Lithium Treatment and Suicide Risk in Major Affective Disorders: Update and New Findings

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Background: Evidence that therapeutic benefits of psychiatric treatments include reduction of suicide risk is remarkably limited and poorly studied. An exception is growing evidence for such suicidal risk reduction with long-term lithium maintenance. This report updates and extends analyses of lithium treatment and suicides and attempts. ***Method:*** We pooled data from studies providing data on suicidal acts, patients at risk, and average exposure times with or without lithium maintenance therapy, and considered effects of lithium on selected subgroups. ***Results:*** Data from 34 reported studies involved 42 groups with lithium maintenance averaging 3.36 years, and 25 groups without lithium followed for 5.88 years, representing 16,221 patients in a total experience of 64,233 person-years. Risks for all suicidal acts/100 person-years averaged 3.10 without lithium versus 0.210 during treatment (93% difference) versus approximately 0.315 for the general population. For attempts, corresponding rates were 4.65 versus 0.312 (93% difference), and for completed suicides, 0.942 versus 0.174 (82% difference). Subjects with bipolar versus various recurrent major affective disorders showed similar benefits (95% vs. 91% sparing of all suicidal acts). Risk reductions for unipolar depressive, bipolar II, and bipolar I cases ranked 100%, 82%, and 67%. Suicide risk without lithium tended to increase from 1970 to 2002, with no loss of effectiveness of lithium treatment. ***Conclusion:*** The findings indicate major reductions of suicidal risks (attempts > suicides) with lithium maintenance therapy in unipolar ≥ bipolar II ≥ bipolar I disorder, to overall levels close to general population rates. These major benefits in syndromes mainly involving depression encourage evaluation of other treatments aimed at reducing mortality in the depressive and mixed phases of bipolar disorder and in unipolar major depression.

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Mortality risk is increased substantially in many major psychiatric disorders, owing to increased death rates with stress-sensitive general medical disorders, complications of comorbid substance abuse, accidents, and most importantly, suicide.[1–4] It is therefore remarkable that studies of the effects of treatment on mortality risks in patients with psychiatric disorders remain remarkably uncommon, and limited in the range of treatments and disorders considered.[5,6] Of the rare investigations of psychiatric treatments with substantial information pertaining to suicide risk specifically, long-term prophylactic treatment of patients with recurrent major affective disorders with lithium salts has, by far, the strongest evidence of reduced suicide risk.[7–13] Several decades of clinical and research experience with long-term maintenance treatment in recurrent major affective disorders has encouraged controlled and naturalistic studies of many patient-subjects given sustained and monitored lithium treatment for years. Many of these studies included information about suicidal behavior. Studies reporting on relationships of lithium treatment and suicide in bipolar disorder and other recurrent major affective disorder patients have consistently found much lower rates of suicide and attempts during lithium maintenance treatment than without it.[11–13]

In contrast, there is surprisingly little direct evidence that modern antidepressants lead to consistent reductions of suicidal risk in major depressive disorder patients (references 4 and 5 and R.J.B.; J.H.; K. W. Kwok, M.D.; et al., unpublished manuscript, 2003). There is some evidence that older, but also more toxic and potentially even lethal, antidepressants may have moderate effects of this kind in major depression (R.J.B.; J.H.; K. W. Kwok, M.D.; et al., unpublished manuscript, 2003). Proposed alternatives

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to lithium treatment in recurrent mood disorders, including various anticonvulsants, atypical antipsychotics, and antihypertensives, have not been evaluated for potential effects on suicide, or mortality in general.[4,6] There is emerging evidence that clozapine, in particular, may be associated with reduced risk of suicidal behavior among chronically psychotic patients, with little information available yet about such effects in bipolar disorder patients.[4,15,16] Unlike the typical clinical use of antidepressants for depressive or anxiety disorders, and similar to the use of clozapine for schizophrenia, lithium usually is used consistently over long periods in relatively structured settings, including specialized programs for mood disorders, or in lithium clinics. This practice pattern may itself contribute to reduction of suicide risk during closely medically supervised long-term treatments.

In sum, available information about possible antisuicidal effects of psychotropic medicines in major affective disorder patients suggests that only for long-term lithium maintenance treatment is there substantial evidence of association with reduced suicidal risk. Given the importance of information pertaining to lithium and suicidal risk, we have updated analyses of published data pertaining to suicidal behavior with versus without lithium therapy,[11–13] extended these analyses to consider completed suicides and suicide attempts separately, evaluated effects of lithium treatment in specific types of recurrent affective disorders, and considered possible secular trends[17] related to suicide risk and to lithium therapy over the past several decades.

