

LITHIUM IN THE CENTRAL NERVOUS SYSTEM

Laurie K Mischley, ND, MPH, PhD(c)

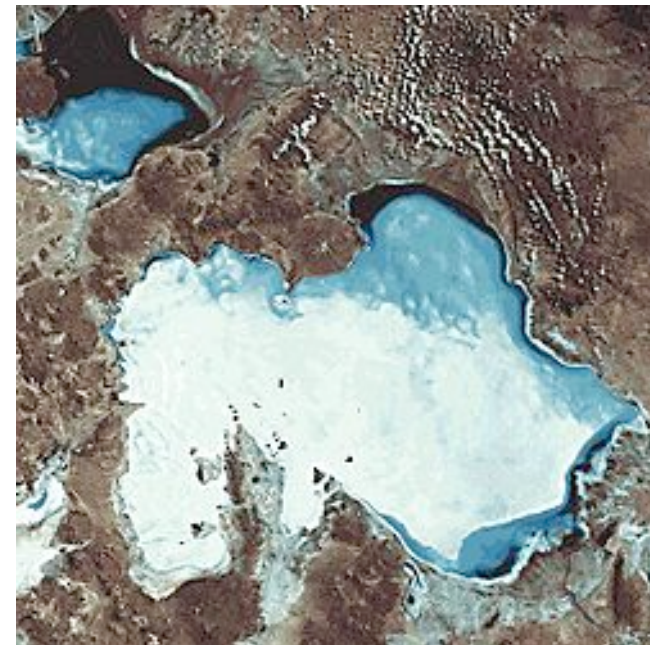
Orthomolecular
Medicine Today
Conference

Vancouver, Canada
April 2014



Geological perspective

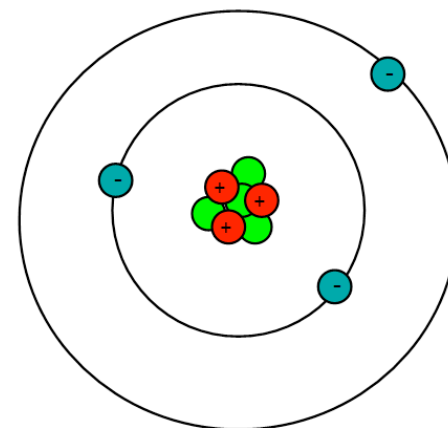
- Unevenly distributed throughout crust
 - Not unique: Iodine, Selenium
 - Medical geography- Harold Foster
- Largest known deposits are Bolivia & Chile
 - Salar- Spanish salt flats



Chemical perspective

Alkali metal, lightest of all the metals

Occurs as a salt



Group	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1	1 H																	2 He
2	3 Li	4 Be								5 B	6 C	7 N	8 O	9 F	10 Ne			
3	11 Na	12 Mg								13 Al	14 Si	15 P	16 S	17 Cl	18 Ar			
4	19 K	20 Ca	21 Sc	22 Ti	23 V	24 Cr	25 Mn	26 Fe	27 Co	28 Ni	29 Cu	30 Zn	31 Ga	32 Ge	33 As	34 Se	35 Br	36 Kr
5	37 Rb	38 Sr	39 Y	40 Zr	41 Nb	42 Mo	43 Tc	44 Ru	45 Rh	46 Pd	47 Ag	48 Cd	49 In	50 Sn	51 Sb	52 Te	53 I	54 Xe
6	55 Cs	56 Ba	*	72 Hf	73 Ta	74 W	75 Re	76 Os	77 Ir	78 Pt	79 Au	80 Hg	81 Tl	82 Pb	83 Bi	84 Po	85 At	86 Rn
7	87 Fr	88 Ra	**	104 Rf	105 Db	106 Sg	107 Bh	108 Hs	109 Mt	110 Ds	111 Rg	112 Cn	113 Nh	114 Fl	115 Mc	116 Lv	117 Ts	118 Og
				* 57 La	58 Ce	59 Pr	60 Nd	61 Pm	62 Sm	63 Eu	64 Gd	65 Tb	66 Dy	67 Ho	68 Er	69 Tm	70 Yb	71 Lu
				** 89 Ac	90 Th	91 Pa	92 U	93 Np	94 Pu	95 Am	96 Cm	97 Bk	98 Cf	99 Es	100 Fm	101 Md	102 No	103 Lr

Swedish chemist Johan August Arfvedison isolated the salt in 1817.



Li Content of Earth's Crust

- Highest where salts have been concentrated by solar evaporation
- Desert, playa, salar



Lithium in Industry

- Lithium is highly anodic in the galvanic series
- Reacts with water something like sodium does
- Not very stable, but excellent energy density
 - Joules of energy per kilogram
 - Offers electronics that are smaller, lighter, thinner
- Widely used battery technology in small electronics



Human Use

Travel to mineral springs dates back ~ 2000 years



Gerhard Schrauzer

Born in Eastern Europe, grew up interested in the local mineral springs purported by locals to having mood-enhancing properties.

German: 'Natalie Quelle'

1948- Dr. Schrauzer analyzed this water while employed as a laboratory chemist at a local research institute specializing in mineral waters.

Lithium in Biology
and Medicine: New
Applications and
Developments

Schrauzer, G. N.

Note: This is not the actual book cover

Downtown Fountain in Lithia Park, OR





LITHIA SPRINGS

RESORT
ASHLAND, OREGON



LITHIUM SCIENCE

Is it essential?

What are the symptoms of deficiency?

How is adequacy assessed?

Li is an Essential Nutrient

- Every cell contains lithium.
- The body does not synthesize it's own lithium.
- Must be exogenously supplied: physiologically essential

- Required dose is estimated to be ~ 1 mg/ d.

Conditional essentiality has yet to be determined:

Are there certain populations who may have unique requirements?

Likely, given what we know about biochemical individuality, SNPs, epigenetics, etc.

Schrauzer GN. J Am Coll Nutr 2002;21(1):14-21.

Where does it come from ?

- WATER

- A function of the natural variation in the Earth's crust
- The higher the rainfall in any region, the lower the lithium level in the water supply.

- FOOD

- Likely a function of the soil the foods were grown in, and how well they are washed before consumed.
- Last analyzed 20+ years ago- farming practices have changed substantially.

Data in humans and rodents suggests the higher the Na content of the diet, the lower the Li.

Pickett EE. Biol Trace Elem Res 1992;34(3):299-319.

Schopfer J, Biol Trace Elem Res 1994;40(1):89-101

Human Intake

- Average US consumption: 650- 3100 $\mu\text{g}/\text{d}$.
Determined by location/ source of water
Soil/ mineral content of diet
- Worldwide variation in intake:

Location	Lithium Intake
Tijuana, Mexico	1485 \pm 1009 $\mu\text{g}/\text{d}$
Glaveston, Texas	821 \pm 684 $\mu\text{g}/\text{d}$
Vienna, Austria	348 \pm 290 $\mu\text{g}/\text{d}$

Schrauzer GN. J Am Coll Nutr 2002

Metabolism

- Absorbed as a salt via Na⁺ channels in the small intestine
- Excreted through the kidneys
- Plasma concentration twice as high as RBC or CSF
- Ubiquitously distributed, highest concentrations in kidney, cerebrum, cerebellum (extra 10-20%)
- Deposited in bone and hair

Assessment

- Goats fed lithium-deficient or lithium-replete diets & then slaughtered
 - Blood serum: 19% reduction ($P < 0.001$)
 - Hair: 30% reduction ($P < 0.001$)
 - Milk concentrations: 31% reduction ($P < 0.001$)
- Supplemental lithium results in a direct dose-response relationship with hair lithium concentrations
 - Up to 2000 $\mu\text{g/g}$
- An ecological study in Texas correlated tap water lithium concentration with body status in urine.

