The Effect of Lithium Carbonate on Affect, Mood, and Personality of Normal Subjects

Lewis L. Judd, MD; Bruce Hubbard, MD; David S. Janowsky, MD; Leighton Y. Huey, MD; Paul A. Attewell, CPhil

• **Data reflecting affect, mood, and personality attributes of 23 normal men were compared after two weeks of placebo administration and two weeks of therapeutic serum lithium levels (mean, 0.91 mEq/liter). The study was a placebo-controlled, split-half crossover, double-blind design. Affect and mood were measured by three self-rating instruments, independent rater observation, and by the subjects' "significant others." Two personality inventories were administered.**

Substantial affect and mood changes are induced by lithium carbonate. Lethargy, dysphoria, a loss of interest in interacting with others and the environment, and a state of increased mental confusion were reported. No generalized effects were found in the responses to the personality inventories.

***(Arch Gen Psychiatry* 34:346-351, 1977)**

One of the major advances in the mental health field during the last decade has been the demonstration of the therapeutic efficacy of lithium carbonate for patients with affect disorder. Since then, controlled clinical trials have been carried out to identify additional specific patient populations whose disorders are responsive to lithium carbonate. A wide variety of metabolic, biochemical, and neurobiological studies have also been initiated to assess the mechanisms by which lithium carbonate may produce its therapeutic effects.

To date, few studies have been reported assessing those psychological and behavioral characteristics changed by lithium carbonate that may underlie therapeutic changes. Even fewer studies are available that have investigated what effects, if any, occur in *normal* individuals who are maintained on therapeutic levels of lithium carbonate. Schou et al[1,2] in 1968 reported three sets of findings concerning mood and affect levels of normal subjects treated with lithium carbonate (approximately 925 mg/day) for seven days in a double-blind experiment. The subjects reported experiencing only tiredness and muscular heaviness from lithium. The authors themselves took 25 mEq/liter/day ("prophylactic dose") for three to six weeks and reported muscular weakness but no subjective or objective evidence of mood or emotional changes. When the three authors subsequently took a "therapeutic dose" of approximately 1,850 mg/day (50 mEq/liter), they experienced a number of symptoms—muscular heaviness, increased irritability, emotional lability, increased mental effort in initiating physical tasks (inertia), indifference, malaise, passivity, increased hypersensitivity alternated with a decreased response to environmental stimuli, being separated from environmental stimuli by a "glass wall," etc.

Linnoila et al,[3] in a double-blind study of 20 normal subjects maintained at therapeutic serum lithium levels (0.75 mEq/liter) for two weeks, reported an increased "choice reaction time" during the lithium carbonate administration.

Bech and colleagues[4] (and unpublished data) have studied the effects of lithium carbonate, both in lithium carbonate-responsive patients (ie, affective disorder) and patients with Meniere disease, and found basically no long-term effects on personality functions. The study of patients with Meniere disease (P Bech et al, unpublished data) focused on the effects of lithium carbonate on driving skills and on personality factors as assessed by the Beck depression scale and the Marke-Nyman personality scale. In this crossover double-blind study, the patients received six months of lithium carbonate administration and six months of placebo administration. The authors reported that they were unable to demonstrate any consistent effects from lithium carbonate on driving skills, nor on the personality of these patients, as measured by the instruments used. Only the side effects of tremor and increased thirst were noted. These findings do not support those of either Linnoila et al[3] or Schou et al[1,2] at "therapeutic" dosage levels of lithium carbonate.

It is apparent that even the most recent evidence available is not conclusive as to whether lithium carbonate exerts effects on normal personality functions. Our interest in this stemmed from a nonblind study[5] of the effects of lithium carbonate on the subjective experiences of pentobarbital-induced euphoria in a group of nine normal male subjects. These subjects were maintained at therapeutic serum levels of lithium (0.8 to 1.2 mEq/liter) for two weeks; during this time, we were impressed with the large number of spontaneous complaints from the group about their personal experiences on lithium carbonate therapy. Statistical analysis permitted isolation of the mood effects of lithium carbonate alone, as measured by a self-rating scale composed of items describing feeling states. To our surprise, the subjects reported the following significant changes while receiving lithium carbonate: decreased "sense of well-being" ($P = .05$); less

Accepted for publication Oct 27, 1976.

From the Department of Psychiatry, University of California, San Diego, School of Medicine, La Jolla.

