

September 28, 2005

VIA TELEFAX

Dockets Management Branch, HFA-305
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

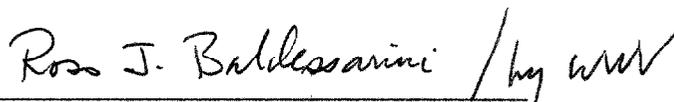
CITIZEN PETITION

It has come to our attention that the Citizen Petition filed on September 27, 2005 failed to contain the following Certification Paragraph:

"The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition."

We are pleased to make this certification. We apologize for the oversight.

Respectfully submitted,



Ross J. Baldessarini, M.D.

Corresponding Petitioner

September 28, 2005

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CITIZEN PETITION

Ross J. Baldessarini, M.D. and Frederick K. Goodwin, M.D. submit this petition under section 505 of the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 C.F.R. § 201.56, and 21 C.F.R. § 10.30 to request the U.S. Commissioner of Food and Drugs to amend or permit amendment of the labeling of all lithium-containing drugs to include the additional indication "to reduce the incidence of suicide and suicide attempts in manic-depressive illness." The Petitioners are internationally known neuroscientists and research psychopharmacologists with extensive training and experience in the evaluation of psychotherapeutic drugs, including clinical studies of the course and treatment of bipolar (manic-depressive) disorder and the therapeutics of suicide, as well as being recognized experts on bipolar disorder. Copies of résumés for Drs. Baldessarini and Goodwin are attached below.

I. ACTION REQUESTED

This Petition requests the FDA Commissioner (1) to determine, based on a comprehensive review of adequate and controlled studies reported in the literature, that lithium is safe and effective for reducing the incidence of suicide and suicide attempts in patients with manic-depressive illness; and (2) on a class-wide basis to order or permit amendment of the labeling of approved lithium carbonate and lithium citrate drug products to include the requested indication and related prescribing information. Currently-marketed lithium drug products potentially affected by this citizen petition include Eskalith[®], Lithobid[®], and several generic short-acting and twice-daily (BID) formulations of lithium carbonate, as well as liquid formulations of lithium citrate. The currently FDA-approved indication for all such products is:

“in the treatment of manic episodes of manic-depressive illness. Maintenance therapy prevents or diminishes the intensity of subsequent episodes in those manic-depressive patients with a history of mania.”

We request that the indication be amended to include that:

Lithium carbonate or citrate is indicated to reduce the incidence of suicide and suicide attempts in patients with manic-depressive illness (bipolar I disorder).

Consistent with current standard American and international diagnostic nomenclature (American Psychiatric Association 2000), this petition uses the term “bipolar disorder” as well as the older term “manic-depressive illness,” which is employed in currently marketed lithium products.

II. STATEMENT OF GROUNDS & NATURE OF THE PROBLEM

A. SUMMARY

1. Overview of Suicide & Illness-burden in Bipolar Disorder (Manic-Depressive Illness)

Suicide is a major public health challenge. Responsible for approximately 32,000 deaths of Americans annually, suicide ranks as the eleventh leading cause of death in the United States, and third among adolescents and young adults (Goldsmith et al. 2002; Jacobs 2003; Kochanek et al. 2004). Rates of medically significant suicide attempts are 10–20-times higher than rates of completed suicide in the general population. Attempts are more likely to be under-reported than suicides, but the total of attempted and completed suicides is estimated at nearly a half-million suicidal events per year (Tondo et al. 2003, 2005; Tondo & Baldessarini 2005). In bipolar (manic-depressive) disorder, the risk of suicide is at least as high as in severe major depressive disorder and higher than in all other psychiatric or general medical disorders (Tondo et al. 2003; Tondo & Baldessarini 2005).

Mortality and morbidity associated with bipolar disorder generate tens of billions of dollars in direct and indirect costs to individuals, their families, and to society annually in the United States (Wyatt & Henter 1995; Baldessarini et al. 1999; Wyatt et al. 2001; Kleinman et al. 2003). In 1990, for which specific estimates are available, the total annual cost of bipolar disorder in the United States was \$45 billion (Wyatt & Henter 1995; Wood 2000). Approximately 83% of these costs were indirect, resulting from lost

productivity caused by unemployment, death from suicide, or burden placed on the family or caregiver, and the indirect costs of suicide and suicide attempts were estimated to account for about 17% of the total (Wyatt & Henter 1995; Wood 2000). Moreover, the mortality and economic figures do not capture the intense suffering, family distress, and disability associated with both suicide attempts and suicides in patients with bipolar disorder (Goldsmith et al. 2002; Tondo et al. 2003).

2. Suicidal Behaviors in Bipolar Disorder

- The rate of suicide is considerably higher in patients with bipolar (manic-depressive) disorder than in most other psychiatric or medical populations, and about equal to the risk with unipolar major depressive illness severe enough as to require hospitalization (Tondo et al. 2003; Tondo & Baldessarini 2005). Suicide occurs at an annual rate of approximately 400/100,000 (0.4%) among patients diagnosed with bipolar disorder, and it accounts for approximately 15% of deaths in such patients. Indeed, suicide is, by far, the leading cause of premature death in patients diagnosed with bipolar disorder (Tondo et al. 1997, 2003; Kasper 2003; Tondo & Baldessarini 2005; Tondo et al. 2005a).
- Recent analyses have estimated the overall annual 0.4% rate of suicide associated with bipolar disorder to be more than 20 times that of the general population, which averages 0.014% internationally, and 0.011% in the U.S. This rate in patients with bipolar disorder is at least as high as in severe forms of major depression, and far greater than in schizophrenia or alcoholism (Harris & Barraclough 1997; Tondo et al. 2003; Tondo & Baldessarini 2005; Tondo et al. 2005a).
- Suicide attempts in patients with bipolar disorder lead to completed suicides more frequently than in the general population. The ratio of attempts to completed suicides in persons with bipolar disorder is about 5 to 1, compared to a ratio of about 18 to 1 in the general population, indicating high lethality of suicidal behavior among persons with bipolar disorder (Tondo et al. 2003; Tondo & Baldessarini 2005; Tondo et al. 2005a).

3. Suicidal Behavior Can Be Treated Effectively With Lithium Salts

Extensive clinical evidence suggests that lithium treatment can reduce the risk of suicidal behaviors, both suicides and attempts, by about 80% (Tondo et al. 2001, 2005; Baldessarini et al. 2003, 2005a). The abundance and consistency of the evidence that treatment with lithium is associated with reduced *mortality* from suicide, as well as the risk of suicide attempts, is unique among pharmacological treatments. Indeed, specific evidence of a reduction of mortality from suicide is not available for *any* other form of treatment for *any* disorder (Tondo et al. 2003; Tondo & Baldessarini 2005; Tondo et al. 2005a). The consistent clinical benefits of long-term treatment with lithium in reducing

recurrences and the proportion of time ill in all phases of illness in patients with bipolar disorder are well-documented, in accord with the FDA-approved status of lithium as the longest-established form of pharmacological maintenance or prophylactic treatment in bipolar (manic-depressive) disorder (Goodwin & Jamison 1990; Tondo et al. 2001; Baldessarini et al. 2002; Geddes et al. 2004; Baldessarini & Tarazi 2005). In a recent meta-analysis of 28 major studies, long-term lithium treatment resulted in an overall sparing of morbidity of at least 50%, reducing the risk of recurrences by more than 3-fold (Baldessarini et al. 2002). When only randomized controlled trials were considered, lithium treatment reduced the risk of all relapses in patients with bipolar disorder (without considering their severity or duration), from 60% (placebo) to 40% (lithium) (Geddes 2004).

Analyses of published evidence have indicated that lithium can reduce rates of suicides and life-threatening attempts by well over 50%, and possibly more than 80%, among patients with bipolar or other major affective disorders (Baldessarini et al. 2001, 2003; Tondo et al. 2001; Kessing et al. 2005). The results of an updated meta-analysis of 31 studies (in 33 non-overlapping reports) confirm and extend these findings, demonstrating that the risk of both completed and attempted suicide was reduced by approximately 80% during lithium treatment in patients with bipolar disorder and other major affective disorders, with similar findings among randomized, controlled trials against other active agents as well as placebo (Table 1; Baldessarini et al. 2005a).

Some data, albeit more limited, suggest that the strong and consistent association of lithium treatment with reduced suicidal risk is specific and not shared by other agents used clinically as antimanic agents or as putative mood stabilizers for long-term prophylactic treatment of patients diagnosed with bipolar disorder. Notably, lithium was associated with several-fold greater reductions in suicidal acts compared to carbamazepine or other medications in a large, randomized, controlled, prospective collaborative German study summarized in a series of reports (Greil et al. 1996, 1997a, 1997b; Thies-Flechtner et al. 1996) or compared to divalproex in a comparison of outcomes in two very large American West Coast health maintenance organization databases (Goodwin et al. 2003). In addition, there is no evidence that either olanzapine or lamotrigine (the only agents other than lithium carbonate or citrate that are currently

FDA-approved for long-term maintenance treatment in bipolar disorder) reduces suicidal risk in any patient group (Baldessarini & Tarazi 2005).

Lithium treatment can substantially reduce the economic burden of bipolar disorder. One analysis estimated that lithium treatment resulted in a savings of nearly \$171 billion over the period 1970–1991 (Wyatt et al. 2001). This savings represented a reduction of nearly 18% of total costs projected in the absence of lithium treatment. Of this total, over \$70 billion (42%) was attributed to the direct and indirect costs associated with suicide.

- The most recent practice guidelines of the American Psychiatric Association (APA 2003) for suicide prevention explicitly noted that strong evidence favors the use of lithium for treating psychiatric patients diagnosed with bipolar disorder, and possibly other major mood disorders, with the aim of reducing risk of suicidal behavior. They state, for example:

“On the basis of present knowledge about pharmacological interventions and risk of suicidal behaviors, prophylactic treatment with lithium salts of patients with recurrent major affective disorders is supported by the strongest available evidence of major reductions in suicide risk of any currently employed psychiatric treatment.” (Jacobs [APA] 2003, page 94).

- Currently the only agent to have an FDA-approved indication pertaining to suicidal risk is Clozaril[®] (clozapine), which is approved for reducing the risk of recurrent suicidal behavior in persons diagnosed with schizophrenia or a schizoaffective disorder, but not bipolar disorder. The manufacturer’s prescribing information (Clozaril[®] 2004) states that the data “should be interpreted only as evidence of the effectiveness of Clozaril in *delaying time to recurrent suicidal behavior.*” [Italics added.] Moreover, data on reduction of *mortality* from suicide, as contrasted to time to clinical interventions were not supportive with respect to clozapine (Meltzer et al. 2003; Hennen & Baldessarini 2005; Modestin et al. 2005). Nevertheless, the availability of at least one drug with FDA approval for the therapeutic management of suicidal behavior is an historically important precedent for this critical clinical indication.

Given these facts and the wealth and consistency of evidence in support of the effectiveness of lithium for prevention of suicide and suicidal behaviors, to be summarized more fully below, it is imperative that the class labeling for lithium salts be amended to address this major public health concern by incorporating a specific indication for suicide prevention in patients with manic-depressive illness (bipolar I disorder). Such an action would accord with the intents and goals of *The Surgeon General's Call to Action to Prevent Suicide* (1999), the Institute of Medicine’s publication *Reducing Suicide: A*

National Imperative (2002), and with the recommended practice guidelines of the American Psychiatric Association (2003), and would provide official guidance to physicians in developing their treatment plans to reduce suicidal behaviors among the high risk population of patients with bipolar manic-depressive disorder that includes a history of mania.

B. BIPOLAR DISORDER & SUICIDE RISK: SCOPE OF THE PROBLEM

1. Epidemiology of Bipolar Disorder

Bipolar (manic-depressive) disorder is relatively prevalent. Although estimates vary with diagnostic criteria and methods of ascertainment, it is generally agreed that the lifetime prevalence of bipolar I disorder (with mania) alone, based on modern diagnostic criteria (American Psychiatric Association 2000), is greater than 1% of the adult population, affecting more than 2 million adults in the United States and a less certain number of juveniles (Faedda et al. 1995, 2004; Goodwin et al. 2003; Kessler et al. 2005). The lifetime prevalence of officially recognized bipolar disorders in the U.S. probably exceeds 3% (as many as 6 million persons) when all age groups and all forms of bipolar disorder identified in the DSM-IV-TR (2000) are considered (Angst 1998; Baldessarini et al. 2002; Tohen & Angst 2002; Akiskal 2003; Tondo et al. 2003; Glick 2004; Kessler et al. 2005). These disorders include the standard diagnostic subtypes, bipolar I (with mania, usually also with major depression) and bipolar II (major depression with hypomania), and cyclothymia (less severe mood swings), as well as pediatric, geriatric, and milder adult forms (APA 2000). The number of affected individuals may be even higher because underdiagnosis of bipolar disorder is common due to both missed and inaccurate diagnoses, notably including non-recognition of depressed or otherwise emotionally or behaviorally disturbed persons of any age as having bipolar disorder (Faedda et al. 2004; Glick 2004; Baldessarini et al. 2005b)

2. Suicide Rates in Bipolar Disorder

As the eleventh leading cause of death in the general United States population, suicide accounts for approximately 32,000 or 1.30% (95%CI, 1.28%–1.31%) of the 2.44 million

deaths in the U.S. annually, with a degree of uncertainty owing to the limits of methods of case identification (Kochanek et al. 2004). As the third leading cause of death among young persons aged 15–24 years in the United States currently, suicide accounts for 10% of deaths in this age group (Kochanek et al. 2004). In comparison, suicide rates in patients with bipolar disorder may reach 15% of all causes of death, which makes it the single most important cause of death within this population, especially among young persons (Goodwin & Jamison 1990; Tondo et al. 1997, 2003; Kasper 2003; NIMH 2004).

Suicide risks sometimes are reported as standardized mortality ratios (SMRs; ratio of observed suicides in at-risk group versus expected suicides in the general population, with approximate matching for age and sex) (Harris & Barraclough 1997; Tondo et al. 2003). The average reported SMR for bipolar disorder in recent reviews was 15 [95%CI, 12.2–18.4] (Tondo et al. 2003, 2005; Tondo & Baldessarini 2005). In a meta-analysis of publications presenting data specifically for patients with bipolar disorder, the suicide rate averaged 0.395% per year (95% CI, 0.32–0.47; Tondo et al. 2003). This rate translated to an overall SMR of 22.1 [95% CI, 20.4–24.1]; Tondo et al. 2003). When compared to an average international general population base rate for suicide, of 0.0143% per year, the annual rate of nearly 0.4% was approximately 28-fold higher than that of the international general population, and 36-times higher than the U.S. rate of 0.011%/year (Tondo et al. 2003, 2005; Tondo & Baldessarini 2005). Despite some quantitative variance, these several methods of estimating the relative suicidal risk among persons diagnosed with bipolar disorder are consistent in indicating very high rates, in the range of 15- to 32-times greater than in the general population.

It is difficult to state precisely the proportion of the approximately 32,000 deaths by suicide officially recorded annually in the United States that are attributable to bipolar disorder, in part because of incomplete or conflicting epidemiological data concerning the prevalence of specific types of bipolar disorder and their associated suicidal risks.

Nevertheless, it is possible to estimate the number of suicides per year associated with bipolar disorder on the basis of the following calculations. Approximately 200 million persons in the United States are at age-risk for bipolar disorder. At any time, approximately 1.5%, or 3 million Americans are afflicted with bipolar disorder (NIMH 2001; Kessler et al. 1994, 2005). If, as reported (Tondo et al. 2003), the risk of suicide

among patients with bipolar disorder is approximately 0.4%/year, then the number of expected suicides could be at least 12,000 per year, or about 38% of the approximately 32,000 annual suicide deaths in the U.S. Given that bipolar disorder is generally considered to be underdiagnosed, the correct number and proportion may well be even higher (American Psychiatric Association 2002; Greil & Kleindienst 2003; Kessler et al. 2005).

It could be argued that the estimated number of suicides associated with bipolar disorder should be adjusted by considering the amount of time ill in such patients. It has been found recently that current treatments reduce total amount of time ill among type I bipolar disorder patients incompletely, to approximately 40% (Judd et al. 2002; Post et al. 2003; Baldessarini et al. 2004; Joffe et al. 2004). Taking this factor of residual (treatment-resistant or inadequately treated), morbidity into account, the number of U.S. citizens who are ill with bipolar disorder each year would be about 1.2 million (40% of 3 million). Even with this adjustment, the number of suicides among such patients yields a conservative estimate of about 4,800 suicides per year, or about 15% of the total. Taken together, the preceding estimates suggest that persons with bipolar disorder account for at least 15% and as many as 38% of all suicides in the U.S. each year.

In summary, the risk of suicide in patients diagnosed with bipolar disorder is consistently calculated to be about 20-fold greater than that of the general population. These rates approach the morbidity and mortality associated with cardiovascular disease and cancer in the American general population (Kasper 2003; Rush 2003).

