“Lithium Treatment: a Lost Art?”

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The Presenter declares no commercial or other conflict of interest, regarding the topic of the talk
If brand names of medications are named, their generic names will also be provided
Overview

- Making the point: *Lithium Treatment soon a “Lost Art”*?
- Historical aspects of Lithium Treatment: 19th Century & beyond
- Mania/Bipolar Disorder: *Acute and prophylactic treatments*
  - John Cade’s re-discovery 1949
  - The *European* Experience: Schou & Baastrup vs. Shephard & Lewis
  - The *American* Experience: Cole, Gershon, Baldessarini, Coppen
  - *Do’s & Don’t’s*: benefits, side-effects, and safe use of Lithium
- Suicide protection/Discontinuation risk: Baldessarini, Viguera
- *Neurotrophic* and other beneficial effects of Lithium
- *Myths and Half-Truths* of Lithium Treatment
- Summary and outlook
Lithium Treatment: A Lost Art?

- With the exception of ECT, lithium is the single most effective treatment in psychiatry (Ed Shorter 2009; David Healy 2009; others).
- Its side effects are easily manageable, and many patients stay safely and beneficially on low-dose lithium for decades.
- Its benefits, in terms of the relief of mania and the prophylaxis of depression, are incalculable.
- The history of the mad campaign of leading British Psychiatrists against Lithium in the 1960’s, the market-driven unscientific preference of less effective “mood-stabilizers” over Lithium in the USA, and the lack of training for US residents in the proper use of Lithium indicate that Lithium Treatment may soon be a “lost art”
Lithium maintenance shows clear superiority ($p=\lt .007$) c/to CMZ (Greil et al. 1997/Goodwin & Jamison 2007)
Incidence of Delirium in elderly new users of lithium, valproate or benztropine. (Shulman et al. 2005/Goodwin & Jamison 2007)
The lithium story raises the question: why in psychopharmacology, scientific evidence—in this case about lithium—often has difficulty in prevailing over commercial messages that run counter to established knowledge?

When Abbott gained FDA approval to market valproate (Depakote) for mania in 1995, a *great shift toward the “mood stabilizers” and away from lithium commenced*. As David Healy points out, the use of valproate off-label for mania had been growing in the late 1980s, and it was *in 1995 that Columbia University closed its lithium clinic*.

Increasingly, *trainees from psychiatry training programs became untutored in lithium use*, and would be uncomfortable about prescribing it in practice.

Is lithium about to be eclipsed by less effective but widely advertised mood stabilizers?

Nobody can definitively answer this question - but it becomes increasingly insistent.
Historical Aspects of Lithium

- Lithium, an element in the alkali metal group (not a molecule) was discovered from Petalite in 1817 by Johan A. Arfvedson, named “lithion” by Berzelius, fully isolated by Th. Brande in 1855, first commercially produced in Germany 1923 (Metallgesellschaft AG)
- **Medicinal** use of Lithium dates back >1,800 years
  - Galenus treated manic patients by having them bathe in alkaline springs and drink the Lithium-containing water
  - 1840ies: Trousseau & Haig proposed lithium treatment of mania & depression (“imbalance-of-uric-acid”- theory)
  - 1870ies: US Surgeon Gen. William Hammond reports Tx of acute mania with Li-Bromide (Bellevue Hospital)
  - 1880/1890ies: Carl Lange (Kopenhagen) systematically used Lithium for Tx and prophylaxis of Depression
Lithium as Food supplement?

Lithium is NOT contained in Vitamine/Mineral supply preparations, but in sea water

Caution: Some OTC Lithium-drugs (Orotate/Aspartate): Maybe risky

Safe: Lithia Springs Water

Would adding Lithium to the drinking water, like Fluoride, help to prevent another “Sandy Hook” or “Ferguson”!? 
generic lithium beverages

- Many Beverages added Lithia water initially, like this Lithia Bock Beer.
- An early version of Coca-Cola available in pharmacies' soda fountains called Lithia Coke was a mixture of Coca-Cola syrup and lithia water.
Lithium-7 Isotope Drink: “7-UP”

- The soft drink 7-up was originally named "Bib-Label Lithiated Lemon-Lime Soda" in 1929: it contained lithium citrate (later removed in 1948).
- It was a patent medicine and cure for hangover.
- 7-up “takes the ‘ouch’ out of ‘grouch’.”
In **natural spring water**, Lithium-concentrations around 0.170 mg/l have been shown to have **strong epidemiological health benefits**:

- **Texas Study 1990**: People whose water had the **least** amount of lithium had the **highest** suicide, homicide and rape levels
- **Corroborating findings** in Japan (x 5 yrs), Greece & Austria:

  Lower all-cause mortality, **better medical & behavioral health** in people with **higher Li-amounts in their drinking water**!
Is there a niche for low-dose Lithium? Ideologists on both sides say “No”!

