

Lithium induced cognitive side-effects in bipolar disorder: a qualitative analysis and implications for daily practice

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Qualitative analysis of the literature on cognitive side-effects of lithium in patients with a bipolar disorder identified four of 17 studies that fulfilled criteria of adequate methodological quality. Analysis of these four studies showed that lithium had a negative effect on memory and speed of information processing, often without subjective complaints or awareness of mental slowness. The consequences of these findings for daily practice are discussed, in particular with respect to driving performance. When neurocognitive complaints or deficits are present, lithium plasma level, thyroid functions and degree of mood disturbance should be assessed. In cases where all these parameters are within normal limits and neurocognitive complaints still persist, dose reduction of lithium, thyroid hormone addition, prescription of a slow release preparation or replacement of lithium by another moodstabiliser should be considered. Guidelines are suggested with respect to further neuropsychological screening. *Int Clin Psychopharmacol* 14:167–171 © 1999 Lippincott Williams & Wilkins

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INTRODUCTION

One of the most often mentioned reasons for non-compliance to lithium treatment are memory complaints (Goodwin and Jamison, 1990). These symptoms are often dismissed as being secondary to affective illness or ageing, rather than as being induced by lithium (Goodwin and Jamison, 1990). Data on lithium related cognitive complaints and deficits are scarce and contradictory. This may be due to the variety of patient populations and applied neurocognitive tests. Furthermore, most studies are poorly designed and often open or retrospective studies. If present, cognitive side-effects related to lithium are subtle and manifest as memory disturbances and diminished speed of information processing (Müller-Oerlinghausen *et al.*, 1977). This qualitative literature analysis addresses the question of whether lithium gives rise to cognitive side-effects and affects the

ability to drive a car. A further meta-analysis with additional statistical evaluation of the pooled data was not possible because of the wide variety of populations, designs and applied methodology. Finally, recommendations are given with respect to the assessment and management of possible cognitive side-effects.

METHODS

The Key words: 'cognition', 'bipolar disorder' and 'lithium' were used to search 'Medline' and 'Psych lit' for articles on cognitive side-effects of lithium in clinical populations from 1977 onwards. A quantitative scoring system (de Vet *et al.*, 1997) was used to score specific aspects of the articles. This scoring system was an adapted version from an earlier published meta-analysis (Menting *et al.*, 1996). The following topics

were scored: number of individuals included, homogeneity of the research population, use of a standardized diagnostic system, research design (prospective or retrospective), use of a placebo-controlled design, duration of lithium therapy, specificity of tests and tasks, and methods used to control for variables that could bias outcome (e.g. mood, co-medication and co-morbidity). The maximum score for each item was 10; the maximum total score was 100. Only those articles with a 'cut-off' score higher than 70 were regarded as of sufficient methodological quality and included in further analyses (see also Table 1).

RESULTS

The results of the literature study are summarized in Table 2. Seventeen articles on cognitive side-effects of lithium were identified, five of which reported no evidence of negative effects of lithium. The other 12 articles reported a negative effect of lithium particularly on memory and speed of information processing.

The design of the studies showed considerable variation and there were no longitudinal or prospective studies. Only four of the 17 articles met the criteria for methodological quality (see Table 1) and were used in the analysis. All of these four studies were (placebo)controlled and/or double blinded. Three articles studied the effect of lithium on memory and motor performance (articles 6, 13, 16 in Table 2); one study focussed on a steering task (article 15 in Table 2). All studies showed a statistically significant negative effect of lithium on memory, vigilance, reaction time and tracking.

The study of Kocsis *et al.* (1993) was one of the best controlled studies (double-blind and placebo-controlled). They found that discontinuation of lithium treatment for 2 weeks in 46 patients with bipolar affective disorder led to a significant improvement of memory, as assessed with memory tasks.

Hatcher *et al.* (1990), for example, found reaction time in a driving simulation task to be increased in 16 lithium-treated patients compared with that of a group of 22 healthy volunteers. Several authors described sedative effects of lithium, although their patients did not complain of mental slowness. This may lead to an increased risk of road accidents (Jauhar *et al.*, 1993).