Reprint requests to Department of Psychiatry, M-003, School of Medicine, University of California, San Diego, La Jolla, CA 92093 (Dr Judd).

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"powerful" ($P = .03$); less "happy" ($P = .01$); less "joyful" ($P = .01$); less "humorous" ($P = .03$); less "clearheaded" ($P = .01$); less "easy to talk to others" ($P = .01$), and a decrease in "ideas flow[ing] easily" ($P = .02$). Thus, there was an indication that lithium carbonate maintenance had resulted in a lowering of more positive affects and a subjective sense that the subjects felt their cognitive processes were not functioning at their usual levels.

In addition, we anecdotally noted an overall dulling and blunting of various personality functions occurring in normal subjects after 14 days' maintenance at therapeutic serum levels of lithium. During the maintenance period, it appeared to us that subjects were slower in their response to interpersonal stimuli, seemed relatively humorless, and less interesting. In short, many of the things that had made them unique and attractive as individuals seemed, under the influence of lithium carbonate, to be subtly blunted. The subjects' observations were qualitatively reminiscent of those feelings anecdotally described by Schou et al[1,2] when taking the "therapeutic dose" of lithium carbonate.

We became curious as to whether these changes observed in a nonblind situation could be objectively demonstrated in a well-controlled clinical study. Therefore, we initiated a placebo-controlled double-blind study to assess the effects of lithium carbonate on levels of affect, mood, and general personality function in a normal subject sample.

SUBJECTS AND METHODS

Subjects

The subjects were obtained through advertisements for a "psychological experiment" in local newspapers and notices posted at local colleges. All subjects were screened by a research psychiatrist, and those with histories of drug and/or alcohol abuse or psychiatric disorder were eliminated. Before admission to the study a medical history, physical examination, and laboratory studies (complete blood cell count, serum electrolytes, blood urea nitrogen, glucose, creatine phosphokinase, 12-factor automated chemical analysis, serum thyroxine (T_4), serum magnesium and calcium, and a routine urinalysis) were done. Psychiatric clearance, normal laboratory values, and an unremarkable history and physical examination were prerequisites for inclusion. Informed consent was obtained from each subject after the nature and outline of the experiment had been explained. This resulted in the selection of 28 normal male volunteers, who were paid for participation.

The subjects ranged in age from 21 to 31 years, with the average being 24 years. The majority were college students (74%).

The basic design was a double-blind crossover using an inactive placebo. It was a within-subjects design, in which the subjects were tested during three different drug conditions: (1) Baseline testing session, during which the subject was completely drug-free, and was tested to establish his baseline or normal responses; (2) second testing session, after the subject had been maintained on either lithium carbonate or placebo for two weeks; and (3) third testing session, after the subject had crossed over from his first drug condition and had been maintained for two weeks on the alternate drug status.

The subjects were randomly assigned to one of two tracks. Track 1 subjects received lithium carbonate during the two weeks following the baseline session and crossed over to placebo for the final two weeks after the second session. In track 2, the presentation order was reversed (ie, placebo first, followed by crossover to the lithium carbonate). Neither the research personnel directly involved with testing sessions nor the subjects had any knowledge of the assignments to track or medication condition.

Lithium carbonate dosage and serum levels were monitored by a research psychiatrist who operated independently of the assessment team. The hospital pharmacy maintained the lithium carbonate-placebo conditions through code. Three or more measurements of serum lithium levels were obtained over the course of each of the two-week periods between the sessions. Serum lithium levels were obtained on each of the testing session days, within ten hours of the last dose (range, nine to ten hours).

Five of 28 subjects who had serum lithium levels of less than 0.7 mEq/liter for the lithium carbonate condition on the testing session day were dropped from the statistical analysis. The serum lithium levels in the remaining 23 subjects ranged from 0.7 to 1.37 mEq/liter with a mean of 0.91 mEq/liter.

Protocol

The total testing battery was divided into two parts, administered at 2 PM on one afternoon and at 9 AM on the following morning, to assess potential diurnal variations in the effects of lithium carbonate and to avoid testing fatigue. Morning and afternoon sessions lasted approximately three hours each and were run in the same quiet, pleasantly appointed room in which three subjects and two research assistants were assembled.

