Effects of Lithium on Cognitive Performance: A Meta-Analysis

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Background: Cognitive impairment is underrecognized among patients with bipolar disorder and may represent not only effects of the illness but also adverse effects of its treatments. Among these, lithium is the best-studied mood stabilizer. As its cognitive effects are mixed and not well-known, we assessed reported effects of lithium on cognitive performance.

Data sources: MEDLINE, PsycINFO, and EMBASE databases (1950 to December 2008) were queried with the keywords *lithium*, *cognit**, *neurocognit**, *neuropsych**, *psycholog**, *attention*, *concentration*, *processing speed*, *memory*, *executive*, and *learning*. Database searches were supplemented with bibliographic cross-referencing by hand. The literature search was conducted independently by 2 authors (A.P.W. and T.S.W.) during August and September 2008, and questions about appropriate inclusion or exclusion were resolved between them by consensus.

Study selection: Of 586 reports initially identified as being of potential interest, 12, involving 539 subjects, met our inclusion criteria: (1) cognitive performance compared between subjects taking lithium and comparable subjects not taking lithium; comparability was assured by: (2) patients with the same affective disorder diagnoses in euthymic or remitted status or healthy volunteers; (3) groups of similar age and sex; (4) similar intelligence, education, or occupation; (5) similar distribution of other concurrent psychotropic drugs; and (6) cognitive abilities (outcomes) assessed with performance-based measures.

Data extraction: Standardized mean-difference effect size (ES), corrected for small-sample bias (Hedges' *g*), was computed for cognitive tasks in each study. ES estimates were transformed so that positive values indicate poorer performance by lithium-treated subjects. Infrequently, when means and standard deviations were not provided, ES was estimated from reported values of *t*, *F*, or *z* tests. For analysis, similar neurocognitive tests were grouped a priori based on the cognitive domains they aimed to assess.

Data synthesis: We identified 12 studies involving 276 lithium-treated and 263 similar or the same subjects, lithium-free. Lithium was taken for a mean duration of 3.9 years by affective disorder patients and 2.5 weeks by healthy volunteers, yielding a mean daily trough serum concentration of 0.80 mEq/L. Overall, lithium treatment was associated with small but significant impairment in immediate verbal learning and memory (ES = 0.24; 95% CI, 0.05–0.43) and creativity (ES = 0.33; 95% CI, 0.02–0.64), whereas delayed verbal memory, visual memory, attention, executive function, processing speed, and psychomotor performance were not significantly affected. Selectively, among the 326 affective-disorder patients, in addition to these overall impairments, long-term lithium treatment also was associated with even greater impairment in psychomotor performance (ES = 0.62; 95% CI, 0.27–0.97), with no evidence of cognitive improvements.

Conclusions: Lithium treatment appears to have only few and minor negative effects on cognition.

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Cognitive impairment is a substantial problem among patients with major mental illnesses, including those with bipolar disorder.[1–3] Nearly two-thirds of euthymic bipolar disorder patients report cognitive problems, usually specific to concentration and memory.[4] Objective neurocognitive assessments suggest that cognitive impairment in bipolar disorder patients exists across mood states, worsens during manic or depressive episodes, and persists substantially during euthymia.[5–7] A recent meta-analysis of 39 studies compared the cognitive performance of 948 euthymic bipolar disorder patients to 1,128 healthy controls, matched for age, sex, education, and estimated IQ.[2] Euthymic bipolar disorder patients were found to have medium-to-large effect sizes ([ESs]; ES = mean difference/standard deviation) for impairment of attention and processing speed (ES = 0.62–0.79), memory (ES = 0.43–0.81), and executive functioning (ES = 0.47–0.71). Another meta-analysis of 20 studies, also comparing cognitive performance among euthymic bipolar disorder patients to matched healthy controls, found deficits of similar magnitude among bipolar disorder patients in measures of executive function, verbal learning and memory, abstraction, sustained attention, and psychomotor speed.[8] Cognitive impairment occurs in both

type I and II bipolar disorder but is typically more severe in type I patients, even when they are euthymic.[9,10] Cognitive impairment was associated with less successful psychosocial functioning, even after adjusting for residual mood symptoms and relevant demographic and clinical variables in 11 of 13 studies.[3]

