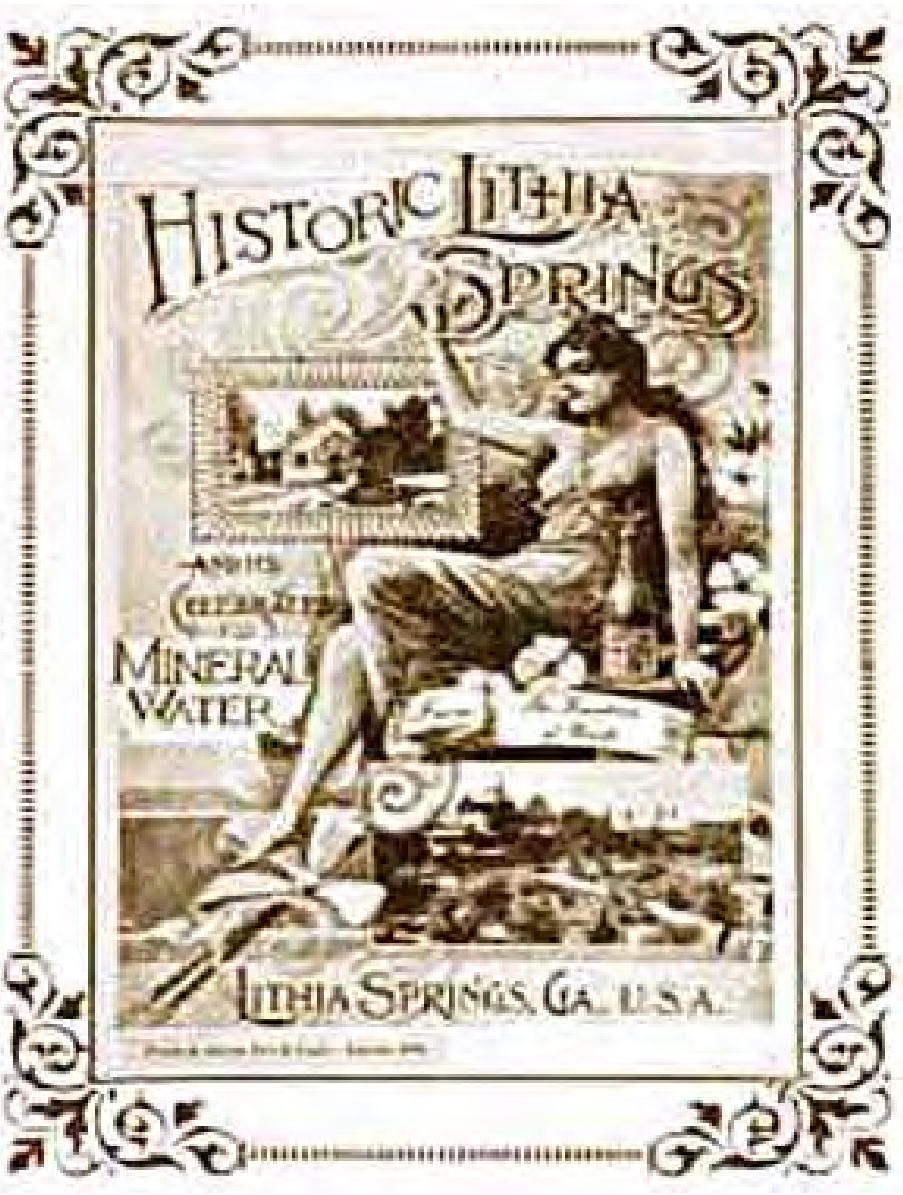
LITHIUM

Side Effects & Medical Benefits

Chris Aiken, MD
Editor-in-Chief, Carlat Psychiatry Report
Assistant Professor of Psychiatry, New York University

AIDDEP Associazione Italiana per i Disturbi Depressivi
Aldo Ravelli Center for Neurotechnology and Experimental Brain therapeutics
UNIVERSITÀ DEGLI STUDI DI MILANO
SINPF


HENNIEZ
Tafelwasser
par excellence
LITHINÉE


HISTORIC LITHIA SPRINGS
MINERAL WATER
LITHIA SPRINGS, GA. U.S.A.

2 liters a day of water from...

Lithium-rich region: 5-23 mg Lithium Carbonate
Lithia Springs: 6 mg Lithium Carbonate
San Pellegrino: 2 mg Lithium Carbonate

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LITHIUM POISONING FROM THE USE OF SALT SUBSTITUTES

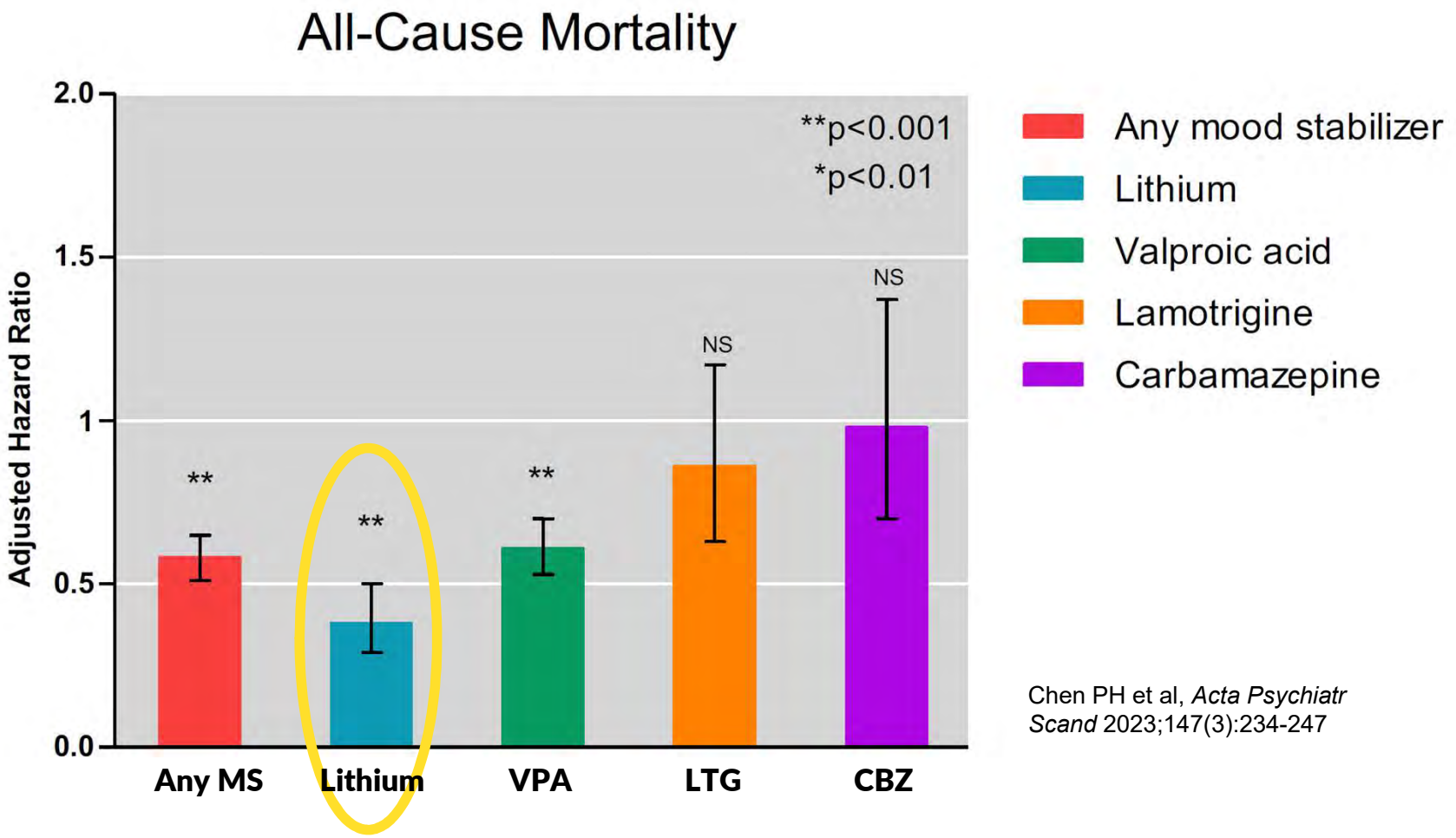
A. C. CORCORAN, M.D.
R. D. TAYLOR, M.D.
and
IRVINE H. PAGE, M.D.
Cleveland

The purpose of this report is to direct attention to lithium intoxication as a complication of the use of lithium chloride as a salt substitute for flavoring low sodium diets. We shall describe the syndrome as it was observed in 7 cases, in 2 of which the intoxication seems to have been a contributory cause of death. The salt substitute used by these patients was westsal,® which is a solution of lithium chloride with citric acid and a small amount of potassium iodide. That the cause

A neurologic consultant noted, "I have never seen such striking muscular irritability in a cerebral lesion. Strychnine poisoning, tetanus and tetany should be considered." An electroencephalogram on August 9 showed a severe generalized slow dysrhythmia with frequencies of 4 to 6 per second and voltages up to 150 millivolts. A neurologic consultant suggested that such an electroencephalogram and clinical state might result from multiple small cerebral emboli. Treatment meanwhile had been supportive, with phenobarbital for restlessness and fluid balance maintained with intravenous fluids (10 per cent dextrose in water and 5 per cent dextrose in 1 per cent solution of sodium chloride). Serum chloride content was 104 milliequivalents per liter and carbon dioxide–combining power 49 volumes per cent on August 9. Serum potassium at the time was 3 milliequivalents per liter.

