Long-term lithium treatment in the prevention of suicidal behavior in bipolar disorder patients

LEONARDO TONDO and ROSS J. BALDESSARINI

Abstract. We reviewed available research findings, including meta-analyses on effects of lithium-treatment associated with rates of suicidal behavior in bipolar disorder or unipolar major depressive disorder patients, and for comparisons of lithium to mood-stabilizing anticonvulsants. Data from meta-analyses consistently indicate marked reductions of suicidal behavior and mortality during long-term treatment with lithium salts in bipolar disorder patients, and possibly also in unipolar, recurrent major depressive, perhaps even more effectively than with anticonvulsants proposed as mood-stabilizers. Suicidal risk is frequently associated with dysphoric-agitated symptoms, anger, aggression, and impulsivity-all of which may respond better to treatment with lithium or other mood-stabilizing medicines than to antidepressants. In these conditions, antidepressant treatment may not provide a beneficial effect on risk of suicidal thoughts and perhaps attempts, particularly in juveniles, whereas, lithium, perhaps even more than anticonvulsants, seems to be remarkably effective in the preventing suicidal behavior. The mechanism of action is not well defined and may be associated with either a prevention of mood recurrences or a more specific "antisuicidal" activity.

Declaration of Interest: Dr. Tondo has received research support from Janssen and Eli Lilly Corporations and has served as a consultant to Glaxo-SmithKline and Merck Corporations. Dr. Baldessarini has recently been a consultant or investigator-initiated research collaborator with: AstraZeneca, Auritec, Biotrofix, Janssen, JDS-Noven, Lilly, Luitpold, NeuroHealing, Novartis, Pfizer, and SK-BioPharmaceutical Corporations. Neither author is a member of pharmaceutical speakers' bureaus, nor do they or any family member hold equity positions in biomedical or pharmaceutical corporations.

INTRODUCTION

As many as 90% of suicides occur in persons with a diagnosable psychiatric disorder (Roy, 2001; Goldsmith *et al*., 2002; Simon & Hales, 2006). Among these, bipolar disorder (BPD) as well as severe (with hospitalization) recurrent major depression (MDD) have the highest standardized mortality ratio (SMR) of any psychiatric disorders compared with the general population (Harris & Barraclough, 1997; 1998). In line with earlier reports, our analysis of 28 studies involving 823 suicides among 21,484 BPD patients at risk for an average of 9.93 years, showed that the pooled, weighted mean annual incidence of suicide in BPD patients was 0.39% (390/100,000), approximately 28 times higher than the international rate for suicide in the general population, of about 14/100,000/year (0.014%; Tondo *et al*., 2003). The very high risk of suicide among BPD patients also was supported by our recent review of the medical records of nearly 3,000 outpatients diagnosed with DSM-IV major mood disorders (Tondo & Baldessarini, 2007). We found substantially greater risk of suicide among BPD patients than those with MDD, in general, but similar rates among those ever hospitalized for either type of mood disorder. The annual risk of *suicide* among 843 bipolar I and II disorder patients in Sardinia was 150/100,000, or more than 15-times higher than in the Italian general population, and three-times greater than among 1,983 patients diagnosed with recurrent major depressive disorder, most of whom were outpatients. The annual rate of *suicide attempts* was 1.26% among BPD patients, versus 0.48% in MDD cases. The ratio of attempts/suicides (A/S), as a proposed *index of lethality* of suicidal behavior (Baldessarini *et al*., 2006), was 8.6:1 in BPD patients, and 9.6:1, in MDD patients, compared to an estimated risk-ratio of 20-30:1 in the general population (Kessler *et al*., 2005), indicating higher lethality of suicide attempts among mood disorder patients.

Depressive phases in BPD patients seem to be more associated with suicidal risk than manic periods, whereas suicide is rare in hypomania, and poorly evaluated in increasingly recognized, mixed manic-depressive states.

