Acta psychiat. scand. (1980) *61*, 96–102

Department of Psychiatry (Chairman: *Albert J. Silverman*), Mental Health Research Institute, The University of Michigan Medical Center, Ann Arbor, Michigan, U.S.A.

Treatment of premenstrual tension with lithium carbonate

A PILOT STUDY

M. STEINER, R. F. HASKETT, J. N. OSMUN AND B. J. CARROLL

Some previous reports have suggested that lithium treatment is of benefit to women with the premenstrual tension syndrome (PMTS). In this study 15 women carefully selected for severe PMTS were given lithium carbonate (600–900 mg/day) continuously for three menstrual cycles. Lithium did not affect physical premenstrual symptoms and was ineffective in most women against behavioral premenstrual symptoms. Despite the low dosage most women also experienced significant drug-related side effects. Although a statistically significant improvement was recorded by several symptom rating instruments, this benefit was of no practical clinical value. The three women who responded best to lithium, and who requested continued treatment beyond 3 months, met diagnostic criteria for subsyndromal affective (cyclothymic) disorder. Lithium is not recommended for the average woman with PMTS.

Key words: Lithium carbonate – premenstrual tension syndrome (PMTS).

Given the cyclic nature of the premenstrual tension syndromes (PMTS), it is surprising that so little has been reported on the effects of lithium on premenstrual dysphoria. *Sletten & Gershon* (1966) reported the first successful trial of lithium in this condition. Eight women with irritability, headaches, explosive emotional outbursts, tension, insomnia and depression during the premenstrual period were given 300 mg of lithium carbonate 3 times daily for 10 days prior to the onset of menses. All eight patients had been previously unresponsive to sedatives, diuretics and psychotherapy and were said to have been treated successfully with this regimen of lithium for 12–18 months. This was an open uncontrolled study and we are unaware of any follow-up reports by this group of investigators. *Fries* (1969) mentioned that lithium had a good effect in two out of five women studied for PMTS. *Tupin* (1972) cites one subject with PMTS who improved partly with lithium therapy. There were no detailed descriptions of symptomatology, treatment schedule, dosage of lithium or lithium plasma levels for either study. *Singer et al.* (1974) compared lithium with placebo in a double-blind multiple random cross-over study involving 19 psychiatric outpatients suffering from PMTS. Lithium treatment was given throughout the month. Patients improved on both lithium and placebo with no recorded differences between treatments. The significance of this study is unclear since 12 of their patients were diagnosed as having concomitant, other psychiatric diagnoses

0001-690X/80/020096-07$02.50/0

(three affective disorders, four neurotics and five remitted schizophrenics). *Mattsson & von Schoultz* (1974) used a double blind cross-over design for a well-controlled study of lithium treatment. Eighteen women received 800 mg lithium carbonate daily beginning 14 days before the expected first day of menstrual flow. Lithium was compared with a diuretic (chlorthalidone) and placebo and each treatment was given over two premenstrual periods. All three treatments improved the symptoms of PMTS. The rank order of effectiveness was placebo first, followed by the diuretic, with lithium least active. Here again the actual symptoms described were a mixture of anxiety-depression-irritability-tension together with physical complaints. *Horrobin et al.* (1973) reported the treatment of one woman with severe premenstrual edema. She was given 500 mg lithium carbonate daily beginning on the day of elevation of basal body temperature and continuing until menstruation occurred. She was reported to be free of edema for two complete cycles, and the severe dysphoria which usually accompanied the premenstrual edema was also relieved during the lithium trial. After 6 months, however, the physical and emotional effectiveness of this treatment was greatly diminished (*Horrobin et al.* (1976)). Since much of the available evidence is contradictory, we decided to further investigate the possible utility of lithium in PMTS.

METHODS

Subjects

Fifteen women suffering severe premenstrual symptoms were selected for this study. Their ages were between 27 and 43 (mean 32 years); 14 were married, 12 with children, and thus constituted a group of mature adult women. They all had regular menses, with no significant abnormal findings at physical examinations with normal laboratory values, and were completely drug free for at least 4 weeks prior to and during the evaluation period. They had premenstrual dysphoric symptoms for at least six consecutive menstrual cycles. Emotional as well as physical symptoms were recorded by the various observers and self-rating scales. These were reported as at least "moderate" to "severe" during the premenstrual period with "marked" or "complete" relief soon after full menstrual flow began. Thus all women studied here suffered a severe premenstrual dysphoria and the disturbance was definitely an on/off phenomenon.

