Lithium Treatment Reduces Suicide Risk in Recurrent Major Depressive Disorder

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Objective: Evidence that clinical treatment reduces suicide risk in major depressive disorder (MDD) is limited and inconsistent. Since lithium shows major antisuicidal effects in bipolar disorders and in heterogeneous mood disorder samples, we evaluated evidence of antisuicidal effects of lithium in patients with recurrent MDD.

Data Sources: We searched MEDLINE (January 1966 to April 2006; search terms: *lithium*, *suicide*, *affective disorder, depression, major depression*, and *mood disorder*) for studies reporting suicides or suicide attempts during treatment with and without lithium in recurrent MDD patients, and we added data for 78 new subjects, provided from the Lucio Bini Mood Disorders Research Center in Sardinia, Italy. Suicide rates were pooled and analyzed by use of incidence-rate ratios (IRRs) and meta-analytic methods.

Data Synthesis: Eight studies involved 329 MDD patients and exposure for 4.56 years (1149 person-years) with, and 6.27 years (1285 person-years) without, lithium. Overall risk of suicides and suicide attempts was 88.5% lower with vs. without lithium: 0.17%/y versus 1.48%/y (IRR = 8.71; 95% CI: 2.10 to 77.2, p = .0005); for completed suicides (85% risk reduction), IRR = 6.77 (95% CI: 1.29 to 66.8, p = .01). Meta-analysis by risk difference and risk ratio supported these findings, and sensitivity analysis yielded similar results with studies omitted serially.

Conclusions: This is the first meta-analysis suggesting antisuicidal effects of lithium in recurrent MDD, similar in magnitude to that found in bipolar disorders.

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Major mood disorders are associated with markedly increased risk of suicide, typically at rates 10 to 20 times above general-population rates, and with severe clinical, social, and economic impact.[1–3] Nevertheless, there is remarkably limited evidence of effectiveness and safety of clinical interventions aimed at suicide prevention.[2,3] A notable exception is that rates of suicides and suicide attempts in bipolar disorder patients or in diagnostically heterogeneous mood disorder samples are markedly reduced during treatment with lithium.[2–10] Antidepressants do not appear to reduce risk of suicide in major depressive disorders (MDD),[11–14] but there is suggestive evidence of protective effects of long-term antidepressant treatment in recurrent MDD.[15] However, it has also been reported that serotonin reuptake inhibitors may increase risk of suicidality in young patients.[16] Since effects of lith-

ium on suicide risk in recurrent MDD patients, specifically, has not been reviewed, we carried out a meta-analysis on this topic, with new data included.

METHOD

Data Sources

We searched MEDLINE (January 1966 to April 2006) for reports and reviews using the terms *lithium, suicide, affective disorder, depression, major depression,* and *mood disorder*. We also obtained supplemental data from several authors of reports of studies on lithium treatment in mood disorder (A. Bocchetta, M.D.; A. Coppen, M.D.; B. Müller-Oerlinghausen, M.D., unpublished data). Additional data on recurrent MDD patients were provided by coauthor L.T. (unpublished data, 2006), from the Lucio Bini Mood Disorders Research Center in Sardinia, Italy, derived by methods detailed previously for DSM-IV bipolar disorder patients.[17] These data involved 78 patients (75.6% female; mean ± SD age, 44.0 ± 14.5 years at intake) with DSM-IV recurrent MDD, exposed for a mean ± SD of 9.10 ± 8.86 years before, and 3.42 ± 2.48 years during, lithium maintenance treatment; other treatments were permitted as required clinically and usually involved intermittent treatment with a variety of antidepressants, typically for 90 to 120 days.

Study Selection and Data Extraction

We included published reports with data for suicidal behaviors among subjects with recurrent MDD (diagnosed by ICD-9 or DSM-III/IV or their equivalent) treated with and without lithium (not excluding other treatments), excluding studies with zero numerators in both treatment arms as noninformative.[18–24] We extracted data to obtain rates of suicide and suicide attempts with vs. without lithium treatment. In 3 studies, the time without lithium treatment (required for incidence-rate analyses only) was not specified,[19–21] and we used a conservative best-estimate of the longest likely exposure time to avoid overestimating the effect of lithium. In addition, authors of 3 studies generously provided supplemental information on (1) the treatment given to a suicidal patient,[20] (2) time with and without lithium and the diagnosis of subjects who discontinued treatment,[22] and (3) the diagnosis of suicidal subjects.[23]

Statistics

Data were pooled to generate an incidence-rate ratio (IRR), its 95% CI, and a 2-tailed exact p value. We also applied the following meta-analytic procedures: (1) a random-effects meta-analysis model (metan, Peto method) to pool risk ratios (RR), (2) a Mantel-Haenszel risk-difference (RD) method that tolerated zero numerators in a study arm, and (3) influence (sensitivity) analysis of omitting 1 study at a time (metainf). Analyses used STATA software, version 8.0 (STATA Corporation, College Station, Tex.).

