Mood Variability in Normal Subjects on Lithium

C. Dennis Barton, Jr., Denise Dufer,† Rachel Monderer, Mitchell J. Cohen, Harold J. Fuller, Michael R. Clark, and J. Raymond DePaulo, Jr.

To investigate the effect of lithium carbonate on normal volunteers' moods, we randomly assigned 30 subjects to 5 weeks each of placebo and lithium treatment with crossover at midstudy. Lithium levels were maintained during the treatment period at a mean serum level of 0.54 mEq/L. All subjects completed visual analogue mood scales (VAMS) daily *throughout the study period; segmented visual analogue scales (SVAS) measuring mood, anxiety, and energy and the Profile of Mood States (POMS) were completed weekly at testing sessions. Neither mean mood nor mood variability as assessed by the delta square (mean square successive difference) differed between placebo and lithium conditions. Segmented visual analogue scale mood ratings were highly correlated with the VAMS and similarly showed no difference between conditions. The self-rated mood variability, however, declined significantly in both experimental conditions as a function of time on study. None of the POMS factors differed between placebo and lithium conditions. These data suggest that lithium, in modest doses administered over 5 weeks, does not have a substantial mood-stabilizing effect in normal subjects.*

Key Words: Mood, mood variability, lithium

Introduction

The efficacy of lithium carbonate in affective disorder has been well established since discovery of its therapeutic effects in 1949 (Cade 1949). Its mechanism of action remains unknown. Schou (1963) included lithium among the drugs he classified as "normothymotic or mood normalizers." As such, he argued, these drugs "do not influence the normal mind and do not level out normal emotions." In contrast, Klein (1970) conceptualized psychotropic drugs as those that "affect normal physiology in a direction similar to their effect on pathophysiological states" (compensatory drugs) and those that have an effect on pathophysiology only (reparative drugs). Regarding lithium as a compensatory drug, one would expect a more general regulating effect on mood variability without respect to psychopathology.

Distinguishing between these two models is useful in conceptualizing the effect of lithium in bipolar disorder. Does lithium "repair" some abnormal physiology in patients, thereby regulating some dysfunctional pathway, or does it have a more general effect on mood that could be shown empirically if given to nonaffectively ill subjects?

Several studies have looked at the effects of lithium on nonpathological mood. Schou (1968) found that, when taken in therapeutic doses by the clinical investigators in his group for 1 to 3 weeks, lithium induced several psychological effects including tiredness, indifference, gen-

From the Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD.
†Deceased.
Address reprint requests to C. Dennis Barton, Jr, MD, Affective Disorders Clinic, The Johns Hopkins Hospital, Meyer 3-181, 600 North Wolfe Street, Baltimore, MD 21287-7381.
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eral malaise, and the feeling that subjects were "separated from their environment by a glass wall." Judd et al (1977) used a double-blind, crossover, placebo-controlled design of 23 normal men in a 4-week study (mean serum lithium level = 0.91 mEq/L). He found that lithium induced dysphoria, lassitude, lethargy, and feelings of negativism and depression. Several other investigators made similar observations in briefer protocols (Kropf and Muller-Oerlinghausen 1979; Muller-Oerlinghausen et al 1977; Karniol et al 1978; and White et al 1979).

Other studies have compared mood states and day-to-day variability of mood between euthymic bipolar patients treated with lithium and control subjects. Folstein et al (1982) reported that mean mood in euthymic bipolar patients taking lithium was similar to nonpatient controls but that daily mood variability was lower, an effect thought to be related to lithium therapy and offered as support of the mood stabilizer concept. Expanding on this, DePaulo et al (1983) studied a group of 17 euthymic bipolar patients while on lithium and compared mood ratings to those of 21 control subjects. Again, mean mood was similar in both groups, while patients on lithium showed statistically significantly lower daily mood variability. The authors called for caution, however, in the interpretation of the data since bipolar patients may rate their euthymic moods in a more narrow range because of their previous experiences of clinical mania or depression, thus giving the appearance of less mood variability when they were euthymic. Bouman et al (1992) compared by *weekly* mood ratings euthymic bipolar patients taking lithium with nonpatient controls and found no significant difference in terms of mood variability—evidence for lithium as a mood normalizer.