Address for correspondence: Professor L. Tondo, Centro Bini, Via Cavalcanti 28, 09128 Cagliari (Italy).
Fax: +39-070-496354
E-mail: ltondo@aol.com

Moreover, suicidal risk and mortality associated with suicide attempts (as reflected in the A/S ratio) with type II BPD patients are at least as high as in type I BPD (Tondo & Baldessarini, 2007). Interestingly, however, even though suicidal behavior occurs mainly in depressive states (Isometsä *et al*., 1994; Tondo *et al*., 1998), antidepressant treatments have failed to demonstrate consistent prevention of such behaviors. Evidence for this impression arises from studies based on retrospective analyses of randomized, placebo-controlled, clinical trials not specifically designed to assess suicidal behaviors, or on non-randomized, clinical studies of groups of treated and untreated patients (Hammad *et al*., 2006; Barbui *et al*., 2009; Zisook *et al*., 2009). Results from some ecological studies of correlations between regional or temporal changes in rates of suicide and of use of modern antidepressant medicines have been favorable when based on North American or Northern European samples, but otherwise inconsistent across countries and years of observation (Baldessarini *et al*., 2007). Such variability may reflect study designs involving lack of randomization or control over important confounding factors, including developmental factors and use of other treatments (mood stabilizers, psychotherapy) that may alter suicidal risk, as well as a lack of information on associations of suicidal behavior and antidepressant treatment at the level of individuals in correlative associational studies. In addition, although *overall* effects of antidepressant treatment on suicidal behaviors and deaths appear to be negligible, there are indications that effects may vary substantially with age, including a lack of reduction of risk in juvenile and young-adult depressed patients, but significant reductions at later years, especially above age 60 (FDA, 2007; Barbui *et al*., 2009).

The inconsistent effects of antidepressant treatment also may reflect the presence of particular symptoms in depressive states associated with suicide behavior, including agitation, dysphoria, restlessness, irritability and anger (Dilsaver *et al*., 1997; Koukopoulos & Koukopoulos, 1999; Akiskal *et al*., 2005; Maj *et al*., 2006). Such affective states are likely to increase risk of aggressive-impulsive acts, including suicidal behavior, are very prevalent among BPD patients, and may sometimes be worsened by antidepresssant treatment (Baldessarini *et al*., 2005). That is, antidepressant treatment may increase the risk of suicidal behavior in vulnerable patients in particular mood-states that can occur spontaneously or perhaps be stimulated by antidepressant treatment itself (Koukopoulos & Koukopoulos, 1999; Akiskal *et al*., 2005; O'Donovan *et al*., 2008; Goldberg *et al*., 2009). This hypothesis may also help to account for the particularly high risk of suicidal behavior among type-II BPD patients (Rihmer & Pestality, 1999) who, like type I BPD patients, are more likely to present agitated-depressive states than are moderately ill MDD patients.

The preceding observations suggest that decreasing suicidal risk may be linked with preventing or managing depressive morbidity in BPD patients generally, or with limiting particular forms of depression. It is striking that depressive or dysphoric morbidity accounts for nearly three-quarters of the 40%-50% of weeks not in euthymia, even if BPD patients are afforded available and clinically favored treatments, not only in the mid-course of such disorders, but also from their onset (Judd *et al*., 2002; Post *et al*., 2003; Baldessarini *et al*., 2004; Joffe *et al*., 2004; Baldessarini *et al*., in press).

An association of reduced suicidal risk during long-term treatment with lithium in BPD patients is supported consistently by nearly three-dozen original studies, meta-analyses, and reviews (Tondo *et al*., 2001; Angst *et al*., 2005; Cipriani *et al*., 2005; Kessing *et al*., 2005; Müller-Oerlinghausen *et al*., 2006). In our own meta-analysis of data from 31 studies (8 were randomized with placebo or active-alternative treatments as controls) we provided data on suicidal behavior in patients treated with long-term lithium treatment for mood disorders or not, and involving more than 110,000 person-years of risk (Baldessarini *et al*., 2006). Averaged crude rates of suicidal acts were 0.56% per year with lithium and 2.64%/year without such treatment, indicating a major overall, crude reduction of suicidal risk of about five-fold, with similar reductions for both suicides and attempts, and among BPD patients and mixed samples of persons with various recurrent major mood disorders. Meta-analysis found a similar risk-reduction by approximately 80% (risk ratio = 4.91, 95%CI: 3.82-6.31; z=12.5; p<0.0001). Results remained highly significant when only randomized, controlled trials (RCTs) were considered (RR=1.76, CI: 1.65-1.88; z=3.51; p=0.001). In a more recent analysis of 34 studies, we found similar reductions of risk, including an even larger number of randomized, controlled trials, and also an estimated number-needed-to-treat (NNT) of 22.6 (CI:21.0-24.6), suggesting that about 23 patients would need to be treated with lithium to avoid one life-threatening or fatal suicidal act (Baldessarini & Tondo, 2008).