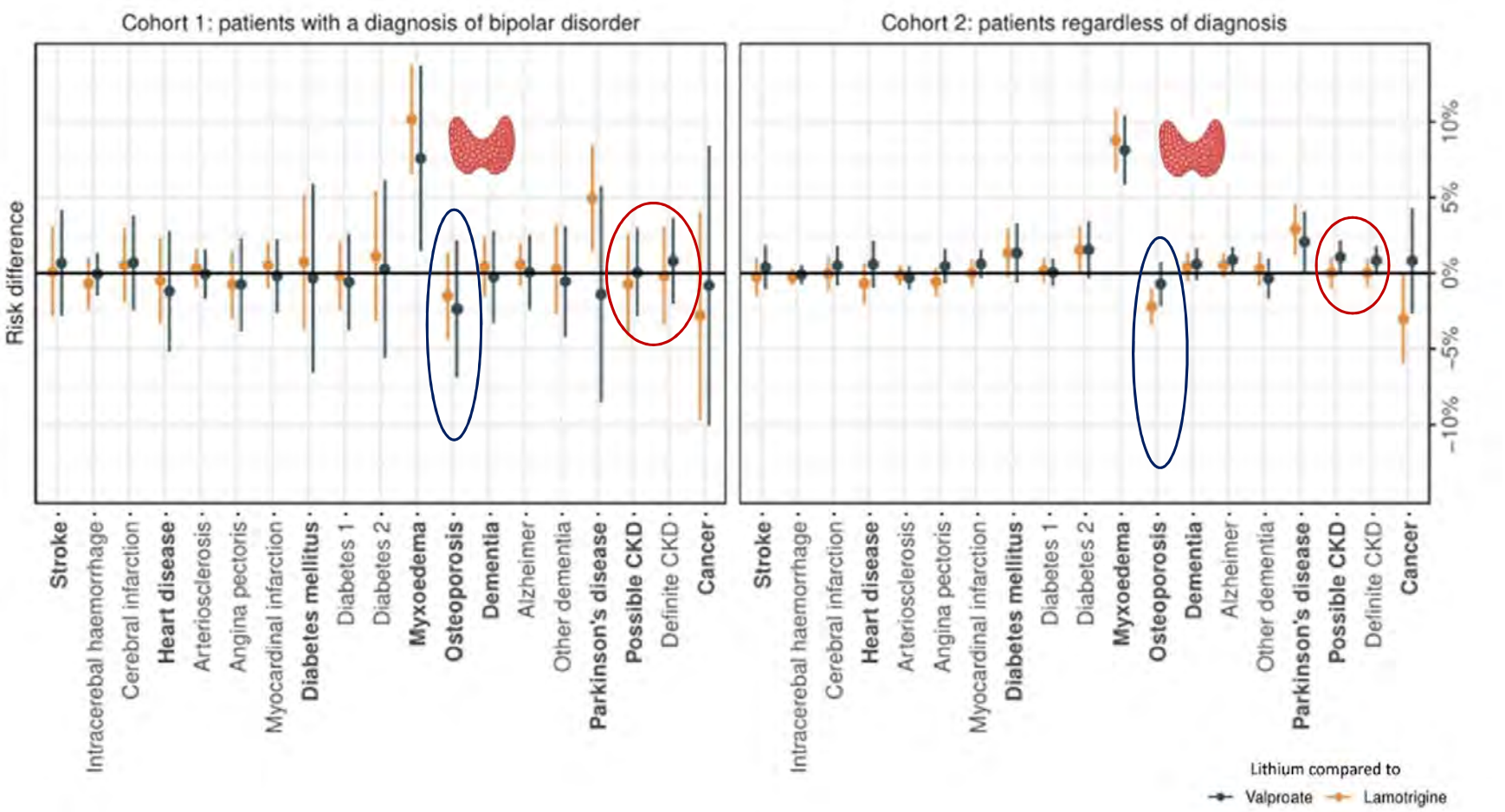
By August 11 she had cleared mentally and was taking fluid by mouth; in succeeding days she improved rapidly, and was discharged in good condition on August 14, having at that time amnesia for the week of her illness. She continued well during the next ten days and resumed her former diet and use of

Lithium lowers medical & suicide mortality in bipolar



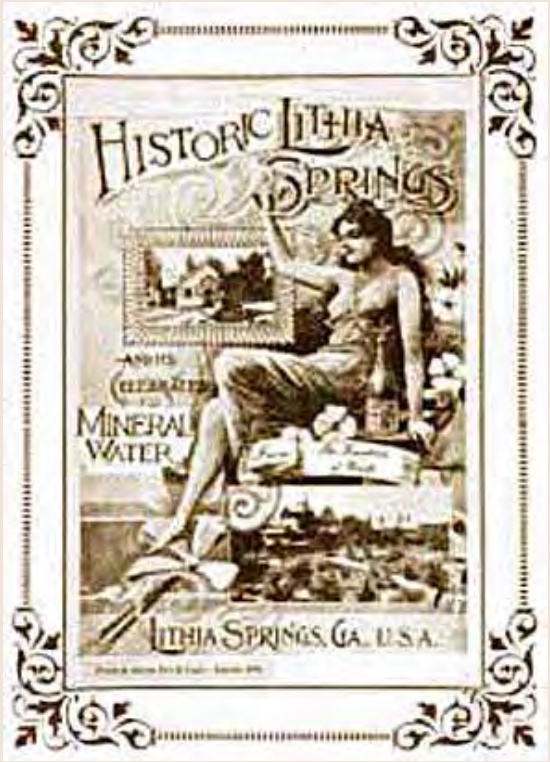
Chen PH et al, *Acta Psychiatr Scand* 2023;147(3):234-247

New Medical Diagnosis on Lithium vs Anticonvulsants



Kessing LV et al, Eur Neuropsychopharmacol. 2024 Jul;84:48-56.

