Neuropsychobiology

Neuropsychobiology 2010;62:43–49
DOI: 10.1159/000314309

Published online: May 7, 2010

Lithium Reduces Pathological Aggression and Suicidality: A Mini-Review

Bruno Müller-Oerlinghausen[a] Ute Lewitzka[b]

[a]Drug Commission of the German Medical Association, Berlin, and [b]Department of Psychiatry and Psychotherapy, Technical University of Dresden, Dresden, Germany

Key Words
Lithium · Pathological aggression · Children · Prisoners · Suicide · Suicide attempt

Abstract
From a practical point of view, the well-proven antisuicidal and anti-aggressive effects of lithium are of utmost importance for a rational, safe and economical treatment of patients with affective disorders. Regular lithium long-term treatment reduces the otherwise 2- to 3-fold increased mortality of untreated patients with severe affective disorders down to the level of the general population. This is mainly due to the reduced suicide risk. Many international studies have confirmed this fascinating property of lithium which so far has not been demonstrated with comparable evidence for any other psychotropic compound. The antisuicidal effects of lithium might possibly be related to its anti-aggressive effects which have been shown in various species, populations and settings, such as animals, inhabitants of nursing homes for the elderly, mentally handicapped subjects, children and adolescents with hyperactive, hostile and aggressive behavior, and particularly in hyperaggressive inmates of correction units and prisons.

Introduction

Sixty years of lithium treatment in psychiatry yielded a still continuing stream of knowledge on the pharmacological and therapeutic effects as well as the effectiveness of this fascinating alkali ion. One of the lightest metallic elements had a heavy impact on the concepts and practice of modern psychiatry. Some scientific studies on lithium and clinical experience collected during recent decades partly confirmed early anecdotal findings, and partly remodeled and integrated them into updated, more precise and comprehensive concepts, thus making previous observations better understood [1, 2]. Other studies detected or redetected important aspects of lithium which either are still to be discussed on a hypothetical level such as its 'neuroprotective' effects, or which are supported by very good scientific evidence but still did not find their way into everyday clinical practice and existing guidelines. The antisuicidal and anti-aggressive properties of lithium reflect this latter situation. Although antidepressants have been in use for more than 50 years, it is disappointing that no valid data exist to prove a suicide- or mortality-reducing effect, with the consequence that usually drug regulatory agencies do not consider reducing the death rate as an essential criterion for approval of a new antidepressant or mood stabilizer. This is rather

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0302–282X/10/0621–0043$26.00/0

Accessible online at:
www.karger.com/nps

Prof. Dr. med. Bruno Müller-Oerlinghausen
Bartningallee 11–13
DE–10557 Berlin (Germany)
Tel. +49 30 2336 2940, Fax +49 30 2336 2935
E-Mail bmoe@zedat.fu-berlin.de

astonishing since for lithium salts such data do exist. In what follows, we will sketch the key studies and the history of this important research area. More comprehensive reviews of the existing literature can be found elsewhere [3].

Does Regular Lithium Long-Term Treatment Diminish the Risk of Suicide in Patients with Affective Disorders?

Suicide Risk and Mortality of Patients with Affective Disorders

Patients with affective disorders exhibit a 2–3 times increased mortality when compared to the general population [4–7]. This excess mortality is caused primarily by the possibly 30- to 70-fold higher suicide-related mortality [8] – which is particularly high in patients with a history of suicide attempts [9, 10]. The meta-analysis by Guze and Robins [11] calculated the lifetime suicide risk as 15% for affective disorders, whereas 20 years later Goodwin and Jamison [12], based on more recent literature, reported an overall risk of 19%.

According to Harris and Barraclough [13], the suicide-related standardized mortality rate (SMR) [14] is 21.24 in major depression and 11.73 in bipolar disorder, with, however, large confidence intervals. Although some studies found a somewhat lower suicide rate in bipolar as compared to unipolar patients [15, 16], others found higher rates in bipolar patients [17–19], particularly in bipolar II patients.

The intriguing question whether long-term medication with lithium salts can improve the course of the manic-depressive disease or of affective disorders in terms of suicide prevention has been given little attention until the 80s.