METHOD

Reports of research pertaining to lithium were updated by MEDLINE computerized literature searching from 1970 through mid-2002, using keywords *lithium* and *suicide*, as well as reviewing the bibliographies of recently published reports. Studies were included if they provided data for subjects treated with, or with and without, lithium, including the numbers of suicidal acts and persons at risk (N), as well as average times at risk, so as to permit computing of rates (events/100 person-years, usually expressed as "%/year" for simplicity). Their variance estimates were expressed as 95% CI derived from random effects, Poisson modeling. Rates for specific comparison groups were compiled by pooling data on suicidal acts/N of subjects and estimating overall exposure times as N-weighted averages from individual studies. Risk ratios and their 95% CI were estimated for comparison groups. These methods are detailed in our previous reviews of aspects of this topic.[11,12]

RESULTS

Data Available for Analysis

We identified 34 reports appearing between 1970 and 2002 (Table 1).[12,18–50] These studies include 67 treatment arms or conditions (42 with and 25 without lithium treatment). The total number of patient-subjects was 16,221 (corrected for appearance of some subjects in both treatment conditions and in separate analyses for suicides and attempts). Exposure during lithium treatment averaged 3.36 years among 15,323 subjects (51,485 person-years of risk exposure), and 5.88 years without lithium maintenance treatment in 2168 subjects (12,748 person-years of exposure), and overall time-at-risk (weighted by subject-N/study) averaged 3.76 years. Total risk exposure was 64,233 patient-years of total experience. Salient characteristics of the 34 studies analyzed are summarized in Table 1.

Overall Rates of Suicides Plus Attempts Without Versus With Lithium Therapy

Data on suicides and attempts, subject Ns under various conditions, and average time-at-risk, were pooled to estimate overall rates of all suicidal acts/100 person-years (or "%/year"). The overall rate for all suicidal acts (completed suicides and attempts) from all identified studies was 3.10 (95% CI = 2.80 to 3.42) %/year without versus 0.210 (95% CI = 0.172 to 0.253) %/year with lithium treatment (Table 2). Risk was reduced by 14.8-fold (95% CI = 8.54 to 25.6) or 93.2% ($p < .0001$; Table 2). Moreover, lower rates of suicides or attempts were found consistently in 24 of the 25 sets of observations with versus without lithium treatment. The single exception was the earliest study,[18] which involved relatively small numbers of patients (39 untreated and 84 treated) and relatively short exposure time without lithium (4.9 months), and encountered no suicidal acts with or without lithium treatment.

Comparisons of Rates of Completed Suicides and Attempts

For both completed suicides and attempts, the lithium-associated lowering of rates was remarkably robust, with a relatively larger reduction, based on risk ratios, for attempts than fatalities (Table 2). For completed suicides considered separately, the pooled rates were 0.942 (95% CI = 0.743 to 1.180) without versus 0.174 (95% CI = 0.138 to 0.215) %/year with lithium treatment (Table 2). This comparison indicates a relative risk-reduction of 5.43-fold (95% CI = 3.57 to 8.25), or an 81.5% lower risk of completed suicides during long-term lithium treatment. For suicide attempts, the rates without versus with lithium maintenance treatment were 4.65 (95% CI = 4.10 to 5.24) versus 0.312 (95% CI = 0.204 to 0.451) %/year, with a risk ratio of 14.9 (95% CI = 8.41 to 26.4), or a reduction of risk by 93.3%. This protection against attempts is 2.74 times (14.9/5.43) greater than that against completed suicides (Table 2).

Rates of Suicides and Attempts in Diagnostic Subtypes

When data for rates of all suicidal acts were split by diagnostic types (Table 3), bipolar disorder (with some schizoaffective) cases showed a reduction of total suicidal acts from 6.10%/year without, to 0.295%/year with lithium

Table 1. Summary of 34 Suicidal Behavior Studies With 67 Subgroups With Lithium (42) and Without Lithium (25) Treatment[a]

