0000-0000/94/4001–0089 $03.60

Effects of Nutritional Lithium Supplementation on Mood

A Placebo-Controlled Study with Former Drug Users

GERHARD N. SCHRAUZER* AND EDMOND DE VROEY

Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Dr., La Jolla, CA 92093-0314

Received September 2, 1993; Accepted November 2, 1993

ABSTRACT

A total of 24 subjects, 16 males and 8 females, average age 29.4 ± 6.5 y, were randomly divided into two groups. Group A received 400 μg/d of lithium orally, in tablets composed of a naturally lithium-rich brewer's yeast, for 4 wk. Group B was given normal, lithium-free brewer's yeast as a placebo. All the subjects of the study were former drug users (mostly heroin and crystal methamphetamine). Some of the subjects were violent offenders or had a history of domestic violence. The subjects completed weekly self-administered mood test questionnaires, which contained 29 items covering parameters measuring mental and physical activity, ability to think and work, mood, and emotionality. In the lithium group, the total mood test scores increased steadily and significantly during the period of supplementation. The 29 items were furthermore placed into three subcategories reflecting happiness, friendliness, and energy, as well as their negative counterparts. In Group A, the scores increased consistently for all subcategories until wk 4 and remained essentially the same in wk 5. In Group B, the combined mood test scores showed no consistent changes during the same period. The only positive change in some members of Group B occurred during wk 1 and was attributed to a placebo effect. In Group B, the placebo effect was noticeable for the subcategories of energy and friendliness; the happiness scores

*Author to whom all correspondence and reprint requests should be addressed.

declined during the entire period of observation. Based on these results and the analysis of voluntary written comments of study participants, it is concluded that lithium at the dosages chosen had a mood-improving and -stabilizing effect.

Index Entries: Drug addict rehabilitation program; drugs; energy; friendliness; happiness; lithium deficiency; lithium; mood; violence.

INTRODUCTION

Several recent studies recognize lithium as a nutritional essential trace element (*1,2*). In animals, lithium deficiency reduces the life span and causes reproductive abnormalities and behavioral changes, notably diminished conditioned avoidance behavior (*2*). A human lithium deficiency syndrome has not been characterized thus far, but results of epidemiological studies reveal a statistically significant inverse correlation between mental hospital admissions, homicides, rapes, and drug-related crimes and the lithium concentration in drinking water (*3,4*). The concentration of lithium in scalp hair from male violent criminal offenders was significantly lower than in male controls (*5*). Since these findings suggest that lithium-deficient human subjects could exhibit a lower threshold level for the development of violent behavior and drug dependency, we attempted to find out whether lithium at nutritional levels, i.e., 1/1000 of the therapeutic dose, would have any effect on the mood and behavior of former drug users. Accordingly, we performed a double-blind placebo-controlled lithium supplementation study with former drug users, from a drug-recovery self-help group. The present article describes the results of this study.

PATIENTS AND METHODS

A total of 24 subjects (16 males and 8 females, average age 29.4 ± 6.5 yr) was consecutively enrolled in the study. Most of the subjects were previous users of stimulant drugs, such as heroin, crystal methamphetamine, PCP, and cocaine. Two were alcoholics and four had a history of domestic violence. None had previously been treated with lithium or was on any psychiatric medication at the time of the study. Each subject was informed about the nature of the study and signed the standard informed consent form required by UCSD Committee on Investigations with Human Subjects. The subjects were asked to take two tablets of a supplement daily for 4 wk. In the verum group each tablet contained 200 μg of lithium in brewer's yeast. The randomly assigned controls received two tablets containing lithium-free brewer's yeast. Each subject agreed to visit the drug rehabilitation center once every week to be

Table 1
NPRU Mood Scale[a]

1. Active	15. Good-natured
2. Alert	16. Grouchy
3. Annoyed	17. Happy
4. Carefree	18. Jittery
5. Cheerful	19. Kind
6. Able to concentrate	20. Lively
7. Considerate	21. Pleasant
8. Defiant	22. Relaxed
9. Dependable	23. Satisfied
10. Drowsy	24. Sleepy
11. Dull	25. Sluggish
12. Efficient	26. Tense
13. Friendly	27. Able to think clearly
14. Full of pep	28. Tired
	29. Able to work hard