Early Studies

Barraclough [20] was one of the first investigators postulating a potential association between lithium long-term medication and suicide prevention. Based on a detailed analysis of the charts of 100 suicide victims he concluded that about 20% of the suicides could have been prevented by adequate lithium medication. The first systematic retrospective study demonstrating a highly significant reduction of suicide attempts in a sample of 64 high-risk patients, 46 bipolar and 11 schizoaffective, during long-term lithium treatment was published in 1992 by the Berlin research group [21]. The authors emphasized that suicides and suicide attempts occurred nearly exclusively in a group of 13 patients who had taken lithium irregularly or had stopped the medication.

Felber's group in Dresden analyzing suicide attempts during accumulated periods on and off lithium had very similar findings: 90% of the suicide attempts occurred in the lithium-free period [22].

Several studies on the mortality of affective disorders during lithium long-term treatment by Coppen et al. [23] and by the International Group for the Study of Lithium-Treated Patients (IGSLI) [14, 24] demonstrated that the SMR of patients with affective disorders during adequate lithium medication is normalized down to the level of the general population[1]. Coppen [25] reviewed the studies existing in the mid-nineties on the suicide rates in patients on versus off lithium and concluded that adequate lithium medication reduces the suicide-related mortality by 82%.

The IGSLI Studies

In the IGSLI main study, well-documented data on the course of illness of 827 patients with affective disorders from lithium clinics in Austria, Canada, Denmark, and Germany, who had been treated with lithium for at least 6 months, were evaluated [14, 24]. Fifty-five percent of the patients were bipolar, 25% unipolar, 2% unipolar-manic, 16% schizoaffective, and 2% had other diagnoses. At onset of the lithium prophylaxis, patients were 41 years old on average. The mean duration of lithium treatment was 81 months (6–21 years), equaling 5,600 patient-years [14, 24].

The ratio of 44 observed and 38 expected cases of deaths is not statistically different from 1.0, which is the mortality of the general population. Thus, the expected 2- to 3-fold excess mortality in patients with affective disorders (see above) does no more exist in this lithium-treated patient sample.

Bipolar patients do not differ essentially from other diagnostic groups in this respect.

Although the specific suicide-related SMR is still higher than in the general population, it can be clearly shown that it is definitely lower in all diagnostic groups compared to what could be expected in untreated patient samples.

To weaken this finding, it might be speculated that patients willing to accept long-term treatment may exhibit a lower suicide risk, although this does not appear very likely when accounting for the fact that those patients would suffer from particularly severe courses of their disease. A further analysis of the IGSLI material could refute this argument: during the first year of lithi-

um treatment, patients showed a 2-fold increased overall mortality and a 17-fold increased suicide-related mortality compared with the general population. During later lithium treatment, the SMR normalized thus indicating that patients who accept lithium prophylaxis actually exhibit a high suicide risk [26]. The Boston group also reported that after abrupt discontinuation of lithium medication the suicide risk rises particularly high [27].

Further Studies and Meta-Analyses

A meta-analysis of the data collected by the late nineties revealed that the risk of suicidal acts in bipolar patients off lithium was 7–8 times higher than in those on lithium [28]. Furthermore, the findings by Guzzetta et al. [29] support the reports by Coppen and the IGSLI that the antisuicidal effect also holds true for patients with recurrent depressions.

Linking regional lithium prescription rates with the Danish suicide register, Kessing et al. [30] added another impressive piece of evidence to the existing data on lithium's antisuicidal effect. There also exist convincing findings from controlled prospective studies. Cipriani et al. [31] reviewed 22 randomized controlled trials and found that patients on lithium were less likely to die from suicide, as compared to other compounds or placebo. Additional proof comes from the first controlled trial with lithium versus placebo as an adjunctive treatment in a large sample of high-risk patients. Suicidal events were defined as the endpoint [32]. Whereas the number of suicide attempts did not differ between treatment groups, a statistically significant superiority of lithium in terms of completed suicides was observed, whereas in a retrospective chart review of long-term treated bipolar patients from a single private practice nonfatal suicidal behavior was not different in patients on lithium and those on anticonvulsants [33].

Questions

There are several intriguing questions related to the mechanism of the antisuicidal effect of lithium and its potential specificity. First of all, is the antisuicidal effect coupled directly to the antidepressant effect of lithium? Several reports point to a mechanism separate from lithium's antidepressant action [34]. It has been speculated that the antisuicidal effect is associated with the well-proven serotonin-agonistic effect in biochemical terms, and with the well-established anti-aggressive effect of lithium in clinical terms [35]. Secondly, is the antisuicidal effect of lithium shared by other compounds such as antidepressants, neuroleptics or mood stabilizers? So far, in various trials using different methodologies, lithium has been shown clearly superior to other mood stabilizers in terms of suicide prevention [36–40].

