Reduced Suicide Risk During Lithium Maintenance Treatment

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Background: About 20% of deaths of bipolar disorder patients are suicides associated with depressive or mixed episodes. Long-term lithium treatment may be associated with reduction of suicidal risk. ***Method:*** We reviewed studies and our previously reported data to quantify relationships of presence versus absence of lithium maintenance and suicides or suicide attempts in bipolar disorder patients. ***Results:*** Results from 22 studies (1974–1998) yielded 7-fold lower suicidal rates for patients during long-term lithium treatment than for these patients when they were not receiving such treatment, patients lacking such treatment, or for patients after lithium discontinuation. ***Conclusions:*** Protection against suicide with lithium is incomplete, but rates of suicides plus attempts during lithium treatment may approach general population base rates. Better protection against bipolar depression is essential for limiting suicidal risk; alternatives to lithium require further study for effects on suicidal behavior.
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The World Health Organization reported that nearly one million persons died of suicide in 1998, making it the second leading cause of death in women aged 15–44 years and ninth in men of the same age.[1] The overall mean ± SD age-adjusted suicide rate in 24 developed nations is 16.6 ± 7.5/100,000 (0.0166%/year). The U.S. suicide rate is approximately 11.2/100,000, but varies markedly by region, age, gender, and race, with elderly white, and Native American men at highest risk.[2–6] Prior suicide attempts are predictive of completed suicides, occurring in 10% to 15% of those who eventually commit suicide.[4] The lifetime prevalence of suicide attempts in the general population is at least 2%, and possibly as high as 15%, but varies with levels of lethality or intent and accuracy of reporting.[3] The reported ratio of attempts to completed suicides averages 18:1 in the general population, but only about 3:1 among persons with mood disorders.[1–5] Overall international annual risk of suicides plus attempts is approximately 0.315%/year (0.0166 + 18 [0.0166]).

INTERNATIONAL VARIATION IN SUICIDE RATES

Since 1945, U.S. annual suicide rates have changed little overall, but tripled among young Americans aged 15 to 24 years between 1956 and 1977 and decreased by a similar amount in the elderly over the last 50 years.[2–4] The increased number of suicides in youth probably reflects psychotropic drug overdoses and increased use of firearms; indeed, nearly 1 of 5 suicides with firearms occurs at ages 15 to 24.[5] Decreasing rates in the elderly may reflect improved access to mental health services in the United States.

Suicide rates vary markedly between countries and regions. In Europe, recent annual suicide rates per 100,000 ranged from 2.6 in Malta to 41.3 in Hungary.[4,6] Furthermore, in striking contrast to the United States, the overall suicide rate in Italy, for example, rose appreciably between 1970 and 1997, from 5.8 to 8.2, whereas rates in adolescents and young adults have held steadier at moderate levels (2.9–3.2) since the late 19th century.[6,7] Differences in prevalence of specific psychiatric disorders, abuse of alcohol and drugs, and access to handguns; cultural and religious differences; and perhaps climatic and other environmental factors probably all contribute to marked differences in suicide rates between countries.[1–6]

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PSYCHIATRIC RISK FACTORS FOR SUICIDE

Diagnosable psychiatric illnesses are found in about 90% of all cases of suicide, based on "psychological autopsies."[4] Affective disorders account for 30% to 80% of suicides, substance use disorders for 19% to 60%, and schizophrenia for 2% to 14%; lower rates are associated with anxiety or personality disorders and various neurologic or medical disorders.[4] In both major depression and bipolar disorder, suicides account for approximately 20% of deaths in severely depressed or ever-hospitalized patients, are less frequent with less severe illness, and are about twice as likely in men than women.[2,8–12]

In a seminal study on suicide as an outcome of psychiatric disorders, Harris and Barraclough[13] compared observed suicide rates with calculated expected rates in an age- and sex-matched sample of the general population to provide a standard mortality ratio for several psychiatric conditions.[14] Standard mortality ratio estimates were markedly increased, on the basis of data collected from 37 studies of major depressive and bipolar disorders. With lifetime prevalence in the general population about 8% for major depression, and approximately 2% for bipolar disorders (types I and II),[14–16] major affective disorders, particularly with comorbid substance abuse, carry the greatest suicidal risk.[2,3,8–12,17] Yet only a minority of persons with highly prevalent and potentially lethal mood disorders are diagnosed, often after years of delay, and only a minority of those are adequately treated.[16,18–23]

