Lithium: evidence reconsidered†

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This review examines the evidence for the main current recommendations for lithium use in psychiatry and briefly summarises the literature on its adverse consequences, in an attempt to develop an overall evaluation of its potential role based on available evidence. An introduction to the history of lithium is given because it is suggested that in both the 19th and 20th centuries the social context in which lithium emerged, rather than the quality of the scientific evidence, was decisive in determining its adoption as a treatment.

HISTORY OF LITHIUM TREATMENT

The history of lithium treatment is thoroughly documented by Johnson (1984). The element was first described in 1818 at around the same period that medical practitioners were engaged in the struggle for professional recognition (Desmond, 1989). As the developing profession became increasingly united and confident, it was able to propagate new explanatory theories with greater credibility than before. When uric acid was discovered to be the cause of gout, its role was elaborated to explain a multitude of conditions, known as the the 'uric acid diathesis'. This included ideas about the aetiology of mood disorders, and terms such as 'gouty mania' were employed. When it was suggested that lithium could dissolve uric acid stones, it began to be used as a treatment for gout and other uric acid diathesis conditions, including depression (Haig, 1888). The popular imagination was also impressed by this new medical theory, and proprietary medications and fashionable mineral spas were marketed as containing lithium and other recommended antidotes to uric acid. The utility of lithium began to be questioned when experiments failed to confirm that it dissolved uric acid stones, and its use also declined along with the influence of the uric acid diathesis theory. Vestiges of the theory remained, however, and lithium continued to be available for gout and 'stones' in non-prescription preparations until the 1970s in the UK.

The first era of lithium use in medicine set a precedent which facilitated its introduction into psychiatric practice. In a concrete sense, it also meant that supplies of lithium were readily available in hospital pharmacies for use and experimentation in mania when this was first suggested. John Cade, who discovered that lithium induced lethargy in guinea pigs and went on to investigate its use in psychiatric patients, also experimented with strontium and cerium in psychiatric disorder, but this line of research never became popular.

In 1949 Cade published a report of 10 manic patients who had improved dramatically with oral lithium treatment (Cade, 1949). His clinical notes, however, recorded little distinction between therapeutic and toxic effects, and the published report failed to mention that there were three cases of severe toxicity with one death and one patient who refused to comply. Johnson (1984) concluded that if the full facts of the cases had been presented, the article would have received little attention. It has also been noted that the original observations on animals were likely to have been the result of lithium toxicity, as high doses were involved (Johnson, 1984; Price & Heninger, 1994).

However, psychiatry was ripe for the introduction of new pharmacotherapies. Other areas of medicine had been invigorated by the development of antibiotics, and with the discovery of chlorpromazine in the 1950s, psychiatry also entered a phase of biologically-oriented therapeutic optimism.

MODERN INDICATIONS FOR LITHIUM TREATMENT

At present, the three main recommended uses of lithium are the treatment of acute mania, prophylaxis of bipolar disorder (BPD) and augmentation of treatment for acute depression in resistant cases. It is also suggested for the control of aggressive or agitated behaviour. There is extensive research on its use as an antidepressant and as a prophylactic in unipolar disorder (UPD), but it is generally accepted that there are more effective alternatives in these situations (Gelder *et al*, 1989).

Treatment of acute mania

Cade's research was enthusiastically received in Denmark, where the first clinical trial was conducted (Schou *et al*, 1954). Placebo-controlled trials are listed in Table 1. A review of the first three found them to be methodologically unreliable (Shull & Sapira, 1970). Schou *et al* (1954) included an unknown number of non-randomised, openly treated patients in the analysis and used vague and subjective outcome measures without the use of statistics. Maggs (1963) selected only 'cooperative' patients and analysed and reported only 18 treatment successes. The small trial by Goodwin *et al* (1969) did not use randomisation, did not report selection procedures and relied on subjective conclusions without presenting data or statistics. The crossover trial by Stokes *et al* (1971), which used alternative patient allocation, was marred by the use of supplementary medication without a record of how this related to experimental treatment. Lithium was significantly more effective than placebo during the first two-week period but during the last two weeks the difference was not significant. Five patients had toxic reactions (one severe), and this may have accounted for the initial superiority of lithium by inducing lethargy. The authors concluded that the superior effect of lithium did not outweigh its disadvantages.