To what extent adverse effects of psychotropic medications, as well as illness effects, may contribute to the cognitive impairment in euthymic bipolar disorder patients is an important question, especially with the increased reliance on combinations of psychotropic medications, such as mood stabilizers, often with antidepressants, antipsychotics, or sedatives.[11,12] Studies examining the cognitive effects of psychotropic medications, particularly those with proposed mood-stabilizing effects, are limited, with inconsistent results. The antimanic anticonvulsant valproate showed impaired mental and psychomotor speed in 4 studies of healthy volunteers and epileptic patients[13] but equivocal cognitive effects in euthymic bipolar disorder patients.[14] Studies of the antimanic anticonvulsant carbamazepine also yielded inconsistent findings: 2 studies in healthy volunteers and epileptic patients suggested no significant cognitive impairment,[15,16] but 2 others in healthy volunteers found impairments in memory, processing speed, and attention.[17,18] In addition, among 34 remitted bipolar disorder patients treated with carbamazepine or lithium as monotherapies with no other psychotropic medications, there were no negative cognitive effects compared to medication-free bipolar disorder controls.[19] Another anticonvulsant mood stabilizer, lamotrigine, had lesser adverse cognitive effects than either carbamazepine or valproate in 33 euthymic bipolar disorder patients.[20]

Among mood stabilizers, lithium has been used longest and studied most extensively, including its effects on cognitive performance. It remains one of the most widely employed mood-stabilizers internationally.[21–24] Lithium has substantial evidence of short- and long-term efficacy against morbidity and mortality associated with depression, mania or hypomania, and mixed-states in both type I and II bipolar disorder.[21,25,26] Lithium also has abundant evidence for major antisuicidal effects in bipolar disorder, which has unusually high suicide rates, and perhaps in other disorders.[27,28] Lithium can be neurotoxic in overdose[22] but may have neuroprotective effects in various neurodegenerative disorders[29–32] and perhaps in bipolar disorder.[33–37] Given the clinical importance of lithium salts and their wide application in the treatment of recurrent affective disorders, we assessed potential effects of lithium on cognitive performance using meta-analytic methods.

METHOD

Study Ascertainment

MEDLINE, PsycINFO, and EMBASE databases (1950 to December 2008) were queried with the keywords *lithium, cognit*, neurocognit*, neuropsych*, psycholog*, attention, concentration, processing speed, memory, executive,* and *learning*. Database searches were supplemented with bibliographic cross-referencing by hand. The literature search was conducted independently by 2 authors during August (A.P.W.) and September (T.S.W.) 2008, and questions about appropriate inclusion or exclusion were resolved between them by consensus.

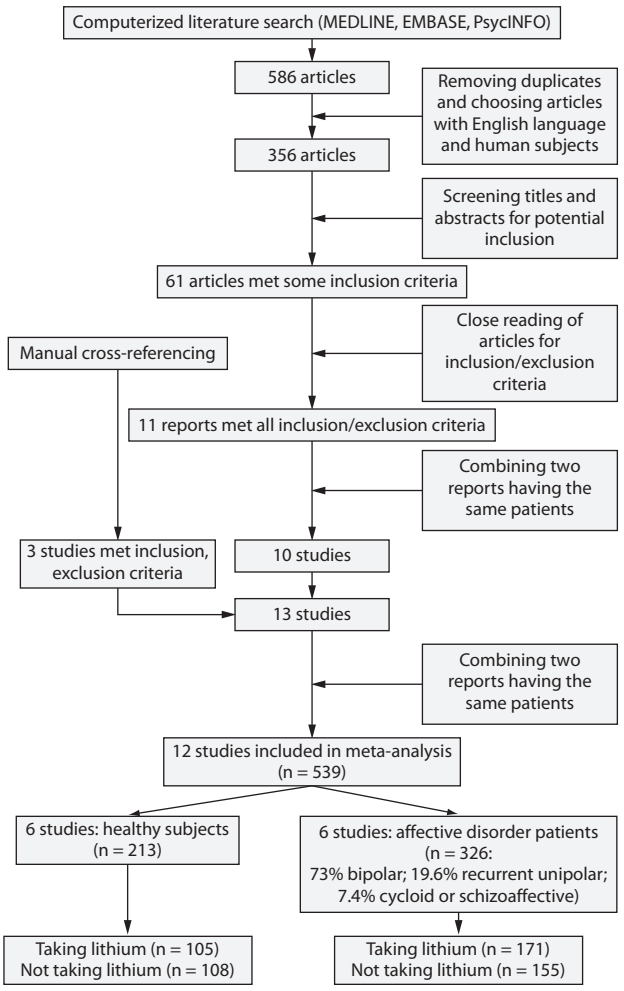
For inclusion in the meta-analysis, studies had to meet 6 criteria: (1) cognitive performance compared between subjects taking lithium and comparable subjects not taking lithium; comparability was assured by (2) patients with the same affective disorder diagnoses in euthymic or remitted status, or healthy volunteers; (3) groups of similar age and sex; (4) similar intelligence, education, or occupation; (5) similar distribution of other concurrent psychotropic drugs; and (6) cognitive abilities (outcomes) assessed with performance-based measures.

Exclusion criteria were (1) comorbid neurocognitive disorders; (2) substance abuse or dependence within 30 days; (3) lithium carbonate given < 1 week; (4) concurrent use of an anticonvulsant (to avoid potential confounding cognitive effects); (5) age < 17 years; (6) data not extractable from reported results; (7) non-English language reports; and (8) reviews, editorials, letters, case reports, or dissertations.