Schrauzer GN et al. Bio Trace Elem Res 1994
Anke MAW, et al. Biological Importance of Lithium. 1991

HAIR ELEMENTS

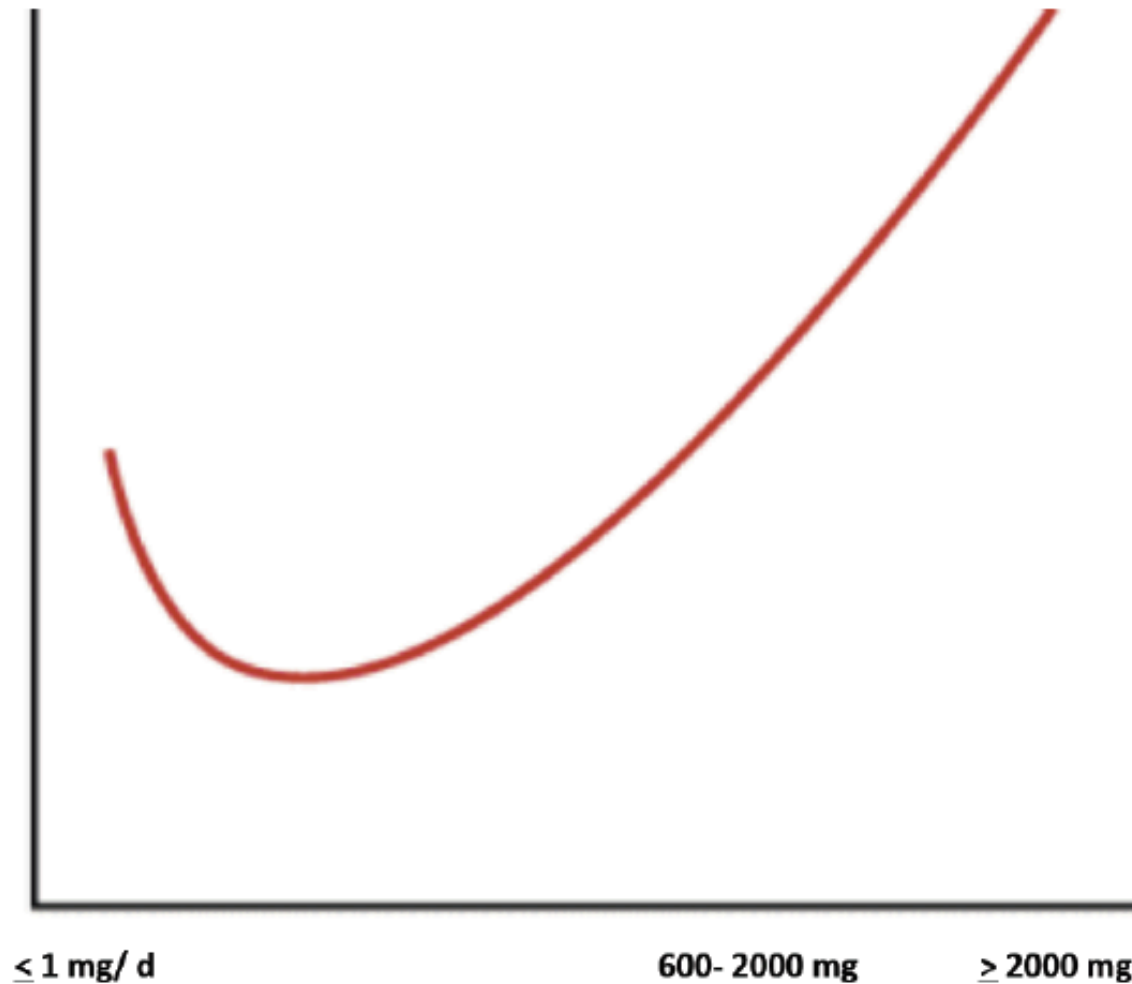


LAB#: H000000-0000-0
PATIENT: Sample Patient
SEX: Male
AGE: 10

CLIENT#: 12345
DOCTOR:
 Doctor's Data, Inc.
 3755 Illinois Ave.
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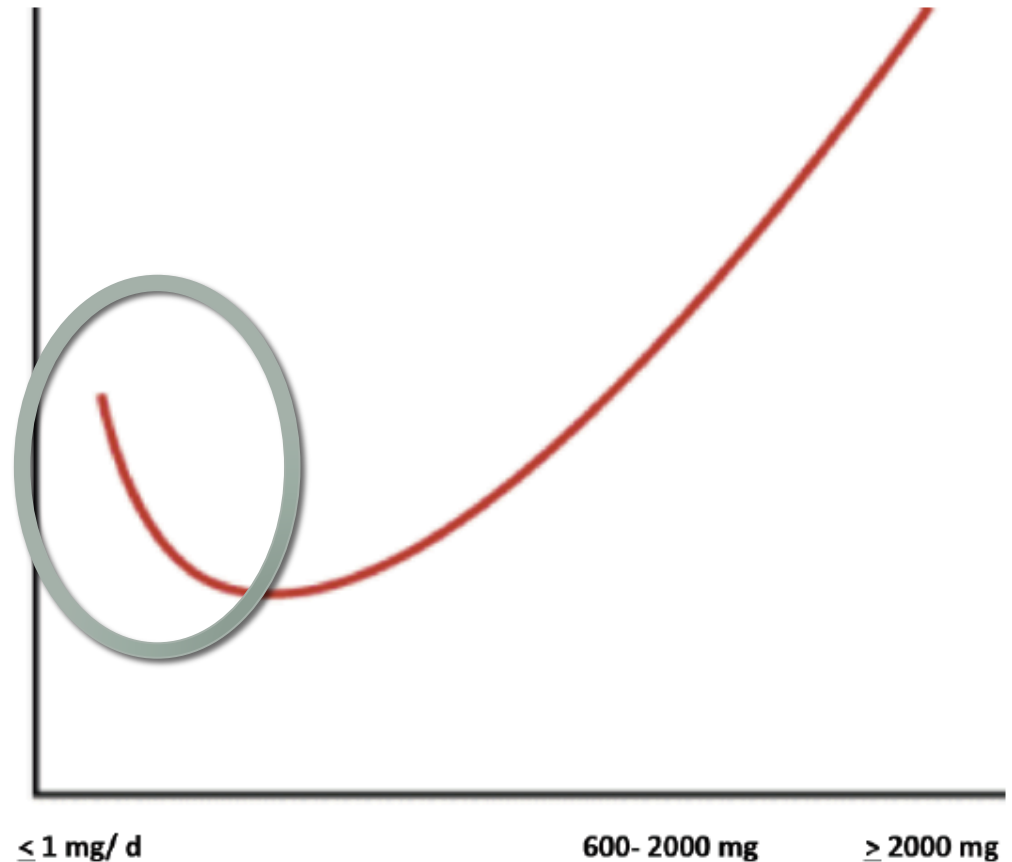
ESSENTIAL AND OTHER ELEMENTS							
ELEMENTS	RESULT µg/g	REFERENCE RANGE	PERCENTILE				
			2.5 th	16 th	50 th	84 th	97.5 th
Calcium	981	160- 500					
Magnesium	68	12- 50					
Sodium	710	12- 90					
Potassium	96	10- 40					
Copper	600	9.0- 30					
Zinc	140	110- 190					
Manganese	0.34	0.18- 0.60					
Chromium	0.45	0.23- 0.50					
Vanadium	0.14	0.025- 0.10					
Molybdenum	0.060	0.040- 0.089					
Boron	2.0	0.50- 3.5					
Iodine	1.0	0.25- 1.3					
Lithium	0.014	0.007- 0.023					
Phosphorus	214	160- 250					
Selenium	0.65	0.95- 1.7					
Strontium	2.4	0.21- 2.1					
Sulfur	51500	45500- 53000					
Barium	0.93	0.19- 1.6					
Cobalt	0.022	0.013- 0.035					
Iron	21	6.0- 17					
Germanium	0.033	0.045- 0.065					
Rubidium	0.10	0.008- 0.080					
Zirconium	0.032	0.060- 0.70					