In one of these studies, initially involving 360 type I or II BPD patients evaluated before, during, and following discontinuation of maintenance lithium monotherapy, rates of suicide and life-threatening attempts were reduced by 6.4-fold, or 83% (Tondo *et al*., 1998). Notably, however, in that study, the risk of suicidal acts

increased by 20-fold within several months after discontinuing lithium maintenance treatment, and later fell back to the same level encountered before lithium treatment had started. This early suicidal risk following discontinuation of long-term treatment with lithium was twice-higher following abrupt or rapid versus gradual (over at least two weeks) discontinuation. Of interest, too, we found more than two-fold increase in the ratio of attempts/suicides (A/S) during treatment with lithium, suggesting *reduced lethality* of suicidal behavior with this treatment even when suicide was attempted. In addition, in data obtained from eight studies and pooled by meta-analysis, we found a substantial reduction of risk of suicide and attempts (by 76%) among patients diagnosed with recurrent MDD, treated with lithium compared to other alternatives, mainly anticonvulsants (Guzzetta *et al*., 2007).

The evident beneficial effects of lithium in reducing mortality as well as morbidity associated with suicidal behaviors are even more remarkable given the potentially lethal toxicity of lithium in acute overdoses. In fact, recent analyses of outcomes of ingestions of potentially toxic substances by the US Centers for Disease Control (CDC) indicate that mortality from overdoses of lithium is similar to that associated with modern antidepressant or antipsychotic agents, or less than expected, possibly owing to protection from lethal effects by vomiting as well as timely treatment by hemodialysis (Baldessarini *et al*., 2006). Despite lithium's potential lethality, suicide attempts with lithium during long-term treatment have been reported to be uncommon (Waddington & McKensie, 1994), and we found none among more than 700 patients with major mood disorders treated with lithium for several years at the Lucio Bini Mood Disorders Center in Sardinia (unpublished observations). It is possible that suicide attempts using this agent are limited by its major antisuicidal effects.

There is little research that directly compares suicidal risks during treatment with mood-stabilizers other than lithium (Oquendo *et al*., 2005), but at least two studies found nearly three-fold average lower risks with lithium than with either carbamazepine or valproate among bipolar or schizoaffective disorder patients (Thies-Flechtner *et al*., 1996; Goodwin *et al*., 2003). Anticonvulsants may have some beneficial effects on suicidal behavior (Yerevanian *et al*., 2003), but our recent meta-analysis of protective effects against suicidal behavior of lithium versus several proved or putative mood-stabilizing anticonvulsants regarding suicidal acts found lithium to be significantly superior (Baldessarini & Tondo 2009). This meta-analysis was based on six studies, mainly involving carbamazepine, divalproex, or lamotrigine (Greil *et al*., 1997; Bowden *et al*., 2003; Calabrese *et al*., 2003; Goodwin *et al*., 2003; Yerevanian *et al*., 2003; Collins & McFarland, 2008), and included more than 30,000 patients treated longer with lithium (31 months) than with an anticonvulsant (19 months); half of the trials involved randomized assignment to treatments. The observed rate of suicidal acts averaged 0.3%/year during treatment with lithium versus 0.9%/year with anticonvulsants, to yield meta-analytically pooled risk ratio of 2.86 (CI: 2.29-3.57; z=9.24; p<0.0001), or nearly three-fold superiority favoring lithium over the few anticonvulsants that have been so-tested.

