

Lithium and Memory: A Long-Term Follow-up Study

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This study examined the effects of long-term lithium therapy on memory functions in 18 patients suffering from bipolar affective disorder. Patients were retested on the Wechsler Memory Scale, Benton Visual Retention Test, and Zung Self-Rating Depression Scale 6 years after initial testing. Mean memory test scores remained remarkably stable over the 6-year interval with only one of the 10 memory subtests showing a statistically, but not clinically, significant decrease. The sample was split at the median duration of lithium therapy into a long- and shorter term group (with means of 12.9 and 5.2 years, respectively). There were no significant differences between these groups on any of the memory tests when controlled

for age and initial memory scores. Negative correlations between several memory test scores and the duration of lithium treatment could in part be explained by the effects of age. Patients' subjective complaints of impaired memory functioning, rated on a visual analogue scale, correlated with the level of depression at the second testing as well as with three memory test scores measuring immediate and short-term visual recall. The results are discussed in view of the demographic and clinical characteristics of the sample and are compared with previous research findings.

(*J Clin Psychopharmacol* 1988;8:207-212)

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THE INCREASING use of lithium carbonate as the treatment of choice for bipolar affective disorder has highlighted a major concern for patients and clini-

cians alike, calling for controlled studies of the long-term effects of lithium therapy on cognitive and memory functioning. Excluding detailed reports of the deleterious effects of acute lithium toxicity,¹⁻³ which recently have been reviewed elsewhere,⁴ several studies have found impaired cognitive and memory functioning in patients receiving lithium therapy.⁵⁻⁸ In particular, the study by Reus and colleagues⁷ demonstrated that patients treated with lithium were unable to recall as many items on a verbal learning task as a control group of patients not receiving lithium. Nair and associates⁸ found correlations between the duration of lithium therapy, severity of EEG abnormalities, and reduced WAIS Performance IQ scores. Episodic slow wave activity in the EEG was associated with mental slowing in the toxicity rating scale. A more recent study by Lund and coworkers⁶ found that patients maintained on long-term lithium therapy scored significantly lower on a test of immediate recall of digits than those receiving lithium for a shorter duration, although the difference in mean number of digits recalled was exceedingly small.

In contrast to these findings, a number of controlled and uncontrolled studies have failed to demonstrate such "lithium-induced" deficits. Ghadirian and colleagues⁹ compared patients receiving long-term lithium therapy with a short-term lithium treatment group and did not find any evidence of memory impairment when the patients were tested on well recognized and widely used tests of memory functioning. Other recent studies have reported similar results.^{10, 11}

Taken together, the results of studies that have examined the effects of lithium on memory functioning in patients are equivocal; some show impaired performance on memory tests, while others find little or no deficits resulting from lithium treatment. The reasons for this lack of empirical consensus are numerous and in part arise from the heterogeneity of patient samples admitted into studies, differences in the classification schemes used in diagnosis, varying durations of lithium treatment, conceptual differences in the definitions of short-term and long-term memory, and a variety of methodological and design problems.

The aim of the present study was to follow-up and retest the patients who participated in a previous study of memory and lithium therapy approximately 6 years ago.⁹ The results of that study demonstrated that the duration of lithium therapy in 30 patients with bipolar affective illness was not found to adversely affect memory functioning when such variables as serum lithium, psychopathology, age, and physical illness were taken into consideration. In the present study, patients were retested on the Wechsler Memory Scale, the Benton Visual Retention Test, and the Zung Self-Rating Depres-

sion Scale under the hypothesis that long-term lithium therapy would not lead to impaired memory functioning. More specifically, based on the previous findings, we tested the hypothesis that memory test scores from the first and second testings would not differ significantly. A second corollary hypothesis predicted that the patients' subjective ratings of their sense of memory impairment would correlate significantly with their level of depression but not with the objective memory test findings.