3. Lethality of Suicidal Intent and Means in Bipolar Disorder

In the general population, the ratio of suicide attempts to completed suicide is high. It is estimated to be at least 10:1 and perhaps as high as 30:1, depending on a number of factors, such as age, sex, ethnicity, comorbid conditions, and the accuracy of case identification, especially for suicide attempts of varied severity and potential lethality (Tondo et al. 2003). General population rates of suicide attempts are estimated to be 0.14% to 0.28%, compared to an average suicide rate of 0.01%/year—a difference of more than 20:1 (Tondo et al. 2003). In contrast, suicide attempts appear to be much

more lethal among patients with bipolar disorder (or other major affective disorders), as indicated by a much lower ratio of attempts/completions.

A new systematic review of 60 published studies of risks of suicide attempts among a total of over 70,000 persons with mood disorders supported comparisons of those with bipolar disorders versus either nonbipolar major depression or a mix of major mood disorders not otherwise separated (Tondo et al. 2005a, Tondo et al., unpublished data, August, 2005). The findings indicated a mean (\pm SD) risk of suicide attempts of $2.13 \pm 2.00\%$ /year in bipolar disorder patients. The risk of suicide attempts was similar among those with depressive or unspecified mood disorders ($2.86 \pm 4.01\%$ /year). The relative risk of suicide attempts was somewhat higher among men with bipolar disorder (crude relative risk [RR] = 1.87), and somewhat higher among women with nonbipolar or unspecified mood disorders (RR=1.18). These findings indicate a ratio of risk of attempts/suicides among bipolar disorder patients averaged only about 5:1 ($2.1/0.4\%$ /year), or several-times fewer attempts per completed suicide than was estimated for the general population. This relatively low ratio of attempts to suicide in bipolar disorder patients is consistent with greater level of lethality in suicide attempts by bipolar disorder patients.

This relative lethality, and the 10-fold higher annual rate of suicide attempts in bipolar disorder patients (2.1%) versus the general population (about 0.21%), are consistent with the conclusion that the risk of suicide is extraordinarily high, and suicide attempts particularly dangerous, in bipolar disorder patients (Tondo et al. 2003). The high rate of attempted plus completed suicide in bipolar disorder patients (approximately 2.5%/year) strongly argues for more intense and systematic efforts to intervene in this potentially preventable cause of excess mortality in this prevalent illness (USPHS 1999; Goldsmith et al. 2002; NIMH, 2004).

C. LITHIUM: BACKGROUND INFORMATION

1. Indications and Current Clinical Usage

Lithium is indicated, with FDA approval, for the treatment of manic episodes of manic-depressive illness (bipolar I disorder) and for long-term maintenance or prophylactic therapy that prevents or diminishes the intensity of subsequent episodes of manic-

depressive illness in patients with a history of mania (Eskalith® 2003; Lithobid® 2004). In current clinical practice, the most important therapeutic application of lithium salts (carbonate or citrate) is for the reduction of long-term risk of illness recurrences. The ability of lithium to reduce recurrence of bipolar mania and hypomania, as well as depression, is well-documented in recent reviews that characterized the broad efficacy profile of lithium (Baldessarini et al. 2002; Tondo et al. 2003; Baldessarini & Tarazi 2005).

2. Morbidity-Sparing Effects and Actions

A meta-analysis of 28 major studies of varying design found that that long-term treatment with lithium salts (almost always lithium carbonate, orally) has resulted in at least 50% sparing of overall morbidity, which was documented primarily as reduction of relapse-risk or the number of recurring episodes of mania or depression over time, independent of episode severity or duration (Baldessarini et al. 2002). The calculated overall rate of recurrences was more than 3-fold lower with lithium than without it (risk ratio = 3.2; 95% CI, 2.7–3.8; $p < 0.0001$). More selective, systematic reviews and meta-analyses only of prospective, randomized, controlled trials confirmed that lithium treatment significantly (risk ratio = 0.65; 95% CI, 0.50–0.84; $p = 0.001$) reduced the overall risk of relapse from about 60% (with placebo treatment) to 40% (with lithium) (Geddes 2004; Geddes et al. 2004).

In addition to these effects on recurrence frequency, another analysis of non-randomized, within-subject comparisons demonstrated that lithium treatment greatly reduced estimated percent-time-ill in patients with either bipolar I or II disorder (Tondo et al. 2001). In that study, among patients with type I bipolar disorder, lithium treatment reduced *time* in mania by 2.5-fold and time in depression by 2-fold. In patients with type II disorder, time in hypomania was reduced by 5-fold, and in depression by 2.5-fold.

Although mechanisms by which lithium treatment exerts its clinical effects are unknown, they have been the subject of a substantial and rapidly expanding body of research. It has been proposed that the mortality-sparing effects of lithium may be distinct from effects on mood and perhaps related to reduced agitation, anger, or impulsivity (Thies-Flechtner et al. 1996; Ahrens & Müller-Oerlinghausen 2001; Ernst & Goldberg 2004). Some

support for this hypothesis comes from the finding that the substantial reduction of suicidal risk among patients with bipolar disorder held regardless of whether patients showed marked, moderate, or poor reductions in risks of recurrences of mania or depression (Ahrens & Müller-Oerlinghausen 2001). It may be that lithium can affect risk of suicidal behaviors through a reduction of agitation, aggression, or impulsivity, rather than purely by limiting depressive and dysphoric morbidity in patients with bipolar disorder.

Multiple molecular and physiological mechanisms of action have been identified, but not definitively linked to specific clinical effects (Jope 1999; Manji et al. 1999; Quiroz et al. 2004; Baldessarini & Tarazi 2005). At clinical doses or tissue concentrations, lithium can alter the release and presynaptic storage of catecholamines to decrease the functional activity of cerebral catecholamine neurotransmission (Baldessarini & Tarazi 2005).

Lithium may also participate in readjusting the balance between excitatory and inhibitory neural activity, decreasing excitatory glutamatergic activity, and modulating several intracellular signal transduction pathways (Jope 1999). Further, lithium can markedly affect brain concentrations of a major neuroprotective protein, B-cell lymphocyte protein 2 (*bcl-2*), and inhibit an enzyme (glycogen synthase kinase-3-beta [$GSK-3\beta$]), both of which are implicated in normal programmed neuronal death as well as in neurodegenerative processes (Manji et al. 1999).

In summary, the well-documented long-term beneficial effects of lithium in mood disorders might be related in part to neuroprotective actions and neurophysiologically stabilizing effects in the central nervous system (CNS), that may contribute to the emotional and behavioral effects of long-term treatment with lithium observed clinically (Manji et al. 1999; Quiroz et al. 2004).

D. LITHIUM AND SUICIDE REDUCTION: REVIEW OF THE DATA

1. Overview

Over a half-century of clinical experience supports the utility of lithium salts as a cornerstone of pharmacotherapy for bipolar disorder. Moreover, extensive research data clearly substantiate the ability of long-term treatment with lithium to reduce the risk of suicidal behavior and completed suicides substantially among patients diagnosed with

bipolar disorder and other major affective disorders. Indeed, data pertaining to suicidal risk are far more extensive and consistent than for any other treatment in any disorder (Tondo et al. 2001, 2003). The evidently unique mortality-sparing effect of lithium is supported by a wealth of evidence that has been evaluated repeatedly in systematic reviews and meta-analyses (Tondo et al. 2001; Baldessarini et al. 2003, 2005a; Ernst & Goldberg 2004), and in a recent Swedish national survey of suicide risks among over 13,000 patients receiving lithium treatment at least twice vs. only once (Kessing et al. 2005). Salient research findings are summarized in this section, and representative abstracts from relevant individual reports are provided in an Appendix below.

The body of evidence pertaining to lithium treatment and risk of suicidal behaviors encompasses various types of published studies, with and without randomization and controls. Several reviews and meta-analyses of various aspects of these findings have been conducted, recently by Baldessarini and colleagues (Baldessarini et al. 2001, 2003, 2005a; Tondo et al. 2001). Their most recent report, updates and extends the information in previous publications, and demonstrates that the risk of both completed and attempted suicide was consistently lower with vs. without lithium treatment, by approximately 80% (a factor of 5) during long-term treatment of patients with bipolar disorder or other major affective disorders (Baldessarini et al. 2005a).

It is important to emphasize that the mortality-sparing effects of lithium treatment occur at standard, recommended therapeutic doses that yield daily minimum concentrations in serum or plasma of 0.6–1.2 mEq/L, and that no new dosing guidelines are required for safe and effective use of lithium salts to limit suicidal risk in bipolar disorder patients.

2. Review and Summary Of Published Data

Published meta-analyses have revealed that lithium treatment is associated with a substantial and statistically significant reduction in suicidal risk, by approximately 80% (Baldessarini et al. 2001, 2003, 2005a; Tondo et al. 2001). Because the most recent analysis encompasses and extends findings from earlier meta-analyses, it is summarized here in some detail.

a. Methods

This new meta-analytical review updated previous reports with computerized literature searching extending from 1970 through February 2005 (Baldessarini et al. 2005a; Table 1). Methods employed, including assessment of study quality, were similar to those of earlier publications (Tondo et al. 2001; Baldessarini et al. 2003). All published studies pertaining to lithium treatment and including information on suicidal behaviors (attempts and completed suicides) were sought. In order to obtain as complete a survey as possible, blind or open, controlled or uncontrolled, and randomized or nonrandomized studies were included. Screening for inclusion in the meta-analysis included the following criteria: publications had to include data that permitted estimates of rates of completed suicides or suicide attempts in patients diagnosed with bipolar disorder or other major affective or schizoaffective disorders; lithium treatment had to be ≥ 3 months; and data on suicidal acts (as well as persons-at-risk and mean exposure times), with or without comparison treatments, were available. Data for inclusion had to be judged to be non-duplicative and reliable. Exposure times were averages based on reported data for each study treatment arm. When precise numbers of treated patients or months of treatment were not provided, conservative estimates were made from the information provided.

As reported previously (Tondo et al. 2001), study-quality was rated as: presence of subjects observed both with and without lithium treatment (1 point), randomized treatment-assignment and blind clinical assessments (1 or 2 points), $N \geq 100$ subjects/treatment group (1 or 2 points), duration ≥ 1 year/treatment group (1 or 2 points). Quality ratings are reported as percentage of the maximum score of 7.0.

Rates of suicidal acts/100 patient-years during maintenance treatment with lithium were tabulated and compared with rates in study arms involving alternative treatment conditions. The initial analysis evaluated crude pooled rates of completed suicides (S) and attempts (A), as well as the ratio (A/S) of rates of attempts to completed suicides as a proposed index of *lethality* of suicidal acts; the 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) were excluded as noninformative, studies involving treatment arms with vs. without lithium treatment were subjected to quantitative meta-analysis (DerSimonian & Laird, 1986). For studies having a study arm without any suicidal acts, the common method of adding 0.5 to *each* cell in the study 2 x 2 table was employed (Sweeting 2004). This continuity-correction was required only for studies in which the lithium treatment arm had no suicidal events, and this method limited the risk of exaggerating antisuicidal effects of lithium.

Risk ratios (RRs) and their standard errors (SEs) for suicidal rates (%/year) were calculated for each of the 31 studies (in 33 non-overlapping reports) included in meta-analyses, based on methods and statistical techniques recommended by DerSimonian & Laird (1986). Preliminary examination of inter-study heterogeneity in RR estimates, based on Q-statistic (degrees-of-freedom [df] = [study number - 1]) methods indicated non-ignorable overall variability ($Q > 90$ th percentile of the χ^2 distribution). Given such heterogeneity, random-effects meta-analysis methods were used to compute a *conservative* pooled RR estimate and its 95%CI, based on study-specific RRs and their SEs. Depending on available data, pooled RRs and their 95%CI estimates for suicides, attempts, and the composite of suicides and attempts were obtained. In these estimation procedures, each study-arm-specific suicidal rate was weighted by the inverse of study variance, to obtain pooled RRs and their variance (SEs and CIs). The computed RR and CIs were summarized in forest plots. The hypothesis (with asymptotic normal z-test) that the overall RR contrasting suicidal rates with versus without lithium treatment was the null value (1.0) was then tested. In order to compare studies falling into major subgroups, notably: [1] studies of BPD patients vs. a mix of manic-depressive types, [2] reports on suicides or attempts vs. both, and [3] studies with above- vs. below-median quality scores (see Table 1), a *stratified* random-effects modeling method for meta-analysis was employed (Bradburn et al. 2005), and heterogeneity between subgroups was examined with χ^2 [df=1] methods. Since all of the randomized, controlled trials identified consistently included zero suicidal events in their lithium arms, they were analyzed separately by use of simple 2x2 contingency analysis to obtain a Fisher exact probability value.

The influence of certain large and atypically heterogeneous studies on pooled RRs was examined by serially including and excluding such studies. Potential publication bias was assessed using funnel-graph 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), and interpreted these results both visually and by use of Begg's test (Begg & Mazumdar 1994) and Eggers test of bias in meta-analysis based on funnel-plot asymmetry (Egger et al. 1997). We also examined results for effects of selected covariates, using meta-regression methods (DerSimonian & Laird 1986).

Statistical analyses used commercial microcomputer programs (Stata[®], Stata Corporation, College Station, TX; Statview-5[®], SAS Institute, Cary, NC). Comparisons with two-tailed $p > 0.05$ at stated degrees-of-freedom were considered not significant (NS).

b. Results

Studies Identified

The 45 studies that provided data on suicidal behavior in mood disorder patients treated with lithium are summarized in Table 1. These 45 studies comprised a total exposure of 113,800 person-years (data were omitted where suicides and attempts, considered separately, were redundant).

Crude rates of suicides and attempts

Overall, crude rates of suicidal acts were 0.437/100 person-years (0.437%/year) with lithium vs. 2.70%/year without lithium treatment, suggesting an overall reduction of risk of suicidal acts during long-term treatment with lithium by more than six-fold (Table 1). Of note, the risk of suicidal acts in all 34 studies providing data for treatment with vs. without lithium was lower with lithium, and risk was zero with lithium in another 6 studies without a comparison treatment arm (Table 1).

Meta-analysis: all suicide acts

Of the 45 studies identified (Table 1), 31 provided one or both non-zero suicidal rates with vs. without lithium treatment and were therefore suitable for meta-analysis (Fig. 1).

Of the 9 studies that involved RCTs, 5 were included in the 31-study meta-analysis (Table 2). These studies represent a total of 40,889 subjects and 84,316 person-years. Crude pooled risks with vs. without lithium were 0.567 vs. 2.71%/year, a greater than six-fold difference favoring lithium (Table 1). Among the 31 studies, there was none in which suicidal risk was higher in the lithium arm than in the non-lithium treatment arm (Fig. 1). The quantitative meta-analysis for all 31 two-armed studies used a conservative, random-effects model indicated by a statistically significant preliminary Q-test of heterogeneity ($Q [df=30] = 44.4, p=0.044$). Overall, there was a highly statistically significant, 4.91-fold (95%CI, 3.82–6.31) lower risk of suicidal acts during long-term treatment with vs. without lithium, or 80% sparing of risk (Fig. 1, Table 2).