One way to control for the bias of past experience would be to study euthymic bipolar patients on lithium and then on placebo to see whether lithium affects mood and its variability between the two treatment conditions. Withdrawing euthymic patients with bipolar disorder, however, puts patients at risk for relapse (Klein et al 1992; Strober et al 1990; Mander and Loudin 1988; Mander 1986). Alternatively, one could study the mood of nonaffectively ill subjects while given lithium and placebo.

With the exception of a recent study (Calil et al 1990), previous attempts to look at lithium's effect on nonpathological mood variation were limited by small numbers of subjects, short study periods, noncontrolled study designs, and nonstandardized tests used to assess mood. We, therefore, examined 30 volunteers without psychiatric disorder in a 3-month, double-blind, placebo-controlled, crossover study to clarify what effect, if any, lithium has on mood and its variability in normal subjects.

Methods

Subjects

Forty-five volunteers were recruited from the hospital and university community of the Johns Hopkins Medical Institutions. An initial contact was made, during which subjects gave informed consent and were screened for psychiatric and medical conditions. All subjects completed the 30-item General Health Questionnaire (GHQ) (Goldberg 1972) and underwent a physical examination and routine laboratory tests of renal, thyroid, and cardiac function. A pregnancy test was given to all female subjects. Subjects were excluded if GHQ scores were 5 or greater of if they had a personal history or family history in a first-degree relative of schizophrenia, major depression, bipolar disorder, or any other psychiatric disorder requiring treatment. Women who were pregnant or lactating or who might become pregnant during the study were excluded. Additional exclusion criteria included age greater than 60 years; history of renal disease, goiter or hypothyroidism, active central nervous system disorders, or psoriasis; abnormal 24-hour creatinine clearance on screening examination; current proteinuria or hematuria; current diuretic use or medically prescribed low sodium diet; cardiac disease (eg, sick sinus syndrome, arrhythmias, abnormal electrocardiogram, history of myocardial infarction or congestive heart disease); current use of indomethacin or phenylbutazone.

Of the 45 volunteers, 4 subjects were excluded: One had a family history of severe psychiataric disorder, one had no significant other to assist in the ratings, one scored greater than 5 on the GHQ, and one had an abnormal creatinine. Eleven subjects, after learning the details of the study, chose not to participate for a variety of reasons, including dislike of frequent blood draws, unwillingness to risk side effects, or the inconvenience of frequent meetings.

Fifteen men and 15 women, with a mean age of 28.8 years (range 20 to 48 years), remained eligible for enrollment into the study and were paid $200 upon its completion. They were asked to designate a "significant other" to assist in ratings of their moods. Subjects were then assigned by lot to a lithium-placebo or placebo-lithium sequence. The subjects, significant others, and the investigators involved in assessing subjects' moods were blind to these assignments. Psychiatrists who were aware of treatment group assignment dispensed the identical-appearing lithium and placebo capsules, monitored lithium levels, and assessed side effects using the same procedures in all subjects across the entire study period (including changing placebo doses and drawing blood samples while subjects took placebo in a manner designed to maintain

the "blind" on subjects, significant others, and other investigators).

Assessment of Mood

The visual analogue mood scale (VAMS), a segmented visual analogue scale (SVAS), and the Profile of Mood States (POMS) were used to assess mood. The VAMS is a 100-mm nonsegmented line on which subjects rated their mood at the same time each day. This method has been shown to be reliable and valid as a repeated measurement of mood (Aitken 1969; Folstein and Luria 1973; Luria 1975). The SVAS (Eastwood et al 1984) consists of three segmented visual analogue scales, on which subjects rated their mood, anxiety, and energy at each weekly testing session. The POMS is a 65-item adjective checklist that has precedence as a quantitative test of mood (Little and Penman 1989) and has previously been shown to be sensitive to drug effects (Johanson et al 1983; deWit et al 1986a; deWit et al 1986b). Furthermore, it has been used in past studies designed specifically to investigate the effects of lithium (Judd et al 1977; White et al 1979). The POMS consists of six mood factors—anger, depression, tension, confusion, fatigue, and vigor. A total mood disturbance (TMD) is obtained by summing each of the above factors, weighting vigor negatively.

