Thomas A. Ban: Lithium in Psychiatry in Historical Perspective

Leonardo Tondo's comment
Lithium and I: Clinical experience with a remarkable ion

Summary

Lithium as a treatment for mood disorders was introduced in Italy in the late 1960s. Interest in lithium was initiated by Drs. Athanasios Koukopoulos who founded and led the Lucio Bini Mood Disorders Center of Rome from 1974 with Drs. Daniela Reginaldi and Paolo Girardi. I was involved with their clinical and research activities from its founding and later established a second such center in Cagliari, Sardinia, in 1977. These activities include my now 45-year long experience with clinical use of lithium in patients with mood disorders and studies of its effectiveness, limitations, and adverse effects, as well as developing evidence for suicide-preventing effects of long-term lithium treatment. Since the early 1990s, these research activities have been strongly stimulated by an ongoing collaboration with Professor Ross Baldessarini at the Mailman Research Center at McLean Hospital and Harvard Medical School, as part of his International Consortium for Mood & Psychotic Disorders Research. This report summarizes highlights of our work with this important orphan treatment.

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The late Drs. Andrea Dotti (1938–2007) and Athanasios Koukopoulos (1931–2013) introduced lithium in Italy in the late 1960s. Koukopoulos heard of lithium from a patient whom he had treated two years earlier for a severe manic episode. Her husband reported that the patient had been taking lithium for two years, prescribed by Dr. Mogens Schou (1918–2005) in Denmark, and had not had her usual annual illness recurrences since starting this treatment. Koukopoulos called and then met Schou. In Rome, he and Dr. Dotti bought an Eppendorf spectrophotometer to assay lithium concentration in serum and started using lithium following Schou's advice. They successfully treated many patients diagnosed with bipolar disorder, but not without encountering

some hostility from colleagues in Rome, who accused them of over diagnosing mood disorders. These skeptics eventually changed their minds after seeing that many patients who had been considered to have "schizophrenia" responded remarkably well to lithium treatment.

In 1973, I started working with Drs. Koukopoulos and Dotti as well as other psychiatrist-colleagues. Among these, Drs. Daniela Reginaldi and Paolo Girardi are still working at the Lucio Bini Mood Disorder Center founded by Dr. Koukopoulos in Rome and named in honor of one of the inventors of ECT, Drs. Lucio Bini (1908–1964) and Ugo Cerletti (1877–1963). While I was a medical student, Mogens Schou visited the Roman Mood Disorder Center to discuss research on lithium in the early 1970s. However, those working at the Bini Center did not carry out research with Dr. Schou, possibly because he was more interested in generating interest in the use of lithium rather than in clarifying what lithium did clinically or for whom it was best suited. Nevertheless, Koukopoulos and Reginaldi discussed their research interests with Schou, who proposed an excellent title for one of their early clinical studies: *Does lithium prevent depressions by suppressing manias?* (Kukopulos and Reginaldi 1973). (Koukopoulos was then using an earlier transliteration of his name from the Greek). In that early report, he and Reginaldi attributed the efficacy of lithium in preventing bipolar depression as a reflection of suppressing manic episodes that often preceded depressions.

Two years later, I participated in a study of effects of lithium on the course of manic-depressive recurrences (Kukopulos, Reginaldi, Girardi and Tondo 1975). We reported that recurring episodes of mania and depression were about 59% shorter (29 weeks before versus 12 weeks with lithium). In particular, reduction of time in manic states was more evident than in the typically longer depressive episodes (62% vs. 50%).

In 1975, we collaborated with Joseph Mendels and Alan Frazer at the University of Pennsylvania to evaluate the significance of intracellular versus circulating concentrations of lithium. We found that, among Lucio Bini Center patients responding poorly to lithium treatment, serum concentrations of lithium were higher than in patients who did well with lithium. Instead, lithium concentrations in corresponding erythrocytes were relatively low in lithium-nonresponders, and the ratio of serum-to-red cell concentrations was higher, even with adjustment for their higher daily doses of lithium carbonate. Of note, however, the ratio of circulating to intracellular lithium was relatively high in the nonresponders, possibly reflecting less efficient

entry of lithium into the central nervous system of poor responders (Mendels, Frazer, Baron et al. 1976).

In further studies of serum concentrations of lithium, Koukopoulos noted that the lithium levels tended to decrease in mania and increase in depression—evidently reflecting corresponding changes in levels of arousal, general metabolic activity, and renal clearance (Kukopulos and Reginaldi 1978). Interestingly, they used this finding to improve treatment by predicting imminent changes of mood before they became clinically manifest.

