Bipolar Disorders 2006: 8: 625–639

BIPOLAR DISORDERS

Review Article

Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review

Baldessarini RJ, Tondo L, Davis P, Pompili M, Goodwin FK, Hennen J. Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review.
Bipolar Disord 2006: 8: 625–639. © Blackwell Munksgaard, 2006

Objectives: To update and extend comparisons of rates of suicides and suicide attempts among patients with major affective disorders with versus without long-term lithium treatment.

Methods: Broad searching yielded 45 studies providing rates of suicidal acts during lithium treatment, including 34 also providing rates without lithium treatment. We scored study quality, tested between-study variance, and examined suicidal rates on versus off lithium by meta-analytic methods to determine risk ratios (RRs) and 95% confidence intervals (CI).

Results: In 31 studies suitable for meta-analysis, involving a total of 85,229 person-years of risk-exposure, the overall risk of suicides and attempts was five times less among lithium-treated subjects than among those not treated with lithium (RR = 4.91, 95% CI 3.82–6.31, $p < 0.0001$). Similar effects were found with other meta-analytic methods, as well as for completed versus attempted suicide, and for bipolar versus major mood disorder patients. Studies with higher quality ratings, including randomized, controlled trials, involved shorter exposures with somewhat lesser lithium superiority. Omitting one very large study or those involving lithium-discontinuation had little effect on the results. The incidence-ratio of attempts-to-suicides increased 2.5 times with lithium-treatment, indicating *reduced lethality* of suicidal acts. There was no indication of bias toward reporting positive findings, nor were outcomes significantly influenced by publication-year or study size.

Conclusions: Risks of completed and attempted suicide were consistently lower, by approximately 80%, during treatment of bipolar and other major affective disorder patients with lithium for an average of 18 months. These benefits were sustained in randomized as well as open clinical trials.

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Key words: bipolar disorder – lithium – major affective disorders – meta-analysis – suicide

Received 22 September 2005, revised and accepted for publication 13 March 2006

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Long-term lithium treatment has been associated with reduced risk of suicide and suicide attempts in patients with bipolar disorder (BPD) or other major affective disorders (1–8). In a previous meta-analysis that included only 22 studies reporting on completed suicides, we found an 82%

RJB consults or engages in collaborative research with companies that produce medicines used to treat major psychiatric disorders (Eli Lilly & Co., IFI SpA, Janssen, JDS, Novartis). LT has served as a consultant to IFI SpA. MP has received research support from Eli Lilly & Co. JH had received grant or contract support from Eli Lilly & Co., JDS and Novartis. PD and JH received contract support from JDS Pharmaceuticals, a manufacturer of lithium products that helped in the preparation of an FDA petition on this topic. FKG has no reported conflict of interest. No author holds any equity positions in pharmaceutical corporations.

lower rate with than without long-term lithium treatment (2). Recently, Cipriani et al. (9) reported a meta-analysis of the few available randomized controlled trials (RCTs), in which they found a four- to five-fold superiority for lithium treatment versus alternatives (placebo, anticonvulsants or antidepressants) with regard to risk of suicide, suicide plus self-harm, or overall mortality. We now report on findings that include both open-label and RCT studies published since our 2001 meta-analysis (3). These expanded analyses consider the effects of lithium treatment: (i) on attempted versus completed suicide; (ii) among BPD versus major affective disorder patients; (iii) in open clinical studies versus RCTs, and (iv) in studies with higher versus lower quality ratings. We also introduce the concept of a 'lethality index' of suicidal behavior, based on the ratio of attempts/suicides.

Methods

Study identification, quality rating, and selection, data analysis and other methods have been detailed in earlier reports on this topic (3, 4). All published studies pertaining to lithium treatment and including information on suicidal behaviors (attempted and completed suicides) were sought. We started from studies considered in our earlier meta-analysis (3) and other reviews (1–10), with extensive updating by open-ended computerized literature searching (MEDLINE–PubMed databases, using lithium, suicide and suicide attempts as search terms) for papers published up to the end of August 2005, and cross-referencing from publications on the topic of lithium treatment. To obtain as complete a survey as possible on the topic of suicide, we considered blind or open, controlled or uncontrolled, and randomized or non-randomized studies. Screening for inclusion in the meta-analysis required data supporting estimates of rates of completed suicides or suicide attempts as defined in each report, as well as persons-at-risk, among patients diagnosed with BPD or other major affective or schizoaffective disorders, treated with lithium for any duration, with or without other treatments, even if these were not specified. Data for inclusion had to be judged to be reliable and non-duplicative (potential multiple publications were verified directly with authors when this was not clear). Exposure times were averages based on reported data for each study treatment arm. When precise months of treatment were not provided, we made conservative estimates based on the information reported.

We rated study quality (3, 4) as: (i) the presence of subjects observed both with and without lithium treatment (1 point); (ii) randomized treatment-assignment and blind clinical assessments (1 or 2 points); (iii) $n \geq 100$ subjects/treatment group (1 or 2 points); and (iv) duration ≥1 year/treatment group (1 or 2 points). Quality ratings are reported as percentage of the maximum score of 7.0.

We tabulated rates of suicidal acts/100 patient-years ('%/year') during maintenance treatment with lithium and compared them with rates in study arms involving alternative treatment conditions. The initial analysis evaluated crude pooled incidence rates of completed suicides (S) and attempts (A), as well as the ratio (A/S) of rates of attempts per completed suicides as a proposed index of *lethality* of suicidal acts; its 95% confidence interval (CI) was estimated by jack-knifing methods.

After studies with only zero rates of suicidal acts in both treatment conditions (with and without lithium) had been excluded as non-informative, studies involving treatment arms with versus without lithium treatment were subjected to quantitative meta-analysis (3, 9, 11). Our primary meta-analytic model is based on the *metan* routine in STATA software. For studies having one study arm with no suicidal acts (usually the lithium-treatment arm), this method employs an arbitrary (12) continuity-adjustment by adding 0.5 to *both* treatment study-arm numerators (suicides or attempts), which should limit the potential risks of exaggerating the antisuicidal effects of lithium based on zero incidence. In addition, we applied alternative meta-analytic models that lack continuity correction, including the Peto method to estimate pooled Odds Ratios (OR), and the Mantel–Haenszel model to estimate pooled Risk Differences (RD).

We calculated risk ratios (RRs) and their standard errors (SEs) for suicidal rates (%/year) for each of the 31 studies (reported in 33 non-overlapping publications cited below) included in meta-analyses, based on techniques recommended by DerSimonian and Laird (11). Preliminary examination of interstudy heterogeneity in the 31 RR estimates, based on χ^2 [Q-statistic (11)] methods [degrees of freedom (df) = (study number − 1)], indicated non-ignorable overall variability ($Q >$ 90th percentile of the χ^2 distribution). Given such heterogeneity, to account for interstudy variation and to limit the risk of overestimating pooled RRs, we employed random-effects meta-analysis methods to compute pooled RR estimates and their 95% CIs, based on study-specific RRs and their SEs (11). Depending on available data, we obtained pooled RRs and their 95% CI

estimates for suicides, attempts, and the composite of suicides and attempts. In these procedures, we weighted each study arm-specific suicidal rate by the inverse of study variance to obtain pooled RRs and their variance (SEs and CIs), and summarized the computed RRs, CIs and weights in forest plots (11). We tested the hypothesis (with asymptotic normal *z*-test) that the overall RR contrasting suicidal rates with versus without lithium treatment was the null value (RR = 1.0).