Study	Diagnosis	Total N	Act Type	With Lithium		Without Lithium	
				Acts/N/y	%/y	Acts/N/y	%/y
Baastrup et al, 1970[18,b]	MAD	123	A	0/84/4.00	0.000	0/39/0.41	0.000
	MAD	123	S	0/84/4.00	0.000	0/39/0.41	0.000
Prien et al, 1974[19,c]	MAD	289	S	0/146/2.00	0.000	2/143/2.00	0.699
Bech et al, 1976[20]	MAD	40	S	1/40/7.00	0.357	...	...
Kay and Petterson, 1977[21]	MAD	192	S	0/123/2.33	0.000	3/69/11.4	0.381
Poole et al, 1978[22]	MAD	99	A	0/99/5.00	0.000	...	...
Glen et al, 1979[23]	MAD	784	S	8/784/4.83	0.211	...	...
Ahlfors et al, 1981[24]	MAD	126	S	0/14/1.33	0.000	3/112/1.25	2.143
Venkoba-Rao et al, 1982[25,b]	MAD	47	A	0/47/8.50	0.000	2/47/8.50	0.501
Hanus and Zapletálek, 1984[26,b]	MAD	95	A	4/95/5.10	0.826	25/95/5.10	5.160
Norton and Whalley, 1984[27,b]	MAD	791	S	8/791/2.17	0.466	...	...
Lepkifker et al, 1985[28,b]	UP	35	A	0/33/8.30	0.000	7/33/8.30	2.556
Jamison, 1986[29]	MAD	9000	S	4/9000/1.00	0.044	...	...
Page et al, 1987[30]	BPD	79	S	6/79/12.1	0.628	...	...
Schou and Weeke, 1988[31,b]	MAD	57	A	0/9/1.00	0.000	10/48/8.58	2.428
Wehr et al, 1988[32]	BPD	70	S	2/70/7.55	0.378	...	...
Coppen et al, 1991[33]	MAD	103	A	0/103/11.0	0.000	...	...
	MAD	103	S	0/103/11.0	0.000	...	...
Nilsson and Axelsson, 1990[34]	MAD	37	A	0/37/7.00	0.000	...	
O'Connell et al, 1991[35]	BPD	248	S	4/248/8.00	0.202	...	...
Vestergaard and Aagaard, 1991[36]	MAD	50	S	5/50/5.00	2.000	...	...
Modestin and Schwartzenbach, 1992[37]	MAD	64	A	0/64/12.1	0.000	...	...
	MAD	64	S	0/64/12.1	0.000	...	...
Müller-Oerlinghausen et al, 1992[38,b,d,e]	MAD	68	A	4/68/8.00	0.735	7/68/8.00	1.287
	MAD	...	S	2/68/8.00	0.368	4/68/8.00	0.735
Rihmer et al, 1993[39,b]	BPD	36	A	6/36/7.20	2.315	61/36/7.20	23.53
	BPD	...	S	1/36/7.20	0.386	3/36/7.20	1.157
Felber and Kyber, 1994[40,b,d,e]	BPD	71	S	1/36/6.98	0.398	3/35/7.19	1.192
	BPD	71	S + A	7/71/6.98	1.412	64/71/7.19	12.54
Lenz et al, 1994[41,b,d]	MAD	695	S	9/695/6.66	0.194	23/430/6.25	0.856
Müller-Oerlinghausen, 1994[42]	MAD	394	S	7/394/14.2	0.125	...	...
Sharma and Markar, 1994[43,d]	BPD	114	S	2/57/9.00	0.390	6/57/9.00	1.170
Ahrens et al, 1995[44]	BPD + SA	611	S	7/611/6.60	0.174	...	...
Koukopoulos et al, 1995[45,b,d]	BPD	432	S	3/343/12.2	0.072	5/89/2.75	2.043
Nilsson, 1995[46,b,d]	MAD	362	S	6/230/14.2	0.184	9/132/8.40	0.812
Thies-Flechtner et al, 1996[47,c]	BPD + SA	285	S + A	0/139/2.50	0.000	8/146/2.50	2.192
	BPD + SA	285	S	0/139/2.50	0.000	...	...
Bocchetta et al, 1998[48,b,d,e]	BPD + SA	115	S	2/68/6.92	0.425	5/47/5.60	1.900
Coppen and Farmer, 1998[49,b,d]	MAD	115	S	1/103/5.25	0.185	1/12/9.00	0.926
Tondo et al, 2001[12,b,d]	MAD	426[f]	A	7/426/4.27	0.385	87/324/6.65	4.038
	MAD	...	S	4/426/4.27	0.220	9/222/3.85	1.053
Rucci et al, 2002[50,b]	BPD-I	170	A	5/166/9.31	0.324	67/170/6.95	5.670

[a]Data include a total of 13,895 subjects, corrected for studies reporting completed suicides and suicide attempts separately in the same persons, and for subjects observed both on and off lithium treatment in some studies.
[b]Data indicate suicidal acts/number of subjects at risk/average years of exposure, with resulting rates (acts/100 patient-years expressed as %/year).
[c]Indicates random-assignment, double-blind trial design.
[d]Nine studies involved lithium discontinuation.
[e]Three studies involved high-risk patients selected for previous suicide attempts.
[f]Not all were at risk for both suicides and attempts.
Abbreviations: A = suicide attempts, BPD = bipolar disorder, BPD-I = bipolar I disorder, MAD = major affective disorder, S = completed suicide, SA = schizoaffective disorder, UP = unipolar major depression.

treatment, a 20.7-fold (95% CI = 11.9 to 35.8), or 95.2% reduction of risk. Studies involving mixed groups of major affective disorder patients, including some with bipolar disorder and others with recurrent depressive or schizoaffective disorders, yielded rates for all suicidal acts of 2.12%/year without versus 0.193%/year with lithium maintenance treatment, indicating an 11.0-fold (95% CI = 5.37 to 22.4), or 90.9% reduction of risk (Table 3).

