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Lithium

- **General**
  - The use of lithium in the treatment of bipolar disorder in the USA has reduced the costs of mental health care by 2.9 billion dollars over a 10-year period. In combination with an additional estimate of savings of 1.3 billion dollars resulting from the return of patients to their functional productive lives, that results in cumulative savings of over 4 billion dollars.
  - One needs to treat only 125 patients with lithium over 1 year to save one patient per year
  - 0.006% of earth's crust
  - Produced from the mineral spodumene in North Carolina or extracted from brine pumped up from a salt desert in Chile.
  - In a review of 32 randomized trials with 1389 patients randomized to lithium and 2069 randomized to active comparator meds, lithium was associated with (Cipriani, 2005):
    - 74% decreased risk of suicide
    - 79% decreased risk of suicide attempt and deliberate self-harm
    - 58% decreased risk of all causes of death

Lithium in Acute Mania


Buffalo Lithia Water.

NATURE'S GREAT REMEDY FOR EXCESS OF URIC ACID IN THE BLOOD.

Its especial value in Nervous Prostration and other Nervous Diseases complicated with Lithæmia. In such cases it accomplishes astonishing results, after a failure of the carbonate of lithia, the phosphate of ammonia, and other so-called solvents of uric acid.

It evidently then possesses some extraordinary virtue apart from that ascribed to Lithia.

Note relative to the Buffalo Litha Water, by William A. Hammond, M.D., Surgeon-General U.S. Army (retired), formerly Professor of Diseases of the Mind and Nervous System, University of New York.

IN AN ARTICLE WIDELY COPIED INTO THE LEADING MEDICAL JOURNALS IN THE COUNTRY.

GOUT, RHEUMATIC GOUT, RHEUMATISM, STONE OF THE BLADDER, RENAL CALCULI, BRIGHT'S DISEASE OF THE KIDNEYS, NEURALGIAS, NERVOUS PROSTRATION, VARIOUS FORMS OF DYSPEPSIA, ETC., HAVE THEIR ORIGIN IN AN EXCESS OF URIC ACID IN THE BLOOD. WE WRITE WITHOUT HESITATION THAT BUFFALO LITHIA WATER IS A POWERFUL REMEDIAL AGENT IN THESE MALADIES.

SPRINGS OPEN FOR GUESTS JUNE 1.

Water in Cases of One Dozen Half-Gallon Bottles, $5.00, f. o. b. Here.
DESCRIPTIVE PAMPHLETS SENT FREE.

THOMAS F. GOODE, Buffalo Lithia Springs, Virginia.

Advertisement from *Harper's New Monthly Magazine*, 1892, from the author's collection.

- Gold standard – benchmark
- Lithium nonresponse differs from other mood stabilizers
- Clinical predictors account for <50% of variance, suggesting genetic factors
- Prophylactic response familial
- Numerous side effects, narrow therapeutic index
- Believed to reduce suicide rates via unknown mechanism

Frye MA et al. 1998; Goodwin FK et al. 1990 APA Practice Guidelines. Bowden CL et al. JAMA.1994;271:918–924.

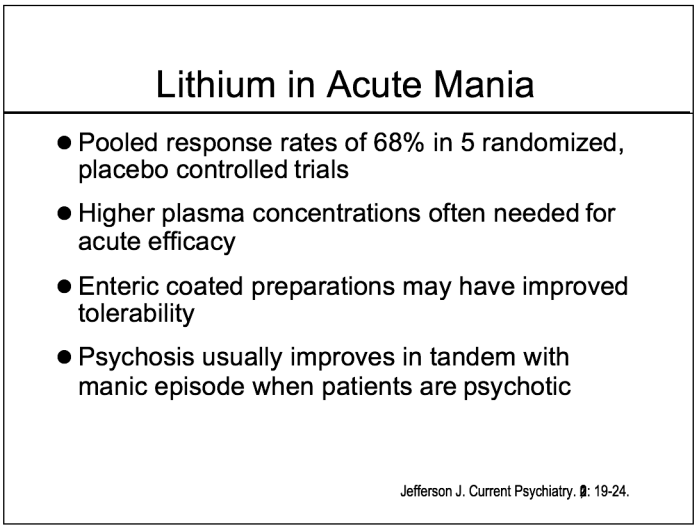
- **History**
  - Second century AD: Greek physician Seranus Ephisios recommended that physicians treating patients suffering from mania should prescribe "natural waters" such as (from) alkaline springs (which are now known to be rich in lithium).
  - Fifth century AD: mineral springs containing small amounts of lithium were recognized as (potentially) therapeutic
  - 1800: obtained from the mineral petalite by Jorge Bonifacio de Andrada e Silva—the Reverend Edward Clarke revealed that part of the sample was unaccounted for by previously identified elements
  - 1818: discovered formally by Arfwedson; originally named lithion
  - 1824: Berzelius describes the mineral springs in Bohemia as a source of lithium
  - 1859: Alfred Garrod proposed it could be used to treat gouty phalanges by topical application
  - Around 1859: Professor A. Trousseau proposed the 'uric acid diathesis' as the root cause of certain mood disorders; he believed 'folie', specifically mania, was the result of excessive uric acid when 'gout retroceded to the head.'
  - Used in medicine since the mid-19th century for bladder stones, rheumatism
  - 1870: S. Weir Mitchell proposed the use of lithium bromide as an antiepileptic
  - 1884: Alexander Haig proposed that the 'uric acid diathesis' accounted for gout, headache, digestive diseases, and depression; he demonstrated that oral lithium citrate decreased uric acid excretion and proposed this as a treatment for these conditions
  - Late 19th century: rise of mineral spas as a fashionable health-promoting activity 1887: Willard Morse proposed that these mineral waters could treat gout and rheumatism