SOCIAL BURDEN OF SUICIDE

Any suicidal act, even if not lethal, represents a disruptive event in the life of the individuals and families involved. In addition to major human tolls, suicide carries heavy social and economic costs.[9,19,24,25] Estimated annual direct (medical costs) and indirect (lost income due to disability and premature mortality) economic costs of bipolar disorder in the United States are $45 billion, with at least 80% of this total due to indirect costs that include the impact of suicide.[26] A similar economic burden has been attributed to major depressive disorders.[27,28] Despite the magnitude of the problem represented by suicide, studies of its prevention or treatment remain too sparse and inadequate to guide either specific clinical recommendations or effective public health policies.[16,25,29]

Reasons for limited research into the effectiveness of interventions into suicide include obvious ethical constraints against controlled studies when a suicidal act is a potential outcome, such as after withholding or removing treatments in persons at high risk for recurrent depression.[16,30] To avoid such risks, most studies of treatment effects on suicide have been naturalistic or have examined suicidal behavior post hoc as an unintended outcome in controlled treatment trials. Treatment studies of suicide are further constrained by emerging recognition of apparently increased risks of early recurrences of acute psychiatric illness following discontinuation of long-term treatment with lithium, antidepressants, or other psychotropic agents.[31–35] Additional practical difficulties for studies of suicide prevention arise from the epidemiology of suicide, with incidence rates that require very large samples or long times of observation.[2,16]

PSYCHIATRIC THERAPEUTICS AND SUICIDE

Suicide remains very strongly associated with depressive illness, despite broad application of treatments with demonstrated effectiveness in clinical depression, including antidepressant drugs, electroconvulsive treatment (ECT), and cognitive-behavioral or interpersonal psychotherapy. Nearly half of a century of routine clinical use of such treatments has not yielded evidence of reductions of long-term suicidal risk or other premature mortality associated with depressive disorders, including from accidents, substance abuse, or stress-related cardiopulmonary diseases (references 1, 10–12, 16, 36–40 and R.J.B.; D. Ioanitescu, M.D.; J. Ragade, M.D.; et al., unpublished data, 2000). Antidepressants may improve suicidal ideation,[41–43] and ECT can be lifesaving in severe acute depression,[42–46] but neither has been demonstrated convincingly to reduce suicide rates in populations of depressive patients (references 41–46 and R.J.B.; D. Ioanitescu, M.D.; J. Ragade, M.D.; et al., unpublished data, 2000).

A rare placebo-controlled United Kingdom study[47] indicated a lowering of risk of suicidal behavior as well as thoughts in depressive patients given long-term treatment with paroxetine. Emerging observations indicate an impact on overall mortality rates by a variety of long-term mood-altering treatments in a large Swiss sample of patients with major affective disorders.[11,12] In addition, several retrospective studies[20,48–50] have found elevated suicidal risk in depressed patients not taking antidepressants or using presumably inadequate doses. Also, local suicide rates varied inversely with the ratio of physicians to regional populations in Hungary.[51] Finally, an inference that treatment may be more effective now than formerly might derive from observations of rather stable overall suicide rates in many countries as the prevalence of identified depression has risen over the past century.[2] However, this potential association is confounded by broadening definitions of clinical depression and improved case identification.