Conclusion

'Does lithium save lives?' – the question raised in an editorial [41], can now be answered conclusively: yes, it does, if the treatment is applied and monitored in a rational, careful and individualized way. While there are rare negative findings in this respect [42], they can most likely be explained by incomplete patient follow-up and insufficient information on patients' compliance with lithium. This saving of lives considerably adds to the preference of lithium when the cost-effectiveness of treatment with various mood stabilizers is assessed [43].

Does Lithium Reduce Pathological Aggression?

The first report on the anti-aggressive effect of lithium was described by John F. Cade [44] who documented that lithium would be effective in cases of restless psychopathic mental defectives in a similar way as a prefrontal leukotomy.

Twenty years later, a number of Scandinavian case reports were published. Forssmann and Walinder [45] tried lithium for various indications. They reported 18 cases with aggression as the predominant clinical feature and pointed to amazingly good results with lithium.

Baastrup [46] characterized a female aggressive patient endangering herself and others. Lithium was the only drug to control this behavior although the patient was not manic-depressive.

Clinical trials on the effect of lithium on aggression included mainly four different groups of patients: (a) children with behavioral disturbances, (b) patients with mental handicaps, (c) adult psychiatric populations, and (d) persons with uncontrolled fit of rage. There is, however, some overlapping between these diagnostic groups.

Children with Behavioral Disturbances

The validity of studies conducted in children with aggressive behavior suffers from methodological problems. Most studies involved extremely heterogeneous patients. At least 4 double-blind, placebo-controlled studies were performed since 1995 [47–50].

Campell et al. [47] examined 61 children aged 5.2–12.9 years with severe aggressiveness, explosiveness and disruptiveness. The children had not responded to previous

treatment. They were treated with lithium or haloperidol or placebo for 4 weeks. Both substances, lithium and haloperidol, reduced target symptoms such as hyperactivity, aggression and hostility, but side effects occurred significantly more often on haloperidol.

In the early 1990s, studies were often published which failed to replicate these results. The study of Carlson et al. [51] only showed 3 of 11 children with significant improvement as to self-control, aggression and irritability.

A second placebo-controlled double-blind trial was performed also by Campbell et al. [48]. Fifty children with severe aggressive and impulsive symptoms as part of a conduct disorder were treated with lithium or placebo for 6 weeks followed by 2 weeks on placebo. The findings were not as much in favor of lithium as those of the former study by Campell et al. [47].

Rifkin et al. [49] included 33 adolescent inpatients and administered lithium or placebo for 2 weeks. 8.3% of those who completed the study receiving placebo versus 21.4% of those receiving lithium were considered responders. The authors assumed the major limitation of this study and the possible reason for the nonsignificant results was the short period of treatment.

Another study conducted by Malone et al. [50] investigated different aggression subtypes related to treatment response. They included 28 aggressive conduct-disordered children (mean age 12.69 years) and treated them in a double-blind manner either with lithium or placebo. They found that treatment response with lithium correlated rather with the affective subtype than with the predatory subtype of aggression. A further study of the same authors [52] on the efficacy of lithium in the treatment of aggression achieved more favorable results for lithium. Lithium turned out to be statistically and clinically superior to placebo. They included 86 inpatients with conduct disorder and treated them in a double-blind manner with lithium or placebo for 4 weeks. Sixteen of 20 subjects in the lithium group were responders versus 6 of 20 in the placebo group. In more than 50% of the subjects in the lithium group adverse side effects like vomiting, nausea and increased urinary frequency were observed.

Patients with Mental Handicaps

Ten to thirty-five percent of patients with mental handicaps show self-injurious behavior like head-banging, biting, and scratching oneself. Explosive behavior complicates the daily life of these patients and their families and hospitalization, therefore, is often unavoidable. The treatment of aggressive behavior presents a challenge to every clinician.

Since the 1970s, lithium therapy was included in pharmacological attempts to reduce the most severe aggressive symptoms. Only studies in which the authors had clearly diagnosed the patients as mentally handicapped are listed in the following paragraph.