Additional analyses were undertaken with data on 426 patients with major affective disorders treated with lithium in our collaborating mood disorders research unit in Sardinia.[12,51,52] The limited number of unipolar cases available was expanded by including data reported earlier by Lepkifker and colleagues.[28] These data supported separate analyses of rates of all suicidal acts (suicides + attempts) in cases diagnosed with bipolar I disorder, bipolar II disorder, or recurrent unipolar depressive disorder (Table 4). Risks for suicidal acts without lithium maintenance treatment ranked as follows: bipolar I (2.73%/year) ≥ bipolar II (1.70%/year) ≥ unipolar depression (1.33%/year). Similarly during lithium treatment, risks ranked as follows: bipolar I (0.90) > bipolar II (0.30) > unipolar (0.00%/year).

Table 2. Estimated Rates of Suicidal Acts With Versus Without Lithium Maintenance Treatment[a]

Outcome	Rates of Suicidal Acts		Risk Ratio	Percent Reduction	z Score	p Value
	With Lithium	Without Lithium				
Suicides						
No. of study arms	27	14				
No. of suicidal acts	83	76				
Subjects, N	14,802	1491				
Exposure, mean, y	3.23	5.41				
Rate, %/y[b]	0.174	0.942	5.43	81.5	7.91	< .0001
95% CI	0.138 to 0.215	0.743 to 1.180	3.57 to 8.25			
General population, %/y	0.0166					
95% CI	0.0136 to 0.0196					
Attempts						
No. of study arms	13	9				
No. of suicidal acts	26	266				
Subjects, N	1267	860				
Exposure, mean, y	6.58	6.66				
Rate, %/y[b]	0.312	4.646	14.9	93.3	9.26	< .0001
95% CI	0.204 to 0.451	4.104 to 5.239	8.41 to 26.4			
General population, %/y	0.299					
95% CI	0.245 to 0.353					
All suicidal acts						
No. of study arms	34	20				
No. of suicidal acts	108	395				
Subjects, N	15,323	2168				
Exposure, mean, y	3.36	5.88				
Rate, %/y[b]	0.210	3.100	14.8	93.2	9.62	< .0001
95% CI	0.172 to 0.253	2.803 to 3.422	8.54 to 25.6			
General population, %/y	0.315					
95% CI	0.258 to 0.353					

[a]Pooled estimates of rates are derived from data summarized in Table 1, with rate estimates and average treatment-exposure times weighted by number of subjects per condition. 95% CIs are not strictly directly comparable since some studies involved patients under both conditions of treatment, and some patients may have made > 1 attempt in some studies. Rates for without versus with lithium treatment differed by 5.43-fold for suicides, 14.9-fold for attempts, and 14.5-fold overall (all of these differences are highly statistically significant, $p < .0001$), and the ratio of attempt/suicide rates without lithium treatment (4.646/0.951) was 4.89.
[b]Rates are suicide attempts before treatment and suicides or attempts during treatment, per 100 person-years of risk exposure (%/year).

Table 3. Estimated Rates of All Suicidal Acts With Versus Without Lithium Maintenance Treatment in Bipolar Disorder Versus Mixed Major Affective Disorder Patients[a]

Outcome	Rates of Suicidal Acts		Risk Ratio	Percent Reduction	z Score	p Value
	With Lithium	Without Lithium				
Bipolar disorder						
No. of study arms	11	7				
No. of suicidal acts	46	219				
Subjects, N	1924	651				
Exposure, mean, y	8.09	5.51				
Rate, %/y[b]	0.295	6.102	20.7	95.2	10.8	< .0001
95% CI	0.216 to 0.394	5.320 to 6.966	11.9 to 35.8			
General population rate,[b] %/y	0.315					
95% CI	0.258 to 0.353					
Major affective disorders						
No. of study arms	23	13				
No. of suicidal acts	70	192				
Subjects, N	13,435	1501				
Exposure, mean, y	2.69	6.04				
Rate, %/y[b]	0.193	2.119	11.0	90.9	6.58	< .0001
95% CI	0.151 to 0.244	1.829 to 2.441	5.37 to 22.4			
General population rate,[b] %/y	0.315					
95% CI	0.258 to 0.353					

