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Lithium Treatment in Post-psychotic Depression

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SUMMARY Six of eleven drug-free schizophrenic patients who were depressed following remission of their illness showed a significant decrease in their depressive symptomatology during a double-blind, placebo substitution lithium trial. Traditional indicators of prognosis did not predict lithium response in this small sample; the schizophrenic patients tolerated the lithium well. Lithium should be studied further in a larger patient sample as an adjunct in the treatment of post-psychotic depression, which frequently is treatment resistant.

Schizophrenic patients frequently manifest a depressive syndrome when their psychosis has abated (Mayer-Gross, 1920; Semrad, 1966; Steinberg *et al*, 1967; Bowers and Astrachan, 1967; Donlon and Blacker, 1973; Rada and Donlon, 1975; McGlashan and Carpenter, 1976a; McGlashan and Carpenter, 1976b; MacKinnon, 1977; Docherty *et al*, 1978). This syndrome may differ amongst patients and may last from a few weeks to over a year. Most of the time, it appears as a retarded depression with gross inertia, neurasthenic complaints, feelings of emptiness, anger, guilt, anhedonia or absence of feelings, an urge to withdraw to bed and suicidal ideation. Only a few systematic reports about this depressive syndrome have appeared in the literature. McGlashan and Carpenter (1976a, b) reported on this syndrome in their remitted psychotic patients, half of whom had suffered a post-psychotic depression. Post-psychotic depression poses a serious treatment problem for both the clinician and the patient; most clinicians have found that these patients, for the most part, are unresponsive to tricyclic antidepressants and psychotherapy.

In a recent study, we found that lithium may have an antipsychotic effect in drug-free psychotic schizophrenic and schizoaffective patients (Alexander *et al*, 1979). This paper reports on a double-blind pilot study evaluating clinical variables in response to lithium carbonate treatment for the depressive syndrome in residual (i.e. non-psychotic) schizophrenia (Spitzer *et al*, 1977).

Method

The subjects were four men and seven women (mean age 23 ± 1.3 years) who had been diagnosed as schizophrenic according the the Research Diagnostic Criteria (RDC) for schizophrenia (N = 1) or schizoaffective disorder mainly schizophrenic (N = 10) (Spitzer *et al*, 1975). Except for one patient who received a diagnosis of paranoid schizophrenia (Spitzer *et al*, 1975), all patients were diagnosed as schizoaffective disorder (depressed)—a result mainly of the presence of depression in the post-psychotic period. In the RDC 1977 edition (Spitzer *et al*), used as the basis for the APA Diagnostic and Statistical Manual (DSM III), the post-psychotic depressive syndrome in residual schizophrenia is separated from the schizoaffective disorder group. Additionally, for inclusion in the study, patients had to have shown five or more of the 12 differential symptoms of the International Pilot Study of Schizophrenia (IPSS) during the last two months (Carpenter, Strauss, Bartko, 1973). Patients were clinically depressed and in remission from an acute psychotic episode or an exacerbation of

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psychosis with some residual symptoms as described above. They were physically healthy and were admitted voluntarily to a clinical research unit of the National Institute of Mental Health. They had been informed fully about the research projects and had signed consent forms before participating in the studies. In addition to the clinical programme they participated in an ongoing weekly meeting with clinical, research and nursing staffs during which research issues were discussed.

All patients were off neuroleptic drugs for at least two weeks prior to the study. Lithium carbonate capsules (300 mg) were given for three weeks with a starting dose of 1800 mg/day; the dose was changed three days later according to blood levels. Lithium was administered during the third week in doses ranging from 900 to 2,100 mg and yielded plasma levels ranging from 0.7 to 1.3 mEq/l (mM/l). Identical placebo capsules were given at least two weeks before, during, and for two weeks after the lithium trials. Patients, thus, could receive a constant number of capsules, i.e., two capsules q.i.d. To maintain the double-blind procedure, blood for lithium level determinations was drawn once or twice weekly, between 0800 and 0830 am, throughout the patient's stay in hospital. The nursing staff had no access to laboratory reports. The prescribing psychiatrist carefully evaluated the patients for central nervous system (CNS) toxicity and other side effects.