- NO: For the opinion leaders in Psychiatry, guidelines are to be followed strictly, all other evidence is ignored
  - But not all Lithium treatments are given to control mania or prevent relapse of Bipolar Illness (where optimal serum levels are important: 0.6-0.8 mEq/l)!
- NO: The counterculture/holistic medicine movement will also not consider Lithium at all, regardless the dose, as it seems tainted to them as a psychiatric power drug to control manic-depressive patients

- Caveat: Beware of “natural” OTC Lithium drugs – they’re uncontrolled, often ineffective, and some are unsafe
## Contemporary Timeline of the Medical History of Lithium
(modified from: Mohandas & Rajmohan 2007)

<table>
<thead>
<tr>
<th>Year</th>
<th>Landmark</th>
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<tbody>
<tr>
<td>1817</td>
<td>Johan August Arfvedson discovers lithium</td>
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<tr>
<td>1843</td>
<td>Alexander Ure introduces lithium in modern medicine (uric acid stones)</td>
</tr>
<tr>
<td>1855</td>
<td>William Thomas Brande fully isolates lithium</td>
</tr>
<tr>
<td>1870s</td>
<td>William Hammond - <em>anecdotal</em> evidence of lithium bromide in treatment of acute mania</td>
</tr>
<tr>
<td>1890s</td>
<td>Carl Lange - <em>systematic</em> use of lithium in the acute and prophylactic treatment of depression</td>
</tr>
<tr>
<td>1900s</td>
<td><em>Toxicity reports</em> – weakness, tremor, diarrhea, vomiting and deaths</td>
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<tr>
<td>1932</td>
<td><em>Lithium disappears from British Pharmacopoeia</em></td>
</tr>
<tr>
<td>1940s</td>
<td><em>Use as sodium substitute in low-sodium diets for hypertensive patients</em></td>
</tr>
<tr>
<td>1949</td>
<td><em>Removal from American markets following reports of severe intoxication</em></td>
</tr>
<tr>
<td>1949</td>
<td>John F. J. Cade - use of lithium in acute mania</td>
</tr>
<tr>
<td>1955</td>
<td>Mogens Schou’s Monography on Lithium Tx, Lithium data bank</td>
</tr>
<tr>
<td>1950-74</td>
<td>Intense clinical research into safety and efficacy of lithium</td>
</tr>
<tr>
<td>1968</td>
<td>American J Psychiatry recognizes the clinical significance of lithium</td>
</tr>
<tr>
<td>1970</td>
<td>USFDAQ approval for treatment of mania</td>
</tr>
<tr>
<td>1974</td>
<td>USFDAQ approval for maintenance therapy of patients with mania</td>
</tr>
</tbody>
</table>
From Lithium Springs to “Brain Gout”

- Many mineral springs contain lithium, among other elements, and some of them, such as Mineral Wells in Texas, have age-old reputations as “crazy waters”
John Cade, aware of Garrod’s success in using lithium a century previously in the treatment of “brain gout”, hypothesized that some condition involving uric acid might lie behind his manic patients’ “psychotic excitement”

Cade began treating 10 of them with lithium citrate and lithium carbonate. Some responded remarkably well, becoming essentially normal and capable of discharge after years of illness

Lithium did not help schizophrenic patients

John Cade

Dr John Frederick Joseph Cade AO was an Australian psychiatrist credited with (re-)discovering the effects of lithium carbonate as a mood stabilizer in the treatment of bipolar disorder in 1949.
European Story: Prophylactic Li

- After Cade’s paper, many groups confirmed Lithium’s anti-manic benefits (f.i. Schou and Stroemgren 1952, Aarhus)
- During the early 1960s, G. P. Hartigan, Poul Chr. Baastrup and Mogens Schou independently made sporadic observations that were suggestive of lithium also having prophylactic properties in manic-depressive illness.
- Subsequently, Baastrup and Schou joined together and in a non-blind lithium trial saw their preliminary observations confirmed.
- They even deemed the results so significant that they concluded that “lithium is the first drug demonstrated as a clear-cut prophylactic agent against one of the major psychoses”
European Story (cc): Politics of Li

- To leading British psychiatrists M. Shephard & A. Lewis, lithium was
  "dangerous nonsense"
- Michael Shepherd, seconded by Harry Blackwell, simply characterized it as ‘a therapeutic myth’, which, in their opinion, was based on ‘serious methodological shortcomings’ and ‘spurious claims’.
- Even terms such as “unethical” and “unscientific” were used.
- After consideration of the ethical aspects invoked, Schou and Baastrup undertook a double-blind trial of prospective-discontinuation design and with random allocation of manic-depressive patients (already on lithium) to lithium or placebo.
- It confirmed their hypothesis, published in *The Lancet 1970*
The American Story