- 1889:
    - Mineral waters shown to contain very little lithium
    - Emil Kraepelin works on development of classification of manic-depressive illness as distinct from schizophrenia
    - Carl Lange begins to explore the use of lithium as a treatment for affective illness; he found that patients with depression AND gout treated with lithium showed an improvement in their mood
- 1894: Fritz Lange, Carl's brother, publishes *The Most Important Groups of Insanity* in which he listed lithium carbonate as an antidepressant
- 1897: Carl Lange reported 10 patients hospitalized for suicidal, recurrent depression treated successfully with lithium, light therapy and exercise; the patients relapsed when lithium was stopped; this is the first report of lithium used in the treatment of recurrent depression
- 1936: found to have a salty taste
- 1946-9: John Cade, an Australian state hospital superintendent in the Mental Hygiene Department of Victoria, Australia:
    - Was investigating the "toxicity" of urine from patients with mania, depression and schizophrenia by injecting the urine samples into guinea pigs
    - Urine from folks with mania was more "toxic" to the animals (due to urea)
    - He added lithium urate (the most soluble of the urates) to the urine to render it more soluble and injected into guinea pigs
    - ~2 hours post-injection, the guinea pigs became more docile and lethargic for a period of 1-2 hours
    - Since the uric acid was less toxic with the lithium; he assumed that the lithium component must have had a protective effect
    - In controlled experiments, lithium carbonate was injected (the carbonate ion is harmless and found in things such as baking soda), and it was noted that "after a latent period of about 2 hours the animals, although fully conscious, became extremely lethargic and unresponsive to stimuli for one to two hours before once again becoming normally active."
    - Cade himself self-administered lithium carbonate for a few weeks and found it to have no ill effects
    - He later administered lithium citrate to a 51 y.o. man "who had been in a state of chronic manic excitement for 5 years, restless, dirty, destructive, mischievous and interfering, had been regarded as the most troublesome patient in the ward. His response was highly gratifying. From the start of treatment on March 29, 1948, with lithium citrate he steadily settled down and in three weeks was enjoying the unaccustomed surroundings of the convalescent ward. He remained perfectly well and left the hospital on indefinite leave with instructions to take a dose of lithium carbonate, five grains, twice-a-day. He was soon back working at his old job. However, he became lackadaisical about his medicine and finally ceased taking it. His relatives reported that he had not taken any for at least six weeks prior to his readmission on January 30, 1949 and was becoming steadily more irritable and erratic. On readmission to the hospital he was at once started on lithium carbonate, ten grains three times-a-day, and in a fortnight had again settled down to normal. He is now (February 28, 1949) ready to return to home and work."
    - Cade had treated ten manic patients with lithium (either 1200 mg of lithium citrate or 600 mg of lithium carbonate), and all ten had shown the same dramatic improvement; he had also given lithium to six patients with "dementia praecox" (schizophrenia) and three patients with "chronic depressive psychoses," but with less effect. The agitated patients with schizophrenia became less agitated but had "no fundamental improvement" in their psychosis; the depressed patients had "no improvement"
    - Cade concluded lithium did not have antidepressant effects
    - September 3, 1949, published article in the Medical Journal of Australia called "Lithium Salts in the Treatment of Psychotic Excitement."
    - The first patient died from lithium toxicity later; the last patient died in 1980 at the age of 76 from myocardial infarction
- 1948: marketed as a salt substitute in patients with cardiac failure and hypertension; banned by FDA in 1949 as a result of lithium-induced fatalities
- 1951-3: increasing evidence from Noack and Trautner, Despinois, Reyss-Brion, Deschamps, Duc, Lafon, Passouant, Glesinger and Carrere.
- 1953: Danish psychiatrist Mogens Schou's trial on the treatment of 35 patients with mania with lithium citrate and lithium carbonate; all patients improved. He wrote: "it is rather astonishing that (Cade's) observation has failed to arouse greater general interest among psychiatrists."
    - Schou and colleagues did the careful clinical trials that eventually resulted in the development of recommended dosages and preparations of lithium for the treatment of bipolar disorder:
        - of the thirty-nine patients whose lithium was replaced with the placebo, twenty-one relapsed within five months
        - of the forty-five other patients, those whose lithium was not replaced, none had a relapse.
    - 1955: 81% of 48 patients with mania improved and demonstrated lower rate of relapse
    - He was also able to show that lithium can prevent the recurrence of episodes as well; this was published in 1970
- 1954: GP Hartigan showed a positive treatment effect of lithium for both mania and depression
- 1956+: groundwork for prophylaxis done by Schou, Hartigan, Rice, Baastrup, Angst and Grof
- 1966: over 100 articles published on lithium in this year
- 1969: Baastrup and Schou, double-blind study of lithium treatment of mood disorders

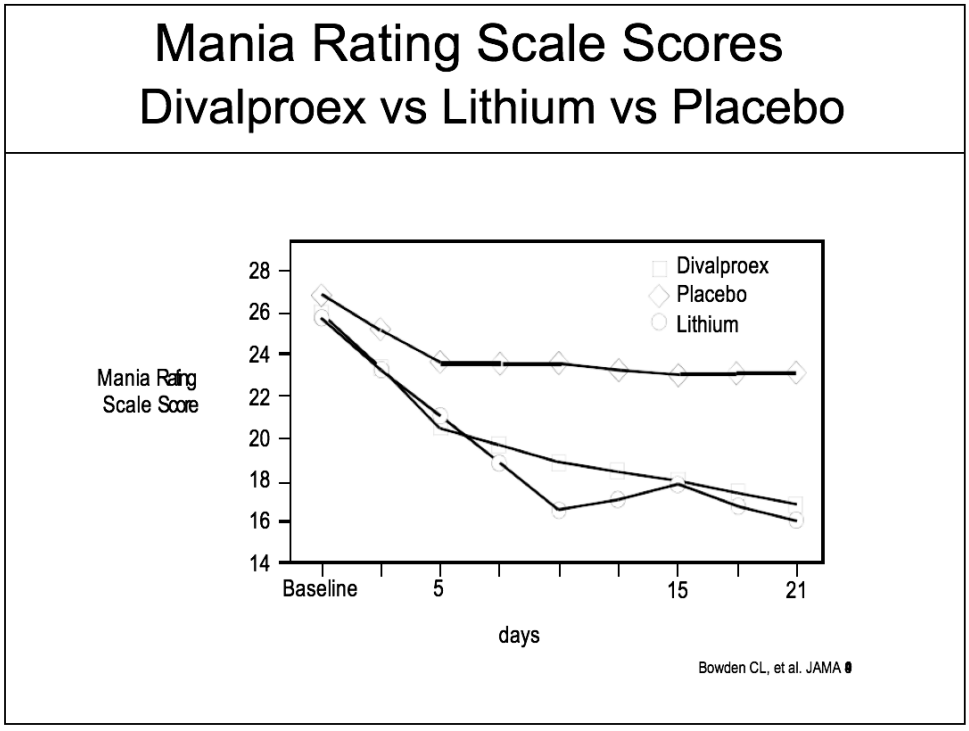
- 1970, 4: due to, among other studies, the VA-NIMH study, the FDA finally gave approval for lithium in the treatment of bipolar disorder

- **FDA-approval**
  - Mania in 1970
  - Maintenance treatment in bipolar disorder in 1974.
  - Bipolar disorder in children 12 years of age and older (though the indication for children 12 years of age and older is not based on adequate evidence of safety and efficacy).
- **Evidence of safety and efficacy in bipolar disorder in adults**
  - **Less response if**
    - anxiety present
    - substance abuse present
    - the sequence of episodes tends to be depression first followed by mania then well intervals (euthymia) (D-M-I, where "I" = well interval (aka, euthymia))
    - rapid cycling
    - presence of dysphoric mania (mixed episodes)
    - > 3 episodes
  - **More response if**
    - positive history of lithium efficacy
      - Alda et al, 2018
        - Good response in 68.6% of patients with a family history of positive response to lithium
        - Good response in 22% of patients without a family history of positive response to lithium
    - family history of mood disorder
    - classical euphoric mania with clear-cut well intervals between episodes (I-M-I)
    - starting lithium early in the course (as opposed to later, after many episodes)
    - sequence of mania followed by depression, followed by euthymia (M-D-I)
  - **Adults**
    - General
      - 79% response rate overall in adult bipolar disorder. Some antidepressant properties; can augment antidepressant efficacy
      - Nierenberg et al, 2009, LiTMUS study:
        - Lithium plus optimized treatment (OPT)
        - OPT without lithium
        - Conclusions
          - No significant differences in primary or secondary outcomes
          - Clinically significant (30-60%) improvements in
          - Mood
          - Quality of life
          - Suicidality
      - Two recent (?2010?) large, placebo-controlled, randomized, parallel-group, double-blind studies provide good evidence for effectiveness of lithium in prophylaxis (the study was better constructed than earlier studies which had inadvertently artifactually increased rates of relapse in the placebo group)
        - Lithium extended time to relapse of 25% of the patients by 55% over placebo.
        - Less effective (and in many cases ineffective for extending time to relapse depression
      - Markku Lahteenvuo et al, 2018
        - Lithium and injectable antipsychotics were best at preventing re-hospitalization in 18,018 Finnish patients (with an average of 7 years of follow up

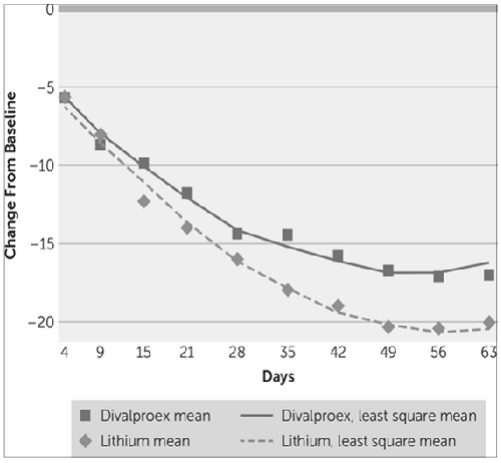
- **Mania, adults**



- Maggs; Bowden; Stokes; Johnson; Platman; Spring; Johnson; Prien; Takahashi; Shopshin
- Schou, 1954
  - confirmed efficacy in mania.
- Compared to standard antipsychotic medications in reducing mania symptoms in 6 studies
  - lithium overall outperformed antipsychotic medications
  - antipsychotic meds acted more quickly and was more helpful with agitation.
- Decreases time ill with mania 2.5-fold in bipolar I
- Decreases time ill with hypomania 2.5-fold in bipolar II