Interpretation of the results of the 21-day randomised controlled trial (RCT) by Bowden *et al* (1994) is also complicated by omission of details of the supplementary medication required. Despite calculations that estimated that the study had 95% power to detect differences between lithium and placebo, the lithium group was significantly better than placebo on only one of the four measurement days. The proportions of premature terminations were also similar in the lithium and the placebo groups, at 61 and 75%, respectively (or 56 and 61%, excluding terminations due to recovery).

†See Cookson, J. 'Lithium: balancing risks and benefits', pp. 120–124, this issue.

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Table 1 Trials comparing lithium with placebo or neuroleptics for treatment of acute mania

Trial	*n*	Design	Treatment comparisons
Schou *et al*, 1954	38	Crossover (random allocation for some patients)	Li *v.* placebo
Maggs, 1963	28	Random crossover	Li *v.* placebo
Goodwin *et al*, 1969	8	Non-random crossover	Li *v.* placebo
Stokes *et al*, 1971	28	Non-random crossover	Li *v.* placebo
Johnson *et al*, 1968, 1971	42	RCT	Li *v.* CPZ
Spring *et al*, 1970	30	RCT	Li *v.* CPZ
Platman, 1970	30	RCT	Li *v.* CPZ
Prien *et al*, 1972	255	RCT	Li *v.* CPZ
Takahashi *et al*, 1975	80	RCT	Li *v.* CPZ
Shopsin *et al*, 1975	30	RCT	Li *v.* CPZ *v.* HAL
Garfinkel *et al*, 1980	21	RCT	Li *v.* HAL *v.* HAL+Li
Braden *et al*, 1982	78	RCT (mixed sample of psychotic admissions)	Li *v.* CPZ
Bowden *et al*, 1994	176	RCT	Li *v.* placebo *v.* SV

RCT, randomised controlled trial (parallel group design); Li, lithium; CPZ, chlorpromazine; HAL, haloperidol; SV, sodium valproate.

Table 1 also shows RCTs that have compared lithium and neuroleptics in the treatment of acute mania. Although earlier smaller studies reported that lithium was equal or superior to neuroleptics, all suffered from methodological problems such as prolonged wash-out periods prior to randomisation, which are likely to have excluded the most disturbed patients, failure to do intention-to-treat analyses and selective reporting or highlighting of outcomes favourable to lithium (Johnson *et al*, 1968; Spring *et al*, 1970; Platman, 1970; Shopsin *et al*, 1975). The large study by Prien *et al* (1972) found that chlorpromazine was markedly superior to lithium for highly active manic patients although it was equally effective in the mildly active. The authors emphasised that highly disturbed patients in the lithium group were extremely difficult to manage and many required seclusion to keep them in the trial. The mean daily dose was 1.8 mg chlorpromazine. Another study, with a mixed group of admissions for manic and schizophrenic psychoses, found the same picture, with mean doses of 1.4 g lithium and 682 mg chlorpromazine (Braden *et al*, 1982). Between 21 and 68% of the sample were categorised as having affective psychoses according to various diagnostic systems, but diagnosis did not predict drug response. The effect of lithium may have been overestimated, as many eligible patients were not included because of a need for emergency sedation, and during the study patients on lithium were prescribed additional sedatives (Braden *et al*, 1982). A small study using haloperidol found it to be significantly superior to lithium in a three-week trial, with patients on lithium showing no overall improvement (Garfinkel *et al*, 1980). Opposite findings emerged from the trial by Takahashi *et al* (1975), with 32% of patients improving on lithium compared with only 12% on chlorpromazine. However, after a long wash-out period the majority of the sample had only moderate symptoms, and the mean dose of chlorpromazine was only 250 mg per day compared with 1.1 g lithium.

Several trials have compared lithium with the anticonvulsants carbamazepine and sodium valproate (Lerer *et al*, 1987; Small *et al*, 1991; Freeman *et al*, 1992; Bowden *et al*, 1994). All these studies used supplementary benzodiazepines or barbiturates for sedation and those studies that provided details revealed that substantial doses were used (Small *et al*, 1991; Freeman *et al*, 1992). In the smallest study, lithium was superior to sodium valproate on some measures (Freeman *et al*, 1992) but in the others no differences were found.