Lithium and Health



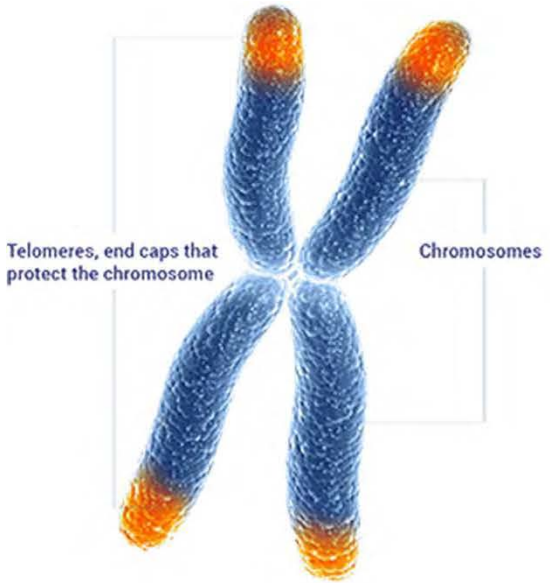
Confirmed

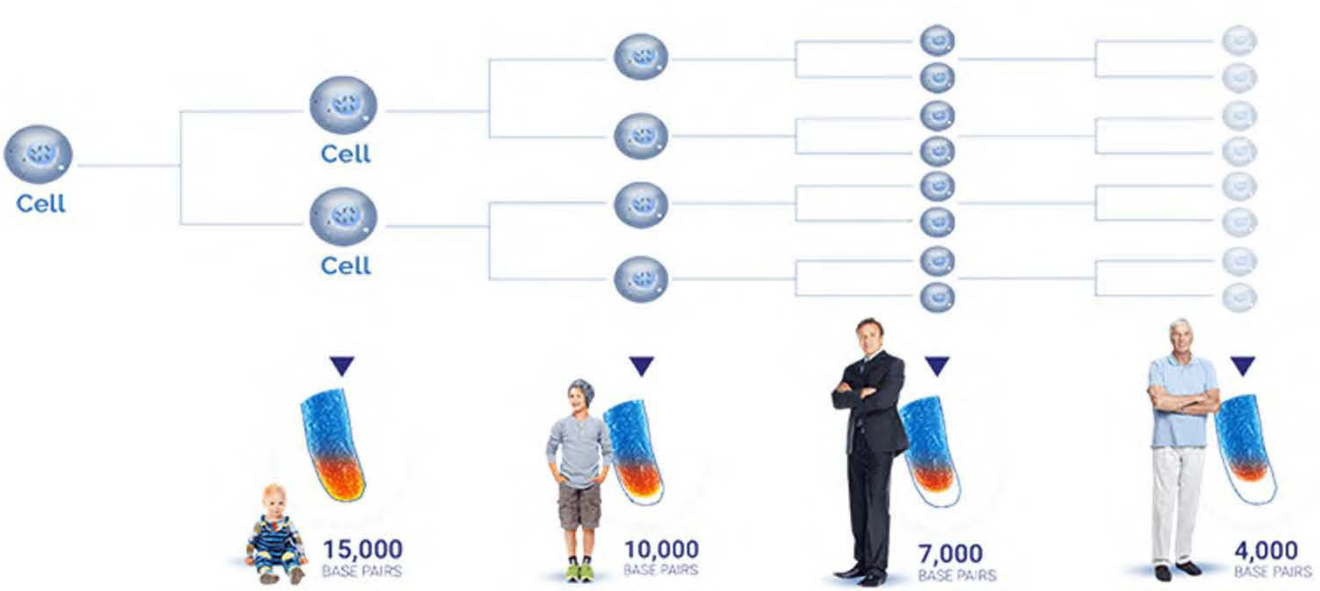
- Prevents suicide
- Lowers dementia risk (neuroprotective)
- Improves cardiac remodeling
- Antiviral effects, anti-COVID

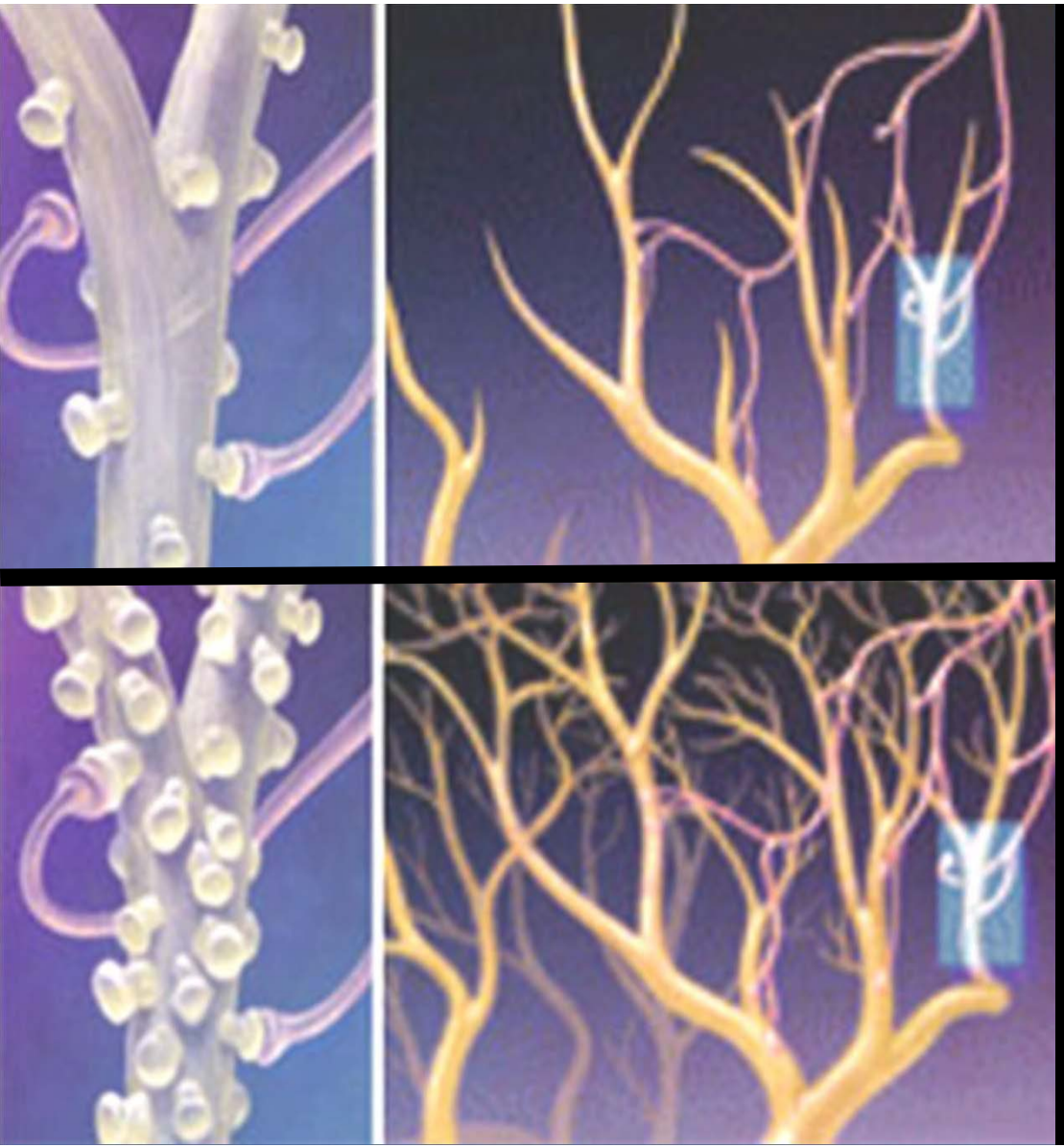
Possible

- Lower cancer risk
- Anti-aging effects (protects telomeres)
- Lower risk of stroke and neurologic illness
- Lower risk of osteoporosis (2022)

Shortening of Telomeres with Age







Neuroprotection

Clock Genes

Uncommon...

Weight gain, Sedation, Cognitive problems

Lithium and Weight Gain

More variability in long term trials

Short (< 12 wks)

Long (> 12 wks)

Group by Length 12 weeks	Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
< 12 weeks	Geller. 2012	1.420	0.206	0.042	1.017	1.823	6.902	0.000
< 12 weeks	Findling. 2015	0.900	1.600	2.560	-2.236	4.036	0.563	0.574
< 12 weeks	Amsterdam. 2016	-0.240	0.311	0.097	-0.850	0.370	-0.771	0.441
< 12 weeks	Keck. 2009	0.620	0.076	0.006	0.472	0.768	8.207	0.000
< 12 weeks	Bowden. 2010	0.200	0.289	0.084	-0.367	0.767	0.691	0.490
< 12 weeks		0.552	0.277	0.077	0.010	1.095	1.995	0.046
>12 weeks	Gao. 2018	-1.590	1.132	1.282	-3.809	0.629	-1.404	0.160
>12 weeks	Yaramala. 2020	2.400	0.544	0.296	1.333	3.467	4.408	0.000
>12 weeks	Findling. 2019	1.800	0.849	0.721	0.136	3.464	2.120	0.034
>12 weeks	Tohen. 2005	-1.400	0.342	0.117	-2.070	-0.730	-4.096	0.000
>12 weeks		0.336	1.174	1.379	-1.966	2.638	0.286	0.775
Overall		0.541	0.269	0.073	0.013	1.069	2.008	0.045

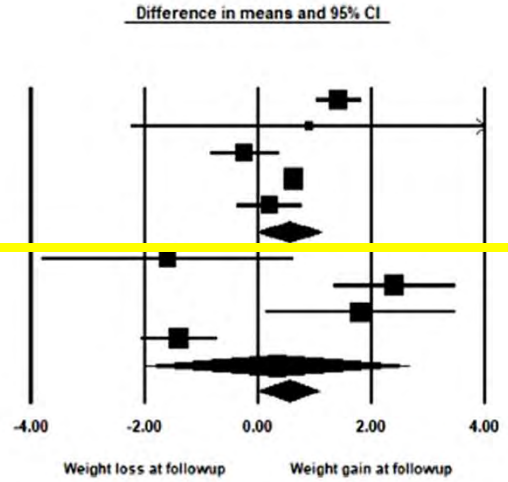


Fig. 3. Weight change during lithium treatment according trial length – Forest plots with the summary effect size (Difference in means) of weight gain, between patients treated with lithium in 2 subgroups: shorter than 12 weeks and longer than 12 weeks.

Gomes-da-Costa S et al, Neurosci Biobehav Rev. 2022;134:104266.

Greil W et al, Int J Bipolar Disord. 2023;11(1):34.