[a]Subjects ranked all items from "not at all" (0), to "a little" (1), "quite a bit" (2), and "extremely" (3).

checked for compliance and to complete the Naval Psychological Research Unit (NPRU) Mood Scale questionnaire (*6*). We also asked each subject to write down any additional items of self-observation concerning his or her mood and behavior that were not covered by the test. The NPRU Mood Scale test questionnaire contains 29 mood- and behavior-related positive or negative items (Table 1). The 19 positive mood items are: active, alert, carefree, cheerful, able to concentrate, considerate, dependable, efficient, friendly, full of pep, good natured, happy, kind, lovely, pleasant, relaxed, satisfied, able to think clearly, and able to work hard. The sum of the responses to the positive items is the *P* score. The 10 negative mood items are: annoyed, defiant, drowsy, dull, grouchy, jittery, sleepy, sluggish, tense, and tired. The sum of the responses to the negative items is the *N* score. In our study, the test scores results integrate both *P* and *N* scores. We have given the weights 0, 1, 2, and 3 to positive mood items and the weights 3, 2, 1, and 0 to negative mood items of intensity; extremely, quite a bit, a little, and not at all. In this manner, the higher intensity of a positive item influences the total score toward the same direction as the lower intensity of a negative item. The weekly scores were added for all subjects and controls. Retaining the same weighting scheme, the 29 mood items were further subdivided into three groups comprising the parameters of happiness (alert, annoyed, carefree, good-natured, happy, relaxed, satisfied, and tense), the parameters of friendliness (cheerful, considerate, defiant, dependable, friendly, grouchy, kind, and pleasant), and the parameters of energy (active, able to concentrate, drowsy, dull, efficient, full of pep, lively, sleepy, sluggish, able to think clearly, tired, and able to work hard).

Table 2
Changes in the NPRU Scores in the Subjects of the Lithium Group During the 4 wk of Observation

Start	Wk 1	Wk 2	Wk 3	Wk 4
49	51	64	67	68
35	53	65	69	75
17	49	55	68	68
24	16	25	36	52
53	63	72	75	82
43	49	60	63	69
47	56	72	76	70
25	43	59	69	69
49	79	75	78	73
46	63	69	68	67
40	36	51	62	68
40	59	67	65	66

Table 3
Changes in the NPRU Scores in the Subjects of the Placebo Group During the 4 wk of Observation

Start	Wk 1	Wk 2	Wk 3	Wk 4
50	79	52	65	71
33	74	44	45	44
55	79	81	77	71
81	71	71	72	68
73	65	65	65	52
53	79	67	71	71
77	68	68	69	60
60	74	64	66	62
40	60	55	53	59
65	65	56	54	58
54	55	45	43	34
68	64	54	48	52

RESULTS

Table 2 shows the NPRU scores of the lithium group. Table 3 shows those of the placebo group. Figure 1 displays the evolution of NPRU scores in the lithium group during a 4-wk period. Figure 2 displays the evolution of NPRU scores in the placebo group. In Figs. 1 and 2, the initial score of each subject was reduced to zero and its original value subtracted from the scores of the following weeks. In the lithium group (Table 2 and Fig. 1), the response to lithium supplementation was uniformly positive. No consistent mood changes were observed in the placebo group (Table 3 and Fig. 2). In the placebo group, an apparent placebo effect was noticeable in some subjects after the first week of