“In the international history of lithium, the United States was more or less the last in, first out, in the sense that “the United States is one of the few countries—perhaps the only one—where other drugs, such as valproate and antidepressants, are given to bipolar patients much more often than lithium”

_E. Shorter Bipolar Disorder 2009 June; 11(02): 4-9_
Lithium had long become registered elsewhere: lithium gluconate in 1961 in France, lithium carbonate in 1966 in the United Kingdom, lithium acetate in 1967 in Germany, and lithium glutamate in 1970 in Italy.

Under the leadership of William Bunney and Frederick Goodwin, the NIMH became actively involved in lithium studies in the 1960s.

At a meeting of the Psychopharmacologic Drugs Advisory Committee of the Food and Drug Administration (FDA) in the early 1970s, opinion was divided on the use of lithium for “the prevention of recurrent mania.”

Gerald Klerman, professor of psychiatry at Harvard, was strongly in favor.

But the FDA believed the indication ill justified because of a “lack of studies”.
Gershon, familiar with lithium from working with a group at the University of Melbourne introduced lithium to his hospital in Ypsilanti, MI.

In a program financed by Jonathan Cole at the National Institute of Mental Health (NIMH) and directed by Ralph W. Gerard, the investigators at Ypsilanti bought lithium by the kilo from a chemical supply store, then had the local pharmacy put it into capsules.

In 1960, Gershon and Arthur Yuwiler, also at Ypsilanti, brought out the first North American publication on lithium.

At the FDA, it was Merle Gibson who finally overcame internal agency apprehensions and pushed for approval of lithium for acute mania.

However, Gibson is also said to have held back the Rowell company’s lithium New Drug Application to give Smith Kline and Pfizer a chance to bring their own products to market (J. O. Cole, telephone interview with Ed Shorter, 17 July 2002).
Question to our US audience:

- Have you been aware of a >10x reduction in suicidal acts in patients on Lithium maintenance treatment?
- Do you realize that none of the other mood stabilizers comes even close? So why are they “preferred” in the US?
- How do you explain that many current US residency training programs don’t provide adequate teaching and clinical experience, and leave graduating residents scared and unprepared regarding Lithium treatment?
- What are your ideas of potential harm to patients?
- Is there a potential benefit in adding low levels of Lithium to the drinking water, similar to Iodine?
Anti-Suicidal Benefit of Lithium

- In 1971, Alec Coppen followed up a group of patients with recurrent affective disorders, using as a measure the number of deaths by suicide:
  - “Instead of having a suicide rate of seven per thousand, which is the norm, we had a suicide rate of less than one per thousand” (seven-fold reduced suicide risk)
Ross Baldessarini and his group (Adele Viguera, L. Tondo, J. Hennen, & others) conducted many studies on Lithium discontinuation, and suicide risk >30 years.

In a review from 2003 (J Clin Psychiatry) data from 34 studies of patients with affective disorders averaging 42 groups on Lithium x 3.36 years and 25 groups without Lithium x 5.88 years found:

- **Risk for all suicidal acts/100 person years** averaged
  - 3.10 without Lithium, vs. 0.210 during Lithium treatment, vs. 0.315 for the general population!

Baldessarini RJ, Tondo L, Hennen J Lithium Treatment and Suicide Risk in Major Affective Disorder J Clin Psychiatry 2003;64/suppl 5/:44-52
Figure 1. Rates of Suicides (S) or Attempts (A) or Both (S + A) Without Lithium Maintenance Treatment, With Lithium Treatment, and Approximately Equivalent Rates for the International General Population

*Estimated upper 95% CI based on findings summarized in Tables 2–4.
### Table 1

#### Research findings on anti-suicidal effects of lithium treatment

<table>
<thead>
<tr>
<th>Groups</th>
<th>No. of studies</th>
<th>RR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All trials</td>
<td>24</td>
<td>4.14 (3.02 - 5.67)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Suicide completions</td>
<td>25</td>
<td>4.89 (3.46 - 6.91)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Suicide attempts</td>
<td>20</td>
<td>4.86 (3.58 - 6.59)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>15</td>
<td>5.53 (3.72 - 8.20)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Major affective disorder</td>
<td>19</td>
<td>4.58 (3.38 - 6.21)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Unipolar major depressive disorder</td>
<td>8</td>
<td>4.24 (1.49 - 12.0)</td>
<td>.007</td>
</tr>
<tr>
<td>Randomized controlled trials</td>
<td>8</td>
<td>4.29 (1.46 - 12.6)</td>
<td>.008</td>
</tr>
<tr>
<td>Open trials</td>
<td>26</td>
<td>5.00 (3.86 - 6.53)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Lithium vs anticonvulsants</td>
<td>6</td>
<td>2.86 (2.29 - 3.57)</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

RR, ratio of risk with/without lithium; CI, confidence interval.