Common...
Thirst, nausea, tremor

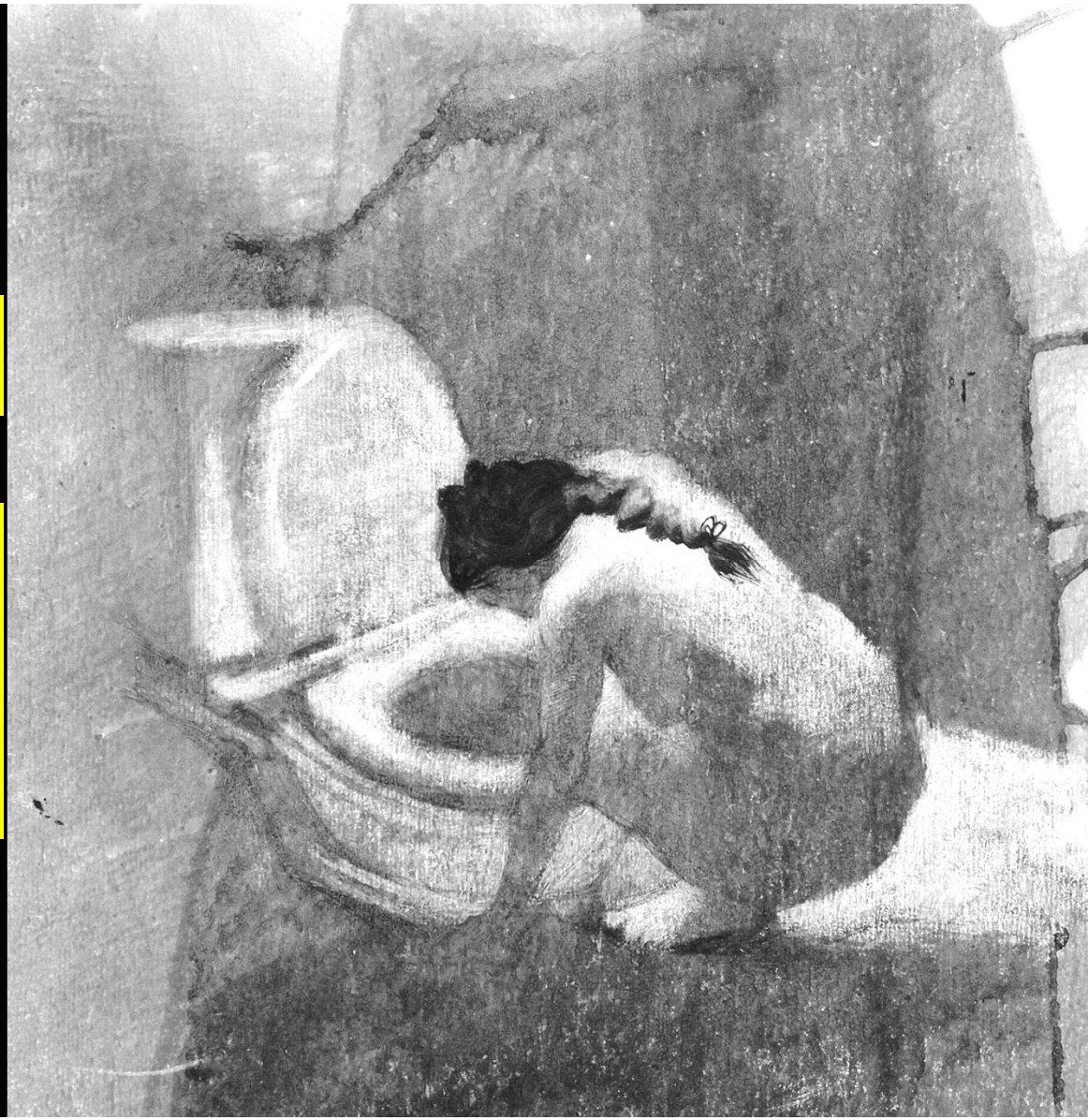
Polydipsia, Polyuria

Avoid caloric beverages (drink water)
Address dry mouth (xylitol gum, biotene rinse)

Assess for nephrogenic diabetes insipidus (NDI):
urine osmolality/Na, serum osmolality and basic chemistry panel
Treat NDI: Amiloride

Nausea

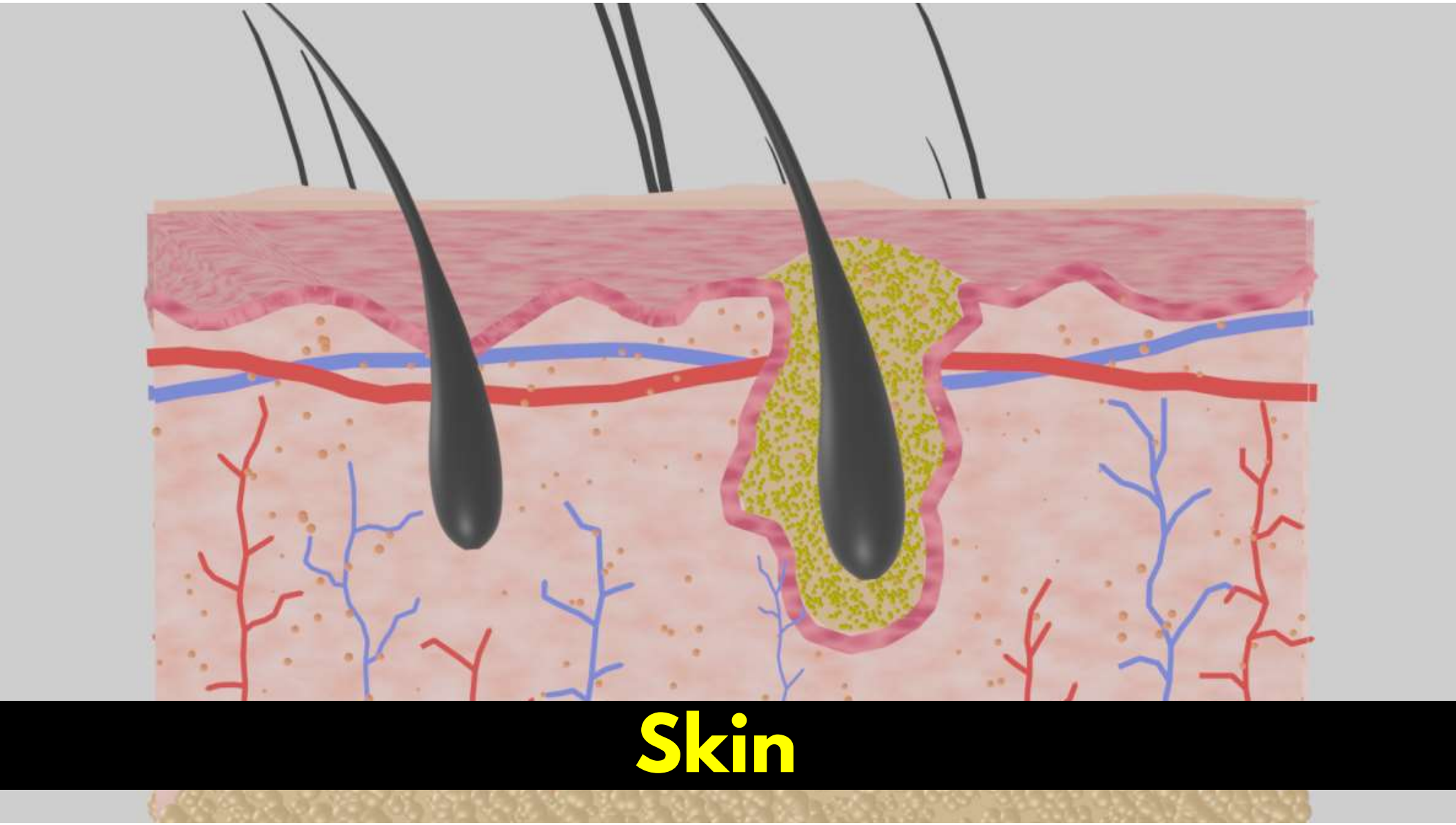
Use ER formulation
Take after a meal
Ginger (1-2,000 mg q12hr)
Ondansetron (4 mg q8hr)



