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A Review of Clinical Trials of Lithium in Neurology

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YUNG, C Y *A review of clinical trials of lithium in neurology* PHARMACOL BIOCHEM BEHAV **21**: Suppl. 1, 57–64, 1984 —Lithium has been put to clinical trials in no less than fifteen neurological disorders. They are Huntington's chorea, tardive dyskinesia, spasmodic torticollis, Tourette's syndrome, L-dopa induced hyperkinesia and the "on-off" phenomenon in parkinsonism, organic brain disorders secondary to brain-injury, drug induced delusional disorders, migraine and cluster headache, periodic hypersomnolence, epilepsy, meniere's disease and periodic hypokalemic paralysis This paper gives a brief summary of the clinical trials with lithium salts reported in the literature There are encouraging results on the use of lithium in cluster headaches, cyclic form of migraine and hypomanic mood disorders due to organic brain disorders The trials with lithium and amitriptyline in tardive dyskinesia needs independent confirmation The effect of lithium on seizure disorders needs to be addressed too

Cluster headache Lithium Movement disorders Parkinsonism Tardive dyskinesia

SINCE the introduction of lithium (Li) in treatment of manic episodes of bipolar affective disorders by Cade in 1949, [7] there have been numerous clinical trials of Li in various psychiatric, medical and neurological disorders [75, 78, 84]. The rationale of these trials is primarily based on the clinical observations and findings of the multiple side effects in various organ systems during Li therapy [44,85]. Clinicians make use of these side effects to counteract or to reverse the pathophysiological processes in some of the medical disorders. These side effects then, become a desired effect. Furthermore, Li is postulated to have effects on the central nervous system and on the receptors involving the dopaminergic and serotonergic systems [65]. This leads to the use of Li on those neurological disorders whose conditions are presumed to be dysfunctions of the dopaminergic and serotonergic systems This paper is a concise summary of case reports and studies from the literature on clinical trials of Li in neurological disorders.

LITHIUM TRIALS IN DISORDERS OF ABNORMAL MOVEMENTS

Lithium therapy has been shown to induce abnormal movement disorders involving the extrapyramidal system; such as tremor, cogwheel rigidity, parkinsonism, pseudoparkinsonism and choreoathetosis [90]. These observations led to the postulation that Li may be affecting the release, uptake and turnover rate of brain amine metabolism. It may even decrease receptor sensitivity or stabilize the dopaminergic receptors [65]. Thus, Li has been used in a group of movement disorders as: (a) Huntington's Chorea, [HC] (b) tardive dyskinesia, [TD] (c) spasmodic torticollis, [ST] (d) Tourette's syndrome, (e) L-dopa induced hyperkinesia and (f) "on-off" phenomenon during the course of treatment of Parkinsonism.

Huntington's Chorea

The biochemical basis of HC is unknown. There are postulations that there is hypersensitivity of dopaminergic receptor in the striatum; or involvement of the serotonergic and GABA systems.

The earlier case reports with a total of 12 patients were encouraging (Table 1). However, a subsequent four double-blind cross over studies with a total of 27 patients showed that Li has no effect on abnormal movements [2, 8, 16, 49] This discrepancy may be due to a number of factors, namely, the group of patients improved on Li, who were also found to be receiving haloperidol concommitantly (n=4) both in the case report samples and in some of the designed group On the other hand, the designed groups were given tetrabenazine concommitantly (n=7). There may be drug interactions differentiating between Li and haloperidol vs. Li and tetrabenazine which is a dopamine depleting drug. Lithium and baclofen (n=2) also gave negative results [3] Another study on 6 patients on a double-blind study showed no improvement in abnormal movement, but did show improvement in irritability and angry outbursts, if these two were present at the baseline [40]. It also showed that Li and haloperidol combined is more effective than either alone

Table 1 summarizes the reports on HC and Li therapy. The results are contradictory, i e., non-blind case studies show improvement and double-blind studies indicate mostly lack of therapeutic response

Tardive Dyskinesia

In animal studies, Li is found to attenuate or prevent some of haloperidol-induced biochemical, behavioral and neurophysiological effects. Tardive dyskinesia is hypothesized to be a result of dopaminergic receptor supersensitiv-