Li vs Valproate in Older Persons with Bipolar I Mania



224 in- and out-patients ≥60 years of age with hypo/mania (YMRS ≥18)

Divalproex (started at 500 mg/kg/d) or Li (started at 300 mg/d) for 9 weeks

Primary outcome: Change in YMRS

Treatments comparable, though Li a little better

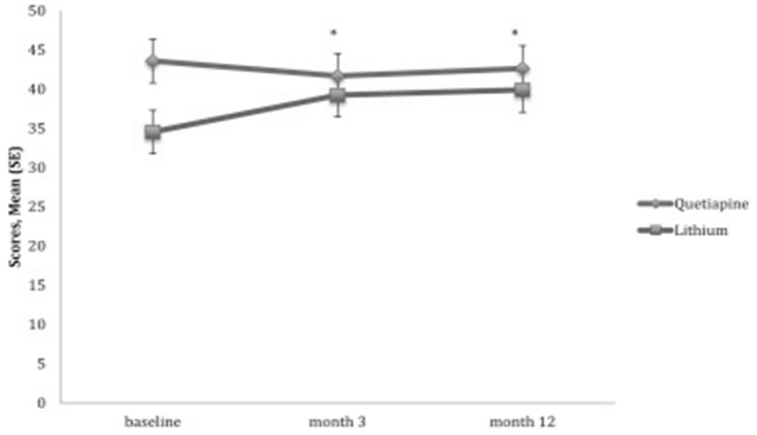
Similar discontinuation rates, including for side effects

Young R C et al. Am J Psychiatry. 1974:1086-93

- Bowden, 1994:
  - randomized, parallel-group, double blind, mania
  - lithium superior to placebo
  - lithium equivalent to Depakote
  - confirmed levels of 0.8 or higher necessary for efficacy
- (Date?) RCT comparing Zyprexa to lithium; manufacturer-sponsored
  - Zyprexa with 87% response rate
  - 73% response rate with lithium
  - no difference on depressive symptoms
  - weight gain more with Zyprexa (4 lbs vs. 1.6 lbs)
- It's often necessary to get the blood level of lithium closer to 1.0 to optimally treat mania

- **Bipolar depression, adults**
  - 36% overall response rate
  - 38% relapse rate vs. 75% rate with placebo
  - Decreases time ill with depression 2-fold in both bipolar I and II
  - Fieve, 1968, Dunner, 1976
    - positive antidepressant properties
    - less robust or slower onset than standard antidepressants.
  - Nemeroff, 2001
    - antidepressants added to patients on high doses of lithium
    - 39-46% response rate with imipramine or Paxil; not statistically significant
    - Perhaps more useful in folks who can't tolerate high doses of lithium
  - Tohen, 2005
    - evidence of efficacy
- **Maintenance treatment, adults**
  - Lithium improves impulsivity and other functional benefits when continued in maintenance treatment even in the absence of formal episodes
  - Lithium treatment over 12 months helps with recovery of cognitive functioning

Li vs QTP on trajectory of cognitive function in 1st episode mania



R Daglas et al. European Psychiatry, Volume 31, 2016, 20–28

- Lithium has at 8-10+ placebo-controlled, randomized trials demonstrating efficacy in maintenance treatment, including Baastrup and Schou; Coppen; Cundall; Prien; Prien; Stallone; Kane; Dunner; Bowden; Calabrese; Gelenberg
- Still, only 50% or less of patients with bipolar disorder have complete suppression of all future episodes.
- Schou, 1970
  - first to report compelling evidence that lithium carbonate dramatically reduced the incidence and duration of serious affective episodes in bipolar patients
- Lithium especially helpful in maintenance treatment of bipolar II, especially if have not used antidepressants in the past; efficacy improves on discontinuation of antidepressants.
  - Dunner, 1976: lithium helpful for prevention of depression, not for hypomania
  - Fieve, 1976: lithium helpful for depression
  - Kane, 1982: lithium helpful for both
  - Tondo, 1998: lithium helpful especially in bipolar II (more than I)
  - Greil, 1999: lithium and Tegretol equally helpful
  - Suppes, 2008: lithium and Lamictal equally helpful
  - Amsterdam, 2010: Prozac > lithium, placebo
- Goodwin and Jamison, 1990; summary of 12 double blind studies of lithium vs. placebo in maintenance treatment:
  - Overall: 34% relapse rate with lithium, 81% with placebo
  - Relapse into depression: 21% with lithium, 37% with placebo
  - Relapse into mania/hypomania: 23% with lithium, 56% with placebo
- Grell, 1998:
  - Lithium better than Tegretol in bipolar I (with no mood-incongruent delusions or co-morbidity)
  - Tegretol better than lithium in bipolar II/NOS (with presence of mood incongruent delusions or co-morbidity
- Baldessarini, 2001 looked at 29 major studies of maintenance lithium treatment
  - 2986 patients (23,263 patient-years)
  - 78% had bipolar disorder
  - 3.2-fold decreased risk of recurrence overall
  - 3.6-fold decreased risk of recurrence in the 12 placebo-controlled studies
  - 80% reduction in hospitalization
- Hennen, 2001, meta-analysis of 16 studies, ~1800 patients
  - lithium was superior to Depakote/Tegretol in rapid cycling patients
- Two large, placebo-controlled, randomized, parallel-group, double-blind studies (2010+?)
  - provide good evidence for effectiveness of lithium in prophylaxis (the study was better constructed than earlier studies which had inadvertently artifactually increased rates of relapse in the placebo group)
  - Lithium extended time to relapse of 25% of the patients by 55% over placebo.

        - Less effective (and in many cases ineffective) for extending time to relapse depression.
    - Geddes, 2010 (BALANCE study), lithium as adjunct to Depakote vs. either one alone in maintenance treatment/relapse prevention:
        - overall: combination > lithium > Depakote
        - time to relapse into mania: combination > lithium > Depakote
        - time to relapse into deprn: lithium ~> combination > Depakote
    - Markku Lahteenvuo et al, 2018
        - Lithium and injectable antipsychotics were best at preventing re-hospitalization in 18,018 Finnish patients (with an average of 7 years of follow up)
    - Markku Lahteenvuo et al, 2019
        - From 2018 cohort
        - Lithium → lowest rate of suicide
        - Depakote → second lowest rate of suicide
        - Antidepressants → highest rate (but most severe depressions?)
- **Reduction of suicide risk, neuroprotection, and protection of medical health**
    - Lithium is associated with
        - A four-fold reduction in mood episode relapse versus placebo (at 1 year)
        - A 6-8.6 fold reduction in suicide; elsewhere: 60-82% reduction in completed suicide and 70% reduction in self-harm
        - An 8.6-fold reduction in the recurrence of suicide attempts
        - Lithium 2.86-fold decreased risk suicide/suicide attempt vs anticonvulsant treatment
        - Upon discontinuation
            - a nine-fold increase in the rate of complete suicide
            - a seven-fold increase in the rate of suicide attempts
            - greatly and rapidly increases the risk of florid relapse
        - Of 33 studies from 1970-2000, 18 of 19 studies which compared groups with and without lithium treatment confirmed the reduction in suicide rates.
        - Fewer deaths overall
        - Note, however, that while the risk of complete suicide is reduced with lithium treatment of bipolar disorder, the risk is still 10-fold greater than the international baseline rate of suicide: 0.109-0.224% annually with lithium treatment versus baseline rate of 0.017%.
        - Lithium might reverse the risk of mortality from other medical causes as well
        - Increases the length of telomeres (bits of DNA at the end of each chromosome; longer telomeres are protective against medical and psychiatric ilneses
    - Thies-Flechtner, 1994
        - lithium >> Tegretol for suicide/suicide attempts in bipolar disorder
    - Tondo and Baldessarini, 2000
        - 7-fold reduction in suicide rate (in review of 22 studies)
        - 0.227%/year on lithium versus 1.778% (plus/minus 1.444%) for bipolar patients not on lithium
    - Goodwin, 2003
        - lithium > lithium + Depakote >>> Depakote for suicide/suicide attempts in bipolar disorder
    - Goodwin, 2004
        - 20,638 members of two HMO's:
        - ER admissions for attempts:
            - 10.8/1000 persons/year for lithium
            - 31.3 for Depakote
        - Suicide attempts resulting in hospitalization
            - .4.2/1000 persons/year for lithium
            - 10.5 for Depakote
        - Complete suicide (2.7-fold reduction if on lithium versus Depakote
            - 0.7/1000 persons/year for lithium
            - 1.7 for Depakote
    - Cipriani, 2005
        - in 32 trials, 1389 patients received lithium and 2,069 received other compounds
        - odds ratio (odds on lithium versus odds on other compounds) of dying by suicide were 0.26 on lithium
        - odds ratio of "suicide plus deliberate self harm" also lower at 0.22
        - fewer deaths overall on lithium (odds ratio 0.42)
    - Baldessarini, 2006
        - analysis of 31 studies
        - 4.91-fold decrease in rates of suicide/suicide attempts
    - Guzetta, 2006
        - analysis of 8 studies of recurrent unipolar depression
        - 2-fold decreased risk of suicide/suicide attempts
    - Meta-analysis, 2007