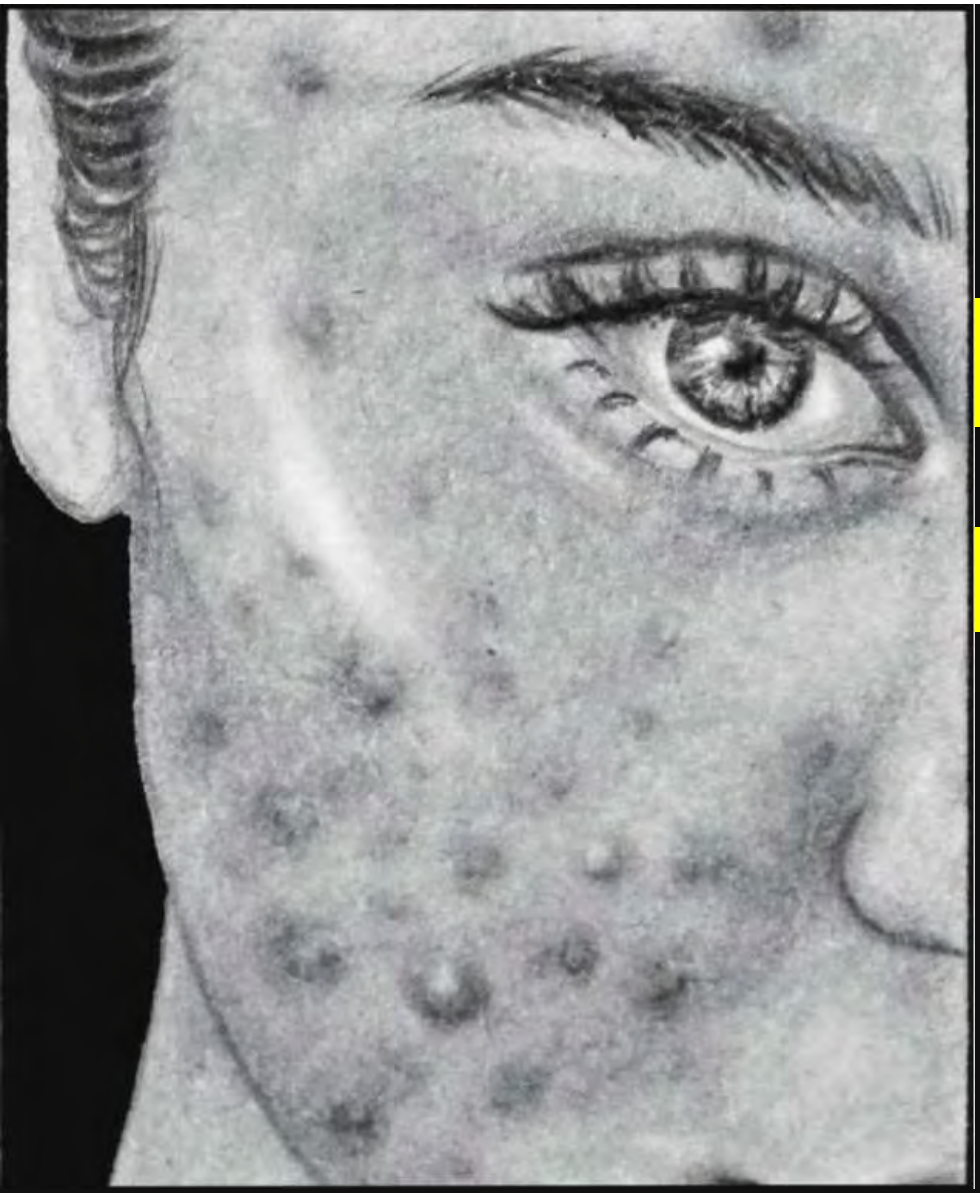
Tremor

ER formulation, Caffeine reduction

Propranolol, Vitamin B6, Nimodipine, Gabapentin

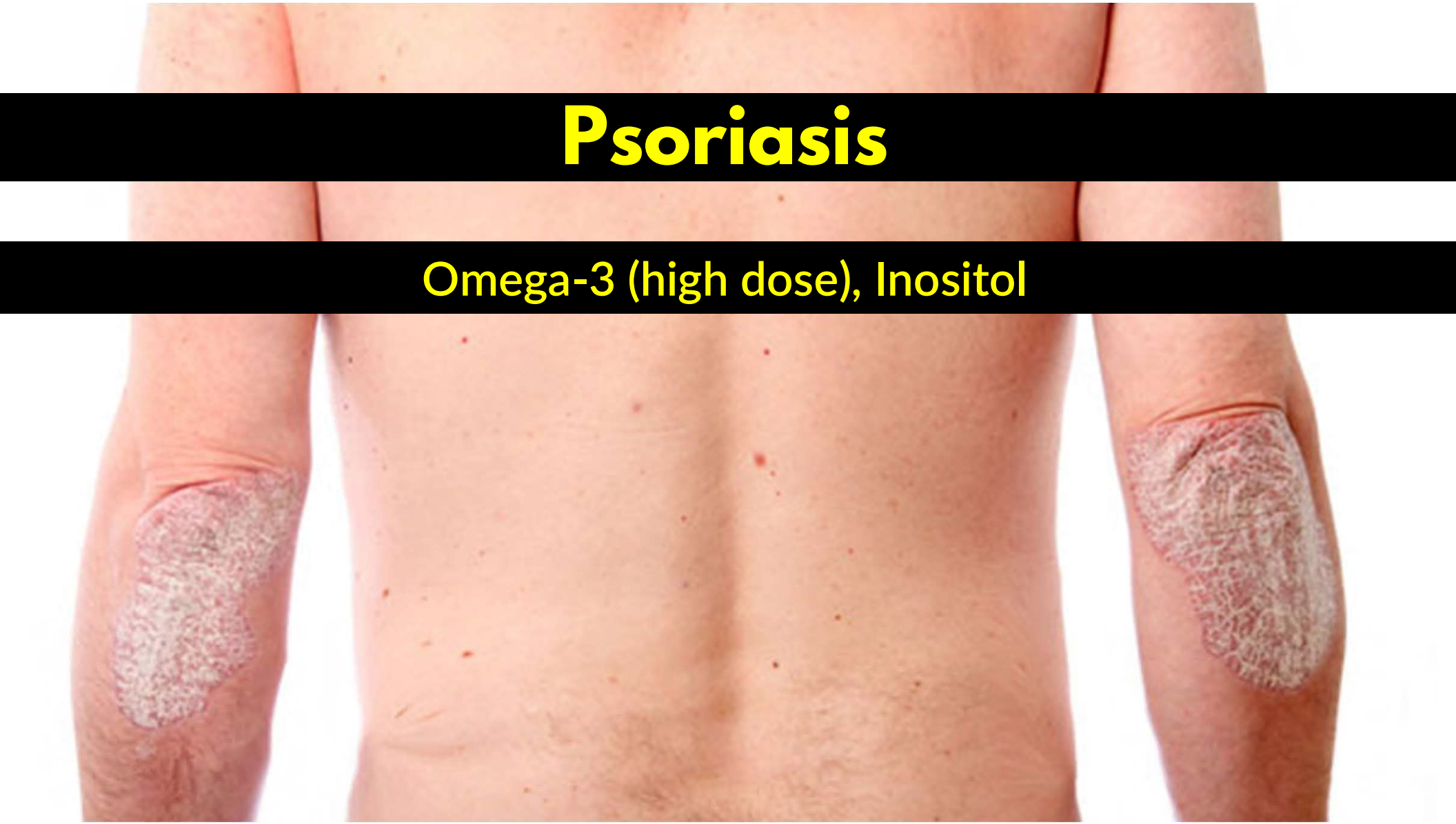


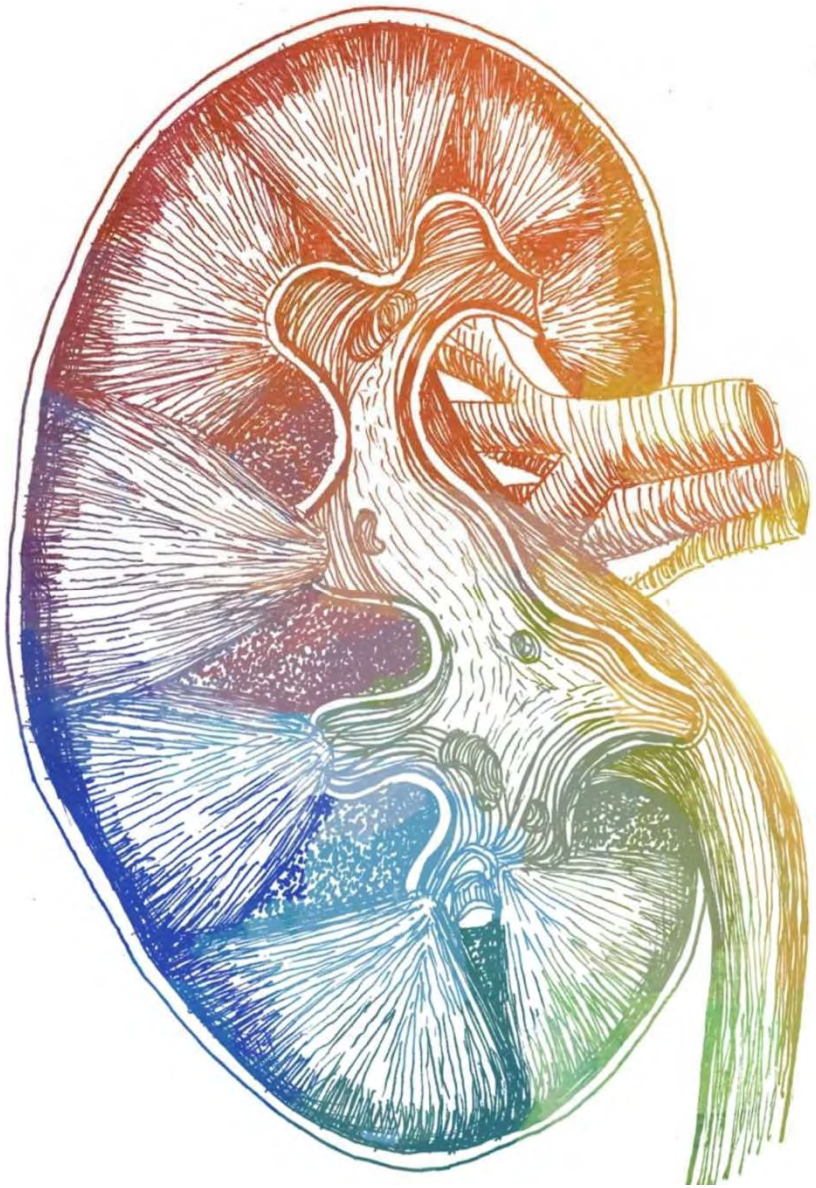
Skin



Acne

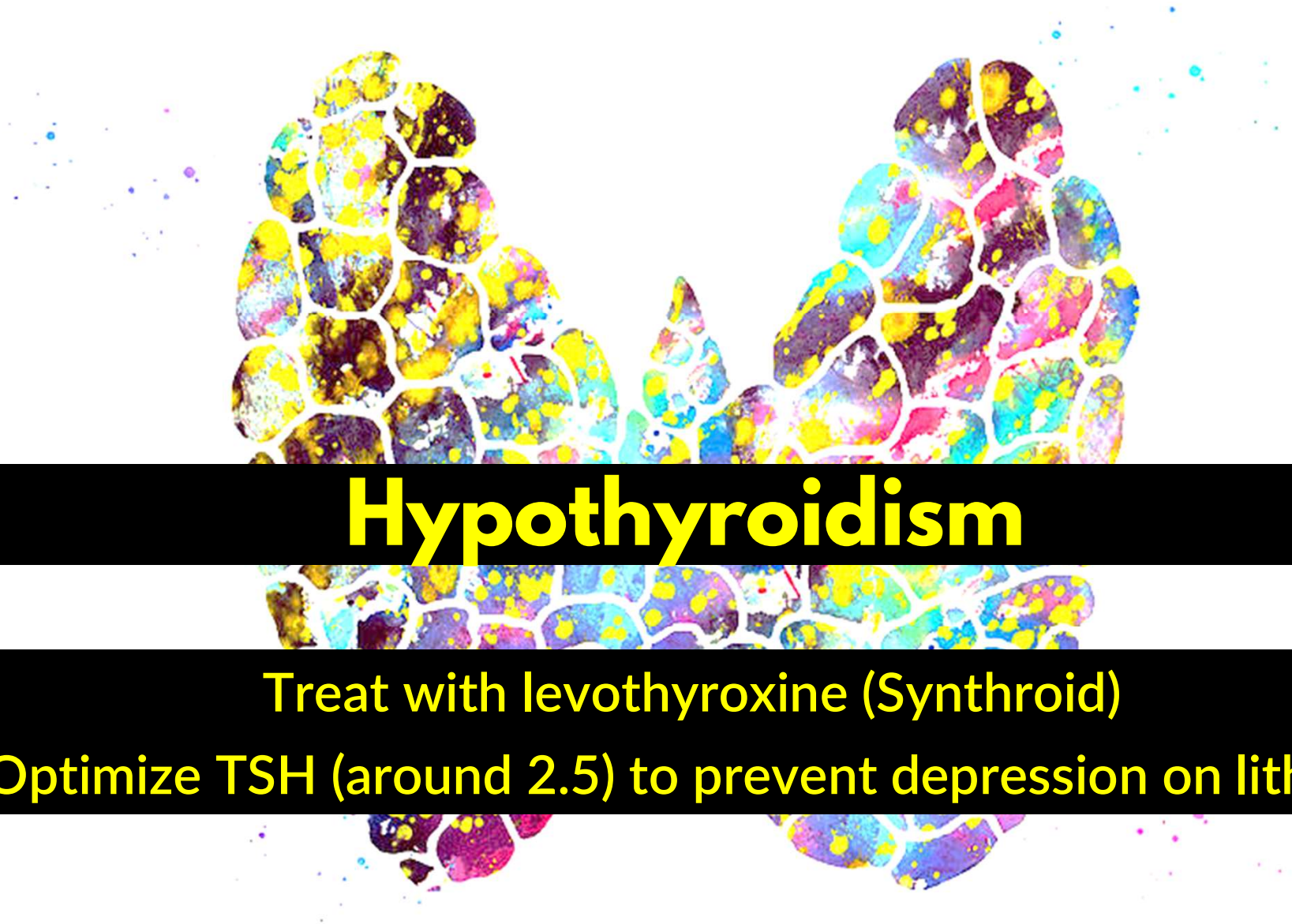
Minocycline, Omega-3, Probiotics


Psoriasis