U-shaped curve: Deficiency & Toxicity



Deficiency

- Infertility
- Aggressive behavior
- Diminished impulse control
- Depression
- Increased suicide risk



Pharmacological use

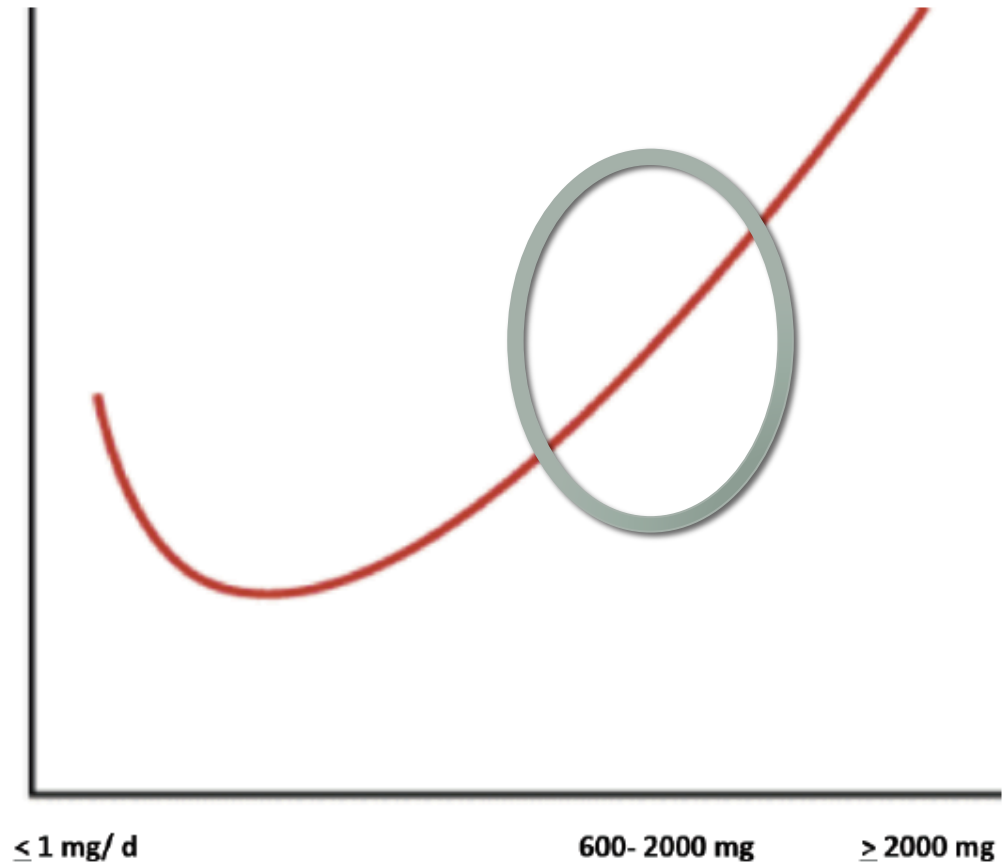
- Bipolar disorder
- Depression
- Seborrhea (topical)
- Dystonia?