Based on these early studies, Koukopoulos instilled in his colleagues and students consideration of the greater clinical importance of the course of manic-depressive illness than its acute symptomatic presentations. Arising from this interest was an early description of five characteristic course sequences in bipolar disorder: [a] depression–mania–free interval (DMI), [b] mania–depression–free interval (MDI), [c] continuous-circular (CC), [d] rapid-cycling (RC), and [e] erratic or irregular (Kukopulos, Reginaldi, Laddomada et al. 1980; Koukopoulos, Reginaldi, Tondo et al. 2013). These course-patterns had important predictive associations with overall morbidity and treatment responses, notably including less favorable results with DMI than MDI patients.

This work also led to the observation that lithium often failed to prevent mood-disorder recurrences in manic-depressive disorder patients being concomitantly treated with antidepressants, and to the hypothesis that antidepressants may induce mood-switches from depression to hypomania or mania that often were poorly responsive to lithium (Reginaldi, Tondo, Floris et al. 1981).

Long-term treatment with lithium was widely employed by the Lucio Bini group and was found to help many difficult patients, including some who had been hospitalized for years. Lithium treatment also was a prevalent option at a new Lucio Bini Mood Disorder Center, which I co-founded in 1977 in Cagliari, Sardinia. By the 1980s, lithium treatment had become well established internationally, and the research interests of the Rome and Cagliari Centers moved to nosological topics, including the importance of mixed or agitated depression.

In 1992, I was mentoring Dr. Gianni Faedda at University of Cagliari. After his medical training, he received a fellowship from the Sardinia Region which could be applied for research training only at Harvard Medical School. We contacted Ross Baldessarini who accepted Faedda's candidacy for postdoctoral training in psychopharmacology at the Mailman Research Center at

Harvard-affiliated McLean Hospital, initially to pursue laboratory studies of the pharmacology of D_1 dopamine receptors.

This development initiated a long and fruitful association with Baldessarini that continues to the present time. I am indebted to him for encouraging discipline in research and rigorous objectivity in the collection, analysis, and interpretation of clinical and research data, and consistent awareness that there were real, suffering persons behind the numbers.

As Faedda's primary interests were clinical, we initiated a study based on patient data from the Bini Center in Cagliari to pursue my idea that the rate of discontinuing lithium treatment might have important clinical consequences. Faedda and Baldessarini noted that patients relapsed much sooner after abrupt or rapid discontinuation of lithium, compared to gradual dose-reduction and discontinuation over at least two weeks. In particular, recurrence rates (new illness episodes per time) were much greater within the initial months following rapid discontinuation of lithium, and risk of recurrences remained parallel (evidently reflecting the natural history of the course of untreated bipolar disorder) but much lower following gradual discontinuation for up to five years of follow-up. This pattern suggested that rapid treatment discontinuation acted as an iatrogenic stressor and that gradual discontinuation not only delayed, but actually *reduced* risks of later illness recurrences (Faedda, Tondo, Baldessarini et al. 1993). The median time to an illness recurrence was 5.0-times longer following gradual than after rapid discontinuation (20.0 ± 5.8 vs. 4.0 ± 0.7 months; $p<0.0001$), the mean cycling interval also was shorter after rapid discontinuation than before lithium treatment was started (6.3 vs. 14.6 months; $p<0.0001$), adding to the impression that rapid treatment discontinuation was an adjunctive stressor to effects of nontreatment. Over several years of follow-up, patient-subjects remained stable without lithium treatment 20 times more frequently after gradual than rapid discontinuation (37% vs. 1.8% of cases; $p<0.0001$) (Baldessarini, Tondo, Faedda et al. 1996). This study was replicated with an independent sample of Bipolar Disorder subjects the following year (Baldessarini, Tondo, Floris and Rudas 1997). We also found that Bipolar I disorder patients were 1.5-times less likely than Bipolar II subjects to remain in remission during long-term treatment with lithium, and that the polarity of their first recurrences during treatment was 81% concordant with that of their first-lifetime episode (Faedda, Tondo, Baldessarini et al. 1993).

A related question was whether trials of re-treatment following discontinuation of lithium were less effective, as had been claimed by some colleagues, based mainly on clinical impressions.

Instead, we found little difference in average clinical responses between initial treatment and second or even later trials of re-treatment with lithium (Tondo, Baldessarini, Floris and Rudas 1997). Notably, the mean number of episodes/year was similar with first versus second trials of lithium treatment (0.83 vs. 0.94), as was the proportion of time ill with treatment (18.0% vs. 24.2%), with no differences in numbers of manic and depressive episodes, duration of the treatments, interval between treatment trials, or discontinuation rate. However, there was 12.8% more use of adjunctive medication in the second treatment.

