The Highs and Lows of Lithium Therapy

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Abstract

The study of lithium in medicine dates back to the late 1800s in the treatment of gout and psychiatric disorders. Lithium in the form of lithium carbonate is frequently employed in manic depression. Other forms of lithium including lithium orotate and lithium succinate have different properties. The biochemistry of these salts will be discussed. Lithium has been studied in psoriasis, hyperthyroid, alcoholism, herpes simplex and cluster headaches. This paper will review the research in these areas, in addition to published case studies.

RESEARCH REVIEW

Introduction

In the late 1800s and early 1900s, lithium was popular as a treatment for gout because of its ability to form lithium urate which is very soluble (1). It was said that soaking in lithia springs could relieve a patient of gout pain and other arthritides (2). At this time, lithium was frequently prescribed as a lithium bromide, which led to a "hypnotic" effect, and reportedly had a beneficial effect on epilepsy. Robert Cade was the first to utilize lithium salts for the treatment of psychiatric disorders in 1949 (3). This continues to be the most common use for lithium.

Lithium remains a beneficial treatment for bipolar disorder in the form of lithium carbonate. Research has also demonstrated lithium to be a promising treatment for immune incompetence (4), viral disease (5), seborrheic dermatitis (6), hyperthyroidism (7), alcoholism (8), cluster headaches (9) and possibly autoimmune disorders (10). Lithium appears to have differing therapeutic effects depending on the salt form. Lithium in minute levels in the drinking water has the potential to significantly alter behavior of those drinking it (11). Nutritional levels—versus pharmacologic doses—of lithium may be used safely by a practitioner of nutritional medicine in assisting patients with anger or a familial tendency toward alcoholism or other addictive behaviors. This paper will discuss this aspect of lithium, as well as its mechanism of action, laboratory monitoring, potential toxicity and contraindications of lithium therapy.

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Biochemistry

Lithium is a class 1-A metal and therefore has the ability to interact with other class 1-A metals. It also shares many properties with the group II metals, and can compete with sodium, potassium, magnesium, and calcium (12). In particular, symptoms of dehydration are noticed when taking this medication due to lithium's ability to upset sodium transport into the cell. Lithium in doses at or exceeding the upper therapeutic range may lead to a hypopotassemia. This has reportedly resulted in cardiac arrhythmia (13). Lithium's effect on magnesium balance can upset numerous enzymatic pathways including viral replication, and immune-mediated processes. By competing for calcium-binding sites, lithium can affect calcium dependent processes including cAMP production and the calcium-dependent release of neurotransmitters (12).

It is known that manic patients have elevated levels of prostaglandin (PG) E1, and that depressed patients have subnormal levels of PGE1. Lithium in therapeutic doses suppresses the synthesis of PGE1 from dihomo gamma linolenic acid (DGLA) by interacting with the cyclo-oxygenase enzyme (a magnesium-dependent enzyme) (14). It is thought that this interaction with the prostaglandin pathway may explain lithium's benefits in the treatment of mania (15).

Dr. Hans Nieper is credited with studying the orotate form of lithium. He has found that the orotate molecule (when compared to the carbonate molecule) demonstrates a preference for the brain glia and vascular walls (including the blood brain barrier). By using

lithium in an orotate form he was able to minimize the elevation in serum lithium to only 30% above normal (0.2-0.5mM/L) levels, in contrast to the pharmacologic elevation of 0.8-1.0mM/L when the carbonate form is used. This nominal elevation with orotate maintains serum lithium levels without side effects. Dr. Nieper's research indicates that by using lithium in the orotate form rather than the carbonate, lithium dosage can be scaled down to 1/ 20th of the usual amount prescribed (16).

Studies have shown that lithium helps to increase the uptake of vitamin B12 (17,18), and enhances the transport of folate into cells. It is suggested that its ability to increase cellular uptake of vitamin B12 may benefit patients with marginal B12 stores (18). This is interesting considering the clinical overlap of vitamin B-12 and lithium in the treatment of both depression (19,20) and herpes (21,22). Indeed, studies reveal that psychiatric patients taking lithium had an average increase in their serum B12 levels over controls not ingesting lithium (23) and a decreased incidence of herpes outbreaks (24).