Patients were rated daily for global depression and psychosis by the nursing staff, using the 15-point Bunney–Hamburg Rating Scale (Bunney and Hamburg, 1963). Only patients who had a mean psychosis score of four or less (mean 2.0 ± 0.3, range 1.0 to 4.0), which indicates absence of or some residual psychotic symptoms and is considered to be non-psychotic on our unit, and who had a mean depression score of four or more were included (mean 6.5, range 4–8.3). Similarily, one point on the depression scale indicates absence of depression, while 2–3 points are normal fluctuations of affect. A decrease in depression ratings of more than 1.5 during the third week of lithium treatment, compared to the week prior to the lithium trial, was considered a clinically significant improvement (Bunney and Hamburg, 1963; van Kammen and Murphy, 1978).

Clinical description of patients

Before they participated in the study, patients were rated on the Phillips Scale (1953). This divides patients into 'process' (more than 15 points) and 'reactive' (less than 15 points). In addition, they were rated on the Vaillant Scale (1963) and on the MODPROG Scale (a modification of a prognostic scale of Strauss and Carpenter, 1972, 1974). The following items were also rated: age of onset of psychosis, month of previous admission, years since onset of illness and Schneiderian first-rank symptoms. To illustrate behavioural changes during the study, examples are given of some double-blind observations that had been entered into the patients' medical charts by a psychiatrist and by the nursing staff, as well as some patients' statements made during the last two weeks of their lithium trial.

Data analysis

Paired and group data were analyzed using Student's t-test. Fisher's Exact Test was used to evaluate the sex difference between the lithium responders and non-responders.

Results

Six patients were designated responders (1 man and 5 women) and five designated non-responders (3 men and 2 women). Fig 1 shows the weekly means of the daily depression ratings of the two groups. During the third week, responders were significantly less depressed (4.1 ± 0.7 vs. 7.0 ± 1.1).

Two patients (C.M. and D.W.) experienced a decrease of more than three points in depression ratings that was reflected in the double-blind notes made in the chart:

C.M.—"I don't need to be hospitalized any more. I'm better". No signs of confusion or memory lapses. Difficulty in flow of speech improved markedly; much warmer; less dependent and less depressed.

D.W.—"Sometimes I still hear voices but they are not of the threatening nature they once were". Despite minor residual hallucinations, patient got a job and functions on a

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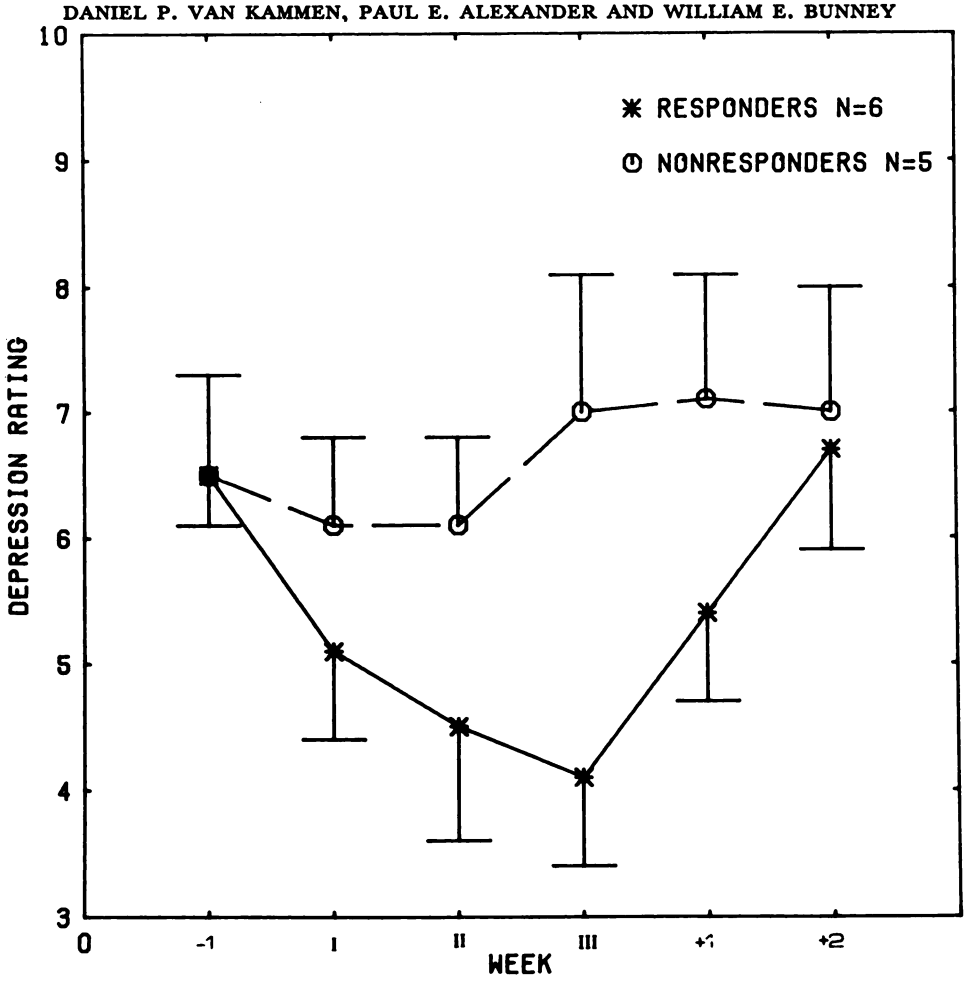