We also compared responses to lithium treatment in Bipolar Disorder types I and II patients and found that lithium had superior benefits in type II patients, with significantly greater reduction of episodes per year and a lower percentage of time ill, probably because of a greater effect of lithium on hypomanias (prevalent in Bipolar-II disorder) compared to manias (only in Bipolar-I disorder), whereas reduction of depressive morbidity was somewhat less but similar with both diagnostic types. Moreover, during treatment, Bipolar II patients had 5.9-fold longer inter-episode intervals and were twice as likely as type I patients to have no new episodes (Tondo Baldessarini, Hennen and Floris 1998b).

Following-up on reports that lithium was becoming less effective in recent years, we reviewed published reports on long-term lithium treatment from 1970 to 1996, seeking evidence of a secular decline in response that was not found (Baldessarini and Tondo 2000). We proposed that unfavorable results with any treatment may occur in some settings with heavy representation of patients with complex and less treatment-responsive illnesses, particularly in specialized institutions, but that benefits of long-term maintenance treatment with lithium had changed little in recent decades. We also tested a frequently repeated idea that delay of treatment of Bipolar Disorder results in a decline of effectiveness of treatment and found that latency from illness onset to diagnosis and sustained treatment, though typically delayed for 6–8 years (and longer after juvenile onset), as well as pre-treatment episode counts, were not significantly associated with the quality of clinical responses to treatment with lithium or other mood-stabilizing treatments (Baldessarini, Tondo, Hennen and Floris 1999b; Baethge, Tondo, Bratti et al. 2003; Bratti, Baldessarini, Baethge and Tondo 2003).

We also reviewed studies of the effectiveness of lithium and other treatments in rapid cycling (RC), compared with non-RC Bipolar Disorder patients. We found that 13.7% fewer RC than non-RC patients experienced full protection from all recurrences during maintenance treatment with

lithium (Baldessarini, Tondo, Floris and Hennen 2000). Moreover, we compared responses with other treatments among RC (n=905) versus non-RC (n=951) Bipolar Disorder patients in 16 reports involving use of carbamazepine, lamotrigine, lithium, topiramate, or valproate, alone or with other agents, over an average of 47.5 months. Across all treatments, lack of substantial clinical benefit averaged 2.9-times more prevalent with RC than non-RC status. Moreover, contrary to expectation, responses with lithium in RC patients were somewhat greater than with anticonvulsant mood-stabilizers (Tondo, Hennen and Baldessarini 2003). These findings challenged marketing claims that anticonvulsant were more effective than lithium for RC Bipolar Disorder patients.

Noting in the 1990s that patients treated with lithium seemed clinically to have less suicidal ideation and behavior than without lithium or with other treatments, with Drs. Baldessarini and Kay Jamison, we reviewed the then very limited research literature on this topic and found evidence favoring an association of long-term lithium treatment lithium with lower risk of suicidal behavior (Tondo, Jamison and Baldessarini 1997). In 28 research reports based on 17,000 subjects with major affective illnesses, the risk of suicides and attempts averaged 3.2 versus 0.37 per 100 patient-years without versus with lithium—a striking, 8.6-fold difference. The finding encouraged further research on effects of lithium treatment on suicidal risk. These studies included a systematic review on this topic (Tondo and Baldessarini 2000), and a first meta-analysis of research findings (Tondo, Hennen and Baldessarini 2001), as well as reporting of original data from the Centro Lucio Bini Centers (Tondo, Baldessarini, Hennen et al. 1998a).

The original data were based on 5233 patient-years of observation and indicated that of 58 patients who made suicide attempts (8 were fatal), there was a highly significant, 6.4-fold lower adjusted hazard ratio for suicidal acts during treatment with lithium versus before treatment, as well as 7.5-fold greater risk after discontinuing lithium treatment, particularly during the initial 12 months post-discontinuation, with a twice-greater risk after discontinuing abruptly or rapidly (Baldessarini, Tondo and Hennen 1999a). We also reported another review (Tondo, Isacsson and Baldessarini 2003) and another meta-analysis on this topic (Baldessarini, Tondo, Davis et al. 2006) which both supported a substantial reduction of risks of suicide and attempts with long-term lithium treatment. Risk of suicide fatality was lower with lithium than with placebo in several randomized, controlled treatment trials, in which suicidal behaviors were reported passively and incidentally as "adverse outcomes" rather than as a pre-planned and explicitly determined outcome

measure (Tondo, Isacsson and Baldessarini 2003; Baldessarini, Tondo, Davis et al. 2006). We also found that risks of suicidal behavior were lower with lithium than during treatment with mood-altering anticonvulsants (Baldessarini and Tondo 2009; Tondo and Baldessarini 2018). In addition, with Dr. Francesca Guzzetta, we extended evidence of an antisuicidal effect of lithium treatment to patients with nonbipolar Major Depressive Disorder (Guzzetta, Tondo, Centorrino and Baldessarini 2007).