RESULTS

We obtained relevant data from 7 published reports[18–24] and from previously unreported observations by L.T. based on assessment methods detailed elsewhere.[17] Among a total of 329 subjects (N = 252 with lithium, N = 205 without lithium; 128 were evaluated both with and without lithium), treatment exposure-observation times were a mean ± SD of 4.56 ± 2.53 years with, and 6.27 ± 4.84 years without, lithium. Exposure totaled 2434 person-years (1149 with vs. 1285 without lithium; Table 1).

There was a highly significant pooled IRR of 8.71 (95% CI: 2.10 to 77.2; exact p = .0005; Table 1), indicating 88.5% lower risk of suicidal acts with vs. without lithium treatment (Table 1). A random-effects model to compute a pooled RR also strongly favored lithium (RR = 4.24; 95% CI: 1.49 to 12.0; z = 2.71, p = .007; Figure 1). Mantel-Haenszel RD meta-analysis also indicated lower suicide risk with vs. without long-term lithium treatment (RD = 8.03; 95% CI: 3.82 to 12.2; z = 3.74, df = 7, p < .0001). Among 6 reports involving completed suicides,[18,20–24] pooled suicide rates with vs. without lithium were 0.33%/y versus 2.22%/y (85% reduction), with a large IRR of 6.77 (95% CI: 1.29 to 66.8; 2-sided exact p = .01; Table 1).

Given the limited number of studies, we tested for possibly excessive influence of individual studies using a meta-analysis influence test. This analysis indicated little or no effect of eliminating each of the 8 studies, 1 at a time, notably including the 2 largest studies (Greil et al.[21] and Tondo [L.T., unpublished data, 2006]; Table 1). When we omitted 3 trials[20,22,23] in which lithium discontinuation may have contributed to risk without lithium, the antisuicidal effect of lithium was still evident (RD = 7.03; 95% CI: 2.64 to 11.4; z = 3.14, df = 4, p = .002).

DISCUSSION

The present findings indicate much lower risk of suicide and suicide attempts during treatment with lithium among patients diagnosed with recurrent MDD. This effect was observed even in 2 studies that selected subjects at high suicide risk, with particularly high rates of suicide without lithium.[20,22] Moreover, alternative treatments (including antidepressants, anticonvulsants, antipsychotics, sedatives) often were given with or without lithium, making the antisuicidal effects of lithium seem all the more remarkable.

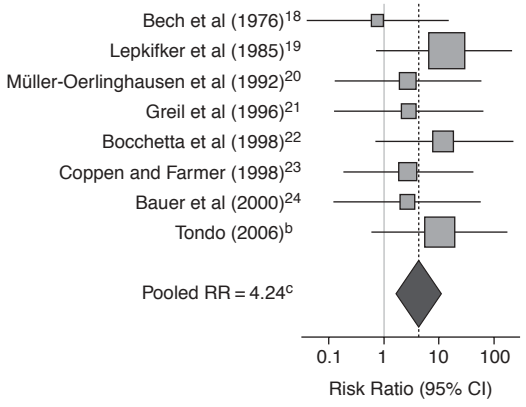
Limitations of this analysis include the relatively small numbers of available studies and subjects and the methodological heterogeneity of the studies. In most studies, suicidal behavior was observed incidentally and not as a

Table 1. Suicidal Behavior Among Recurrent Major Depressive Disorder Patients Treated With vs. Without Lithium

			With Lithium			Without Lithium		
			Rate			Rate		
Study	Subjects, N	Act Type	Acts/N/y	%/y	Other Treatments	Acts/N/y	%/y	Other Treatments
Bech et al (1976)[18,a]	14	S	1/10/7.0	1.43	Some AD	0/4/2.0	0.00	Some AD
Lepkifker et al (1985)[19]	33	A	0/33/8.3	0.00	AD, other	7/33/7.9	2.69	AD, other
Müller-Oerlinghausen et al (1992)[20,b,c]	11	S	0/11/8.0	0.00	Various	1/11/2.5	3.64	AD, AP
Greil et al (1996)[21,d]	81	S	0/40/2.5	0.00	Some other	1/41/2.5	0.98	AD
Bocchetta et al (1998)[22,b,c]	16	S	0/16/5.5	0.00	AD, AP, other	3/6/3.2	15.6	AD, AP, other
Coppen and Farmer (1998)[23,b]	67	S	1/50/5.2	0.40	AD, AP	1/17/9.0	0.65	AD, AP
Bauer et al (2000)[24,d]	29	S	0/14/0.3	0.00	AD	1/15/0.3	22.2	AD + PBO
Tondo (2006)[e]	78	A	0/78/3.4	0.00	AD, AP, other	5/78/9.1	0.70	AD, AP, other
Total (8 studies)[f]	329[g]	S + A	2/252/4.56	0.17	Various	19/205/6.27	1.48	Various