- data from 7 studies on recurrent depression
- 88.5% reduction in the risk of suicidal acts
- completed suicide rates were
  - 0.33% with lithium treatment
  - 2.22% without

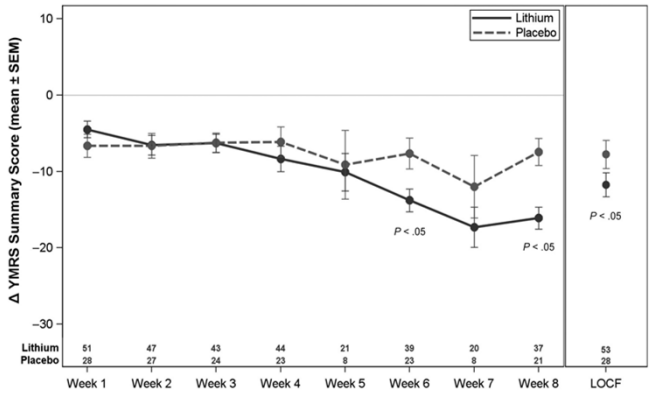
- Song et al, 2017; Suicidal Behavior During Lithium and Valproate Treatment: A Within-Individual 8-Year Prospective Study of 50,000 Patients With Bipolar Disorder
  - 51,535 folks with bipolar disorder followed from 2005-2013 for treatment with lithium and valproate
  - 10,648 suicide-related events occurred
    - The incidence rate was decreased by 14% during lithium treatment, but not during valproate treatment
- Markku Lahteenvuo et al, 2019
  - From 2018 cohort
  - Lithium → lowest rate of suicide
  - Depakote → second lowest rate of suicide
  - Antidepressants → highest rate (but most severe depressions?)

- **Evidence of safety and efficacy in bipolar disorder in youth**

  - **Mania, youth**
    - Gram and Rafaelsen, 1972
    - DeLong, 1978,
    - Hassanyeh, 1980
    - McKnew et al, 1981
    - McKnew, 1981
    - Hsu, 1986
    - Delong and Aldershof, 1987
    - Varanka, 1988
    - Strober, 1988
    - Strober et al, 1990
      - 49% response rate in youth less than 12 yo
      - 80% in adolescent patients
    - Carlson et al, 1992
    - Strober et al, 1995
      - 68% response rates in
      - 92.3% relapse rate upon discontinuation against medical advices compared
      - 37.5% relapse rate with lithium maintenance treatment
    - Hagino et al, 1995
      - anecdotal evidence in open treatment in in children aged 4-6 who were hospitalized for aggression and/or mood disorder
    - Geller et al, 1998
      - not statistically superior to placebo in 30 prepubertal youth
    - Geller et al, 1998; double blind, placebo-controlled 6 week study of lithium for adolescent bipolar disorders with secondary substance dependency (alcohol or marijuana)
      - 25 adolescents (12 bipolar I, 5 bipolar II, 8 depression with risk factors for bipolar disorder)
      - ages ~15-17
      - average onset of bipolar disorder 10 yo (range 7-13 yo)
      - average onset of substance use disorder 15.3 yo (range 14-16.6 yo)
      - results
        - decreased drug use
        - improved mood symptoms
    - Stober et al, 1998; State et al, 2004
      - ADHD might predict poor response to lithium (but this has not been found in all studies
    - Kowatch, 2000
      - 38% response rate
    - Wagner, 2002
    - Davanzo, 2003, naturalistic study, 44 hospitalized youth aged 5-12 years
      - effective by, by week 2
      - lithium equivalent to Depakote
      - lithium more effective than Tegretol
    - Kafantaris et al, 2003/2004: lithium treatment of acute mania in adolescents; placebo-controlled discontinuation study, 40 adolescents, bipolar I, manic episode, average age 15 (range 13.3-16.7 yo)
      - effective over 5-8 weeks in adolescents at levels ~0.99

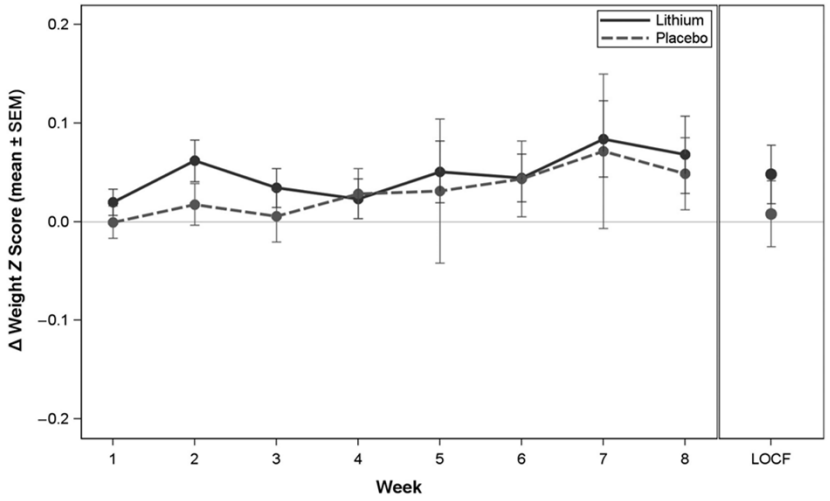
- when treatment was randomized to lithium vs. discontinuation of lithium, relapse rates were equivalent
- Kafantaris, other:
  - 100 hospitalized teens with bipolar I (32% had co-morbid ADHD; 35% psychotic; 11% aggressive without psychosis)
  - 64% response rate by 4 weeks when treated openly with lithium and an antipsychotic
  - 28.6% maintained response after antipsychotic discontinuation.
- Dickstein et al, 2009
- Kowatch et al, 2009
  - Pediatric Bipolar Collaborative Trial (Lithium vs Depakote vs Placebo)
  - Depakote>lithium>placebo
- Geller et al, 2012/Vitello et al, 2012; TEAM Study (Risperdal vs Lithium vs Depakote in bipolar I mania/mixed episodes, 279 youth, 6-15
  - Response rates at 8 weeks:
    - Risperdal (avg dose 2.6) 68.5%
    - Lithium (avg bld level 1.1) 35.6%
    - Depakote (avg bld level 114) 24%
  - For non-responders and partial responders:
    - Non-responders (89) were switched; response rates according to what they were switched to:
      - Risperdal switch 47.6%
      - Lithium switch 12.8%
      - Depakote switch 17.2%
    - Partial responders (65) were augmented with 1 of the other agents that they were not on; response rates according to what med was added on:
      - Risperdal add-on 53.3%
      - Lithium add-on 26.7%
      - Depakote add-on 0%
- Findling et al, 2005, 2011, 2013, 2015; Findling et al, 2011; COLT Study (published in 2015)
  - 8-week trial; double-blind, placebo controlled
  - Ages 7-17
  - 64% also had ADHD
  - Lithium levels as high as 1.4
  - Lithium improved symptom scores but not functioning
    - Lithium 37.7%
    - Placebo 28.6%
  - Side effects
    - Vomiting 45% vs. 10.7% placebo
    - Nausea 43.4% vs. 17.9% placebo
    - Tremor 32% vs. 7.1% placebo
    - Thirst 28% vs. 10.7% placebo
    - Diarrhea 28% vs. 14.3% placebo
    - Urinary frequency 26% vs. 7.1% placebo
    - Dizziness 22.6% vs. 7.1% placebo
    - Fatigue OR sedation 20.7% vs. 3.6% placebo
    - TSH increase 17% vs. 0% placebo
    - Abdominal pain 11.3% vs. 3.6% placebo
    - Rash 11.3% vs. 0% placebo
    - Decreased appetite 9.4% vs. 3.6% placebo
    - Vision blurred 9.4% vs. 0% placebo