Laboratory Evaluation

Laboratory monitoring of lithium carbonate is necessary in the dosage range of 300-1200 mg daily, which is the usual dose for the treatment of manic depression. The normal serum concentration of lithium is 0.2-0.5 mM/L whereas the active concentration for safe dosing is 0.8-1.0 mM/L (25). Beyond this range, signs of toxicity may become prominent. Monitoring of these laboratory measures is necessary every 2-6 months depending on the patient. Other pertinent laboratory measures include creatinine clearance or serum creatinine and thyroid stimulating hormone (TSH). When utilizing lithium in a nutritional range, rather than a pharmacologic one; it is not necessary to monitor these laboratory measures, as supplementation is only slightly above that found in the food and water supply, and adverse changes are not apparent.

Nutritional Doses of Lithium

There is debate about whether lithium is an essential or non-essential nutrient. Some studies indicate a reduced reproductive rate and higher mortality in goats when a lithium deficiency is induced (26). As of yet there is no direct evidence that lithium is essential for humans. Nevertheless, using data for 27 Texas counties from 1978-1987 it was shown that the incidence of suicide, homicide, and rape were significantly higher in counties whose drinking water supplies contained little or no lithium than in counties with water lithium levels ranging from 70-170 (mg/L ($p<0.01$). These results suggest that nutritional levels of lithium, as found in the water supply, can have significant moderating effects on both suicide and violent crime (27) and thus human physiology. The lithium levels found in plants are dependent on the content of the minerals found in the soil and the water source supplying the vegetation (28).

Therapeutic Lithium

I. Psychiatry

The first study of lithium for the treatment of manic depression utilized lithium **citrate** (20 grains TID, on a tapering schedule). It is interesting to note that Dr. JF Cade discusses his choice of lithium **citrate** over lithium **carbonate** thoroughly in his research, stressing that in this form the ion appears to be more soluble and better absorbed (3).

Lithium is primarily used in the treatment of manic depression, and is particularly beneficial in lowering the manic phase. Although lithium use continues to be associated with psychiatry, lithium therapy has been well studied for a variety of conditions. Because of lithium's effect at the cellular level on electrolytes, it is not a surprise that it functions throughout the body from neurology to the immune system to dermatology.

II. Dermatologic effects

Lithium succinate (8%) in a topical form has been shown to be beneficial in the treatment of seborrheic dermatitis (6). In a study of 73 patients with genital herpes, this ointment was applied four times a day for seven days. This regimen reduced the duration of pain and discomfort (from seven to four days), and significantly reduced viral shedding (by the fourth or fifth days) (29). Other studies demonstrate an antipruritic effect in such conditions as exfoliative dermatitis, vaginal pruritus, heat rash, contact dermatitis and acne vulgaris (30). Lithium use may cause a flare up of psoriasis, which is likely due to a decreased production of cAMP (31).

III. Viral/immune mechanisms

Both *in vitro* and *in vivo* studies have demonstrated inhibition of herpes simplex virus (both HSV1 and HSV2) replication (5,32). This may be due to an interaction between lithium and magnesium-dependent enzymes or enhanced immune function (33). An *in vivo* study reported in the *New England Journal of Medicine* demonstrated a decreased recurrence of HSV with oral lithium (34). A study of 236 patients (90 of whom had recurrent labial herpes infections) demonstrated a significant decrease in the number of episodes per year for patients on lithium (n=63) compared to patients using other antidepressants (n=27, $p<0.001$) (35). A study using topical lithium **chloride** showed a decrease in healing time, pain and excretion of viral particle (5). Other studies have shown an effect on measles virus replication (36).

Numerous studies have utilized lithium **chloride** to enhance hematopoiesis following chemotherapy and/or radiation causing bone marrow toxicity (300 mg TID-QID). These studies demonstrated an increase in eosinophil production, both increase and decrease in monocyte production, no change in basophils, an increase in platelets and a statistically significant increase in neutrophils (4,37,38). It has been suggested that increased neutrophil production is due to an increased production of colony stimulating factor (CSF), a glycoprotein which affects differentiation of the stem cells in the bone marrow (39).

It has been suggested that lithium may benefit autoimmune diseases (particularly those with a relapsing and remitting nature) via inhibition of DGLA induced production of PGE1, and thus suppression of mobilization of arachidonic acid (a PGE2 precursor) (10).

A case study of a patient with both chronic active ulcerative colitis for seven years and affective disorder reported that the patient experienced relief from his gastric symptoms following 12 days of lithium carbonate treatment. A sigmoidoscopy two months later revealed marked improvement. Remission was maintained for the year and several months prior to the reporting of this case (40).