In order to compare studies falling into major subgroups, notably: (i) studies of BPD patients versus a mix of manic-depressive types; (ii) reports on suicides versus attempts versus both, and (iii) studies with above- versus below-median quality scores (Table 1), we employed a *stratified* random-effects modeling method for meta-analysis (13), and heterogeneity between subgroups was examined with χ^2 (df = 1) methods. Since all of the RCTs identified consistently included zero suicidal events in their lithium arms, they were analyzed separately by use of contingency tables to obtain a Fisher's exact probability value and an estimated probability for incidence rates, as well as being subjected to meta-analysis.

We examined the potential influence of certain large and atypically heterogeneous studies on pooled RRs by serially including and excluding such studies (influence or sensitivity analysis). We also assessed potential publication bias with funnel-graph (11, 14, 15) methods [plotting study-specific $\log_{10}$-RR estimates (x) against their $\log_{10}$-SEs (y), derived from fixed-effect meta-analysis, with estimated 95% confidence limits]. We interpreted the results both visually and by use of Begg's test (14), as well as Egger's test of bias in meta-analysis based on funnel-plot asymmetry (15). We also examined results for effects of selected covariates, using meta-regression methods (11).

Statistical analyses used commercial microcomputer programs (STATA®, Stata Corporation, College Station, TX, USA; STATVIEW-5®, SAS Institute, Cary, NC, USA). Comparisons with two-tailed $p > 0.05$ at stated df were considered not significant (NS).

Results

Studies identified

We identified 45 studies with data on suicidal behavior (attempted or completed suicide) in mood disorder patients treated with lithium (Table 1) (1, 2, 16–60). These studies comprised a total exposure of 114,736 person-years (mean exposure time of 1.52 years), based on only non-redundant data in studies that considered subjects exposed or not exposed to lithium treatment.

Crude rates of suicides and attempts

Overall, across all 45 reports analyzed, crude pooled rates per 100 person-years (%/year) of suicidal acts were 0.436%/year with lithium versus 2.63%/year without lithium treatment, indicating a six-fold reduction of risk of suicidal acts during treatment with lithium (Table 1).

Meta-analysis: all suicide acts

Of the 45 studies identified (Table 1), 31 (including 5 RCTs), presented in 33 reports, provided one or both non-zero suicidal rates with versus without lithium treatment and were therefore suitable for meta-analysis (2, 18, 20, 21, 23, 24, 26, 28, 31, 35–38, 40, 42–60). These studies included a total of 33,340 subjects and 85,229 person-years of exposure (averaging 2.08 years). Of note, in all 31 studies, suicidal risk was consistently lower in the lithium versus the non-lithium treatment arms (Fig. 1). Crude pooled risks with versus without lithium were 0.563%/year versus 2.64%/year, indicating a 4.7-fold risk ratio favoring lithium (Table 1).

Quantitative meta-analysis for all 31 two-armed studies was based on random-effects modeling indicated by a statistically significant preliminary Q-test of heterogeneity [Q (df = 30) = 44.4, p = 0.044]. This method of pooling across the 31 studies yielded a highly statistically significant, 4.91-fold [95% CI 3.82–6.31; $z = 12.5$ (df = 30); $p < 0.0001$] lower risk of suicidal acts during long-term treatment with versus without lithium, or an 80% sparing of risk (Fig. 1, Table 2). This conclusion was further supported by methods that do not require continuity corrections for zero numerators, including both the Peto fixed-effect OR method (OR = 4.42; 95% CI 2.79–5.15; $z = 19.0$; $p < 0.0001$) and the Mantel–Haenszel Risk Difference method (RD = 0.043; 95% CI 0.038–0.048; $z = 17.9$; $p < 0.0001$).

Meta-analysis: completed versus attempted suicide

The pooled, estimated RR for *completed suicides* in 24 studies with at least one non-zero numerator (2, 18, 20, 23, 31, 35–38, 40, 42–53, 56, 57, 59, 60; items 'S', Table 1) was 4.86 (95% CI 3.36–7.02; Fig. 2, Table 2), or virtually identical to the pooled estimate of RR (4.91) for all suicidal acts. A similar and highly significant effect of lithium on *suicide*

Table 1. Summary of reports on lithium and suicidal behavior (all studies)