In recent years, our research on lithium has included reassessments of adverse effects on renal function. This work included an international collaborative study of 312 patients (mean age, 56 years) who produced 2,669 assays of serum lithium concentration. We found that over 8–48 (mean, 18) years, 29.5% of subjects experienced at least one low value of eGFR (<60 mL/min/1.73 m^2), mostly after ≥15 years of treatment and age >55 years; risk of ≥2 low values was 18.1%, and there were no cases of end-stage renal failure (which may well have been avoided by clinically appropriate interventions including discontinuation of lithium before renal dysfunction became severe). Further of note, these encouraging data were obtained in highly specialized clinical settings where the patients were closely followed and monitored and may or may not generalize to other circumstances. Independent risk factors for declining eGFR ranked: longer exposure to lithium, lower lithium dose (probably related to lesser baseline clearance), higher serum lithium concentration, older age, and medical comorbidity. Later low eGFR also was predicted by lower initial eGFR and starting lithium at age ≥40 years (Tondo, Abramowicz, Alda et al. 2017). An important conclusion was that advancing age was a major risk factor confounding the role of lithium in the decline of renal function.

Recently, we collaborated with colleagues from the International Group for The Study of Lithium (IGSLi) to develop a clinical advisory report on use of lithium aimed at guiding patients and prescribing clinicians to its safe and effective use to treat patients with major mood disorders (Tondo, Alda, Bauer et al. 2019).

Having treated approximately 1800 patients with lithium, I understand that it may be not be as easy to use this mood-stabilizer compared to other agents that can be administered without the requirement of monitoring serum drug levels, and assays for renal and thyroid function. However, alternatives have medical risks, too but they do not achieve the same beneficial effects. Mood-stabilizing anticonvulsants can interact with the metabolism of other drugs, and some have extraordinarily high teratogenic risk. Second-generation antipsychotics can increase risk of

weight-gain, metabolic syndrome, excessive sedation, and akathisia. Moreover, lithium remains one of the most effective and versatile treatments aimed at long-term mood-stabilization and its evident antisuicidal effect is virtually unique among treatments widely used to treat major mood disorders.

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References:

Baethge C, Tondo L, Bratti IM, Bschor T, Bauer M, Viguera AC, Baldessarini RJ. Prophylaxis latency and outcome in bipolar disorders. Can J Psychiatry 2003; 48:449-57.

Baldessarini RJ, Tondo L. Does lithium still work? Evidence of stable responses over three decades. Arch Gen Psychiatry. 2000; 57:187-90.

Baldessarini RJ, Tondo L. Suicidal risks during treatment of bipolar disorder patients with lithium versus anticonvulsants. Pharmacopsychiatry. 2009; 42:72-5.

Baldessarini RJ, Tondo L, Davis P, Pompili M, Goodwin FK, Hennen J. Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review. Bipolar Disord. 2006; 8(5 Pt 2):625-39.

Baldessarini RJ, Tondo L, Faedda GL, Suppes TR, Floris G, Rudas N. Effects of the rate of discontinuing lithium maintenance treatment in bipolar disorders. J Clin Psychiatry. 1996; 57: 441-8.

Baldessarini RJ, Tondo L, Floris G, Hennen J. Effects of rapid cycling on response to lithium maintenance treatment in 360 bipolar I and iI disorder patients. J Affect Disord. 2000; 61:13-22.

Baldessarini RJ, Tondo L, Floris G, Rudas N. Reduced morbidity after gradual discontinuation of lithium treatment for bipolar I and II disorders: a replication study. Am J Psychiatry. 1997; 154:551-3.

Baldessarini RJ, Tondo L, Hennen J. Effects of lithium treatment and its discontinuation on suicidal behavior in bipolar manic-depressive disorders. J Clin Psychiatry. 1999a; 60(Suppl 2):77-84.

Baldessarini RJ, Tondo L, Hennen J, Floris G. Latency and episodes before treatment: response to lithium maintenance in bipolar I and II disorders. Bipolar Disord. 1999b; 1:91-7.