A 55 year old female suffered from recurrent episodes of fever,

arthralgia, wheezing, abdominal pain with diarrhea, and dark urine. When she was hospitalized, it was discovered that within an hour after her temperature started to rise, her WBC count fell from 5000 to 300/cu mm, with a drop in neutrophils by 50%. Abnormalities in thermoregulation have many different possible etiologies, one of which is abnormal metabolism of norepinephrine and serotonin (biogenic amines). A disruption of biogenic amines has been associated with manic depression. This led the reporting physicians in this case to attempt a trial of lithium carbonate (300 mg QID, later reduced to TID) to treat the recurring fevers. The patient had no fevers or known neutropenic episodes after the lithium therapy was initiated. Seven months later, lithium therapy was discontinued due to the development of a rash. Eight months later the episodes of fever and associated symptoms returned, and with time became present on a weekly basis (41).

IV. Alcoholism

A study of 42 patients with chronic alcoholism and a variety of systemic complaints (including liver dysfunction, alcoholic cardiomyopathy, seizure disorders, and headaches) reported on clinical trial. The patients were treated with 150 mg lithium **orotate** daily, and a diet high in complex carbohydrates. Ten of the patients had no relapse for over three and up to ten years; 13 patients remained without relapse for one to three years; 12 had relapses between six to 12 months. Improvements were also noted in many of the aforementioned symptoms (8).

In 1973 studies by Kline on US Veterans, the use of lithium was beneficial in 50% (n=70) of alcoholics (43). Sartori studied 42 patients using 150 mg/day of lithium **orotate** and found mood improved in all patients. Liver enzymes, headaches, seizures, and behavior also improved (8).

A double-blind placebo-controlled trial of lithium **carbonate** on alcoholics demonstrated a decrease in drinking episodes in the treatment group relative to the placebo group ($p<0.05$). The dosage range was 600-1500 mg lithium carbonate daily. Blood levels were maintained within a range of 0.6-1.2 mEq/L (43).

V. Thyroid/TSH

Studies on rats have demonstrated that lithium has an effect on the pineal gland. Administration of lithium to rats resulted in hyperplasia of the pineal gland (and adrenal gland), and a resultant increase in both melatonin and serotonin production (44). This is particularly interesting considering the therapeutic overlap of both melatonin and L-tryptophan (45,46).

It is well documented that lithium has an adverse effect on the functioning of the thyroid gland. The two most common side effects are goiter and hypothyroidism. It is estimated that 25-30% of patients on lithium therapy (lithium **carbonate** 600-1200 mg daily) will demonstrate abnormal thyroid function. Lithium blocks the release of thyroid from the thyroid gland, and thus has been used successfully for the treatment of hyperthyroidism (7).

VI. Endocrinology

A recent study of 38 patients with diabetes demonstrated an improvement in fasting and postprandial blood sugar levels with the addition of lithium **carbonate** (100 mg) to the current therapeutic regime (Group 1: diet, Group 2: oral hypoglycemic agents, Group 3: insulin injection). The levels of both fasting blood glucose (FBG) and one-hour postprandial blood glucose (PBG) decreased significantly in all groups with the exception of the fasting blood glucose of the diet group (Group 1). In group 3 the levels declined by 37.2% (FBG) $p<0.001$, and by 26.3% (PBG) $p<0.01$. The dosage of insulin was reduced by 16.7% (47).

A placebo-controlled study of rats demonstrated a statistically significant increase in the production of corticosterone with administration of lithium **chloride** (versus sodium chloride) (48).

VII. Neurology

The pineal gland regulates circadian rhythm by secreting the hormone melatonin. Manic depression has a cyclic nature similar to that of cluster headaches (CH). Lithium carbonate is a drug used successfully in the treatment of manic depression. Therefore, it has been suggested that the pineal gland may be involved in the cycling of CH, and lithium may be of benefit (49). In fact, the administration of lithium to rats resulted in an increased secretion of melatonin (49).

A study was performed in 1979 by Klimek et al. on 15 patients suffering from CH (eight were chronic and seven episodic) (9), where 250 mg of lithium **carbonate** was given daily. In the chronic CH group, a complete resolution of symptoms was observed in one patient, and a decrease in frequency of attacks in four patients. The lithium was ineffective in the other three patients. In the episodic group, a complete remission of symptoms was demonstrated in four patients and significant improvement in one patient. The drug was ineffective in two patients.