The first open trial on aggression was conducted by Dostal and Zvolsky [53]. They investigated 14 adolescent, mentally handicapped patients and showed a beneficial effect under lithium therapy. Most of the patients suffered from side effects like polydipsia and polyuria.

In an open study conducted by Micev and Lynch [54], these positive results could be confirmed. Six out of 8 patients experienced complete remission of self-harming behavior.

An equal reduction in aggression and self-injurious behavior was shown in a retrospective study by Luchins and Dojka [55] who assessed the effect of lithium and propanolol in subjects with mental retardation.

In 1989, Glenn et al. [56] published case reports of 10 brain-injured patients with severe aggressive behavior. Five of these patients showed a dramatic response after onset of lithium treatment.

A decrease in the frequency of aggressive outbursts was also demonstrated by Bellus et al. [57] in patients following brain injury. The authors concluded that the use of lithium may yield positive effects in the control of aggressive behavior, even in the long term.

Adult Psychiatric Population

One of the first studies in this field was conducted by van Putten and Sanders [58]. They treated 35 patients with chronic and incapacitating mental illness and reported a favorable change in aggressive behavior during lithium medication. None of their patients was suffering from manic-depressive illness.

Likewise remarkable results were found by Rifkin et al. [59]. This research group in 1972 conducted a 6-week double-blind crossover trial with random allocation comparing lithium to placebo in patients with emotionally unstable character disorder. In the view of Rifkin et al. [59], the persuasive improvement during the lithium treatment had to be explained either by hidden manic-depressive illness or by a closely related condition.

In 2001, Prado-Lima et al. [60] examined 8 mothers with child abuse. Lithium significantly reduced their abusive behavior towards their children at day 30 and day 60 of treatment compared with baseline. Especially the score for physical aggression towards other people showed a statistically significant reduction.

Adult patients with an attention-deficit/hyperactivity disorder were treated in a randomized double-blind crossover design by Dorrego et al. [61] with lithium or methylphenidate. They received 8 weeks of methylphenidate hydrochloride treatment and 8 weeks of lithium treatment by random assignment. Aggression was measured with the Overt Aggression Scale. The authors concluded that lithium might be beneficial in the treatment of adult attention-deficit/hyperactivity disorder and that lithium significantly alleviated a couple of behavioral problems including aggressive outbursts.

Persons with Uncontrolled Rage Outbursts

One interesting approach towards the effectiveness of lithium in the treatment of aggression is to study individuals with uncontrolled rage outbursts such as inmates of prisons or correctional institutions. In the 1970s, a number of 'prisoner studies' were conducted to investigate the effect of lithium on aggression.

Twelve inmates with personality disorders (aggressive, sociopathic and schizoid) from a maximum security prison in Connecticut were investigated by Sheard [62] who was the first to present study results comparing lithium with placebo. Lithium reduced self-rated aggressive affect while also being associated with a lower incidence of disciplinary sanctions.

Tupin et al. [63] treated 27 inmates of the California Medical Facility selected because of serious repeated violent behavior with lithium for 10 months. The anti-aggressive effect of lithium could be replicated. Participants of this study described an increased capacity to reflect on the consequences of actions and to control angry feelings while taking lithium.

The only clinical trial on lithium and aggression involving outpatients with uncontrolled fits of rage was conducted by Sheard [64]. Twelve inmates with aggressive behavior were treated with lithium for 4 months and after their release the patients were followed as outpatients during 1–2 months of lithium treatment. A decreased number of serious aggressive episodes could be shown.

The same authors conducted a 3-month, double-blind, placebo-controlled trial with 66 inmates from a medium-security prison [65]. Significantly fewer major infractions occurred in the lithium as compared to the placebo group. These results strengthen the evidence that lithium can have an inhibitory effect on impulsive aggressive behavior.

Potential Mechanism: The Role of Serotonin

The potential mechanisms of the anti-aggressive effects of lithium are unclear. Some authors [66] pointed to the frequently combined occurrence of impulse control disorder and bipolar disorder and suggested a relationship between both disorders. They discussed an underlying common pathophysiological pathway. Animal and clinical studies have suggested a critical role for central serotonin function in this context. Lithium exerts serotonin-enhancing effects [67] and this might provide an explanation for a possible working mechanism in the reduction of aggressive behavior.