Lithium vs Placebo in Manic Youth



Robert L. Findling et al. Pediatrics 2015;136:885-894

Change in weight z score during the efficacy phase



Robert L. Findling et al. Pediatrics 2015;136:885-894

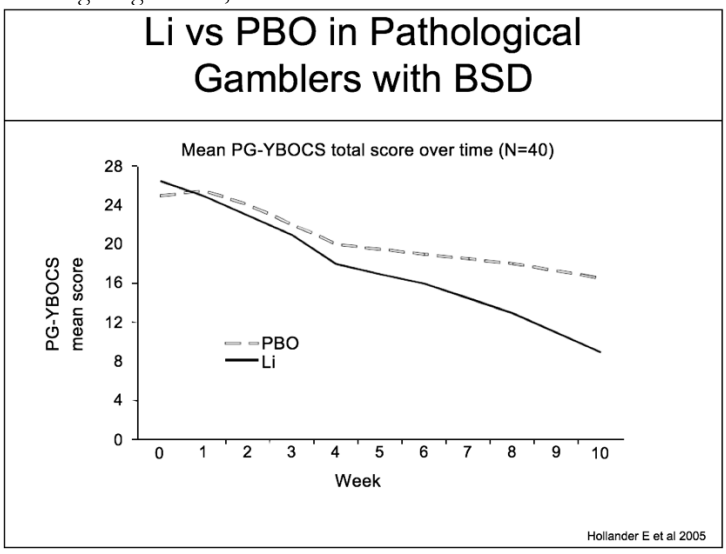
- Hafeman et al, 2018; Course and Outcome of Bipolar Youth (COBY) study
  - 413 youth, 7-17 yo
  - lithium use (more than 75% of time) (vs. other mood stabilizer use (more than 75% of time) →
    - fewer suicide attempts
    - fewer depressive symptoms
    - fewer psychosocial difficulties

- **Bipolar depression, youth**
  - Patel, 2006
    - open-label lithium, 27 adolescents
    - 48% response and 30% remission
    - headache 74%, nausea/vomiting 67%, stomachache 30%, abdominal cramps 19%.

- Hafeman et al, 2018; Course and Outcome of Bipolar Youth (COBY) study
  - 413 youth, 7-17 yo
  - lithium use (more than 75% of time) (vs. other mood stabilizer use (more than 75% of time) →
    - fewer suicide attempts
    - fewer depressive symptoms
    - fewer psychosocial difficulties
- **Maintenance treatment, youth**
  - Strober, 1990:18 month lithium-discontinuation study of adolescents with bipolar disorder
    - 92% of those that discontinued lithium relapsed
    - 38% of those who continued lithium relapsed
  - Geller, 1998: Adolescents with bipolar disorder *or* chronic recurrent depression *and* substance abuse
    - showed some positive efficacy in terms of reduced substance abuse and global improvement.
  - Findling, 2003
    - safety and efficacy of the combination of Depakote and lithium in the treatment of bipolar disorder in children.
  - Findling, 2005: double-blind, 18-month trial of lithium versus Depakote in pediatric bipolar disorder
    - both medications were equally effective
    - time to intervention for any mood episode in ***youth***:
      - Lithium: 16.3 weeks before 50% of clients require intervention
        - Preventative effect plateaus at ~30 weeks where 70% of clients required intervention
        - From 30 weeks through >70 weeks, just under 30% did NOT require intervention
      - Depakote: 16.0 weeks before 50% of clients require intervention
        - Preventative effect plateaus at ~55 weeks where >80% of clients required intervention
        - From ~55 weeks through >70 weeks, just under 20% did NOT require intervention
  - Findling, 2006:
    - children stabilized on combination lithium and Depakote who relapsed on taper of either the lithium OR the Depakote stabilized on re-introduction of the tapered agent.

- Recurrent depression
  - often there is a family history of bipolar disorder
  - onset is similar to onset of bipolar disorder (teens and 20's)
  - episode frequency in the range of patients with bipolar disorder
  - lithium prophylaxis better than imipramine
  - meta-analysis of 10 augmentation studies adding lithium to antidepressants, 269 patients total
    - 3.11 odds ratio of response vs. placebo
      - 40.5% pooled response rate for lithium
      - 17.4% for placebo
  - meta-analysis of 9 randomized placebo-controlled studies (229 patients)
    - relapse rates 36% with lithium treatment, 75% with placebo
    - 78% reduction in new episodes in another analysis of 10 studies
    - 30% fewer episodes with lithium vs. antidepressants in another analysis of 7 studies
  - levels between 0.4-0.6
  - usually requires 6 weeks at appropriate lithium level

- Other benefits
  - **Conduct disorder, youyh**
    - Improving benefit though at least the fourth week
  - Pathological gamblers, **adults**