Side Effects

Weight gain

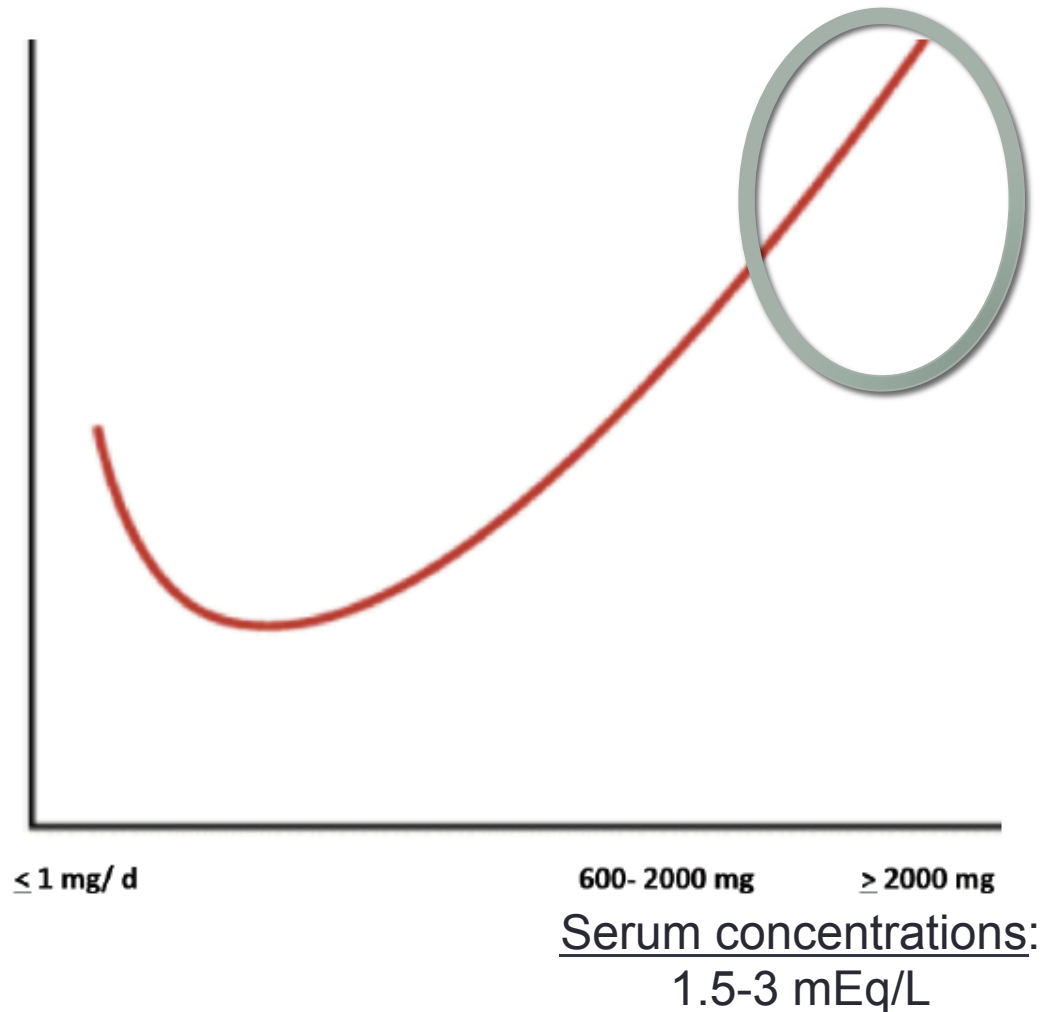
Hypothyroidism

Hyperparathyroidism



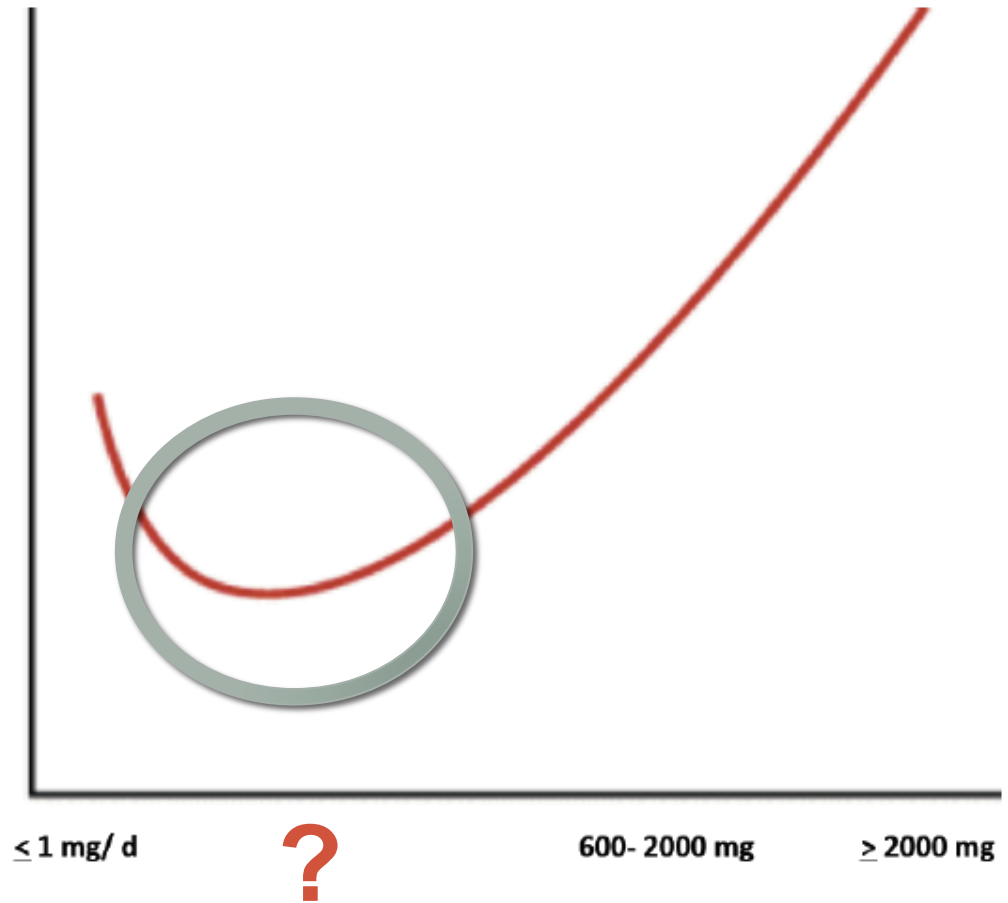
Toxicity

- Increase blood Ca
- Gastrointestinal complaints
- Tremor
- Confusion/somnolence
- Seizure
- Death



Maintenance

- Cell growth
- Electrolyte regulation across neuron membranes
- Neurorepair
- Regulate autophagy



EPIDEMIOLOGY

Lithium status across populations

Ecological Studies of Deficiency

- Lithium mapped across Texas, concentrations of urine lithium were inversely proportional to regional rainfall.

Counties with the lowest vs. highest $[\text{Li}_{\text{urine}}]$ had statistically significant increase in:

- All mental hospital admissions ($P < 0.001$)
- Psychosis ($P < 0.01$)
- Neurosis ($P < 0.001$)
- Personality disorders ($P < 0.001$)
- Schizophrenia ($P < 0.01$)
- Homicide ($P < 0.01$)

Dawson EB. Li in Biology & Medicine, 1991

Table 2: Population Reference Ranges of Hair Lithium. Diseased populations are in red.

	Year	N	Median	Mean (SD)
				µg/g ppm
New York, USA (68)	1975	206		0.009-0.228
Montreal, Canada(6)		53		
Healthy control children	1977	22		.40 ppm
Children with learning disorder	1977	31		.22 ppm
Vienna, Austria	1992	20		0.030 (0.025)
Munich, Germany	1992	18		0.035 (0.033)
Tokyo, Japan	1992	20		0.070 (0.033)
Galveston, Texas	1992	25		0.080 (0.059)
Culiacan, Mexico	1992	21		0.081 (0.080)
Kopenhagen, Denmark	1992	20		0.087 (0.021)
Stockholm, Sweden	1992	10		0.094 (0.028)
Tijuana, Mexico	1992	60		0.128 (0.087)
California, USA, Healthy males		82		0.099 (0.126)
California, USA, Violent offenders	1992	49		0.028 (0.029)
Florida, USA, Prisoners	1992	48		0.032 (0.031)
Oregon, USA, Prisoners	1992	31		0.051 (0.052)
California, USA, Heart patients	1992	42		0.028 (0.025)
National sample, USA, Doctor's Data(69)	1998	150		.015 (.008)
Tokyo, Japan(5)		200		
Males	2011	n=100	0.011	0.019 (0.025)
Females	2011	n=100	0.017	0.0275 (0.029)

Li Deficiency in Tokyo

Background: High rate of suicide in Japan

Hypothesis: High frequency of deficiency

Aim: Li scalp hair in 100 male & 100 female residents of the Tokyo Prefecture.

Results: Below lower limit of detection in more than half of samples, in both genders.

Conclusion: Consider lithiation of the water supply.

[Schöpfer J](#), [Schrauzer GN](#). Biol Trace Elem Res. 2011 Dec; 144(1-3):418-25.