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

Study, year	Quality Score	Other Rx	Trial Design	Diagnosis	Suicidal Type	<i>With Lithium</i>		<i>Without Lithium</i>	
						Acts/N/y	Rate (%/y)	Acts/N/y	%/y
Baastrup 1970	57.1	Pbo	RCT	MAD	S+A	0/84/0.42	0.000	0/39/0.42	0.000
Coppen et al. 1971	57.1	Pbo	RCT	MAD	S+A	0/28/2.00	0.000	0/37/2.00	0.000
Prien et al. 1974*	100	Pbo/IMI	RCT	MAD	S	0/146/2.00	0.000	2/181/2.00	0.552
Bech et al. 1976	14.3	—	Open	BPD	S	1/40/7.00	0.357	—	—
Kay & Petterson 1977*	57.1	No-Li	Open	MAD	S	0/123/4.56	0.000	3/69/22.3	0.195
Poole et al. 1978*	28.6	Pre-Li	Open	MAD	A	7/99/5.00	1.414	21/99/5.00	4.24
Glen et al. 1979	28.6	—	Open	MAD	S	8/784/4.83	0.211	—	—
Ahlfors et al. 1981*	57.1	APD	Open	MAD	S	0/14/1.33	0.000	3/112/1.18	2.27
Venkoba-Rao et al. 1982*	28.6	Off-Li	Open	MAD	A	0/47/8.50	0.000	2/47/8.50	0.501
Glen et al. 1984	57.1	Pbo/AMI	RCT	MAD	S+A	0/12/3.00	0.000	0/9/3.00	0.000
Hanus & Zapletálek 1984*	14.3	Pre-Li	Open	MAD	A	4/95/5.10	0.826	25/95/5.10	5.16
Norton & Whalley 1984	28.6	—	Open	MAD	S	8/791/2.17	0.466	—	—
Lepkifker et al. 1985*	14.3	Pre-Li	Open	MDD	A	0/33/8.30	0.000	7/33/8.30	2.56
Jamison 1986	28.6	—	Open	MAD	S	4/9000/1.00**	0.044	—	—
Page et al. 1987	14.3	—	Open	BPD	S	6/79/12.1	0.628	—	—
Wehr et al. 1988	14.3	—	Open	BPD	S	2/70/7.55	0.378	—	—
Nilsson & Axelsson 1990*	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	28.6	—	Open	MAD	S+A	0/103/11.0	0.000	—	—
O'Connell et al. 1991	28.6	—	Open	BPD	S	4/248/8.00	0.202	—	—
Vestergaard & Aagard 1991	14.3	—	Open	MAD	S	5/50/5.00	2.00	—	—
Modestin & Schwarzenbach 1992*	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*	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

Study, year	Quality Score	Other Rx	Trial Design	Diagnosis	Suicidal Type	With Lithium		Without Lithium	
						Acts/N/y	Rate (%/y)	Acts/N/y	%/y
Rihmer et al.1993*	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*	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*	71.4	Off-Li	Open	MAD	S	9/695/6.66	0.194	23/430/6.25	0.856
Müller-Oerlinghausen 1994	28.6	—	Open	MAD	S	7/394/14.2	0.125	—	—
Sharma & Markar 1994*	42.9	No-Li	Open	BPD	S	2/57/8.50	0.413	6/57/9.00	1.17
Ahrens et al. 1995	28.6	—	Open	BPD+SzA	S	7/611/6.60	0.174	—	—
Koukopoulos et al. 1995*	57.1	Off-Li	Open	BPD	S	4/343/12.2	0.096	6/110/2.75	1.98
Nilsson 1995*	71.4	Off-Li	Open	MAD	S	6/230/14.2	0.184	9/132/8.40	0.812
Greil et al. 1996, 1997a, 1997*	80.9	CBZ,ADD	RCT	MAD	S+A	0/157/2.50	0.000	7/158/2.50	1.772
					S	0/157/2.50	0.000	0/158/2.50	0.000
					A	0/157/2.50	0.000	1/158/2.50	0.253
Bocchetta et al. 1998*	42.9	Pre/Off-Li	Open	BPD+SzA	S+A	12/73/9.48	1.73	81/73/11.0	10.1
					S	1/73/9.48	0.145	9/73/3.62	3.41
					A	11/73/9.48	1.59	72/73/11.0	8.97
Coppen & Farmer 1998*	71.4	No-Li	Open	MAD	S	1/103/5.25	0.185	1/12/9.00	0.926
Tondo et al. 1998*	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*	42.9	Pbo	RCT	MDD	S	0/14/0.33	0.000	1/15/0.33	20.2
Brodersen et al. 2000*	42.9	Less-Li	Open	MAD	S	2/77/2.00	1.30	6/48/2.00	6.25
Kallner et al. 2000*	57.1	Off-Li	Open	BP-I	S	11/405/10.1	0.269	7/106/8.26	0.800
Coryell et al. 2001*	42.9	No-Li	Open	MAD	S	6/14/4.67	9.177	8/16/3.80	13.2
Rucci et al. 2002*	71.4	No-Li	Open	BP-I	A	1/119/2.0	0.420	67/166/13.1	3.08
Bowden et al. 2003*	71.4	Pbo/LTG	RCT	BP-I	A	0/46/0.82	0.000	1/127/0.82	0.960

Study, year	Quality Score	Other Rx	Trial Design	Diagnosis	Suicidal Type	With Lithium		Without Lithium	
						Acts/N/y	Rate (%/y)	Acts/N/y	%/y
Calabrese et al. 2003*	100.0	Pbo/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*	85.7	VPA	Open	BPD	S+A	217/29,617/1.00	0.733	95/4453/1.00	2.13
					S	9/13,597/1.00	0.066	3/2040/1.00	0.147
					A	208/16,020/1.00	1.30	92/2413/1.00	3.81
Yerevanian et al. 2003*	71.4	No-Li	Open	BPD	A	5/140/14.6	0.245	6/140/5.61	0.764
Angst et al. 2005*	42.9	No-Li	Open	BPD	S	5/76/34.5	0.191	66/84/30.0	2.62
Gonzalez-Pinto et al. 2005*	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

Legend for Table 1:

Quality in the 45 reports was scored as: presence of subjects observed both with and without lithium treatment (1 point), randomized treatment-assignment and blind clinical assessments (1 or 2 points), N≥100subjects/treatment group (1 or 2 points), duration ≥1 year/treatment group (1 or 2 points), and presented as percentage of the maximum score of 7.0. Rates for suicides (S) and attempts (A) are shown separately only when the total (S+A) rate is >0.

Abbreviations: AMI = amitriptyline; APD = antipsychotic drug; BPD = bipolar disorder; CBZ = carbamazepine; IMI = imipramine; Less-Li = poorly adherent to lithium treatment; LTG = lamotrigine; MAD = major affective disorders; MDD = unipolar major depressive disorder; Pbo = placebo; Pre/Off = before starting and after stopping lithium; RCT = randomized controlled trial; SzA = schizoaffective; VPA = valproate.

[*] Reports (N=31) included in meta-analyses.

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

The 45 reports with data re. completed or attempted suicide include 53,268 patients observed for a weighted average of 2.14 years (total exposure: 113,822 person-years). Suicide rates were lower with vs. without lithium in 34/34 trials (100%) with both conditions, and in another 6, there were no acts during treatment with lithium. The overall crude risk for suicidal acts with vs. without lithium was 388/45,607/1.95 years (0.437%/year) vs. 675/7661/3.26 years (2.70%/year), a crude risk difference of 6.18.

The 31 reports used for meta-analyses included 40,889 subjects observed for a weighted average of 2.06 years (total exposure: 84,316 person-years). The crude risk for suicidal acts with vs. without lithium was 336/33,313/1.78 years (0.567%/year) vs. 675/7576/3.29 years (2.71%/year), a crude risk ratio of 4.78

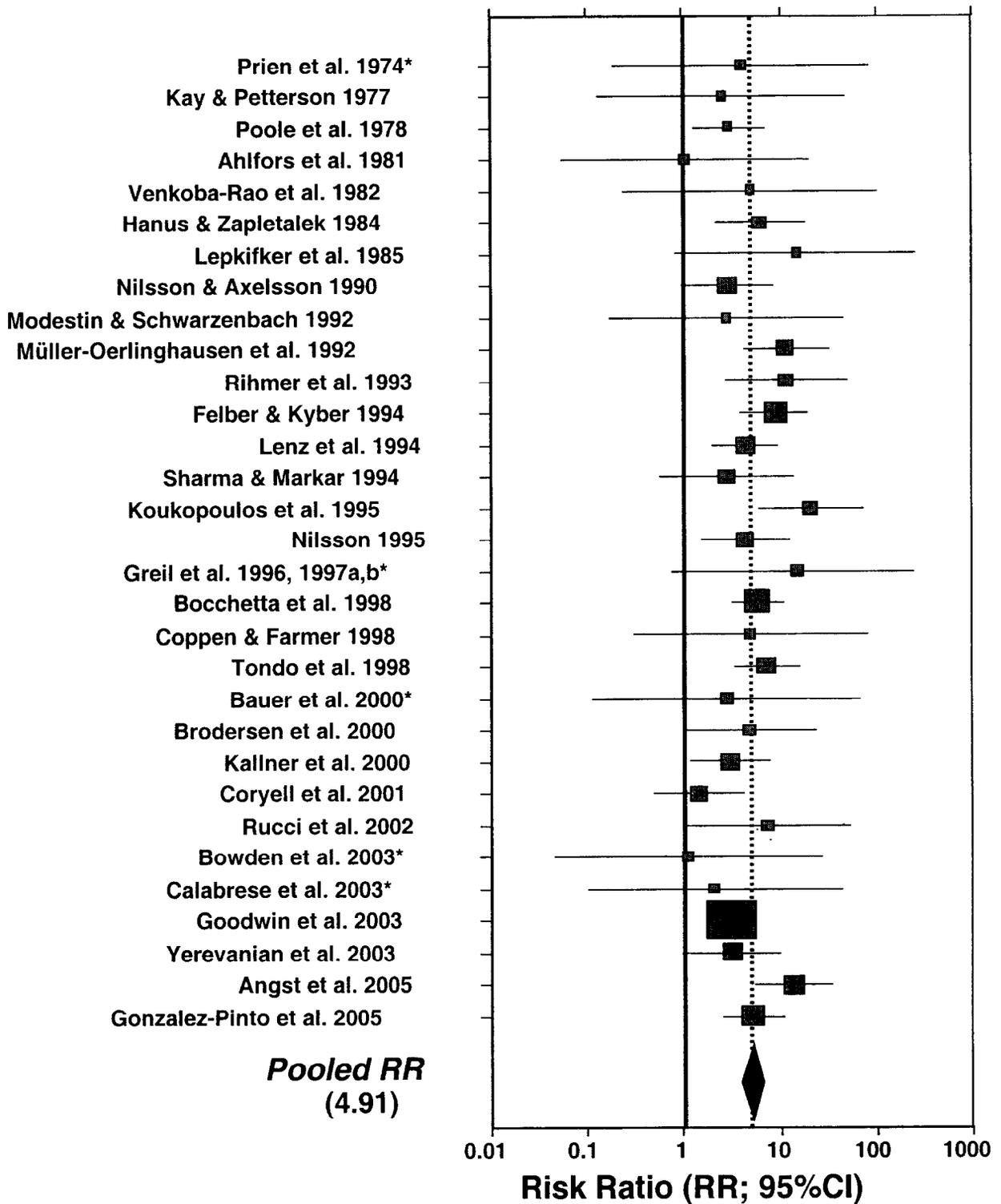


Figure 1. Overall random-effects meta-analysis of 31 studies of risks of suicides and/or attempts, with versus without lithium: RR with 95%CI for each study (shaded squares proportional to study-weight); computed pooled (black diamond) RR = 4.91 (CI: 3.82-6.31; z=12.5, p<0.0001). [*] = RCTs.

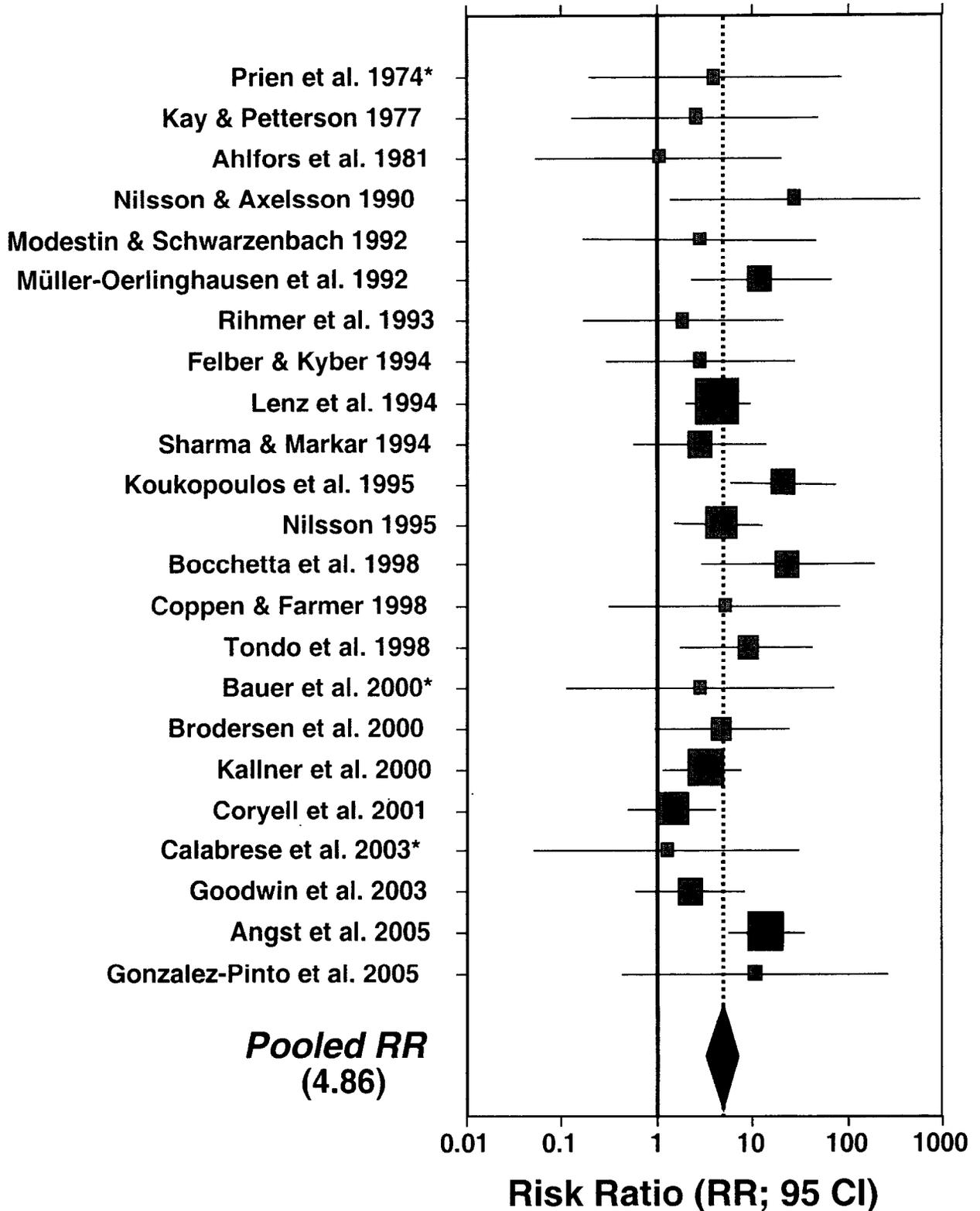


Figure 2. Overall random-effects meta-analysis of 23 studies of risks of suicides, with versus without lithium: RR with 95% CI for each study (shaded squares proportional to study-weight); computed pooled (black diamond) RR = 4.86 (CI: 3.36-7.02, z=8.42, p<0.0001). [*] = RCTs.

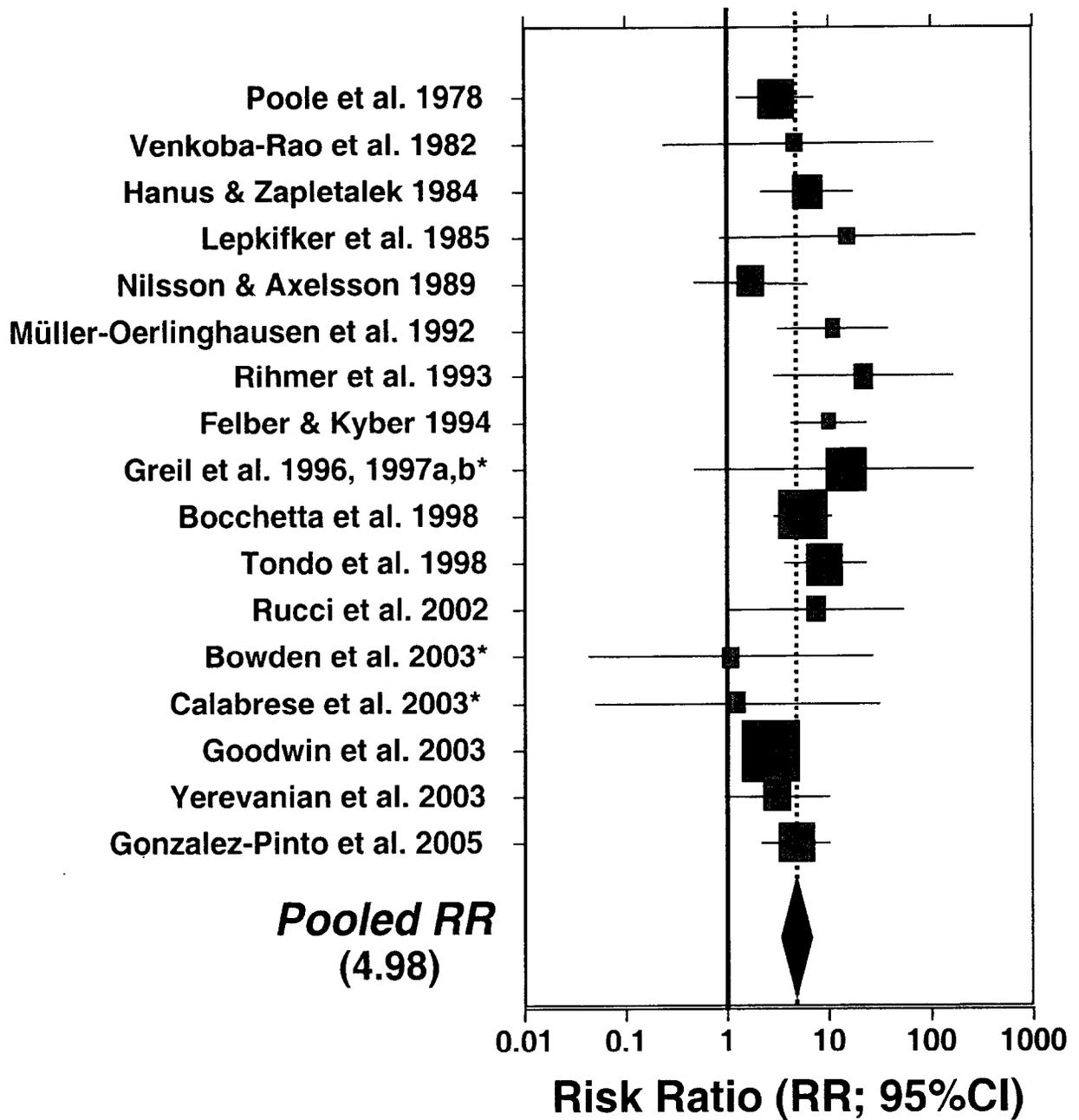


Figure 3. Overall random-effects meta-analysis of 17 studies of risks of suicide attempts, with versus without lithium: RR with 95% CI for each study (shaded squares proportional to study-weight); computed pooled (black diamond) RR = 4.98 (CI: 3.56-6.96; z=9.42, p<0.0001). [*] = RCTs.