Study, year	Quality score	Other Rx	Trial design	Diagnosis	Suicidal type	With lithium		Without lithium	
						Acts/n/year	Rate (%/year)	Acts/n/year	Rate (%/year)
Baastrup 1970 (16)	57.1	Pbo	RCT	MAD	S + A	0/84/0.42	0.000	0/39/0.42	0.000
Coppen et al. 1971 (17)	57.1	Pbo	RCT	MAD	S + A	0/28/2.00	0.000	0/37/2.00	0.000
Prien et al. 1974 (18)[a]	100.0	Pbo or IMI	RCT	MAD	S	0/146/2.00	0.000	2/181/2.00	0.552
Bech et al. 1976 (19)	14.3	Clinical	Open	BPD	S	1/40/7.00	0.357	–	–
Kay & Petterson 1977 (20)[a]	57.1	No-Li	Open	MAD	S	0/123/4.56	0.000	3/69/22.3	0.195
Poole et al. 1978 (21)[a]	28.6	Pre-Li	Open	MAD	A	7/99/5.00	1.414	21/99/5.00	4.24
Glen et al. 1979 (22)	28.6	Clinical	Open	MAD	S	8/784/4.83	0.211	–	–
Ahlfors et al. 1981 (23)[a]	57.1	APD	Open	MAD	S	0/14/1.33	0.000	3/112/1.18	2.27
Venkoba-Rao et al. 1982 (24)[a]	28.6	Off-Li	Open	MAD	A	0/47/8.50	0.000	2/47/8.50	0.501
Glen et al. 1984 (25)	57.1	Pbo or AMI	RCT	MAD	S + A	0/12/3.00	0.000	0/9/3.00	0.000
Hanus & Zapletálek 1984 (26)[a]	14.3	Pre-Li	Open	MAD	A	4/95/5.10	0.826	25/95/5.10	5.16
Norton & Whalley 1984 (27)	28.6	Clinical	Open	MAD	S	8/791/2.17	0.466	–	–
Lepkifker et al. 1985 (28)[a]	14.3	Pre-Li	Open	MDD	A	0/33/8.30	0.000	7/33/8.30	2.56
Jamison 1986 (1)	28.6	Clinical	Open	MAD	S	4/9000/1.00[b]	0.044	–	–
Page et al. 1987 (29)	14.3	Clinical	Open	BPD	S	6/79/12.1	0.628	–	–
Wehr et al. 1988 (30)	14.3	Clinical	Open	BPD	S	2/70/7.55	0.378	–	–
Nilsson & Axelsson 1990 (31)[a]	28.6	Off-Li	Open	MAD	S + A	10/39/7.00	3.66	5/18/2.60	10.7
					S	0/39/7.00	0.000	2/18/2.60	4.27
					A	10/39/7.00	3.66	3/18/2.60	6.41
Coppen et al. 1991 (32)	28.6	Clinical	Open	MAD	S + A	0/103/11.0	0.000	–	–
O'Connell et al. 1991 (33)	28.6	Clinical	Open	BPD	S	4/248/8.00	0.202	–	–
Vestergaard & Aagard 1991 (34)	14.3	Clinical	Open	MAD	S	5/50/5.00	2.00	–	–
Modestin & Schwarzenbach 1992 (35)[a]	57.1	No-Li	Open	Mixed Dxs	S	0/7/1.00	0.000	21/121/1.00	17.4
Müller-Oerlinghausen et al. 1992 (2)[a]	14.3	Off-Li	Open	MAD	S + A	6/68/8.00	1.10	11/68/1.29	12.5
					S	2/68/8.00	0.368	4/68/1.29	4.56
					A	4/68/8.00	0.735	7/68/1.29	7.98
Rihmer et al. 1993 (36)[a]	28.6	Pre-Li	Open	BPD	S + A	2/36/7.20	0.772	25/36/7.60	9.14
					S	1/36/7.20	0.386	2/36/7.60	0.731
					A	1/36/7.20	0.386	23/36/7.60	8.41
Felber & Kyber 1994 (37)[a]	42.2	No-Li	Open	MAD	S + A	7/71/6.98	1.43	64/71/7.20	12.5
					S	1/71/6.98	0.202	3/71/7.20	0.587
					A	6/71/6.98	1.21	61/71/7.20	11.9
Lenz et al. 1994 (38)[a]	71.4	Off-Li	Open	MAD	S	9/695/6.66	0.194	23/430/6.25	0.856
Müller-Oerlinghausen 1994 (39)	28.6	Clinical	Open	MAD	S	7/394/14.2	0.125	–	–
Sharma & Markar 1994 (40)[a]	42.9	No-Li	Open	BPD	S	2/57/8.50	0.413	6/57/9.00	1.17
Ahrens et al. 1995 (41)	28.6	Clinical	Open	BPD + SzA	S	7/611/6.60	0.174	–	–
Koukopoulos et al. 1995 (42)[a]	57.1	Off-Li	Open	BPD	S	4/343/12.2	0.096	6/110/2.75	1.98
Nilsson 1995 (43)[a]	71.4	Off-Li	Open	MAD	S	6/230/14.2	0.184	9/132/8.40	0.812
Greil et al. 1996, 1997 (44–46)[a]	80.9	CBZ or ADD	RCT	MAD	S + A	0/157/2.50	0.000	7/158/2.50	1.772
					S	0/157/2.50	0.000	2/158/2.50	0.506
					A	0/157/2.50	0.000	5/158/2.50	1.266

Table 1. Continued

Study, year	Quality score	Other Rx	Trial design	Diagnosis	Suicidal type	With lithium		Without lithium	
						Acts/n/year	Rate (%/year)	Acts/n/year	Rate (%/year)
Bocchetta et al. 1998 (47)[a]	42.9	Pre + Off-Li	Open	BPD + SzA	S + A	12/100/9.48	1.27	81/100/14.6	5.55
					S	1/100/9.48	0.105	9/100/3.62	2.49
					A	11/100/9.48	1.16	72/100/14.6	4.93
Coppen & Farmer 1998 (48)[a]	71.4	No-Li	Open	MAD	S	1/103/5.25	0.185	1/12/9.00	0.926
Tondo et al. 1998 (49)[a]	71.4	Pre + Off-Li	Open	BPD	S + A	7/310/6.36	0.355	83/310/10.5	2.55
					S	2/310/6.36	0.101	6/185/3.70	0.877
					A	5/310/6.36	0.254	77/310/10.5	2.37
Bauer et al. 2000 (50)[a]	42.9	Pbo	RCT	MDD	S	0/14/0.33	0.000	1/15/0.33	20.2
Brodersen et al. 2000 (51)[a]	42.9	Less-Li	Open	MAD	S	2/77/2.00	1.30	6/48/2.00	6.25
Kallner et al. 2000 (52)[a]	57.1	Off-Li	Open	BP I	S	11/405/10.1	0.269	7/106/8.26	0.800
Coryell et al. 2001 (53)[a]	42.9	No-Li	Open	MAD	S	6/14/4.67	9.177	8/16/3.80	13.2
Rucci et al. 2002 (54)[a]	71.4	No-Li	Open	BP I	A	1/119/2.00	0.420	67/166/13.1	3.08
Bowden et al. 2003 (55)[a]	71.4	Pbo or LTG	RCT	BP I	A	0/46/0.82	0.000	1/127/0.82	0.960
Calabrese et al. 2003 (56)[a]	100.0	Pbo or LTG	RCT	BP I	S + A	0/120/0.24	0.000	2/290/0.24	2.87
					S	0/120/0.24	0.000	1/290/0.24	1.44
					A	0/120/0.24	0.000	1/290/0.24	1.44
Goodwin et al. 2003 (57)[a]	85.7	VPA	Open	BPD	S + A	217/29,617/1.00	0.733	95/4,453/1.00	2.13
					S	9/13,597/1.00	0.066	3/2,040/1.00	0.147
					A	208/16,020/1.00	1.30	92/2,413/1.00	3.81
Yerevanian et al. 2003 (58)[a]	71.4	No-Li	Open	BPD	A	5/140/14.6	0.245	6/140/5.61	0.764
Angst et al. 2005 (59)[a]	42.9	No-Li	Open	BPD	S	5/76/34.5	0.191	66/84/30.0	2.62
Gonzalez-Pinto et al. 2006 (60)[a]	42.9	Less-Li	Open	BP I	S + A	12/56/9.74	2.20	17/16/9.16	11.6
					S	0/56/9.74	0.000	1/16/9.16	0.682
					A	12/56/9.74	2.20	16/16/9.16	10.9

The total of 45 reports with data concerning suicidal acts (completed or attempted suicide) include 114,736 person-years of exposure, and overall crude risks for suicidal acts with versus without lithium of 388/45,634/1.95 years (0.436%/year) versus 675/7,688/3.34 years (2.63%/year), yielding a crude risk ratio of 6.03.

Among the 33 studies involving treatment with and without lithium, 31 had a non-zero risk in at least one treatment condition, and so were suitable for meta-analyses; they included 85,229 person-years of exposure, with crude risks for suicidal acts with versus without lithium of 336/33,340/1.79 years (0.563%/year) versus 675/7,603/3.36 years (2.64%/year), for a crude risk ratio of 4.69.