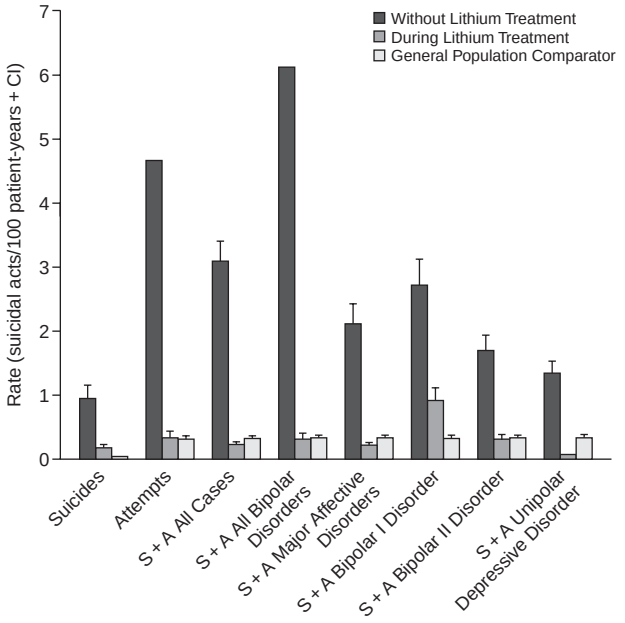
[a]Pooled estimates of rates are derived from data summarized in Table 1, with rate estimates and average treatment-exposure times weighted by the number of subjects per condition. 95% CIs are not strictly directly comparable since some studies involved patients under both conditions of treatment, and some patients may have made > 1 attempt in some studies. Differences in risks with versus without lithium were 20.7-fold for bipolar disorder patients and 11.0-fold in mixed affective disorder patients. These rate differences (risk ratios) within diagnostic group are highly statistically significant ($p < .0001$), but not between diagnostic groups. However, the untreated risk in bipolar disorder patients was significantly greater (by 3.31-fold) than among the mixed affective disorder patients ($p < .05$). Note that the number of studies and subjects with bipolar disorder diagnoses was much smaller than for combined mood disorders.
[b]Rates are suicide attempts before treatment and suicides or attempts during treatment, per 100 person-years of risk exposure (%/year).

Table 4. Rates of All Suicidal Acts With Versus Without Lithium Maintenance Treatment in Bipolar I, Bipolar II, or Unipolar Depressive Patients[a]

Outcome	Rates of Suicidal Acts: With Lithium	Rates of Suicidal Acts: Without Lithium	Percent Reduction
Bipolar I disorder			
No. of suicidal acts	10	50	
Subjects, N	263	263	
Exposure, mean, y	4.23	6.97	
Rate, %/y[b]	0.898	2.728	67.1
Bipolar II disorder			
No. of suicidal acts	2	25	
Subjects, N	153	153	
Exposure, mean, y	4.28	9.59	
Rate, %/y[b]	0.305	1.703	82.1
Recurrent major depression			
No. of suicidal acts	0	10	
Subjects, N	80	86	
Exposure, mean, y	5.72	8.72	
Rate, %/y[b]	0.000	1.333	100

[a]Data for bipolar disorder patients are based on experience in Sardinian patients before versus during maintenance treatment with lithium, based on methods reported previously.[11,51] Includes unipolar depressive Sardinian subjects (N = 53) plus data from Lepkifker et al.[28] for similar patients with (N = 35) and without (N = 33) lithium treatment. Note that the rates during treatment among both unipolar depressive and bipolar II (but not bipolar I) patients are below the general population estimate of 0.315%/year.
[b]Rates are suicide attempts before treatment and suicides or attempts during treatment, per 100 person-years of risk exposure (%/year).

Figure 1. Rates of Suicides (S) or Attempts (A) or Both (S + A) Without Lithium Maintenance Treatment, With Lithium Treatment, and Approximately Equivalent Rates for the International General Population[a]



[a]Estimated upper 95% CI based on findings summarized in Tables 2–4.

Reductions of risk were high in all subtypes, and ranked as follows: unipolar depression (100%) > bipolar II (82.1%, 5.57-fold) > bipolar I disorder (67.1%, 3.04-fold).