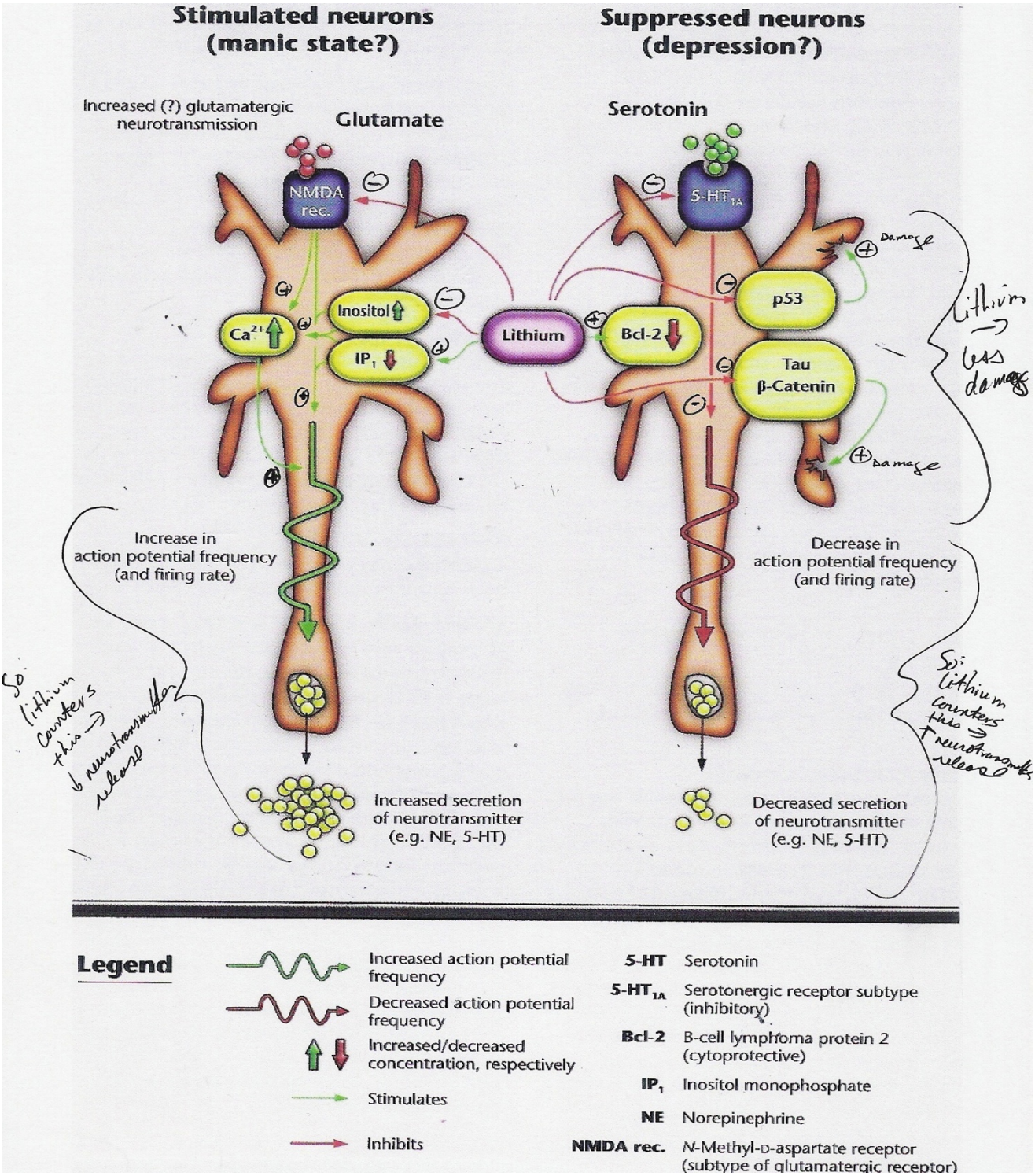


- **Some of the side effects and risks:**
  - General
    - increased white blood cells (all but basophils) 75-100%—no association with leukemia
    - stomach upset/nausea/vomiting (extended release preparations can reduce these side effects) 69%
    - "chemical" thyroid dysfunction (asymptomatic) 50%
    - transient muscle weakness during the first two weeks 40%; rarely observed in long-term studies
    - increased thirst 36%
    - increased frequency urination 30%
      - can be severe (e.g., diabetes insipidus)
      - can treat with:
        - 50 mg chlorothiazide with subsequent reduction of lithium dosage by 50% followed by careful restabilization of desired lithium level.
        - can carefully use amiloride 5-10 mg 1-3X/day, but levels must be watched closely
        - furosemide
    - memory problems/cognitive impairment 28%
      - 75% of patients note no change or an improvement in their creativity (Schou, 1979)
      - Bauer, 2005: improves immediate recall and organizational capacity
    - tremor 26% (fuller range is 4-65%)
      - occurs at rest and while moving
      - could use propanolol 30-80 mg/day (but contraindicated in asthma)
    - increased number of platelets 24% (81% with slightly elevated platelets but within normal range)
    - increased urination 20% (but generally only with levels above 0.8)
    - weight gain 19%
      - may relate to insulin-like effects that lead to hypoglycemia with consequent overeating
      - average of 16 pounds when occurs
    - bed wetting 17%
    - drowsiness/fatigue 12%
    - slightly elevated calcium, reduced phosphorous, and increased parathyroid hormone 10-25% (of adult patients)
      - 10-25% of adult patients
      - most often occurs after several years of treatment
      - lithium interferes with the calcium-sensing receptor in the parathyroids, reducing the sensitivity of the parathyroid glands to the negative feedback exerted on parathyroid hormone (PTH) secretion by calcium, and raising the calcium set point around which PTH secretion is regulation.
      - often, discontinuation of lithium may restore normocalcemia, but it can become independent of lithium
      - the parathyroids may become hyperplastic with the risk of developing adenomas
      - surgical parathyroidectomy may be needed in some cases
      - most often aymptomatic
      - can → sad, apathetic, or ataxic
      - some risk of kidney stones
      - get endo consult
    - diarrhea 9%

- balance problems 6.5%
- thyroid dysfunction
    - 6%: goiter without hypothyroidism (fuller range 0-61%)
        - 4.5% of men
        - 21% of women
    - 3.4%: symptomatic hypothyroidism
    - Over time, up to 23% adults (10% by 2 years, 23% by 10 years), 24% of children develop clinical hypothyroidism
    - Female to male ratio 5:1
    - even with normal thyroid, thyroxine (T4) replacement ay help, especially with rapid cycling (0.075-0.14 mg/day)
    - lithium inhibits the release of thyroid hormone from the gland→ high TSH→ increased thyroid gland growth and nodularity
    - 10-33% incidence of thyroid antibodies vs. 10% in controls
- double vision 2.2%
- malaise
- acne, worsening of dermatological problems; could use
    - omega 3 fatty acids
    - benzoyl peroxide (5% topical 1-2 times-a-day)
    - tetracycline 500-1500 mg/day
    - topical retinoic acid
- hair loss
- kidney changes (after years of use)
    - Kessing et al, 2015
        - Massive population-based study
        - Risk of chronic renal disease
            - Lithium
                - In folks with >60 prescriptions, risk is 3.65-fold higher for definitive chronic renal disease and 2.88-fold higher for possible chronic renal disease than folks with 0 scripts
                - Not associated with end stage renal disease
            - Anticonvulsants in bipolar disorder
                - In folks with >60 prescriptions, risk is 2- and 2.3-fold higher risk for definitive or possible chronic renal disease than folks with 0-2 scripts
                - Risk of end stage renal disease is 2- to 3-fold in folks with 30 to >60 prescriptions for anticonvulsants
            - Results may partly be due to bias
    - 1984 Consensus Development Conference of the NIMH concluded that there are few significant permanent risks from long-term lithium therapy
    - renal tubular acidosis—usually clinically insignificant
    - glomerular filtration rate does not appear to be affected
    - increased urination/nephrogenic diabetes insipidus
    - interstitial fibrosis, tubular atrophy, glomerular sclerosis, distal nephron lesions (not solely seen in lithium-treated patients)
    - up to 5% develop some degree of renal insufficiency; often it is clinically insignificant
    - creatinine can creep up in 20% of patients using lithium for 20+ years
    - slow-release preparations have less effect on urine concentrating ability
    - once-daily dosing of lithium may be better for kidney
- no link with cancer
    - Martinsson et al, 2018
    - 2.6 million Swedes aged 50-84 years with 4 years of follow-up
    - 2,393 patients with bipolar disorder on long-term lithium
    - 3,049 patients with bipolar disorder not on lithium
    - cancer risk, overall
        - 5.9% for those on lithium
        - 6% for those not on lithium
        - similar to those in the general population
    - cancer risk in those with bipolar disorder, NOT on lithium
        - 72% greater risk of lung cancer and cancers of the respiratory system than the general population
        - 47% greater risk of gastrointestinal cancers than the general population
        - 150% greater risk of endocrine organ cancers than the general population
        - Is lithium protective against some cancers?
- Congenital malformations