Bratti IM, Baldessarini RJ, Baethge C, Tondo L: Pretreatment episode count and response to lithium treatment in manic-depressive illness. Harv Rev Psychiatry. 2003; 11:245-56.

Faedda GL, Tondo L, Baldessarini RJ, Suppes T, Tohen M. Outcome after rapid vs. gradual discontinuation of lithium treatment in bipolar disorders. Arch Gen Psychiatry. 1993; 50:448-55.

Guzzetta F, Tondo L, Centorrino F, Baldessarini RJ. Lithium treatment reduces suicide risk in recurrent major depressive disorder. J Clin Psychiatry. 2007; 68:380-3.

Koukopoulos A, Reginaldi D, Tondo L, Visioli C, Baldessarini RJ. Course sequences in bipolar disorder: depressions preceding or following manias or hypomanias. J Affect Disord. 2013; 151:105-10.

Kukopulos A, Reginaldi D. Does lithium prevent depressions by suppressing manias? Int Pharmacopsychiatry. 1973; 8:152-8.

Kukopulos A, Reginaldi D. Variations of serum lithium concentrations correlated with the phases of manic-depressive psychosis. Agressologie. 1978; 19:219-22.

Kukopulos A, Reginaldi D, Girardi P, Tondo L. Course of manic-depressive recurrence under lithium. Compr Psychiatry. 1975; 16:517-24.

Kukopulos A, Reginaldi D, Laddomada P, Floris G, Serra G, Tondo L. Course of the manic-depressive cycle and changes caused by treatment. Pharmakopsychiatr Neuropsychopharmakol. 1980; 13:156-67.

Mendels J, Frazer A, Baron J, Kukopulos A, Reginaldi D, Tondo L, Caliari B. Letter: Intra-erythrocyte lithium io concentration and long-term maintenance treatment. Lancet. 1976; 1(7966):966-7.

Reginaldi D, Tondo L, Floris G, Pignatelli A, Kukopulos A. Poor prophylactic lithium response due to antidepressants. Int Pharmacopsychiatry. 1981; 16:124-8.

Tondo L, Abramowicz M, Alda M, Bauer M, Bocchetta A, Bolzani L, Calkin CV, Chillotti C, Hidalgo-Mazzei D, Manchia M, Müller-Oerlinghausen B, Murru A, Perugi G, Pinna M, Quaranta G, Reginaldi D, Reif A, Ritter P Jr, Rybakowski JK, Saiger D, Sani G, Selle V, Stamm T, Vázquez GH, Veeh J, Vieta E, Baldessarini RJ. Long-term lithium treatment in bipolar disorder: effects on glomerular filtration rate and other metabolic parameters. Int J Bipolar Disord. 2017; 5:27–38.

Tondo L, Alda M, Bauer M, Bergink V, Grof P, Hajek T, Lewitka U, Licht RW, Manchia M, Müller-Oerlinghausen B, Nielsen RE, Selo M, Simhandl C, Baldessarini RJ; International Group for Studies of Lithium (IGSLi).Clinical use of lithium salts: guide for users and prescribers. Int J Bipolar Disord. 2019; 7:16-25.

Tondo L, Baldessarini RJ. Reduced suicide risk during lithium maintenance treatment. J Clin Psychiatry. 2000; 61 (Suppl 9):97-104.

Tondo L, Baldessarini RJ. Antisuicidal Effects in Mood Disorders: Are They Unique to Lithium? Pharmacopsychiatry. 2018; 51:177-88.

Tondo L, Baldessarini RJ, Floris G, Rudas N. Effectiveness of restarting lithium treatment after its discontinuation in bipolar I and bipolar II disorders. Am J Psychiatry. 1997; 154:548-50.

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. 1998a; 59:405-14.

Tondo L, Baldessarini RJ, Hennen J, Floris G. Lithium maintenance treatment of depression and mania in bipolar I and bipolar II disorders. Am J Psychiatry. 1998b; 155:638-45.

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; 104:163-72.

Tondo L, Hennen J, Baldessarini RJ. Rapid-cycling bipolar disorder: effects of long-term treatments. Acta Psychiatr Scand. 2003; 108:4-14.

Tondo L, Jamison KR, Baldessarini RJ. Effect of lithium maintenance on suicidal behavior in major mood disorders. Ann N Y Acad Sci. 1997; 836:339-51.

Tondo L, Isacsson G, Baldessarini R. Suicidal behavior in bipolar disorder: risk and prevention. CNS Drugs. 2003; 17:491-511.

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