TABLE 1
LITHIUM TRIALS IN HUNTINGTON'S CHOREA

Treatment Outcome	Author	Year	Reference No	(n)	Method	Remarks
Improvement	Dalen	1973	[16]	(6)	CR	One of the 4 improved patients received haloperidol with Li_2CO_3
	Manyam and Bravo-Fernandez	1973	[46]	(1)	CR	Li and haloperidol
	Mattsson	1973	[49]	(4)	CR	Marked improvement in 3 cases
	Schenk and Keignse-Yhema	1974	[77]	(1)	CR	Li and haloperidol
Non-improvement	Aminofff and Marshall	1974	[2]	(9)	DB	4 cases were given Li and tetrabenazine 2 cases were given Li and thiopropazate
	Anden *et al*	1974	[3]	(3)	CR	2 cases' hyperkinesis were worse when Li was given concurrently with baclofen
	Carman	1974	[8]	(6)	DB and CO	Worsening of motor and cognitive performance
	Leonard *et al*	1974	[40]	(6)	DB	Patients became worse, Li and haloperidol together were effective to control anger and irritability
	Vestergaad *et al*	1977	[87]	(6)	DB and CO	3 cases were given Li and tetrabenazine 1 case was given Li and perphenazine

Case Reports (CR), double-blind (DB), cross-over design (CO), placebo-controlled (PC) studies for the number (n) of patients given between parenthesis

ity from long term receptor blockade by neuroleptics. As Li is reported to interfere with the presynaptic release of monoamines and to facilitate catecholamine reuptake, it is used in TD to counteract the dopaminergic supersensitivity Table 2 summarizes the reports related to the use of Li salts in TD [15, 26, 34, 45, 66, 67, 68, 74, 80, 81]. The improvement of TD seems to be due to a combination of Li with another drug, i e , one group received Li and haloperidol and the other received Li and amitriptyline [15, 31, 73, 74] The former study showed improvement could be due to haloperidol's suppressing effect and the latter is based on an underlying depressed affective component in TD Thus, clinical trials on 2 groups of patients appear to support the effectiveness of Li and amitriptyline combinations [71, 73, 74] This requires the initiation of a double-blind cross-over placebo-controlled studies confirmation Another hypothesis by Pert *et al* [65] is that Li co-administration with haloperidol blocked the hypersensitivity of striatal dopamine receptors, whereas Li alone had no effect on dopamine receptor sensitivity There are a few studies suggesting Li's augmentation of tricyclic antidepressant effect It should be mentioned that there was one case report of Li induced aggravation of TD [15] and another case of Li reinduced TD which had been quiescent for several years [4]

Spasmodic Torticollis

Lithium therapy for ST has essentially been negative [14, 24, 42] as shown in Table 3

Tourette's Syndrome

Lithium was used in 3 patients with good responses [56] However, long-term follow-up reports and additional clinical trials are necessary to establish its efficacy

L-Dopa Induced Hyperkinesia

Lithium's effect on the dopaminergic system is evidenced by the reduction of akinesia and increased dyskinesia in patients after Li therapy The speculation that Li may stabilize striatal dopamine receptor and may therefore prevent L-dopa desensitization The effect of Li on L-dopa induced hyperkinesia is still very meager Dalen and Steg [17] reported two patients had decreased hyperkinetic involuntary movement and Van Woert and Ambani [86] had only 2 out of 4 patients showing slight reduction. McCaul and associates [50,51] reported negative results on 16 patients with parkinsonian symptoms, except some relief in muscle spasms and cramps were noted. For the past ten years, there have been no reports on this subject

TABLE 2

LITHIUM TRIALS IN TARDIVE DYSKINESIA

Treatment Outcome	Author	Year	Reference No	(n)	Method	Remarks
Improvement	Dalen	1973	[16]	(1)	CR	Li + Haloperidol
	Ehrensing	1974	[18]	(1)	CR	Li + melanocyte-stimulating-hormone releasing-inhibiting hormone
	Gerlach *et al*	1975	[26]	(15)	DB and PC	Haloperidol is better than Li 4 cases improved markedly
	Prange *et al*	1973	[66]	(2)	DB and CO	Li versus Placebo
	Reda *et al*	1974	[68]	(20)	CR	6 Dyskinetic patients improved markedly
	Rosenbaum *et al*	1977	[73]	(19)	CR	Li + Amitriptyline 58% marked to moderate improvement 37% minimal to no change 5% worsened conditions
	Rosenbaum *et al*	1980	[74]	(25)	CR	Li + Amitriptyline Only 5% relapses after 1 year
	Simpson	1973	[80]	(7)	CR	All Improved
Non-improvement	Jus *et al*	1978	[34]	(29)		Li versus deanol and placebo No significant changes for all 3 drugs
	Mackey and Sheppard	1980	[45]	(11)	CR	5 cases developed parkinsonism
	Simpson *et al*	1976	[81]	(10)	DB and PC	No improvement or exacerbation