Also, no convincing evidence exists that specific antidepressants, such as fluoxetine, increase risk of suicidal or other violent behavior, although induction of agitation and insomnia in some vulnerable patients, including those with undiagnosed bipolar disorder, may sometimes contribute to potentially dangerous reactions to antidepressant treatment.[36,43,52] Paradoxically, introduction of safer modern antidepressants with very low lethality in acute over-

Table 1. Studies of Lithium and Suicide Rates (% of cases/y) in Major Affective Disorders[a]

Study	Diagnosis	N	Risk Type	Time at Risk (y)	Rates (% of cases/y) Lithium	Rates (% of cases/y) No Lithium
Prien et al, 1974[62]	BP + UP	327	Deaths	2.0	0.000	0.306
Bech et al, 1976[63]	MAD	74	Deaths	6.0	0.386	NA
Kay and Petterson, 1977[64]	BP	187	Deaths	≤ 11.0	0.000	0.721
Glen et al, 1979[65]	BP	784	Deaths	≤ 9.6	0.186	NA
Venkoba-Rao et al, 1983[66]	MAD	47	Attempts	≈ 8.5	0.000	0.501
Lepkifker et al, 1985[67]	UP	33	Attempts	8.3	0.000	2.556
Jamison, 1986[68]	MAD	9000	Deaths	NA	0.044	NA
Schou and Weeke, 1988[69]	BP + UP	2640	Deaths	≈ 1.0	0.341	3.137[b]
Nilsson and Axelsson, 1990[70]	MAD	37	Attempts	7.0	0.000	NA
Coppen et al, 1991[71]	MAD	103	Attempts	11.0	0.000	NA
Vestergaard and Aagaard, 1991[72]	MAD	133	Deaths	5.0	1.353	NA
Modestin and Schwartzenbach, 1992[73]	MAD	64	Deaths	12.1	0.000	NA
Müller-Oerlinghausen et al, 1992[74]	MAD	68	Attempts + deaths	8.0	1.471	2.022
Rihmer et al, 1993[75]	BP I + II	36	Attempts	7.2	0.386	5.482
Coppen, 1994[76]	MAD	103	Deaths	16.0	0.066	0.910
Felber and Kyber, 1994[77]	MAD	36	Deaths	7.1	0.404	1.158[c]
Lenz et al, 1994[78]	MAD	265	Deaths	> 0.5	0.194	0.856
Müller-Oerlinghausen, 1994[79]	MAD	394	Deaths	14.2	0.125	NA
Ahrens et al, 1995[80]	MAD	827	Deaths	6.8	0.125	NA
Nilsson, 1995[81]	MAD	362	Deaths	14.2	0.184	0.812
Thies-Flechtner et al, 1996[82]	BP + SA	378	Deaths	2.5	0.000	1.905[d]
Tondo et al, 1998[60]	BP I + II	310	Attempts	14.6	0.355	2.752
Summary (22 reports), mean ± SD		16,208	All acts	≈ 8.22 ± 4.53	0.255 ± 0.403	1.778 ± 1.444
Apparent risk reduction					6.97-fold	

[a]Adapted from Tondo et al.[29,30] Abbreviations: BP = bipolar I or II disorder, MAD = major affective disorders, NA = not available, SA = schizoaffective disorders, UP = recurrent unipolar major depression. Many studies include various affective disorders, lack direct comparisons with untreated individuals, give only approximate times at risk, and vary in reporting suicides and attempts. Overall, risk of suicidal acts or deaths was 6.97-fold (t = 3.73, df = 34, p < .001) lower during treatment. All 22 studies favored lithium by direct comparisons with untreated individuals or lower rates than in untreated patients in other studies. These 22 studies of suicide attempts or suicides involve over 16,000 manic-depressive patients; 15 of the studies report on rates of suicides among > 5900 manic-depressive patients, and 7 studies report on attempts.
[b]Untreated rate uncorrected for time at risk.
[c]With all attempts included, difference = 8.74-fold.
[d]Treated without lithium but with carbamazepine or amitriptyline and antipsychotic agents.

dose uncomplicated by other toxins, notably the serotonin reuptake inhibitors, since the 1980s has not been followed by measurable reduction of suicide rates. Evidently, a formerly strong association of suicide with overdoses of older, potentially more lethal antidepressants has shifted toward other means of self-destruction.[53,54] In addition, a clinically suspected association of increased suicide risk with emerging recovery from acute depression has not been verified, although there may be a link between suicide and recent hospital discharge, particularly in chronically ill and psychotic patients.[43,55]