*a Based on reported meta-analyses.*

Note: These findings show striking consistency over several decades, despite changes in diagnostic criteria, suicide rates, and other treatments.
Kurt Cobain in “Nevermind” 1992
Kurt Cobain never took Lithium

- Kurt Cobain was diagnosed with ADD at a young age, and with bipolar d/o thereafter, according to an interview with Kurt’s cousin Bev Cobain.

- What if Kurt Cobain took Lithium instead of heroin? Would he still be alive today?

HOW does it work?

Postulated mechanism of action

- Lithium is just a metal salt – how can it beneficially modify complex human behavior?

- Answer: WE DON’T REALLY KNOW!!

- But we know it works! Here’s some data:
  - Li has effects on Serotonin
  - Lithium increases BDNF/new brain cells (hippocampus)
  - Lithium inhibits PK-C
Postulated mechanisms of Lithium

- **Macro-effects:** Preservation or increase of the volume of brain structures involved in emotional regulation such as
  - the prefrontal cortex, hippocampus and amygdala, possibly reflecting its neuroprotective effects.
- **Neuronal level:** Lithium reduces excitatory (dopamine and glutamate) but increases inhibitory (GABA) neurotransmission, and inhibits Protein-Kinase C
- **These broad effects are underpinned by complex neurotransmitter systems that strive to achieve homeostasis by way of compensatory changes.**
  - Lithium targets second-messenger systems that further modulate neurotransmission:
    - effects of lithium on the adenyl cyclase and phospho-inositide pathways, as well as protein kinase C, may serve to dampen excessive excitatory neurotransmission.
- **In addition to these many putative mechanisms, it has also been proposed that the neuroprotective effects of lithium are key to its therapeutic actions.**
  - Lithium has been shown to reduce the oxidative stress that occurs with multiple episodes of mania and depression; it increases mitochondrial metabolism (decreases tau protein that way: Newest MAYO Clinic study: Tau’s primary role in Alzheimer’s)
  - Lithium increases protective proteins such as brain-derived neurotrophic factor and B-cell lymphoma 2, and reduces apoptotic processes through inhibition of glycogen synthase kinase 3 and autophagy

Lithium Pharmacokinetics

- Half-life 8 – 55 hours, mean about 24 hours
- Peak levels after 4 – 4.5 hours (12 hrs after last intake)
- Brain Li-levels are 50% of Serum Li-levels
- Steady state reached after 5 - 7 days
- Therapeutic level for prophylaxis: The doyen of lithium researchers, Mogens Schou recommended that: “... between 0.5 and 0.8 mmol l−1 is appropriate for most patients, but adjustment to values outside this range is necessary for some.”
Lithium Serum Level Monitoring

- Lithium serum levels should be taken 12 hours (10-14 hours) post-dose.
- Lithium serum levels should be measured:
  - If there are signs of lithium toxicity (see below)
  - Five days after initiation or change in dose, change in brand, change in dosage regimen (e.g. twice daily to once daily) or change to potentially interacting medication
  - Weekly during acute treatment
  - Every three months once patient’s mental state and lithium serum level are stable
Evidence-based Indications for Lithium Treatment

- Treatment of Acute Mania
- Prevention of relapse in Bipolar I and Bipolar II d/o
- Prevention of relapse in frequently recurring Major Depression
- Augmentation of AD treatment in patients with partial or no AD response
- Treatment of Cluster Headaches
- Treatment of some forms of Neutropenia
- Reducing Suicidal and homicidal risk, violent behaviors
Table 1
Benefits and Limitations of the Practice Guideline

Benefits
- Extends beyond the research evidence base
- Involves clinical opinion/experience, eg:
  - Gabapentin
  - Topiramate
  - Lamotrigine for mania
  - Other anticonvulsants? Oxcarbazepine?