Study quality (scored as stated in Methods) is percentage of maximum (7.0). Rates for suicides (S) and attempts (A) are shown separately only if total (S + A) rate is >0.

A = suicide attempts; ADD = antidepressant drugs; AMI = amitriptyline; APD = antipsychotic drug; BPD = bipolar disorder; CBZ = carbamazepine; Clinical = unstated, clinically-based treatments; Dxs = diagnoses; IMI = imipramine; Less-Li = poorly adherent to lithium treatment; Li = lithium salt; LTG = lamotrigine; MAD = major affective disorders; MDD = major depressive disorder; Pbo = placebo; Pre/Off = before starting and after stopping lithium; RCT = randomized controlled trial; Rx = treatment; S = completed suicides; SzA = schizoaffective disorder; VPA = valproate.

[a]Reports (n = 31) included in meta-analyses.

[b]Exposure time is undefined and a *minimal* value is indicated, although treatment typically continued for several years.

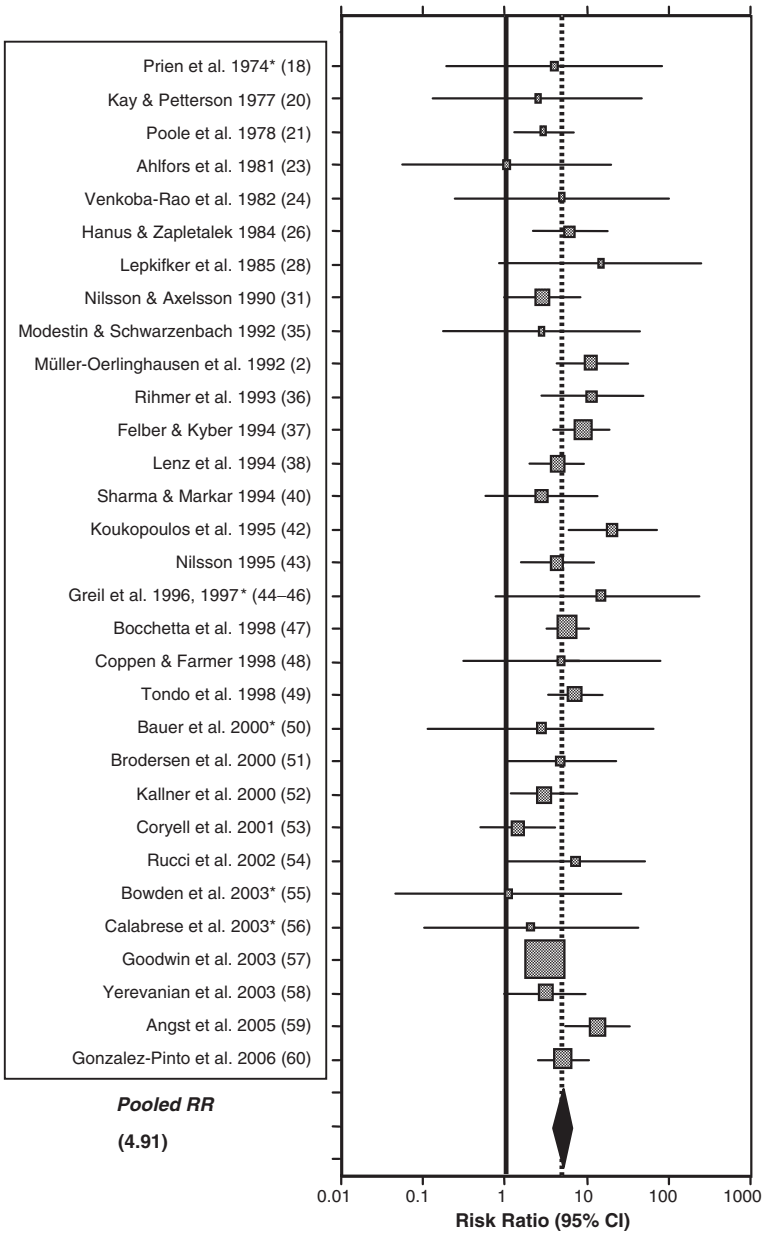

Fig. 1. Forest plot Risk Ratios (RR) as shaded squares proportional to study weight and their 95% confidence intervals (CI) based on random-effects meta-analysis of suicidal risk [rates of suicides and/or attempts per 100 person-years ('%/year')] in 31 studies, with two arms (with and without lithium treatment) and non-zero suicidal risk in at least one arm (see Table 1) (2, 18, 20, 21, 23, 24, 26, 28, 31, 35–38, 40, 42–60). The computed pooled risk ratio (RR) (black diamond) = 4.91 (95% CI 3.82–6.31, $z = 12.5$, $p < 0.0001$). *Randomized, controlled trials.

attempts was also detected (RR = 4.98, 95% CI 3.56–6.96; Fig. 3, Table 2) on the basis of 17 studies (2, 21, 24, 26, 28, 31, 36, 37, 44–47, 49, 54–57, 60; items 'A', Table 1). In these analyses, random-effects modeling was used to avoid overestimating the effect of lithium, although preliminary Q-tests indicated limited heterogeneity of findings across studies (for completed suicides: Q [df = 22] = 26.5, p = 0.23; for attempts: Q [df = 16] = 26.2, p = 0.051).

Subgroup comparisons

The apparent reduction of overall suicidal risk during long-term treatment with lithium was only slightly greater in 14 studies of patients diagnosed with BPD (RR = 5.34, 95% CI 3.59–7.93) than in 17 studies including a mix of patients with major affective or schizoaffective disorders (RR = 4.66, 95% CI 3.43–6.33; p = 0.34 for the comparison; Table 2). Studies with quality ratings of ≥50%

Table 2. Summary of meta-analyses: lithium treatment versus suicidal risk

Conditions[a]	Studies (n)	Risk Ratio		z	p
		RR	95% CI		
All two-armed studies[b]	31	4.91	3.82–6.31	12.5	<0.0001
Omitting Goodwin et al. 2003 (57)[b]	30	5.34	4.27–6.68	14.7	<0.0001
Open clinical studies	26	3.41	2.61–4.46	8.98	<0.0001
Randomized, controlled trials	5	1.76	1.65–1.88	3.51	0.001
Suicides only	24	4.86	3.36–7.02	8.42	<0.0001
Attempts only	17	4.98	3.56–6.96	9.42	<0.0001
Bipolar disorder[c]	14	5.34	3.59–7.93	8.28	<0.0001
Major affective disorders[c]	17	4.66	3.43–6.33	9.82	<0.0001
Quality score ≥50%[d]	16	3.92	2.94–5.23	9.33	<0.0001
Quality score <50%[d]	15	5.56	3.98–7.76	10.1	<0.0001

