Brit. J. Psychiat. (1981), **139**, 255–264

Correspondence

Correspondents should note that space is limited and shorter letters have a greater chance of publication. The Editors reserve the right to cut letters and also to eliminate multitudinous references. Please try to be concise, strictly relevant and interesting to the reader.

LITHIUM WITHDRAWAL TRIGGERS PSYCHOTIC STATES

DEAR SIR,

The authors conducted a controlled trial to determine psychopathological, neurophysiological and biochemical changes during long-term lithium treatment and particularly its reversibility when lithium medication is interrupted.

Twenty-one patients (13 females; mean age 43 years) with several previous manifestations of an affective illness and at least seven months continuously maintained on lithium were included in the study (mean duration of lithium therapy 3.9 years, mean lithium plasma level 0.68 mmol/l). These patients stabilized on lithium were switched to placebo for a period of five weeks.

Within 14 days on placebo 11 patients relapsed into severe psychotic states with paranoid, manic and depressive syndromes. The various psychopathological syndromes erupting after lithium withdrawal corresponded to the previous features of the disease of the individual patient.

The mean scores of standardized rating scales applied showed a highly significant increase in psychopathological symptoms during the placebo period (see Table).

TABLE

Mean scores of rating scales in 21 patients during lithium and after lithium withdrawal

Mean score (n = 21)	During lithium maintenance	After lithium withdrawal	
HAM-D	3.5± 4.9	11±10.9	P <0.002
AMP III/IV	4.0± 4.7	17±16	P <0.0001
GAS	81±12	59±28	P <0.00001 (student's t-test)

HAM-D: Hamilton Depression Scale; AMP III/IV: Arbeitsgemeinschaft f. Methodik u. Dokumentation in der Psychiatrie; GAS: Global Assessment Scale.

Most of the other patients not relapsing into psychotic states (n = 10) reported anxiety, nervousness, increased irritability and alertness, sleep disturbances and occasionally elated mood. These minor symptoms began several days after lithium withdrawal and endured over one to two weeks.

When lithium was reinstituted a rapid remission occurred in a majority of patients. Retrospectively we analysed the data in an attempt to detect those patients prone to prompt relapse of psychosis after lithium withdrawal. It appears that those patients who exhibited mood swings and minor affective disturbances during previous lithium therapy, bear a considerably higher risk to relapse when lithium therapy is interrupted.

After discontinuation of lithium, measures of thyroid function showed an increase of the ratio T_4/TBG from 3.42±0.70 to 4.19±1.11 ($P < 0.005$), a decrease of TSH from 1.89±0.78 to 0.94±0.29 μU/ml ($P < 0.001$) and a decrease of TSH response to TRH from 14.0±8.7 to 4.5±4.4 μU/ml ($P < 0.0005$). Similarly prolactin response to TRH decreased from 1189±843 to 794±466 μU/ml ($P < 0.05$) during placebo.

The immediate onset of psychotic symptoms suggests rebound effects due to lithium withdrawal rather than a spontaneous recurrence of the underlying disease during lack of lithium protection. This is in accordance with findings of Small *et al* (1971) who reported five patients relapsing within six weeks after lithium withdrawal, although previously well stabilized on lithium. Alexander *et al* (1979) tried lithium therapy in schizophrenic patients and found that four out of seven responders relapsed within two weeks after lithium withdrawal. Recently Lapierre *et al* (1980) reported a 20 per cent relapse rate with mania in manic-depressive patients during experimental lithium withdrawal of only five days.

It is generally assumed that if lithium maintenance is no longer indicated in an individual patient it may be stopped abruptly with no adverse effects. It has been stated by Schou (1980) that neither abstinence phenomena nor any accumulation of relapses (rebound) during the period immediately after discontinuation of lithium were observed. Sporadic reports in the literature (Lapierre *et al*, 1980; Small *et al*, 1971; Wilkinson, 1979) and our own findings, however, seriously question this widely accepted assumption. It may be suggested that a stepwise

https://doi.org/10.1192/bjp.139.3.255 Published online by Cambridge University Press

withdrawal of lithium with intensive supervision during the period of reduction and discontinuation may be a more adequate approach to preventing relapses.

HELMFRIED E. KLEIN
BRIGITTE BROUCEK
WALDEMAR GREIL

Psychiatrische Klinik der Universitat Munchen,
Nussbaumstrasse 7,
D-8000 Munchen 2,
W-Germany

References

ALEXANDER, P. E., KAMMEN, D. P. v. & BUNNEY, W. E. (1979) Antipsychotic effects of lithium in schizophrenia. *American Journal of Psychiatry*, **136**, 283–7.