Overall therefore, the evidence that lithium is superior to placebo in the treatment of acute mania is not compelling. Results of comparisons with other drugs are conflicting, but most studies suggest that lithium is at least inferior to neuroleptics in the treatment of severe mania. Practical reasons, such as the frequent need for rapid parenteral sedation and likely non-compliance, reduce the feasibility of lithium treatment for mania, but it is still recommended as the principal element in the management of this condition by some authors (Cook & Winokur, 1990).

Much of the original appeal of lithium was its claimed specificity for affective psychosis. This helped to validate psychiatric classification at a time (in the 1960s) when the concept of mental illness and psychiatric diagnosis was under attack from sociological theories of labelling and deviance and the 'anti-psychiatry' movement. However, as the efficacy of lithium in mania is unproved, its relative specificity for this condition cannot be surmised. It has also been claimed that lithium has a selective effect on the affective symptoms of mania when compared with neuroleptics (Goodwin & Zis, 1979) but the largest trial found no such effect (Prien *et al*, 1972) and evidence from the other trials is confusing and inconclusive.

Prophylaxis of bipolar disorder

Over the past 25 years the most uncontroversial indication for lithium has been the prophylaxis of bipolar disorder. A recent review re-examined nine placebo-controlled RCTs of lithium prophylaxis and uncovered some serious methodological problems (Moncrieff, 1995). Five of the nine studies used a discontinuation design, which is problematic in view of the mounting evidence, discussed below, suggesting that lithium withdrawal precipitates mania. Recurrence of illness after discontinuation does not necessarily provide evidence of efficacy, as it is possible that the process of drug withdrawal may itself have a negative impact on the course of the disorder. Psychotic episodes have also been noted in predisposed individuals after withdrawal of benzodiazepines (Tyrer *et al*, 1983). The only large prospective trial, by Prien *et al* (1973*a*), had two important methodological weaknesses. First, it was only single-blind, and treating physicians had instructions to alter the dose of lithium according to symptomatology, which was done for up to 28% of patients in the lithium group, thereby diminishing the comparability of the groups; trials that are not double-blind have been found to yield significantly higher treatment effects in other areas of medicine (Schultz *et al*, 1995). Second, all patients were stabilised on lithium during the index hospital admission prior to randomisation, creating the possibility that withdrawal-

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induced mania occurred in some placebo group patients. This possible explanation would be in accordance with the finding that the relapse rate in the placebo group during the study was higher than during the corresponding period before the trial, although the difference was not significant (67% of placebo subjects had a severe relapse during the trial versus 54% before). A further small prospective trial was subject to the same methodological problems (Prien *et al*, 1973*b*) and the others were also small and had other weaknesses. Small studies must be interpreted with caution because of possible publication bias. This was thought to be the explanation of the misleading results produced by a meta-analysis of small trials of magnesium treatment in myocardial infarction (Yusuf & Flather, 1995).

Subsequent trials, which are listed in Table 2, have compared lithium with other drugs or combinations of drugs. These trials are instructive because lithium-treated groups performed less well than in placebo-controlled trials. Some of these trials also excluded early treatment failures by selecting patients who had been stable on lithium for a period of time before randomisation (Quitkin *et al*, 1981; Prien *et al*, 1984). A re-analysis of the data from the largest study by Prien *et al* (1984), done with the authors' agreement, found that only 18% of the lithium group, 22% of the combined group and 9% of the imipramine group completed the trial and remained well (Shapiro *et al*, 1989). One comparison of lithium with carbamazepine in patients with bipolar and schizoaffective disorder found lower relapse rates as defined by re-admission, but 78% and 44% of the lithium group required additional treatment with neuroleptic and antidepressant medication, respectively (Placidi *et al*, 1986). Loss to follow-up was also high, with no indication about how this was managed in the analysis. Overall, therefore, evidence for the superiority of lithium over placebo in the prophylaxis of bipolar disorder is inconclusive, and results in later comparative studies have been disappointing.

Research on the natural history of bipolar disorder raises further doubts about the impact of lithium. Lack of efficacy was one explanation suggested for the increased frequency of admissions for mania in relation to schizophrenia that was found to occur between 1970 and 1985 (Symonds & Williams, 1981; Dickson & Kendell, 1986). In the ensuing correspondence it was suggested that this observation was due to changing patterns of diagnosis, which has been recognised in the USA (Schou, 1986; Grof, 1987), but Kendell & Dickson (1987) found no evidence to support this theory in Scotland.