Meta-analysis: completed and attempted suicide

The pooled estimated RR for *completed suicides* in 23 studies with at least one non-zero numerator was 4.86 (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 attempts* also was detected on the basis of 17 studies (RR=4.98; CI: 3.56–6.96; Fig. 3, Table 2). In these analyses, conservative random-effects modeling was used although preliminary Q-tests indicated nonsignificant heterogeneity of results across studies (for completed suicides: $Q [df=22] = 26.5, p=0.23$; for attempts: $Q [df=16] = 26.2, p=0.051$).

Table 2. Summary of meta-analyses: Lithium treatment vs. 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 ^b	30	5.34	[4.27–6.68]	14.7	<0.0001
Suicides only	23	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 conservative, random-effects modeling.

b. Results with Goodwin et al. 2003 (58) omitted indicate that this very large study did not exert a misleading influence on the overall findings.

c. For studies with bipolar disorder vs. major affective disorder patient samples: $\chi^2 (df=1) = 0.91, p=0.34$; 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 vs. below median

Attempt/suicide ratio (lethality)

Risk-rates were calculated across all studies providing risk data for suicides and attempts separately (Table 3). For completed suicides, the crude risk was 0.141%/year with lithium treatment versus 1.38%/year without lithium—a ten-fold difference. For attempted suicide, the respective crude rates were 1.24%/year versus 3.63%/year, a three-fold difference in favor of lithium. In addition, the ratio of attempts to completed suicides (A/S) was more than twice-*higher* (2.21-fold) during lithium treatment (6.48 vs. 2.93; Table 3), suggesting *reduced* lethality of suicidal acts with lithium treatment.

The finding that the ratio of attempts/suicides (A/S) was greater during lithium treatment was sustained when only the 9 studies with data for all four cells of interest (suicides and attempts, with and without lithium) were considered in order to avoid biasing that might arise by including data from studies without all four cells. For suicide attempts, these 9 studies yielded a pooled crude rate of 4.62%/year (352 acts/3295 persons/2.31 years) without lithium treatment vs. 1.23%/year (257/16,793/1.24) with lithium, and for completed suicides, rates of 0.0869 %/year (16/14,370/1.28) with lithium vs. 0.752%/year (31/2797/1.47) without it. The A/S ratios without vs. with lithium were 6.14 vs. 14.2, or 2.31-times greater with lithium. Among patients with bipolar disorder, analyzed separately, the A/S ratio was 2.50-fold higher with lithium treatment (1.214/0.076%/year = 16.0) vs. without it (4.036/0.632%/year = 6.39; not shown).

Random-effects meta-regression modeling methods, with adjustment for clustering on study, were used to test for an interaction of treatment-type by attempted vs. completed suicides in the 9 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 to nonfatal suicide attempts. Together, these findings are consistent with the proposal that *lethality* of suicidal acts as well as their frequency may be reduced by long-term treatment with lithium.

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 bipolar disorder

(RR=5.41 [CI: 3.60–8.14]) than in 17 studies with a mixture of patients with major affective disorders (RR=4.60 [CI, 3.38–6.26]); χ^2 [df=1] = 0.91, $p=0.34$; Table 2). Studies rated at above-median quality yielded significantly more conservative results than those with lower quality scores (RR=3.92 vs. 5.56; χ^2 [df=1] = 8.39, $p=0.004$). We also found that removing the unusually large study by Goodwin and colleagues (Goodwin et al. 2003) had little effect on the reported findings (Table 2).

There were 10 reports involving 8 randomized, controlled trials (RCTs) providing direct contrasts pertaining to suicide or suicide attempts (Baastrup 1970; Coppen et al. 1971; Prien et al. 1974; Glen et al. 1984; Greil et al. 1996, 1977a, 1977b; Bauer et al. 2000; Bowden et al. 2003; Calabrese et al. 2003). Among these 8 studies, 3 could provide no risk contrast data because they had no suicidal outcomes in either lithium or comparator arm (Baastrup 1970; Coppen et al. 1971; Glen et al. 1984). In the other 5 studies, there were no suicide deaths in the lithium arms, thus obviating risk ratio estimation. A risk-difference contrast between lithium and non-lithium arms in these 5 studies also proved uninformative because of the zero outcomes in all 5 lithium arms. Accordingly, a simple contingency table analysis using Fisher's exact methods were used to assess relative lithium vs. comparator suicide risk in these 5 studies. In the non-lithium arms of these 5 studies, there were 11 suicides or attempts. Based on the aggregate 2x2 tabulation (11/590 [1.86%] vs. 0/337 [0.00%]), the associated Fisher's exact p -value was 0.0093. When this contingency table was extended to include consideration of exposure times (ranging from 0.24 to 2.5 years), this lithium vs. non-lithium risk difference was even more pronounced (Fisher's exact $p<0.001$).

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 nearly balanced around the centerline defined as the overall, fixed-effect pooled RR of 4.10. In addition, Begg's test for publication bias was not significant ($z = 1.29$, $p=0.20$), nor was Egger's test for funnel-plot asymmetry (not shown; Baldessarini et al. 2005a).

Meta-regression analyses

Several trial-specific factors that might tend to confound the reported outcomes were examined by meta-regression modeling. Factors considered were year of publication, bipolar disorder vs. any other diagnostic category, number of subjects/study, RCT vs. open-label-clinical study design, assessment of suicides-plus-attempts vs. suicides or attempts separately, and higher vs. lower quality ratings. None of these factors alone, or combined, was even marginally correlated with the contrast in outcomes with vs. without lithium treatment, indicating that the effect of lithium on suicidal risk was very robust.

Table 3. Relationships of attempts and suicides

Measures	Attempts (A)	Suicides (S)	A/S Ratio
<i>Without lithium</i>			
Studies		17	23
Proportions	482/4072/3.07	194/4360/3.38	
Rate (%/year)	3.63	1.38	2.93
[95% CI]	[2.60–4.67]	[0.0–2.75]	[2.89–2.98]
<i>With lithium</i>			
Studies		17	23
Proportions	274/17,446/1.43	114/28,815/2.35	
Rate (%/year)	1.24	0.141	6.48
[95% CI]	[1.09–1.40]	[0.0–0.39]	[6.39–6.58]
<i>Relative Risk</i>	2.93	9.79	2.21

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, and *excluding* data pertaining to combined A+S.

The A/S ratio is 2.21-times (CI: 2.17–2.25) *higher* with lithium treatment, suggesting *decreased* lethality of suicidal acts, as reflected in the greater relative reduction of risk for suicides than attempts.

III. ADDITIONAL SUPPORTING COMMENTS

Suicide is now unequivocally recognized as a serious national and international public health problem, but one that can be treated. On that principle, the Surgeon General's *Call to Action to Prevent Suicide* (USPHS 1999) and the *National Strategy for Suicide Prevention* (USPHS 2001), the National Academy of Sciences Institute of Medicine (Goldsmith et al. 2002), the *Practice Guideline for the Assessment and Treatment of Patients With Suicidal Behaviors* (APA 2003), and the World Health Organization (WHO 2005), as well as numerous professional and community advocacy groups have made strong recommendations to increase efforts to prevent suicide. In all of these official statements, both pharmacologic and nonpharmacologic interventions were considered to play potential roles. However, a constant among these recommendations is acknowledgment that an extensive, consistent, and highly significant body of research documents the unique effectiveness of lithium in reducing suicidal acts, both attempts and completions, among persons with recurrent major affective disorders, and particularly bipolar disorder. The consistency and strength of the data remain very high despite acknowledged difficulties in assessing the risks of suicidal behavior and in conducting ethical and feasible therapeutic studies aimed at reducing suicidal risk. These publications also note that research findings pertaining to reduction of suicidal risk in association with other pharmacologic or other therapeutic interventions, in the treatment of any psychiatric disorders, are either weak or not available.

As a result, lithium is recommended by national and international health-care professionals as an appropriate, clinically indicated intervention for suicide prevention. For example, Müller-Oerlinghausen and his collaborators (2003) concluded that lithium is the only pharmacologic agent with sufficient evidence of suicide risk reduction and that its use should be greater than it is currently. Along with nonpharmacological interventions, lithium is also recommended in *Reducing Suicide: A National Imperative* (2002), developed by the U.S. Institute of Medicine on behalf of the U.S. National Institute of Mental Health, the National Institute of Drug Abuse, the U.S. Veterans Affairs Administration, The National Institute on Alcohol Abuse, and the Centers for Disease Control and Prevention (Goldsmith et al. 2002). Support for lithium also was

provided in a very recent, comprehensive review of treatment effects on suicidal risk (Ernst & Goldberg 2004).

In 2003, the American Psychiatric Association (APA) published *Practice Guideline for the Assessment and Treatment of Patients With Suicidal Behaviors* (Jacobs 2003). All specific recommendations were coded into one of 3 categories:

- I. Recommended with substantial clinical confidences;
- II. Recommended with moderate clinical confidence;
- III. May be recommended on the basis of individual circumstances.

The recommendations of the APA for pharmacological interventions to reduce the risk of suicide are as follows:

“There is strong evidence that long-term maintenance treatment with lithium salts is associated with major reductions in the risk of both suicide and suicide attempts in patients with bipolar disorder (I), and there is moderate evidence for similar risk reductions in patients with recurrent major depressive disorder.(I.)”(Jacobs 2003, page 6).

“Specific anticonvulsants have been shown to be efficacious in treating episodes of mania (i.e., divalproex) or recurrences of bipolar depression (i.e., lamotrigine), but there is no clear evidence that their use alters rates of suicide or suicidal behaviors (II)” (Jacobs 2003, page 6).

“Evidence for a lowering of suicide rates with antidepressant treatment is inconclusive. (Jacobs 2003, page 6).

IV. ENVIRONMENTAL IMPACT

The action requested of the FDA will not result in the introduction of any substance into the environment and is thus categorically excluded under the provisions of 21 CFR 525.30. The request is for an extension of the current therapeutic indications for lithium (carbonate or citrate in various formulations), which are already approved by the U.S. FDA and which are within the context of widespread use of this agent for nearly 50 years.

V. SUMMARY & CONCLUSIONS

Suicide and suicide attempts are a major health concern, are strongly associated with common psychiatric illnesses, most often mood disorders, and are of particular concern among patients with bipolar disorder, whose risks at least meet, and probably exceed those of any other major psychiatric or substance-use diagnostic group with increased risks for suicidal behavior.

Lithium is the only psychopharmacologic agent with substantial and consistent evidence of ability to reduce significantly rates of completed suicides as well as suicide attempts in patients with bipolar disorder, specifically, and indeed the *only* treatment of any kind with evidence of reduced risk of completed suicide in any clinical disorder. Lithium treatment is associated with a reduction of all suicidal acts by about 80% and a reduction in mortality by suicide by a very similar amount (Table 3). These effects occurred at standard, currently recommended therapeutic doses, yielding daily trough or minimum concentrations in serum or plasma of 0.6–1.2 mEq/L. Consequently, no new dosing guidelines are required for safe and effective use of lithium salts to limit suicidal risk.

Therefore, this Petition seeks to have the U.S. Commissioner of Food and Drugs to act immediately to order or permit amendment of the labeling for all lithium agents indicated for the treatment of bipolar I (manic-depressive) disorder to include an indication for suicide prevention in order to provide official guidance to physicians to help reduce suicidal behaviors in a known high risk population:

Indication: Lithium carbonate or citrate is indicated to reduce the incidence of suicide and suicide attempts in patients with manic-depressive illness (bipolar I disorder)
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V. INTEREST OF THE PARTIES

Ross J. Baldessarini, M.D., D.Sc. (hon.), DLFAPA, FACP, FACNP, FCINP

Dr. Baldessarini, an internationally known neuroscientist and research psychopharmacologist, has made many contributions related to the basic scientific understanding of monoaminergic neurotransmission systems in the brain, their involvement in the pathophysiology of major neuropsychiatric disorders, and their interactions with antipsychotic and mood-altering medicines. His recent laboratory interests have focused on central dopaminergic systems of the brain and their relevance to the actions, side effects, development, and clinical application of antipsychotic and antimanic agents. He has also contributed extensively in studies of the course and treatment of bipolar disorder, and to the therapeutics of suicide. He was a Career Investigator of the NIMH from 1970–2000. He has over 1650 publications, including the chapters on psychopharmacology in standard American textbook of pharmacology, *Goodman & Gilman's The Pharmacologic Basis of Therapeutics*, through its last six editions, as well as his own monograph *Chemotherapy in Psychiatry: Principles and Practice* (Harvard University Press), and serves on editorial boards of several leading neuroscience and psychiatric journals, including the *Archives of General Psychiatry*. Among his recognitions was election to the Scholars of Johns Hopkins University, the Falcone Prize for Bipolar Disorders Research of the American National Alliance for Research in Schizophrenia and Depression (NARSAD), the American Foundation for Suicide Prevention (AFSP) Research Prize, and listing on the *ISI* roster of most-frequently cited scientists.

Dr. Baldessarini graduated from Williams College in Massachusetts with highest honors in chemistry in 1959. He completed medical education at Johns Hopkins University in Baltimore in 1963, where he began training in neuroscience with Professor Vernon Mountcastle in neurophysiology, as well as spending a year at the National Institutes of Health with Drs. Julius Axelrod, Seymour Kety, and Irwin Kopin in neuropharmacology. After graduation, he completed internship at Boston City Hospital in internal medicine and then returned to the NIMH for additional training in biochemical neuropharmacology in 1964–66. In 1966 he returned to Johns Hopkins Hospital for training in psychiatry

with Professor Joel Elkes, and was Chief Resident Psychiatrist of the Henry Phipps Psychiatric Clinic there in 1968–1969.

He moved to Massachusetts General Hospital (MGH) in Boston in 1969 to help Professor Seymour Kety establish the Laboratories for Psychiatric Research (LPR), which he directed following Dr. Kety's retirement in 1983. In 1988, Professor Baldessarini was named permanent Director of the LPR as well as Director of a new Bipolar & Psychotic Disorders Program, which he founded. In 1989, also became Co-Director of the Psychopharmacology Program and Psychopharmacology Training at the McLean Psychiatric Division of MGH, and has directed that Program since 1996. He is a tenured Professor of Psychiatry and in Neuroscience at Harvard Medical School and Senior Consulting Psychiatrist at Massachusetts General Hospital. He founded the International Consortium for Bipolar Disorder Research in 1995 with colleagues from the US, Canada and Europe, and serves as a consultant to numerous scientific, industrial, and clinical organizations.

Frederick K. Goodwin, MD

Dr. Goodwin's spent most of his long research career at the National Institute of Mental Health (NIMH), initially as a clinical and laboratory scientist. He later served as Director of the NIMH Intramural Research Program, and was next appointed by the President to head of the Alcohol, Drug Abuse and Mental Health Administration (ADAMHA), a 2.3 billion dollar agency that incorporated the NIMH and was, like the NIH and FDA, an agency of the U.S. Department of Health and Human Services. Finally, he held the position of Director of NIMH in the year that ADAMHA was reorganized into a services agency, and its three research Institutes (NIMH, NIAAA, and NIDA) returned to NIH.