Limitations
- Perpetuates myths
- May be overutilized
- Quickly obsolete—a continuous work in progress
- Biased by commercial influence
- Addresses medication side effects poorly

Figure 1
Treatment of Acute Mania: Divalproex and Lithium Versus Placebo


Caution/Contra-Indication

- No Lithium in dehydrated patients, severe renal or CV disease, Addison’s disease, breastfeeding mothers
- Consultation with a cardiologist is recommended if:
  - 1) treatment with Lithium is under consideration for patients suspected of *having Brugada Syndrome* (syncope & abnormal EKG: incomplete RBBB and pronounced elevation of the J point (arrow), a coved-type ST segment, and an inverted T wave in V1 and V2)
  - 2) or patients who have *risk factors* for Brugada Syndrome, e.g., unexplained syncope, a family history of Brugada Syndrome, or a family history of sudden unexplained death before the age of 45 years
  - 3) patients who develop unexplained syncope or palpitations after starting Lithium therapy.
Cardiovascular effects of lithium
(modified from: Mohandas & Rajmohan 2007)

Hypotension
Bradycardia

Decreased cardiac output
Clinically insignificant effect on blood pressure
Nonspecific T-wave flattening

Sick Sinus syndrome/ sinus node dysfunction
AV conduction disturbances
Cardiac arrhythmias (heart blocks and brady-arrhythmias)
Possible anti-arrhythmic action

Reversible premature ventricular contractions
? QT interval changes
Endocrine effects of lithium
(modified from: Mohandas & Rajmohan 2007)

Thyroid:
- Lithium interferes with glandular release of thyroid hormones
- Lithium at higher doses blocks iodine uptake
- R/o Lithium-induced thyroid autoimmunity (controversial)
- *Clinical* Hypothyroidism - 2 to 15%; *Subclinical* Hypothyroidism - approximately 19% *Chemical* hypothyroidism - 50%; Goiter - 5%
- Hyperthyroidism - 0.7%

Para-Thyroid:
- *Subclinical* increase of the levels of calcium and PTH
- Very rarely: hypercalcemia and hyperparathyroidism

BS: Increased, decreased and unchanged glucose tolerance (anecdotal)

CBC: Increase of WBC (neutrophilia), CD34 cells and G-CSF (Lithium can be therapeutic in some forms of neutropenia)

- Thyroid function test (TFT) every 6 to 12 months
- Females over the age of 45 or 50 - every 3 months
Renal effects of lithium
(modified from: Mohandas & Rajmohan 2007)

Polyuria, nocturia and polydipsia – 70%
Nephrogenic diabetes insipidus (NDI) – 12 to 20%
Reduced renal concentrating ability by 7 to 10%
  - Raises the urine volume by 10 to 20%
Very rarely, nephrotic syndrome
No increase in glomerular filtration rate (GFR)

Histological changes
Freely filtered by the glomerulus
80% reabsorbed in the proximal tubule
20% reabsorbed between the loop of Henle and the collecting duct ↓ GFR and ↑ proximal tubular reabsorption → ↑ serum lithium levels
Lithium intoxication ↑ in acidosis or urinary acidification defects
Inhibitory cAMP-dependent action of ADH causing NDI

Cautious use in hemodialysis and transplant cases
Absolutely contraindicated in acute renal failure
Cautious use in chronic renal failure

Serum creatinine levels monitoring (first every three months, later once a year)
Dermatologic effects of lithium
(modified from: Mohandas & Rajmohan 2007)

Dermatologic adverse effects:
- 3 to 45% acneiform eruptions: Lithium causes follicular plugging and occlusion
  - Exfoliative dermatitis
  - Psoriasis
  - Pityriasis versicolor
  - Pruritic maculopapular erythematous eruption
  - Dermatitis herpetiformis
  - Darier's disease
  - Alopecia (diffuse non-scarring type) – 12 to 19%

Lithium used to treat (historic):
- seborrheic dermatitis,
- eczematoid dermatitis, and
- genital herpes

Aggravates cutaneous conditions associated with neutrophilic infiltration:
Lithium ↓ cAMP level and ↑ neutrophil chemotaxis and lysosomal release
Lithium in pregnancy and lactation
(modified from: Mohandas & Rajmohan 2007)

Category D drug
(known adverse effects, but treatment benefits may warrant risk)

- Incidence of major malformations low, varies from 4% to 12% in older studies
- Ebstein's anomaly risk “20 to 40 times the risk in general population”, but absolute risk of Ebstein's anomaly low: – 0.05% to 0.1%

Effects on pregnant mother:
- NDI
- Thyroid dysfunctions
- Polyhydramnios (rare)
- Premature delivery

Not many reports of detrimental effects in newborns
- Floppy infant syndrome
- No significant increase of congenital anomalies
- Transient neurodevelopmental deficits
- Reports of lethargy, hypothermia, hypotonia and T-wave modifications

AAP recommendation – breast-feeding with caution
- Infant serum one quarter the concentration of lithium in maternal serum
Lithium: **Low** Teratogenic Risk (1)

- **Old:** International Register of Lithium Babies:
  Of 217 infants exposed to lithium (Eskalith, Lithobid) during the first trimester
  - 25 (11.5%) had malformations. 18 had cardiovascular anomalies, including 6 cases of the rare Ebstein anomaly (occurred only once in 20,000 in the nonexposed population)
  - Of 60 unaffected infants who were followed-up until age 5 years, no increased mental or physical abnormalities were noted compared with unexposed siblings (this is much different to VA which may cause cognitive deficits!).
Lithium: **Low** Teratogenic Risk (2)

- **New** reports suggest a *bias of ascertainment in the registry*: the risk of anomalies is *lower than previously thought*.