[a]Analyses are based on random-effects modeling; p is based on testing against the null RR = 1.0. Note that, within each comparison, the overlapping CIs indicate close similarity of RR values.
[b]Results with Goodwin et al. 2003 (57) omitted indicate that this very large study did not exert a misleading influence on the overall findings.
[c]For studies with bipolar disorder versus major affective disorder patient samples: χ^2 (df = 1) = 0.91, p = 0.34; cases of bipolar I and II disorders and some schizoaffective disorders, in various combinations, are included.
[d]For studies with quality ratings (Table 1) at or above versus below the median: χ^2 (df = 1) = 8.39, p = 0.004.

versus < 50% yielded significantly more conservative results than those with lower quality scores (RR = 3.92 versus 5.56; p = 0.004). It may also be important that *exposure times* in studies rated as higher quality (including RCTs) were 5.5 times shorter than in open-label clinical studies (1.41 ± 1.09 years versus 7.77 ± 6.54 years), with no difference in exposure time for with versus without lithium (not shown). Studies with specified *alternative treatments* to lithium yielded somewhat lower rates of suicides and attempts (2.16%/year) than those without specified alternatives (2.79%/year), but also involved 7.2 times shorter average exposure times (1.16 years versus 8.41 years). An influence or sensitivity analysis involving the omission of an unusually large health care database study (57) yielded an even higher RR of 5.34 (95% CI 4.27–6.68; Table 2), as did the removal of other individual studies (not shown).

We tested for potential differences in suicidal risks without lithium among studies involving risks *before* lithium treatment (n = 14) versus those involving its *discontinuation* (n = 5), including two studies that included both types of data (47, 49) to address the possibility that rates after stopping lithium might be inflated by the effects of treatment discontinuation (49, 61). Since only suicide attempts could be compared before versus after treatment, we compared attempt rates *before* versus *after discontinuing* lithium. The respective incidence rates were 3.14%/year *before* versus 3.75%/year *after stopping* lithium (incidence RR = 1.19, 95% CI 0.86–1.63). These observations provide only limited support for higher risks expected within the initial months following lithium discontinuation (49, 61), possibly owing to the relatively long exposure times involved, which averaged 2–3 years (Table 1). Moreover, studies involving lithium discontinuation represented only 11% of the total number of studies (5/45), and the resulting RRs versus during lithium treatment were very similar (4.98 for before versus during lithium treatment and 5.17 for after discontinuing versus during treatment).

Finally, we compared suicidal risks in non-lithium study arms involving other defined drugs or placebo; n = 9) versus undefined alternative treatments (n = 22). The incidence for attempts plus suicides was only slightly lower under defined treatment conditions (2.16%/year) than in undefined treatment conditions (2.79%/year). However, as already noted, the former trials were also much shorter in duration, which tended to limit opportunities to observe suicidal behavior.

Randomized controlled trials

We found 10 reports involving 8 RCTs providing direct contrasts pertaining to suicide or suicide attempts (16–18, 25, 44–46, 50, 55, 56; Table 3). Among these eight trials, three provided no risk-contrasts because they had no suicidal outcomes in either the lithium or the comparator arm (16, 17, 25). The other five studies also reported no suicidal acts in any lithium arm, but ≥ 1 act (total of 13) without lithium (Table 3). Given the small number of studies and the lack of events during lithium treatment, we used a simple contingency table

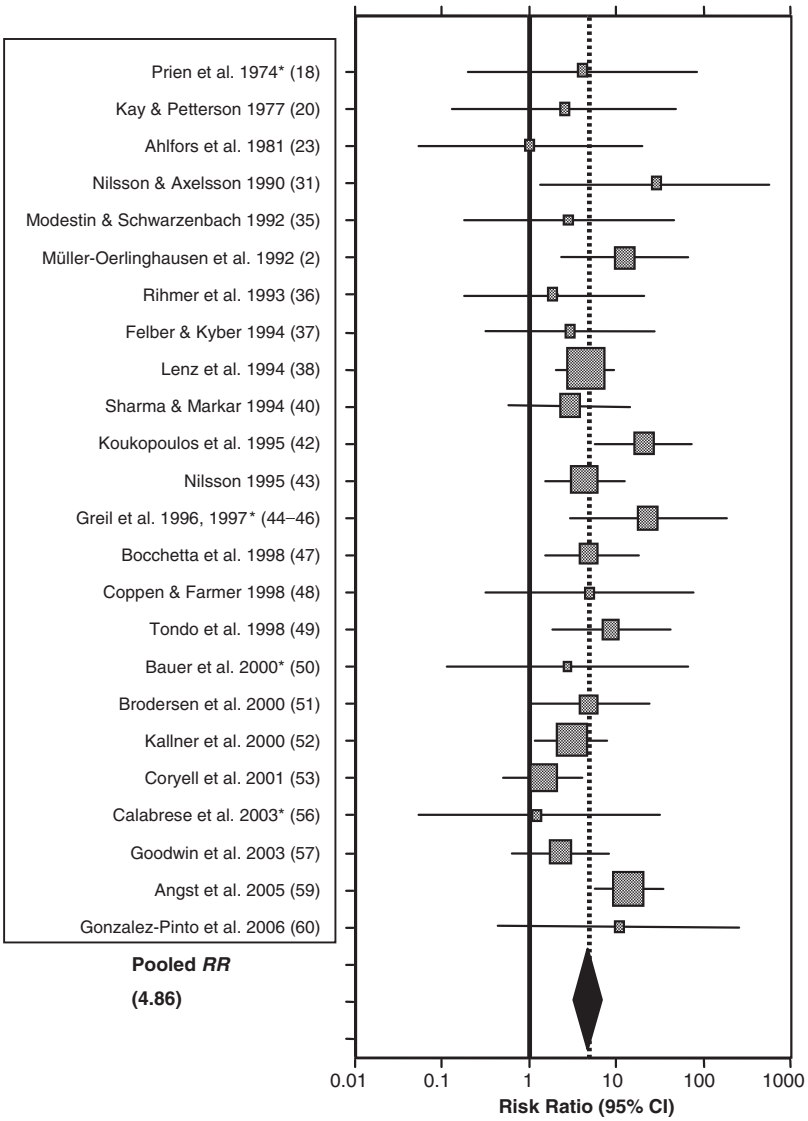

Fig. 2. Forest plot constructed as for Fig. 1, showing results of random-effects meta-analysis of 24 studies of risks of *suicides*, with versus without lithium (see Table 1) (2, 18, 20, 23, 31, 35–38, 40, 42–53, 56, 57, 59, 60). The computed pooled risk ratio (RR) (black diamond) = 4.86 (95% CI 3.36–7.02, $z = 8.42$, $p < 0.0001$).
*Randomized, controlled trials.

analysis to assess relative lithium versus comparator suicide risk in these five studies, in addition to applying meta-analysis (Table 3). Given matched exposure times, we compared aggregate risks with lithium [0/463 (0.00%)] versus with other treatments (anticonvulsants, antidepressants or placebo; 13/771 (1.69%); Fisher's exact-p = 0.003; Table 3). Comparison of pooled incidence rates (with weighted-average exposure times) also yielded a significantly lower rate with lithium (0%/year versus 1.39%/year estimated exact-p = 0.005). The superiority of lithium treatment was further supported by meta-analysis (Tables 2 and 3).