A second study was performed in 1980 on 21 patients (12 chronic (C) and nine episodic (E)) with CH (50). The patients were given lithium **carbonate** at a dose of 600mg. The following results were obtained: 11 patients (six C and five E) had absolute improvement, (defined by the patient becoming symptom free), five patients had partial improvement (two C and three E) (defined by a marked decrease in both severity and frequency of symptoms to a tolerable level), and five patients (three C and two E) had no lasting improvement. In fact three of the five patients with no lasting improvement, initially showed signs of improvement but the results could not be maintained. All of the patients improved with doses of 600 mg of the lithium **carbonate**. These benefits were noted within the first week of treatment. In six of the patients a maintenance dose of 900 mg was necessary to achieve maximal improvement.

Further research was performed on 19 patients given 168 mg of lithium **carbonate** daily (eight chronic CH, and 11 episodic) (51). Within two weeks after the onset of treatment, all eight chronic CH patients had an improvement of symptoms by at least 75% (based on a headache index). The long-term study performed at 18 months post-treatment showed that only two of the eight patients had resumed symptoms; however, they now suffered from episodic rather than chronic CH. In the seven patients suffering from episodic CH no benefit was demonstrated.

Because of the consistent problems of side effects noted in previous studies of cluster headache treated with lithium **carbonate**, it would be of great benefit to utilize lithium at a lesser dose if

improvement could still be maintained. A dramatic study of 44 patients with migraine, utilizing lithium **orotate** at a dose of 150 mg (five-six capsules per week) revealed efficacy in 39 patients. These patients were previously unresponsive to conventional treatment (17). At this low dose side effects were not provoked.

VIII. Case Reports documented in the literature

Three women with fibromyalgia, previously unresponsive to tricyclic antidepressants, were given lithium **carbonate** therapy (300 mg QID). Pain resolved after three months. One of the patients developed side effects from the lithium. When the dose was lowered, however, pain and stiffness were still reduced (52).

As lithium appears to be of benefit in diseases of a cyclic nature, studies have been performed to determine if it may be beneficial in the treatment of premenstrual syndrome. Some studies have demonstrated a positive response utilizing lithium **carbonate** (53), while other studies have not been able to reproduce these results (54).

Contraindications, Interactions and Toxicity

Contraindications to both therapeutic and nutritional doses of lithium include kidney disease, fever, diuretic use, a low sodium diet, and pregnancy/lactation. Interactions with theophylline, diuretics, caffeine in drugs, chlorpromazine, iodide preparations, norepinephrine, and possibly acyclovir may occur (55).

Lithium toxicity generally occurs when serum concentration is elevated beyond 1.0 mM/L. Signs and symptoms of toxicity include hand tremor, weight gain, polyuria, polydypsia, visual changes, dehydration (and related symptoms), gastrointestinal upset, and decreased thyroid function (21). The signs of toxicity are due to changes in the electrolyte balance and fatty acid metabolism. Toxicity can be minimized with the use of bouillon soup and some form of essential fatty acids (i.e., flaxseed oil). Elevated levels of serum lithium also upset potassium balance, which can cause serious cardiac disorders and arrhythmias (13).

Pharmacologic doses of lithium may affect renal concentrating ability, and thus patients should be warned to drink plenty of fluids or dehydration can occur. Case reports have linked renal insufficiency with long-term lithium use. However these events are rare and generally occur at the higher doses used in psychiatry (56).

Studies performed on rats demonstrated lithium has a teratogenic effect (57). This has led to concern for the infants born to women with bipolar disorder. Most recently, this concern has been re-evaluated, and recommendations for lithium treatment are now based upon the severity of symptoms exhibited by the mother. The risks of major malformations among infants born to women taking pharmacologic doses of lithium during the first trimester are 4-12%, as compared to 2-4% among women taking no lithium (58).

Conclusions

Lithium salts have a colorful history in medicine dating back to the 1800s when they were used to treat gout and other arthritic complaints. Lithium carbonate is used primarily for the treatment of bipolar illness, although side effects are frequent and close laboratory monitoring is necessary. Studies have demonstrated a significant difference in the uptake of lithium orotate versus lithium carbonate, and these differences may be utilized to decrease dosage and side effects of treatment and improve patient compliance. Lithium has been well studied in the treatment of hyperthyroidism, alcoholism, cluster headaches, and neutropenia. Other smaller studies have demonstrated benefit in the treatment of herpes virus, seborrheic dermatitis, and perhaps autoimmune disorders. Lithium in nutritional doses can have a significant impact on violent behavior and crime.