Despite the strong association between suicidal behavior and depressive-dysphoric states in both bipolar and unipolar mood disorders, treatment of bipolar depression remains remarkably poorly studied.[16,29,30,56–58] Indeed, bipolarity, as well as psychosis and even suicidality itself, is a traditional exclusionary factor in most trials of antidepressant treatments.[21,22] Moreover, studies of proposed mood-stabilizing agents have tended to focus on acute and recurring mania rather than the more lethal condition of bipolar depression, and even lithium continues not to carry an FDA-sanctioned indication for depression, despite abundant evidence of its effectiveness in both phases and subtypes of bipolar illness.[10,12,16,21,56–58]

EFFECTS OF LITHIUM TREATMENT ON SUICIDAL BEHAVIOR

Rare information indicating beneficial therapeutic effects on suicide derives from research literature on long-term lithium treatment.[59] Long-term lithium treatment shows a strong, and possibly unique, protective effect against suicidal behavior in major affective disorder patients and particularly in bipolar manic-depressive illness. We have recently reviewed much of this literature and now summarize previous findings.[16,29,30,60,61]

In computerized literature searches and references cited in identified reports, we found 22 studies (1974–1998) with data permitting estimation of annual rates of suicide attempts or fatalities in persons with bipolar or allied major affective illnesses treated with lithium (Table 1).[30,60,62–82] Direct comparisons were provided for risks with and without lithium maintenance treatment under matching conditions of diagnosis, follow-up, and assessment in 13 re-

ports.* All but 2 of the 13 reported on suicidal risks during versus after discontinuing lithium maintenance (1 compared before vs. during treatment[60]; the other compared lithium with other treatments[82]) and may inflate risks due to specific effects of treatment discontinuation.[34,35]

The results of these studies require cautious interpretation: many did not aim to study effects of treatment on suicidal risk or they have limitations, including (1) a broad diagnostic concept not distinguishing unipolar and bipolar disorders or bipolar subtypes I and II, (2) lack of specification of lethality of suicidal acts, (3) nonseparation of high-risk cases with comorbid substance use or prior suicide attempts, (4) use of standardized mortality ratios or other lack of direct comparisons of subjects with and without lithium treatment, (5) lack of precise times at risk, (6) lack of drug assays or estimates of adherence to prescribed treatment, (7) lack of control over other treatments, (8) possible confounding effects of treatment discontinuation, and (9) limited numbers of subjects.

Despite their methodological limitations, overall, the 22 studies with data concerning suicidal acts with or without lithium maintenance treatment yielded substantially lower annual rates of suicidal behavior during maintenance treatment with lithium, with consistent differences in the 13 reports of risks with and without lithium treatment (see Table 1). The mean ± SD rate of suicide attempts or deaths with lithium treatment was 0.255% ± 0.403% of subjects per year (22 studies), compared with 1.778% ± 1.444% per year without lithium treatment in 13 of the reports—a 6.97-fold difference (see Table 1 and Table 2).

Based on a reported average annual suicide rate in affective disorder patients of 0.523% (32 times higher than the average population rate of 0.0166%/year),[4] apparent protection against suicides afforded by lithium treatment was 56.6% ([0.523–0.227]/0.523). However, based on direct comparisons of subjects with and without lithium-treatment (see Table 2), observed protection against suicide attempts was greater (23-fold, or 95.6% reduction) than for fatalities (5.40-fold, or 81.5%), with a large overall reduction of all suicidal acts (6.97-fold, or 85.7%).

It is important to emphasize that the suicide rate found during lithium treatment (0.227%/year) was 13.7 times greater than that in the general population (0.0166%/year; see Table 2). Moreover, the risk without lithium (1.226%/year) exceeds that estimated for the broad population of persons with major affective disorders (1.226/0.523; 2.34-fold), as well as far exceeding the general population risk (1.226/0.0166; 74-fold). This excess may reflect lithium discontinuation—the without-lithium condition in 11 of the 13 studies cited (see Table 1). Alternatively, affectively ill patients who eventually are treated long term with lithium or who were studied (typically at academic referral centers that may tend to accumulate patients with especially difficult illnesses) may be at higher baseline suicidal risk than many other affectively ill persons, and some studies selected high-risk cases with prior suicide attempts.[74,75]