His research contributions on biological and pharmacological aspects of mental disorders began in 1969 with the first double-blind, controlled study of the efficacy of lithium in bipolar depression. Well before techniques were available to explore directly for biochemical abnormalities in patients, he and his colleagues carried out a series of studies using pharmacologic probes (such as L-dopa and other monoamine neurotransmitter precursors and synthesis inhibitors) to test the monoamine theories of depression and mania. These efforts resulted both in an A.E. Bennett Research Award in 1970, and the

major international award in this field, the Anna-Monika Prize for Research in Depression, in 1971.

The next phase of the research led by Dr. Goodwin included attempts to unravel the biological meaning of clinical subtypes of the several manic-depressive disorders. He considered selective pharmacological response as a probe, and demonstrated a selective antidepressant response to lithium in bipolar but not in unipolar major depression. He also defined the precise clinical phenomena of the stages of mania, and he offered pharmacological evidence that these stages were associated with increased noradrenergic or dopaminergic activation. He also explored how such clinical variables as diagnosis, symptoms, illness-stages and severity, treatment, diet, and activity each contributed to observed biochemical measures in cerebrospinal fluid.

His studies of effects of sleep deprivation on biochemistry and mood marked a transition from cross-sectional studies to correlates of natural course of manic-depressive illness. He and his colleagues demonstrated that antidepressants can induce rapid cycling between mania and depression, that an imposed phase-advance of the circadian sleep-wake cycle exerts mood-elevating effects, and the unexpected finding that bright light can suppress melatonin secretion in humans. This work led to his group's identification of the new syndrome Seasonal Affective Disorder (SAD) and its treatment with bright artificial light.

Dr. Goodwin's research led to the discovery of a powerful relationship between the central serotonergic system and the traits of aggression and impulsivity. This line of inquiry has proven particularly fruitful in leading to evidence of an important association between the function of central serotonin systems and suicide.

The predominant themes of Dr. Goodwin's research career are integrated in his authoritative textbook, *Manic-Depressive Illness*, co-authored with Kay R. Jamison, Ph.D. (Oxford University Press, 1990, and in press). This volume was the first comprehensive, non-multiauthored work on bipolar disorder designed to cover most of the important period of research on the illness since its recognition as a separate entity in the mid-20th century. This massive project entailed extensive reinterpretation of original data and presented significant new contributions to the knowledge base. The Association

of American Publishers designated *Manic-Depressive Illness* as the "best medical book of 1990." It was the first psychiatry text ever to win the award.

Dr. Goodwin was elected to membership in the Institute of Medicine of the U.S. National Academy of Sciences. He has served on editorial boards of leading journals in his field and is a founder of the research journal, *Psychiatry Research*. He was recognized by *Current Contents* as one of the 1,000 (99.9th percentile) most frequently cited international scientists during the last 15 years, and one of only five psychiatrists on that distinguished roster. Their most recent listing of most highly cited scientists continues to include Dr. Goodwin.

He has been active in encouraging further integration of psychiatry into the mainstream of medicine. In 1992, he played a pivotal role in achieving the return, after a quarter-century of dualistic isolation, of the NIMH to the NIH. He became the first psychiatrist to be honored by the Federation of American Societies for Experimental Biology (FASEB), and the National Association for Biomedical Research (NABR) for contributions to supporting the infrastructure of the American biomedical research enterprise, including his leadership in establishing U.S. PHS-based, science education programs for schools and the general public. He has also played an important role in developing sensible regulations for the protection of human subjects. In addition, he assumed a critical role in developing a balance between concern for animal rights and the needs of biomedical research.

After retiring from active service in the federal government in 1994, Dr. Goodwin moved to the George Washington University (GWU) Medical Center in D.C., as a Research Professor of Psychiatry and Behavioral Sciences, and founded and has directed the Psychopharmacology Research Center and the Center on Neuroscience, Medical Progress and Society. At GWU he has remained active in research and teaching while continuing to be active on the national scene in science and health policy issues and in public education.

In 2003, he reported in *JAMA* on a major study of over 25,000 patients with bipolar disorder in large West- Coast HMOs that compared the incidence of suicidal behaviors during treatment with the two mood-stabilizers most widely used in the U.S. (lithium and sodium valproate). This study revealed that the rate of suicide and suicide attempts was nearly three times lower during treatment with lithium than with valproate. He is currently completing the second edition of his comprehensive book with Kay R. Jamison, Ph.D., *Manic-Depressive Illness*, which is due to appear in 2006.

Respectfully submitted,

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References Cited

([*] Reports included in meta-analyses)

- *Ahlfors UG, Baastrup PC, Dencker SJ, Elgen K, Lingjaerde O, Pedersen V, Schou M, Aaskoven O. Flupenthixol decanoate in recurrent manic-depressive illness. A comparison with lithium. *Acta Psychiatr Scand* 1981; 64: 226–237.
- Ahrens B, Müller-Oerlinghausen B, Schou M, Wolf T, Alda M, Grof E, Grof P, Lenz G, Simhandl C, Thau K. Excess cardiovascular and suicide mortality of affective disorders may be reduced by lithium prophylaxis. *J Affect Disord* 1995; 33: 67–75.
- Ahrens B, Müller-Oerlinghausen B. Does lithium exert an independent antisuicidal effect? *Pharmacopsychiatry* 2001; 34: 132–136.
- Akiskal HS. Validating 'hard' and 'soft' phenotypes within the bipolar spectrum: continuity or discontinuity? *J Affect Disord* 2003; 73: 1–5.
- APA (American Psychiatric Association). *Diagnostic and Statistical Manual of Mental Disorders*. Fourth edition (DSM-IV). Arlington: American Psychiatric Press, 2000.
- *Angst J. The emerging epidemiology of hypomania and bipolar II disorder. *J Affect Disord* 1998; 50:143–151.
- Baastrup PC, Poulsen JC, Schou M, Thomsen K, Amdisen A. Prophylactic lithium: double blind discontinuation in manic-depressive and recurrent-depressive disorders. *Lancet* 1970; 2: 326–330.
- Baldessarini RJ, Tondo L, Viguera AC. Discontinuing lithium maintenance treatment in bipolar disorders: risks and implications. *Bipolar Disord* 1999; 1: 17–24.
- Baldessarini RJ, Tondo L, Hennen J. Treating the suicidal patient with bipolar disorder: reducing suicide risk with lithium. *Ann N Y Acad Sci* 2001; 932: 24–38.
- Baldessarini RJ, Tondo L, Hennen J, Viguera AC. Is lithium still worth using? An update of selected recent research. *Harvard Rev Psychiatry* 2002; 10: 59–75.
- Baldessarini RJ, Tondo L, Hennen J. Lithium treatment and suicide risk in major affective disorders: update and new findings. *J Clin Psychiatry* 2003; 64 (Suppl 5): 44–52.
- Baldessarini RJ, Salvatore P, Tohen M, Khalsa HMK, Hennen J, González-Pinto A, Baethge C, Tohen M. Morbidity from onset in first-episode bipolar I disorder patients: The International-300 study. *Neuropsychopharmacology* 2004; 29 (Suppl 1): S88.
- Baldessarini RJ. Drug therapy of depression and anxiety disorders. Chapt 17 in Hardman JG, Limbird LE, Gilman AG, editors. *Goodman & Gilman's The Pharmacologic Basis of Therapeutics*. New York: McGraw-Hill Press, 2005, pp 429–459.
- Baldessarini RJ, Tondo, Hennen J, Pompili M, Davis PG. Decreased suicidal risk during long-term lithium treatment: a meta-analysis. *Bipolar Disord* 2005a; in press.
- Baldessarini RJ, Faedda GL, Hennen J: Risk of mania with antidepressants. *Arch Pediatr Adolesc Med* 2005b; 159: 298–299.

- Baldessarini RJ, Tarazi FI. Pharmacotherapy of psychosis and mania. Chapt 18 in: Hardman JG, Limbird LE, Gilman AG, editors. Goodman & Gilman's The Pharmacologic Basis of Therapeutics. New York: McGraw-Hill Press, 2005, pp 461–500.
- Baldessarini RJ, Pompili M, Tondo I. Management of suicidal risk in bipolar disorder patients. Chapt 13 in Simon RI, Hales RE, editors. American Psychiatric Press Textbook of Suicide Assessment and Management. Arlington, VA: American Psychiatric Press, 2005a, in press [Note: This text is not yet available. It will be provided as soon as it is published.]
- *Bauer M, Bschor T, Kunz D, Berghofer A, Strohle A, Müller-Oerlinghausen B. Double-blind, placebo-controlled trial of the use of lithium to augment antidepressant medication in continuation treatment of unipolar major depression. *Am J Psychiatry* 2000; 157: 1429–1435.
- Bech P, Vendsborg PB, Rafaelsen OJ. Lithium maintenance treatment of manic-melancholic patients: its role in the daily routine *Acta Psychiatr Scand* 1976; 53: 70–81.
- Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; 50: 1088–1101.
- *Bocchetta A, Ardaur R, Burrai C, Chillotti C, Quesada G, Del Zompo M. Suicidal behavior on and off lithium prophylaxis in a group of patients with prior suicide attempts. *J Clin Psychopharmacol* 1998; 18: 384–389.
- *Bowden CL, Calabrese JR, Sachs G, Yatham LN, Asghar SA, Hompland M, Montgomery P, Earl N, Smoot TM, DeVeaugh-Geiss J. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. *Arch Gen Psychiatry* 2003; 60:392-400.
- Bradburn MJ, Deeks J, Altman D. Updated and new commands for meta-analysis in Stata®. 2005. Oxford, UK: UK Cancer Research Medical Statistics Group, Center for Statistics in Medicine, 2005.
- *Brodersen A, Licht RW, Vestergaard P, Olesen AV, Mortensen PB. Sixteen-year mortality in patients with affective disorder commenced on lithium. *Br J Psychiatry* 2000; 176: 429–433.
- *Calabrese JR, Bowden CL, Sachs G, Yatham LN, Behnke K, Mehtonen OP, Montgomery P, Ascher J, Paska W, Earl N, DeVeaugh-Geiss J. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *J Clin Psychiatry* 2003; 64: 1013–1024.
- Clozaril® (clozapine) Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals, 2003.
- *Coppin A, Noguera R, Bailey J, Burns BH, Swani MS, Hare EH, Gardner R, Maggs R. Prophylactic lithium in affective disorders. Controlled trial. *Lancet* 1971; 2: 275–279.
- Coppin A, Standish-Barry H, Bailey J, Houston G, Silcocks P, Hermon C. Does lithium reduce the mortality of recurrent mood disorders? *J Affect Disord* 1991; 23: 1–7.
- *Coppin A, Farmer R. Suicide mortality in patients on lithium maintenance therapy. *J Affect Disord* 1998; 50: 261–267.
- *Coryell W, Arndt S, Turvey C, Endicott J, Solomon D, Mueller T, Leon AC, Keller M. Lithium and suicidal behavior in major affective disorder: a case-control study. *Acta Psychiatr Scand* 2001; 104: 193–197.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7: 177–188.

- Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315: 629–634.
- Ernst CL, Goldberg JF. Antisuicide properties of psychotropic drugs: a critical review. *Harvard Rev Psychiatry* 2004; 12: 14–41.
- Eskalith® Prescribing Information. Research Triangle Park, NC: GlaxoSmithKline Pharmaceuticals, 2004.
- Faedda GL, Baldessarini RJ, Suppes T, Tondo L, Becker I, Lipschitz DS. Pediatric-onset bipolar disorder: a neglected clinical and public health problem. *Harv Rev Psychiatry* 1995; 3: 171–195.
- Faedda GL, Baldessarini RJ, Glovinsky IP, Austin NB. Pediatric bipolar disorder: phenomenology and course of illness. *Bipolar Disord* 2004; 6: 305–313.
- *Felber W, Kyber A. Suizide und Parazuide während und ausserhalb einer Lithium prophylaxe. In: Müller-Oerlinghausen B, Berghöfer A (eds). *Ziele und Ergebnisse der Medikamentösen Prophylaxe Affektiver Psychosen*. Stuttgart, Germany: G.Thieme Verlag, 1994, pp 53–94.
- Geddes J. Relapse prevention in bipolar disorder: The contribution of systematic reviews and meta-analyses. *Acta Psychiatrica Scandinavica* 2004; 110 (Suppl 423): 8
- Geddes JR, Burgess S, Hawton K, Jamison K, Goodwin GM. Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. *Am J Psychiatry* 2004; 161: 217–222.
- Glen AI, Dodd M, Hulme EB, Kreitman N. Mortality on lithium. *Neuropsychobiology* 1979; 5: 167–173.
- Glen AI, Johnson AL, Shepherd M. Continuation therapy with lithium and amitriptyline in unipolar depressive illness: a randomized, double-blind, controlled trial. *Psychol Med* 1984; 14: 37–50.
- Glick ID. Undiagnosed Bipolar Disorder: New Syndromes and New Treatments. *Prim Care Companion J Clin Psychiatry* 2004; 6: 27–33.
- Goldsmith SK, Pellman TC, Kleinman AM, Bunney WE (eds). *Reducing Suicide: A National Imperative* (2002). Washington: U.S. Institute of Medicine–National Academies Press, 2002.
- *Gonzalez-Pinto A, Mosquera F, Alonso M, López P, Ramírez F, Vieta E, Baldessarini RJ. Increased suicidal risk in bipolar-I disorder patients nonadherent to long-term lithium treatment. Manuscript in review 2005.
- Goodwin FK, Jamison KR. *Manic-Depressive Illness*. New York: Oxford University Press, 1990.
- *Goodwin FK, Fireman B, Simon GE, Hunkeler EM, Lee J, Revicki D. Suicide risk in bipolar disorder during treatment with lithium and divalproex. *JAMA* 2003; 290: 1467–1473.
- *Greil W, Ludwig-Mayerhofer W, Erazo N, Engel RR, Czernik A, Giedke H, Müller-Oerlinghausen B, Osterheider M, Rudolf GA, Sauer H, Tegeler J, Wetterling T. Comparative efficacy of lithium and amitriptyline in the maintenance treatment of recurrent unipolar depression: a randomised study. *J Affect Disord* 1996; 40: 179–190.
- *Greil W, Ludwig-Mayerhofer W, Erazo N, Engel RR, Czernik A, Giedke H, Müller-Oerlinghausen B, Osterheider M, Rudolf GA, Sauer H, Tegeler J, Wetterling T. Lithium vs carbamazepine in the maintenance treatment of schizoaffective disorder: a randomised study. *Eur Arch Psychiatry Clin Neurosci* 1997a; 247: 42–50.

- *Greil W, Ludwig-Mayerhofer W, Erazo N, Schochlin C, Schmidt S, Engel RR, Czernik A, Giedke H, Müller-Oerlinghausen B, Osterheider M, Rudolf GA, Sauer H, Tegeler J, Wetterling T. Lithium versus carbamazepine in the maintenance treatment of bipolar disorders: a randomized study. *J Affect Disord* 1997b; 43: 151–161.
- Greil W, Kleindienst N. Concepts in the treatment of bipolar disorder. *Acta Psychiatr Scand* 2003; (Suppl 418): 41–46.
- *Hanus K, Zapletal M. [Suicidal activity of patients with affective disorders during the preventive use of lithium]. *Cesk Psychiatr* 1984; 80: 97–100.
- Harris EC, Barraclough B. Suicide as an outcome for mental disorders. A meta-analysis. *Br J Psychiatry* 1997; 170: 205–228
- Hennen J, Baldessarini RJ. Suicidal risk during treatment with clozapine: a meta-analysis. *Schizophrenia Res* 2005; 73: 139–145.
- Jacobs D (ed): American Psychiatric Association (APA): Practice guideline for the assessment and treatment of patients with suicidal behaviors. *Am J Psychiatry* 2003; 160 (11 Suppl): 1–44.
- Jamison KR. Suicide and bipolar disorders. *Ann N Y Acad Sci* 1986; 487: 301–315.
- Joffe RT, MacQueen GM, Marriott M, Trevor YL. A prospective, longitudinal study of percentage of time spent ill in patients with bipolar I or bipolar II disorders. *Bipolar Disord* 2004; 6: 62–66.
- Jope RS. Anti-bipolar therapy: mechanism of action of lithium. *Mol Psychiatry* 1999; 4: 117–128.
- Judd LL, Akiskal HS, Schettler PJ, Endicott J, Maser J, Solomon DA, Leon AC, Rice JA, Keller MB. The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Arch Gen Psychiatry* 2002; 59: 530–537.
- *Kallner G, Lindelius R, Petterson U, Stockman O, Tham A. Mortality in 497 patients with affective disorders attending a lithium clinic or after having left it. *Pharmacopsychiatry* 2000; 33: 8–13.
- Kasper S. Issues in the treatment of bipolar disorder. *Eur Neuropsychopharmacol* 2003, 13 (Suppl 2): S37–S42.
- *Kay DWK, Petterson U. Manic-depressive illness. *Acta Psychiatr Scand* 1977; 269 (Suppl): 55–60.
- Kessing LV, Sondergard L, Kvist K, Andersen PK. Suicide risk in patients treated with lithium. *Arch Gen Psychiatry* 2005; 62: 860–866.
- Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994; 51: 8–19.
- Kessler RC, Berglund P, Demler O, Jin R, Walters EE. Lifetime prevalence and age-of-onset distributions of *DSM-IV* disorders in the National Comorbidity Survey replication. *Arch Gen Psychiatry* 2005; 63: 593–602.
- Kleinman L, Lowin A, Flood E, Gandhi G, Edgell E, Revicki D. Costs of bipolar disorder. *Pharmacoeconomics* 2003; 21: 601–622
- Kochanek KD, Murphy SL, Anderson RN, Scott C. Deaths: final data for 2002. *Natl Vital Stat Rep* 2004; 53: 1–115.