HAIR ELEMENTS

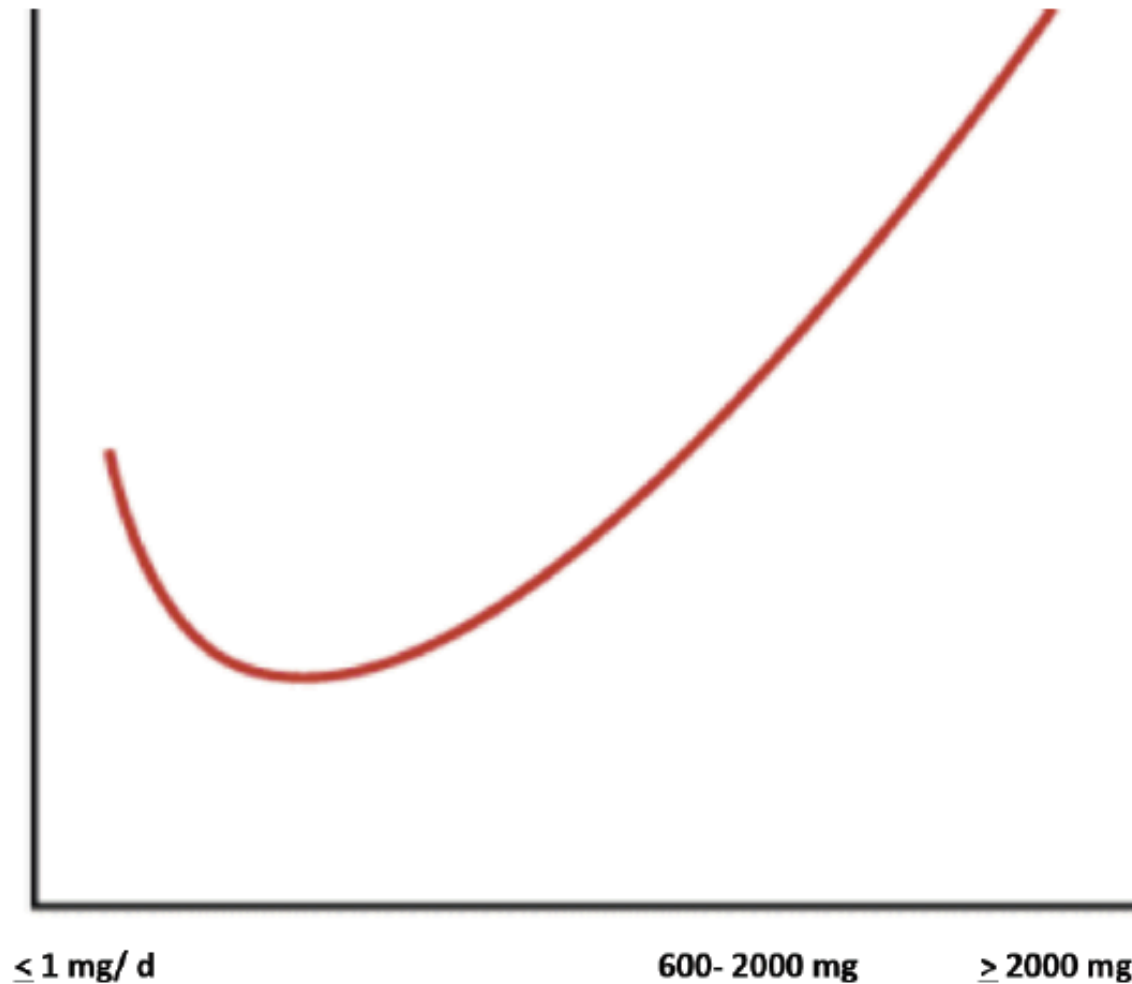


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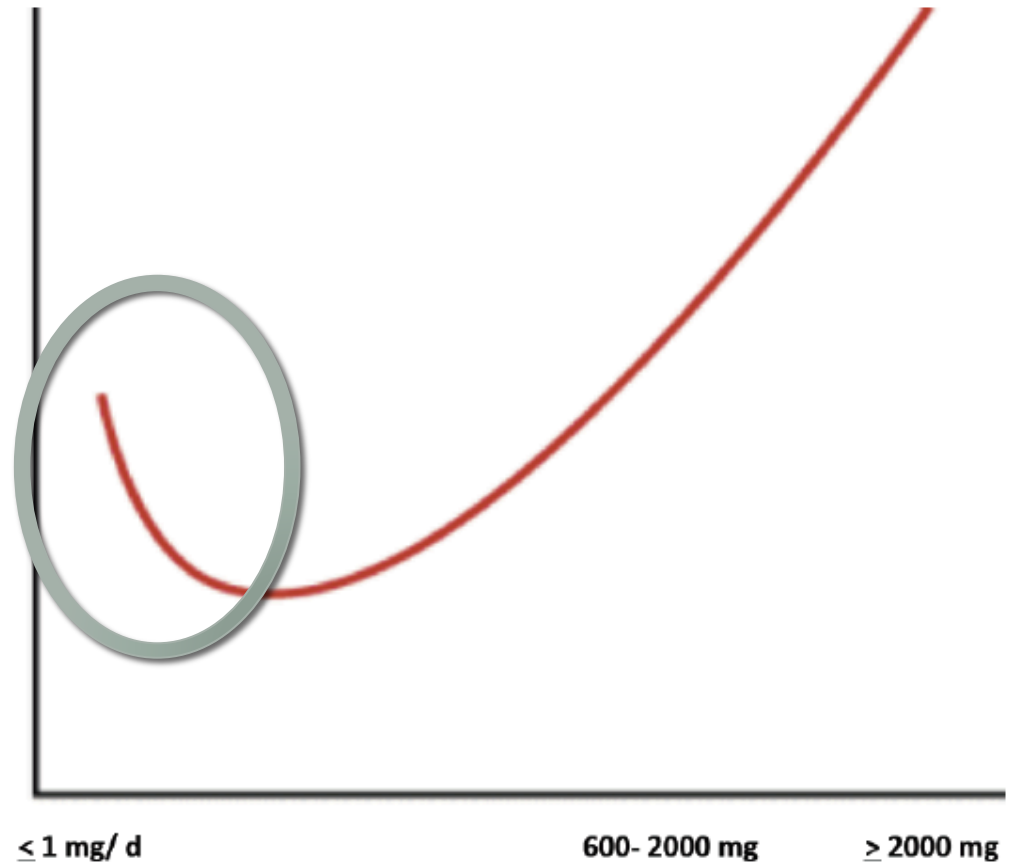
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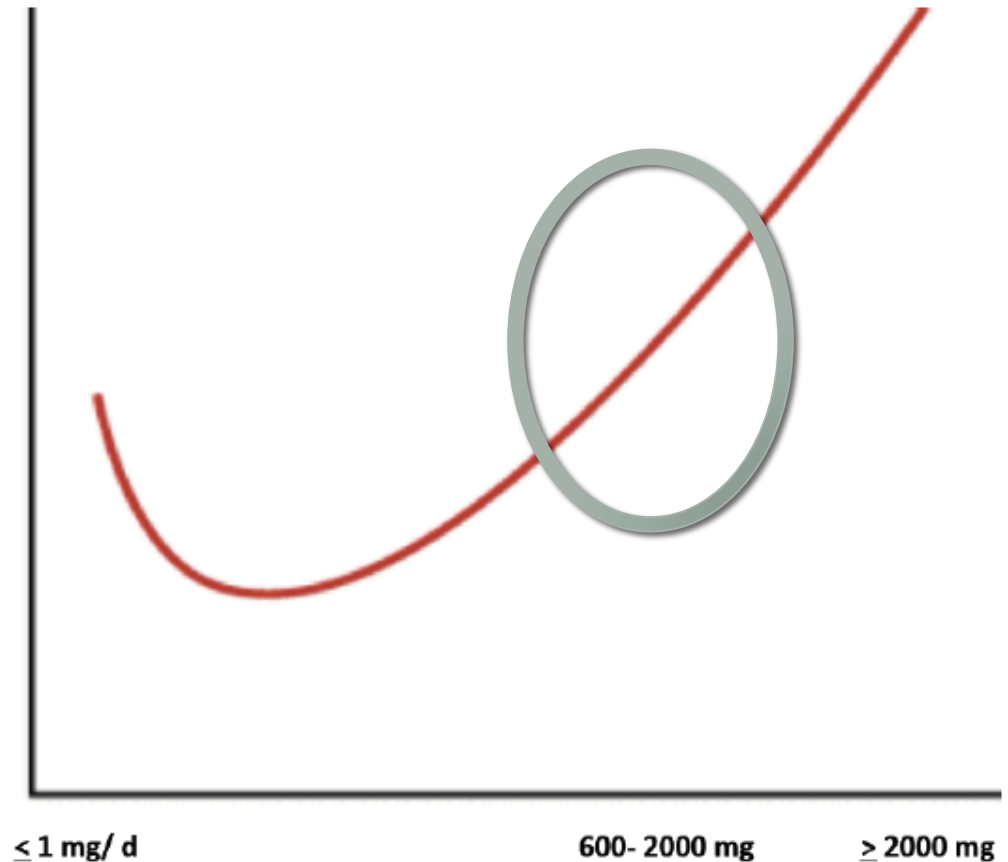