Coccaro and colleagues [68–70] could show an inverse covariation between peripheral markers of central 5-HT functions and impulsive aggressive behavior such as a reduced number of 5-HT transporters on platelets correlated with aggressive behavior. However, the validity of studies allegedly corroborating these rather populist concepts has been questioned [71].

References

1 Grof P, Müller-Oerlinghausen B: A critical appraisal of lithium's efficacy and effectiveness: the last 60 years. Bipolar Disord 2009; 11(Suppl 2):10–19.
2 Grof P: Sixty years of lithium responders. Neuropsychobiology 2010;62:8–16.
3 Bauer M, Grof P, Müller-Oerlinghausen B (eds): Lithium in Neuropsychiatry. London, Informa, 2006, pp 33–42.
4 Lundquist G: Prognosis and cause of manic depressive psychosis. Acta Psychiatr Neurol Scand 1945;35:1–96.
5 Petterson U: Manic-depressive illness: a clinical, social and genetic study. Acta Psychiatr Scand Suppl 1977;269:55–60.
6 Tsuang MT, Woolson RF: Excess mortality in schizophrenia and affective disorders. Do suicides and accidental deaths solely account for this excess? Arch Gen Psychiatry 1978;35: 1181–1185.
7 Weeke A: Causes of death in manic depressives; in Schou M, Strömgren E (eds): Origin, Prevention and Treatment of Affective Disorders. London, Academic Press, 1979, pp 289–299.
8 Hagnell O, Lanke J, Rorsman B: Suicide rates in the Lundby study: mental illness as a risk factor for suicide. Neuropsychobiology 1981; 7:248–253.
9 Tuckman J, Youngman W: Identifying suicide with groups among attempted suicide. Public Health Rep 1963;78:763–766.
10 Motto I: Suicide attempts: a longitudinal view. Arch GenPsychiatry 1965;13:516–520.
11 Guze SB, Robins E: Suicide in primary affective disorders. Br J Psychiatry 1970;117:437–438.