Table 2. Reported Rates of Suicidal Acts With and Without Lithium Maintenance Treatment (acts/100 patient-years)

Measure	All Acts	Attempts	Suicides
Without lithium[a]	1.778 ± 1.444	2.823 ± 2.044	1.226 ± 0.897
With lithium[a]	0.255 ± 0.403	0.124 ± 0.192	0.227 ± 0.341
Risk reduction			
Fold	6.97-fold	22.8-fold	5.40-fold
%	85.7	95.6	81.5
No. of studies	22; 13[b]	6	15
F (p Value)	22.0 (< .0001)	11.0 (.011)	15.0 (.0009)
Population rates (%/y)[c]	0.315	0.299	0.0166
Ratio vs without lithium	5.64	9.44	73.9
Ratio vs with lithium	0.81	0.41	13.7

[a]Mean ± SD rates are derived from a meta-analysis of the reports summarized in Table 1.
[b]All 22 studies reported rates on lithium; only 13 of these provided rates off lithium.
[c]Based on international general population rates cited in the text.

Based on epidemiologic information reviewed above, the estimated international risk of attempts-plus-suicides is about 0.315%/year. This estimate suggests that the overall risk of suicidal acts during lithium maintenance may be close to, or even below, the base rate in the general population (0.255% vs. 0.315%/year, respectively; see Table 2). However, population base rates include risk associated with major affective and substance use disorders. Attainment of illness-corrected population base rates or, ideally, reaching zero risk during treatment is obviously far from having been accomplished. It may not even be a realistic goal, given limitations of case finding and treatment in persons with mood disorders. The therapeutic challenge is greater still owing to limited adherence to recommended treatment among the minority who accept treatment at all and to imperfect clinical protection afforded by available treatments for bipolar disorder.[22] Failure rates involving at least one recurrence of mania or bipolar depression during closely supervised lithium maintenance treatment in our research center averaged 38% within 1 year and 54% by 2 years. Many of these episodes were depressive-dysphoric, representing increased suicidal risk.[83]

ADDITIONAL SUPPORT FOR A PROTECTIVE EFFECT OF LITHIUM AGAINST SUICIDE

In addition to the studies summarized above (see Table 1), 5 other reports[84–88] with data unsuitable for comparisons of rates during and without treatment provide support for a reduction of suicide risk during long-term treatment with lithium. Only Norton and Whalley[89] found no evidence of a protective action of lithium against suicide; suicide rates in nearly 800 lithium-treated patients with major affective

*References 60, 62, 64, 66, 67, 69, 74–78, 81, and 82.

disorders were 48.5 times above those expected in the general population.[89] However, they provided no direct comparisons of treated versus untreated subjects. Such comparisons are important (particularly in evaluating risks for events of infrequent occurrence) to control for variance in sampling methods between populations. For example, suicide rates with lithium in at least 2 studies listed in Table 1,[72,80] as well as the average rate across all studies, were above those expected in the general population, but both studies and the overall results found lower rates than in untreated subjects under comparable conditions.

BASIS OF PROTECTION AGAINST SUICIDE BY LITHIUM TREATMENT

The results summarized here indicate substantial protection against suicide attempts and fatalities with long-term lithium treatment in patients with a variety of severe, recurrent mood disorders. It is plausible that antisuicidal effects are merely incidental to the overall clinical benefits of long-term mood stabilization with lithium. This view is supported by strong associations between suicidal behavior and recurrences of depressive or mixed mood states in bipolar disorder patients.* Moreover, close personal monitoring of patients receiving lithium maintenance treatment and improvements in overall emotional stability, interpersonal relationships, vocational functioning, self-esteem, and perhaps reduced comorbid substance abuse all may contribute potentially important benefits. Conversely, the residual suicidal risk encountered during lithium treatment may reflect the typically incomplete protection against recurrences of depressive, dysphoric, and agitated mood states associated with all currently available methods of treatment for bipolar disorder, assuming adequate dosing and compliance.[10,11,21,22,43,57,83]