Table 2 Comparative randomised controlled trials of lithium prophylaxis in bipolar disorder

Trial	*n*	Length of follow-up	Comparison groups	Outcome in lithium-treated patients
Ahlfors *et al*, 1981	33	16 months (mean)	Li *v.* flupenthixol	Mean episodes per patient-year: 0.6
Quitkin *et al*, 1981	75	19 months (mean)	Li *v.* Li+IM	27% relapsed, 21% completed trial and remained well
Prien *et al*, 1984	117	24 months	Li *v.* Li+IM *v.* IM	25% relapsed into depression and 27% into mania; 18–22% completed trial and remained well
Placidi *et al*, 1986	83	36 months	Li *v.* CA	20% relapsed, 34% completed trial
Luznat *et al*, 1988	40	12 months	Li *v.* CA	50% relapsed, 25% had 'satisfactory' outcome.
Coxhead *et al*, 1992	31	12 months	Li *v.* CA	53% relapsed

Li, lithium; IM, imipramine; CA, carbamazepine.

Table 3 shows the studies that provide information on the frequency of relapses in bipolar disorder. Comparison of studies is hazardous because of varying diagnostic practices and definitions of relapse. For example, Lundquist (1945) found that only 21% of first admissions for mania had a subsequent attack in a period of 23 years, suggesting a far broader definition of mania than the modern one. However, in the subset of patients who had a second episode, 50% relapsed in three years. A similar relapse rate was found in a retrospective case note study (Winokur, 1975). In a modern study of the history of the disorder prior to lithium treatment, there was a mean rate of 0.54 episodes per patient-year, meaning that on average, patients experienced one episode every two years (Dunner *et al*, 1979). When started on long-term lithium treatment, 46% of this sample had relapses in a two-year period. In a famous follow-up study of admissions between 1959 and 1963, in a clinic in which studies of lithium were also conducted, bipolar patients had an average of 10 episodes in approximately 20 years and the mean cycle length was 2.8 years (Angst, 1986). There was no marked difference in the course of bipolar I and bipolar II disorder in this study. Coryell *et al* (1989) also found little difference in overall outcome, but patients with bipolar I disorder were more likely to have a manic or hypomanic relapse, with 70% of them having such a relapse within the first two years. An earlier paper specified that 78% of this sample had taken lithium for at least some of the initial follow-up period (Coryell *et al*, 1987). Direct comparisons of patients prescribed and not prescribed lithium have found no difference in relapse rate and no indication of other confounding factors which might conceal the superiority of lithium (Marker & Mander, 1989; Harrow *et al*, 1990). A study with patients from a lithium clinic who had been on lithium for at least one year, with a mean of eight years, found a high rate of relapses which were mostly manic in one year of observation (O'Connell *et al*, 1991).

In summary, follow-up studies suggest that the natural history of bipolar disorder has not improved since the introduction of lithium, and patients who are taking lithium appear to be little better than those who are not. Some authors have suggested that non-compliance and underprescribing might explain these disappointing findings (Guscott & Taylor, 1994) but another explanation could be the ineffectiveness of the drug itself.

Lithium augmentation

Although lithium is rarely used as a treatment for acute depression, it has become common to add it to antidepressant regimes in resistant cases. A meta-analysis of five RCTs of lithium augmentation concluded that there was a small but significant effect when compared with placebo (Austin *et al*, 1991). However, the trials reviewed were short-term and

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Table 3 Relapse frequency in bipolar disorder

Trial	*n*	Design	Subjects	Period of observation	Outcome
Lundquist, 1945	36	Retrospective	Subjects with 2 episodes of mania	3 years	50% relapsed
Winokur, 1975	100	Retrospective	Manic probands admitted 1934–1944	Mean 3.2 years	57% men relapsed 42% women relapsed
Dunner *et al*, 1976	96	Prospective	Patients on long-term lithium attending a lithium clinic	2 years	46% relapsed
Dunner *et al*, 1979	140	Retrospective	Patients from a lithium clinic prior to starting lithium	5 years after admission mean 11.4 years	mean 2.2 relapses 0.54 episodes/patient year
Angst, 1986	215 (BP I & II)	Prospective	Admissions 1959–63	Mean 20 years	Median 10 episodes
Coryell *et al*, 1989	117 (BP I & II)	Prospective	Admissions for depression (most subjects on lithium for some time)	2 years 5 years	70–80% relapsed 90–95% relapsed
Marker & Mander, 1989	83	Retrospective	Recurrent affective disorder (41 on lithium 42 not on lithium)	2 years	60% relapse both groups
Harrow *et al*, 1990	73	Prospective	Admissions for mania	Mean 1.7 years	40% manic relapse
O'Connell *et al*, 1991	248	Prospective	Attenders at lithium clinic (all on lithium > 1 year)	1 year	44% relapsed