Afternoon Test Battery.—*The Subjective State Questionnaire (SSQ).*—This is a self-rated inventory consisting of 74 dimensions, each of which denotes a mood state phenomenon (S. Erwin, PhD, written communication). Each dimension is expressed as a continuum between two opposite phrases, eg, "can't concentrate" and "easy to concentrate." The subject marks on a continuous 130-mm line where he feels himself to be. The basic structure of each dimension is as follows:

$$\text{Feeling (A)} \quad \underset{\substack{100\% \quad 0\% \quad 100\%}}{\overset{\text{Neither A}}{\text{nor B}}} \quad \text{Feeling (B)}$$

As an appendix to the SSQ there is an Adverse Symptom Checklist (ASC) consisting of 32 items. Subjects rate each item as a continuum from "no effect" to "intense effect," eg, nausea, dizzy.

The California Psychological Inventory (CPI).—This is a standardized paper-and-pencil psychometric instrument consisting of 480 items, which attempts to assess those personality characteristics and adaptive qualities important for successful social living and psychosocial interaction.[6] Each of the 18 scales is intended to cover a salient facet of interpersonal coping style and psychological maturity.

The CPI, designed to tap aspects of normal psychological functioning, might more likely elicit change in personality function than scales oriented to psychopathology.

Holtzman Inkblot Technique.—This is a standardized psychometric form of the Rorschach test with parallel equivalent forms for repeated trials.[7] Responses are coded on 22 variables, such as reaction time, the structural nature of the stimuli utilized to reach a conclusion, the nature of the subjects' conclusions. Unlike the Rorschach procedure, the subject can give only one response per card, and a brief inquiry is given immediately after each response. The examiner's questions during inquiry are limited in scope and are asked with the same regularity to avoid inadvertent verbal conditioning.

Morning Test Battery.—*Profile of Mood States (POMS).*—This is a standardized adjective checklist of 65 descriptive items on which the subject indicates intensity or degree on a five-point scale.[8] The items can be analyzed individually or grouped for analysis (Tension, Depression, Anger, Vigor, Frustration, and Confusion scales).

The Subjective High Assessment Scale (SHAS).—Thirty-eight

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items are rated by subjects on a six-point scale. This scale was built utilizing both our own[5] and others'[9-12] experience to capture the individual's own assessment of his subjective state as it is being experienced. This scale was a complement to the POMS, which by design emphasizes descriptive terms reflecting more negative and unpleasant experiences and feelings. Dittrich et al,[12] indicated that when measuring drug-induced changes of subjective state, the inclusion of a full-range of negative and positive affects to be rated is essential in order to give a total picture of a drug-induced change.

Rater Observation.—Along with the self-reports of feelings (POMS and SHAS), we used a Behavioral Observation Scale for an independent evaluation of behavioral changes in the subjects. Two trained observers, blind to the placebo-lithium carbonate conditions, independently rated the subjects' behavior and mood on the basis of a short, interpersonal interaction and observation of the subjects performing the various tests. The scale lists 20 adjective phrases describing states of individuals amenable to behavioral observation, eg, happy, talkative, angry. The instrument also rates the frequency of each behavior on a six-point scale. Training sessions were conducted prior to the experiment to ensure that raters agreed on definitions of each behavioral item and with the dimensions of the intensity scale.

Data Obtained Apart From the Testing Sessions.—*The "Significant Other" Questionnaire.*—The purpose of this questionnaire was to determine whether lithium carbonate-induced changes in emotions or mood were also apparent to persons interpersonally close to the subjects. A subset of 28 descriptive items from the SHAS and POMS were chosen that denoted mood attributes visible to an outside observer, eg, drowsy, grouchy, happy. Each subject was asked at the beginning of the experiment to choose an intimate with whom they had daily contact as their "significant other." In most cases this was a spouse, girlfriend, roommate, or close friend who completed the questionnaire after two weeks of lithium carbonate maintenance, and again after two weeks of placebo maintenance. The "significant others" and subjects were blind as to lithium carbonate and placebo conditions. Questionnaires were filled out in private at home and returned to the research group in sealed envelopes.

One week after the final session, subjects' serum lithium levels were obtained as a final check to ensure that they had returned to medication-free levels. Serum T_4 levels were monitored throughout for the possibility that mood changes could result from lithium carbonate-induced thyroid dysfunction.