Comparison of Suicide Rates With and Without Lithium to General-Population Rates

International annual suicide rates among 24 developed nations were recently reported to average (± SD) 16.6 (± 7.5) per 100,000 population, or 0.0166 ± 0.0075 (95% CI = 0.0136 to 0.0196) %/year, with substantial variation among countries, regions, ethnic groups, ages, and the sexes.[52,53] The general population risk of suicide attempts varies with the level of lethality of means and apparent seriousness of intent, as well as variable reporting accuracy.[52] The attempt rate in the general population is about 10 to 20 times (median estimate, 18 times) greater than the suicide rate, or about 0.299 (95% CI = 0.245 to 0.353) %/year.[52] In contrast, the reported ratio of attempts to completed suicides averages only about 3:1 among persons with mood disorders,[52] and in the studies of lithium treatment considered here, the ratio of attempts to suicides (A/S) in major affective illnesses, untreated, was 4.89-fold (A/S = 4.65/0.951; Table 2). These lower ratios, averaging about 4:1 among affective disorder patients than in the general population, suggest greater lethality of attempts in major affective disorder patients. The total rate of all suicidal acts in the general population is approximately 0.315%/year (0.0166 for suicides + 0.299 for attempts).

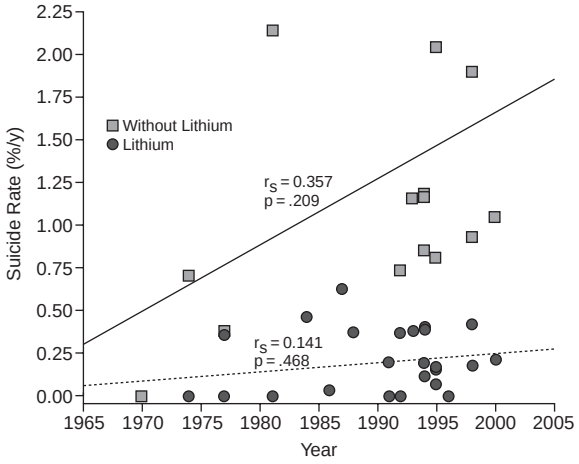
In comparison, the total pooled rate of all suicidal acts with lithium treatment (0.210%/year), remarkably, is 33.3% lower than the estimated general population risk of 0.315%/year (Table 2). For completed suicides, the overall rate during lithium treatment (0.174%/year) is much lower than the untreated risk of 0.942%/year, but still 10.5 times above the general population average of 0.0166%/year. The treated rate for suicide attempts of 0.312%/year, however, is very close to the estimated risk for the general population (0.299%/year; Table 2), again suggesting a relatively greater impact of lithium treatment on attempts than suicides.

Overall, these data indicate a substantial reduction in risk of suicides and attempts during treatment with lithium in a range of major affective disorders to overall levels (suicides + attempts) close to those in the general population (Tables 2–4). Relationships among untreated, treated, and population rates for suicide, attempts, and overall risks for specific subtypes of mood disorder patients are summarized in Figure 1.

Secular Trends in Suicide Rates and Effects of Lithium Treatment

In view of recent discussions of the consistency of therapeutic effects of lithium over the past half century of its use,[13,17] we considered whether reductions of suicidal risk have been sustained over the past several decades, based on comparisons of patients treated with lithium or not. We found that the percentage reduction of risk of all

Figure 2. Rates of Suicides/100 Person-Years (%/year) Among Patients With a Major Affective Disorder Versus Year Reported[a]



[a]Based on data summarized in Table 1, without lithium treatment (13 arms) and with lithium treatment (24 arms). There may be a tendency toward an increase in untreated suicide risk over time, but neither function indicates a significant secular trend: without lithium maintenance treatment, Spearman r_s = +0.357, p = .209; during lithium maintenance treatment, r_s = + 0.141, p = .468.

suicidal acts did not degrade across the years (Spearman nonparametric r_s = +0.007 for 25 contrasts, p = .974; not shown). Moreover, for completed suicides specifically, the rate during lithium treatment was consistently low across the decades since 1970 (Spearman r_s = +0.141; p = .468; Figure 2). However, an unexpected finding was an apparent, but nonsignificant, tendency toward rising rates of completed suicides across the years among major affective disorder patients not maintained on long-term lithium treatment (r_s = +0.357; p = .209). The last trend may reflect growing bias in recruitment to more recent studies of more severely ill patients, particularly at academic or specialized referral centers.[54]

DISCUSSION

Recapitulation of Major Findings

The present findings extend the large body of evidence supporting major reductions of risk of suicidal behavior in patients with recurrent major affective disorders of various types, based on data found in 34 studies published through mid-2002 (Table 1). Pooled reduction of risk of suicide attempts (93%) was somewhat greater than for suicides (82%; Table 2), but reduction of rates of suicidal acts was similar in both bipolar (95%) and mixed (91%) samples of major affective disorder patients (Table 3). Separate analysis of smaller subsamples of specific types of mood disorder patients suggested a rank-order of benefit, as follows: recurrent major depression (100%) ≥ bipolar II disorder (82%) ≥ bipolar I disorder (67%; Table 4).