Extraction of Effect Size

Standardized mean-difference effect size (ES), corrected for small-sample bias (Hedges' *g*), was computed for cognitive tasks in each study, using the methods of Hedges and Olkin.[38] Standardized ES does not depend on the scaling of individual cognitive tests, allowing the combination of data from studies using different instruments to measure similar cognitive domains.[38] ES estimates were transformed so that positive values indicate poorer performance by lithium-treated subjects. Infrequently, when means and standard deviations were not provided, ES was estimated from reported values of *t*, *F*, or *z* tests, using the methods of Rosnow and Rosenthal.[39] For analysis, similar neurocognitive tests were grouped a priori based on the cognitive domains they aimed to assess. For each study, we selected only 1 neurocognitive test per domain for pooled analyses. If a study used more than 1 test per cognitive domain, we selected the most commonly employed among the included studies. In addition, to maximize the likelihood of meeting the methodological assumption that ES values from individual studies were independent of each other,[40] we used only 1 comparison/study when, rarely, cognitive performance was assessed at multiple times, selecting the longest lithium exposure or largest number of subjects tested. Two of the authors (A.P.W. and T.S.W.) carried out ES calculations independently to minimize errors, with consensus to resolve discrepancies. Mood-disordered patients and healthy control subjects were considered separately as well as in pooled analyses.

Figure 1. Flow Chart of Studies Considered and Finally Selected for Meta-Analysis, Based on Consolidated Standards of Reporting Trials[41] Recommendations



Statistical Analyses

Mean ES for each cognitive domain was calculated from unbiased standardized ES estimates across studies by weighted linear combination.[38] ES homogeneity across studies was tested for each cognitive domain using *Q* statistics.[38] Homogeneous ES values were then combined using a fixed-effects model; heterogeneous values were combined using a random-effects model, all with corresponding 95% CIs.[38] Apparent publication bias was assessed by inspection of funnel plots.[40]

RESULTS

Search Results

We initially identified 586 reports of potential interest; 356 in English involved human subjects and 178 contained duplicate information, leaving 61 studies that met some inclusion criteria, and only 11 that met all inclusion/exclusion criteria (Figure 1).[41] Of the 11 studies, Judd et al 1977[42] and Judd 1979[43] involved the same patients and are reported as the 1979 study only.[43] Hand checking yielded 3 other additional studies: Marini and Sheard 1977,[44] Shaw et al 1986,[45] and Calil et al 1990.[46] Shaw et al 1986 involved the same patients as their 1987 study[47] among the 11 identified by computer searching, and so were reported as from the 1987 study. This process yielded a total of 12 studies (from 14 reports) for meta-analysis, involving 539 subjects.[19,43,44,46–54]

Characteristics of Included Studies

Of the 12 included studies, 6 involved 213 healthy volunteers,[43,44,46,48,52,54] and 6 others involved 326 affective disorder patients,[19,47,49–51,53] yielding a total of 539 adults (Figure 1); 276 received lithium carbonate, and 263 did not. Among affective disorder patients, 238 of 326 (73.0%) were diagnosed with bipolar disorder, 64 of 326 (19.6%) with recurrent unipolar major depressive disorder, and 24 of 326 (7.4%) with cycloid or schizoaffective psychoses. Mean ± SD age was 37.4 ± 12.6 years; 61% were men. All included affective disorder patients were required to be euthymic or in clinical remission, usually supported by depression and mania rating-scale measures (Table 1). These patients received lithium carbonate for a mean ± SD duration of 3.9 ± 3.5 years at a mean serum lithium concentration of 0.82 mEq/L. Healthy volunteers were exposed to lithium for a mean ± SD duration of only 2.52 ± 1.05 (range, 1–4) weeks, at a mean serum level of 0.78 mEq/L. Overall, mean ± SD daily-trough lithium concentrations were 0.80 ± 0.12 (range, 0.50–1.20) mEq/L (Table 1).

Most studies (9 of 12) compared cognitive performance of individuals taking lithium to themselves when not taking lithium, assuring very similar age, sex, intelligence, education, and diagnosis between those compared (Table 1). In such studies, a mean ± SD duration of 2.78 ± 1.05 weeks of washout was allowed between sampling with/without lithium. Among healthy subjects, the sequence was off-to-on lithium; among affective disorder patients, on-to-off (Table 1). In 3 other studies, subjects receiving lithium were paired with others not given lithium but similar in age, sex distribution, intelligence, education or occupation, diagnosis, and current clinical status (Table 1). Study subjects received no other psychotropic medications in 9 of 12 studies (Table 1). In 2 studies[47,53] in which subjects taking lithium were compared to themselves when lithium-free, few were exposed to the same medicines with and without lithium, thus limiting potential confounding effects of other medications. In a third study,[51] an unstated proportion of subjects who acted as their own controls were given an antidepressant or antipsychotic when not given lithium. Most studies (8/12 = 66.7%) employed double-blinded designs, with placebo capsules replacing lithium (Table 1). Visual inspection of funnel plots (not shown) indicated approximately symmetrical distribution of measures of variance of ES around median ES, suggesting a low likelihood of publication bias.