Design

Following a baseline/screening week for each volunteer (week 1), each volunteer entered two 5-week active treatment periods with lithium or placebo according to lot (weeks 2–6 and weeks 7–11). Week 7 was designated as the crossover week; week 12 as the washout week. A baseline assessment of mood was obtained at the beginning of the study using the VAMS, SVAS, and POMS. Thereafter, subjects met weekly with blinded investigators to submit the VAMS from the preceding week and to complete their weekly POMS and SVAS.

During the titration weeks (2 and 7), subjects were begun on lithium carbonate at a dosage of 300 mg bid (9 AM and 9 PM) or placebo and returned once to nonblinded psychiatrists for measurement of serum lithium levels. Blood obtained from subjects on placebo was discarded. Lithium levels were obtained twice during the second week of the treatment phase and then weekly; lithium carbonate dosages were adjusted to achieve a serum lithium level above 0.4 mEq/L and below 0.9 mEq/L. (Note: Lithium level 1 corresponds to the end of the titration week; lithium levels 2 and 3 to the first week of the treatment period; level 4 to week 2, level 5 to week 3, and level 6 to week 4). Subjects received an average dose of 765 mg/d.

Significant others completed the POMS at baseline, at the midpoint of each treatment period, and at the completion of the study at an exit interview. At the exit interview, the subjects and significant others were asked whether they could identify when the subject was on lithium and, if so, during which treatment period.

Data Analysis

The mean and standard deviations for each week of VAMS were computed. To assess the degree of mood variability, from each week of VAMS, the delta square statistic (ie, the mean square successive difference) was also computed (Rifkin et al 1972). The delta square statistic is an index of absolute change between successive measurements. In this study, the delta square statistic reflects the day-to-day mood change over 1-week intervals. Results were compared from baseline, end of placebo treatment, and end of lithium treatment, using a repeated measures analysis of variance on each week's mean VAMS and SVAS and each POMS factor as well as the POMS TMD. In reporting POMS scores, we have used T scores rather than raw scores, as this population was without psychiatric disorder.

Results

Twenty-nine subjects completed the study. One volunteer was withdrawn because of complaints of poor concentration. Unblinding her drug sequence code revealed that she was on placebo and that her serum lithium level was zero.

Mean serum lithium levels were 0.5 ± 0.2 mEq/L for weeks 1 to 3 and 0.6 ± 0.2 mEq/L for weeks 4 and 5.

Mean VAMS, delta squared values, and POMS scores (at baseline, end of placebo treatment period, and end of lithium treatment period for both experimental groups) are reported in Table 1 for the 29 volunteers completing the study. Repeated measures analysis of variance (ANOVA) revealed no significant differences between treatment groups across time for mean VAMS scores or for mood variability (represented by the weekly delta squared statistic).

Neither the TMD nor any of the mood factors on the POMS showed significant changes between the placebo and lithium treatment conditions with the exception of a reduction in the tension scores during both placebo and lithium treatment. However, the difference between week 5 of placebo treatment and week 5 of lithium treatment was not statistically significant (Student's $t = -1.17$, $p = 0.25$).

Ratings on POMS done by significant others were analyzed and similarly showed no significant difference between treatment periods. Correlations between volunteers' reports on the POMS and significant others' reports generally were low and not significant for the factors depres-

Table 1. Mean Visual Analogue Mood Scale (VAMS) Scores, Standard Deviations, and Profile of Mood Scale (POMS) Scores at Baseline, at End of Placebo Period, and at End of Lithium Period.*