Omega-3 (high dose), Inositol



Medical

Thyroid
Parathyroid
Renal
Cardiac
Lithium Toxicity

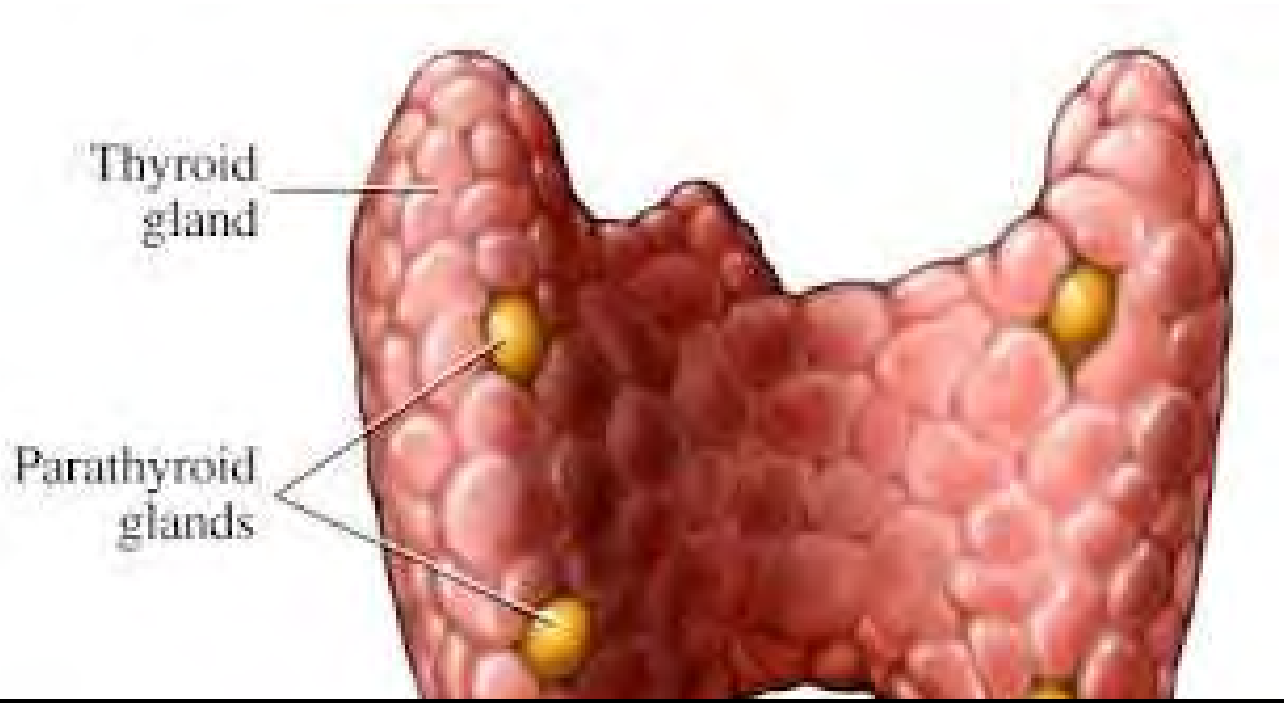


Hypothyroidism

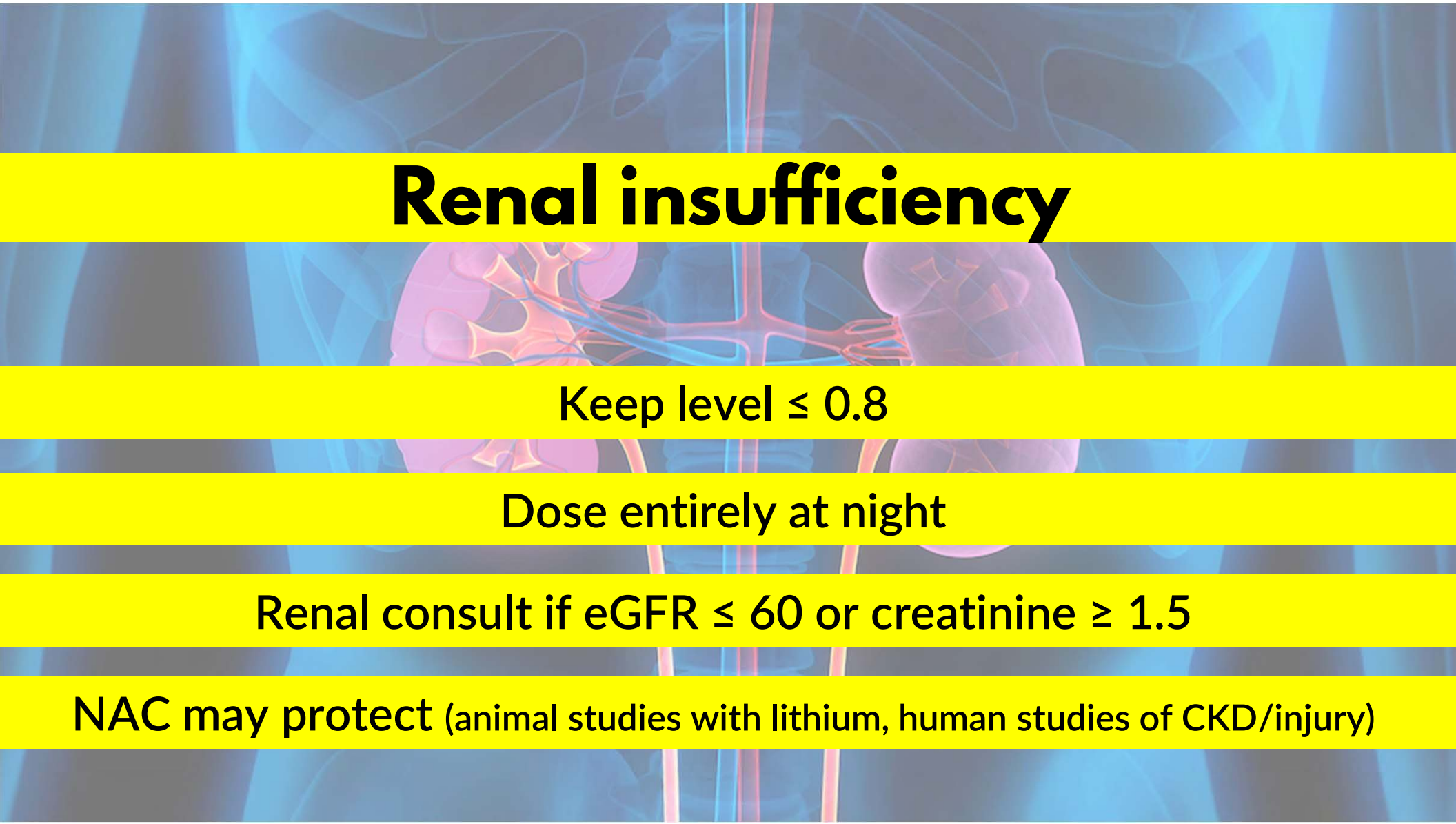
Treat with levothyroxine (Synthroid)

Optimize TSH (around 2.5) to prevent depression on lithium

Hyperparathyroidism



Monitor Ca. If elevated check parathyroid.