Lithium may exert specific or unique effects on suicidal and other aggressive behavior that can not be assumed to occur equally with all proposed mood-stabilizing treatments.[30,74,90] In a large collaborative European program[82,91] comparing 2 years of randomly assigned maintenance with lithium versus other options, suicides and attempts were virtually absent from bipolar or schizoaffective disorder patients maintained on lithium treatment, but occurred in approximately 2% of similar patients given carbamazepine and patients with unipolar depression maintained on amitriptyline treatment with or without an antipsychotic. These provocative observations require verification, and extension to other proposed mood-stabilizing treatments.[83]

If reduction of suicidal risk associated with long-term lithium treatment is not shared with other treatments, it would be important to consider distinct pharmacodynamic actions of lithium not produced by other agents, particularly anticonvulsants. Possibilities include serotonin-enhancing actions of lithium in limbic forebrain[16,21,92] that may offset deficiencies in cerebral serotonergic functioning tentatively associated with suicidal and other violent behavior.[93,94] Such serotonin-mediated effects are unknown with anticonvulsants. At least moderate mortality-reducing and possibly specific antisuicidal actions have also been associated with the atypical antipsychotic agent clozapine.[95–97] Instead of enhancing cerebral serotonergic activity, clozapine is an antagonist of some serotonin receptors.[98] Nevertheless, clozapine has been associated with depression-improving effects that might in part reflect antagonism of serotonin-2A receptor activity.[99]

LITHIUM DISCONTINUATION AND SUICIDAL RISK

We also examined suicidal risk in association with discontinuing lithium to follow up previous findings indicating an excess of early recurrences within several months of discontinuing lithium and other psychotropic agents.[31–35] In our clinical sample of 310 bipolar patients, the risk of suicide attempts before lithium maintenance treatment versus attempts plus suicides during treatment differed by a 6.48-fold overall reduction—very similar to the 6.97-fold reduction of suicidal acts derived from the literature (see Tables 1 and 2).[30,60,61]

A total of 165 of our patients discontinued lithium maintenance treatment clinically, either electively after doing well for prolonged periods and wishing to avoid side effects, or as indicated by compelling medical conditions including pregnancy or important adverse effects. We excluded cases involving emerging hypomania or depression that might impair judgment about continuing treatment and inflate risks of morbidity. In addition, patients who continued and discontinued lithium treatment were very similar in a variety of demographic and clinical variables, including past-episode frequency and severity.[30,60,61] Finally, it is important to emphasize that treatment discontinuation was not initiated for research purposes and that such experimental designs now seem to be contraindicated by our findings.

We found that rates of all suicidal acts rose nearly 14-fold after discontinuing lithium. This increase was especially striking within 12 months of discontinuation (20-fold), whereas at follow-up times later than 12 months off lithium treatment, the rate fell to match that found by largely retrospective analysis for years from illness onset to the start of maintenance treatment (Table 3). A particularly ominous finding was that risk of fatalities rose nearly 13-fold after discontinuing lithium. We also found a strong trend toward limiting risk by slow (> 2 weeks) discontinuation of lithium, after which rates of suicidal acts were half those following abrupt or rapid discontinuation (Figure 1; see Table 3).[30,61] Even though the numbers involved were

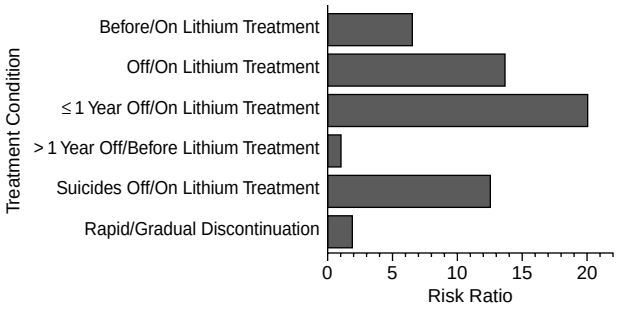
*References 1, 4, 8, 14, 16, 30, 34, 57, 60, and 61.