- A *case-control study* of 59 patients with *Ebstein anomaly* showed no difference in the rate of lithium exposure in pregnancy from a control group of 168 children with neuroblastoma.

- A *prospective study of 148 women exposed to lithium in the first trimester* showed *no difference in the incidence of major anomalies compared with controls*.
  - Details: One fetus in the lithium-exposed group had Ebstein anomaly, and one infant in the control group had a ventricular septal defect.
  - *The authors conclude that lithium is not a major human teratogen.*

- Nevertheless, we still recommend that women exposed to lithium be offered ultrasound and fetal echocardiography.
Lithium use in elderly and adolescents
(modified from: Mohandas & Rajmohan 2007)

As a rule, in *elderly* individuals use *lower doses of lithium* to attain adult serum concentrations
- 65 to 75 years: dose 300 to 600 mg/day; maximum 900 mg/day
- >80 years or frail elderly – 150 to 300 mg/day and rarely exceed 450 mg/day

Bioavailability of lithium is not altered by increasing age
Elderly have ↓ volume of distribution and ↓ GFR; this ↑ S. Li levels

Risk: Higher incidence of neurotoxicity in the elderly (Ataxia, Delirium, [progressive] Encephalopathy)

Adolescents: dosage and serum levels comparable with those of adults

Caution: Cannot be recommended for children under 12 years of age
Thiazide diuretics are thought to lower lithium clearance by increasing proximal tubular reabsorption.

ACE inhibitors also increase concentrations of concomitant lithium, but the mechanism is yet to be determined.

Non-steroidal anti-inflammatory drugs (NSAIDs) also reduce lithium clearance. Although the mechanism of the latter effect is not clear, one hypothesis is that NSAIDs inhibit renal production of endogenous prostaglandins, thereby mediating either sodium retention or reduced renal blood flow and consequently reduced glomerular filtration rates.

Other causes of increased serum lithium concentrations include any cause of reduced glomerular filtration and sodium depletion, vomiting and diarrhoea, or fever.
Lithium toxicity
(modified from: Mohandas & Rajmohan 2007)

75 to 90% of patients may show temporary symptoms and signs of toxicity at some point during lithium treatment (mostly mild tremor and diuresis)

- **Mild intoxication** – tremor, nausea, diarrhea, blurred vision, vertigo, confusion and increased deep tendon reflexes

- **Severe intoxication**: >2.5 mEq/L – seizures, coma, cardiac dysrrhythmia and permanent neurological impairment (especially cerebellar)

Risk factors:
- **General risk** increase: Diuretics, ACE inhibitors, CCBs, NSAIDs, Haloperidol, thioridazine, chlorpromazine, clozapine, risperidone
- **Neurotoxicity risk**: Preexisting EEG abnormalities, seizures, any cerebral impairment, old age

Mortality: Overall less than 1%

Treatment by gastric lavage, whole bowel irrigation with polyethylene glycol, rehydration, **Hemodialysis**
Incidence of Delirium in new users of lithium, valproate or benztropine. (Shulman et al. 2005/Goodwin & Jamison 2007)
Neurotoxicity of Lithium Tx

- Neurotoxicity at excessive Lithium levels (>1.5 mEq/l) are well known (cerebellar ataxia, delirium, seizures, death)
- Toxicity at normal Li-levels: Baldessarini’s group reviewed 12 studies involving 276 lithium-treated and 263 similar or the same subjects, lithium-free.
- Lithium was taken for a mean duration of 3.9 years by affective disorder patients and 2.5 weeks by healthy volunteers, yielding a mean daily trough serum concentration of 0.80 mEq/L.

- Results: Overall, lithium treatment was associated with
  - small but significant impairment in immediate verbal learning and memory (ES = 0.24; 95% CI, 0.05-0.43) and creativity (ES = 0.33; 95% CI, 0.02-0.64),
  - but delayed verbal memory, visual memory, attention, executive function, processing speed, and psychomotor performance were not significantly affected.
  - Selectively, among the 326 affective-disorder patients, in addition to these overall impairments, long-term lithium treatment also was associated with even greater impairment in psychomotor performance (ES = 0.62; 95% CI, 0.27-0.97), with no evidence of cognitive improvements.

- CONCLUSIONS: Lithium treatment appears to have only few and minor negative effects on cognition.