VAMS Scores			
	Baseline	Week 5 placebo	Week 5 lithium
Mean VAMS	56.5 ± 10.6 (50–68)	56.5 ± 13.4 (49–69)	55.2 ± 15.7 (50–66)
Delta square	242 ± 251 (43–345)	145 ± 177 (29–162)	123 ± 146 (21–157)
POMS Scores			
Subscale	Baseline	Week 5 placebo	Week 5 lithium
Anger	44.01	43.64	43.05
Confusion	39.10	39.87	38.89
Depression	42.57	40.72	41.42
Fatigue	41.96	40.63	40.75
Tension	44.54	41.00	39.90†
Vigor	53.34	51.70	50.98
Total mood disturbance	158.9	154.2	154.9

*For VAMS scores, the interquartile ranges are given in parentheses. Daily VAMS ratings and weekly POMS scores for other weeks are not shown.

†Significant repeated measures analysis of variance (ANOVA), f = 1.84, $p = 0.0028$.

sion, fatigue, and tension. Significant correlations were seen only at the midpoint of placebo treatment for the factors anger ($r = .41$, $p = 0.03$) and vigor ($r = .50$, $p = 0.006$); and in the posttreatment assessment for confusion ($r = .41$, $p = 0.03$) and vigor ($r = 0.61$, $p = 0.0006$), but not at other assessment periods.

Each of the three scales of the SVAS (mood, energy, and anxiety) was analyzed and revealed no significant change among baseline, last week of placebo, and last week of lithium treatment. The mean weekly VAMS ratings were significantly correlated with each week's SVAS mood rating ($r = 0.547$, $p < 10^{-5}$).

To investigate the effect of time on repeated measurements of mood, we analyzed the data by repeated measures ANOVA in the sequence in which volunteers did the study without regard for whether they were on lithium or placebo. Figure 1 depicts this analysis. The ANOVA was significant (f = 1.84, $p = 0.05$), indicating that, as time progressed, subjects rated their mood as less variable, regardless of treatment sequence.

Complaints of side effects were not significantly different between periods on lithium and placebo (mean side effect checklist on placebo = 1.32 ± 1.66; on lithium, 1.74 ± 2.50; $t = -0.929$, NS). The reporting of side effects was not correlated with serum lithium levels ($r = 0.0041$, NS).

Twenty-three of the 29 volunteers completing the study reported when asked that they "knew" when they were on lithium and when on placebo. Of these 23, only 12 were correct (chi-squared = 0.043, NS). Twenty-six significant others also reported that they "knew" when their subject had been on placebo and on lithium. Only 16 of the 26 correctly identified the time when the subject was on lithium (chi-squared = 0.61, NS).

Discussion

The present data suggest that lithium does not have a substantial effect on mood or mood variation in normal subjects, at least when given in modest doses for 5 weeks. This conclusion was supported by both visual analogue rating scales as well as POMS scores.

Our finding of no significant difference in mood variability (as assessed by the mean square successive difference) between lithium and placebo treatment periods does not support our previous hypothesis that lithium acts as a general mood stabilizer. The lack of a significant difference also would appear to replicate the work of Calil et al (1990), although they noted a significant decrease in mean mood at the end of the lithium treatment period. We noted that our subjects rated their mood with less variability as a function of time but not treatment status.

Any study of mood variability must address the issue of what measurement best reflects the phenomenon of mood variability. The delta square statistic, spectral analysis, time-series measurements, and nonlinear mathematical models have been proposed as means of measuring frequency of changes (Moller and Leitner 1988; Larsen 1987). The delta square statistic was chosen because it is easily employed and because we were primarily interested in this study in how mood varied from day to day under both placebo and lithium conditions. It is also unclear what time frame is best for this measurement. We may have missed an effect on mood variability if it occurred from