For details see legend to Table 1

The "On-Off" Phenomenon in Parkinsonism

The "on-off" phenomenon associated with L-dopa therapy for parkinsonism is characterized by periods of dyskinesia (on) and sudden switches to akinesia with rigidity (off), which can occur several times daily. Some patients tend to have akinesia between doses (end of dose akinesia), while others do not. It is postulated that alterations in striatal dopamine receptor sensitivity may be involved in this phenomenon. The rationale of using Li for control of "on-off" phenomenon is based on two experimental findings in animals Namely, pretreatment with Li prevents haloperidol induced striatal dopamine receptor sensitivity [25] and secondly, it prevents dopamine receptor and alpha-beta norepinephrine receptor supersensitivity followed by 6 hydroxydopamine lesions of the nigrostriatal pathway [65].

Clinical reports [11,12] suggest that Li may be a valuable adjunct in management of "on-off" phenomenon This is demonstrated by administration of Li_2CO_3 to 5 patients (1 open study and 4 with double-blind cross over design) with severe idiopathic parkinsonism treated with L-dopa, carbidopa and bromocriptine and 4 of the patients showed 62–85% reduction in akinesia. However, 3 patients developed a marked increase in dyskinesia [12] In another report [13] Li salt was given to 6 patients (double-blind cross-over, Li vs. placebo) produced a 70% decrease in akinesia in 5 patients. A similar effect was also reported in one case studied [76]. There is only one study showing 8 of 12 patients studied experienced no improvement while 2 were improved but declined after a few months of Li therapy [41].

LITHIUM AND ORGANIC BRAIN SYNDROMES

Case reports relevant to the use of Li salts in organic brain disorders, secondary to brain injury are summarized in Table 4. A total of 23 patients in 8 separate reports responded to Li treatment. These patients developed hypomanic mood and behavior as a result of structural damages to the brain. The damages were due to physical trauma, tumor, haemorrhage and surgery [10, 28, 31, 47, 61, 70, 72, 88, 89]. Most of these patients described could be diagnosed as organic affective syndromes with the Diagnostic and Statistical Manual III criteria. There were no negative results found in the literature on Li efficacy which may be due to non-reporting rather than the absence of it. However, Li seems to have therapeutic effect on patients with an affective psychosis that is secondary to neurological condition and a special caution should be taken to avoid toxicity. The find-

TABLE 3

LITHIUM TRIALS IN SPASMODIC TORTICOLLIS

Author	Year	Reference No	(n)	Method	Remarks
Couper-Smartt	1973	[14]	(1)	CR	Improved
Foerster and Regli	1977	[24]	(2)	CR	Only 1 patient improved
Lippman and Karens	1983	[42]	(1)	CR	Improved for 6 months, then relapsed
McCaul and Stern	1974	[51]	(11)	CR	No improvement in all cases 9 Patients on Li + Haloperidol 1 Patient had torsion dystonia 1 Patient had bilateral choreoathetosis

For details see legend to Table 1

TABLE 4

LITHIUM TRIALS IN ORGANIC BRAIN SYNDROMES WITH BRAIN INJURY

Author	Year	Reference No	(n)	Nature of Brain Injury and Psychiatric Symptoms
Cohen *et al*	1977	[13]	(1)	Head trauma, temporal hematoma Hypomania
Cohens and Niska	1980	[10]	(1)	RT cerebral hemisphere dysfunction Mania
Hale and Donaldson	1982	[31]	(5)	Mixed group (car accidents, aneurysm, steroid psychoses, multiple sclerosis) Hypomania
Massey and Lowe	1981	[47]	(1)	Pseudobulbar palsy Afffective disturbance
Oyewumi and Lapierre	1981	[61]	(1)	Brain-stem medulloblastoma post-operation Cyclothymia
Rosenbaum and Barry	1975	[72]	(1)	Post traumatic subaranoid hemorrhage and basilar artery aneurysm, with RT temporal lobe resection Hypomania
Williams and Goldstein	1979	[88]	(10)	Mixed groups (6 alcoholics, 6 with abnormal C A T scan, 2 had craniotomies) Hypomania
Young *et al*	1977	[89]	(3)	Affective illness associated with organic brain syndrome