Subjects and Methods

Subjects

Eighteen of the 30 patients who participated in the earlier study were retested. The remainder were either unwilling to participate or could not be reached. The present sample consisted of 12 men and six women ranging in age from 28 to 67 years, with a mean age of 45.8. All patients were treated at the Allan Memorial Institute Affective Disorders Clinic and were included in the study with their consent. The diagnosis of affective disorder was made on the basis of clinical assessment and personal and family history and according to DSM-III¹² criteria. The criteria for exclusion were acute physical illness, organic brain syndrome, perceptual disorders, acute psychopathology, electroconvulsive therapy during the past 3 months, and large dosages of concomitant psychotropic medication. At the second testing, one patient was on a modest dosage of antidepressant medication and two were receiving small dosages of anxiolytic medication.

Test battery

The following tests were readministered to the patients.

Wechsler Memory Scale (WMS). This test is widely used with clinical populations to measure short-term and long-term memory functions and yields a memory quotient (corrected for age) and scores in the following subtests: information, orientation, mental control, logical memory, digit span, visual reproduction, and associate learning.

Benton Visual Retention Test (BVRT). This is a performance test consisting of 10 cards with geometric designs graded in difficulty ranging from one single figure to three complex figures on a card. The test requires spatial perception, immediate recall, and visual-motor skills to reproduce the drawing after 10 seconds of exposure and a 15-second delay (form D). Scoring consists of the number of cards correctly reproduced (0 to 10) and the number of errors within each reproduction (ranging from a total of 0 to 26). The test retest reliability of the BVRT is quite high. Coefficients of concordance be-

tween the BVRT scores at two testings 1 year apart were 0.74 for the number of correct designs and 0.77 for the number of errors.¹³

Zung Self-Rating Depression Scale (SDS). This scale consists of 20 items yielding a total raw score and an index (raw score multiplied by a coefficient of 1.25 for normalization purposes). The Zung SDS is widely used in clinical studies of depressed psychiatric patients with satisfactory reliability for a self-report instrument.¹⁴ An SDS index of 60 indicates the presence of moderate to marked depression and serves as a cutoff point in clinical and research studies.

Structured Interview Schedule (SIS). This schedule aided in gathering the following data: age, sex, education, duration of lithium treatment since the first testing, lifetime duration of lithium treatment, serum lithium level on the morning of the day of testing, subjective awareness of memory impairment (measured on a visual analogue scale), other current medication, the number of major manic and/or depressed episodes since the first testing, and the number of hospitalizations since the first testing (both obtained from the patient's clinical records).

Procedure

When the patients arrived, the examiner described the nature and objectives of the study, outlined the procedures involved, and obtained their informed written consent to participate. Serum lithium levels were measured in the morning on the day of testing after a brief clinical examination. The Zung SDS was completed by the patient, followed by the administration of the SIS, BVRT, and WMS. Patients were reimbursed for their transportation costs to and from the hospital on the day of testing.

Results

Reliability check

Although both the WMS and the BVRT have been shown to have relatively high test-retest reliability, we computed the interrater reliability for the BVRT since the records for the two testing occasions were scored by different individuals. One of us (J.K.) rescored the BVRT records from the first testing of 10 randomly selected patients and computed the Pearson product moment correlation coefficient between his results and those obtained by the first examiner. The correlation coefficients for the Correct Cards and Error Design scores were 0.94 and 0.97, respectively, indicating a very high degree of interrater reliability.

Sample description

Table 1 contains relevant demographic and clinical variables for the sample of 18 patients at the second test-

TABLE 1. Demographic and clinical variables for the 18 subjects at the second testing

Variables	Mean	SD
Age	45.8	13.7
Education	13.8	3.2
Subjective sense of memory impairment (0-100)	22.9	17.5
Serum lithium (mEq/liter)	0.61	0.27
Months of lithium in lifetime	108.9	63.5
Months of lithium between testings	66.0	15.9
No. of manic/depressed episodes between testings	0.67	0.77
No. of hospitalizations between testings	0.22	0.43

ing. It is evident that as a group this sample has been relatively healthy since the first testing as indicated by the small mean number of major episodes (0.67) and hospitalizations (0.22). Although retesting was done approximately 6 years later, the average duration of lithium treatment for this interval was 5.5 years, indicating that not all patients had been maintained on continuous lithium therapy.