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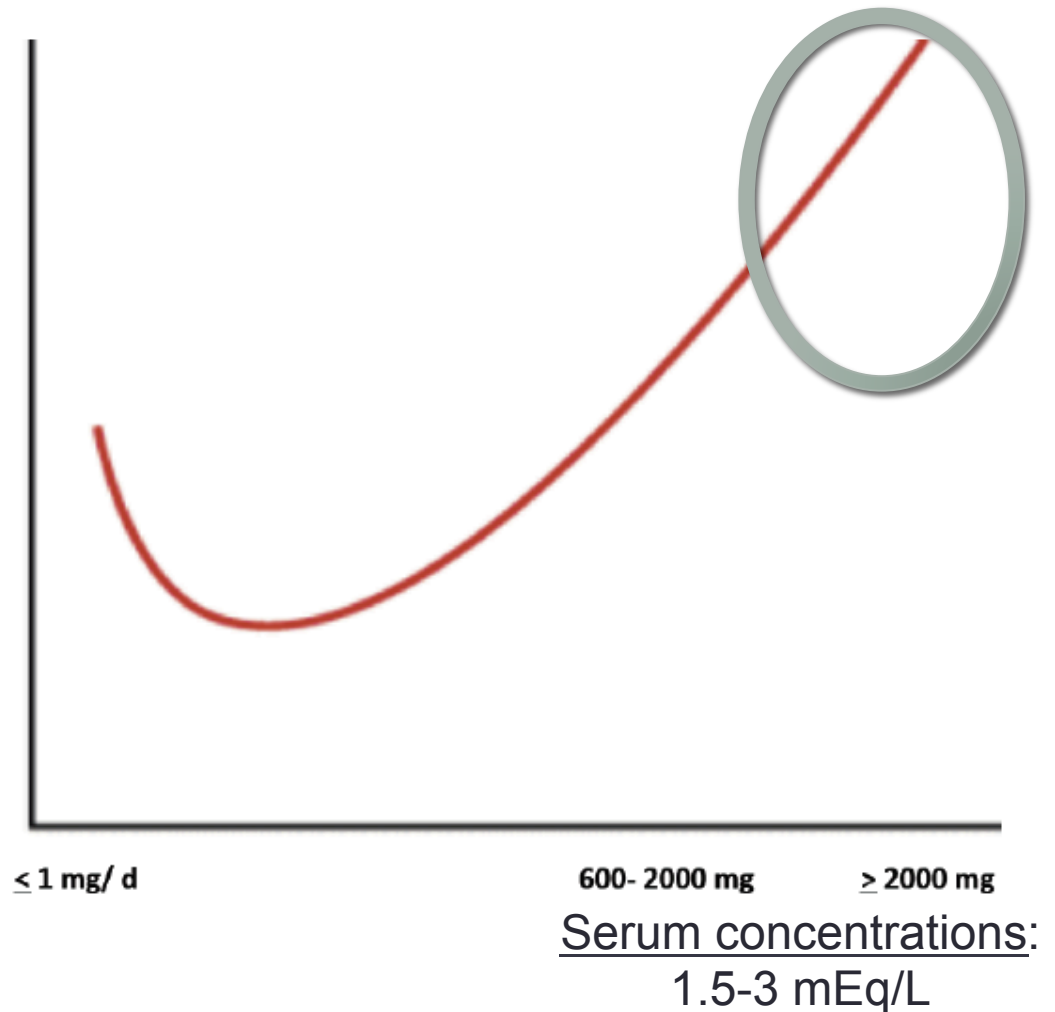
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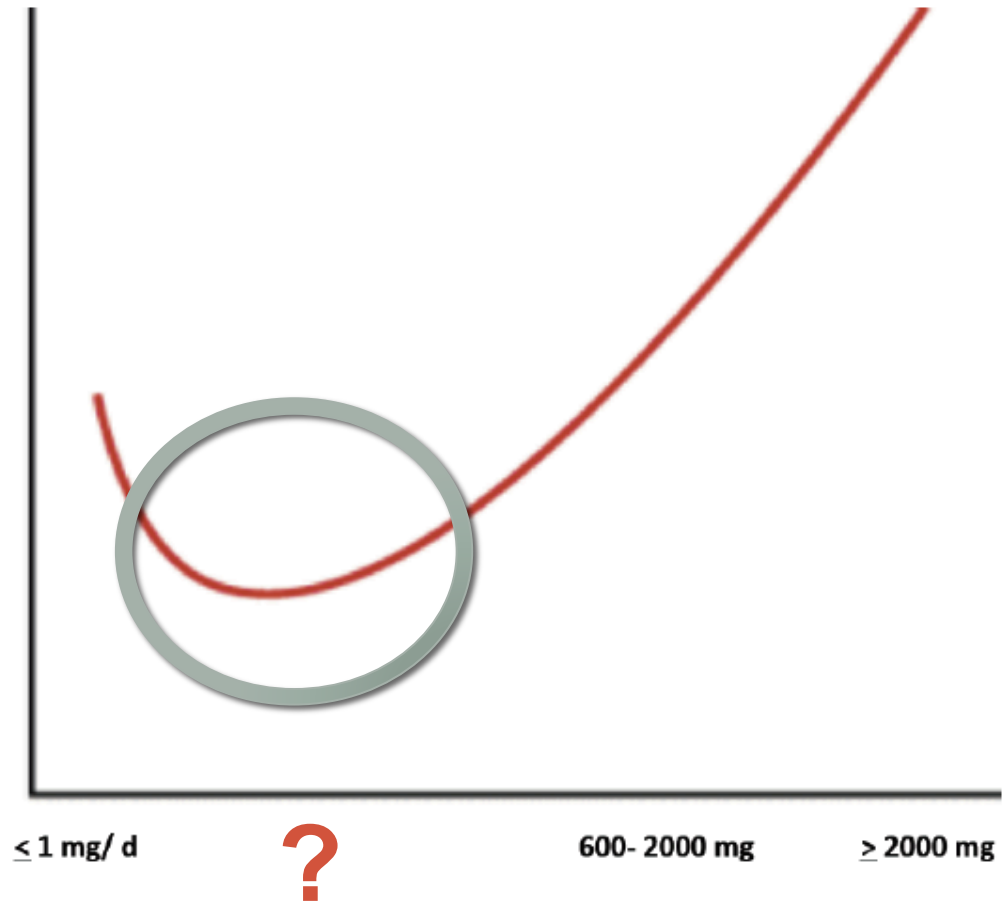
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Clinical Case Series