Table 1. Study Design and Clinical Characteristics of Included Studies of Cognitive Effects of Lithium[a]

Study	Design	Other Rxs	Blinding	Clinical State	Mood Rating	Diagnosis (n)	Lithium Exposure, mo	Mean Serum Lithium Level, mEq/L	Lithium Status, n		Age, y	Men, %
									Taking	Not Taking		
Marini & Sheard,[44] 1977	Drug-free healthy subjects vs themselves after 3 wk taking lithium	None	Double	Nm vs Nm	NA	H (65)	0.75	0.81	31	34	19.4	100
Judd,[43] 1979	Drug-free healthy subjects vs themselves after 2 wk taking lithium	None	Double	Nm vs Nm	Scale	H (44)	0.5	0.90	22	22	24	100
Kropf & Müller-Oerlinghausen,[48] 1979	Drug-free healthy subjects vs comparable healthy subjects taking lithium × 2 wk	None	Double	Nm vs Nm	NA	H (24)	0.5	0.54 ± 0.15[b]	12	12	20–30	100
Reus et al,[49] 1979	Patients taking lithium vs comparable patients not taking lithium ≥ 3 wk	None	Single	E vs E	Self-report	BPD (24)	12–108	0.8–1.2	17	7	39.5	46
Christodoulou et al,[50] 1981	Patients taking lithium vs themselves after 2 wk not taking lithium	None	Single	Nm vs Nm	Scale	BPD (28) UD (2)	26.3 ± 20.3[b]	0.92 ± 0.15[b]	15	15	47 ± 12.9[b]	25
Smigan & Perris,[51] 1983	Patients taking lithium vs themselves after 1 mo not taking lithium	Yes[c]	NP	R vs R	Scale	BPD (40) UD (42) Other[d] (24)	4	0.62 ± 0.16[b]	53	53	42	43
Weingartner et al,[52] 1985	Drug-free healthy subjects vs themselves after taking lithium × 8 d	None	Double	Nm vs Nm	NA	H (20)	0.27	0.82 ± 0.17[b]	10	10	21–27	100
Shaw et al,[47] 1987	Patients taking lithium vs themselves after 2 wk not taking lithium	Some[e]	Single, Double	E vs E	Scale	BPD (42) UD (2)	113 ± 70[b]	0.80 ± 0.23[b]	22	22	51.2 ± 15.0[b]	55
Joffe et al,[19] 1988	Patients taking lithium vs comparable patients not taking lithium	None	NP	R vs R	NP	BPD (30)	≥ 1	0.70–0.90	18	12	36.2 ± 10.0[b]	47
Calil et al,[46] 1990	Drug-free healthy subjects vs themselves after 4 wk taking lithium	None	Double	Nm vs Nm	NA	H (34)	1	0.80 ± 0.10[b]	17	17	22.9 ± 2.5[b]	65
Kocsis et al,[53] 1993	Patients taking lithium vs themselves after 2wk not taking lithium	Some[f]	Double	R vs R	Scale	BPD (74) UD (18)	72 ± 68[b]	0.75 ± 0.32[b]	46	46	54 ± 16[b]	39
Stip et al,[54] 2000	Drug-free healthy subjects vs themselves after 3 wk taking lithium	None	Double	Nm vs Nm	NA	H (26)	0.75	0.80	13	13	33.1	50
Total/weighted mean	12 studies comparing cognition between subjects taking lithium vs themselves or comparable subjects not taking lithium	75% None	58% Double-blind	All Euthymic	Rating Scales	Total N = 539	Patients: 46.8 ± 42.7[b] Healthy: 0.63 ± 0.26[b]	0.80 ± 0.12[b]	276	263	37.4 ± 12.6[b]	61

[a]Subjects (N = 539): 44.2% bipolar I disorder, 11.9% unipolar major depression, 4.5% other disorders, 39.5% healthy volunteers.
[b]Mean ± SD.
[c]With lithium, some patients also received antidepressants (n = 11), antipsychotics (n = 7), or both (n = 2); without lithium, some patients also received antidepressants (n = 22), antipsychotics (n = 16), or both (n = 2).
[d]Other = cycloid or schizoaffective psychosis.
[e]Some subjects (n = 7) received other medications throughout study (4 thyroxin, 1 metoprolol, 1 nitroglycerin, 1 thiothixene), both while taking and not taking lithium.
[f]Some subjects (n = 12) received an antidepressant throughout study (fluoxetine, phenelzine, nortriptyline, or trazodone), both with and without lithium.
Abbreviations: BPD = bipolar disorder, E = euthymic, H = healthy volunteer, NA = not applicable, Nm = normothymic (lacking mood abnormality at the time of assessment), NP = not provided, NS = not statistically significant, as defined in Method, R = mood-disorder patients in remission when tested, Rx = psychotropic medication, UD = unipolar depression.