From previous experience and because of the within-subjects design, the method of statistical analysis selected was matched or correlated t tests. Data from the pilot study[5] permitted us to hypothesize the direction of the changes of affect and mood secondary to the lithium carbonate. Therefore, significance levels based on one-tailed t tests were used. However, no previous data were available on the impact of lithium carbonate on personality measures. Therefore, two-tailed levels of significance were used in reporting these data. Only those significant interactions at or beyond the .05 level of significance are reported, but when interesting trends are included they will be identified as such.

RESULTS

Because there were two tracks in this repeated measures design, the initial statistical analysis searched for whether or not order effects could be identified; they could not. The next analysis focused on differences between the baseline testing sessions and the placebo testing sessions (ie, "placebo effect"). Again, no statistically significant differences emerged, and therefore only the results from the two experimental sessions, placebo vs lithium carbonate, are reported. Since the subjects' serum T_4 levels did not change, the reported affect and mood changes do not appear to be related to lithium carbonate influences on thyroid function.

Table 1.—Self-Rated Effects of Lithium Carbonate: SHAS* and POMS* Combined†

Item	Mean Values: Placebo Condition	Mean Values: Lithium Carbonate Condition	t	P (One-Tailed)
Lethargic	1.61	2.13	2.41	.01
Exhausted	0.48	0.87	1.68	.05
Bewildered	0.17	0.52	2.91	< .01
Muddled	0.39	0.83	2.01	.03
Clearheaded	2.74	2.26	−2.42	.01
Ideas flow easily	2.00	1.48	−1.91	.03
Good sexual feelings	1.47	1.22	−1.82	.04
Wish it would last for days	1.78	1.26	−1.96	.03
Lonely	0.39	0.65	1.82	.04
Nauseous	1.22	1.48	2.02	.03
Shaky	0.35	0.91	2.13	.02

*SHAS indicates Subjective High Assessment Scale; POMS, Profile of Mood States.
†N = 23; df = 22.

The data recorded in Table 1 compiled all those self-rated response items from the SHAS and POMS, filled out during the morning session, that were significantly changed after two weeks' lithium carbonate maintenance. Subjects reported experiencing the following general changes: increased lethargy and exhaustion; less clearheaded, more confused and bewildered; generally dysfunctional and would like the experience to stop. The more commonly reported lithium carbonate side effects of nausea and shakiness were also experienced. Furthermore, these effects were strong enough to result in significantly elevated scores on both the POMS Tension Scale (P = .04) and on the POMS Frustration Scale (P = .02).

In Table 2 are listed all the mood-related items from the SSQ that the subjects reported as changing during the lithium carbonate condition. This questionnaire was filled out by the subjects on a different day and at another time of day (2 PM) than the SHAS and POMS. Twenty-five of the 74 total items were rated by the subjects as being altered after 14 days of maintenance on lithium carbonate. In this table the descriptive phrases have been grouped into four relatively homogeneous clusters of feeling tones. In the first grouping, the subjects reported an increase in those feelings that are more negativistic and depressive in nature. In the second, they indicated an increase in feelings of agitation, anxiety, restlessness, and tension. The third group of items potentially reflect how the subjects felt in regard to interpersonal closeness and feelings of social relatedness. It is interesting that in this case they indicated they felt that they did not want to be bothered by environmental demands, nor to have to deal with other people, nor to have to respond to new stimuli. Finally, in the last grouping, they indicated that their cognitive processes were disrupted and that they were experiencing noticeable difficulty in thinking. In summary, in every instance the effects from lithium carbonate were experienced by the subjects as being quite dysphoric,

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Table 2.—Self-Rated Items From the Subjective State Questionnaire That Were Changed by Lithium Carbonate*