Despite these several findings, a direct role of lithium treatment in decreasing suicide risk is not securely demonstrated. A major limitation of studies that indicate less suicidal risk during long-term treatment with lithium involve incidental findings since they were usually not designed to test for suicidal behavior as an outcome. An additional limitation to these studies – and, indeed, of all studies of therapeutic effects – is that the patients who accept, tolerate, and sustain long-term treatment with lithium may well be self-selected and not entirely representative of the full spectrum of clinically encountered mood-disorder patients. Moreover, such factors as female sex, being married, having more education and employment, the presence of certain personality traits, relative improvement of depressive versus other symptoms with treatment, and the occurrence of side-effects, as well as being less severely ill or ill for less time, all might affect suicidal risk and so tend to confound interpretation of the observed effects of lithium treatment. Whether the same patients were assessed with and without lithium, or randomly assigned to particular treatments in parallel groups, those who accept and continue the treatment may differ from others who fail to adhere to lithium treatment, tolerate it poorly, or discontinue treatment early. Nevertheless, in order to test for long-term effects of *any* treatment, only patients who accept and tolerate it can be considered for analysis. Since a growing number of BPD and other mood disorder patients are reluctant to be treated with lithium, or to accept it for prolonged periods, it is important to identify alternative treatments that can reduce suicidal risk.

Ideal studies of such treatment would involve randomized assignment to specific treatment conditions for prolonged periods, and would involve outcome measures that are specific to suicidal behavior (Baldessarini *et al*., in press). However, use of a placebo-control condition is unlikely to be feasible owing to ethical constraints when death is a possible outcome, and due to difficulties of recruiting patients into placebo-controlled treatment trials, especially over long times. Nevertheless, trials

involving randomization to different but similarly plausible, even if unproved, treatments might be practically and ethically feasible. So far, however, trials that compare, for example, lithium to an anticonvulsant or antipsychotic agent are rare and almost never continued for more than several months. Moreover, head-to-head comparisons of different companies' products are unlikely to be favored by the pharmaceutical industry.

The effectiveness of lithium treatment in preventing suicide is likely to be associated with reduction of risk or severity of recurrences in depression or mixed dysphoric-agitated states in BPD, probably also with reduced impulsivity and aggressiveness in various types of mood disorders (Baldessarini *et al*., 2006). Some experts have suggested that lithium may have specific effects against suicide, independent of its mood-stabilizing actions (Müller-Oerlinghausen, 2001; Ahrens & Müller-Oerlinghausen 2001), based on reductions of suicidal risk even among patients considered clinical "nonresponders" to lithium in not showing substantial prevention of recurrences of episodes of mood disorder. Regarding biological hypotheses, decreased intensity of impulsive, hostile or aggressive behavior may be mediated through enhanced functioning of the central serotonin system that has been identified as an action of lithium (Bschor & Bauer, 2006).

Finally, lithium treatment requires closer monitoring of patients than with most other mood-stabilizing agents. This added level of clinical follow-up might facilitate identification of emerging symptoms associated with suicidal behavior, including suicidal ideation, and early agitation, dysphoria, and anger, or otherwise provide protective influences. We reported previously that various measures that can be considered indices of access to clinical care were closely correlated with state suicide rates in the United States (Tondo *et al*., 2006). However, the value of additional clinical contact and close supervision required by lithium treatment is not likely to be a critical factor, given experience in the InterSePT trial for schizophrenia patients, which found superior antisuicidal effects of clozapine over olanzapine, despite matching for clinician contact-time (Meltzer *et al*., 2003).

In conclusion, major mood disorders are associated with important increases of suicide behavior, especially when the illnesses present as mixed, dysphoric-agitated, states, perhaps also with anger, aggression, or impulsivity. In such conditions, antidepressant treatments may lack a beneficial effect or even increase suicide risk, and mood-stabilizers, and particularly lithium salts maintained for prolonged times, may be more effective treatments, as a component of more comprehensive clinical management aimed at suicide prevention.