12 Goodwin FK, Jamison KR: Manic-Depressive Illness. New York, Oxford University Press, 1990.
13 Harris EC, Barraclough B: Excess mortality of mental disorder. Br J Psychiatry 1998;173: 11–53.
14 Ahrens B, Müller-Oerlinghausen B, Schou M, et al: Excess cardiovascular and suicide mortality of affective disorders may be reduced by lithium-prophylaxis. J Affect Disord 1995;33:67–75.
15 Newman S, Bland R: Suicide risk varies by subtype of affective disorder. Acta Psychiatr Scand 1991;83:420–426.
16 Ösby U, Brandt L, Correia N, et al: Excess mortality in bipolar and unipolar disorder in Sweden. Arch Gen Psychiatry 2001;58:844–850.
17 Lester D: Suicidal behavior in bipolar and unipolar affective disorders: a meta-analysis. J Affect Disord 1993;27:117–121.
18 Angst J, Sellaro R, Angst F: Long-term outcome and mortality of treated vs untreated bipolar and depressed patients: a preliminary report. Int J Psychiatry Clin Pract 1998; 2:115–119.
19 Bottlender R, Jager M, Strauss A, et al: Suicidality in bipolar compared to unipolar depressed inpatients. Eur Arch Psychiatry Clin Neurosci 2000;250:257–261.
20 Barraclough B: Suicide prevention, recurrent affective disorder and lithium. Br J Psychiatry 1972;121:91–392.
21 Müller-Oerlinghausen B, Müser-Causemann B, Volk J: Suicides and parasuicides in a high-risk patient group on and off lithium long-term medication. J Affect Disord 1992; 25:261–270.
22 Felber W, Kyber A: Suizide und Parasuizide während und ausserhalb einer Lithiumprophylaxe; in Müller-Oerlinghausen B, Berghöfer A (eds): Ziele und Ergebnisse der medikamentösen Prophylaxe affektiver Psychosen. Stuttgart, Thieme, 1994, pp 53–59.
23 Coppen A, Standish-Barry H, Bailey J, et al: Does lithium reduce the mortality of recurrent mood disorders? J Affect Disord 1991; 23:1–7.
24 Müller-Oerlinghausen B, Ahrens B, Grof E, et al: The effect of long-term lithium treatment on the mortality of patients with manic-depressive and schizo-affective illness. Acta Psychiatr Scand 1992;86:218–222.
25 Coppen A: Depression as a lethal disease: prevention strategies. J Clin Psychiatry 1994; 55(suppl 4):37–45.
26 Müller-Oerlinghausen B, Wolf T, Ahrens B, et al: Mortality during initial and during later lithium treatment. A collaborative study by the International Group for the Study of Lithium-treated Patients. Acta Psychiatr Scand 1994;90:295–297.
27 Baldessarini RJ, Tondo L, Hennen J: Effects of lithium treatment and its discontinuation on suicidal behaviour in bipolar manic-depressive disorders. J Clin Psychiatry 1999; 60(suppl 2):77–84.
28 Baldessarini RJ, Tondo L, Hennen J: Effect of lithium treatment and its discontinuation on suicidal behavior in bipolar manic-depressive disorders. J Clin Psychiatry 1999;60(suppl 2):77–84.
29 Guzzetta F, Tondo L, Centorrino F, et al: Lithium treatment reduces suicide risk in recurrent major depressive disorder. J Clin Psychiatry 2007;68:380–383.
30 Kessing LV, Sondergard L, Kvist K, et al: Suicide risk in patients treated with lithium. Arch Gen Psychiatry 2005;62:860–866.
31 Cipriani A, Pretty H, Hawton K, et al: Lithium in the prevention of suicidal behavior and all-mortality in patients with mood disorders: a systematic review of randomized trials. Am J Psychiatry 2005;162:1805–1819.
32 Lauterbach E, Felber W, Müller-Oerlinghausen B, et al: Adjunctive lithium treatment in the prevention of suicidal behavior in depressive disorders: a randomized, placebo-controlled 1 year trial. Acta Psychiatr Scand 2008;118:469–479.
33 Yerevanian BI, Kock RJ, Mintz J: Lithium, anticonvulsants and suicidal behaviour in bipolar disorder. J Affect Disord 2003;73: 223–228.
34 Ahrens B, Müller-Oerlinghausen B: Does lithium exert an independent antisuicidal effect? Pharmacopsychiatry 2001;34:132–136.
35 Bierbrauer J, Nilsson A, Müller-Oerlinghausen B, et al: Therapeutic and prophylactic effects of lithium on pathological aggression; in Bauer M, Grof P, Müller-Oerlinghausen B (eds): Lithium in Neuropsychiatry. London, Informa, 2006, pp 227–236.
36 Goodwin FK: Anticonvulsant therapy and suicide in affective disorders. J Clin Psychiatry 1999;60(suppl 2):89–93.
37 Thies-Fletchner K, Müller-Oerlinghausen B, Seibert W, et al: Effect of prophylactic treatment on suicide risk in patients with affective disorders: data from a randomized prospective study. Pharmacopsychiatry 1996; 29:103–107.
38 Goodwin FK: Rationale for using lithium in combination with other mood stabilizers in the management of bipolar disorder. J Clin Psychiatry 2003;64:18–24.
39 Sondergard L, Lopez AG, Andersen PK, et al: Mood-stabilizing pharmacological treatment in bipolar disorders and risk of suicide. Bipolar Disord 2008;10:87–94.
40 Collins JC, McFarland BH: Divalproex, lithium and suicide among Medicaid patients with bipolar disorder. J Affect Disord 2008; 107:23–28.
41 Joffe R: Does lithium save lives? J Psychiatry Neurosci 2004;29:9.
42 Licht RW, Vestergaard P, Brodersen A: Long-term outcome of patients with bipolar disorder commenced on lithium during hospitalization: a complete 15-year register-based follow-up. Bipolar Disord 2008;10:79–86.
43 Soares-Weiser K, Bravo Vergel V, Revnun S, et al: A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder. Health Technol Assess 2007;11:206.
44 Cade JF: Lithium salts in the treatment of psychotic excitement. Med J Aust 1949;36: 349–352.
45 Forssman H, Walinder J: Lithium treatment of atypical indications. Acta Psychiatr Scand Suppl 1969;207:34–40.
46 Baastrup P: Practical clinical viewpoints regarding treatment with lithium. Acta Psychiatr Scand Suppl 1969;207:12–18.
47 Campbell M, Small AM, Green WH, et al: Behavioral efficacy of haloperidol and lithium carbonate. A comparison in hospitalized aggressive children with conduct disorder. Arch Gen Psychiatry 1984;41:650–656.
48 Campbell M, Adams PB, Small AM, et al: Lithium in hospitalized children with conduct disorder: a double-blind and placebo controlled study. J Am Acad Child Adolesc Psychiatry 1995;34:445–453.
49 Rifkin A, Karajgi B, Dicker R, et al: Lithium treatment of conduct disorders in adolescents. Am J Psychiatry 1997;154:554–555.
50 Malone RP, Bennett DS, Luebbert JF, et al: Aggression classification and treatment response. Psychopharmacol Bull 1998;34:41–45.
51 Carlson GA, Rapport MD, Pataki CS, et al: Lithium in hospitalized children at 4 and 8 weeks: mood, behavior and cognitive effects. J Child Psychol Psychiatry 1992;33:411–425.
52 Malone RP, Delaney MA, Luebbert JF, et al: A double-blind placebo-controlled study of lithium in hospitalized aggressive children and adolescents with conduct disorder. Arch Gen Psychiatry 2000;57:649–654.
53 Dostal T, Zvolsky P: Antiaggressive effect of lithium salts in severe mentally retarded adolescents. Int Pharmacopsychiatry 1970;5: 203–207.
54 Micev V, Lynch DM: Effect of lithium on disturbed severely mentally retarded patients. Br J Psychiatry 1974;125:111.
55 Luchins DJ, Dojka D: Lithium and propanolol in aggression and self-injurious behaviour in the mentally retarded. Psychopharmacol Bull 1989;25:372–375.
56 Glenn MB, Wroblewski B, Parziale J, et al: Lithium carbonate for aggressive behaviour or affective instability in ten brain-injured patients. Am J Phys Med Rehabil 1989;68: 221–226.
57 Bellus SB, Stewart D, Vergo JG, et al: The use of lithium in the treatment of aggressive behaviours with two brain-injured individuals in a state psychiatric hospital. Brain Inj 1996; 10:849–860.
58 Van Putten T, Sanders DG: Lithium in treatment failures. J Nerv Ment Dis 1975;161:255–264.