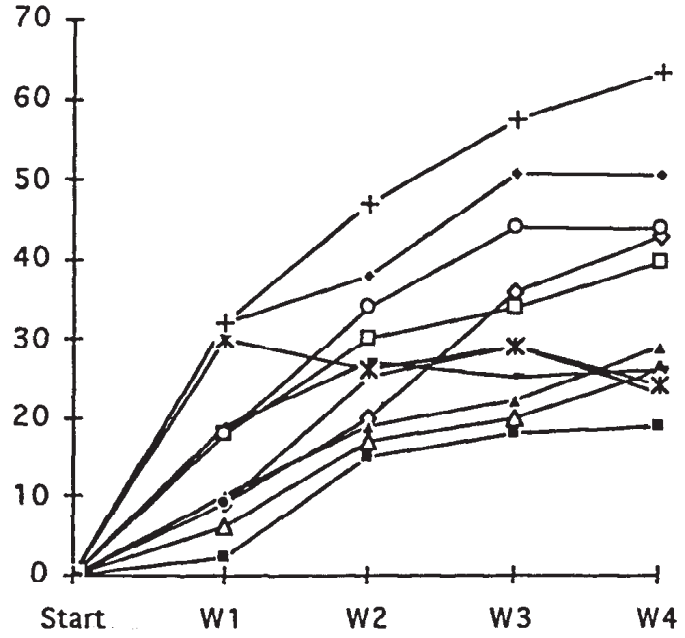

Fig. 1. Changes in the NPRU scores in 12 subjects on lithium during the 4 wk of observation.

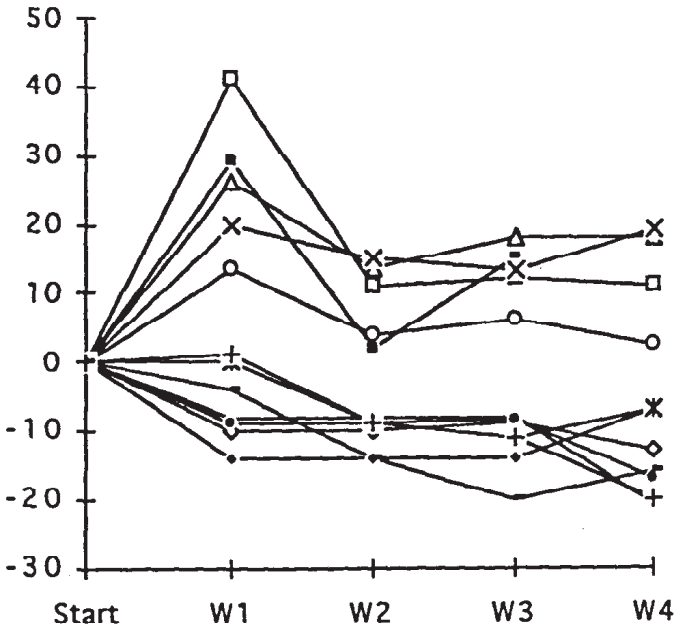

Fig. 2. Changes in the NPRU scores in 12 subjects on placebo during the 4 wk of observation.

taking the yeast tablet (Fig. 2). Paired sample *t*-tests (Table 4) of the NPRU scores in the lithium group (Table 2) show that the mood improvement was statisticallly significant after 1 wk of lithium supplementation already and remained so until the end of the experiment. Comparison between the paired sample *t*-tests (Table 4) of the scores from the lithium group (Table 2) and the paired sample *t*-tests (Table 5) of the scores from

Table 4
Paired Sample *t*-Tests of the Scores in the Lithium Group

Pairs	Mean diff.	SD	*t*	DF	*P*
Start/Wk 1	−17.917	10.900	−5.694	11	0.000
Start/Wk 2	−27.000	9.254	−10.107	11	0.000
Wk 1/Wk 2	−9.083	6.842	−4.599	11	0.001
Start/Wk 3	−32.917	12.457	−9.154	11	0.000
Wk 1/Wk 3	−15.000	9.686	−5.365	11	0.000
Wk 2/Wk 3	−5.917	5.282	−3.880	11	0.003
Start/Wk 4	−34.417	13.827	−8.623	11	0.000
Wk 1/Wk 4	−16.500	12.796	−4.467	11	0.001
Wk 2/Wk 4	−7.417	8.185	−3.139	11	0.009
Wk 3/Wk 4	−1.500	4.927	−1.055	11	0.314