Procedure

All subjects were evaluated for at least one complete menstrual cycle before beginning treatment. Visits were scheduled to coincide as closely as possible with two specific points in the menstrual cycle: a follicular phase visit on Day 9 (where Day 1 was the onset of menses) and a luteal phase visit on, or around, Day 26 but always 2–6 days premenstrual.

To measure the phenomenology at each visit and record the change occurring between the follicular and luteal phases the following rating scales were used:

1. Visual Analogue Scale (VAS) (*Maxwell* (1978)).
2. Menstrual Distress Questionnaire (MDQ) (*Moos* (1969)).
3. Multiple Affect Adjective Checklist (MAACL) (*Zuckerman & Lubin* (1965)).

4. State-Trait Anxiety Inventory (STAI) (*Spielberger et al.* (1970)).
5. Hamilton Depression Scale (HDS) (*Hamilton* (1960)).
6. Carroll Depression Scale (CDS) (*Feinberg et al.* (1979)).

The total scores obtained on the various rating scales were used as an index of global severity as well as a measure of change between follicular and premenstrual visits.

After completion of the initial evaluation ("cycle 0") all patients were given 600 mg lithium carbonate daily (300 mg caps. b.i.d.) for one menstrual cycle ("cycle 1"). If there was "No change" in symptomatology after one menstrual cycle the dose was increased to 900 mg daily (300 mg t.i.d.) for two additional cycles ("cycles 2" and "3").

Lithium plasma levels were monitored on each visit to the clinic, i.e. bimonthly. Samples were drawn 12 h after the last dose of the drug was taken by the patient. Clinical global impression and side effects were independently recorded by the psychiatrist and the research nurse during each visit.

The rating scale total scores during the premenstrual visit of "cycle 0" were compared with the mean total scores for the premenstrual visits of "cycles 1" through "3" and analyzed statistically by a 1-way ANOVA.

RESULTS

The course of treatment and some of the clinical observations are summarized in Table 1.

All patients received 600–900 mg lithium carbonate daily and the plasma lithium levels ranged between 0.3 and 0.85 mEq/l (average 0.54). Six patients were unable to complete the 3-month study, three because of drug related side-effects and three for other reasons. Six patients reported significant side-effects but were willing to complete the 3-month schedule. Five patients seemed to benefit from the treatment but only three requested to be maintained on lithium past the study period. None of the patients experienced any beneficial effects on the physical premenstrual symptoms, and in five patients lithium seemed to have aggravated the symptoms.

The change in symptomatology as measured by the various rating scales is shown in Table 2.

Combined Rating Scale total score changes failed to show that lithium carbonate produced a significant beneficial effect (0.087). Comparison of score changes on individual rating scales revealed a few in which the difference reached a statistical significance. The clinical implications of these results are unclear because these instruments were not designed primarily for PMTS (e.g. HDS change from 10.5 to 5.0, $P < 0.002$).

The VAS and the MDQ give a global measure of PMTS and show some degree of statistical significance. This, however, seems to be the result of a change from "extremely severe" to "moderate" symptomatology. A final MDQ mean score of 114 ± 32 or a mean of 43 ± 27 on the VAS while on lithium carbonate does not indicate symptom resolution.

Table 1. *Course of treatment*

Patient No.	Age	Lithium		Effect on emotional PMTS symptoms	Effect on physical PMTS symptoms	Persistent side-effects	Dropouts	
		Max. dose mg/d	Max. plasma level mEq/l				Drug related	Non-drug related
1	28	900	0.4	no change	no change			
2	31	900	0.42	beneficial*	no change	nausea dizziness tremor		
3	28	900	0.75	beneficial	no change	nausea tremor		
4	27	900	0.61	beneficial	no change	dizziness tremor		
5	40	900	0.45	somewhat beneficial	worse	blurred vision		
6	34	600	0.75	beneficial*	no change			
7	43	900	0.6	no change	no change	nausea		
8	39	600	0.3	somewhat beneficial	worse	water retention	after 2 months	
9	27	600	0.36	no change	no change			after 1 month
10	29	600	0.51	beneficial*	no change			
11	29	600	0.63	somewhat beneficial	worse	blurred vision	after 2 months	
12	36	900	0.58	worse	worse	nausea sweating palpitations urin. freq.	after 2 months	
13	31	600	0.41	no change	no change			after 1 month
14	32	900	0.85	somewhat beneficial	worse	tremors edema		
15	33	900	0.46	somewhat beneficial				after 2 months

* Requested to be maintained on lithium past the study period.