BP I disorder is classical bipolar disorder with severe episodes of mania and depression and at least one episode of mania requiring admission. BP II disorder is defined by milder episodes of mania which have not required admission.

small, admitting the possibility of publication bias. The largest and longest of them, which followed up 34 patients for three weeks, was negative (Stein & Bernadt, 1988). Of the two trials that produced statistically significant results favouring lithium, one produced an effect of only two points average decrease in a 15-point nurses' rating scale in a sample of 15 (Heninger *et al*, 1983). The other trial by Schopf *et al* (1989), with 27 subjects, found a significant difference between lithium and placebo groups in one week of treatment. Subsequently, the placebo group was prescribed lithium but continued to have a significantly poorer outcome. A more recent trial of lithium augmentation, with a total of 61 subjects and a six-week follow-up, was negative with respect to the overall scores on the Hamilton Rating Scale for Depression, and response rates as defined *a priori* (Katona *et al*, 1995). In a *post hoc* analysis with response re-defined, significant differences were obtained in favour of lithium, but there is potential for bias in this sort of procedure and it should not therefore obscure the essentially negative findings.

Some of these trials reported low compliance rates (Stein & Bernadt, 1988; Katona *et al*, 1995). Although compliant subjects did relatively well, this cannot be attributed with certainty to the effect of the drug, as compliant behaviour has been associated with better outcome in a variety of conditions (Fuller *et al*, 1986; O'Sullivan *et al*, 1991).

Genuinely double-blind studies of lithium are difficult to conduct because side-effects may reveal the identity of medication to patients and investigators, and this was noted in the trial by Katona *et al* (1995) (Edwards *et al*, 1994). This introduces the possibility of an 'amplified placebo effect' in patients (Thomson, 1982) and measurement bias by investigators. This may partly explain the persisting differential in outcome performance between lithium and placebo groups after the end of one of the trials (Schopf *et al*, 1989). The negative findings of the larger trials are even more remarkable in view of these potential biases in favour of lithium.

ADVERSE EFFECTS OF LITHIUM

Withdrawal-induced mania

Evidence that mania is precipitated by withdrawal of lithium is now substantial. Suppes *et al* (1991) reviewed the literature and found that 50% of new illness episodes occurred within 10 weeks of discontinuation of lithium and that mania was more likely than depression. In 16 patients in whom a previous cycle length was known, the cycle length after lithium withdrawal was significantly shorter than before lithium was started. Mander (1986) retrospectively compared 29 patients who had discontinued lithium while asymptomatic with 50 patients who were not on lithium, and found a significantly higher relapse rate in the former. In the discontinuation study of lithium prophylaxis by Cundall *et al* (1972) there was a higher ratio of manic to depressive episodes after lithium discontinuation (3.5:1) than before (0.67:1) and the authors concluded that withdrawal-induced mania was a possible explanation of their findings. Goodwin (1994) described how lithium discontinuation could be conceptualised as bringing forward the risk of mania, and even assuming efficacy, treatment was likely to confer a net disadvantage on patients treated for less than three years continuously because of this phenomenon.

Not all authors accept this hypothesis. In an earlier review Sashidharan & McGuire (1983) concluded that there was no evidence of an increased risk of relapse within six weeks of discontinuation, but fewer data were available to them than to later reviewers, and it now appears that the increased risk associated with discontinuation persists for longer than a few weeks. Schou (1993) presented data which showed that the number of relapses was not greater one year after discontinuation than it had been in the year before lithium treatment was commenced. However, since lithium is

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likely to be started during or after a relapse, this inflates the apparent pre-lithium relapse rate, making it invalid as a comparison.