References

1. Baldessarini RJ, Lipinski JF. Lithium salts: 1970-1975. Ann Intern Med 1975; 83:527-533.
2. Georgotas A, Gershon S. Historical perspectives and current highlights on lithium treatment in manic-depressive illness. J Clin Psychopharmacol 1981;1(1):27-31.
3. Cade JFJ. Lithium salts in the treatment of psychotic excitement. Med J Aust 1949; 36:349-352.
4. Birch NJ. Lithium and the Cell: Pharmacology and Biochemistry. Wolverhampton Polytechnic, United Kingdom:Academic Press:1991:186.
5. Skinner GRB, Hartley C, Buchan A, et al. The effect of lithium chloride on the replication of herpes simplex virus. Med Microbiol Immunol Berl 1980;168(2):139-148.
6. Boyle J, Burton JL, Faergemann J. Use of topical lithium succinate for seborrhoeic dermatitis. Br Med J 1986;292:28.
7. Schrauzer GN. Lithium in Biology and Medicine: new applications and developments. New York, NY: VCH Verlagsgesellschaft: 1991:81-101.
8. Sartori HE. Lithium orotate in the treatment of alcoholism and related conditions. Alcohol 1986;3(2):97-100.
9. Klimek A, Szulc-Kuberska J, Kawiorski S, et al. Lithium Therapy in cluster headache. Eur Neurol 1979;18:267-8.
10. Horrobin DF. A biochemical basis for the actions of lithium on behaviour and on immunity: relapsing and remitting disorders of inflammation and immunity such as multiple sclerosis or recurrent herpes as manic-depression of the immune system. Med Hypotheses 1981;7:891-905.
11. Dawson EB, Moore TD, McGanity WJ. The mathematical relationship of drinking water lithium and rainfall to mental hospital admission. Dis Nerv Syst 1970;31:1-10.
12. Bunney WE, Pert A, Rosenblatt J, et al. Mode of action of lithium: some biological considerations. Arch Gen Psychiatry 1979;36:898-901.
13. Habibzadeh MA, Zeller NH. Cardiac arrhythmia and hypopotassemia in association with lithium carbonate overdose. South Med J 1977;70(5):628-630.
14. Bach RO, Gallicchio VS. Lithium and cell physiology. New York, NY: Springer-Verlag 1990: 10-12.
15. Lee RE. The influence of psychotropic drugs on prostaglandin biosynthesis. Prostaglandins 1974;5(1):63-68.
16. Nieper HA. Clinical applications of lithium orotate: a two year study. Agressologie 1973;14 (6):407-411.
17. Schrauzer GN. Lithium in Biology and Medicine: new applications and developments. New York, NY: VCH Verlagsgesellschaft; 1991: 17-30.
18. Chikkappa G, Corcino L, Greenberg ML, et al. Correlation between various blood white cell pools and the serum B-12 binding capacities. Blood 1971;37(2):142-151.
19. Birch NJ. Lithium and the Cell: Pharmacology and Biochemistry. Wolverhampton Polytechnic, United Kingdom:Academic Press:1991:1-6.
20. Smith ADM. Megaloblastic madness. Br Med J 1960;2:1840.
21. Parks, DG, Greenway FL, Pack AT. Prevention of recurrent herpes type II infection with lithium carbonate. Clin Res 1988;36:147A (abstract).
22. Gupta AK, Mital HS. Cyanocobalamin (vitamin B-12) in the management of herpes zoster. Indian pract 1967; 20(7):457-459.
23. Tisman G, Herbert V, Rosenblatt S. Evidence that lithium induces human granulocyte proliferation: elevated serum vitamin B 12 binding capacity in vivo and granulocyte colony proliferation in vitro. Br J Haematol 1973; 24(6):767-771.
24. Lieb J. Remission of recurrent herpes infection during therapy with lithium. N Engl J Med 1979; 301:942.