LAPIERRE, Y. D., GAGNON, A. & KOKKINIDIS, L. (1980) Rapid recurrence of mania following lithium withdrawal. *Biological Psychiatry*, **15**, 859–64.

SCHOU, M. (1980) *Lithium Treatment of Manic Depressive Illness. A Practical Guide*, p 27. Basel: S. Karger.

SMALL, J. G., SMALL, I. F. & MOORE, D. F. (1971) Experimental withdrawal of lithium in recovered manic-depressive patients: A report of five cases. *American Journal of Psychiatry*, **127**, 1555–8.

WILKINSON, D. G. (1979) Difficulty in stopping lithium prophylaxis. *British Medical Journal*, **1**, 235–6.

LITHIUM THERAPY AND THE RISK FOR LEUKEMIA

DEAR SIR,

There are now several case reports raising the question of a relationship between lithium and leukemia, Orr and McKernan (1979), Hammond and Appelbaum (1980), Nielsen (1980). Levitt and Quesenberry (1980) have shown that lithium *in vivo* increases granulocyte production, and this mechanism might explain the mild leukocytosis noted in many patients on lithium maintenance therapy (Gallagher and Gleaves, 1979).

One hypothesis is that chronic marrow stimulation by lithium may induce leukemia, especially of the myelogenous subtype. In order to examine this question we decided to search for any overlap in the diagnoses of bipolar affective disorder and leukemia among patients in our institution. Over the past 10 years our hospital has treated 710 in-patients with bipolar affective disorder and 571 patients with leukemia. Data obtained from the State Tumor Registry indicates that our hospital treats approximately half of all leukemia patients in Iowa. Our experience is that patients treated in this hospital for a major medical or psychiatric problem usually receive treatment here for other illnesses that develop. Our anticipated incidence of leukemia in the bipolar sample was 1–2 cases (Gallagher and Gleaves, 1979) and we therefore would expect to identify 0–1 case by our survey. Another assumption was that almost all of the bipolar patients would have been exposed to lithium at one time or another, and many would be on chronic therapy. Support for the hypothesis would come by finding a significantly increased incidence of leukemia in the lithium-treated patients.

We found no cases of leukemia in the group of bipolar patients. This finding speaks against an association of lithium treatment with leukemia. However, a well-designed, prospective study that specifically follows up on each subject would put the hypothesis to its proper test.

JOHN LYSKOWSKI
HENRY A. NASRALLAH

University of Iowa College of Medicine,
Department of Psychiatry,
Iowa City, Iowa, U.S.A.

References

GALLAGHER, R. P. & GLEAVES, K. (1979) *Cancer Patterns in Iowa 1973–77*. National Cancer Institute.

HAMMOND, W. P. & APPELBAUM, F. (1980) Lithium and acute monocytic leukemia. *New England Journal of Medicine*, **302**, 808.

LEVITT, L. J. & QUESENBERRY, P. J. (1980) The effect of lithium on murine hematopoiesis in a liquid culture system. *New England Journal of Medicine*, **302**, 713–19.

NIELSEN, J. L. (1980) Development of acute myeloid leukaemia during lithium treatment. *Acta Haematologica*, **63**, 172–3.

ORR, L. E. & MCKERNAN, J. F. (1979) Lithium reinduction of acute myeloid leukaemia during lithium treatment. *Lancet*, *i*, 449–50.

IDENTIFICATION OF DISEASE ENTITIES

DEAR SIR,

We have been surprised at the lack of correspondence relating to Kendell and Brockington's paper on the identification of disease entities (*Journal*, 1980, **137**, 324–31). Apart from one letter which is critical on broadly philosophical issues, there has been little discussion of the statistical basis of the proposed technique, which, since the authors invite its use by others, has considerable importance.

It seems to us that the authors oversimplify by implication the interpretation which would be made had even a clear nonlinearity been observed. The situation is complicated by the fact that the scales used in psychiatric research are seldom natural interval scales analogous to those found in the physical sciences (e.g. weight). The intervals between points on the scales cannot be guaranteed to be of equal size—any given interval can be arbitrarily stretched or squashed, making a nonsense of any assessment of linearity of the resulting plot. Admittedly some of the scales referred to are weighted averages (the discriminant functions) and the averaging process

https://doi.org/10.1192/bjp.139.3.255 Published online by Cambridge University Press