Toxicity

Deaths due to lithium toxicity occur at a rate of 14 per million prescriptions of lithium (Henry, 1996, personal communication). This fatal toxicity index compares with figures of 46.5 for amitriptyline, 50.0 for dothiepin, 11.1 for clomipramine and 3.7 for lofepramine (Cassidy & Henry, 1987). These figures may conceal a higher death rate per person treated with lithium relative to other drugs, as it is probable that long-term prescriptions for lithium are not issued to as many people as long-term prescriptions for antidepressants. Permanent neurological sequelae are also increasingly recognised as possible consequences of toxicity (Schou, 1984; Sansone & Ziegler, 1985), and renal damage may occur. Toxicity is more commonly due to long-term therapeutic administration than intentional overdose (Dyson *et al*, 1987) but lithium blood-level monitoring is not always preventive, as several cases of toxicity and neurological damage have been reported at normal blood levels (Nagaraja *et al*, 1987; Bell *et al*, 1993). Lithium also appears to be mildly neurotoxic at normal therapeutic doses, as placebo-controlled experiments with normal volunteers find it produces subjective dysphoria and impairment of some aspects of cognitive function in conjunction with physiological measurements showing reduced nerve conduction velocity and increased EEG slow waves (Small *et al*, 1972; Girke *et al*, 1975; Karniol *et al*, 1978; Kropf & Muller-Oerlinghausen, 1979; Weingartner *et al*, 1985; Calil *et al*, 1990). The significance of these effects is debated (Calil *et al*, 1990) but the frequency of poor compliance with lithium treatment may be a further indication of their importance.

Other physical complications

Oliguric renal failure occurs in acute intoxication and may result in a persistent reduction in creatinine clearance (Hestbech *et al*, 1977). Chronic renal lesions consisting of interstitial nephritis have been shown to occur in association with reduced renal concentrating ability in patients on long-term lithium treatment (Hestbech, 1977). The clinical significance of these changes has been questioned and some reviewers have concluded that they are unlikely to lead to severe renal failure (Hwang & Tuason, 1980), although it is probable that vulnerability to lithium toxicity and other renal insults is increased.

Lithium may cause cardiac conduction defects, most commonly sinus node dysfunction (Mitchell & Mackenzie, 1982), and it has been associated with sudden death in people with pre-existing cardiovascular abnormalities or risk factors such as a family history of cardiovascular disease (Shopsin *et al*, 1979; Lyman *et al*, 1984). It is also a well-known teratogen which causes cardiac abnormalities and an increased risk of Ebstein's anomaly (Cohen *et al*, 1994). Interactions with other drugs producing increased vulnerability to lithium toxicity are well recognised, as is lithium-induced impairment of thyroid function. Side-effects such as tremor and weight gain, which are common, may be less severe in medical terms but may substantially impair quality of life and normal functioning.

CONCLUSIONS

Studies which showed an effect of lithium may have had biased results due to certain methodological problems. Overall there appears to be little evidence that lithium is effective for three of its commonly recommended uses: treatment of acute mania, prophylaxis of bipolar disorder and augmentation of treatment in resistant depression. In addition, naturalistic follow-up studies fail to reveal any beneficial effect of lithium on the course of bipolar disorder. Negative consequences of using lithium are an independent cause for concern, especially the risk of toxicity and the possibility of mania provoked by lithium withdrawal. There are also long-term physical complications and side effects, while for some, taking lithium is a subjectively unpleasant experience.

It appears that social and historical factors may have enabled lithium treatment to become established on the basis of insubstantial evidence, despite its known dangers. At a time when other pharmaceutical products were improving the outlook for some psychiatric conditions, lithium held out hope for the long-term suffering associated with bipolar disorder. It also presented an opportunity to psychiatrists at a time when the anti-psychiatry movement was at its height, and its claimed specificity in affective disorder was used as a weapon against critics of psychiatric nosology (Spitzer, 1976). The serendipity of its introduction into psychiatry and the enthusiasm with which it was adopted closely paralleled the 19th century experience of lithium therapy.

I have suggested that there is inadequate evidence that lithium has a beneficial effect, that there are indications that it is ineffective in the long-term outlook of bipolar disorder, and that it is known to be associated with various forms of harm. Its place in psychiatry needs discussion and re-evaluation and there may come a time to abandon this "old but flourishing blunder" (*Chemist & Druggist*, 1888; quoted in Johnson, 1984) for the second time in history.

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