If hyperparathyroidism, refer to endocrinology.



Renal insufficiency

Keep level ≤ 0.8

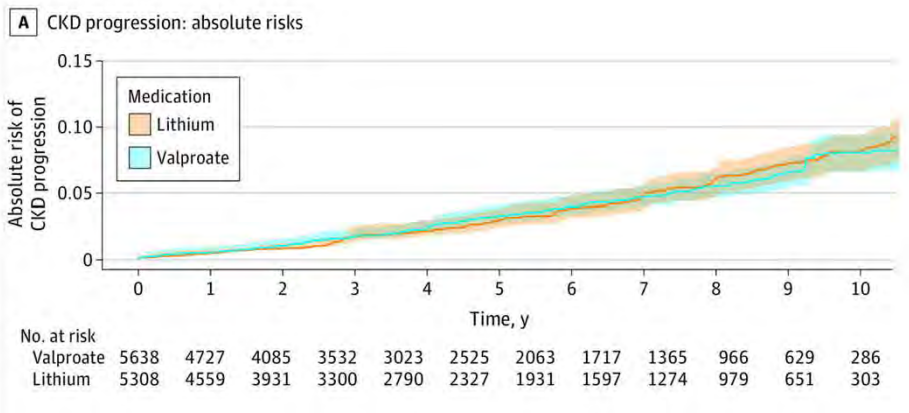
Dose entirely at night

Renal consult if eGFR ≤ 60 or creatinine ≥ 1.5

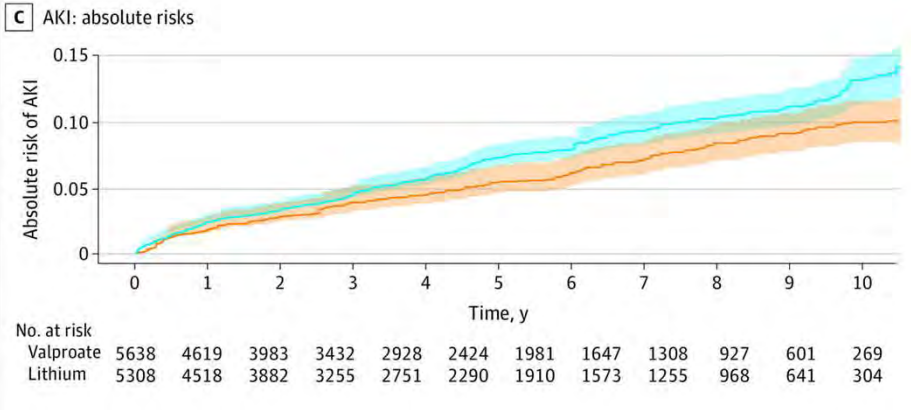
NAC may protect (animal studies with lithium, human studies of CKD/injury)