Serum lithium levels were within therapeutic limits for all subjects at both testings, ranging from 0.60 to 1.2 mEq/liter at the first testing and from 0.26 to 1.1 mEq/liter at the second. All patients were clinically evaluated prior to testing. There were no symptoms of lithium toxicity or any abnormal serum lithium levels to suggest toxicity.

Memory functions over time

Table 2 shows the means and standard deviations for the BVRT, WMS, and the Zung SDS Index at the two testings for the sample of 18 subjects. These data show a remarkable stability over time: the mean WMS memory quotients for the first and second testings were 112.4 and 112.8, respectively. A statistical comparison of the change in performance over the 6-year interval was computed for each memory score shown in Table 2 by a

TABLE 2. A comparison of the mean memory test scores and the Zung SDS Index at the two testings

	First testing: mean (SD)	Second testing: mean (SD)
BVRT		
No. correct cards score	6.8(2.3)	6.5(1.9)
Error design score	5.1(4.9)	4.9(3.7)
WMS		
Information	5.8(0.5)	5.0(0.0)
Orientation	4.9(0.2)	4.9(0.2)
Mental control	7.4(1.9)	7.3(1.9)
Logical memory	9.3(2.9)	9.6(3.9)
Digit span	11.7(2.3)	10.6(1.8)
Visual reproduction	10.2(3.6)	9.5(3.9)
Associate learning	15.4(3.6)	16.1(3.1)
Memory quotient	112.4(17.1)	112.8(17.8)
Zung SDS Index	39.4(9.1)	37.9(7.9)

univariate one-way repeated measurement ANOVA. The only variable that showed a significant decrease over the testings was the information subtest of the WMS ($F(1,17) = 47.20, p < 0.0001$: At the second testing, all subjects failed on the WMS information subtest item, which requests the name of the former Prime Minister of Canada: and instead, all named his predecessor. Lack of variation in responses for this subtest is seen in a standard deviation of zero in Table 2. The statistically significant difference observed between testings on the information subtest is best interpreted as an artifact of recent public events in Canada; the clinical significance of this difference is negligible. It is important to note that there were no significant differences between testings on any other variable measuring memory functioning.

To further assess the effects of long-term lithium therapy on memory functioning the sample was split, at the median, into two groups of equal size based on the patients' lifetime duration of lithium therapy (median, 7.6 years of lithium treatment). This resulted in a "long-term" group with a mean duration of 12.9 years of lithium therapy and a "shorter-term" group with a mean of 5.2 years. Mean memory test scores from the second testing were compared by a series of univariate one-way ANCOVAs using age and the first testing memory scores as covariates. There were no significant differences between the two groups on any of the 10 memory measures.

Table 3 contains the significant ($p < 0.05$) correlations found between the clinical variables obtained from the SIS, the memory test scores, and the Zung SDS Index. For ease of reading in the table, all nonsignificant correlations have been omitted and replaced by empty cells. Correlations involving the information and

orientation subtests and the number of hospitalizations and manic or depressed episodes between testings were not computed given the extremely small range of observed values for these variables.

Several findings in Table 3 are noteworthy. First, there is a negative relationship between five memory test scores and the duration of lithium therapy (as measured by the total lifetime duration as well as the duration between testings). These findings indicate that, in general, the longer a patient received lithium, the poorer was his or her memory test performance on the BVRT error design score, three WMS subtests, and the WMS memory quotient. However, three of these memory scores were also positively correlated with the patients' ages. Thus, age may account in part for the relationship between the duration of lithium treatment and memory performance.

Second, the patients' subjective sense of memory impairment correlated with the Zung SDS Index ($r = 0.52$) as well as with age ($r = 0.62$). In addition, subjective sense of memory impairment was significantly correlated with three of the objective memory test scores measuring immediate and short-term visual reproduction but not with duration of lithium therapy. None of the 10 memory subtests correlated significantly with scores on the Zung SDS Index.

Finally, performance on the digit span subtest correlated positively with both the lifetime duration of lithium therapy ($r = 0.40$) and serum lithium level just prior to testing ($r = 0.72$).