Attempt/suicide ratio (lethality)

We calculated incidence rates across all studies providing risk data (acts/subjects/time) for suicides (24 studies) and attempts separately (17 studies), among the 31 reports involving paired treatment conditions for with versus without lithium used in the preceding meta-analyses (Table 1). For suicide attempts, the respective crude rates for with versus without lithium treatment were 1.08%/year versus 3.63%/year, representing a 3.4-fold difference; for completed suicides, the corresponding rates were 0.155%/year versus 1.30%/year, representing a larger, 8.4-fold difference; both treatment-related

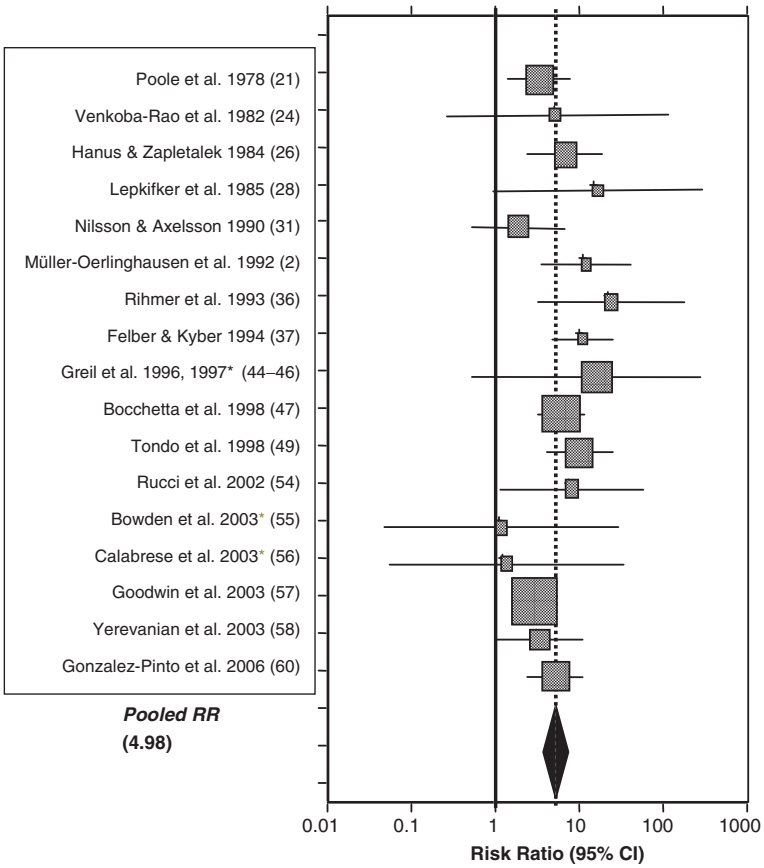

Fig. 3. Forest plot constructed as for Fig. 1, showing results of random-effects meta-analysis of 17 studies of risks of suicide *attempts*, with versus without lithium (see Table 1) (2, 21, 24, 26, 28, 31, 36, 37, 44–47, 49, 54–58, 60). Risk ratio (RR) with 95% CI for each study (shaded squares proportional to study weight). The computed pooled RR (black diamond) = 4.98 (95% CI 3.57–6.40, $z = 9.42$, $p < 0.0001$).
*Randomized, controlled trials.

Table 3. Risk of suicide or attempts in randomized, controlled trials of lithium

Studies	Lithium	Other treatments
Prien et al. 1974 (18)	0/146/2.0	2/181/2.0[a]
Greil et al. 1996, 1997 (44–46)	0/157/2.5	7/158/2.5[b]
Bauer et al. 2000 (50)	0/14/0.33	1/15/0.33[c]
Bowden et al. 2003 (55)	0/26/0.82	1/127/0.82[d]
Calabrese et al. 2003 (56)	0/120/0.24	2/290/0.24[d]
Totals	**0/463/1.60**[e]	**13/771/1.21**[e]
Incidence rate (%/year)	0	1.39
Exact-p	0.005	

Data are from five RCTs, each with at least one arm with a non-zero risk of suicides or attempts; there were no suicidal acts during lithium treatment versus 13 with other treatments.
[a]Placebo or imipramine as other treatment.
[b]Carbamazepine or antidepressants as other treatment.
[c]Placebo as other treatment.
[d]Placebo or lamotrigine as other treatment.
[e]Exposure time is an N-weighted average.
Statistical testing shown is for incidence rate ratio with exact-p. In addition, random-effects meta-analysis yielded RR = 1.62 (95% CI: 1.23–2.13, $z = 3.51$, $p < 0.001$).

differences strongly favored lithium (Table 4). In addition, the ratio of attempts to completed suicides (A/S) was 2.5-fold *higher* during lithium treatment (6.94%/year versus 2.79%/year; Table 4), supporting the potential utility of this ratio as an *index of lethality* of suicidal behavior. With lithium treatment, there were fewer deaths per suicide attempt, indicating *decreased* lethality as an evident additional therapeutic benefit of lithium treatment.

The finding that the attempts/suicides ratio was *greater* during lithium treatment was sustained when only the 10 studies with data for all four cells of interest (suicides and attempts, with and without lithium) and non-zero numerators in at least one of each pair of treatment arms were considered in order to avoid biasing that might arise by including data from studies without all four cells (2, 31, 36, 37, 44–47, 49, 56, 57, 60). For suicide attempts (A), these 10 studies yielded a pooled crude incidence of 1.19%/year (257 acts/16,977 subjects/1.27 years) with lithium versus 3.88%/year (336 acts/3,480

Table 4. Relationships of attempts and suicides

Measures	Attempts (A)	Suicides (S)	A/S ratio
Without lithium			
Studies	17	24	
Proportions	486/4,187/3.20	195/4,475/3.36	
Rate (%/year) (95% CI)	3.63	1.30	2.79 (2.36–3.32)
With lithium			
Studies	17	24	
Proportions	274/17,556/1.45	62/16,858/2.37	
Rate (%/year) (95% CI)	1.08	0.155	6.94 (5.25–9.29)
Relative risk (95% CI)	3.37 (2.90–3.92)	8.35 (6.25–11.3)	2.49

The 'proportions' are acts/subjects/mean exposure times (weighted by subject numbers), and corresponding crude rates (acts/100 person-years, or '%/year') are based on all available data from Table 1 pertaining to attempted (A) and completed suicides (S) considered separately (*excluding* data pertaining to combined A + S), for 31 studies included in the preceding meta-analyses. The A/S ratio is nearly 2.5 times *higher* with lithium treatment, suggesting *decreased* lethality of suicidal acts, as reflected in the greater relative reduction of risk for suicides than attempts.

subjects/2.49 years) without lithium treatment, and for completed suicides (S), rates of 0.084%/year (16 acts/14,554 subjects/1.31 years) with lithium versus 0.714%/year (33 acts/2,982 subjects/1.55 years) without it. The corresponding A/S ratios for with versus without lithium were 14.2%/year (1.19/0.084) versus 5.43%/year (3.88/0.714), or 2.6 times greater with lithium. Among patients with BPD from six studies (36, 47, 49, 56, 57, 60), analyzed separately, the A/S ratio was 2.9 times higher with lithium treatment (1.20/0.075%/year = 16.0) versus without it (3.41/0.616%/year = 5.54).