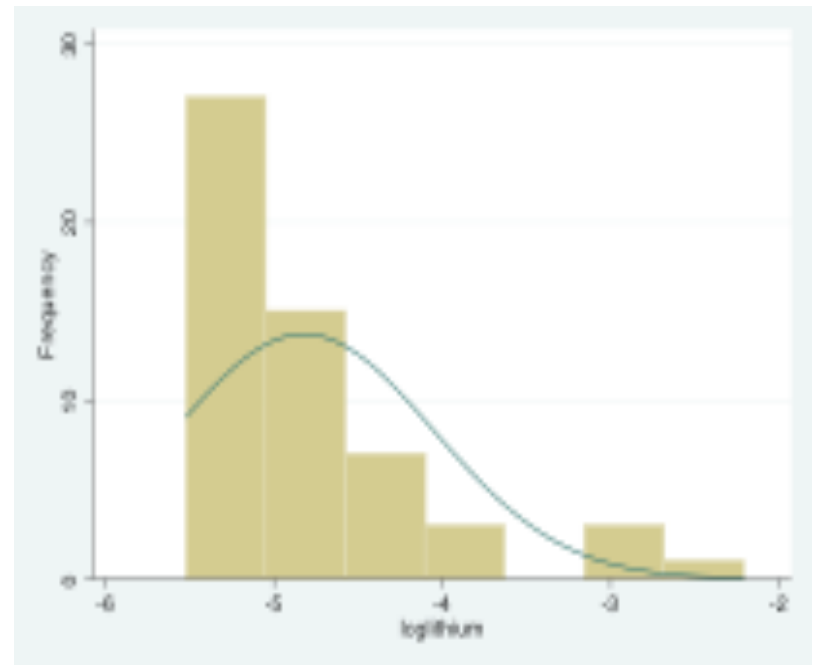
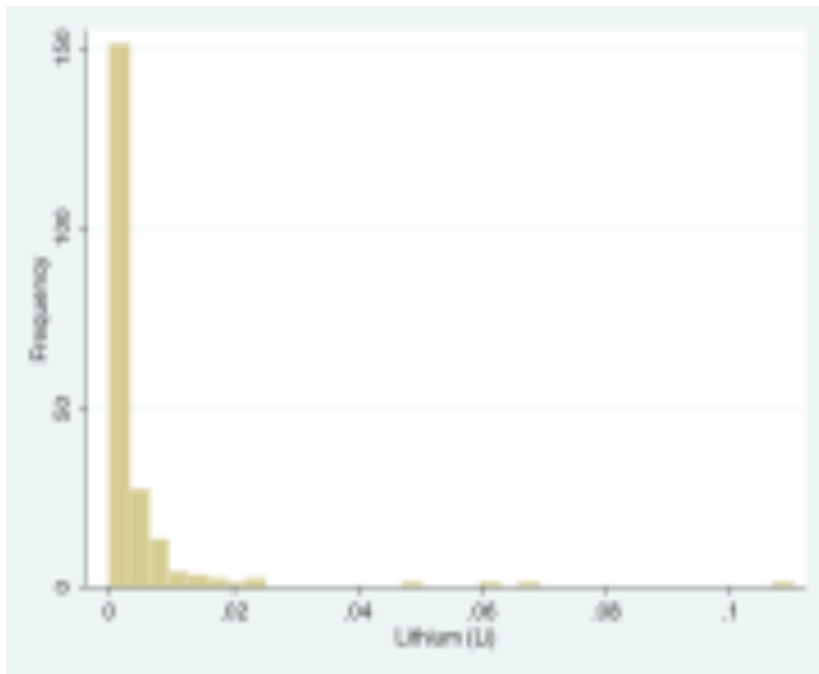
METHODS

- 711 clinical records identified by disease-
 - Chief complaint neuro disorder: PD, MS, ALS, HD, epilepsy, etc.
 - Secondary: fatigue, depression, myalgia, ... up to 10. (data avail)
- First test only
- Scalp hair only
- Untreated hair
- ICP-Mass spect

N= 419

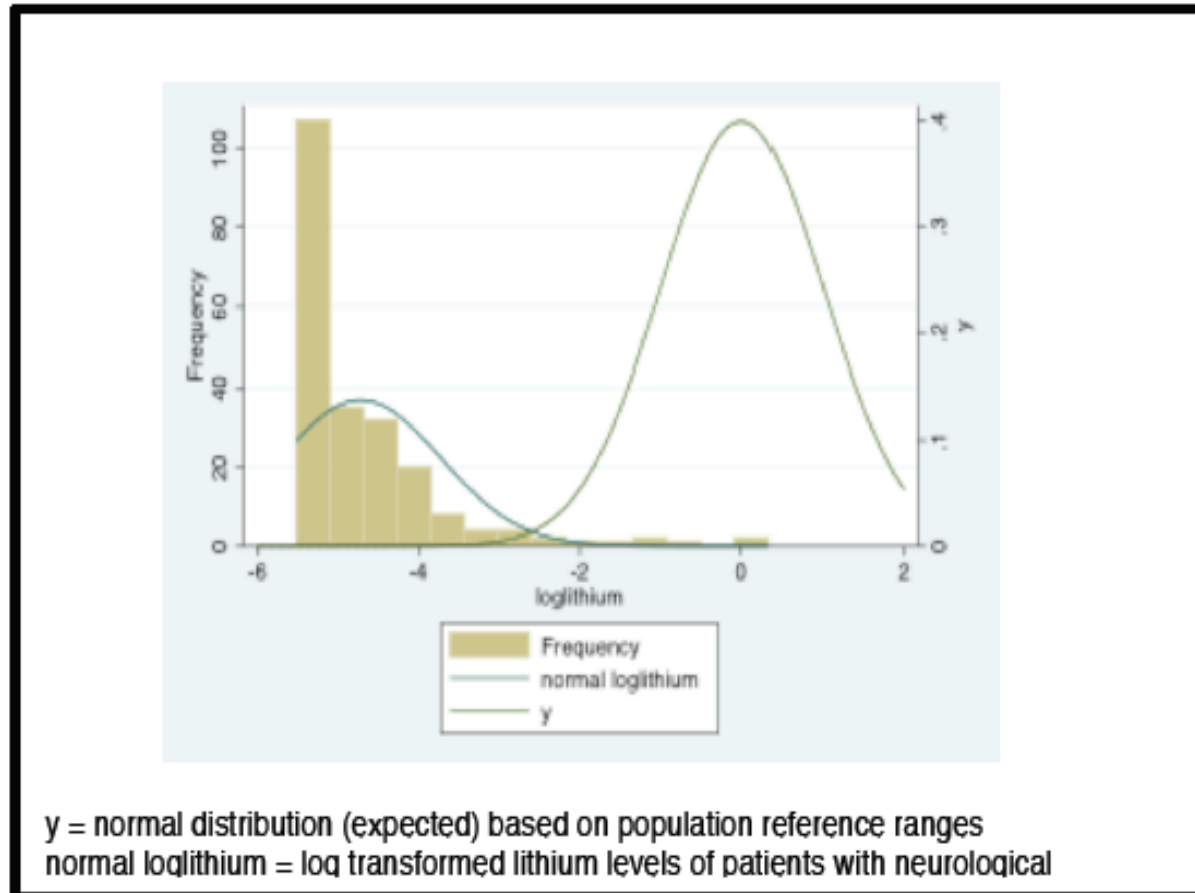
(MS= 94, PD=80, Seizures=22, Autism=24)

Lithium concentration distribution



Li Status of Neuro Patients in the Pacific NW

Figure 1: Log-transformed lithium levels of patients with neurological disorders compared to expected reference ranges from general population, as defined by laboratory reference ranges.



Frequency of Li Deficiency by Disease

Deficiency described as 2 or more standard deviations below the laboratory reference range (DDI).

Disease	N	Number Deficient (%)
Multiple Sclerosis	94	62 (66%)
Parkinson's Disease	80	51 (64%)
Autism	24	10 (42%)
Seizures	22	16 (73%)
A neurological patients	419	324 (77%)
Clinic-based controls	19	11 (58%)

LITHIUM REPLETION AS A THERAPEUTIC STRATEGY

Physiologic doses

Emerging Understanding

“It is likely that the ancestral role of this ion as a modulator of cell survival, cell growth, movement, and mood impact on a variety of behavioral issues, which are the expression of similar cell mechanisms operating in different neuronal networks.”