Table 5
Paired Sample *t*-Tests of the Scores in the Placebo Group

Pairs	Mean diff.	SD	*t*	DF	*P*
Start/Wk 1	−2.250	23.457	−0.332	11	0.746
Start/Wk 2	5.250	10.056	1.809	11	0.098
Wk 1/Wk 2	7.500	13.568	1.915	11	0.082
Start/Wk 3	4.750	10.376	1.586	11	0.141
Wk 1/Wk 3	7.000	13.273	1.827	11	0.095
Wk 2/Wk 3	−5.000	0.522	−3.317	11	0.007
Start/Wk 4	7.500	12.303	2.112	11	0.058
Wk 1/Wk 4	9.750	14.271	2.367	11	0.037
Wk 2/Wk 4	2.250	7.509	1.038	11	0.322
Wk 3/Wk 4	2.750	7.473	1.275	11	0.229

the placebo group (Table 3) indicates that the differences between the verum and the placebo group are statistically highly significant. It should be added that all the subjects in the control group eventually recognized that they had been receiving a placebo, and some demanded to receive the other tablets. After receiving the lithium tablet, all former placebo group subjects responded positively to the lithium intake in the same way as the subjects in the verum group. In the verum group, no subject mistook his lithium-containing tablets for placebo and requested a change. Voluntary comments of the subjects on lithium were all positive. The apparent mood-improving effects of lithium were observed without exception. Plots of the evolution of the scores for the categories of happiness, friendliness, and energy in the lithium group are shown in Fig. 3, and for the categories of happiness, friendliness, and energy in the placebo group are shown in Fig. 4. Plots of the evolution of the scores in the lithium group and in the placebo group for each category are given in Fig. 5–7.

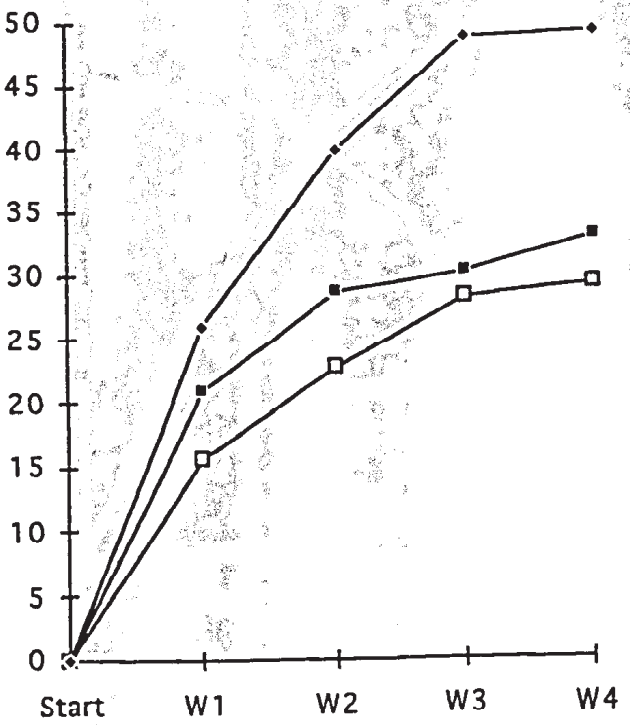

Fig. 3. Changes of the NPRU scores for the categories happiness (■), friendliness (□), and energy (◆) in the lithium group during 4 wk of observation.

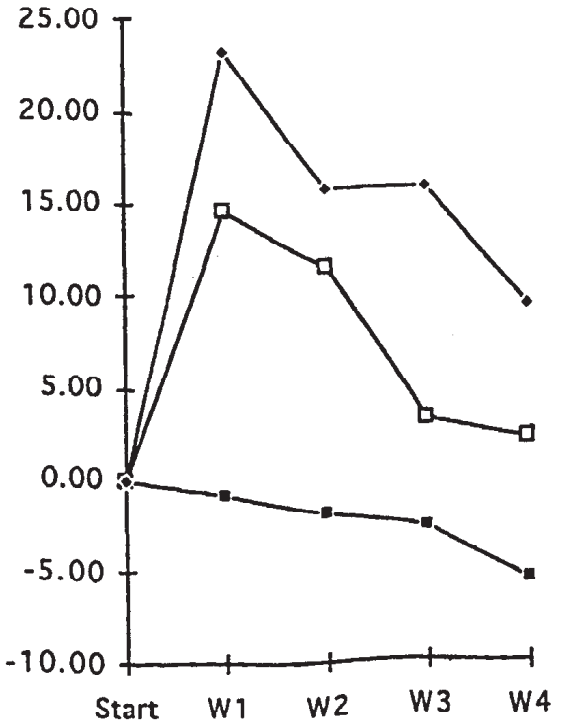

Fig. 4. Changes of the NPRU scores for the categories happiness (■), friendliness (□), and energy (◆) in the placebo group during 4 wk of observation.