Neuroprotective Effects of Lithium

- Lithium reduces elevated rates of dementia in patients with bipolar disorder down to levels of the general population
- Lithium counteracts glutamatergic activity
- Lithium increases BDNF, inhibits PK-C
- Greater volume of cortical and subcortical structures in patients on Lithium (DLPFL, Hippocampus)
Plate 1. Brain gray matter volume is increased following 4 weeks of lithium administration at therapeutic levels in patients with bipolar disorder. Brain tissue volumes were examined by means of high-resolution three-dimensional magnetic resonance imaging (MRI) and validated quantitative brain tissue segmentation methodology to identify and quantify the various components by volume, including total brain white and gray matter content. Measurements were made at baseline (medication-free, after a minimum 14-day washout) and then repeated after 4 weeks of lithium treatment at therapeutic doses. Chronic lithium significantly increases total gray matter content in the human brain of patients with bipolar disorder. No significant changes were observed in brain white matter volume or in quantitative measures of regional cerebral water. (Source: Gould, T.D., and Manji, H.K. (2002). Signaling networks in the pathophysiology and treatment of mood disorders. J Psychosom Res, 53, 687–697. Reprinted by permission of SAGE Publications, Inc.)
Lithium leads to 25% increase in +BrdU cells in the dentate gyrus of mice (Chen et al. Bipolar Dis. 2000)
Increased dendritic arborization and BDNF in the Hippocampus (Nestler, EJ et al. Neuron 2002)
Lithium Treatment and Risk of Dementia

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Figure Legend: Rate ratios (bars represent 95% confidence intervals) of dementia according to the number of prescriptions for lithium (the period with 1 prescription is used as the reference). Findings are adjusted for the effect of age, sex, calendar period, and purchase of antidepressants or anticonvulsants. Subjects: 16,238 persons who purchased lithium at least once and 1,487,177 persons from the general population who did not purchase lithium.
Rate ratios (bars represent 95% confidence intervals) of dementia according to the number of prescriptions for anticonvulsants (the period with 1 prescription is used as the reference). Findings are adjusted for the effect of age, sex, calendar period, and purchase of antidepressants or lithium.

Figure Legend:
Do’s and Don’t’s of Lithium Tx

- Regular f/u visits and PE, serum Li-levels, Labs
- Educate about (de-)hydration/medication interactions
- Be cautious combining Lithium with Haloperidol/Risperidone
- Avoid ECT in patients still on Lithium (d/c Li first)
- Educate about early relapse signs, seasonal fluctuations
- Don’t ever suddenly stop Lithium: Suicide risk becomes very high, so does relapse!
- IF you discontinue Lithium: Taper over >1 year!
Li-Prophylaxis: Right Levels Matter

- **Nolan and Weisler (2013)** compared the effect of lithium within the presumed therapeutic range of 0.6-1.2 mEq/L and below 0.6 mEq/L with that of placebo.
  - Methods: post hoc analysis of a double-blind trial in which patients aged ≥18 years with bipolar I disorder (DSM-IV) who had achieved stabilization from a manic, depressive, or mixed episode during open-label treatment with quetiapine were randomized to continue quetiapine or to switch to lithium or placebo for up to 104 weeks.
  - Of patients randomized to lithium, 201 obtained median lithium levels between 0.6 and 1.2 mEq/L, and 137 obtained median lithium levels < 0.6 mEq/L. Their outcomes were compared with those of patients receiving placebo (n=404).
  - The primary outcome was time to recurrence of any mood event; additional outcomes included time to recurrence of a manic or depressive event.

- **Results:** Times to recurrence of any mood event as well as a manic or depressive event were **significantly longer for the lithium 0.6-1.2 mEq/L group** versus placebo and versus lithium < 0.6 mEq/L.

- **Conclusions:** The results support and expand previous findings that lithium monotherapy should be dosed high enough to achieve plasma levels ≥ 0.6 mEq/L in order to achieve an effect in the prevention of both manic and depressive recurrences of **bipolar I disorder**.
However... lower doses maybe effective as well

- Jerram & McDonald found no differences in recurrence rates between the following groups:
  - 0.49 mmol/l; 0.50–0.69 mmol/l; and 0.70 mmol/l.

- Similarly, Coppen et al. found no difference in the outcome of bipolar patients randomly allocated to either continue lithium at a level of 0.8–1.2 mmol/l or to decrease to 0.45–0.79 mmol/l.

- Vestergaard et al. found no difference in recurrence rates between groups randomly allocated (in an open study) to 0.8–1.0 mmol/l or 0.5–0.8 mmol/l.

- For lithium augmentation of antidepressants, serum lithium concentrations of about 0.4 mmol/l are recommended.