- *Koukopoulos A, Reginaldi D, Minnai G, Serra G, Pani L, Johnson N. The long-term prophylaxis of affective disorders. In: Gessa G, Fratta W, Pani L, eds. *Depression and Mania: From Neurobiology to Treatment*. New York: Raven Press, 1995, pp 127–147.
- *Lenz, G., Ahrens B, Denk E, Müller-Oerlinghausen B, Stratzberger-Topitz A, Simhandl C, Wancata J. Mortalität nach Ausschneiden aus der Lithiumambulanz [Increased mortality after drop-out from lithium clinic]. In Müller-Oerlinghausen B, Berghöfer A (eds). *Ziele und Ergebnisse der Medikamentösen Prophylaxe Affektiver Psychosen Ziele und Ergebnisse der Medikamentösen Prophylaxe Affektiver Psychosen*. Stuttgart, Germany: G. Thieme Verlag, 1994, pp 49–52. [Note: An English translation is not available. If FDA finds one is necessary, the Petitioners will have one prepared.]
- *Lepkifker E, Horesh N, Floru S. Long-term lithium prophylaxis in recurrent unipolar depression. A controversial indication? *Acta Psychiatr Belg* 1985; 85: 434–443.
- Lithobid® Prescribing Information. New York, NY: JDS Pharmaceuticals, 2004.
- Manji HK, Moore GJ, Chen G. Lithium at 50: have the neuroprotective effects of this unique cation been overlooked? *Biol Psychiatry* 1999; 46: 929–940.
- Meltzer HY, Alphas L, Green AI, Altamura AC, Anand R, Bertoldi A, Bourgeois M, Chouinard G, Islam MZ, Kane J, Krishnan R, Lindenmayer JP, Potkin S. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry* 2003; 60: 82–91.
- *Modestin J, Schwarzenbach F. Effect of psychopharmacotherapy on suicide risk in discharged psychiatric inpatients. *Acta Psychiatr Scand* 1992; 85: 173–175.
- Modestin J, Dal Plan D, Agarwalla P. Clozapine diminishes suicidal behavior: Retrospective evaluation of clinical records. *J Clin Psychiatry* 2005; 66:534–538.
- *Müller-Oerlinghausen B, Muser-Causemann B, Volk J. Suicides and parasuicides in a high-risk patient group on and off lithium long-term medication. *J Affect Disord* 1992; 25: 261–269.
- Müller-Oerlinghausen B. Die "IGSLI" zur Moralität Lithium behandelter Patienten mit affektiven Psychosen. In: Müller-Oerlinghausen B, Berghöfer A, editors. *Ziele und Ergebnisse der Medikamentösen Prophylaxe Affektiver Psychosen*. Stuttgart, Germany: G. Thieme Verlag, 1994; pp 35–39. [Note: An English translation is not available. If FDA finds one is necessary, the Petitioners will have one prepared.]
- Müller-Oerlinghausen B. How should findings on antisuicidal effects of lithium be integrated into practical treatment decisions? *Eur Arch Psychiatry Clin Neurosci* 2003; 253: 126–131.
- *Nilsson A. Mortality in recurrent mood disorders during periods on and off lithium. A complete population study in 362 patients. *Pharmacopsychiatry* 1995; 28: 8–13.
- *Nilsson A, Axelsson R. Lithium discontinuers: Clinical characteristics and outcome. *Acta Psychiatr Scand* 1990; 82: 433–438.
- NIMH. *Going To Extremes: Bipolar Disorder*. NIH Publication Number: 01-4595. 2001. Available at: <http://www.nimh.nih.gov/publicat/manic.cfm>. Accessed August 18, 2005
- NIMH. *Bipolar Disorder Research at the National Institute of Health*. National Institute of Mental Health. NIH Publication No. 00-4502. 2000. Available at: <http://www.nimh.nih.gov/publicat/bipolarresfact.cfm>. Accessed May 10, 2005

- Norton B, Whalley LJ. Mortality of a lithium-treated population. *Br J Psychiatry* 1984; 145: 277–282.
- O'Connell RA, Mayo JA, Flatow L, Cuthbertson B, O'Brien BE. Outcome of bipolar disorder on long-term treatment with lithium. *Br J Psychiatry* 1991; 159: 123–129.
- Page C, Benaim S, Lappin F. A long-term retrospective follow-up study of patients treated with prophylactic lithium carbonate. *Br J Psychiatry* 1987; 150: 175–179.
- *Poole AJ, James HD, Hughes WC. Treatment experiences in the lithium clinic at St Thomas Hospital. *J Roy Soc Med* 1978; 71: 890–894.
- Post RM, Denicoff KD, Leverich GS, Altshuler LL, Frye MA, Suppes TM, Rush AJ, Keck PE, Jr., McElroy SL, Luckenbaugh DA, Pollio C, Kupka R, Nolen WA. Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH life chart method. *J Clin Psychiatry* 2003; 64: 680–690.
- *Prien RF, Klett CJ, Caffey EM Jr. Lithium prophylaxis in recurrent affective illness. *Am J Psychiatry* 1974; 131: 198–203.
- Quiroz JA, Gould TD, Manji HK. Molecular effects of lithium. *Mol Interv* 2004; 4: 259–272.
- *Rihmer Z, Szanto K, Barsi J. Suicide prevention: fact or fiction? *Br J Psychiatry* 1993; 162:130–131.
- *Rucci P, Frank E, Kostelnik B, Fagiolini A, Mallinger AG, Swartz HA, Thase ME, Siegel L, Wilson D, Kupfer DJ. Suicide attempts in patients with bipolar I disorder during acute and maintenance phases of intensive treatment with pharmacotherapy and adjunctive psychotherapy. *Am J Psychiatry* 2002; 159: 1160–1164.
- Rush AJ. Toward an understanding of bipolar disorder and its origin. *J Clin Psychiatry* 2003; 64 Suppl 6:4–8.
- *Sharma R, Markar HR. Mortality in affective disorder. *J Affect Disord* 1994; 31: 91–96.
- Sweeting MJ. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of rare events. *Statist Med.* 2004; 23: 1351–1375
- Thies-Flechtner K, Muller-Oerlinghausen B, Seibert W, Walther A, Greil W. Effect of prophylactic treatment on suicide risk in patients with major affective disorders. Data from a randomized prospective trial. *Pharmacopsychiatry* 1996; 29: 103–107.
- Tohen M, Angst F. Epidemiology of bipolar disorder. Chapt. 17 in Tsuang MT, Tohen M, editors. *Textbook of Psychiatric Epidemiology*. New York: Wiley-Liss, 2002, pp 427–444.
- Tondo L, Jamison KR, Baldessarini RJ. Effect of lithium maintenance on suicidal behavior in major mood disorders. *Ann N Y Acad Sci* 1997; 836: 339–351.
- *Tondo L, Baldessarini RJ, Hennen J, Floris G, Silvetti F, Tohen M. Lithium treatment and risk of suicidal behavior in bipolar disorder patients. *J Clin Psychiatry* 1998; 59: 405–414.
- Tondo L, Hennen J, Baldessarini RJ. Lower suicide risk with long-term lithium treatment in major affective illness: a meta-analysis. *Acta Psychiatr Scand* 2001; 104: 163–172.
- Tondo L, Baldessarini RJ, Floris G. Long-term clinical effectiveness of lithium maintenance treatment in types I and II bipolar disorders. *Br J Psychiatry* 2001; 178 (Suppl 41): S184–S190.

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- Tondo L, Isacsson G, Baldessarini R. Suicidal behaviour in bipolar disorder: risk and prevention. *CNS Drugs* 2003; 17: 491–511.
- Tondo L, Baldessarini RJ. Suicidal risk in bipolar disorder. *Clin Neuropsychiatry* 2005; 2:55–65
- USPHS. The Surgeon General's Call to Action to Prevent Suicide. Washington, DC: US Public Health Service, 1999.
- *Venkoba-Rao A, Hariharasubramanian N, Parvathi-Devi S, Sugumar A, Srinivasan V. Lithium prophylaxis in affective disorder. *Indian J Psychiatry* 1982; 24: 22–30.
- Vestergaard P, Aagaard J. Five-year mortality in lithium-treated manic-depressive patients. *J Affect Disord* 1991; 21: 33–38.
- Wehr TA, Sack DA, Rosenthal NE, Cowdry RW. Rapid cycling affective disorder: contributing factors and treatment responses in 51 patients. *Am J Psychiatry* 1988; 145: 179–184.
- Wood SW. The economic burden of bipolar disease. *J Clin Psychiatry* 2001; 61 (Suppl 13): 38–41.
- WHO. Suicide Prevention. Geneva, Switzerland: World Health Organization, 2005, Available at: http://www.who.int/mental_health/prevention/suicide/supresuicideprevent/en/ Accessed May 10, 2005.
- Wyatt RJ, Henter ID. An economic evaluation of manic-depressive illness–1991. *Soc Psychiatry Psychiatr Epidemiol* 1995; 30: 213–219.
- Wyatt RJ, Henter ID, Jamison JC. Lithium revisited: savings brought about by the use of lithium, 1970–1991. *Psychiatr Quart* 2001; 72: 149–166.
- *Yerevman BI, Koek RJ, Mintz J. Lithium, anticonvulsants and suicidal behavior in bipolar disorder. *J Affect Disord* 2003; 73: 223–228.

APPENDIX**(Abstracts of representative studies)**

1. **Ahlfors UG, Baastrup PC, Dencker SJ, Elgen K, Lingjaerde O, Pedersen V, Schou M, Aaskoven O. Flupenthixol decanoate in recurrent manic-depressive illness. A comparison with lithium. Acta Psychiatr Scand 1981; 64: 226-237.**
Abstract: The hypothesis that flupenthixol decanoate may serve as an alternative to prophylactically administered lithium in recurrent manic-depressive illness, bipolar and unipolar type, was tested in two groups of patients. In Group I the patients were allocated randomly to maintenance treatment with either lithium or flupenthixol decanoate. The patients in Group II had previously been given lithium and were switched to flupenthixol decanoate because of unsatisfactory prophylactic effect of lithium, doubtful tablet compliance, troublesome side effects, or fear of later harmful effects. The flupenthixol decanoate dosage was 20 mg every 2-3 weeks. The study was not blind. In Group I neither lithium treatment (14 patients) nor treatment with flupenthixol decanoate (19 patients) led to a significant fall of mean episode frequency or mean per cent time ill. The reasons for this lack of response are not clear, but prognostically negative selection of the patients presumably took place before and possibly also during the hospitalization. Since absent effects cannot be compared, this part of the trial remains inconclusive. In Group II (93 patients) treatment with flupenthixol decanoate was associated with significant falls of the frequency of manic episodes and per cent time ill in mania and with significant rises of the frequency of depressive episodes and per cent time ill in depression. Increase of depressive morbidity was seen only in patients who had been given lithium during the pre-trial period and was presumably a result of the discontinuation of lithium. It is not known whether flupenthixol decanoate is of value in the prophylactic treatment of recurrent manic-depressive illness, but the drug may be worth trying in patients whose disease is dominated more by manic than by depressive recurrences and who do not respond to lithium or do not tolerate it or do not take it.

2. **Ahrens B, Müller-Oerlinghausen B, Schou M, Wolf T, Alda M, Grof E, Grof P, Lenz G, Simhandl C, Thau K. Excess cardiovascular and suicide mortality of affective disorders may be reduced by lithium prophylaxis. J Affect Disord 1995; 33: 67-75.**
Abstract: The mortality of patients suffering from affective disorders is much higher than that of the general population; this excess is due to both suicides and cardiovascular disease. During long-term lithium treatment, the overall mortality has not been found to differ significantly from that of the general population but the question remains whether this lowering, if it is in fact caused by lithium, is due to a reduction in suicide frequency or cardiovascular mortality, or both. We analysed data from 827 previously studied patients and used a procedure that estimated both overall mortality and cause-specific mortalities by single-case analysis. For overall mortality, the ratio of observed deaths (among the patients) to expected deaths (in the general population) was 1.14, which is not significantly different from 1.0; this was also found in our previous analysis. In the whole patient group, comprising 5600 patient years under lithium treatment, seven suicides were observed and 1.3 expected, resulting in a standard mortality ratio of 5.22; this is significantly > 1.0, but markedly lower than that found in patients with affective disorders not given lithium. Cardiovascular mortality was not found to be higher in our patients than in the general population. In view of the fact that a placebo-controlled mortality study under long-term conditions is neither ethically nor practically feasible, our findings cannot prove definitively that long-term lithium treatment counteracts factors responsible for the excess suicide and cardiovascular mortality of affective disorders. However, our observations are compatible with such a notion.

3. **Bauer M, Bschor T, Kunz D, Berghofer A, Strohle A, Müller-Oerlinghausen B. Double-blind, placebo-controlled trial of the use of lithium to augment antidepressant medication in continuation treatment of unipolar major depression. Am J Psychiatry 2000; 157: 1429–1435.**

Abstract: OBJECTIVE: Use of lithium to augment antidepressant medication has been shown to be beneficial in the acute treatment of depression. The authors examined the efficacy of lithium augmentation in the continuation treatment of unipolar major depressive disorder. METHOD: Thirty patients with a refractory major depressive episode who had responded to acute lithium augmentation during an open 6-week study participated in a randomized, parallel-group, double-blind, placebo-controlled trial of lithium augmentation during continuation treatment. After a 2-4-week stabilization period following remission, patients were randomly assigned to receive either lithium or placebo for a 4-month period. Antidepressant medication was continued throughout the study. RESULTS: Relapses (including one suicide) occurred in seven (47%) of the 15 patients who received placebo in addition to antidepressants. None (0%) of the 14 patients who received lithium augmentation with antidepressants suffered a relapse during the double-blind phase of the study. Five of the seven relapsing patients in the placebo group developed a depressive episode, and the other two experienced a manic episode. CONCLUSIONS: Lithium augmentation in the continuation phase of treatment of unipolar major depressive disorder effectively protects patients against a relapse. Patients who respond to lithium augmentation should be maintained on lithium augmentation for a minimum of 6 months or even longer.

4. **Bech P, Vendsborg PB, Rafaelsen OJ. Lithium maintenance treatment of manic-melancholic patients: its role in the daily routine. Acta Psychiatr Scand 1976; 53: 70–81.**
5. **Bocchetta A, Ardaù R, Burrai C, Chillotti C, Quesada G, Del Zompo M. Suicidal behavior on and off lithium prophylaxis in a group of patients with prior suicide attempts. J Clin Psychopharmacol 1998; 18: 384–389.**

Abstract: The purpose of this study was to evaluate the desired and undesired effects of relapse-preventive lithium treatment given routinely to manic-melancholic patients who had accepted the necessity of a strict tablet regime. The evaluation was based upon case record data and various rating scales, and 76 patients took part in the investigation. Our results showed that in 24% of the patients treatment was discontinued. This was due to side effects in 16% and to insufficient effect in 8% of the cases. The suicide risk was not eliminated, and 29% of the patients were receiving additional antidepressive or antimanic treatment at the test day. On the other hand, 78% of the patients rated the relapse-preventive lithium effect as moderate to excellent. Indirect evidence was obtained in support of a stabilizing effect of lithium on the emotional control in bipolar patients. The most frequent complaints during lithium treatment were tremor and increased thirst.

Abstract: One hundred patients who had attempted suicide before commencing lithium prophylaxis were followed up. Outcome was analyzed in terms of attempted or completed suicide after a mean of 10 years since admission to the lithium clinics. Of 10 patients who committed suicide, 9 had discontinued adequate lithium prophylaxis for a period ranging from 2 weeks to 7 years before death. Having discontinued lithium therapy was associated with suicide also in the subgroup of patients for whom lithium had not completely prevented episodes during lithium treatment. Suicide risk was 24 times as high during periods off compared with periods on adequate lithium prophylaxis. Incidence of attempting suicide was similar during the periods before receiving or after discontinuing lithium treatment, whereas it was 5 to 6 times lower during prophylaxis. Continuous and adequate lithium prophylaxis should be considered in the presence of high suicide risk, even if the prophylactic effect on the underlying mood disorder may be incomplete.