DISCUSSION

Lithium has a negative effect on memory, as concluded from a relative small number of well designed and controlled studies that showed an improvement of memory functions after temporary discontinuation of

Table 1. Qualitative scoring system

		Points	
1	Number of individuals	$n > 20$	10
		$n \leq 20$	5
2	Selection of population	Homogeneous (with reference to age, education and diagnosis)	10
		Heterogeneous	5
3	Diagnosis	Standardized	10
		Non-standardized	5
4	Data selection	Prospective	10
		Retrospective	5
5	Research design	Double-blind – placebo	10
		Control group	5
6	Duration of trial	> 2 weeks	10
		≤ 2 weeks	5
7	Lithium level	> 0.6 mmol/l	10
		≤ 0.6 mmol/l	5
8	Mood	Depression and mania	10
		Depression or mania	5
9	Neurocognitive tasks	Specific (15 word task, steering task, etc.)	10
		Battery (e.g. WAIS)	5
10	Confounding variables	Co-medication and co-morbidity (drug treatment and thyroid function)	10
		Co-medication or co-morbidity	5

Score = 0, in cases not mentioned and/or not controlled for. Maximum score = 100 points. 'Cut-off'-score > 70 points.

lithium. Inconsistent findings concerning memory effects seem to be related to differences in methodology and research design (see also Ghadirian *et al.*, 1983).

Lithium slows information processing, which may have a detrimental effect on driving ability. The observation that lithium has no subjective sedative effects, but at the same time slows information processing,

Table 2. Summary of research data from literature

Author	n	Duration lithium	Lithium level	Diagnosis	Research design	Methodology tests	Results	Total score
1 Kusumo and Vaughan (1977)	13	-	0.6-1.2	MD	Control group	STM LTM Vigilance	Recall STM ↓	No
2 Friedman <i>et al.</i> (1977)	13	3 years (x)	0.4-1.0	MD	Retrospective Open study	Halstead Reitan battery WMS	'Cortical dysfunction' Vigilance ↓	40 60
3 Müller-Oerlinghausen <i>et al.</i> (1977)	18	1.3 years	0.6-1.4	MD	Retrospective Open study	RT EEG WMS tapping	No effect	60
4 Telford and Worral (1978)	7	2.8 years (x)	0.83	MD	'Single-blind' repeated: measures following stop lithium	WALS 20-WT	Retrieval LTM ↓ Slowness ↑	65 70
5 Reus <i>et al.</i> (1979)	24	1-9 years	0.8-1.2	MD	MD patients with and without lithium	Trailmaking memory tasks	No effect	35
6 Squire <i>et al.</i> (1980)	16	2 weeks	0.94	Alcoholic MD Schizo-affective MD	Double-blind cross-over	20-WT	Memory effects ↑ RT ↑	65 60
7 Marusz <i>et al.</i> (1981)	13	2 years	-	MD	MD patients with and without lithium	WMS Benton RT	No effect	35
8 Christodoulou <i>et al.</i> (1981)	15	2 years	0.92	MD	Stop lithium, repeated measures			
9 Elsass <i>et al.</i> (1981)	22	4.5 years	-	MD	MD patients with and without lithium control individuals 'Double-blind'			
10 Lund <i>et al.</i> (1982)	50	8 years	-	MD		'Story Recall' Stroop 'Digit Span'	No effect	35
11 Ghadinian <i>et al.</i> (1983)	30	10 months	0.6-1.2	MD	Open study > 10 months ≤ 10 months lithium	WMS Benton	No effect	70
12 Kropf and Müller- Oerlinghausen (1985)	14	-	-	MD	Dose reduction lithium (20%) retesting	Tachistoscope 'backward marking'	Visual perception ↑	45
13 Shaw <i>et al.</i> (1987)	22	9 years	0.4-1.2	MD	Double-blind/placebo (2 weeks stop lithium)	Tapping 20-WT	Motor speed ↑ 'retrieval' LTM ↑	90
14 Engelsmann <i>et al.</i> (1988)	18	9 years	0.61	MD	Retesting after 6 years lithium	WMS Benton	No effect	50
15 Hatcher <i>et al.</i> (1990)	16	> 3 months	0.61	MD	Healthy control individuals	Steering task	RT ↑	75
16 Kocsis <i>et al.</i> (1993)	46	6 years	0.5-1.5	MD; depression	Double-blind stop lithium	Tapping 16-WT	Memory motor speed RT ↑	90 65
17 Jauhar <i>et al.</i> (1993)	20	-	0.84	MD	Healthy control individuals	Steering task RT 14-WT	No effect on memory	