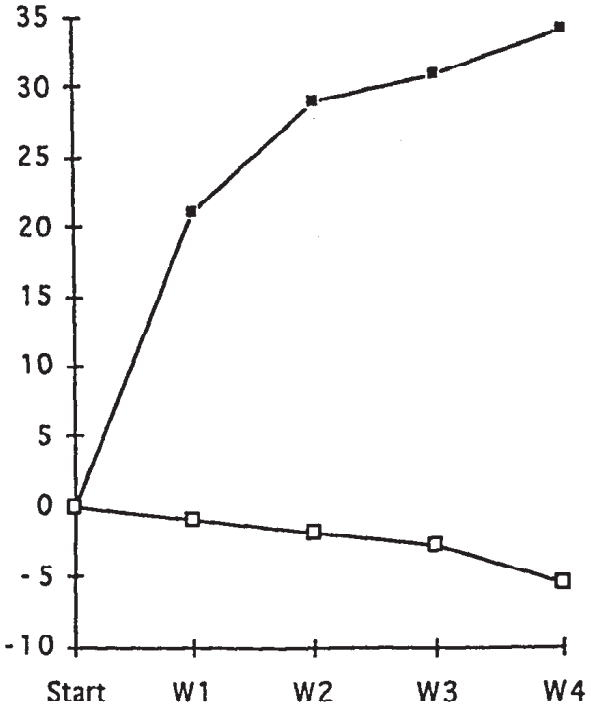

Fig. 5. Changes of the NPRU scores for the category happiness in the lithium (■) and the placebo (□) group during 4 wk of observation.

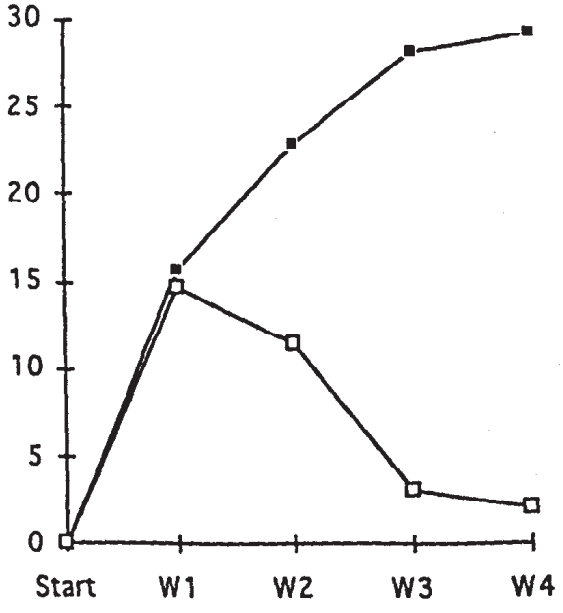

Fig. 6. Changes of the NPRU scores for the category friendliness in the lithium (■) and in the placebo (□) group during 4 wk of observation.

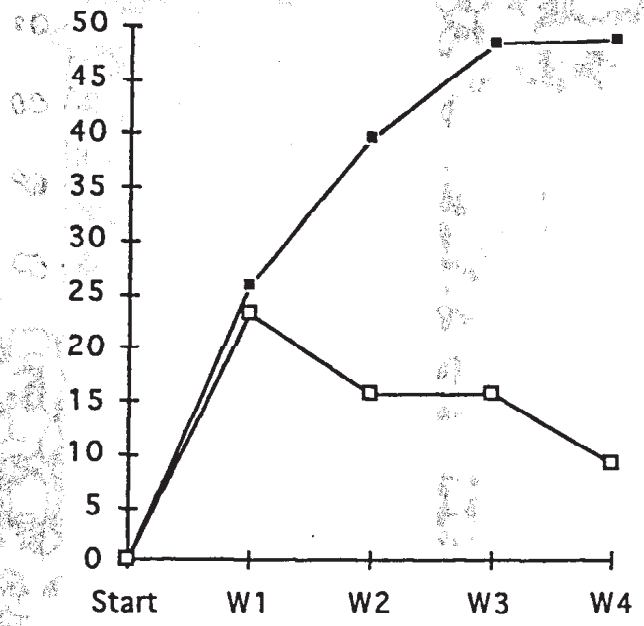

Fig. 7. Changes of the NPRU scores for the category energy in the lithium (■) and in the placebo (□) group during 4 wk of observation.