Table 2. Neurocognitive Tests and Corresponding Cognitive Domains

Tasks by Cognitive Domains[a]
Immediate verbal learning and memory
Buschke Selective Reminding Test
30 Word-Pair Test
Word List Recall
Auditory Verbal Learning Test
Delayed verbal memory
Auditory Verbal Learning, delayed recall test
30 Word-Pair, delayed recall test
Immediate visual memory
Benton Visual Retention Test
30-Figure Test
Delayed visual memory
Benton Visual Retention Test, delayed recall
30-Figure Test, delayed recall version
Attention
Digit Span (forward)
Cancellation Test
Processing speed
Digit Symbol Substitution Test
Executive function
Trail-Making Test B (completion time)
Digit Span (backward)
Creativity (aka associative productivity)
Associational Fluency
Verbal Association
Psychomotor performance
Finger Tapping Test
Minnesota Rate of Manipulation Test

[a]These tests were used in the 12 included studies.

Effects of Lithium on Cognitive Performance

Nine cognitive domains—immediate verbal learning and memory, delayed verbal memory, immediate visual memory, delayed visual memory, attention, processing speed, executive function, creativity, and psychomotor performance—were assessed in the 12 analyzed studies (Table 2). We calculated unbiased, standardized measures of ES (Hedges' *g*) for different cognitive domains in each study (Table 3). Weighted mean ES for each cognitive domain, its CI, the associated *P* value, and a statistical test of ES homogeneity (*Q* test) are reported (Table 4).

The results summarized (Tables 3 and 4; Figure 2) indicate that subjects taking lithium had a small but statistically significant impairment in immediate verbal learning and memory (ES = 0.24; 95% CI, 0.05–0.43) and creativity (ES = 0.33; 95% CI, 0.02–0.64) compared to similar subjects not taking it. Otherwise, there were no significant overall differences with respect to delayed verbal memory (ES = 0.17; 95% CI, −0.18 to +0.52), immediate visual memory (ES = 0.45; 95% CI, −0.82 to +1.71), delayed visual memory (ES = 0.41; 95% CI, −0.79 to +1.60), attention (ES = −0.05; 95% CI, −0.34 to +0.23), processing speed (ES = 0.16; 95% CI, −0.44 to +0.75), executive function (ES = 0.07; 95% CI, −0.23 to +0.38), or psychomotor performance (ES = 0.35; 95% CI, −0.43 to +1.13) between subjects taking and not taking lithium.

Cognitive effects of lithium among affective disorder patients with far more prolonged exposures to lithium were also considered when there were ≥ 2 studies per cognitive domain (Table 4). In addition to immediate verbal learning and memory and creativity, long-term lithium treatment (weighted mean ± SD = 46.8 ± 42.7 months) was also associated with substantial impairment in psychomotor performance (ES = 0.62; 95% CI, 0.27–0.97). Otherwise, no other cognitive impairments or benefits were found in association with lithium treatment among affective disorder subjects. Among healthy volunteers, short-term exposures to lithium (weighted mean ± SD = 2.5 ± 1.0 weeks) did not yield significant effects on immediate verbal learning and memory (ES = 0.09; 95% CI, −0.30 to 0.47), attention (ES = −0.17; 95% CI, −0.52 to 0.17), processing speed (ES = 0.13; 95% CI, −0.65 to 0.90), or executive function (ES = 0.03; 95% CI, −0.34 to 0.41; Table 4). Meta-regression analysis was not considered due to the small number of available studies and incomplete information concerning predictor variables.

DISCUSSION

This meta-analysis of 12 studies met stringent inclusion/exclusion criteria and compared results of cognitive testing in adult subjects taking lithium versus the same or similar subjects not receiving lithium. Among all 539 subjects, small impairments were detected in immediate verbal learning and memory and creativity among persons taking lithium. No other significant differences were found in delayed verbal memory, visual memory, attention, executive functioning, processing speed, and psychomotor performance. Healthy subjects gave no indication of altered cognition with short-term exposure (2.5 weeks) to lithium, and long-term exposure (47 months) in affective-disorder patients was associated with only minor adverse effects on immediate verbal learning and memory and creativity and a moderate negative effect on psychomotor performance (Table 4). Neither short- nor long-term lithium treatment was associated with altered delayed verbal memory, visual memory, attention, executive functioning, or processing speed. The adverse cognitive effects of lithium in affective disorder patients appeared to be strongly associated with long-term exposure to the mood stabilizer. It may be that duration of lithium exposure, rather than tissue concentrations of the cation, contributes to emergence of adverse cognitive effects; however, data were not sufficient to test for dose effects.