FIG 1.—Weekly means of depression ratings from one week prior (−1) to two weeks after (+1, +2) double-blind lithium treatment. Patients were divided into responders (decrease of > 1.5 points) and non-responders (others). (At week three of lithium treatment, the depression ratings of the responders and non-responders were significantly different).

high social and intellectual level; his mood is stable, not depressed or self-accusatory.

The following statements were recorded on four other responding patients during the third week of lithium treatment:

M.W.—"I'd like to come off eye contact; I feel I can accept responsibility for myself now; I don't feel the urge to hurt myself now; I feel more a part of the community". The patient appears more interested in other patients, with some improvement in depression. "Lately, everything is out in the open and I don't feel alone".

B.J.—Less angry, more cooperative, less retarded and withdrawn. When asked about her mood changing by Monday evening, she replied: "The depression ran out".

C.V.—Less angry effect. He requested a pass for the first time in weeks in an appropriate and pleasant manner, in contrast to previous withdrawn behaviour.

H.H.—Recent depression came to an end gradually some time last weekend. Patient stated that depression for the last two months was qualitatively different from what she has ever experienced before, especially in its quality of hopelessness. Current mood and

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TABLE I

	Age	Sex	RDC '75°	Baseline† depression ratings	Depression*** rating on lithium	Changes in* depression ratings	Li level 3rd week (mEq/l)	Depression** ratings post-lithium
D.W.	31	M	SA-D	5.0±.7	1.3±.2	3.7	0.8	9.7±.4
C.M.	22	F	SA-D	6.0±.9	2.5±.4	3.5	0.9	6.7±.9
M.V.	28	F	SA-D	7.2±.4	4.8±.5	2.4	1.2	4.7±.5
B.J.	27	F	SA-D	7.7±.7	5.7±.3	2.0	1.0	8.5±.3
H.H.	18	F	SA-D	7.0±.7	5.3±.7	1.7	1.1	4.8±.4
C.V.	20	F	SA-D	6.3±.3	4.7±1.1	1.6	0.8	6.0±.6
S.R.	23	M	SA-D	7.0±.9	6.3±.6	0.7	1.0	5.0±.4
O.S.	19	F	PAR	4.0± 0	3.3±.6	0.7	1.3	4.0±.3
R.M.	18	F	SA-D	8.3±.5	7.7±.4	0.6	0.7	9.0±.5
M.E.	24	M	SA-D	7.5±1.1	9.7±.6	−2.2	0.9	8.3±.7
F.L.	23	M	SA-D	5.5±.9	7.9±.3	−2.4	0.7	8.7±.6

† Baseline depression ratings are the mean ±SEM daily nursing ratings of the week preceding the double-blind lithium trial.

* Changes in the depression ratings indicate the difference between the baseline rating means and the means of the daily ratings during the third week on lithium treatment. A positive sign indicates improvement.

** Post-lithium depression ratings are the means ±SEM of the daily nursing ratings for depression during the second week after lithium treatment.

*** Third week lithium treatment depression ratings.

° SA-D: schizoaffective disorder—depressed, mainly schizophrenic.
PAR: paranoid schizophrenia.

energy level are close to normal, and interest in her activities has returned.

Third-week serum lithium levels did not differ between responders and non-responders (.98±.07 vs. .91±.12 mEq/l, P = NS), nor did the third-week lithium dose (1200±164 vs. 1300±142 mg/day, P = NS). There was no sex difference between the number of responders and the non-responders (Fisher's Exact Test, P = NS).

During the third-week lithium treatment, one patient (M.E.) had an increase to above four (from 3.7 to 6.3) in psychosis ratings, although no organic brain syndrome was observed. Two patients (M.E., F.L.) became somewhat more depressed (Table I). One responding patient (H.H.) experienced a coarse finger tremor and some indication of cogwheeling, but that abated later when the lithium was replaced by placebo. No other CNS toxicity was observed. Two weeks after lithium was discontinued, she again became depressed; however, she responded to a second trial and was discharged on lithium.