Item	Mean Values: Placebo Condition	Mean Values: Lithium Carbonate Condition	t	P (One-Tailed)
Helpless	2.68	3.86	−2.08	.03
Depressed	9.50	11.95	−2.03	.03
Miserable	7.41	12.45	−3.01	<.01
Negative toward life	7.71	10.29	−2.46	.01
Interested	25.90	22.82	2.86	<.01
Active	25.27	21.36	3.22	<.01
Empty	10.50	14.14	−2.02	.03
Sick	7.41	11.09	−2.38	.02
Restless	14.68	17.36	−1.88	.04
Anxious	12.45	16.95	−2.65	<.01
Agitated	11.95	15.91	−3.03	<.01
Out of control	2.54	4.09	−2.58	<.01
Tense	9.77	14.55	−2.68	<.01
Distress	8.14	11.18	−2.19	.02
Suspicious	9.67	11.71	−2.07	.03
Want excitement	24.50	22.27	1.95	.03
Be with people	24.55	20.68	2.71	<.01
Want attention	22.36	19.05	3.38	<.01
Want physical contact	23.32	19.82	2.01	.03
Attentive	26.59	23.59	2.49	.01
Rapidly changing thoughts	7.59	12.05	−2.61	<.01
Easy to remember	25.05	20.68	2.24	.02
Confusion	7.27	10.27	−1.72	.05
Can't function	2.73	4.68	−2.75	<.01
Drug effect	7.14	13.29	2.89	<.01

*N = 23; *df* = 22.

unpleasant, and disruptive.

The items in Table 3 are those from the ASC that were rated as changing because of lithium carbonate. The subjects reported that 14 of the possible 32 items were altered during the lithium carbonate condition, and all were rated as being increased. Certain of these are the common side effects that have been spontaneously reported by patients receiving lithium carbonate, but others have not commonly been identified as such. Again, the lithium carbonate is experienced as promoting physically dysphoric symptoms in these normal subjects.

It is interesting that lithium carbonate effects are clearly evident in the subjects' self-reports, but are not apparent to objective observation. The two independent raters were unable to distinguish differences in the subjects' behavior or moods while on or off lithium carbonate therapy. However, statistical analysis of the "significant other" questionnaire showed that individuals who know the subjects more intimately were able to identify differences in their behavior and mood during the lithium carbonate maintenance condition. They indicated that to them the subjects appeared more "drowsy" ($P = .03$), less "able to work hard" ($P = .03$), and less "able to think clearly" ($P = .03$) during the time they were receiving lithium carbonate. In addition, there was a trend for the "significant other" to see the subjects as less "relaxed" ($P = .055$) and less "full of pep" ($P = .054$) while receiving lithium carbonate. While these findings are not

Table 3.—Items From the Adverse Symptom Checklist That Changed on Lithium Carbonate Maintenance*

Item	Mean Values: Placebo Condition	Mean Values: Lithium Carbonate Condition	t	P (One-Tailed)
Twitching	1.95	6.05	−1.96	.04
Numb	1.33	2.33	−1.77	.05
Headache	2.05	6.57	−3.10	<.01
Pain	1.48	2.67	−2.18	.02
Itchy	3.24	4.76	−1.74	.05
Dizzy	1.33	4.62	−2.00	.03
Faint	1.91	3.67	−2.07	.03
Stuffy nose	6.38	10.76	−2.10	.03
Stuffy head	4.00	7.71	−2.14	.03
Hard breathing	1.43	4.04	−2.33	.02
Heart pounding	1.86	4.14	−1.97	.04
Stomach ache	1.71	3.14	−3.14	<.01
Dry mouth	2.38	5.38	−1.73	.05
Nausea	1.33	4.00	−2.59	<.01

*N = 23; *df* = 22.

strong, they are consistent with the self-rated changes and serve as a further confirmation of the affect and mood changes seen after two weeks' maintenance on lithium carbonate.

Statistical analysis of the personality assessment instruments revealed few significant differences between lithium carbonate and placebo conditions. All subjects scored within the accepted norms on all 18 of the scales in the CPI. Of 22 scoring dimensions in the Holtzman Inkblot Technique, only two dimensions were significantly changed during the lithium carbonate condition: Subjects were more likely to select a "popular" response while receiving lithium carbonate ($P = .048$, two-tailed t test), and subjects had a longer delay in their response to the stimulus inkblot ($P = .022$, two-tailed t test). In the former category, subjects receiving lithium carbonate were more prone to respond with images that were typical and more commonplace than they did while receiving a placebo. In the latter case, subjects receiving lithium carbonate had a mean reaction time of 23.48 seconds; subjects receiving placebo, 18.83 seconds. Thus there was a 4.65-second delay in reaction time on the Holtzman during the lithium carbonate condition. In summary, apart from the two Holtzman dimensions, lithium carbonate did not alter the response patterns of these normal subjects in the two psychometric personality instruments.