The analyzed studies appear to be of high quality: (1) most were double-blinded; (2) most compared lithium-treated subjects to themselves without such treatment; (3) the few studies (25%) involving separate comparison subjects were similar in diagnosis, mood state, age, sex distribution, and tested intelligence, education, or occupation; (4) outcomes as cognitive abilities were assessed by performance-based neurocognitive tests, not subjective self-reports or rating scales; (5) both positive and negative cognitive effects of lithium treatment (usually minor) were

Table 3. Standardized Effect Sizes for Cognitive Domains

Study	Cognitive Domains	Effect Size[a]	Subjects, n	
			Taking Lithium	Not Taking Lithium
Healthy Volunteers				
Marini & Sheard,[44] 1977	Attention	−0.47	31	34
	Executive function	−0.16		
	Processing speed	−0.56		
	Psychomotor performance	−0.40		
Judd,[43] 1979	Processing speed	0.60	22	22
	Executive function	0.34	14	14
	Creativity	0.26		
Kropf & Müller-Oerlinghausen,[48] 1979	Immediate verbal learning and memory	0.59	12	12
	Delayed verbal memory	−0.33		
Weingartner et al,[52] 1985	Immediate verbal learning and memory	−0.19	10	10
Calil et al,[46] 1990	Immediate verbal learning and memory	0	17	17
	Processing speed	0.42		
	Attention	0.22		
Stip et al,[54] 2000	Immediate verbal learning and memory	0	13	13
	Attention	0.09		
Affective Disorder Patients				
Reus et al,[49] 1979	Immediate verbal learning and memory	1.15	17	7
Christodoulou et al,[50] 1981	Immediate verbal learning and memory	0.35	15	15
	Immediate visual memory	1.14		
	Delayed visual memory	1.07		
	Attention	−0.03		
	Executive function	0.35		
Smigan & Perris,[51] 1983	Immediate verbal learning and memory	0.14	53	53
	Delayed verbal memory	0.29		
	Immediate visual memory	−0.15		
	Delayed visual memory	−0.16		
Shaw et al,[47] 1987	Immediate verbal learning and memory	0.50	22	22
	Psychomotor performance	1.10		
	Creativity	0.51		
Joffe et al,[19] 1988	Immediate verbal learning and memory	0.00	18	12
	Attention	0.50		
	Processing speed	0.30		
	Executive function	−0.06		
Kocsis et al,[53] 1993	Immediate verbal learning and memory	0.28	46	46
	Psychomotor performance	0.41		
	Creativity	0.26		

[a]Effect sizes are unbiased standardized estimates (Hedges' *g*). Positive effect size indicates *poorer* performance in lithium-treated subjects; N = number of subjects.

found across studies, along with symmetrical funnel plots, indicating a low risk of publication bias. In most cognitive domains, *Q* statistics indicated that ES estimates were homogenous, except for visual memory, processing speed, and psychomotor performance. Heterogeneity may reflect numbers of available studies sometimes as small as 2 or 3, making between-study differences more prominent.

Limitations

The relatively small number of qualified studies is a limitation of this meta-analysis, which reflects the challenge of conducting studies on cognitive effects of medicines in patients with recurrent mood episodes, who often require multiple psychotropic agents for clinical stabilization. Bipolar disorder patients, in particular, often receive combinations of antidepressants, anticonvulsants or lithium, antipsychotics, and sedative-anxiolytic agents.[11,12] Adverse cognitive effects can be exerted by some of these agents, including valproate,[13] tricyclic antidepressants,[55,56] and benzodiazepines.[57] It follows that cognitive complaints of such patients may reflect effects of depressive symptoms,[5,6] abuse of alcohol or drugs,[58] effects of lithium or other medications, hypothyroidism, effects of bipolar disorder illness states,[59,60] or a combination of these factors.

Despite the relative high quality and sound designs of the studies considered, several potential confounding factors also warrant consideration: (1) in 3 of 12 studies in which subjects were not their own controls,[19,48,49] despite matching the compared groups by age and years of education or intelligence, cognitive differences may still exist; (2) there may have been subtle symptomatic differences among mood-disorder patients, despite nominal euthymia; (3) in 2 studies in which affective disorder patients given lithium were compared with similar patients not given lithium,[19,49] there may have been unspecified differences in illness parameters.