Comment and Conclusions

The results of the present study supported the hypothesis of no difference in memory test performance

TABLE 3. Correlations of the memory test results with the clinical and demographic variables at the second testing^a

Variables	Age	Education	Serum lithium (mEq/liter)	Lifetime lithium (months)	Lithium between testings (months)	Subjective memory impairment
BVRT						
Correct cards	-0.47	0.54				-0.52
Error design	0.58	-0.60		0.44		0.55
WMS						
Information						
Orientation						
Mental control				-0.42		
Logical memory	-0.50				-0.62	-0.45
Digit span			0.72	0.40		
Visual reproduction		0.67				0.40
Associate learning	-0.40	0.46		-0.61	-0.49	
Memory quotient		0.40			-0.56	
Subjective memory impairment	0.62	-0.40				
Zung SDS Index						0.52
Age				0.43		0.62

^aAll correlation coefficients are significant at the 5% level or less.

over time, demonstrating that after a mean duration of 5.5 years of lithium treatment spanning a 6-year interval between testings, memory functions remained remarkably stable and unchanged. With the exception of the poorer performance on the information subtest of the WMS at the second testing, there were no significant changes in any of the remaining nine memory test scores. Furthermore, comparisons of the long-term and shorter term lithium therapy groups (with means of 12.9 and 5.2 years of lithium treatment, respectively) yielded no significant memory score differences. Clearly, these findings do not support the claim that long-term lithium therapy results in impaired memory performance.

Despite these unequivocal findings, the negative correlations between several of the memory test scores and the duration of lithium treatment would seem to indicate that long-term lithium use is associated with poorer memory performance. However, these correlations should be interpreted cautiously since both the lifetime duration of lithium treatment and four of the memory test scores were also significantly related to the patients' ages. Thus, it seems reasonable to conclude that the association between memory performance and lithium duration can, in part, be accounted for by the patients' ages.

Our second hypothesis was only partially confirmed. As predicted, the patients' ratings of their subjective sense of memory impairment correlated with scores on the Zung SDS Index (as well as with age). The most likely explanation of these findings is that the combined effects of age and level of depression are in part responsible for the subjective sense of impaired memory functioning that these patients report. However, contrary to our expectation, these subjective ratings were also associated with poorer performance on three memory tasks involving focused attention and visual-motor coordination in reproducing designs. Taken together, these results indicate that when patients with bipolar disorder report a sense of impaired memory functioning, their reports may accurately reflect their performance on objective memory tests. Whereas age and level of depression may contribute to a sense of impaired memory functioning, and age to lowered performance on objective tests of memory, there is no evidence that this is the case for duration of lithium treatment.

The finding that serum lithium levels were highly correlated with performance on the digit span subtest indicated that higher lithium levels were associated with better performance on this subtest. In addition to being a test of immediate memory, the digit span subtest requires focused attention and concentration for successful performance. Factor-analytic studies reveal that the digit span subtest loads most highly on factors

that measure "freedom from distractibility."¹⁵ Thus, patients with higher serum lithium levels may have benefited from the stabilizing effects of lithium and performed better with fewer internal or external distractions.

Results from the original study⁹ showed that at the first testing digit span test scores correlated significantly with duration of lithium therapy ($r = 0.42$). At that time patients had been receiving lithium treatment for an average of approximately 2 years. The present study demonstrated at follow-up, after an additional 5.5 years of lithium treatment, that these variables were still significantly correlated. This finding provides further evidence of the stability of memory functions over time despite the intervening years of lithium treatment.

Finally, it is evident from the demographic and clinical variables presented in Tables 1 and 2 that the present sample was overrepresented by males, who were relatively well educated, showed an above average WMS memory quotient, and did not demonstrate much psychopathology over the 6-year interval between testings. This latter finding, however, is probably evidence of the prophylactic effect of lithium. Further long-term evaluations of the effects of lithium treatment on memory functioning in larger samples of patients with bipolar affective disorder are warranted.

Acknowledgments

This study was supported in part by a Medical Research Council of Canada Studentship (J.K.).

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