Table 2. *Lithium trial* (n = *15)*

Rating scale	Pretreatment cycle 0		Treatment mean of cycles 1–3		Significance of change
VAS	62.0	24.0	43.0	27.0	0.046
MDQ	139.0	27.0	114.0	32.0	0.034
HDS	10.5	5.0	5.0	4.0	0.002
CDS	19.0	9.0	11.0	7.0	0.005
STAI	58.0	11.0	45.0	10.0	0.002
MAACL-A	13.6	3.5	9.2	3.2	0.001
MAACL-D	22.7	7.0	17.4	5.0	0.020
MAACL-H	15.0	5.4	11.0	5.6	0.052
Total change for the group					0.087

Table 3. *Comparison of ratings in 12 women subjectively unimproved with lithium*

Rating scale	Pretreatment cycle 0		Treatment mean of cycles 1–3		Significance of change
VAS	61.0	24.0	48.0	23.0	0.240
MDQ	142.0	29.0	120.0	35.0	0.120
HDS	12.0	5.0	6.0	4.5	0.007
CDS	21.0	8.0	12.0	7.0	0.017
STAI	59.0	11.0	46.0	11.0	0.007
MAACL-A	14.0	3.7	9.5	3.3	0.006
MAACL-D	23.0	7.6	17.4	5.0	0.060
MAACL-H	15.0	5.8	11.4	6.1	0.190
Total change for the group					0.220

For additional analysis we excluded the three patients who requested to be maintained on lithium past the study period (which we interpreted to be a strong indication as to the clinical efficacy of the drug in these women) so as to further examine the characteristics of definite non-responders. The data for the remaining 12 subjects are summarized in Table 3. In these 12 patients the changes in global symptomatology as rated by the MDQ and the VAS, are statistically non-significant.

As shown in Table 1 only nine patients completed the 3-month treatment trial. In Table 4 the premenstrual total scores of the six women who completed the study and then withdrew are compared with the scores recorded from the three women mentioned earlier who requested to be maintained on lithium beyond the study period.

When the various ratings on these three women are compared with the other six women there is no difference whatsoever between the two groups. Thus we were unable to show by the instruments used that lithium had a beneficial effect on any of the specific premenstrual tension symptoms.

Table 4. *Average premenstrual scores during treatment for nine women who completed the study*

Rating scale	Completed study but declined continuation ($n = 6$)		Completed study and requested continuation ($n = 3$)		Significance of change
VAS	47.0	9.0	44.0	37.0	0.84
MDQ	112.0	23.0	107.0	24.0	0.76
HDS	8.0	3.0	3.5	1.0	0.05
CDS	13.0	4.0	9.0	3.0	0.14
STAI	46.0	8.0	45.0	11.0	0.88
MAACL-A	9.8	1.6	9.6	3.3	0.93
MAACL-D	19.0	4.4	18.2	6.5	0.84
MAACL-H	11.0	2.4	11.3	4.2	0.86

DISCUSSION

A standard procedure for screening and selecting women suffering from severe PMTS was utilized in this study. In contrast to anecdotal clinical studies we have studied only women who have not experienced major psychiatric disorders in the past. Changes in symptomatology and response to treatment were monitored with existing validated rating scales in addition to global clinical impressions. Most of the women experienced severe side-effects even on low dose lithium, reminiscent of observations in normal volunteers (*Judd et al.* (1977)). The three women who clearly benefited from the treatment would probably qualify as "subsyndromic" affective disorders (*Akiskal et al.* (1977)). Two of them had first degree relatives with diagnosed affective illness. We believe that these women comprise a specific subgroup. Lithium seems to help some cyclothymic features without directly affecting their premenstrual tension. Consequently, while on lithium they seem to be able to better cope with the PMTS symptoms. The remaining 12 women noted no beneficial effect and most experienced a worsening in some of the physical symptoms. We believe that the non-specific emotional symptoms which disappeared in some of the women while on lithium cannot be completely attributed to a specific effect of medication. A general placebo effect seems to play a major role in PMTS treatments (*Smith et al.* (1975)), the full meaning of which needs further clarification.