Illness factors that might influence cognitive performance, including age at onset, illness duration, episode count, and history of psychosis, have yielded inconsistent support from previous studies.[61] For example, more manic recurrences were associated with poorer verbal memory

Table 4. Mean Weighted Effect Size by Cognitive Domain

Cognitive Domain	Studies, no.	Subjects, n		Effect Size[a] (95% CI)	*P* Value	Q
		Taking Lithium	Not Taking Lithium			
Analysis for All Subjects						
Immediate verbal learning and memory	10	223	207	0.24 (0.05 to 0.43)	.01	7.72
Delayed verbal memory	2	65	65	0.17 (–0.18 to 0.52)	.34	1.98
Immediate visual memory	2	68	68	0.45 (–0.82 to 1.71)	.49	8.83*
Delayed visual memory	2	68	68	0.41 (–0.79 to 1.60)	.50	7.95*
Attention	5	94	91	–0.05 (–0.34 to 0.23)	.71	5.76
Processing speed	4	88	85	0.16 (–0.44 to 0.75)	.61	11.11*
Executive function	4	86	83	0.07 (–0.23 to 0.38)	.64	2.33
Creativity	3	82	82	0.33 (0.02 to 0.64)	.04	0.47
Psychomotor performance	3	99	102	0.35 (–0.43 to 1.13)	.38	14.21*
Subgroup Analysis for Healthy Subjects						
Immediate verbal learning and memory	4	52	52	0.09 (–0.30 to 0.47)	.65	1.90
Attention	3	61	64	–0.17 (–0.52 to 0.17)	.32	3.24
Processing speed	3	70	73	0.13 (–0.65 to 0.90)	.75	10.55*
Executive function	2	53	56	0.03 (–0.34 to 0.41)	.87	1.62
Subgroup Analysis for Affective Disorder Subjects[b]						
Immediate verbal learning and memory	6	171	155	0.29 (0.07 to 0.51)	.01	5.00
Attention	2	33	27	0.22 (–0.30 to 0.73)	.41	1.00
Executive function	2	33	27	0.15 (–0.37 to 0.66)	.58	0.59
Creativity	2	68	68	0.34 (0.00 to 0.68)	.05	0.44
Psychomotor performance	2	68	68	0.62 (0.27 to 0.97)	.0005	3.13

[a]Hedges' *g*.
[b]Subgroup analysis of affective disorder subjects was made with ≥ 2 studies per cognitive domain.
*Effect sizes not homogeneous, based on homogeneity statistic (Q).

and executive functions in 7 of 10 studies; more depressive episodes were associated with deficiencies in executive functioning, verbal learning and memory, and visual memory in 6 of 10 reports; however, in only 1 of 4 studies was total episode count associated with any significantly impaired cognition. Younger age at onset of bipolar disorder was a risk factor for cognitive impairment in only 1 of 6 studies, whereas more total years of illness predicted reduced cognitive performance in 5 of 11 studies. Previous psychosis was associated with impaired executive functioning and verbal memory in 3 of 4 studies of bipolar disorder patients.[62–65] Acute bipolar illness, including manic, mixed, and depressive episodes, can adversely affect cognitive functions.[5,6]

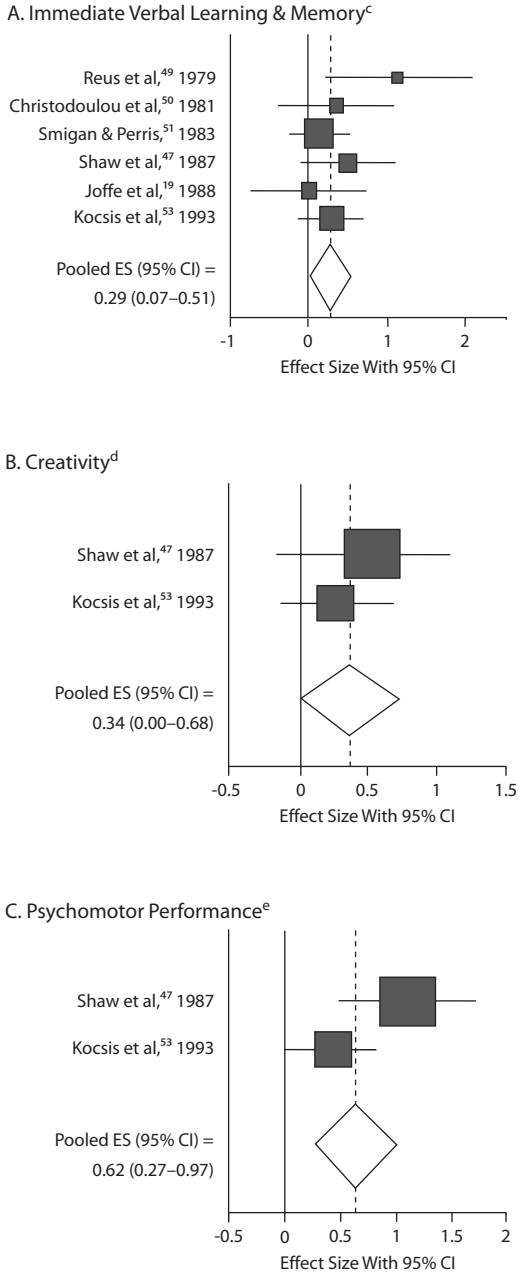
Concurrent treatments did not appear to be an important confounding factor in the present analyses, as they were absent in 9 of 12 studies, and 2 other studies compared subjects to themselves, of whom only a few (32% and 26%) received the same adjunctive psychotropic medicines with and without lithium.[47,53] In 1 other study using a within-subject design,[51] only a minority (38%) of mood-disordered patients had an antidepressant or antipsychotic added after discontinuing lithium. None of these 3 studies involved anticholinergic-antiparkinsonism agents or benzodiazepines.