[a]Study includes observations after discontinuing lithium, but no suicides occurred in that phase.
[b]Includes observations following discontinuation of lithium that may affect risk.
[c]High-risk sample (prior suicide attempts).
[d]Randomized trial.
[e]L.T., unpublished data.
[f]Incidence-rate ratio (IRR) = 8.71, 95% CI = 2.10 to 77.2, df = 7, 2-tailed exact p = .0005; for studies with only completed suicide (S) as outcome, the rate with vs. without lithium = 0.33%/y vs. 2.22%/y, IRR = 6.77, 95% CI = 1.29 to 66.8, df = 5, 2-tailed exact p = .01.
[g]Subject total excludes those represented with and without lithium.
Abbreviations: A = suicide attempt, AD = antidepressants, AP = antipsychotics, other = anticonvulsants or sedatives, PBO = placebo, S = completed suicide.

Figure 1. Risk of Suicide Attempts and Suicides[a]



[a]Forest plot of risk ratios (RRs) (risk of suicide attempts and suicides without vs. with long-term lithium treatment in major depressive disorder patients) and their 95% confidence intervals (CIs), based on a Peto random-effects meta-analysis model with continuity correction for zero numerators in single study arms.
[b]L.T., unpublished data.
[c]95% CI: 1.49 to 12.0; z = 2.71, p = .007.

primary outcome measure, risking underreporting, especially of suicide attempts of less severity or less potential lethality. Only 2 reports involved a randomized trial,[21,24] and only 1 of these was double-blind and placebo-controlled.[24] Another possible confound is that 3 studies[20,22,23] included patients discontinuing lithium, which itself has been associated with transiently increased suicide risk.[17,25] Removing these 3 studies[20,22,23] from meta-analysis still yielded a significant reduction of suicide risk with lithium.

Despite their limitations, the present findings indicate that lithium may exert antisuicidal effects in recurrent MDD patients, as suggested by analyses including diagnostically heterogeneous major mood disorder patients.[6–10] Factors contributing to an antisuicidal effect may include long-term prophylactic clinical benefits in recurrent MDD,[5,26] although some patients benefiting from lithium treatment might have had undiagnosed or subtle bipolar disorders.[27,28] Other effects of lithium, not related to its mood-stabilizing properties, also may be involved. These may include reduction of aggression and impulsivity,[2,29] which are typically associated with suicidal behavior, as opposed to suicidal ideation.[10] Antidepressant treatment is less likely to modify aggression and impulsivity, and that characteristic may help to account for evidence that risk of suicidal behavior is not reduced by antidepressant treatment.[11–14,16,30] It is noteworthy, nevertheless, that suicidal ideation has improved with antidepressant treatment, including in randomized, placebo-controlled trials.[31,32]

It is important to point out that the observed suicide rate during treatment of MDD patients with lithium (0.33%/y), though 85% lower than without lithium, remained much higher than in the general population (0.015%/y), similar to findings in bipolar disorder patients.[3,8–10,15,29] Since lithium can be neurotoxic and even lethal on overdose,[12,13,33–35] its benefits require balancing against potential risks. However, the reported use of lithium for deliberate self-poisoning has been relatively infrequent, perhaps reflecting its antisuicidal effects.[35,36] Moreover, the lethality of lithium overdoses has been remarkably limited and, reportedly, not different from that of modern antidepressants, mood-altering anticonvul-

sants, and second-generation antipsychotics.[36] Protection is afforded by initial vomiting and by the effectiveness of hemodialysis.[12,13,37]

The hypothesis that lithium reduces risk of suicide and suicide attempts in recurrent MDD patients requires further testing. Such studies may be ethically feasible; a precedent for randomized trials with suicidal behavior as an explicit, primary outcome measure is the International Suicide Prevention Trial (InterSePT) comparing clozapine with olanzapine in highly suicidal schizophrenic patients.[38] Similar trials could, for example, randomly assign MDD patients to treatment with an antidepressant alone versus with lithium added. The findings reported here support the conclusion that lithium may represent a useful supplemental or alternative treatment for potentially suicidal patients with recurrent MDD, as has been found in patients with bipolar disorders.

Drug names: clozapine (Clozaril, FazaClo, and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa).

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