Acknowledgements. Supported by the Centro Bini Private Donors Research Fund (LT), by a grant from the Bruce J. Anderson Foundation and by the McLean Private Donors Research Fund (RJB).

REFERENCES

Ahrens B. & Müller-Oerlinghausen B. (2001). Does lithium exert an independent antisuicidal effect? *Pharmacopsychiatry* 34,132-136.

Akiskal H.S., Benazzi F., Perugi G. & Rihmer Z. (2005). Agitated "unipolar" depression re-conceptualized as a depressive mixed state: implications for the antidepressant-suicide controversy. *Journal of Affective Disorders* 85, 245-258.

Angst J., Angst F., Gerber-Werder R. & Gamma A. (2005). Suicide in 406 mood-disorder patients with and without long-term medication: a 40-44 years follow-up. *Archives of Suicide Research* 9, 279-300.

Baldessarini R.J. & Tondo L. (2008). Lithium and suicidal risk. *Bipolar Disorders* 10, 114-115.

Baldessarini R.J. & Tondo L. (2009). Suicidal risks during treatment of bipolar disorder patients with lithium versus anticonvulsants. *Pharmacopsychiatry* 42, 72-75.

Baldessarini R.J., Salvatore P., Tohen M., Khalsa HMK. & Hennen J. (2004). Morbidity from onset in first-episode bipolar I disorder patients: The International-300 study. *Neuropsychopharmacology* 29, Suppl. 1, S88.

Baldessarini R.J., Pompili M., Tondo L., Tsapakis E., Soldani F., Faedda G.L. & Hennen J. (2005). Antidepressants and suicidal behavior: are we hurting or helping? *Clinical Neuropsychiatry* 2, 73-75.

Baldessarini R.J., Tondo L., Davis P., Pompili M., Goodwin F.K. & Hennen J. (2006). Decreased suicidal risk during long-term lithium treatment: meta-analysis. *Bipolar Disorders* 8, 625-639.

Baldessarini R.J., Tondo L., Strombom I., Dominguez S., Fawcett J., Oquendo M., Tollefson G.D., Valuck R.J. & Tohen M. (2007). Ecological studies of antidepressants and suicide risks. *Harvard Review of Psychiatry* 15, 133-145.

Baldessarini R.J., Vieta E., Calabrese J.R., Tohen M. & Bowden C. (in press). Bipolar depression: overview and commentary. *Harvard Review of Psychiatry*.

Barbui C., Esposito E. & Cipriani A. (2009). Selective serotonin reuptake inhibitors and risk of suicide: a systematic review of observational studies. *Canadian Medical Association Journal* 180, 291-297.

Bowden C.L., Calabrese J.R., Sachs G., Yatham L.N., Asghar A., Hompland M., Montgomery P., Earl N., Smoot T.M. & De Veaugh-Geiss J. (2003). Placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. *Archives of General Psychiatry* 60, 392-400.

Bschor T. & Bauer M. (2006). Efficacy and mechanisms of action of lithium augmentation in refractory major depression. *Current Pharmaceutical Design* 12, 2985-2992.

Calabrese J.R., Bowden C.L., Sachs G., Yatham L.N., Behnke K., Mehtonen O.P., Montgomery P., Ascher J., Paska W., Earl N. & DeVeaugh-Geiss J. (2003). Placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. *Journal of Clinical Psychiatry* 64, 1013-1024.

Cipriani A., Pretty H., Hawton K. & Geddes J.R. (2005). Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: Systematic review of randomized trials. *American Journal of Psychiatry* 162, 1805-1819.

Collins J.C. & McFarland B.H. (2008). Divalproex, lithium and suicide among Medicaid patients with bipolar disorder. *Journal of Affective Disorders* 107, 23-28.

Dilsaver S.C., Chen Y-W., Swann A.C., Shoaib A.M., Dilsaver Y.T. & Krajewski K.J. (1997). Suicidality panic disorder and psychosis in bipolar depression, depressive-mania and pure mania. *Psychiatry Research* 73, 47-56.