CASE REPORTS

The comments of a former crystal methamphetamine and alcohol user, with a history of domestic violence were: "I feel a lot of difference in the respect that I do not fly off the handle as much." Figure 8 displays the evolution of the NPRU score of this subject. Other comments of subjects after 1 or 2 wk on lithium were: "My mood is stable and I can think more clearly now. I feel pretty good." "I have had tempers, but I have made a drastic difference since I am taking these vitamins." A subject suicidal before lithium stated after 4 wk: "I am no longer depressed. I see a light at the end of the tunnel." Interesting also are the comments of a subject taking his lithium irregularly: "My mood is a little down today. I believe the reason is I have missed the food supplement for two days. When steadily taking these vitamins I seems to be in better spirit." In other subjects the improvement was slower to develop as indicated by the evolution of the score in a former crystal methamphetamine, PCP, and alcohol user (Fig. 9). A former heroin and alcohol user and violent offender had stated during placebo: "I am always extremely moody and fight with my girlfriend frequently." Switched to lithium he stated after 1 wk: "I noticed changes in my attitude." After 4 wk: "I do not get so mad about stupid things as I did before" and "I am in a much better mood most of the time." The evolution of his NPRU score is illustrated in Fig. 10.

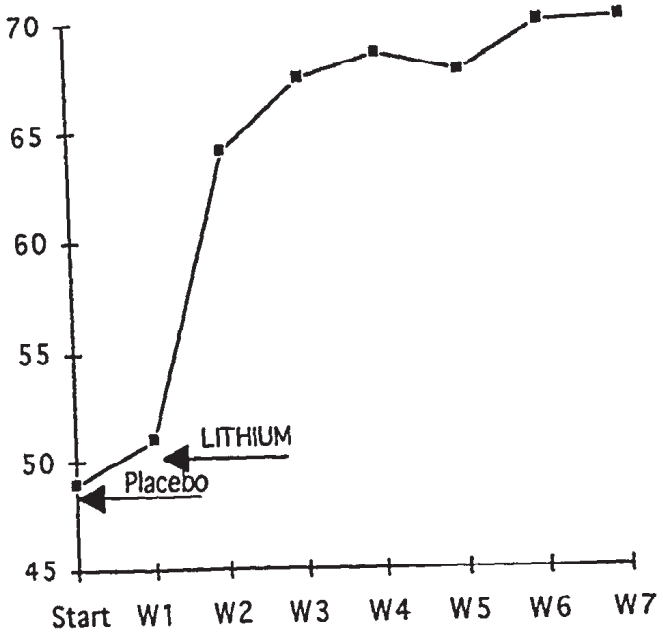

Fig. 8. Changes in the NPRU score in a former crystal methamphetamine and alcohol user. The subject was on placebo during wk 1, and on lithium thereafter.

