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A Review of Clinical Trials of Lithium in Medicine

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YUNG, C Y *A review of clinical trials of lithium in medicine* PHARMACOL BIOCHEM BEHAV **21**: Suppl 1, 51–55, 1984 —Since the approval of lithium use in treatment of acute mania, there have been numerous clinical trials of lithium in medical and psychiatric disorders. This paper gives a brief review of the literature on lithium trials in approximately fourteen medical conditions These are: hyperthyroidism, metabolizing thyroid cancer, syndrome of inappropriate secretion of antidiuretic hormone, premenstrual tension syndrome, anorexia nervosa, Felty's syndrome, chemotherapy-induced neutropenia, aplastic anemia, seborrheic dermatitis, eczematoid dermatitis, cyclic vomiting, diabetes mellitus and asthma. Most of the case reports cited showed the efficacy of the side effects from lithium salt in the management of the symptoms and signs of these disorders, however, well-designed and controlled studies give negative results The positive results are reported in the group of disorders having an underlying subdromal affective syndrome such as premenstrual tension syndrome and anorexia nervosa Other encouraging reports include the effect of lithium to induce leucocytosis in Felty's syndrome and chemotherapy-induced neutropenia

Anorexia nervosa Chemotherapy-induced neutropenia Felty's syndrome Lithium Metabolizing thyroid cancer

LITHIUM (Li) was first introduced into clinical use in psychiatry by Cade in 1948 [16], and approved by the Food and Drug Administration in the U.S. in 1970 for treatment of acute mania and as prophylaxis against recurrent mania. Since then there have been experimental trials of Li salts in other psychiatric and medical disorders. There are excellent review articles on some of the specific psychiatric disorders such as schizophrenic disorder, schizoaffective disorder, periodic catatonia [27], anxiety disorder [30], emotionally unstable character disorders [7,63], borderline personality disorder [77], obsessive-compulsive disorder [85], alcohol dependence [55], cocaine abuse, lysergic acid diethylamide intoxication [30], violent behaviors [30] and psychiatric disorders in children and adolescents [17, 42, 82]. Recently, there are reports to suggest that Li is also effective in prophylaxis against relapses of depression in unipolar depression [22,26], and augments the antidepressant effects of tricyclic antidepressants in a group of non-responsive patients [43]. There are also a number of comprehensive reviews on clinical trials of Li in medical disorders [30, 64, 70, 91]. This review is an update on the recent studies and reports on clinical trials of Li therapy in various medical disorders, excluding the psychiatric and neurological diseases.

The rationale of using Li in these disorders is based on the application of the specific side-effects of Li to counteract or reverse the pathophysiological changes in these conditions. Thus a specific side-effect of Li therapy became a desired effect (positive side effect) [59], e.g , the antithyroid property of Li is used to suppress hyperthyroidism, and the leucocytosis effect of Li is used to overcome cancer drug induced neutropenia.

LITHIUM TRIALS IN HYPERTHYROIDISM

Approximately 15–25% of patients on Li maintenance therapy experience abnormal thyroid function and some develop goitres and hypothyroidism [73]. This is due to inhibition of iodine release from the thyroid gland of thyroid response to Thyroid-Stimulating Hormone (TSH) by lithium [6, 14, 87].

Based on these mechanisms, clinical case reports have shown beneficial use of Li salts alone, in combination with thiocarbamide [10] or with radio-iodide [15] in management of hyperthyroidism [94], thyrotoxicosis [49] and metabolizing thyroid cancer [14,32].

Boehm [10] reported the use of Li and iodine combination therapy for thyrotoxicosis on 17 patients. There is an additive inhibition of thyroid release only when Li is used before iodine is administered. The use of Li in hyperthyroidism is still uncertain, since the following effects have yet to be addressed, (1) the side effects of Li therapy on other organs (2), the potential risk and adverse effects of iodine accumulation in the gland (3), the masking of hyperthyroidism which may evolve into a thyroid storm, upon withdrawal of Li [65] and (4), re-evaluation of the negative studies of Li in treatment of thyrotoxicosis [46]

LITHIUM TRIALS IN METABOLIZING THYROID CANCER

Taking advantage of Li inhibition of hormonal release from the thyroid gland, some investigators have used Li with radioactive iodine in treatment of metabolizing thyroid cancer, in order to increase the ratio of gland irradiation to body irradiation by trapping the iodine in the gland [15,32].

LITHIUM AND ANTIDIURETIC HORMONE

The polyuria (10–40%) from Li therapy is presumably due to its effect on inhibiting the renal response to antidiuretic hormone (ADH), through the ADH activation of adenylate cyclase in the distal tubule [23,95]. This mechanism becomes the rationale of using lithium in the syndrome of inappropriate secretion of antidiuretic hormone. Treatment outcome is contradictory, ranging from no effect [25,28] to prompt water diuresis, normalization of urine osmolarity and serum sodium [1, 41, 97] Lithium has been recommended for patients who cannot comply with long-term fluid restriction [1]

LITHIUM TRIALS IN PREMENSTRUAL SYNDROMES (PMS)

Rubinow [66] has reviewed the use of Li in PMS in a recent article and found three open trials with positive results [25, 29, 76, 83], but two double-blind, placebo-controlled cross over studies showed no significant differences between Li and placebo [54,74]. There are reports of placebo response as high as 40–60% and the possibility that some patients with PMS may have an underlying affective disorder responding to Li therapy [54]