Long-Term Cognitive Effects of Lithium

We found only 2 longitudinal, repeat-assessment studies of cognitive effects of long-term lithium treatment.[51,66] Tests of visual and verbal memory of 53 euthymic, mood disorder patients in one study found little difference just before starting lithium treatment versus at 4 and 12 months of continuous exposure at mean serum concentrations of ≥ 0.60 mEq/L and even slight improvement in some measures of visual memory during treatment.[51] In the other study, 18 bipolar disorder patients showed stable cognition at several points over 6 years of continuous lithium treatment.[66] In both studies, mood symptoms and use of psychotropic medicines other than lithium remained similar over time. Though limited, these observations suggest that cognitive performance of affective disorder patients taking lithium was stable over several years.

Some evidence suggests that lithium may exert neuroprotective effects on the central nervous system. For example, a case-control study of 114 euthymic elderly bipolar disorder patients found that long-term lithium treatment reduced the risk of dementia from 33% to 5%.[34] Similarly, a large Danish cohort study found that long-term lithium treatment was associated with a risk of dementia not greater than that in the general population,[37] even though bipolar disorder patients may have increased risk of dementia.[34,67] Additionally, imaging studies suggest that lithium treatment in bipolar disorder patients is associated with increased cerebral gray-matter volume[35] and elevated cortical concentrations of *N*-acetyl-l -aspartate, a putative marker of neuronal viability.[33,36] In genetically modified mice, doses of lithium considered clinically therapeutic in humans reduced cerebral concentrations of beta-amyloid and levels of tau-protein phosphorylation, likely through inhibition of glycogen synthase kinase-3.[31,68] Together, accumulation of beta-amyloid and tau-protein phosphorylation are believed to represent key steps in the pathogenesis of Alzheimer's

Figure 2. Forest Plots of Meta-Analyses for Selected Cognitive Measures With Versus Without Long-Term Lithium Treatment in Affective-Disorder Subjects Only and Involving ≥2 Comparisons[a,b]



[a]A positive value (falling to the right of the null value of zero) indicates a decrease in cognition with lithium, which was found and was statistically significant with all testing shown.
[b]Gray squares (size reflects weighting by subject count) are ESs with 95% CIs for each with/without lithium comparison; widths of white diamonds are 95% CIs; vertical broken lines are pooled ESs. Vertical solid line is the null ES value of zero.
[c]N = 326.
[d]N = 136.
[e]N = 136.

disease, and tau-protein phosphorylation has been implicated in other neurodegenerative diseases.[69] Based on these and other preliminary findings, potential for exerting beneficial effects on neurodegenerative diseases has led to clinical trials of lithium in Alzheimer's disease,[70] progressive supranuclear palsy,[71] corticobasal degeneration,[71] amyotropic lateral sclerosis,[72,73] and Huntington's disease.[74]

CONCLUSIONS

Cognitive impairment is a significant aspect of all phases of bipolar disorder, including acute illness and euthymia. The present findings suggest that lithium carbonate, a widely used treatment for bipolar disorder and other recurrent mood disorders, had only mild negative effects on immediate verbal learning and memory and creativity and an expected, moderate adverse effect on psychomotor performance in euthymic bipolar disorder patients. Lithium treatment did not appear to adversely impact performance in tests of visual memory, attention, executive function, or mental processing speed in patients treated with lithium long-term or in healthy subjects exposed to similar serum concentrations of lithium but only briefly. Studies are needed to evaluate cognitive effects of other mood stabilizers and their interactions with aspects of bipolar disorder itself, including illness duration, episode counts, and effects of particular acutely abnormal mood states as well as clinical euthymia. Potential neuroprotective effects of lithium may seem at odds with the mild adverse effects it has on selected cognitive domains. A likely explanation is that lithium acts on multiple cerebral sites and molecular targets, with various negative and positive effects.[75] Additional studies are required to address the apparent paradox of mild cognitive effects of lithium and growing evidence of its possible central neuroprotective actions.

Drug names: carbamazepine (Carbatrol, Equetro, and others), lamotrigine (Lamictal and others), lithium (Lithobid, Eskalith, and others).
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