FDA (US Food and Drug Administration). (2007). Antidepressant use in children, adolescents, and adults. Retrieved February 18, 2009, from http://www.fda.gov/cder/drug/antidepressants/default.htm

Goldberg J.F., Perlis R.H., Bowden C.L., Thase M.E., Miklowitz D.J., Marangell L.B., Calabrese J.R., Nierenberg A.A. & Sachs G.S. (2009). Manic symptoms during depressive episodes in 1,380 patients with bipolar disorder: findings from the STEP-BD. *American Journal of Psychiatry* 166, 173-181.

Goldsmith S.K., Pellmar T.C., Kleinman A.M. & Bunney W.E. (2002). *Reducing Suicide*. Institute of Medicine of the US National Academy of Science: Washington, DC.

Goodwin F.K., Fireman B., Simon G.E., Hunkeler E.M., Lee J. & Revicki D. (2003). Suicide risk in bipolar disorder during treatment with lithium and divalproex. *Journal of American Medical Association* 290, 1467-1473.

Greil W., Ludwig-Mayerhofer W., Erazo N., Schochlin C., Schmidt S., Engel R.R., Czernik A., Giedke H., Müller-Oerlinghausen B., Osterheider M., Rudolf G.A., Sauer H., Tegeler J. & Wetterling T. (1997). Lithium versus carbamazepine in the maintenance treatment of bipolar disorders: randomized study. *Journal of Affective Disorders* 43, 151-161.

Guzzetta F., Baldessarini R.J, Tondo L. & Centorrino F. (2007). Lithium treatment and suicidal risk in recurrent unipolar major depression. *Journal of Clinical Psychiatry* 68, 380-383.

Hammad T.A., Laughren T.P. & Racoosin J.A. (2006). Suicide rates in short-term randomized controlled trials of newer antidepressants. *Journal of Clinical Psychopharmacology* 26, 203-207

Harris E.C. & Barraclough B. (1997). Suicide as an outcome for mental disorders. a meta-analysis. *British Journal of Psychiatry* 170, 205-228.

Harris E.C. & Barraclough B. (1998). Excess mortality of mental disorder. *British Journal of Psychiatry* 173, 11-53.

Isometsä E.T., Henriksson M.M., Aro H.M., Heikkinen M.E., Kuoppasalmi K.I. & Lönnqvist J.K. (1994). Suicide in major depression. *American Journal of Psychiatry* 151, 530-536.

Joffe R.T., MacQueen G.M., Marriott M. & Trevor Young L. (2004). Prospective, longitudinal study of percentage of time spent ill in patients with bipolar I or bipolar II disorders. *Bipolar Disorders* 6, 62-66.

Judd L.L., Akiskal H.S., Schettler P.J., Endicott J., Maser J., Solomon D.A., Leon A.C., Rice J.A. & Keller M.B. (2002). The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Archives of General Psychiatry* 59, 530-537.

Kessing L.V., Søndergard L., Kvist K. & Andersen PK. (2005). Suicide risk in patients treated with lithium. *Archives of General Psychiatry* 62, 860-866.

Kessler R.C., Berglund P., Borges G., Nock M. & Wang P.S. (2005). Trends in suicide ideation, plans, gestures, and attempts in the United States, 1990-1992 to 2001-2003. *Journal of American Medical Association* 293, 2487-2495.

Koukopoulos A. & Koukopoulos A. (1999). Agitated depression as a mixed state and the problem of melancholia. *Psychiatric Clinics of North America* 22, 547-564.

Maj M., Pirozzi R., Magliano L., Fiorillo A. & Bartoli L. (2006). Agitated "unipolar" major depression: prevalence, phenomenology, and outcome. *Journal of Clinical Psychiatry* 67, 712-719.

Meltzer H.Y., Alphs L., Green A.I., Altamura A.C., Anand R., Bertoldi A., Bourgeois M., Chouinard G., Islam M.Z., Kane J., Krishnan R., Lindenmayer J.P., Potkin S. & International Suicide Prevention Trial Study Group. (2003). Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Archives of General Psychiatry* 60, 82-91.