LITHIUM AND ANOREXIA NERVOSA AND BULIMIA

Four patients with anorexia nervosa [2, 61, 78] were described in three case reports. They had 14–20 years history of the disorder and were unresponsive to previous therapies They were able to gain weight with Li therapy Gross *et al* [34] conducted a double-blind controlled study (n=16) and reported that Li produced a significant weight gain than placebo in anorexia nervosa patients receiving behavior therapy The positive outcome may be due to the probability that a small group of anorexia nervosa patients also have a cyclothymic mood disorder There may be a subgroup of anorexia nervosa patients who are variants of an affective disorder As the depression is being stabilized, so would the anorexia nervosa There are recent reports [13,40] of improvement of anorexia nervosa by tricyclic antidepressants and bulimia by monomine oxidase inhibitors [40]. This seems to support the assumption of an underlying depression in a subgroup of patients with anorexia nervosa and bulimia

LITHIUM AND HAEMATOLOGICAL DISORDERS

The effect of Li on the haemopoetic system has been extensively studied It has no apparent effect on erythrocytes [8, 18, 80]. The li effect on blood platelets is based on clinical reports of thrombocytosis in Li treated patients and of the Li mild protective action against chemotherapy-induced thrombocytopnia in one study [18], but not in two other studies [51,79] Platelet count was unaffected by Li [8,79] There is increased blood neutrophil concentration, marrow neutrophil production and enhancing release of colony stimulating activity [44]

Felty's Syndrome

The rationale of Li therapy in haemotological disorders, such as Felty's syndrome, leukemia, cancer therapy induced granulocytopenia, aplastic anemia, neuroleptic-induced neutropenia, is based on Li induction of neutrophil leucocytosis [88,89], increased production of colony stimulating factor [38], possible stimulation of both pluripotential stem cell [31] and chemotaxis without changes of phagocytosis In Felty's syndrome (rheumatoid arthritis, splenomegaly, and neutropenia), Li therapy induced a rise in leukocyte counts which was sustained throughout treatment, but disappeared after discontinued treatment [35, 47, 53, 58, 60]. There are five reports covering 22 patients showing the efficacy of Li salts in this syndrome and the lack of the therapeutic effect was also reported in 2 patients [45] It has been reported that Li reduced the rate of infection [69]

Chemotherapy-Induced Neutropenia

Trials of Li in chemotherapy induced neutropenia during the course of chemotherapy in acute myelogenous leukemia and systemic chemotherapy in brochogenic cancer, have been attempted in more than a total of 140 patients as reported in the literature Most of these studies reported either amelioration of myelosuppression by the chemotherapy or reduction in duration of neutropenia, less severe febrile episodes and less infection related death [18, 19, 31, 78, 79, 81, 92, 96, 99, 100]

Aplastic Anemia

No definite conclusion could be drawn from the literature Some reports showed improvement with Li [4, 9, 57], while others could not confirm it [3,4]. However, it seems that Li has an effect in stimulation of granulopoiesis in neutropenic state, through an enhancement of colony-stimulating activity production in some reports [44], but not in others related to cyclic neutropenia [11, 37, 48, 98]

LITHIUM IN DERMATOLOGICAL DISORDERS

Various forms of skin reactions have been reported to be aggravated or initiated by Li therapy [24] These reactions include maculopapular, acneiform, follicular eruptions, psoriasis, exfoliative dermatitis, alopecia and generalized pruritis However, early reports of the positive effects of Li on dermatological disorders were incidental findings from psychiatric patients who were inflicted with these disorders and were treated with Li. There were two cases of remission of an oral and of a genital form of herpes, which reoccurred after termination of Li therapy [50]. In addition, improvement in 2 cases of seborrheic dermatitis [21], and 2 cases of abatement of eczematoid dermatitis were reported [59] A recent double-blind cross over, placebo vs Li study on 15 patients with seborrheic dermatitis showed Li to be inferior to placebo in 9 of the cases [20].

A study by Skinner has demonstrated inhibition of replication of herpes simplex and other DNA viruses by LiCl [75] This may explain the clinical observation of certain groups of dermatitis remitted during Li therapy, especially when cutaneous infections were due to herpetic, adenoviral or vaccinial viruses

Miscellaneous Reports on Li (the Gastrointestinal System, Diabetes Mellitus and Asthma)

Gastrointestinal side effects such as nausea, vomiting and diarrhea, occur frequently during the course of Li therapy. A case was reported of a manic depressive patient's concomitant ulcerative colitis condition improved with Li therapy with remission of the affective symptoms [101]. The effect of Li in the management diarrhea in pancreatic chorea remains controversial, as has been reviewed recently by Frost and Messiha [30]

Clinical data gave conflicting results on the effect of Li on glucose tolerance and carbohydrate metabolism There were a few reported cases of diabetes mellitus associated with Li

therapy, including exacerbation and first appearance of the disorder [52]. A case with adult onset diabetes was found to have the blood glucose lowered by Li [68], and was not in need of insulin after Li therapy. Russell and Johnson [67] reviewed 18 animal studies which have shown that Li given acutely inhibits insulin secretion in response to glucose loading Lithium salt appears to possess insulin like effects, i.e., increase glucose utilization and glycogen synthesis. There are two reports of the coincidental improvement in asthma in 4 patients, during the course of Li therapy for psychiatric indications [59]. There is no report on the use of Li alone in treatment of asthma.

In conclusion, there are only a very few new studies on clinical trials of Li salt in medical disorders in the past 10 years. The therapeutic effects of Li_2CO_3 for most of these medical disorders are not curative. It is only a temporary measure to counteract the pathophysiological changes. There are no known or effective medical treatments for some of these disorders, and most of which are invariably in the terminal or severe stages and chronic course of their illnesses. These factors preclude good and long term follow-up studies. The recent laboratory finding of inhibitory effect of Li on herpes simplex and other DNA viruses, may open a new area of investigation of the immunochemistry of Li^+.

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