Random-effects meta-regression modeling methods, with adjustment for clustering on study, were used to test for an interaction of treatment type by attempted versus completed suicides in the same 10 studies selected as having non-zero data in at least one of each pair of cells of interest. In this modeling, there was a significant lithium-by-type-of-suicidal-act interaction effect ($z = 2.73$, $p = 0.006$), indicating that the effect of lithium was disproportionately strong for suicides compared with non-fatal suicide attempts. Together, these findings are consistent with the proposal that the *lethality* of suicidal acts as well as their frequency may be reduced by treatment with lithium.

Meta-regression analyses

We examined several trial-specific factors that might tend to confound the reported outcomes, using meta-regression modeling. Factors considered were: (i) year of publication; (ii) BPD versus any other diagnostic category; (iii) number of subjects/study; (iv) assessment of suicides-plus-attempts versus suicides or attempts separately; (v) higher versus lower quality ratings; and (vi) RCT versus open-label clinical study design.

None of these factors alone, or combined, except the last contrast (see Table 2), was even marginally correlated with the contrast in outcomes for with versus without lithium treatment, indicating that the effect of lithium on suicidal risk was very robust.

Assessment of publication bias

Publication bias was not evident in the analysis of all suicidal acts, based on examination by funnel plot methods. The funnel plot was nearly symmetrical, with outcomes of the 31 meta-analyzed studies balanced around the centerline defined as the overall, fixed-effect pooled RR of 4.10 (Fig. 4). In addition, Begg's test for publication bias (11) was not significant ($z = 1.29$, $p = 0.20$), nor was Egger's test for funnel-plot asymmetry (not shown). Finally, removing the unusually large study by Goodwin and colleagues (57) had little effect on the reported findings (Table 2), nor did the removal of other individual studies (not shown).

Discussion

Based on observations in all 45 identified reports of rates of suicide or attempts during lithium treatment, the crude incidence of suicidal behaviors during long-term lithium treatment averaged 0.436%/year, compared to 2.63%/year without such treatment, suggesting a six-fold lower risk to lithium treatment (Table 1). In quantitative meta-analyses based on 31 of the studies with information about suicidal acts with and without lithium treatment, and with non-zero risks in at least one

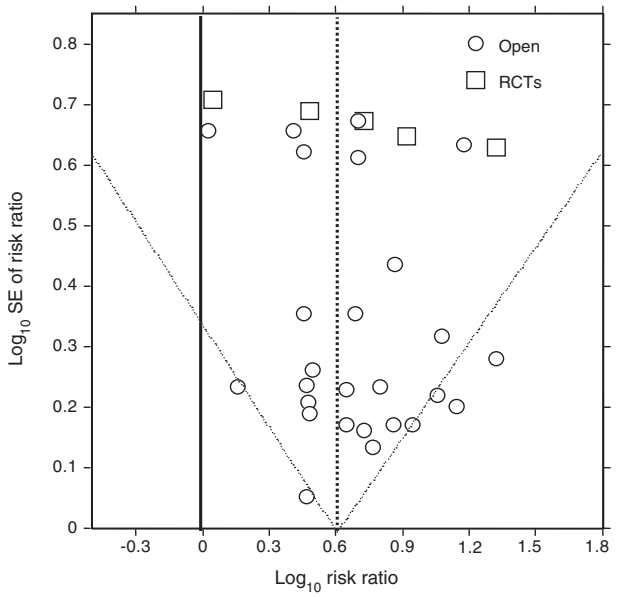

Fig. 4. Funnel plot of values of the $\log_{10}$-SE-of-risk ratios (RR) versus $\log_{10}$-RR for 31 individual studies included in meta-analyses, including five randomized controlled trials (RCTs; squares) and 26 open clinical trials (circles) (2, 18, 20, 21, 23, 24, 26, 28, 31, 35–38, 40, 42–60). The vertical dashed line indicates the pooled RR (4.01, $\log_{10} = 0.603$) based on *fixed-effects* meta-analysis; the vertical solid line is the null (RR = 1.0, $\log_{10}$-RR = 0), and the diagonal dotted lines represent the pseudo-95% confidence limits for the plotted values. The horizontal distribution of the values is quite symmetrical and does not suggest bias toward larger RRs with smaller studies (higher SEs). The distribution of values indicates higher variance in RR estimates from RCTs, reflecting their smaller average size (see Table 1).

study arm, the overall incidence of suicidal acts (suicides and attempts) was nearly five-fold lower during treatment with lithium, indicating an approximately 80% reduction of risk (Fig. 1, Table 2). Very similar results were obtained when completed and attempted suicides were considered separately (Table 2, Figs 2 and 3). Moreover, these results proved to be largely independent of the method of analysis, the type of study (open clinical versus RCT), or diagnosis (BPD only or various major affective disorders), and proved to be robust on removal of individual studies, including one particularly large study (57). Studies with higher quality ratings yielded non-significantly lesser contrasts between lithium and control conditions, and RCTs yielded a significantly smaller RR (Table 2). Both effects may reflect the much shorter duration of treatment in RCTs and higher-quality studies than in open trials, with risk of inflating annualized rates based on short exposures. In addition, there was little inflation of risks after discontinuing lithium in the few studies (all long-term) in which discontinuation was identified, although such effects can be expected in studies following patients for only 3–6 months after discontinuing lithium, and perhaps other treatments, especially abruptly (49, 61).

A potentially important new observation was a strong association of lithium treatment with the ratio (A/S) of attempted to completed suicides, which we propose as an index of 'lethality' of suicidal acts. In the general population, the proportion of attempted to completed suicides (20–30:1) is about four to six times higher than in major affective disorder patients, in whom the A/S ratio averages only about 5:1 or less (10, 62–64) (Table 4), suggesting that a higher lethality of suicidal acts is associated with mood disorders. In the available data, the A/S ratio was 2.5 times *greater* among lithium-treated subjects than among those not treated with lithium (Table 4), and nearly three times higher among BPD cases, suggesting a *reduction* in lethality attributable to lithium treatment, with fewer fatalities per attempt.