To see if any relationship existed between high and low serum lithium levels and the levels of intensity of change in affect and mood, a further statistical analysis was performed. It should be recalled that data had been eliminated from the original analysis if subjects had serum lithium levels less than 0.7 mEq/liter, because we were primarily interested in the effects from lithium carbonate seen at therapeutic levels. For this further analysis all the subjects on whom we had complete data, regardless of their lithium levels on the testing days, were included.

This widened the range of serum lithium levels was between 0.57 to 1.37 mEq/liter. Mean change scores were calculated by subtracting the placebo from the lithium

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carbonate scores on all those reponse items from the SSQ and the ASC on which significant differences from lithium carbonate had been obtained. These mean change scores were then compared to the full range of serum lithium levels, using a Pearson r correlation coefficient technique. A moderate trend was found on six of the 25 SSQ items and one of the 14 ASC items, indicating that higher serum lithium levels related to larger change scores and lower lithium levels to smaller change scores. The range of correlation coefficients was from $r = .35$ to $r = .51$ on these seven items. No findings of this type were found on the remaining 19 SSQ and 13 ASC items. A scattergram analysis showed that there was no clear "threshold" or serum level at which these mood and symptom alterations became more apparent.

COMMENT

The definitiveness with which these results are interpreted should be initially viewed from the perspective of certain issues of design and methodology. The subject sample is a biased one, since volunteers were solicited by advertisement and paid. Careful screening procedures were used to obtain "normals," but it is not possible to totally screen out bias resulting from the motivational and psychological commonalities that occur in a paid volunteer subject sample.

In addition, much of the data base is derived from self-perceived and rated changes as experienced by the subjects themselves. This class of information is vulnerable to a variety of influences in terms of psychological set and setting. In part, the crossover double-blind design helps correct for these factors, in that if psychological set errors are present they are present consistently in each of the conditions and should not influence the data in one direction or the other.

At the time of this study's initiation we were aware that questions had been raised by one group[13] about the completeness of the double-blind in a design utilizing lithium carbonate and an inert placebo. Since these findings were not conclusive, our series of studies was carried out using an inert placebo in the design. Since then, studies by Marini et al[14] and Stallone et al[15] have indicated that the side effects from lithium carbonate are sufficient to reveal to some subjects their medication status in a double-blind procedure. Our own experience would support this conclusion. Thus, the absence of an active placebo may be a weakness in the design, since lithium carbonate's effects were profound enough that subjects at times commented on the disparity between the active medication and the placebo. We did not anticipate that the disparity would be so obvious and therefore did not control for the contrast effects between the lithium carbonate and placebo experiences. This in turn may have resulted in enhancing, by contrast, the subjective experiences due to the lithium carbonate. This design problem is not easily solved, since the addition of an active placebo immensely complicates studies of this type. We have already experimented, on a pilot basis, with subclinical doses of lithium carbonate by maintaining subjects on levels at or below 0.3 mEq/liter as an "active" placebo. This technique proved to be less than satisfactory and equally problematic in our hands.

Despite these caveats, data from every aspect of this study indicate rather profound and consistent effects on normal subjects from two weeks' maintenance at therapeutic serum levels of lithium (range, 0.7 to 1.37 mEq/liter; mean, 0.91 mEq/liter). The qualitative aspects of these self-reported affect and mood alterations actually, extend across two different studies and two different subject samples—the first, an uncontrolled pilot study[5] in which we first demonstrated significant lithium carbonate-induced alterations in mood and feeling tone in normals, and now the controlled study described in this article. In the latter instance, mood and affect changes from lithium were reported by the subjects at both 9 AM and 2 PM on two different experimental days. Further, qualitatively similar self-rated changes were reported by the subjects on the SHAS, POMS, and the SSQ. There appears to be little question that two weeks' maintenance at therapeutic serum lithium levels results in consistent and predictable alterations in the subjective states of normal individuals.

These subjective changes are not mood elevating, but rather mood lowering. In general, these feeling-tone alterations are dysphoric and characterized by lassitude, lethargy, and feelings of negativism and depression. In addition, feelings of agitation, anxiety, tension, and restlessness are related to lithium carbonate maintenance. There is also some evidence that subjects indicated they did not want to have to deal with the demands of interacting with their human environments. Finally, there are consistent self-reports of inability to concentrate, mental confusion, feeling muddleheaded, and a loss of clear-headedness.