Pasquali L, et al. Intracellular pathways underlying the effects of lithium. Behavioural Pharmacology 2010, 21

Drug Addicts: Rx Li for Foul Mood

24 former drug users

Randomized to 400 $\mu\text{g}/\text{d}$ of Li or placebo x 4 weeks

Using the Naval Psychological Research Unit measure, there was a statistically significant improvement in mood scores from baseline, particularly in:

- Energy
- Happiness
- Friendliness

Schrauzer GN et al. Effects of nutritional lithium supplementation on mood. Biol Trace Elem Res 1992

Pharmacological Doses

- Method of Cooper, et al. uses doses of 600-1200 mg/ d, which targets a serum Li level between 0.65-0.85 mEq/L.
 - Just below level of toxicity
- At pharmacological doses, 1-2 week latency for maximum effect
- Clinical efficacy retained for 1-2 weeks following discontinuation
- FDA Approval (used this way) for depression, bipolar disorder

OVERVIEW

USES

SIDE EFFECTS

INTERACTIONS

DOSING

LITHIUM OVERVIEW INFORMATION

Lithium is an element. It gets its name from "lithos," the Greek word for stone, because it is present in trace amounts in virtually all rocks. Lithium works with other elements, [drugs](#), enzymes, hormones, vitamins, and growth factors in the body in many different ways. People use it for medicine.

Lithium is used for mental illnesses, including [bipolar disorder](#), [depression](#), and [schizophrenia](#); for eating disorders, including [anorexia](#) and [bulimia](#); and for blood disorders, including [anemia](#) and low white-cell count ([neutropenia](#)).

Lithium is also used for [headache](#), [alcoholism](#), [epilepsy](#), [diabetes](#), [liver disease](#), [kidney disorders](#), [arthritis](#), a skin condition called [seborrhea](#), and overactive [thyroid](#). Other uses include [treatment of asthma](#), [Huntington's disease](#), [Graves' disease](#), [herpes simplex](#), a movement disorder called [tardive dyskinesia](#), [Tourette's syndrome](#), [cyclical vomiting](#), [Meniere's disease](#), a tingling or "crawling" sensation in the skin ([paresthesias](#)), and aggressive behavior in people with attention deficit-hyperactivity disorder ([ADHD](#)).

CNS:

MECHANISM OF ACTION

Magnesium homeostasis

- Diagonal relationship
- Similar ionic radii and potential (0.60 Å- Li, 0.65 Å- Mg)
- Competition at binding sites
- Displacement of Mg by Li

1.5 g Li/ kg body weight x 14 d

→ Increase plasma Mg & Decrease RBC Mg

Haavaldsen et al. 1973

Li can inhibit Mg-dependent enzymes.

Birch NJ, Lancet 1974; Amari L, Anal Biochem, 1999

GROUP		PERIOD							
1	IA	2	IIA	3	IIIB	4	IVB	5	VB
1	1.0079								
1	H								
	HYDROGEN								
3	6.941	4	9.0122						
2	Li		Be						
	LITHIUM		BERYLLIUM						
11	22.990	12	24.305						
3	Na		Mg						
	SODIUM		MAGNESIUM						
19	39.098	20	40.078	21	44.956	22	47.867	23	50.942
4	K		Ca		Sc		Ti		V
	POTASSIUM		CALCIUM		SCANDIUM		TITANIUM		VANADIUM

RELATIVE ATOMIC M

GROUP IUPAC

ATOMIC NUMBER

SYMBOL

ELEMENT NAME

Decreases neuronal hyperexcitability

Low RBC Mg and Li increase neuronal hyperexcitability.

Neuronal hyperexcitability involved in:

- Migraine

- Seizure

- Neurodegeneration

- Multiple Sclerosis

Protects cells against glutamate-induced excitotoxicity

Bauer M, et al. Pharmacopsychiatry 2003; 36 Supp
3:S250-254.

Regulation of autophagy

Autophagy is the process by which cell lysosomes engulf and digest our used and dysfunctional waste, and recycle it into component parts, e.g. amino acids. (Greek, *auto* “self” and *phagein* “to eat”)

Dysregulated autophagy is a major problem in all of the neurodegenerative diseases.

- In *Caenorhabditis elegans*, lithium supplementation resulted in increase in healthspan and mitochondrial energetic function.

Tam ZY, et al. Effects of Li on Age-related Decline in Mitochondrial Turnover and Function. 2014 J Gerontol A Biol Sci Med Sci.

- Rodent model of Parkinson’s disease, Li improved clearance of α synuclein, ubiquitin, & superoxide dismutase 1.

Fornai F, et al. Autophagy 2008; Sarkar S, et al. J Cell Biol 2008

Glycogen synthase kinase-3 beta

GSK3b is involved in energy production & neurogenesis.

2 mechanisms by which Li inhibits GSK3b:

- Li dislocates Mg binding to the catalytic core of GSK3b
- Li induces conformational change via phosphorylation of the serine-9 residue, rendering it inactive.

Li has been shown to reduce GSK3b at the gene level

Mendes CT. Li reduces GSK3b mRNA levels: implications for Alzheimer's Disease. *Eur Arch Psych Clin Neurosci* 2009

Neuroprotection as a Downstream Effect

- Induces secretion of growth factors (e.g. BDNF)

Su H, et al. 2009

- From adult stem cells, Li enhances the differentiation toward neuronal phenotypes, leading to neurogenesis.

Kim et al., 2004; Fornai *et al.* 2008a)

- Increases neuropil formation, axonal elongation, and motor neuron axon collaterals.

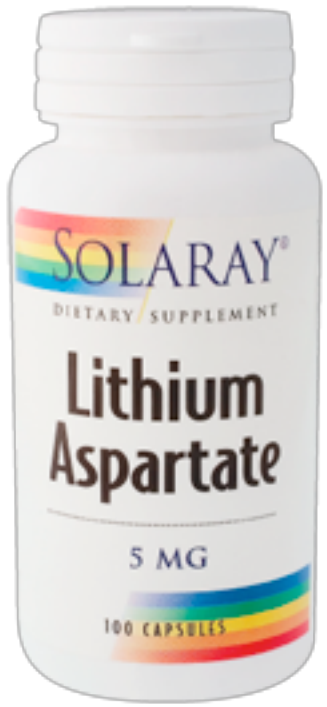
Ferrucci et al, 2010, Gilad and Gilad 2007,

Pasquali L, et al. Intracellular pathways underlying the effects of lithium. Behavioural Pharmacology 2010, 21:473-492.

INDUSTRY PERSPECTIVE

5 mg

300 mg





7up
REG. U.S. PAT. OFF.

Seven-Up
Settles the
Stomach

For Hospital
or home use.

LITHIATED
LEMON SODA

The added citrates neutralize free acid. The sugar is inverted...
burns clean. 7-Up is more than a mixer... It blends out the harsh
features... Dispels hangovers... takes the "ouch" out of grouch.



Slenderizing

Patents have been filed...

- Use patent, for an indication
 - Parkinson's Disease
 - Neurodegenerative Disease
- Should one be granted ownership for nutrient repletion?

PUBLIC HEALTH

Mental Health

Neuroinflammation

Neurodegeneration

PRAGMATIC QUESTIONS:

- Do our patients have lithium deficiency?
- If those who are lithium deficient were not, would the symptoms or course of their disease improve?
- Physiologic lithium treatment for:
 - Psychosis?
 - Depression? Anxiety?
 - Neuroprotection?
 - Levodopa-induced dyskinesia?
 - Dystonia?
 - Infertility?
 - Impulse-control disorders: Tics? Addiction? Seizures?
 - Unfriendliness?

Recommended Dietary Intake

- None exists
- Not added to multivitamins
- Not fortified in water, salt, bread, etc.

Future Research

- Distribution of lithium around the world.
 - Water samples to a central lab. Imagine the ROI...
- Analysis of foods for presence of lithium
 - As has been done for other required minerals. Thyme?
- Cross-sectional studies with disease incidence
- Intervention trials
 - Prevention
 - Lack of progression
 - Symptom Improvement

THANK YOU