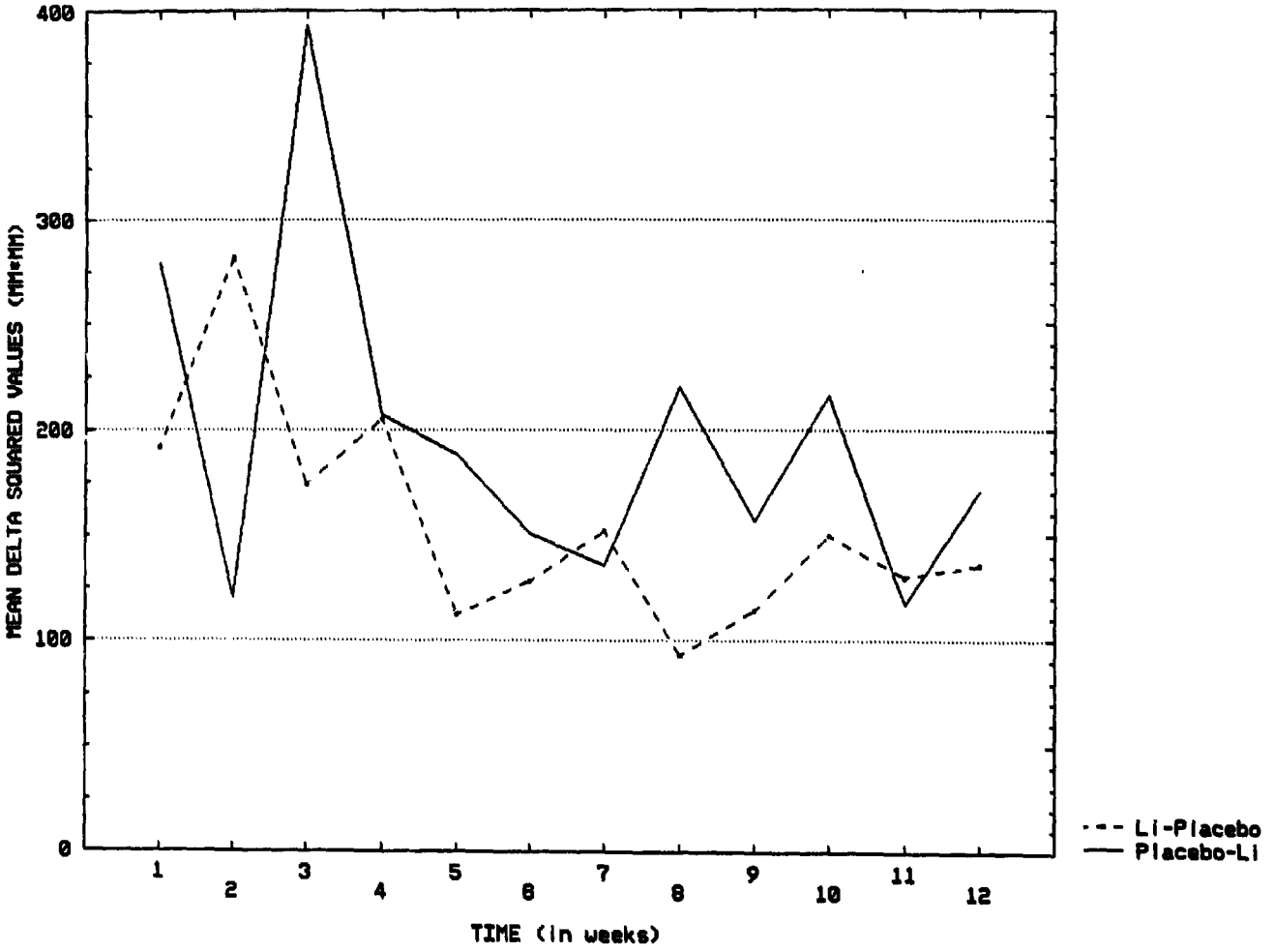

Figure 1. Mean delta square values of daily visual analogue mood scale (VAMS) ratings for each treatment group as a function of time on study.

hour to hour or season to season, for example, rather than day to day.

Our finding that the mean mood does not change with lithium administration does agree with previous work (DePaulo et al 1983), which showed no difference in mean mood between lithium-treated euthymic bipolar patients and nonpatient control subjects, but contradicts the report of Calil et al (1990) that mean VAMS score decreased and most POMS factors and the TMD increased during lithium treatment. Differences between the experimental design of their study and ours may account for this: they elevated the mean serum lithium to higher levels and did so more quickly in their subjects (eg, from 0.4 mEq/L in week 1 to 0.8 mEq/L in week 4). In fact, their subjects were able to distinguish with better than chance probability when they were on lithium. One factor in their results may be lithium-related side effects rather than a "therapeutic" or normative psychotropic effect of lithium on mood.