59 Rifkin A, Quitkin F, Carrillo C, et al: Lithium carbonate in emotionally unstable character disorder. Arch Gen Psychiatry 1972;27:519–524.
60 Prado-Lima P, Knijnik L, Juruena M, et al: Lithium reduces maternal child abuse behavior: a preliminary report. J Clin Pharm Ther 2001;26:279–282.
61 Dorrego MF, Canevaro L, Kuzis G, et al: A randomized, double-blind, crossover study of methylphenidate and lithium in adults with attention-deficit/hyperactivity disorder: preliminary findings. J Neuropsychiatry Clin Neurosci 2002;14:289–295.
62 Sheard MH: Effect of lithium in human aggression. Nature 1971;230:113–114.
63 Tupin JP, Smith DB, Clanon TL, et al: The long-term use of lithium in aggressive prisoners. Compr Psychiatry 1973;14:311–317.
64 Sheard MH: Lithium in the treatment of aggression. J Nerv Ment Dis 1975;160:108–118.
65 Sheard MH, Marini JL, Bridges CI, et al: The effect of lithium on impulsive aggressive behaviour in man. Am J Psychiatry 1976;133:1409–1413.
66 McElroy SL, Pope HG Jr, Keck PE Jr, et al: Are impulse-control disorders related to bipolar disorder? Compr Psychiatry 1996;37:229–240.
67 Müller-Oerlinghausen B: Lithium long-term treatment – does it act via serotonin? Pharmacopsychiatry 1985;18:214–217.
68 Coccaro EF: Central serotonin and impulsive aggression. Br J Psychiatry 1989;8(suppl):52–62.
69 Coccaro EF, Siever LJ, Klar HM, et al: Serotonergic studies in affective and personality disorder patients; correlates with suicidal and impulsive aggressive behavior. Arch Gen Psychiatry 1989;46:587–599.
70 Coccaro EF, Kavoussi RJ, Sheline YI, et al: Impulsive aggression in personality disorder correlates with tritiated paroxetine binding in the platelet. Arch Gen Psychiatry 1996;53:531–536.
71 Roggenbach J, Müller-Oerlinghausen B, Franke L, et al: Peripheral serotonergic markers in acutely suicidal patients. 1. Comparison of serotonergic platelet measures between suicidal individuals, nonsuicidal patients with major depression and healthy subjects. J Neural Transm 2007;114:479–478.