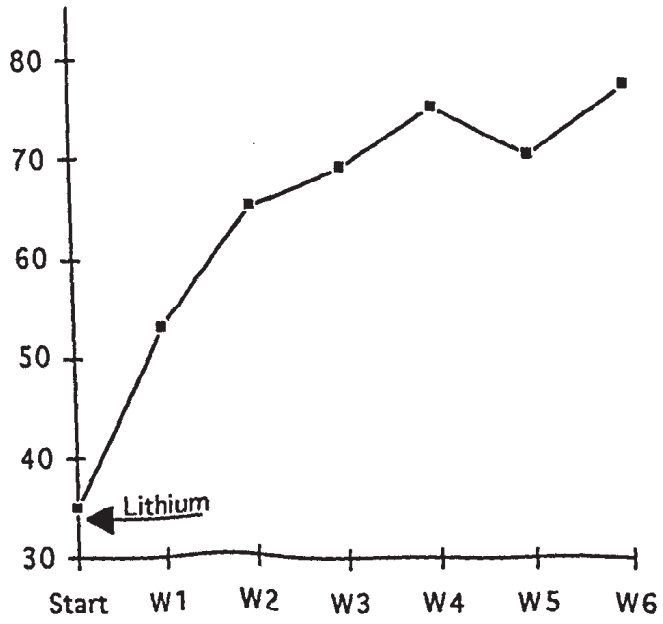

Fig. 9. Changes in the NPRU score in a former crystal methamphetamine, PCP, and alcohol user. The subject was on lithium.

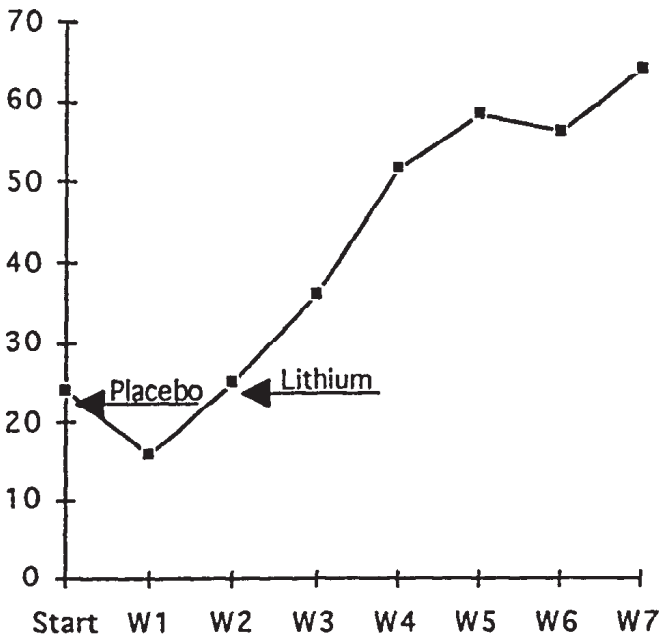

Fig. 10. Changes in the NPRU score in a former heroin and alcohol user. The subject was on placebo during the first 2 wk, and on lithium thereafter.

DISCUSSION

The NPUR Mood Scale test was developed from an experiment on the effects of sleep deprivation in human subjects on mood and behavior (*6*). It therefore seemed to be particularly suited for our purposes because lithium at therapeutic dosages is known to affect circadian rhythms (*7*,*8*). Although our study was conducted in the nutritional dosage range, corresponding only to approx. 1/1000 of the amounts usually prescribed, the NPRU test would still have detected such side-effects. The NPRU Mood Scale test was derived from an original early version of the Profile of Mood State (POMS), buffered with 10 negative items from another 44-item mood scale (*9*) that were found to be as sensitive to sleep deprivation as positive items (*10*). An advantage of the NPRU Mood Scale test, as compared to other similar mood scale tests, is that it contains only 29 items. Other tests list many more items for example: the Profile of Mood State (POMS), 52; the Primary Affect Scale (PAS) (*11*) and the Spielberger State-Trait Inventory (STAI) (*12*), 65 each. Also, the NPRU Mood Scale test can be completed in about 1 min. and has the further advantages that it lacks the learning factor common to many performance tests; it therefore can be given repeatedly without showing practice effects (*13*).

The NPRU Mood Scale items were subdivided into three groups reflecting happiness, friendliness, and energy and the contributions of the respective negative counterparts. Graphic representations of the evo-

lution of the scores for these groups are given in Fig. 3 and 4 for the lithium and the placebo groups, respectively.

Figure 3 shows that lithium raised the scores in all three groups until wk 4 of supplementation, after which the effect seemed to plateau. In those members of the placebo group who exhibited maximum mood scores after 1 wk, as shown in Fig. 2, this was found to be a result of the increase only of the friendliness and energy scores, both of which subsequently declined until wk 4. The happiness scores showed no maximum and declined steadily during the same period of observation (*see* Fig. 4). Lithium, on the other hand, had beneficial effects on all three major mood categories from the beginning, and these effects were additive for about 4 wk of supplementation. In most subjects of the lithium group, the mood improvement was apparent from the beginning of the treatment; an initial placebo effect could not be discerned in this group.