Unlike some previously reported studies we were unable to show that lithium carbonate is indicated in premenstrual tension syndromes.

ACKNOWLEDGMENTS

For excellent technical assistance we are grateful to Ms. *Mary Sies,* Ms. *Ruth Metski,* and Ms. *Anna Babbit.* We wish to thank Ms. *Ann Taylor* for her invaluable assistance in analyzing the data, and Ms. *Ruth Prieskorn* of the Upjohn Center for Clinical Pharmacology for her kind support.

REFERENCES

Akiskal, H. S., A. H. Djenderedjian, R. H. Rosenthal & M. K. Khani (1977): Cyclothymic disorder: validating criteria for inclusion in the bipolar affective group. Amer. J. Psychiat. *134,* 1227–1233.

Feinberg, M., B. J. Carroll, P. Smouse, S. Rawson, R. F. Haskett, M. Steiner, A. Albala & T. Zelnick (1979): Comparison of physician and self-ratings of depression. Abstr. No. 80, Annual Meeting of Society of Biological Psychiatry, Chicago.

Fries, H. (1969): Experience with lithium carbonate treatment at a psychiatric department in the period 1964–1967. Acta psychiat .scand., Suppl. *207,* 41–43.

Hamilton, M. (1960): A rating scale for depression. J. Neurol. Neurosurg. Psychiat. *23,* 56–62.

Horrobin, D. F., M. S. Manku, B. Nassar & D. Evered (1973): Prolactin and fluid and electrolyte balance. In *Pasteels, J. L., & C. Robyn* (eds.): Human prolactin. Excerpta Medica, Amsterdam, pp. 152–155.

Horrobin, D. F., J. P. Mtabaji, R. A. Karmali, M. S. Manku & B. A. Nassar (1976): Prolactin and mental illness. Post-grad. med. J. *52,* Suppl. *3,* 79–85.

Judd, L. L., B. Hubbard, D. S. Janowsky, L. Y. Huey & P. A. Attewell (1977): The effect of lithium carbonate on affect, mood, and personality of normal subjects. Arch. gen. Psychiat. *34,* 346–351.

Mattsson, B., & B. von Schoultz (1974): A comparison between lithium, placebo and a diuretic in premenstrual tension. Acta psychiat. scand., Suppl. *255,* 75–84.

Maxwell, C. (1978): Sensitivity and accuracy of the visual analogue scale: A psychophysical classroom experiment. Brit. J. clin. Pharmacol. *6,* 15–24.

Moos, R. H. (1969): Menstrual Distress Questionnaire. Preliminary manual. Social Ecology Lab., Stanford, California.

Singer, K., R. Cheng & M. Schou (1974): A controlled evaluation of lithium in the premenstrual tension syndrome. Brit. J. Psychiat. *124,* 50–51.

Sletten, I. W., & S. Gershon (1966): The premenstrual syndrome: a discussion of its pathophysiology and treatment with lithium ion. Comprehens. Psychiat. *7,* 197–206.

Smith, S. L., J. M. Cleghorn, D. L. Streiner & E. V. Younglai (1975): A study of estrogens and progesterone in premenstrual depression. In *Hirsch, H.* (ed.): The family. Karger, Basel, pp. 538–542.

Spielberger, C. D., R. L. Gorsuch & R. E. Lushene (1970): STAI Manual, Consulting Psychologists Press, Palo Alto, California.

Tupin, J. P. (1972): Lithium use in nonmanic depressive conditions. Comprehens. Psychiat. *13,* 209–214.

Zuckerman, M., & B. Lubin (1965): Manual for the Multiple Affect Adjective Check List. Educational and Industrial Testing Service, San Diego, California.

Received August 31, 1979

Meir Steiner, M.D.
Roger F. Haskett, M.B.B.S.
Judith M. Osmun, R.N.
Bernard J. Carroll, M.D., Ph.D.
Mental Health Research Institute
Department of Psychiatry
The University of Michigan Medical Center
Ann Arbor, Michigan 48109
U.S.A.