Lithium Discontinuation

- **Prophylactic** effects of Lithium may take 8 – 12 months to fully develop – do not d/c Lithium too early in maintenance/prophylactic Tx of Bipolar d/o
- Safe in Pregnancy (Cat. D: old data); adjust dose upwards during pregnancy (same serum level/more body water); decrease back down after delivery
- **Surgery**: Generally recommended to
  - d/c Lithium 24 hours before surgery or delivery, and then to
  - Resume asap after surgery
OBJECTIVE: The aim of this study was to verify reduction of early affective morbidity by gradual, rather than rapid, discontinuation of lithium treatment.

METHOD: For 78 patients with bipolar disorders, lithium treatment was discontinued either rapidly (over 1-14 days) or gradually (over 15-30 days). The effects of the two schedules were compared by survival analysis of time to first recurrence.

RESULTS: Median time to recurrence was 5.6 times as long for gradual discontinuation (14.0 months) as for rapid discontinuation (2.5 months).

The ratios of the median survival times for gradual and rapid discontinuation were similar in I and II subtypes and in depression and mania (4-6:1).

The polarities of the episodes at onset and at first recurrence after lithium discontinuation were 83.6% concordant.

CONCLUSIONS: These results independently confirm a reduction in morbid risk from slow discontinuation of lithium treatment for bipolar disorders.

Old Myths – new Insights

- Myth: “Lithium levels should be always between 0.6-1.2 mmol/l” or “low-dose Li-Tx does not work”

- Fact: For Bipolar d/o: Li-levels best around 0.6-0.8 mEq/l; higher than 0.8 only increases risk of SE’s, not benefit
Myth: “Lithium is too dangerous”

- Lithium-Facts:
  - For patients with bipolar disorder, NOT to receive appropriate treatment may lead to increased relapse, social and medical harm, and death (suicide)
  - Its side effects are easily manageable, and many patients stay safely and beneficially on low-dose lithium for decades.
  - Its benefits, in terms of the relief of mania and the prophylaxis of depression, are incalculable
  - With the exception of ECT, lithium is the single most effective treatment in psychiatry (Ed Shorter 2009; David Healy 2009; others).
Other old Myth – new Insights

● Myth: “Use Lithium only for severe Bipolar-1 Disorder”

● Facts: Lithium can be successfully and safely used to
  ● Augment Tx-resistant Major Depression
  ● Decrease suicide risk in depressed patients
  ● Reduce impulsivity and violence potential
  ● Decrease cognitive impairment/dementia risk in bipolar patients back to the general population level
Once a day, or twice a day?

- Patient variables (greater irritability and impulsivity in am, sensitivity to tremor) may guide the choice

- But *Kidney concerns seem to favor once-a-day regimen* (Plenge et al. 1982):
  - Renal structure & function were investigated in two groups of long-term lithium treated patients: either in a one-dose per day schedule where the whole dose of lithium was given between 8 and 10 p.m. or in a schedule where the lithium dose was given, divided into two or three doses, during the day.
  - Kidney biopsy was performed, and structural changes in the kidney tissue were determined together with 24-h urine volume in the individual patients.

- Results: The functional as well as the structural changes were most pronounced in patients given lithium in divided doses

- Conclusion: Lithium may be more harmful to the kidney when the lithium is given in divided doses resulting in a relatively constant serum lithium level than when the administration causes greater variations including peak values and low minimum levels in serum lithium.

- The reason for this might be that a number of regenerative processes only occur in periods with low lithium concentrations.
The Art of Lithium Treatment: Summary

- Treatment of manic syndromes and suicidality
- Mood stabilization/relapse prevention in bipolar d/o
- Blood levels: no increase in clinical benefit found beyond 0.8 mEq/l, only more SE’s (Baldessarini)
- Stabilization of recurrent Major Depressive episodes
- Augmentation of Tx resistant MD
- Hypothyroidism: add Thyroid hormone
- NDI: give Amiloride
- The “L-L-Treatment” (Goodwin): Lamictal + Lithium
- Once or twice daily? And: Taper-off SLOWLY (3 months)
“Some guys from the state board of medicine are here to see you.”
• Zarate CA, Manji HK Protein kinase C inhibitors: rationale for use and potential in the treatment of bipolar disorder. CNS Drugs. 2009;23(7):569-82.
• E. Shorter Bipolar Disorder 2009 June; 11(02): 4-9
• Fels, Anna: Should We All Take a Bit of Lithium? New York Times 9/14/2014
References

- Baldessarini RJ, Tondo L, Hennen J Lithium Treatment and Suicide Risk in Major Affective Disorder  J Clin Psychiatry 2003;64/suppl 5/:44-52