Compared to valproate in 10,946, lithium has…

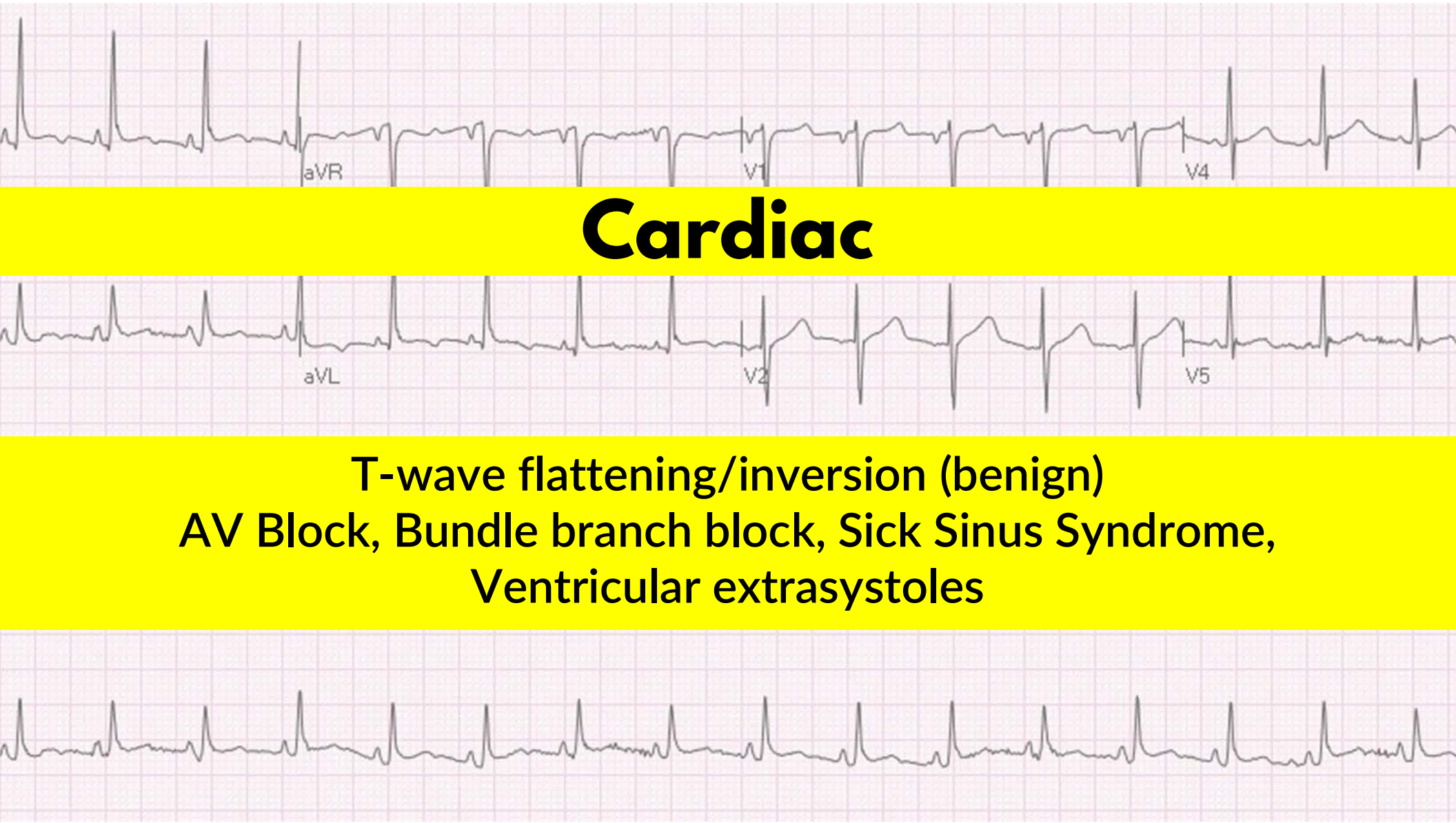
Same risk of chronic kidney disease



Lower risk of acute kidney injury



Bosi A et al, JAMA Netw Open 2023;6(7):e2322056



Cardiac

T-wave flattening/inversion (benign)
AV Block, Bundle branch block, Sick Sinus Syndrome,
Ventricular extrasystoles

Lab Monitoring

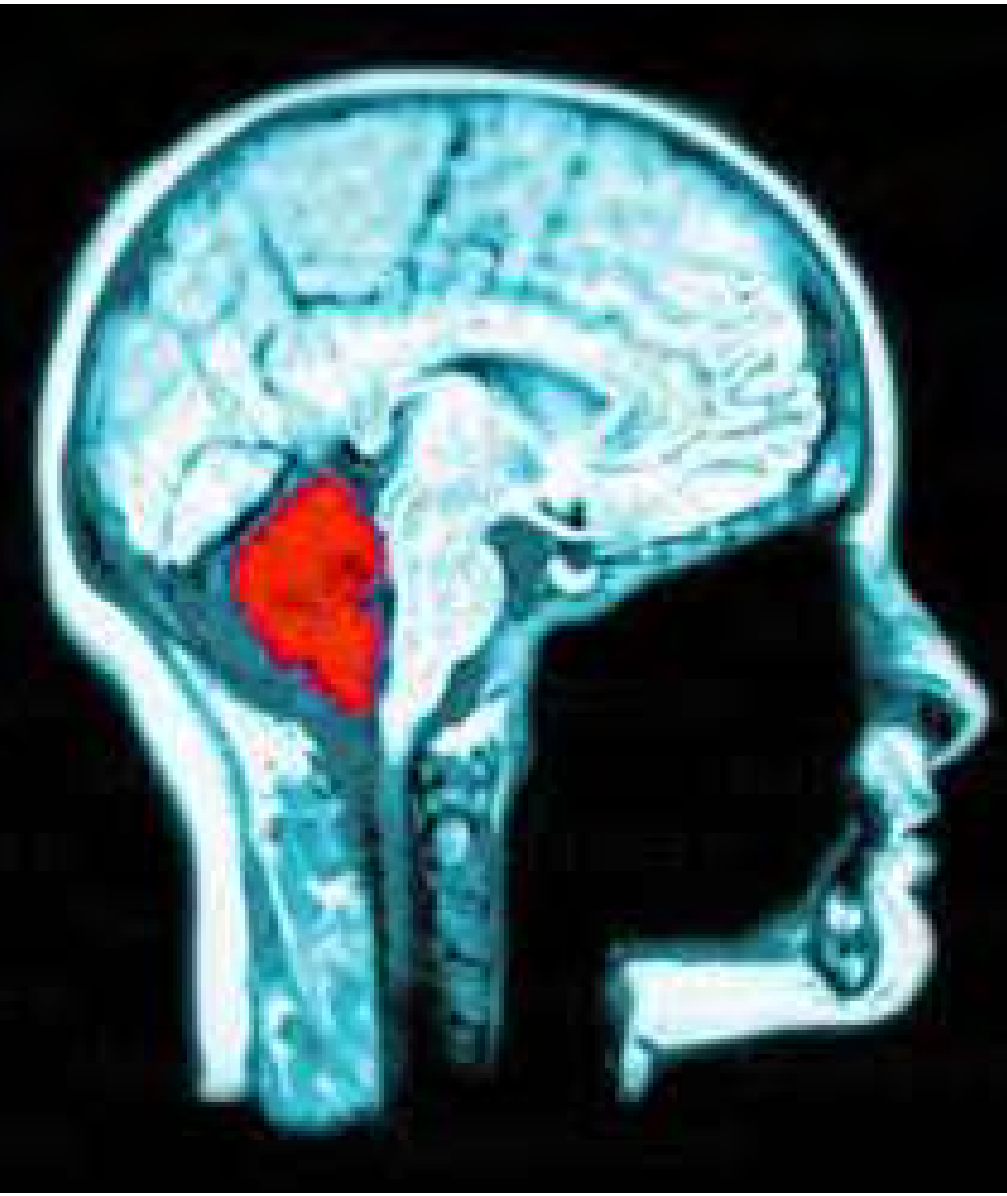
Labs every 6-12 months

(more often in first 3 years or if elderly, renal impairment, unstable, drug interactions)

TSH, creatinine (eGFR), calcium

Optional: WBC (benign neutrophil elevation), pregnancy

Over 50 or heart disease: EKG



Lithium Toxicity

“Can’t walk, can’t talk, shaking”

Ataxia

Slurred speech

Coarse tremor

Hyperreflexia, myoclonus

Diarrhea

Sluggish, somnolence, coma

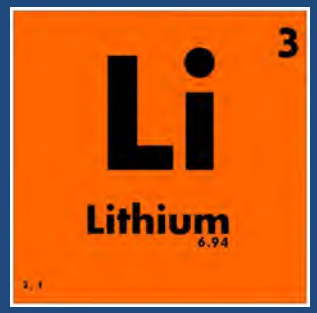
More often, factors raise than lower lithium

Raises Lithium	Lowers Lithium
Drug interactions: antihypertensives, diuretics, NSAIDs, and more (see full list)	Drug interactions: acetazolamide, xanthines (aminophylline, theophylline), mannitol
Dehydration	Caffeine
Aging	Active mania*
Renal slowing	Pregnancy
Low-sodium diet	Going off a low-sodium diet

*Lithium levels fall during active mania, possibly due to increased urination in the manic state

Medications That Raise Lithium	
Class	**Examples**
Thiazides and loop diuretics	The "-ides": bumetanide, chlorothiazide, furosemide, hydrochlorothiazide (potassium-sparing diuretics like amiloride and spironolactone are OK)
ACE inhibitors	The "-prils": benazepril, captopril, enalapril, lisinopril
Angiotensin II antagonists	The "-sartans": azilsartan, losartan, valsartan
NSAIDs and COX-2 inhibitors	**Over the counter:** ibuprofen, naproxen (aspirin is OK) **Prescription:** celecoxib, diclofenac, indomethacin, meloxicam (sulindac is usually OK)
Antibiotics	Metronidazole, tetracycline

Aiken C et al (2022) *Prescribing Psychotropics,* Carlat Publishing



Side Effect Guide

Antidote	Use	Potential Psych Benefits	Dose (mg/day)
Propranolol	Tremor	Anxiety. AP-akathisia.	80-240
Vitamin B6	Tremor	Depression. AP-akathisia, AP-hyperprolactinemia.	500-1,000
Nimodipine	Tremor	Ultra-rapid cycling	240-480 divide TID
Gabapentin	Tremor	Social anxiety, alcohol, cannabis	600-1200 divide BID-TID
Ondansetron	Nausea	OCD, binge drinking, bulimia	4 mg q12 hr
Ginger	Nausea	n/a	1,000-2,000 mg q12hr
Amiloride	NDI*	n/a	5
Aspirin	Sex dys in men	n/a	240
Minocycline	Acne	Depression	100-200
Probiotics	Acne	Depression, anxiety	Take with fiber
Omega-3	Acne, psoriasis	Depression	2000-3600 of EPA + DHA
Inositol	Psoriasis	Depression, bulimia	12,000-18,000
NAC*	Renal protect	Depression	1,200-2,000

*NDI = nephrogenic diabetes insipidus

*NAC (N-acetylcystine) has animal studies for lithium-renal toxicity, human trials in renal failure and bipolar depression

The Future: LiProSal

Branded formulation pairs lithium with the amino acid proline and salicylate (Aspirin) to allow higher CNS levels and lower serum levels, potentially reducing side effects.

Studies underway in bipolar, depression, PTSD, and dementia

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Questions?

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