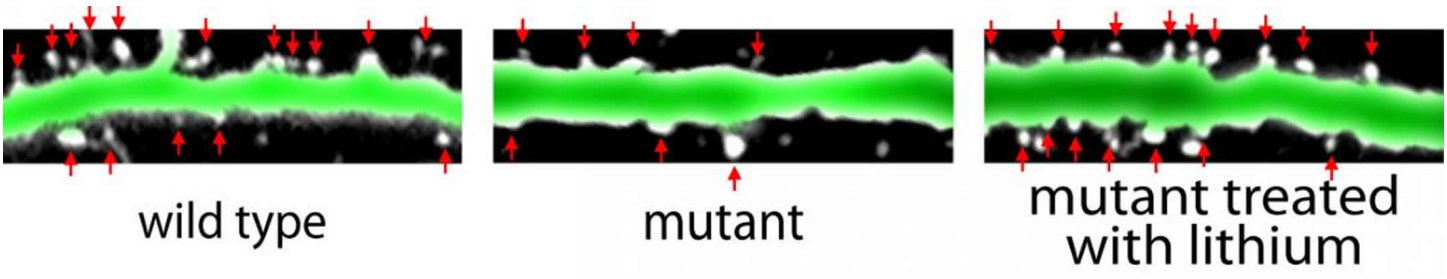
        - Ebstein's anomaly is a cardiac defect characterized by the failure of the tricuspid valves to properly form
            - Ebstein's anomaly occurs in the general population in 1/20,000
            - Cohen, 1994: risk in lithium-exposed infants: 1-2/1000
            - Risk is low, but 20-40 times the rate in the general population (despite earlier studies where the risk was thought to be 400-fold greater)
        - Increased overall risk of congenital anomalies
            - 4-12% in lithium exposed
            - 2-6% in non-exposed
        - AJP, 2014
            - 183 women with bipolar disorder exposed to lithium during pregnancy vs. 748 pregnant women with bipolar disorder not exposed to lithium
            - 5-fold increased risk of miscarriage or elective termination of pregnancy in lithium-exposed women
            - 7-fold increased risk of cardiovascular anomalies during the first trimester in lithium-exposed women
            - 14% rate of preterm delivery in lithium exposed women vs. 6% in those not exposed to lithium
        - Other possible fetal effects
            - "Floppy baby" syndrome
            - Large for gestational age
            - Hypothyroidism in mom
            - Nephrogenic diabetes insipidus in mom
            - No significant differences in developmental milestones in one controlled prospective study of lithium (Gentile, 2010)
        - Lithium level monitoring in pregnancy
            - Monthly until the last month
            - Then weekly in the last month
            - Then every 2-3 days shortly after delivery
        - Also, in pregnancy
            - Cardiac ultrasound, fetal echo at 16-20 weeks
            - Lower dose with onset of labor, avoid dehydration
- More likely with increasing blood levels, especially if levels are becoming toxic
    - fatigue/sleepiness
    - confusion
    - muscle weakness/heaviness of limbs
    - slurred sleep
    - worsening hand tremor/tremor of the lower jaw
    - muscle twitches
    - worsening nausea, stomachache, diarrhea
    - ringing in the ears
    - difficulty with balance/unsteady gait
    - heart rhythm: t-wave flattening and inversion; "sick sinus node" syndrome is very rare.
    - double vision
    - seizures in overdose
    - lethal in overdose

- Mechanisms of action



  - Serotonin (5HT)
    - increases synthesis of serotonin
    - increases tryptophan reuptake in synaptosomes after even short term use
    - enhances the release of serotonin from neurons in the parietal cortex and hippocampus after 2-3 weeks of use
    - chronic use causes a downregulation in 5HT1a, 1b, 2 receptors
  - Norepinephrine (NE)
    - increase rate of synthesis of NE in some parts of the brain
    - increased NE reuptake
    - decreases stimulated-induced release of NE
    - downregulation of NE receptor receptivity
    - inhibits NE turnover

        - reduces excretion of NE in patients with mania but increases the excretion of NE metabolites in patients with depression.
- Dopamine
    - blocks postsynaptic dopamine receptors' supersensitivity
    - decrease dopamine turnover in the nucleus accumbens
    - indirectly block dopaminergic tone
- Glutamate
    - reduces calcium influx via NMDA glutamate receptors,
    - may block reuptake of glutamate in a manner that leads to downregulation of glutamate release (i.e., less glutamate release).
- Acetylcholine
    - Enhances expression of M3 receptors but decreases M2 levels.
    - Enhances cholinergic activity
- Increases bcl-2/BAG-1 (see "Stress, Trauma and Brain")
- G-proteins
    - Blocks inositol transport; decreases coupling to phosphoinositol
    - Decreases coupling to adenylate cyclase (AC)
- Phosphatidyl inositol
    - Decreases inositol monophosphotase
    - Decrease phospholipase C
    - Decreases inositol transport
    - Increases calcium influx
- Adenylate cyclase
    - Increases basal cAMP but decreases stimulation of cAMP and inhibits protein kinase C (PKC), an enzyme found in higher amounts in the hippocampus of adults with bipolar disorder; valproic acid and antipsychotic medications also regulate this enzyme.
- Influence on genes
    - Neuropeptide Y
    - Glucorticoid Type II Receptors
    - G-proteins
    - Adenylate cyclase
    - Decreases alpha2 receptor activity
    - Associated with an increase in brain-derived neurotrophic factor (which is neuroprotective)
        - Excellent response (as opposed to partial and non-response) to lithium is associated with the Val/Met genotype of Val66Met polymorphism (and possible for the C/T genotype and T allele of -270C/T polymorphism) of the gene for BDNF.
- Other
    - increases GABA-B receptors in the hippocampus
    - decreases dopamine
    - decreases C-catenin.
    - Decreases phospholipase A2 and AA.
- Neurotrophic and neuroprotective effects
    - Chronic treatment with lithium:
        - increases the gray matter volume (in the brain) of subjects with bipolar disorder by as much as 15% (which is a remarkable increase)
        - increase a marker of neuronal viability
    - Chronic treatment with lithium and Depakote
        - minimizes reduction of subgenual prefrontal cortex volumes (seen in bipolar disorder)
        - minimizes reduction in glial numbers or glial/neuron ratios in the amygdala
        - → larger anterior cingulate volumes than bipolar patients not treated with lithium
    - Protects against
        - Glutamate, NMDA toxicity
        - Calcium toxicity
        - MPP+ toxicity
        - Beta-amyloid toxicity
        - Aging "toxicity"
        - Growth factor deprivation
        - Cholinergic system lesion toxicity
        - Medial cerebral artery occlusion toxicity
        - Quinolinic acid toxicity
    - Enhances neurogenesis in hippocampus
    - Increases synaptic efficiency and plasticity in the hippocampus (of rats)
    - Does not increase the gray matter in folks without bipolar disorder.



- There is some evidence that people with a certain type of serotonin reuptake transporter (with homozygous 'L' alleles) as well as other genetic traits are more responsive to lithium

- Pharmacodynamics
  - Dose range
    - Target dose 30 mg/kg.day; some begin at 25 mg/kg/day
    - Common range is 300 mg-2400 mg
      - 900 mg tends to produce levels around 0.6-0.7
      - 1200→~0.78
      - 1500→~0.85
      - 1800→~0.92
      - 2100→~0.96
      - 2400→~1.0
  - Effective plasma levels
    - 0.8-1.4 is the broader range
    - 0.9-1.1 is good target level for acute episode
    - 0.7-0.9 for short-term potentiation of antidepressant
    - 0.6-0.8 for bipolar I monotherapy
    - 0.4-0.6 for bipolar II and recurrent unipolar depression monotherapy
    - 0.4-1.2 for maintenance
    - 0.3-0.5 for adjuvant use with another mood stabilizer
    - some patients can avert episodes at levels of 0.4-0.6 and symptoms of irritability can sometimes be treated at even lower levels. Note (from Gelenberg, 1989):

Treatment Group	Any Relapse	Depressed	Manic/Mixed	Hypomanic	Withdrew from Study
Level 0.8-1	12%	6%	6%	0	51%
Level 0.4-0.6	44% (4X increase)	2% (3X decrease)	36% (6X increase)	6% (~6X increase)	23% (2X decrease)

- 7-14 days for onset of action; 6-8 weeks for onset of full action.
- Comes in 150, 300 and 600 mg caps and 300 mg tabs. Comes in extended release tabs of 300 mg. Eskalith CR comes in 450 mg pills. Also comes as syrup (300 mg/5 ml).
- Pregnancy
  - Risk of birth defects
    - Overall risk of a major birth defect appears to be two to three times greater with lithium than in the general population.
    - Cardiovascular defects
      - General population average is 3% (range 1-7%)
      - Historical (but inaccurate) study: risk with lithium 8%
      - More recent data suggests that there is a 1.2-7.7 fold increased risk of cardiac malformations
        - Ebstein's anomaly (right ventricular hypoplasia and displacement of the tricuspid valve)
          - Revised risk: 1/1000 (vs. risk in general population which is 1/20,000)
  - Renal metabolism
    - half-life 20-24 hours (larger range 14-32 hours) in adults
    - half-life 17-19 hours in children—children clear lithium more quickly than adults and may require higher doses
      - Baseline population risk is 1/20,000
      - Initial estimates suggested lithium increase the rate of Ebstein's anomaly 400-fold.
      - Lithium risk more likely to be 1/700-1/1000
      - seems to be associated only with first trimester use.
    - Most common effects associated with fetal exposure to lithium are high birth weight and "floppy baby" syndrome: cyanosis, low tone, slow heart rate, hypothyroidism, atrial flutter, enlarged liver, ECG changes, enlarged heart, gastrointestinal bleeding, nephrogenic diabetes insipidus, polyhydramnios, seizures, and shock—most of these effects are minor and time limited