A particularly striking finding is that overall risk of suicidal behavior (suicides + attempts) during lithium maintenance treatment (0.210%/year) is 33% lower than comparable estimated rates for the international general population (0.315%/year; Table 2).[52] This remarkable outcome of overall treated rates for suicides plus attempts at or below population estimates was found for a pool of all subjects (Table 2), for both bipolar and mixed major affective disorder patients (Table 3), and for bipolar II and recurrent unipolar depressive patients considered separately (Table 4). In contrast, the overall rate of suicidal acts among bipolar I patients treated with lithium was 2.75 times higher than that estimated for the general population (Table 4). If these comparisons to general population risks are valid, they may plausibly reflect the substantial risk of suicidal behavior in the general population associated with untreated affective illness.[3–5] Nevertheless, it is important to emphasize that risk of completed suicides, although markedly reduced with lithium treatment (from 0.942 to 0.174%/year), remained at least 10 times above population base rates averaging 0.0166%/year (Figure 1; Table 2). These findings suggest that lithium treatment–related benefits were greater with suicide attempts, and among patients with disorders with recurrent depression as the primary clinical problem (unipolar major depression and bipolar II disorder).

Another somewhat ominous finding was that, whereas suicide rates and the percentage reduction of suicidal risk remained stable from 1970 to 2002, rates of suicides among major affective disorder patients tended to rise somewhat in that period (Figure 2). It remains to be determined whether this secular trend represents a real change in the nature or epidemiology of major affective illness, including possible effects of comorbid substance abuse.[54] Another plausible explanation is that this trend, found in both treated and untreated cases, represents a sampling artifact involving a growing representation of complex and severe cases of major affective disorders encountered in specialized referral and research settings.[17,55] Similar case selection–related trends for long-term outcomes in schizophrenia through the same historical era have been noted previously.[56,57]

Compared with patients diagnosed with bipolar I disorder, there were somewhat superior lithium-related reductions of suicidal risk among bipolar II and unipolar mood-disordered patients whose illnesses primarily involved recurrent major depressive episodes and dysthymia (Table 4). Importantly, reduction of suicide risk evidently was not unique to bipolar I patients, who have been traditionally considered optimal candidates for long-term lithium therapy. The findings are also consistent with the impression that the depressive or mixed-agitated phases of bipolar disorder, as well as unipolar depression, are critical links to risk of suicide.[3,4,51,52] Moreover, they suggest that other treatments that are beneficial in unipolar or bi-

polar depression should also lead to reductions of suicidal risk and need to be studied further.

However, the available evidence for a suicide-protective effect of modern antidepressants in unipolar depression is very weak, although tricyclic antidepressants may have a moderate effect not yet proved for safer and easier-to-use modern antidepressants (references 2, 4, and 5 and R.J.B.; J.H.; K. W. Kwok, M.D.; et al., unpublished manuscript, 2003). Furthermore, evidence for a suicide-protective effect of putative mood-stabilizing agents other than lithium is extremely limited.[2,4,6] Reports from a long-term collaborative German study that involved randomization of bipolar and schizoaffective patients to 2 years of treatment with either lithium or carbamazepine found no suicidal acts in lithium-treated subjects, but substantial risk with the anticonvulsant,[47,58] possibly reflecting suspected clinical superiority of lithium in protecting against recurrences of acute affective episodes, and especially bipolar depression.[6,59] There are no reports of mortality risks with other proposed mood-stabilizing agents; and indeed, agents such as anticonvulsants and atypical antipsychotic drugs, although often effective in acute mania, are not proved to have long-term protective effects against suicidal acts or even recurrences of bipolar depression.[6,59]

Limitations and Critical Considerations

There are several notable limitations to the studies analyzed and reported here. They include potential lack of control over randomization and retention of subjects in some treatment trials, and inclusion of some patients with very high pretreatment suicide risk. Some studies finding a reduction of suicide risk during lithium treatment also might involve biased self-selection, since patients who remain in any form of maintenance treatment for many months may be more compliant than others who refuse treatment, and conceivably also less likely to become suicidal. However, it is not feasible to evaluate any long-term treatment in patients who do not accept or adhere to the treatment. Moreover, it is important to emphasize that several of the studies analyzed (e.g., references 12, 18, 19, 45, 47, 50; Table 1) involved either randomization to treatment options or assessment of the same persons with and without lithium treatment, and their results were consistent with the overall findings of marked reductions of suicidal risk during lithium treatment, as we have noted previously.[11–13]