It is concluded, therefore, that lithium at the dosage chosen clearly improved and stabilized the mood of our subjects. No evidence for any negative side effects in the lithium-supplemented group was obtained. Further studies are needed to determine the minimum effective dose in applications of this kind. From the response curves in Fig. 1 and 3, it may be judged that the dose could be reduced to ½ or possibly ⅓ of the amount used in the present study, especially for long-term maintenance. The human dietary lithium requirement has not yet been established. Wada and Ono suggested that the requirement is in the order of 60 μg/d for the Japanese adult. Because of the difference in average body weight, this would translate to about 100 μg/d of lithium for American adults. Since hair lithium content correlates well with lithium intake (*14*), and because about 20% of the samples from a collection of American hair had very low lithium levels, a sufficient daily intake is probably not, or not always, reached by a significant percentage of the population in the United States. The same may be true in the populations of other countries. As lithium deficiency is associated with diminished conditioned avoidance behavior in animals, lithium-deficient human subjects could exhibit a greater tendency toward uncontrolled behavior, e.g., resorting to violence in resolving conflicts, or committing suicide, as is also supported by the results of the epidemiological studies (*3,4*). A nutritional lithium supplement may thus be a valuable adjuvant in drug rehabilitation as well as violence and suicide prevention programs.

ACKNOWLEDGMENTS

Support of this work by The Wacker Foundation, Dallas, TX, is gratefully acknowledged. We also thank William Beck, Director of Recovery Lifestyles Institute, Encinitas, California, for making this study possible.

REFERENCES

1. M. Anke, W. Arnhold, B. Groppel, and U. Krause, The biological importance of lithium, in *Lithium in Biology and Medicine* (G. N. Schrauzer and K.-F. Klippel, eds.), VCH, Weinheim, pp. 149–167 (1991).
2. T. Ono and O. Wada, *Biomed. Res. Trace El.* **2** 264, 265 (1991).
3. E. B. Dawson, The relationship of tap water and physiological levels of lithium to mental hospital admission and homicide in Texas, in *Lithium in Biology and Medicine* (G. N. Schrauzer, and K.-F. Klippel, eds.), VCH, Weinheim, pp. 171–187 (1991).
4. G. N. Schrauzer and K. P. Shrestha, *Biol. Trace El. Res.* **25**, 105 (1990).
5. G. N. Schrauzer, K. P. Shrestha, and Flores-Acre, *Biol. Trace El. Res.* **34**, 161–176 (1992).
6. J. M. Moses, A. Lubin, P. Naitoh, and L. C. Johnson, *Subjective Evaluation of the Effects of Sleep Loss: The NPRU Mood Scale*. Technical report no. 74–25, Naval Health Research Center, San Diego, CA (1974).
7. W. Engelmann, Effects of lithium salts on circadian rhythms, *Chronobiology and Psychiatric Disorders* (A. Halaris, ed.), Elsevier, New York, pp. 263–289 (1987).
8. M. S. Kafka, *Acta Pharmacol. Toxicol.* **56**, 162–169 (1985).
9. C. Hendrick and R. S. Lilly, *J. Personality* **38**, 453–465 (1970).
10. D. M. McNair, M. Lorr, and L. P. Droppleman, *Profiles of Mood States*. Educational and Industrial testing Service, San Diego, CA (1971).
11. E. Johnson and T. Myer, The development and use of the primary affect scale (PAS). Naval Medical Research Institute, Bethesda, MD, Research report no. 31 (1967).
12. C. D. Spielberger, *The Spielberger State-Trait Anxiety Inventory*. Consulting Psychologists Press, Palo Alto, CA (1968).
13. A. Lubin, J. M. Moses, L. C. Johnson, P. Naitoh, *Psychophysiology* **11** (1974).
14. G. N. Schrauzer and K. P. Shrestha, Lithium in drinking water and the incidence of crimes, suicides and arrests related to drug addictions, in *Lithium in Biology and Medicine* (G. N. Schrauzer and K.-F. Klippel eds.), VCH, Weinheim, pp. 171–183 (1991).