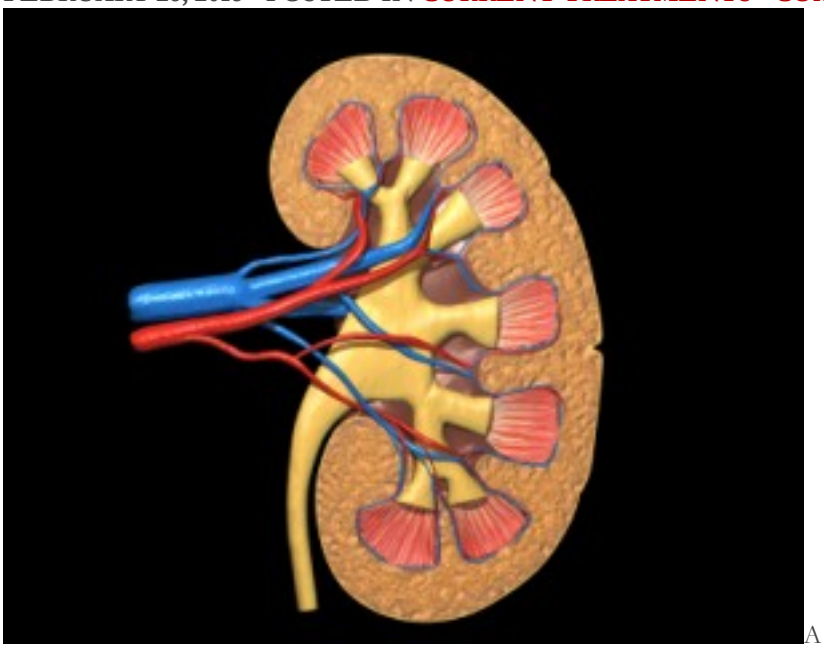
        - Only mood stabilizer for which published neurodevelopmental outcome data show a lack of adverse effects among prenatally exposed children
    - Significantly lower Apgar scores, longer hospital stays, and higher rate of central nervous system and neuromuscular complications observed in infants with higher lithium concentrations (>0.64 meq/liter) at delivery; withholding lithium therapy for 24-48 hours before delivery resulted in a 0.28 meq/liter reduction in maternal lithium concentration.
    - Currently consider safer than anticonvulsants in pregnancy
    - Lactaion
        - Serum lithium levels in nursing infants are low and well-tolerated with no significant adverse clinical or behavioral effects (Viguera et al, 2007)
        - Breast milk level is ½ of maternal serum level
            - Infant serum is ½ of breast milk level (so ¼ of maternal level)
- **In the treatment of bipolar disorder, lithium should always be slowly tapered (if it needs to be tapered) to minimize the chances of relapse.**
- Anti-inflammatory NSAIDs (including cox-2 inhibitors celecoxib and rofecoxib) can raise lithium levels.
- InstaRead Lithium System
    - ReliaLAB (www.relialab.com); 866-467-8273
    - instant finger-stick test to monitor blood lithium
    - FDA-approved in 8/05
- Lithium Information Center
    - 608-827-2470
    - www.healthtechsys.com/mimlithium.html

A 2018 article in the journal *JAMA Psychiatry* reports that lithium and long-acting antipsychotic injections were most effective at preventing re-hospitalizations among people with bipolar disorder. The study by Markku Lähteenvuo and colleagues included 18,018 Finnish patients with bipolar disorder. A national database contained information on any hospitalizations that occurred among the patients and what medications were dispersed to patients. Among the participants, 54% (9,721 patients) were re-hospitalized at least once over a study period of 16 years. Medications associated with the smallest risk of re-hospitalization for psychiatric reasons were long-acting injections of risperidone, gabapentin, long-acting injections of perphenazine, and lithium carbonate.

When the researchers looked at hospitalizations for any cause (not just psychiatric illness), lithium was associated with the least risk of re-hospitalization, while benzodiazepines had the greatest risk, both for psychiatric re-hospitalization and re-hospitalization for any cause. Long-acting injectable medications were associated with less risk of re-hospitalization compared to the identical medications delivered orally. Lähteenvuo and colleagues concluded, "Lithium…should remain as the first line of treatment for bipolar disorder, after decades of underprescription." They suggest that long-acting injectable medications may be a good alternative to prevent relapse in patients for whom lithium is unsuitable.

Continuing Lithium Treatment Does Not Increase Kidney Failure

FEBRUARY 26, 2018 · POSTED IN CURRENT TREATMENTS · COMMENT



A risk of long-term lithium treatment is that it can cause kidney damage. However, a new study suggests that continuing lithium treatment after a diagnosis of chronic kidney disease does not necessarily increase the risk of irreversible end-stage kidney disease, which is defined as either the need for either chronic dialysis or a kidney transplant.

The 2017 study by researcher Lars Kessing and colleagues in the journal *Acta Psychiatrica Scandinavica* used Danish health databases to track data from all individuals who received a diagnosis of chronic kidney disease between 1995 and 2012 and also had a history of lithium treatment (754 patients) or anticonvulsant treatment (5,004 patients). Kessing and colleagues found that **patients who continued taking lithium after an initial diagnosis of chronic kidney disease had decreased rates of end-stage kidney disease.** This also held true for those who continued anticonvulsant treatment after a diagnosis of kidney disease.

One point of uncertainty was introduced by the finding that the subset of participants who were taking lithium specifically to treat bipolar disorder did have a higher rate of end-stage kidney disease. This was not true of the participants who were taking anticonvulsants to treat bipolar disorder.

Kessing and colleagues concluded that after an initial diagnosis of chronic kidney disease, continuing lithium did not necessarily increase end-stage kidney disease. Switching to an anticonvulsant, as is sometimes the practice after a kidney disease diagnosis, may not confer any benefit.

A large study that made use of a Swedish health database has shown that lithium reduces suicide rates in bipolar disorder. The study by researcher Jie Song and colleagues was published in the *American Journal of Psychiatry* in 2017.

The study included eight years of data from 51,535 people with bipolar disorder. During that time, there were 10,648 suicide-related events recorded, such as suicide attempts or completed suicides. **The researchers compared suicide rates when patients were taking lithium to rates when they were off the drug, and found that lithium reduced attempted or completed suicide by 14%.** Song and colleagues also looked at suicide rates for people taking valproate, and found that these were no better than when patients were off valproate, implying that treatment alone is not enough to reduce the suicide rate and the benefit is specific to lithium use.

Song and colleagues estimate that 12% of the suicide-related events among the patients included in the study might have been avoided if the patients had taken lithium for the entire study period. While there are other clinical considerations to make when selecting an appropriate treatment for a given patient, the researchers suggest that lithium treatment should be considered for patients with bipolar disorder who have expressed suicidal intentions or who are otherwise at risk for suicide.

Finnish researchers, 2018:

Prospective national databases, looking at all-cause hospitalizations during ~7.2 years (average) of follow-up in all 18,018 Finns hospitalized for bipolar disorder. Lithium, adjusted for concomitant psychotropic meds, duration of bipolar illness, and intervals of med exposure and non-exposure, was associated with the lowest risks of psychiatric rehospitalization and all-cause hospitalization, with relative risk reductions of 33% and 29% respectively. Seroquel achieved an 8% reduction in the risk of psychiatric rehospitalization and a 7% decrease in all-cause hospitalization. Long-acting injectable antipsychotic meds were more effective in preventing hospitalization than oral antipsychotic medications.