In addition, several trials included potential effects of treatment discontinuation.[12,18,40,41,45,46,48,49] Stopping lithium therapy by clinicians or patients, especially abruptly or rapidly or at times of emerging affective illness, often in association with impaired judgment, can contribute to an excess of early recurrence of affective illness.[51,60–63] We found previously that lithium discontinuation was associated with sharply increased suicidal risk.[51,52] Risk of suicidal acts in those reports increased by 20-fold within 12 months after clinically determined discontinuation of lithium maintenance treatment (usually owing to sustained wellness and refusal to continue or to medically compelling adverse effects, taking care to exclude patients in emerging hypomania or depression).[51,52] Moreover, risk of suicidal behavior within the months after discontinuing lithium was twice as high among patients who discontinued lithium therapy abruptly within several days. At later times, the risk returned to levels virtually identical to those encountered before lithium treatment had been initiated, suggesting that treatment discontinuation itself contributed to the sharp increase of risk.[51,52] The increased suicidal risk in the year after lithium discontinuation was associated with greatly increased risk of affective morbidity including depression, which is probably a critical mediating factor for the increased risk of suicide and attempts shortly after discontinuing lithium maintenance treatment. Although such risks are obviously important to consider in planning for safe clinical management of potentially suicidal patients, excluding studies involving lithium discontinuation had a negligible impact on the reduction of suicide risk associated with treatment, and, specifically, was not associated with inflated risks in the untreated condition, as noted previously.[12]

These several methodological limitations may be partly mitigated by several indications of a high degree of consistency of the major findings. There was no evidence that the time at risk influenced the annualized computed suicide or attempt rates, in that Spearman nonparametric correlation of suicidal rates (as percentages, respectively, of the most recently reported rate for suicides or attempts to enable their pooling) versus study length was nonsignificant ($r_s = –0.051$, $p = .804$). In addition, lower or absent suicide risks during lithium treatment were found consistently among 13/13 studies in which treated and untreated conditions were directly compared (Table 1),* and 5 other trials found no suicidal acts during lithium treatment[19,22,33,34,37] (Table 1).

Possible Action Mechanisms of Lithium Against Suicide

If lithium is indeed effective in preventing suicide in patients with broadly defined, recurrent major affective syndromes, as it appears to be based on the evidence reviewed here, it seems likely that this effect operates through reduction of risk or severity of recurrences in depression or mixed dysphoric-agitated states.[3,51,52] Additional factors may be reduction of impulsivity or of aggressive and hostile behavior, possibly mediated through the central serotonergic neurotransmission system, which may be facilitated by lithium.[3,14,64,65] Inconsistent with this

*References 12, 18, 19, 21, 24–26, 28, 31, 37, 39, 40, and 47.

hypothesis are the lack of evidence that serotonin reuptake inhibitor antidepressants have a beneficial effect on suicidality (reference 5 and R.J.B.; J.H.; K. W. Kwok, M.D.; et al., unpublished manuscript, 2003) and evidence that the antiserotonergic agent clozapine may reduce suicide risk in schizophrenia.[15,16] An additional nonspecific, but potentially important, benefit may arise from supportive, long-term therapeutic relationships associated with typically structured and relatively closely medically monitored lithium maintenance treatment of patients with recurrent major mood disorders, as well as in the long-term use of clozapine for patients with schizophrenia.

CONCLUSIONS

The present evidence supports the conclusion that long-term maintenance treatment with lithium salts is associated with major reductions in risks of suicides and attempts, not only in bipolar I disorder, but possibly even more effectively in other forms of recurrent major affective illness (unipolar depressive and bipolar II disorders) that mainly involve depression. Lithium stands virtually alone as a treatment with substantial and consistent evidence of having such an apparent suicide-protection effect. For the future, given the widespread and growing empirical, long-term use of divalproex, lamotrigine, oxcarbazepine, topiramate, and other anticonvulsants to treat bipolar disorder, often instead of lithium, it is extremely important to include assessments of mortality risk and suicidal behavior in long-term studies of the effectiveness of these and other emerging alternatives to lithium. It is also important to clarify whether modern antidepressants reduce suicidal risk in recurrent unipolar major depressive illnesses, as well as being much safer in acute overdoses formerly commonly employed as a means of committing suicide.[3–5] Finally, the potential adjunctive role of lithium or other mood-stabilizing agents as a means of reducing risk of suicide in recurrent unipolar depression suggested by some of the findings presented requires additional study.

Drug names: carbamazepine (Tegretol, Epitol, and others), clozapine (Clozaril and others), divalproex sodium (Depakote), lamotrigine (Lamictal), oxcarbazepine (Trileptal), topiramate (Topamax).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, lamotrigine is not approved by the U.S. Food and Drug Administration for the treatment of bipolar depression; and lithium is not approved for the treatment of unipolar depression and bipolar II disorder.

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