25. Gelenberg AJ, Kane JM, Keller MB, et al. Comparison of standard and low serum levels of lithium for maintenance treatment of bipolar disorder. N Engl J Med 1989; 321(22):1489-1493.
26. Bach RO, Gallicchio VS. Lithium and cell physiology. New York, NY: Springer-Verlag 1990: 1-3.
27. Schrauzer GN, Shrestha KP. Lithium in drinking water and the incidences of crimes, suicides, and arrests related to drug addictions. Biol Trace Elem Res 1990; 25(2):105-113.
28. Bach RO, Gallicchio VS. Lithium and cell physiology. New York, NY: Springer-Verlag 1990: 25-46.
29. Skinner GRB. Lithium ointment for genital herpes. Lancet 1983;ii(8344):288.
30. Lieb J. Lithium and immune function. Med Hypotheses 1987;23(1):73-93.
31. Sasaki T, Saito S, Aihara M, et al. Exacerbation of psoriasis during lithium treatment. J Dermatol 1989;16(1):59-63.
32. Trousdale MD, Gordon YJ, Peters ACB, et al., Evaluation of lithium as an inhibitory agent of herpes simplex virus in cell cultures and during reactivation of latent infection in rabbits. Antimicrob Agents Chemother 1984;25(4):522-523.
33. Birch NJ. Lithium and the Cell: Pharmacology and Biochemistry. Wolverhampton Polytechnic, United Kingdom:Academic Press: 1991:99-112.
34. Amsterdam JD, Maislin G, Hooper MB. Suppression of herpes simplex virus infections with oral lithium carbonate—a possible antiviral activity. Pharmacother 1996;16(6):1070-1075.
35. Amsterdam JD, Maislin G, Rybakowski J. A possible antiviral action of lithium carbonate in herpes simplex virus infections. Biol Psychiatry 1990;27:447-453.
36. Cernescu C, Popescu L, Constantinesu ST, et al., Antiviral effect of lithium chloride. Virologie 1988;39(2):93-101.
37. Schrauzer GN. Lithium in Biology and Medicine: new applications and developments. New York, NY: VCH; 1991:3-14.
38. Ricevuti G, Mazzone A, Rizzo SC. The effects of lithium on platelet count. Acta Haematol 1985;74:118-119.
39. Jim RT. Leukocytosis: side effect of lithium. Blood 1979;53(5):1031.
40. Zinook S. Ulcerative colitis: case responding to treatment with lithium carbonate. JAMA 1972;219(6):755.
41. Gerner RH, Wolff SM, Fauci AS, et al. Lithium carbonate for recurrent fever and neutropenia. JAMA 1981;246 (14):1584-1586.
43. Kline NS, Wren JC, Cooper TB, et al. Evaluation of lithium therapy in chronic and periodic alcoholism. Am J Med Sci 1974;268 (1):15-22.
44. Devi SP, Hariharasubramanian N, Rao AV. Pineal gland responses to lithium and chlorpromazine. Indian J Psychiat 1976;18:208-214.
45. Leone M, DiAmico D, Moschiano F, et al. Melatonin versus placebo in the prophylaxis of cluster headache: a double-blind pilot study with parallel groups. Cephalgia 1996;16:494-496.
46. Benedittis GD, Massei R. Serotonin precursors in chronic primary headache. J Neurosurg Sci 1985;29:239-248.
47. Hu M, Wu H, Chao C. Assisting effects of lithium on hypoglycemic treatment in patients with diabetes. Biol Trace Elem Res 1997;60:131-137.
48. Jacobs JJ. Effect of lithium chloride on adrenocortical function in the rat (40013). 1977; Proc Soc Exp Biol Med 1978; 157(2): 163-167.
49. Sandyk, R. The influence of the pineal gland on migraine and cluster headaches and effects of treatment with Pico Tesla magnetic fields. Int J Neuroscience 1992;67(1-4):145-71.
50. Damasio, H. Lyon L. Lithium Carbonate in the Treatment of Cluster Headaches. J Neurol 1980;224:1-8.
51. Ekbom, K. Lithium for Cluster Headache: Review of the Literature and Preliminary Results of Long-term Treatment. Headache 1981;July;132-9.
52. Tyber MA. Lithium carbonate augmentation therapy in fibromyalgia. Can Med Assoc J 1990;143(9):902-904.
53. Sletten IW, Gershon S. The premenstrual syndrome: a discussion of pathophysiology and treatment with lithium ion. Compr Psychiatry 1966;7(3):197-206.
54. Singer K, Cheng R, Schou M. A controlled evaluation of lithium in the premenstrual tension syndrome. Br J Psychiatry 1974;124:50-51.
55. Schou M, Mult HC. Forty years of lithium treatment. Arch Gen Psychiatry 1997;54(1):9-13.
56. Okusa MD, Crystal LJ. Clinical manifestations and management of acute lithium intoxication. Am J Med 1994 Oct; 97(4): 383-9.
57. Kallen B, Tandberg A. Lithium and pregnancy. A cohort study on manic-depressive women. Acta Psych Scand 1983;68(2):134-139.
58. Cohen LS, Friedman JM, Jefferson JW, et al. A reevaluation of risk of in utero exposure to lithium. JAMA 1994;271(2):146-150.

Biography

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