Table 3. Suicide Rates and Treatment Status in Bipolar Disorder Patients[a]

Treatment Status	Suicidal Acts/per 100 Patient-Years
Before lithium treatment[b]	2.30
During lithium maintenance[c]	0.36
After discontinuing lithium[d]	4.86
First year off lithium treatment	7.11
Later times off lithium treatment	2.29
Fatal suicides on lithium treatment	0.10
Suicides after stopping lithium treatment	1.27
Rapid discontinuation (1–14 d)	4.96
Gradual discontinuation (15–30 d)	2.55

[a]Adapted from Baldessarini et al.[30, 61]
[b]310 subjects for 8.28 years.
[c]310 for 6.36 years.
[d]165 subjects for 3.70 years.

Figure 1. Relative Risks of Suicidal Acts Under Different Conditions of Lithium Maintenance Treatment[a]



[a]Based on rates shown in Table 3.[30,61] All comparisons differ highly significantly except > 1 year after discontinuation vs. before treatment (both rates are virtually identical) and the risk of fatalities off vs. during lithium treatment (a nonsignificant 2-fold trend). Results are based on methods reported by Tondo et al.[60] and Baldessarini et al.[61]

insufficient to yield statistical significance of the effect of discontinuation rate, clinical prudence, coupled with highly statistically significant reduction of morbidity by slow discontinuation of lithium, strongly supports gradual discontinuation whenever clinically feasible.[31,34,35,100]

Increased risk of suicides and life-threatening suicide attempts after lithium discontinuation is consistent with results from other studies, including 11 of 13 trials reporting risks on and off lithium treatment (see Table 2). This phenomenon does not involve emergence of suicidality in isolation, but instead parallels emerging recurrences of depressive or mixed dysphoric-agitated states that call for immediate clinical intervention.[34,35,101–104] Recurrences of bipolar depression and mania after lithium discontinuation probably exceed risks of morbidity associated with untreated illness, particularly within several months after discontinuation and after abrupt or rapid discontinuation.[34,35,83,101–105] While awaiting verification of these findings concerning apparently increased early risk of recurrences of depressive illness with attendant increases in suicidal risk, particular caution is needed in managing maintenance treatment and its discontinuation with potentially suicidal patients. Evidently important benefits of sustained treatment and close clinical monitoring need to be balanced against the potential for increasing risks following abrupt discontinuation of treatment, particularly in high-risk patients who are impulsive, abuse alcohol or drugs, are nonadherent to medical recommendations, or have had prior suicide attempts.

CONCLUSIONS

Despite limitations of studies indicating reduction in suicidal risk during long-term treatment with lithium, the weight of the evidence is compelling and the effect is substantial. Nearly 2 dozen studies accumulated over a quarter century consistently found much lower rates of suicides and potentially lethal attempts during lithium maintenance treatment in patients with bipolar and other recurrent major affective disorders than without such treatment. This effect of lithium may not generalize to other mood-stabilizing or antidepressant therapies. Moreover, the protection afforded with lithium was incomplete, although rates of suicides plus attempts with lithium approached base rates estimated for the general population. Ethical considerations severely constrain controlled studies when suicide is an anticipated outcome. Nevertheless, the present findings indicate that naturalistic studies of the therapeutics of suicide are feasible, and even controlled comparisons of clinically plausible alternative treatments can be carried out. Finally, since suicidal risk is associated mainly with depressive or mixed bipolar episodes, it follows that better protection against bipolar depression is a key to limiting suicidal behavior in bipolar disorders. Further studies of treatment effects on suicide risk require carefully designed, long-term studies comparing clinically and ethically plausible treatment options, with much greater consideration of the special problems and challenges of bipolar depression and mixed-dysphoric bipolar mood states.

Drug names: amitriptyline (Elavil and others), carbamazepine (Tegretol and others), clozapine (Clozaril and others), fluoxetine (Prozac), paroxetine (Paxil).

Disclosure of off-label use: The authors have determined that, to the best of their knowledge, the specified uses of the following agents are not approved by the U.S. Food and Drug Administration: carbamazepine and clozapine for mood stabilization, lithium for the prevention of recurrent depression.

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