6. **Bowden CL, Calabrese JR, Sachs G, Yatham LN, Asghar SA, Hompland M, Montgomery P, Earl N, Smoot TM, DeVeaugh-Geiss J. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. Arch Gen Psychiatry 2003; 60: 392–400.**

Abstract: BACKGROUND: Lamotrigine has been shown to be an effective treatment for bipolar depression and rapid cycling in placebo-controlled clinical trials. This double-blind, placebo-controlled study was conducted to assess the efficacy and tolerability of lamotrigine and lithium compared with placebo for the prevention of relapse or recurrence of mood episodes in recently manic or hypomanic patients with bipolar I disorder. METHODS: After an 8- to 16-week open-label phase during which treatment with lamotrigine was initiated and other psychotropic drug regimens were discontinued, patients were randomized to lamotrigine (100-400 mg daily), lithium (0.8-1.1 mEq/L), or placebo as double-blind maintenance treatment for as long as 18 months. RESULTS: Of 349 patients who met screening criteria and entered the open-label phase, 175 met stabilization criteria and were randomized to double-blind maintenance treatment (lamotrigine, 59 patients; lithium, 46 patients; and placebo, 70 patients). Both lamotrigine and lithium were superior to placebo at prolonging the time to intervention for any mood episode (lamotrigine vs placebo, $P = .02$; lithium vs placebo, $P = .006$). Lamotrigine was superior to placebo at prolonging the time to a depressive episode ($P = .02$). Lithium was superior to placebo at prolonging the time to a manic, hypomanic, or mixed episode ($P = .006$). The most common adverse event reported for lamotrigine was headache. CONCLUSIONS: Both lamotrigine and lithium were superior to placebo for the prevention of relapse or recurrence of mood episodes in patients with bipolar I disorder who had recently experienced a manic or hypomanic episode. The results indicate that lamotrigine is an effective, well-tolerated maintenance treatment for bipolar disorder, particularly for prophylaxis of depression.
7. **Brodersen A, Licht RW, Vestergaard P, Olesen AV, Mortensen PB. Sixteen-year mortality in patients with affective disorder commenced on lithium. Br J Psychiatry 2000; 176: 429–433.**

Abstract: BACKGROUND: Lithium treatment is claimed to reduce mortality in patients with affective disorder, but the evidence is conflicting. AIM: To estimate mortality rates from a cohort of patients with affective disorder commenced on lithium with an observation period of two years and a follow-up after 16 years. METHOD: The mortality rates of patients were compared with those of the general Danish population, standardised for age, gender and calendar time with respect to death from all causes, suicide and death from cardiovascular disease. RESULTS: Forty of the study's 133 patients died during the 16-year observation period (11 from suicide). Mortality among patients commenced on lithium was twice that of the general population. The statistically significantly elevated mortality was due largely to an excess of suicides; mortality from all other causes was similar to the background populations. Thirty-two patients died after the first two years of observation and were included in the analysis of the association between death and treatment compliance. Suicide occurred more frequently among those patients not complying with treatment. CONCLUSION: Mortality, especially suicide, was significantly increased in unselected patients with affective disorder commenced on lithium relative to the general population.
8. **Calabrese JR, Bowden CL, Sachs G, Yatham LN, Behnke K, Mehtonen OP, Montgomery P, Ascher J, Paska W, Earl N, DeVeaugh-Geiss J. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. J Clin Psychiatry 2003; 64: 1013–1024.**

Abstract: BACKGROUND: The anticonvulsant lamotrigine was previously shown to be effective for bipolar depression. This study assessed the efficacy and tolerability of lamotrigine and lithium compared with placebo for the prevention of mood episodes in bipolar disorder. METHOD: During an 8- to 16-week open-label phase, lamotrigine (titrated to 200 mg/day) was added to current therapy for currently or recently depressed DSM-IV-defined bipolar I outpatients ($N = 966$) and concomitant drugs were gradually withdrawn. Patients stabilized on open-label treatment ($N = 463$) were then randomly assigned to lamotrigine (50, 200, or 400 mg/day; $N = 221$), lithium (0.8-1.1 mEq/L; $N = 121$), or placebo ($N = 121$) monotherapy for up

to 18 months. The primary outcome measure was time from randomization to intervention (addition of pharmacotherapy) for any mood episode (depressive, manic, hypomanic, or mixed). Data were gathered from September 1997 to August 2001. RESULTS: Time to intervention for any mood episode was statistically superior ($p = .029$) for both lamotrigine and lithium compared with placebo—median survival times were 200, 170, and 93 days, respectively. Intervention for depression was more frequent than for mania by a factor of nearly 3:1. Lamotrigine was statistically superior to placebo at prolonging the time to intervention for a depressive episode ($p = .047$). The proportions of patients who were intervention-free for depression at 1 year were lamotrigine 57%, lithium 46%, and placebo 45%. Lithium was statistically superior to placebo at prolonging the time to intervention for a manic or hypomanic episode ($p = .026$). The proportions of patients who were intervention-free for mania at 1 year were lamotrigine 77%, lithium 86%, and placebo 72%. Headache was the most frequent adverse event for all 3 treatment groups. CONCLUSION. Lamotrigine and lithium were superior to placebo for the prevention of mood episodes in bipolar I patients, with lamotrigine predominantly effective against depression and lithium predominantly effective against mania.

9. **Coppen A, Standish-Barry H, Bailey J, Houston G, Silcocks P, Hermon C. Does lithium reduce the mortality of recurrent mood disorders? *J Affect Disord* 1991; 23: 1–7.**
Abstract: Numerous follow-up studies have shown that patients with mood disorders who do not receive prophylactic medication are at increased risk of death, particularly from suicide. After 11 years follow-up we compared the mortality of 103 patients attending a lithium clinic with that expected on the basis of age/sex/year-specific rates for England and Wales. Only 10 patients died during the study, although the expected number of deaths was 18.31 ($P = 0.052$, two-tailed) and no deaths from suicide were observed. After correcting for the prevalence of mood disorder in the general population, the relative risk was 0.60 (95% CI 0.29–1.12) which suggests that lithium reverses the excess mortality associated with recurrent mood disorders, including that from suicide.
10. **Coppen A, Farmer R. Suicide mortality in patients on lithium maintenance therapy. *J Affect Disord* 1998; 50: 261–267.**
Abstract: Mood disorders are frequently recurrent and it has been shown that maintenance treatment can reduce long-term morbidity in this condition. It has also been shown that mood disorders carry an increased risk of suicide and that a significant proportion of individuals who commit suicide suffer from a mood disorder. This paper reports the results of a long term follow-up of a cohort of patients attending a specialist mood disorder clinic over a period of 18 years. Sixty-seven suffered from unipolar depression and 36 had bipolar or schizo-affective disorders. In order to qualify for entry to the cohort the unipolar patients had to have had at least three episodes of depression and those with bipolar disorders had to have had at least three episodes - with at least one manic episode and one depressive episode. All patients were treated with lithium. The initial treatment refusal rate and drop out rates were low. The mortality from suicide in this group was compared with that reported in five recent studies - all of which involved patients who had not been given maintenance therapy. The standardised mortality ratio (SMR) for all causes for the whole group was 0.93. There were two suicides. In one case the patient had continued treatment with lithium until death and in the other the patient had discontinued treatment 12 months before death. The overall suicide rate was 1.3 per 1000 patient years. Amongst similar groups of patients who had not been given maintenance therapy suicide rates of about 5.5 per 1000 patient years have been reported. It is concluded that maintenance treatment of mood disorders reduces the suicide rate in this vulnerable group of patients.
11. **Coryell W, Arndt S, Turvey C, Endicott J, Solomon D, Mueller T, Leon AC, Keller M. Lithium and suicidal behavior in major affective disorder: a case-control study. *Acta Psychiatr Scand* 2001; 104: 193–197.**
Abstract: OBJECTIVE: A number of studies have suggested that lithium may be particularly effective in reducing suicide risks among patients with major affective disorders. The design of many of these studies left them open to biases associated with treatment compliance, however. METHOD: Subjects were drawn from a naturalistic, long-term follow-up of patients with major

affective disorders. Fifteen who committed suicide while receiving somatotherapy where matched to non-suicidal patients who were similarly receiving somatotherapy at the same point in follow-up. The same procedure was followed for 41 patients who made a serious suicide attempt during follow-up. RESULTS: Six (40.0%) of the patients who committed suicide, and eight (53.3%) of their controls, were thought to have been taking lithium in the preceding week. Among attempters and their controls, nine (22.0%) and eight (19.5%), respectively, were taking lithium. CONCLUSION: These results do not support previous suggestions that lithium has uniquely antisuicidal properties. Other existing datasets should be explored with this design to establish whether lithium does, or does not, offer special protection against suicide.

12. **Glen AI, Dodd M, Hulme EB, Kreitman N. Mortality on lithium. Neuropsychobiology 1979; 5: 167-173.**
Abstract: A register of patients receiving lithium in the Edinburgh and Lothian area of Scotland has been kept by the Medical Research Council Brain Metabolism Unit since 1967. Using this register, information was obtained on 784 patients receiving lithium for a period of up to 115 months (97.4% of the population available for study). 33 patients died during the period of study due predominantly to cardiovascular causes or to suicide. There was nothing to suggest that long-term exposure caused more deaths than short-term exposure and the pattern of mortality resembled that found in other studies of manic-depressive illness, i.e. the majority of deaths occurred in the early stages of follow-up.
13. **Glen AI, Johnson AL, Shepherd M. Continuation therapy with lithium and amitriptyline in unipolar depressive illness: a randomized, double-blind, controlled trial. Psychol Med 1984; 14: 37-50.**
Abstract: A detailed analysis of the results of a multi-centre clinical trial shows that, while the relapse rate following recovery from an operationally defined depressive illness was smaller among patients subsequently treated with either amitriptyline or lithium than with a placebo, there was no clinically significant difference between the prophylactic efficacy of the 2 antidepressants. An account is given of the relative adverse effects of the treatments, and the implications of the findings are discussed.
14. **Goodwin FK, Fireman B, Simon GE, Hunkeler EM, Lee J, Revicki D. Suicide risk in bipolar disorder during treatment with lithium and divalproex. JAMA 2003; 290: 1467-1473.**
Abstract: CONTEXT: Several studies have suggested that lithium treatment reduces risk of suicide in bipolar disorder, but no research has examined suicide risk during treatment with divalproex, the most commonly prescribed mood-stabilizing drug in the United States. OBJECTIVE: To compare risk of suicide attempt and suicide death during treatment with lithium with that during treatment with divalproex. DESIGN AND SETTING: Retrospective cohort study conducted at 2 large integrated health plans in California and Washington. PATIENTS: Population-based sample of 20 638 health plan members aged 14 years or older who had at least 1 outpatient diagnosis of bipolar disorder and at least 1 filled prescription for lithium, divalproex, or carbamazepine between January 1, 1994, and December 31, 2001. Follow-up for each individual began with first qualifying prescription and ended with death, disenrollment from the health plan, or end of the study period. MAIN OUTCOME MEASURES: Suicide attempt, recorded as a hospital discharge diagnosis or an emergency department diagnosis; suicide death, recorded on death certificate. RESULTS: In both health plans, unadjusted rates were greater during treatment with divalproex than during treatment with lithium for emergency department suicide attempt (31.3 vs 10.8 per 1000 person-years; $P < .001$), suicide attempt resulting in hospitalization (10.5 vs 4.2 per 1000 person-years; $P < .001$), and suicide death (1.7 vs 0.7 per 1000 person-years; $P = .04$). After adjustment for age, sex, health plan, year of diagnosis, comorbid medical and psychiatric conditions, and concomitant use of other psychotropic drugs, risk of suicide death was 2.7 times higher (95% confidence interval [CI], 1.1-6.3; $P = .03$) during treatment with divalproex than during treatment with lithium. Corresponding hazard ratios for nonfatal attempts were 1.7 (95% CI, 1.2-2.3; $P = .002$) for attempts resulting in hospitalization and 1.8 (95% CI, 1.4-2.2; $P < .001$) for attempts diagnosed in

the emergency department. **CONCLUSION:** Among patients treated for bipolar disorder, risk of suicide attempt and suicide death is lower during treatment with lithium than during treatment with divalproex.

15. **Greil W, Ludwig-Mayerhofer W, Erazo N, Engel RR, Czernik A, Giedke H, Müller-Oerlinghausen B, Osterheider M, Rudolf GA, Sauer H, Tegeler J, Wetterling T. Comparative efficacy of lithium and amitriptyline in the maintenance treatment of recurrent unipolar depression: a randomised study. J Affect Disord 1996; 40: 179–190.**
 Abstract: The present study, including 81 depressive patients, compares the prophylactic efficacy of lithium and amitriptyline in recurrent unipolar depression over a treatment period of 2.5 years in a randomised multicentre design. Hospitalisation, re-emergence of depressive or subdepressive recurrences, unwanted side-effects and need of concomitant psychotropic medication were considered to indicate treatment failures. Average dosage for amitriptyline was 98 +/- 37 mg/day, average lithium blood level was 0.59 +/- 0.12 mmol/l. Survival analyses demonstrated a significant superiority of lithium ($P = 0.015$) regarding the outcome criteria 'recurrences and/or subclinical recurrences' and non-significantly better results of lithium compared to amitriptyline concerning 'recurrence' ($P = 0.059$) or 'recurrence and/or concomitant medication' ($P = 0.066$).

16. **Greil W, Ludwig-Mayerhofer W, Erazo N, Engel RR, Czernik A, Giedke H, Müller-Oerlinghausen B, Osterheider M, Rudolf GA, Sauer H, Tegeler J, Wetterling T. Lithium vs carbamazepine in the maintenance treatment of schizoaffective disorder: a randomized study. Eur Arch Psychiatry Clin Neurosci 1997a; 247: 42–50.**
 Abstract: In a randomised multicentre study, the prophylactic efficacy of lithium and carbamazepine was compared in schizoaffective disorder. A total of 90 ICD-9 schizoaffective patients were included in the maintenance phase (2.5 years). They were also diagnosed according to RDC and DSM-III-R and classified into subgroups. Mean serum levels were 0.58 +/- 0.12 mmol/l for lithium and 6.4 +/- 1.5 micrograms/ml for carbamazepine (mean dose 643 +/- 179 mg/d). Outcome criteria were hospitalisation, recurrence, concomitant psychotropic medication and adverse effects leading to discontinuation. There were more non-completers under carbamazepine than under lithium ($p = 0.02$). Survival analyses demonstrated no significant differences between lithium and carbamazepine in treatment outcome. Patient's ratings of side effects ($p = 0.003$) and treatment satisfaction ($p = 0.02$) favoured carbamazepine. Following the RDC criteria, patients of the schizodepressive and non-classifiable type did better under carbamazepine ($p = 0.055$ for recurrence), whereas in the schizomanic patients equipotency of both drugs was found. Applying DSM-III-R, carbamazepine demonstrated a superiority in the patient group with more schizophrenia-like or depressive disorders ($p = 0.040$ for recurrence), but not in patients fulfilling the DSM-III-R criteria of bipolar disorder. Lithium and carbamazepine seem to be equipotent alternatives in the maintenance treatment of broadly defined schizoaffective disorders. However, in subgroups with depressive or schizophrenia-like features and regarding its long-term tolerability carbamazepine seems to be superior.

17. **Greil W, Ludwig-Mayerhofer W, Erazo N, Schochlin C, Schmidt S, Engel RR, Czernik A, Giedke H, Müller-Oerlinghausen B, Osterheider M, Rudolf GA, Sauer H, Tegeler J, Wetterling T. Lithium versus carbamazepine in the maintenance treatment of bipolar disorders: a randomised study. J Affect Disord 1997b; 43: 151–161.**
 Abstract: In a randomised multicentre study, the prophylactic efficacy of lithium and carbamazepine was compared in 144 patients with bipolar disorder (74 vs. 70 patients; observation period: 2.5 years; lithium serum level: 0.63 +/- 0.12 mmol/l, carbamazepine dose: 621 +/- 186 mg/day). Hospitalisations, recurrences, need of psychotropic comedication and adverse effects prompting discontinuation were defined as treatment failures. Survival analyses regarding hospitalisations and recurrences showed no statistically significant differences between both drugs. Results were distinctly in favour of lithium, considering recurrences combined with comedication ($P = 0.041$) and/or adverse effects ($P = 0.007$). Whereas adverse effects prompting discontinuation were more frequent under carbamazepine (9 vs. 4, ns), lithium patients reported more often slight/moderate side effects (61% vs 21% after 2.5 years; $P = 0.0006$). In completers,

recurrences occurred in 28% (lithium) vs. 47% (carbamazepine) of the patients ($P = 0.06$). Lithium seems to be superior to carbamazepine in maintenance treatment of bipolar disorder, in particular when applying broader outcome criteria including psychotropic comedication and severe side effects.