It is noteworthy that the observed crude suicide rate of 1.30%/year among samples of broadly defined manic-depressive patients treated without lithium (Table 4) was more than 90 times above the base rate of circa 0.014%/year (14/100,000/year) in the international general population (10, 62, 63). With lithium, this rate was 8.4 times lower, at 0.155%/year (Table 4), but still around 10 times above the general population risk, as noted previously (4, 10). Estimates of suicide attempt rates in the general population are less secure, but are approximately 20–30 times higher than rates of completed suicides, or about 0.3–0.5%/year (4, 6, 10, 62, 64). The observed rate of suicide attempts among major affective disorder patients not treated with lithium, at 3.63%/year (Table 4), was therefore about 10 times higher than in the general population. With lithium, that risk fell to 1.08%/year, which is relatively closer to the general population rate, as noted earlier (4, 10).

The present findings strongly and consistently support the proposal that lithium has substantial suicide risk-reducing effects. There is also suggestive evidence that it may be more effective for this indication in comparison to other mood stabilizing treatments, including carbamazepine, divalproex and lamotrigine (44–46, 55–57, 65). The basis of this beneficial effect of lithium treatment is not clear. Risk of suicidal behavior in BPD and other forms of major affective illness is strongly associated with depressive-dysphoric phases of illness and rare in mania/hypomania (10), and lithium has substantial ability to limit recurrences of depressive illness in both BP I and II syndromes,

and perhaps also in non-bipolar major depression (66–69). Nevertheless, the depressive component of BPD remains the least successfully managed aspect of the illness (10, 69). Residual morbidity can account for as much as 40% of time during long-term follow-up of BP I patients treated clinically by current community standards, and approximately three-quarters of this morbidity is accounted for by depression and dysthymia (65, 70–73), even early in the course of the illness (73), when the risk of suicide is particularly high (10, 49).

Ahrens and Müller-Oerlinghausen (74) reported evidence supporting the view that the antisuicidal effect of lithium may be somewhat independent of its effects on affective morbidity in BPD patients. Other effects of potential importance may include beneficial effects of lithium treatment on the impulsive and aggressive tendencies commonly encountered in BPD and other major affective disorder patients, as well as the non-specific effects of the close clinical monitoring required for safe long-term treatment with lithium (10, 66, 68, 75). Close clinical and chemical monitoring may also enhance adherence to long-term lithium treatment, a factor known to contribute to antisuicidal effects (51). Impulsivity and aggression may be particularly important for both risk and timing of suicidal acts, and may help to account for the striking disparity between the effectiveness of lithium in reducing suicidal risk and the lack of evidence of such an effect for antidepressants in the treatment of unipolar or bipolar major depression (69, 75–82).

It should also be pointed out that clinical use of lithium with the hope of reducing suicidal risk may seem paradoxical, in that lithium has a very limited therapeutic index or margin of safety, can be lethal in acute overdoses (69), and can be used deliberately for suicidal purposes. However, the choice of lithium as a toxin for suicide attempts appears to be uncommon, an observation that, itself, may reflect an antisuicidal effect of lithium (83). Moreover, the fatality risk of lithium overdoses is only moderate, and very similar to those of modern antidepressants and second-generation antipsychotics (84), both generally considered relatively safe drugs (69, 82).

Limitations to the present findings include some imprecise definitions of actual exposure times and of numbers of subjects remaining at risk for prolonged periods of time. Further, since suicidal events were rarely the primary outcomes of interest, the *incidental* reporting of suicide attempts, in particular, may be incomplete or inaccurate.

An additional limitation is that reported information regarding *treatments other than lithium* is so limited as to preclude any analysis of their potential impact on the reported findings. Despite the potentially confounding effects of uncontrolled treatments, our findings regarding lithium in open studies are consistent with those of RCTs (Tables 2 and 3) and congruent with recent meta-analyses of relevant RCTs by Cipriani et al. (9). In such trials, access to alternative treatments with lithium was excluded or limited. However, lithium was compared to other active mood stabilizing agents, including carbamazepine (44–46, 66) and lamotrigine (55, 56); such conditions might well yield lesser effects of lithium than would be apparent without an active treatment comparison. It is indeed remarkable that in all 31 studies analyzed, lithium outperformed conditions that included both clinically selected as well as randomly assigned active treatments. Additional RCTs comparing other treatments, involving longer exposure times, and including suicidal behaviors as an explicit outcome measure would be welcome, although they will present practical and ethical challenges in design and conduct.

As already noted, the *duration* of studies used to evaluate the risk of relatively rare suicidal events appears to be an important variable, as shorter studies (including RCTs and others with relatively high quality scores) yielded somewhat lower rates of suicidal acts in the present data, presumably due to more limited opportunities to observe suicidal behavior. Moreover, longer lithium treatment has been associated with superior separation of antisuicidal effects from alternative treatments (85).

A final limitation is that some of the studies analyzed may overrepresent patients who were relatively tolerant of, or clinically responsive to, lithium treatment, thus perhaps tending to exaggerate the benefits actually attainable under broader clinical conditions, including in relatively complex BPD patients, such as those with rapid-cycling, substance use and other comorbidities, or prominent psychotic or mixed manic-depressive features, all of whom may be at particularly high suicidal risk (10). Such subgroups could not be evaluated in the present analysis because the required clinical information was lacking in most reports. Nevertheless, variance in the actual taking of a treatment is an inescapable factor in evaluating the effectiveness of any long-term medical regimen, and our findings of positive results in both RCTs and open studies, as well as in studies involving the same persons treated with versus without lithium, support the overall validity of the conclusion that long-term treatment with lithium is associated with major reductions in rates of suicidal behaviors.

In conclusion, the present findings provide strong support for major reductions in the risk of completed and attempted suicides among BPD and other major affective disorder patients during long-term treatment with lithium, and suggest that the lethality of suicidal acts may also be reduced, perhaps by limiting impulsivity and aggressiveness. The findings were remarkably consistent in various types of assessments, as well as in open clinical observations and in the fewer available RCTs that included a lithium arm, even against other active mood stabilizing treatments. It is noteworthy that no study found a greater risk of suicidal behavior during treatment with lithium than without it, nor even in comparison to alternative active treatments. For the future, we recommend that mortality in general, and that due to suicide in particular, be considered important and ethically feasible targets for therapeutic research in patients with BPD and other major psychiatric disorders, as has also been done with clozapine in schizophrenia patients, the first FDA-approved treatment for reducing suicidal risk (86–88). Based on the evidence reviewed here, and other recent findings with lithium (5–9), we encourage further studies directly comparing lithium with other modern alternatives, including anticonvulsants and antipsychotics with proposed mood stabilizing properties.

Acknowledgements

This study was supported in part by grants from the Bruce J. Anderson Foundation and the McLean Private Donors Neuropsychopharmacology & Bipolar Disorder Research Fund (RJB), awards from NARSAD, the Stanley Medical Research Institute (LT), and by contract support from JDS Pharmaceuticals (JH, PD). Information reviewed in this report was included in a citizens' petition by RJB and FKG to the FDA to recognize an antisuicide effect for all lithium products used to treat bipolar manic-depressive disorder in 2005. This report is dedicated to the memory of our late, esteemed colleague, senior biostatistician John Hennen, PhD.

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