Müller-Oerlinghausen B. (2001). Arguments for the specificity of the antisuicidal effect of lithium. *European Archives of Psychiatry and Clinical Neuroscience* 251, Suppl. 2, 72-75.

Müller-Oerlinghausen B., Ahrens B. & Felber W. (2006). The suicide-preventive and mortality-reducing effect of lithium. In *Lithium in Neuropsychiatry* (ed. M. Bauer., P. Grof, B. Müller-Oerlinghausen), pp 179-192. Informa Healthcare: London.

O'Donovan C., Garnham J.S., Hajek T. & Alda M. (2008). Antidepressant monotherapy in pre-bipolar depression: predictive value and inherent risk. *Journal of Affective Disorders* 107, 293-298.

Oquendo M.A., Chaudhury S.R. & Mann J.J. (2005). Pharmacotherapy of suicidal behavior in bipolar disorder. *Archives of Suicide Research* 9, 237-250.

Post R.M., Denicoff K.D., Leverich G.S., Altshuler L.L., Frye M.A., Suppes T.M., Rush A.J., Keck P.E. Jr., McElroy S.L., Luckenbaugh D.A., Pollio C., Kupka R. & Nolen W.A. (2003). Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH life chart method. *Journal of Clinical Psychiatry* 64, 680-690.

Rihmer Z. & Pestality P. (1999). Bipolar II disorder and suicidal behavior. *Psychiatric Clinics of Nord America* 22, 667-673.

Roy A. (2001). Suicide. In *Kaplan and Sadock's Comprehensive Textbook of Psychiatry* (ed. B.J. Sadock and V.A. Sadock), pp. 2031-2040. Lippincott-Williams & Wilkins: Philadelphia.

Simon R.I., Hales R.E. (2006). *Textbook of Suicide Assessment and Management*. American Psychiatric Press: Washington, DC.

Thies-Flechtner K., Müller-Oerlinghausen B., Seibert W., Walther A. & Greil W. (1996). Effect of prophylactic treatment on suicide risk in patients with major affective disorders: Data from a randomized prospective trial. *Pharmacopsychiatry* 29, 103-107.

Tondo L. & Baldessarini RJ. (2007). Suicidal risks among 2826 Sardinian major affective disorder patients. *Acta Psychiatrica Scandinavica* 116, 419¬428.

Tondo L., Baldessarini R.J., Hennen J, Floris G., Silvetti F. & Tohen M. (1998). Lithium treatment and risk of suicidal behavior in bipolar disorder patients. *Journal of Clinical Psychiatry* 59, 405-414.

Tondo L, Hennen J. & Baldessarini R.J. (2001). Reduced suicide risk with long-term lithium treatment in major affective Illness: A meta-analysis. *Acta Psychiatrica Scandinavica* 104, 163-172.

Tondo L., Isacsson G. & Baldessarini R.J. (2003). Suicide in bipolar disorder: risk and prevention. *CNS Drugs* 17, 491-511.

Tondo L., Albert M.J. & Baldessarini R.J. (2006). Suicide rates in relations to health care access in the United States: an ecological study. *Journal of Clinical Psychiatry* 67, 517-523.

Waddington D. & McKensie I.P. (1994). Overdose rates in lithium-treated vs. antidepressant-treated outpatients. *Acta Psychiatrica Scandinavica* 90, 50-52.

Yerevanian B.I., Koek R.J. & Mintz J. (2003). Lithium, anticonvulsants and suicidal behavior in bipolar disorder. *Journal of Affective Disorders* 73, 223-228.

Zisook S., Trivedi M.H., Warden D., Lebowitz B., Thase M.E., Stewart J.W., Moutier C., Fava M., Wisniewski S.R., Luther J. & Rush AJ. (2009). Clinical correlates of the worsening or emergence of suicidal ideation during SSRI treatment of depression: An examination of citalopram in the STAR-D study. *Journal of Affective Disorders*, Epub ahead of print.