18. **Kallner G, Lindelius R, Petterson U, Stockman O, Tham A. Mortality in 497 patients with affective disorders attending a lithium clinic or after having left it. *Pharmacopsychiatry* 2000; 33: 8–13.**

Abstract: The impact of lithium prophylaxis on mortality has been studied in 497 patients, 405 bipolars and 92 unipolars, who attended the same out-patient lithium clinic for up to 30 years. In order to avoid preselection, no minimum period of lithium treatment was required in our study. Of a total of 6014 patient-years, 4330 were spent in regular contact with the study clinic. General mortality due to natural causes was not significantly increased; among cardiovascular diseases, only pulmonary embolism showed an excess mortality. No patients died of lithium intoxication or chronic renal insufficiency. Patients were divided into three groups: Group A, 277 patients, attended the study clinic until death or the end of the study, Group B, 86 patients, left the clinic but continued to take lithium, and Group C, 134 patients, both left the clinic and stopped taking lithium. Among bipolars, the suicide rate compared to the general population was in excess in all three groups. Among unipolars, suicides occurred only after the patients had left the study clinic and stopped taking lithium. A special analytical method was used for intergroup comparisons of suicide rates. Bipolars in Group A attending the study clinic regularly had a suicide rate of 3.5 per 1000 patient-years. The rate increased to 6.3 or by 80 % if patients had left the clinic and did not take lithium any longer as in Group C. The suicide rate in Group C increased by 45% compared to Group B, patients who left the clinic but continued to take lithium. Our results support the hypothesis that lithium has a significant antisuicidal effect in bipolars as well as in unipolars. The suicide mortality can be further.

19. **Lepkifker E, Horesh N, Floru S. Long-term lithium prophylaxis in recurrent unipolar depression. A controversial indication? *Acta Psychiatr Belg* 1985; 85: 434–443.**

Abstract: The authors assessed results obtained with long-term lithium maintenance in a group of 33 recurrent unipolar patients, followed regularly in the outpatient clinic of the Chaim Sheba Medical Center for 1-15 years. They analyzed changes of frequency, severity and duration of depressive relapses, rate and duration of hospitalization, suicidal ideas or attempts, and various assessments of outcome. A significant reduction was found on all indices during lithium management as compared to before lithium treatment, attesting to the efficacy of long-term prophylactic lithium in recurrent unipolar depression. These results are discussed and compared with those from other reports

20. **Modestin J, Schwarzenbach F. Effect of psychopharmacotherapy on suicide risk in discharged psychiatric inpatients. *Acta Psychiatr Scand* 1992; 85: 173–175.**

Abstract: We investigated 64 former psychiatric inpatients who had committed suicide within 1 year after their discharge and compared them with a carefully matched control group of patients who did not commit suicide. One third of the patients in both groups were no longer in treatment at the time of the suicide or, for controls, at the corresponding point in time. At that time, a significantly higher proportion of controls had been receiving psychopharmacotherapy and a significantly higher proportion of them were on lithium.

21. **Müller-Oerlinghausen B, Muser-Causemann B, Volk J. Suicides and parasuicides in a high-risk patient group on and off lithium long-term medication. *J Affect Disord* 1992; 25: 261–269.**

Abstract: 68 patients with affective disorders, and receiving lithium prophylaxis in a specialized lithium clinic were followed up for 8 years on average. Patients were selected for this study according to 2 criteria: They had been given lithium for at least 12 months, and they had attempted suicide at least once before onset of lithium prophylaxis. Outcome was analysed in terms of suicidal and parasuicidal behaviour. 55 patients took their lithium regularly, 13 discontinued or dropped the medication. One third of those patients having discontinued the

medication died from suicide. Only one suicide occurred in patients with regular lithium intake and proven compliance during the last check before death. An impressive drop of parasuicides was observed in responders as well as in apparent non-responders. In total, 11 of 13 patients showed suicidal or parasuicidal behaviour 2 weeks-44 months after lithium discontinuation, which in about half of these cases took place on advice or with consent of the treating psychiatrist. It is concluded that lithium may have specific anti-suicidal properties, possibly related to its anti-aggressive effect, and that patients apparently not responding satisfactorily in terms of reduced number of episodes may still be protected against suicide or parasuicide.

22. **Nilsson A, Axelsson R. Lithium discontinuers: clinical characteristics and outcome. Acta Psychiatr Scand 1990; 82: 433-438.**
Abstract: Eleven patients with major affective disorder (DSM-III) were investigated after a mean of 6.7 years on lithium prophylaxis and reinvestigated 7 years later, at which time they had discontinued lithium for a mean 2.3 years. Outcome was assessed by the Comprehensive Psychopathological Rating Scale, by relapse frequencies, by need for psychotropic medication and for inpatient treatment. The study period was associated with an increase in the rated score for depression, as previously observed also in lithium discontinuers. Although the relapse frequencies remained largely unchanged, a significantly increased number of inpatient treatment days indicated considerably more severe episodes after the discontinuation of lithium. Long periods without lithium were associated with higher doses of neuroleptic drugs.
23. **Nilsson A. Mortality in recurrent mood disorders during periods on and off lithium. A complete population study in 362 patients. Pharmacopsychiatry 1995; 28: 8-13.**
Abstract: Recent studies have suggested that long-term lithium treatment reduces the high mortality rates of recurrent mood disorders in patients selected for and compliant with treatment at specialized lithium clinics. Whether lithium also generally reduces mortality in this diagnostic category under less select treatment conditions is a question of vital public health interest. The impact of prophylactic lithium on mortality was studied in a complete population of 362 unselected patients with DSM-III-R diagnoses of mood disorders or schizoaffective disorder, hospitalized at least once between 1970 and 1977 and treated with lithium for a minimum of one year. The patients were followed until 1991 or until date of death. The final analyses included 3911 patient years with lithium and, because of temporary or permanent discontinuations, 1274 patient years without lithium prophylaxis. A total of 129 deaths were recorded, compared with the 60.7 deaths that would normally be expected in the general population, yielding a Standard Mortality Ratio (SMR) of 2.1, significantly different from 1.0 ($p < 0.001$, 95% confidence limits 1.8-2.5). The relative risk of death was 1.7 times higher ($p < 0.01$, 95% confidence limits 1.2-2.6) during periods off lithium than during periods on lithium. The relative risk of suicide was 4.8 times higher off lithium than on lithium ($p < 0.02$, 95% confidence limits 1.1-12.6). Suicide, pneumonia, pyelonephritis, and, unexpectedly, pulmonary embolism contributed to the excess mortality both on and off lithium.(ABSTRACT TRUNCATED AT 250 WORDS).
24. **Norton B, Whalley LJ. Mortality of a lithium-treated population. Br J Psychiatry 1984; 145: 277-282.**
Abstract: In South-East Scotland, 791 subjects treated with lithium for more than two months during 1967-76 were traced, using public and health service records; 751 were traced alive, 33 had died, and seven remained untraced. The standardised mortality rate was 2.83, and excess mortality was attributable to suicide (increased 36-times) and cardiovascular disease (increased 2.15-times); deaths from nephropathy, cancer or leukaemia were not increased. Comparison of the 33 deaths and 33 matched patients, selected from the 751 survivors, showed that patients dying on lithium were similar in most respects to survivors, but when first starting lithium, they had more signs of physical disease.

25. **O'Connell RA, Mayo JA, Flatow L, Cuthbertson B, O'Brien BE. Outcome of bipolar disorder on long-term treatment with lithium. Br J Psychiatry 1991; 159: 123–129.**
Abstract: The long-term treatment outcome of 248 bipolar patients in an out-patient lithium programme was assessed. Over half of the patients (138 or 56%) had no affective episodes in the year observed. Patients were divided into outcome groups according to GAS scores: the outcome for 40% of patients was good, for 41% fair, and for 19% poor. More frequent psychiatric admissions before starting lithium treatment was the best predictor of poor outcome, followed by a negative affective style in the family and lower social class. Current alcohol and drug abuse was associated with poor outcome. Although familial and psychosocial factors were significantly associated with outcome, the findings suggest there may be inherent differences in the pathophysiology of bipolar disorder reflected in an increased frequency of episodes which account for a large variance in lithium treatment outcome.
26. **Page C, Benaim S, Lappin F. A long-term retrospective follow-up study of patients treated with prophylactic lithium carbonate. Br J Psychiatry 1987; 150: 175–179.**
Abstract: Patients suffering from unipolar and bipolar affective illness, who began treatment with prophylactic lithium carbonate during a 5-year period, were followed up and 59 out of 101 interviewed. Most had been taking lithium for at least 13 years: 49% had a complete remission, 41% a partial but significant response, and 10% no response. No specific individual or illness factor was found to correlate with favourable outcome, and no correlation between average serum lithium level and outcome. No side-effects could be associated specifically with the long-term use of lithium, but there was a surprisingly high incidence of clinical hypothyroidism.
27. **Rucci P, Frank E, Kostelnik B, Fagiolini A, Mallinger AG, Swartz HA, Thase ME, Siegel L, Wilson D, Kupfer DJ. Suicide attempts in patients with bipolar I disorder during acute and maintenance phases of intensive treatment with pharmacotherapy and adjunctive psychotherapy. Am J Psychiatry 2002; 159: 1160–1164.**
Abstract: OBJECTIVE: Lifetime rates of suicide attempts among patients with bipolar I disorder were compared to rates during a 2-year period of intensive treatment with pharmacotherapy and with one of two adjunctive psychosocial interventions. METHOD: Subjects entered the study during an acute mood episode. Subjects were treated with primarily lithium pharmacotherapy and with either psychotherapy specific to bipolar disorder, which included help in regularizing daily routines, or nonspecific, intensive clinical management involving regular visits with empathic clinicians. Data on prior suicide attempts were obtained retrospectively from interviews with the NIMH-Life-Chart method. Data on suicide attempts during the clinical trial were collected systematically throughout the protocol. RESULTS: The rate of suicide attempts was 1.05 per 100 person-months before patients entered the trial. Patients experienced a threefold reduction in the rate of suicide attempts during the acute treatment phase (until the patient achieved stabilization, defined by completion of 4 weeks during which the patient had a mean score of ≤ 7 on the 17-item Hamilton Depression Rating Scale and ≤ 7 on the Bech-Rafaelsen Mania Scale) and a 17.5-fold reduction during maintenance treatment. Poisson loglinear regression analysis modeling the relationship between the observed rates and the three protocol stages (pretreatment, acute, and maintenance) showed that the reductions were significant in the acute and maintenance phases, compared with the pretreatment phase. No patient with one or more suicide attempts before entering the trial attempted suicide during the protocol. CONCLUSIONS: A treatment program in a maximally supportive clinical environment can significantly reduce suicidal behavior in high-risk patients with bipolar I disorder.
28. **Sharma R, Markar HR. Mortality in affective disorder. J Affect Disord 1994; 31: 91–96.**
Abstract: 472 bipolar patients were followed up retrospectively over 17 years. The patients that died were compared with the general population and a control group. The former comparison showed greater mortality from suicide, cardiovascular and respiratory causes in the index population and the latter, that the deceased were more likely to have been unmarried, with greater frequency and duration of admissions, a shorter follow-up period and were less likely to have received lithium treatment. The suicides were significantly younger at onset and death than

the index and control groups, and suicide was uncommon where follow-up extended over 10 years.

29. **Thies-Flechtner K, Müller-Oerlinghausen B, Seibert W, Walther A, Greil W. Effect of prophylactic treatment on suicide risk in patients with major affective disorders. Data from a randomized prospective trial. *Pharmacopsychiatry* 1996; 29: 103–107.**
Abstract: Recent findings have indicated that lithium treatment markedly reduces suicide risk in major affective disorders. To compare the effect of lithium with carbamazepine and amitriptyline, suicidal behavior was analyzed during the randomized prospective long-term MAP study (N = 378; duration 2.5 years). Of the nine suicides and five attempted suicides, none took place during lithium treatment. The findings support the view that lithium has a specific antisuicidal effect over and above its prophylactic benefit.
30. **Tondo L, Baldessarini RJ, Hennen J, Floris G, Silvetti F, Tohen M. Lithium treatment and risk of suicidal behavior in bipolar disorder patients. *J Clin Psychiatry* 1998; 59: 405–414.**
Abstract: BACKGROUND: Lithium may exert an antisuicidal effect in bipolar disorder patients, but this hypothesis requires further testing by direct comparison of patients with and without lithium treatment. METHOD: Risk of life-threatening suicidal acts over time and associated factors were analyzed in 310 patients with DSM-IV bipolar I (N = 186) or II (N = 124) disorder evaluated for a mean of 8.3 years before, and prospectively during, a mean of 6.4 years of lithium maintenance in a mood disorder clinic; 185 were also followed for a mean of 3.7 years after clinically discontinuing lithium. RESULTS: In 5233 patient-years of observation, 58 patients made 90 suicide attempts (8 were fatal). Survival analyses with Weibull modeling with adjustments for covariates indicated a highly significant 6.4-fold adjusted hazard ratio during versus before and 7.5-fold ratio after versus during lithium maintenance. Suicidal acts were more common early in the course of illness before lithium and were associated with prior suicide attempts, greater proportion of time depressed, and younger age. After the discontinuation of lithium, suicidal acts were more frequent in the first year than at later times or before start of lithium treatment. Fatalities were 9 times more frequent after versus during treatment. CONCLUSION: Lithium maintenance was associated with marked reduction of life-threatening suicidal acts, the number of which sharply increased after discontinuing lithium. Suicidal behavior was strongly associated with prior suicide attempts, more time depressed, and younger age or recent onset. Greater attention to suicidal risk in patients with bipolar depression and assessment of all proposed mood-stabilizing agents for antisuicidal effects are strongly encouraged.
31. **Vestergaard P, Aagaard J. Five-year mortality in lithium-treated manic-depressive patients. *J Affect Disord* 1991; 21: 33–38.**
Abstract: A hundred and thirty-three affective disorder patients who received prophylactic treatment with lithium were followed prospectively for 5 years and their mortality was recorded. Twenty-two patients died during the period, 13 from natural causes and nine from definite or probable suicide. The observed mortality was significantly greater than the expected overall, and also when natural causes and suicide were considered independently. No patients died from lithium intoxication or lithium-induced side effects. Patients who died from suicide were all bipolars or suffered from affective disorder with uncertain polarity. They were significantly younger than the patients who died from natural causes, they tended to lead isolated lives and they suffered a violent death. The older patients who died from natural causes had often had physical illness and alcohol abuse prior to the start of lithium treatment. The results of the study speak in favour of the establishment of comprehensive treatment programmes possibly in the framework of specialised affective disorder clinics.
32. **Wehr TA, Sack DA, Rosenthal NE, Cowdry RW. Rapid cycling affective disorder: contributing factors and treatment responses in 51 patients. *Am J Psychiatry* 1988; 145: 179–184.**
Abstract: For 51 patients with rapid cycling affective disorder, clinical and family history data indicated that the illness was phenotypically and genetically related to more typical forms of

affective disorder, was characterized by a bipolar course (100%), and was more common in women (92%). Manic-depressive cycles were separate from menstrual cycles. At the time of onset of rapid cycling, 73% of the patients were taking antidepressant drugs; the continuation of rapid cycling was associated with antidepressant drug therapy in 51% of the patients. Although most patients had been referred to a research ward because they were considered to be refractory to treatment, 37% attained essentially complete remissions, usually during treatment with lithium and/or monoamine oxidase inhibitors.

33. **Yerevanian BI, Koek RJ, Mintz J. Lithium, anticonvulsants and suicidal behavior in bipolar disorder. *J Affect Disord* 2003; 73: 223–228.**

Abstract: **BACKGROUND:** Lithium has been found to be effective in reducing suicide rates during long term treatment of patients with bipolar disorders. Data on the efficacy of anticonvulsant mood stabilizers in reducing suicide risk are sparse. **METHOD:** Charts of 140 bipolar patients treated continuously for a minimum of 6 months during a 23-year period of private practice by the senior author were extracted from nearly 4000 patient records. Data extracted from the charts were incidence of completed suicide, number of suicide attempts, and number of hospitalizations for suicidal ideation or behavior per 100 patient-years of either 'on' or 'off' lithium or anticonvulsant mood stabilizer monotherapy. **RESULTS:** Only one completed suicide (during a period off of lithium) occurred in the patients studied. Incidence of non-lethal suicidal behavior was not different during treatment with lithium, compared with anticonvulsants. Being on a mood stabilizer significantly protected against suicidal behavior. The relative protective effect was more modest than in reports from other treatment settings. **LIMITATIONS:** This was a retrospective chart review study of naturalistically treated patients. **CONCLUSIONS:** Treatment of patients with bipolar disorder with either lithium or anticonvulsant mood stabilizers was associated with reduced risk of suicidal behavior. This study did not find evidence for a difference in the protective effect of the two types of mood stabilizing medications against non-lethal suicidal behavior in the naturalistic setting of private practice.