STM, short-term memory; LTM, long-term memory; RT, reaction time; 20-WT, 20-words task; MD, manic depressive illness.

suggests that the use of lithium may be associated with an increased risk of road accidents. Longitudinal, prospective research with respect to the effects of lithium on cognitive functions is clearly needed.

Recommendations

Separate from normal routine laboratory testing, the serum lithium concentration should be measured in patients with bipolar disorder treated with lithium who present themselves with memory problems and mental slowness (or whose partner or relatives report a diminished cognitive functioning) in order to rule out the possibility of lithium intoxication. Thyroid (hypo)function and mood disturbance, especially depressive symptoms, should also be evaluated. If cognitive complaints persist after correction of hypothyroidism or depressive symptoms, further investigation of cognitive functioning by a neuropsychologist may be indicated. It is difficult to indicate when a patient should be referred, because subjective cognitive complaints are not directly correlated with objective cognitive deficits. This referral is highly dependent on the clinical judgement of the therapist. It may be useful to ask the patient to complete a questionnaire focussed on limitations in daily functioning imposed by the subjective cognitive complaints or to get confirmation of cognitive dysfunctioning from a partner or another person who is in daily contact with the patient. A more than average severity of number of complaints on the Cognitive Failure Questionnaire (CFQ) is an indication for referral. The CFQ is a 25-item self-report questionnaire measuring failures in perception, memory, attention and motor functioning (e.g. inability to remember a name, inability to remember items one wants to buy in a shop, failure to notice a signpost in the street). Normative data are available for people aged 25–80 years (Ponds, 1990). More general and routine cognitive screening instruments, such as the Mini-Mental State Examination (Joffe *et al.*, 1988), are inappropriate because lithium causes subtle cognitive changes. Driving ability could be 'assessed' by asking patients to take a test-lesson at a recognized driving school.

Specialized cognitive screening should focus primarily on memory, speed of simple and complex information processing and attention and other tasks that are relevant for driving ability. Examples of tests that could be used are the Trial Making Test (attention and conceptual shifting), the Symbol Digit Modalities Test (speed of complex information processing), or the California Verbal Learning Test (encoding and retrieval of verbal information). An extensive description of these tests and other related tests and tasks are

described by Lezak (1995).

If subjective complaints are not substantiated, the patient should be reassured, which may enhance medication compliance. If, however, cognitive complaints are substantiated, the following options should be considered: (1) The dose of lithium could be reduced (Squire *et al.*, 1980 and Kocsis *et al.*, 1993) because cognitive functioning improves when serum lithium concentrations are lowered. (2) A slow-release formulation (Litarex) could be used so that serum lithium concentrations are more constant, without peaks. (3) Addition of thyroidhormone (T_3 , liothyronine) even in the absence of subclinical thyrotoxicity is reported to enhance cognitive functioning (Tremont and Stern, 1997) in a dosage of 25–50 μg per day. (4) Lithium could be replaced by valproic acid or carbamazepine. However, research data on the cognitive side-effects of these drugs in patients with epilepsy are inconsistent (Vermeulen and Aldenkamp, 1995; Cochrane *et al.*, 1998). In a case series of seven bipolar patients with lithium associated cognitive and functional deficits, Stoll *et al.* (1996) described an improvement in cognitive functioning after switching to valproate.

In all cases, patients should be given psycho-education about cognitive deficits in an attempt to make them aware of implications of these deficits for their ability to drive, thereby decreasing the risk of road accidents.

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