It is interesting that the self-rated findings in both the pilot study and the controlled study are basically in agreement with the anecdotal reports from the original study of Schou et al[1,2] who reported a rather large number of subjective state changes when they, the authors, received "therapeutic" doses of lithium carbonate. Clearly, from our results and from those anectotally reported by Schou and colleagues, lithium carbonate does produce subjectively profound affect and mood changes in normal subjects after two to three weeks' maintenance at therapeutic serum levels.

It was of interest to find that the effects of lithium carbonate in normal subjects were not perceptible to trained independent observers in the experimental situation. We initially speculated that these changes, although profound to the individual experiencing them, were not such that they were easily discernible, even to trained observers. In contrast to this was the fact that the "significant other," an individual who had a much more extensive interpersonal experience with the subject, was able to identify alterations in behavior and mood during the time the subjects were being maintained on lithium carbonate. Further, their observations were completely consistent with qualitative changes obtained from the self-rating data from the subjects themselves. Thus, these changes due to lithium carbonate are not just subjectively experienced, but are apparent to independent observers who are well acquainted with the normal range of behavior of each of the subjects. This conclusion is supported by Stallone et al,[15] who found that family members were quite accurate

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($P = .001$) in identifying placebo vs lithium carbonate status of patients who were being studied in a double-blind procedure.

Apart from the two dimensions on the Holtzman, we found that lithium carbonate did not influence our subjects' response patterns to the personality inventories (CPI and Holtzman Inkblot Technique). These findings are consistent with those of Bech et al,[5] who also found no lithium carbonate-related changes in personality function as measured by the Marke-Nyman scale. It would appear that the subjective state alterations due to lithium carbonate are either not robust enough to be tapped by use of personality inventories or that, more likely, these inventories, by design, are not meant to be responsive nor sensitive to evanescent or more subtle shifts in feeling tone and mood.

Given the weakness of the correlation trends and the small number of items involved, it is our conclusion that within the range of 0.57 to 1.37 mEq/liter, high serum lithium levels are no more likely than low serum lithium levels to be significantly related to the appearance or intensity of lithium carbonate's effect on mood. This would indicate that the demarcation point at which these changes become apparent to normal subjects is somewhere below a serum level of 0.57 mEq/liter.

It is possible that the 14-day period of maintenance may have been a particularly unfortunate choice since this may be the peak time for lithium carbonate's dysphoric effects to occur. There is some evidence from animal studies by Mandell and Knapp[16] indicating that certain neurochemical adaptive mechanisms appear just after this period of time. It is our impression that we may be describing subacute effects of lithium carbonate secondary to 14 days of therapeutic blood levels and that these effects will attenuate progressively over time and eventually disappear. Further, it may be that patients with lithium carbonate-responsive conditions do not experience the same type of dysphoric state reported by normals.

Results of this study may have clinical relevance since if an unpleasant or dysphoric state is created in patients as well as in normal subjects during the early phases of lithium carbonate maintenance, it could be discussed with them. It has been our clinical experience that when this is acknowledged as a specific probable reality, response compliance to lithium carbonate maintenance is noticeably improved.

While it is true that very solid research has been reported in regard to the effects of certain other psychotropic drugs on normal subjects,[17-23] previous studies have been based primarily on acute dose regimens rather than on dose ranges and durations necessary to achieve therapeutic effects in a clinical situation.

It is our impression that methodological advantages may accrue from a research design that contrasts how normal subjects, compared to medication-responsive patients, respond to the same medications given in therapeutic doses. In this case, how do patients with lithium carbonate-responsive disorders respond differently to the drug as compared to a normal population? We suggest that an approach answering such questions may help elicit mechanisms for identifying the behavioral, cognitive, and mood-modulating changes by which psychotropic medications mediate their desired therapeutic changes. In turn, eliciting aspects of how these compounds influence behavior may indirectly reveal something about the disease processes themselves.

This investigation was supported in part by grant IH81-DA01467 from the National Institute of Drug Abuse (ADAMHA), a Polydrug Demonstration and Research Project (Friends of Psychiatric Research of San Diego).

Kenneth I. Takahashi, Richard Anderson, Christopher Maloy, Winifred B. Riney, MA, and William G. Lee provided technical assistance throughout this study.

Nonproprietary Name and Trademarks of Drug

Lithium carbonate—*Eskalith, Lithane, Lithotabs, PFI-Lithium.*

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