Because previous studies have found that side effects from lithium were sufficient to "unblind" subjects (Marini et al 1976), we monitored side effects under both lithium and placebo treatment conditions and asked subjects to attempt to identify the sequence in which they completed the study. Neither the subjects nor their significant others could distinguish between the placebo and lithium treatment periods. Likewise, complaints of side effects did not differ significantly between the two periods. Given this, any difference between treatment periods is more likely due to direct psychotropic effects rather than clinical side effects of lithium.

Apart from the occurrence of more side effects with increasing serum lithium levels, it is possible that effects of lithium on normal mood may be observed only above

a certain serum level. Schou (1968) noted irritability, emotional lability, and diminished responsiveness to environmental stimuli at doses of 1850 mg/d but not at doses of 925 md/d. Judd et al (1977) found dysphoria, lassitude, and feelings of negativism and depression in subjects with mean lithium levels of 0.91 mEq/L. However, White et al (1979) found that although lithium induced dysphoric mood and psychomotor slowing at serum levels from 0.65 to 1.30 mEq/L, these changes were not related either to plasma or to red blood cell lithium concentrations. Only one study to our knowledge has reported change in mood with lower lithium levels, 0.54 mEq/L (Kropf and Muller-Oerlinghausen 1979). Future studies of lithium in nonpatients should address the issue of whether higher blood concentrations of lithium will produce greater mood stability.

In addition to differing lithium levels, the length of time subjects were treated with lithium has varied among studies. Most have assessed changes induced in normals after only a few days to weeks of treatment with lithium. Because acute clinical effects of lithium may take 2 to 3 weeks to develop (Mandell and Knapp 1975) and prophylactic response may not be manifest for months or even a year or more, a longer study period may be necessary to observe any effect in normals. In this study, we provide data collected over a 5-week treatment period with lithium. Any transient side effects should have resolved by the last week of treatment for both placebo and lithium conditions. Nonetheless, we acknowledge that effects of lithium may have a slow onset and thus confound measurements of mood in two ways in study designs such as ours. First, effects on mood may be missed altogether for those volunteers in the placebo-lithium group because of limited duration of lithium administration. Second, for those volunteers in the lithium-placebo group, mood ratings during the "placebo" period may actually reflect delayed effects of lithium. Future studies of lithium in nonpatients should allow for a more extended washout period between lithium and placebo treatments and for an extended period of monitoring after lithium has been discontinued, although the cost of such a study and the time required of volunteers to take medication are two obstacles to such an experimental design.

Our study, unlike others (White et al 1979; Judd et al 1977; Calil et al 1990), failed to show changes in POMS ratings between lithium and placebo conditions. Because POMS has previously been shown to be sensitive to drug effects, we take this as further evidence that lithium at modest serum levels does not affect subjective mood states.

Although results of the study by Calil et al (1990) and of the present study suggest that lithium does not significantly affect mood variability in normal subjects, more research is needed to establish lithium's psychotropic effect on mood variation. Studies designed to distinguish the effects of lithium on normal mood in nonpatients from the effect on normal and pathologic moods in patients allow us, on one level, to characterize lithium as a reparative drug, regulating mood variability only in the pathologic state. On another level, these studies may provide clues to laboratory researchers searching for lithium's therapeutic mechanism of action, who have thus far been stymied by ignorance of the pathophysiology of the affective disorders. Clinical studies such as ours can define populations who respond differently to lithium and allow us to specify these differences. Making this clinical distinction may, in turn, direct us to more relevant questions in investigating the pharmacology of lithium's effect on mood variability and, ultimately, to an understanding of the fundamental psychotropic properties of lithium.

It is with sadness that the authors acknowledge the death during the preparation of this paper of Denise Dufer, without whose original proposal and inspiration this study would not have been possible.

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