There were no clinical differences between the lithium responders and non-responders for the following variables: 12 differential symptoms (IPSS) (6.8±.6 vs. 6.4±.5); Schneiderian first-rank symptoms (3.2±.2 vs. 3.2±1.0); age of onset (21.7±1.7 vs. 18.8±1.0); months of previous hospitalization (5.9±4.1 vs. 4.9±2.1); years since onset of illness (2.7±1.1 vs. 2.6±1.4); Vaillant scores (4.4±.75 vs. 3.6±.93); Phillips scores (13.3±1.9 vs. 13.6±2.4); MOD-PROG (8.3±.9 vs. 8.8±1.9). Four of the six responding patients showed re-emergence or intensification of depressive symptomatology after discontinuation of lithium (mean depression ratings of third week of lithium treatment vs. second week post-lithium ratings of the six responding patients: 4.1±.7 vs. 6.7±.8, P <.1).

Discussion

Six of the eleven patients who were depressed following a psychotic exacerbation experienced a significant decrease in depressive symptomatology during lithium treatment. Two patients

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became almost symptom-free of depression (C.M. and D.W.). One of them (D.W.) retained some non-affective auditory hallucinations as his major residual symptom; however, he was less bothered by them than before and after lithium treatment. He expressed more interest in his environment and was less angry. One (non-responding) patient (M.E.) also experienced an increase in psychosis (delusional ideation) that continued after lithium withdrawal. In contrast to other reports, no organic brain syndromes (neurotoxicity) were observed (Shopsin *et al*, 1971; Johnson *et al*, 1968).

Although Stephens *et al* (1966, 1972, 1974) and others linked affective symptomatology to good prognosis, McGlashan and Carpenter (1976a) and Kayton *et al* (1976) pointed out in their reports that the presence or absence of this depressive syndrome had no prognostic value. Abrams *et al* (1974) and Sovner and McHugh (1974) linked good premorbid functioning to bipolar affective illness, inasmuch as these patients frequently tended to respond to lithium. Clinical descriptors—particularly good premorbid functioning—were not predictive of lithium response in our patients. We suggest that it is premature to equate lithium response with an affective disorder prognosis as long as there is no way of biologically validating the diagnosis of schizophrenia or affective disorder. According to their ratings on the Phillips Scale (1953), there were two 'process' patients amongst our responders and two 'reactives' amongst the non-responders, which tends to confirm the relative unimportance of good premorbid functioning as a predictor of lithium response. This needs to be studied in a larger patient population.

Some authors (e.g., Murphy *et al*, 1974) have reported that manic patients with paranoid symptoms are less likely to respond to lithium; others have observed that patients with paranoid features in atypical affective or psychotic disorders(Perris, 1978; Forssman and Wålinder, 1969) may improve with lithium. The one patient in our study who was diagnosed as a paranoid schizophrenic did not respond to lithium. This contrasted with a psychotic patient with chronic paranoid schizophrenia who became less psychotic (Alexander *et al*, 1979). These contrasting findings suggest that the presence of paranoid symptoms is nonspecific and may not be a good indicator of diagnostic sub-groups or prognosis.

Although a diagnosis of schizophrenia usually indicates that the patient will not respond fully to lithium (Cade, 1949; Johnson *et al*, 1968), it is conceivable that some patients with aggressive behaviour (Sheard, 1975; Tupin, 1973), catatonic features (Petursson, 1976; Wald and Lerner, 1978), psychomotor excitement (Cade, 1949; Prien *et al*, 1972) or confusion (Perris, 1978), who also have a diagnosis of schizophrenia or schizoaffective disorder, may benefit from lithium treatment (Alexander *et al*, 1979; van Kammen and DeFraites, in press). Small *et al* (1975) and Belmaker (personal communication, 1978) reported that chronic schizophrenic patients who had been on neuroleptics and were still symptomatic improved somewhat more when treated with lithium. The moderate antidepressant response reported in our study suggests that lithium may be of help in the management of schizophrenic and schizoaffective patients. Because this study dealt with just a small group of patients who were treated for only three weeks, further studies are needed to define this lithium-responsive population. Only four of the six patients improved more than two points.

Although three weeks are enough to show improvement in most depressed and manic patients, it remains to be seen whether patients on longer lasting lithium treatment will show a sustained or even a complete remission and prophylaxis. Our data suggest that lithium should be evaluated further as an adjunct in the clinical management of schizophrenia.

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