All reports showed improvement in their affective symptoms
For details see legends to Table 1

ings from these reports are at variance with the considerations by some that Li is contraindicated in organic brain syndrome [27]

Lithium trials in substance-induced organic mental disorder is summarized in Table 5 Lithium has been used to control steriod-induced psychoses (steroid delusional disorder) during the course of steroid therapy in multiple sclerosis, as well as in the prophylaxis against steroid-induced psychosis [23, 36, 39] Furthermore, one case of L-dopa induced psychoses delusional disorder was reported to respond to Li [6] In addition, one report showed Li to be effective in 4 patients with manic psychotic symptoms [32] which was due to lysergic acid diethylamide delusional disorder

LITHIUM TRIALS IN HEADACHES

The exact pathophysiology of headache is not clear There is some evidence to suggest that migraine is associated with vasodilation of the extracranial and meningeal vasculature Headache can also be a side effect of Li therapy The basis of using Li in cluster headaches with some form of periodic attacks and symptom free intervals was thought of as an analogy to Li in an affective disorder with a cyclic

TABLE 5

LITHIUM TRIALS IN SUBSTANCE-INDUCED ORGANIC BRAIN DISORDER

Author	Year	Reference No	(n)	Nature of Illness and Drugs Involved
Blaser *et al*	1976	[5]	(1)	An affective psychosis following renal transplant improved with Li_2CO_3
Falk *et al*	1979	[23]	(27)	All Li_2CO_3-treated cases of multiple sclerosis receiving ACTH therapy, did not develop psychoses, while 14% of cases receiving ACTH only developed psychoses
Goggans *et al*	1983	[29]	(1)	Li_2CO_3 improved prednisone induced psychoses in a patient with pulmonary disease
Kemp *et al*	1977	[36]	(1)	Improvement in a case of ACTH treated multiple sclerosis
Kuehnle	1981	[39]	(1)	Ineffective
Siegal	1978	[79]	(1)	Improvement in a case receiving lymphoma therapy

For details see legend to Table 1

TABLE 6

LITHIUM TRIALS IN MIGRAINE

Author	Year	Reference No	(n)	Remarks
Chazot *et al*	1979	[9]	(25)	50% of patients had decreased number of attacks
Medina	1982	[52]	(22)	19 patients with the cyclic form responded
Nieper	1978	[58]	(44)	Used Li orotate which was thought to enter the brain through a specific carrier mechanism 39 patients had decreased in severity and in frequency of attacks
Peatfield	1981	[63]	(5)	All showed worsened conditions

All trials were open noncontrolled studies

nature, such as bipolar disorders Li trials in headaches falls into three major varieties· migraine, cyclic migraine and cluster headaches

Migraine

The clinical trials with Li salts on migraine were essentially discouraging. Table 6 summarizes all these reports Generally, Li aggravates or exacerbates the symptoms of migraine [37, 38, 62, 64].

Cyclic Migraine

The Li trials in cyclic migraine had better results Cyclic migraine is characterized by daily attacks of two weeks or longer, having a recurrence rate on an average of five times a year with headache free periods in between Medina *et al* [52–55] reported the remission of 5 subjects of 27 patients studied with this disorder with Li therapy and the reduction in duration of attacks by the remaining patients.

Cluster Headaches

There were 6 studies with a total number of 113 patients, (Table 7) with most of them showing good responses to Li therapy [19, 20, 21, 37, 45]. The lack of clinical response to Li therapy derives from a group of episodic cluster headaches. It seems that Li may have a place in the chronic cluster headache, after the failure of the more conventional methods and drugs

The general consensus is that Li may have a role in prophylaxis of chronic cluster headaches. The efficacy of Li in cyclic migraine needs further confirmation, and Li may exacerbate migraine symptoms [62, 63, 64]

TABLE 7
LITHIUM TRIALS IN CLUSTER HEADACHES (CH)

Author	Year	Reference No	(n)	Remarks
Ekbom	1977	[19]	(5)	3 patients with chronic CH had 70% improvement 2 with episodic had no improvement
Ekbom	1981	[20]	(19)	All 8 patients with chronic CH improved 7 patients with episodic symptoms had no improvement 4 chronic CH with psychiatric disorders improved
Kudrow	1978	[37]	(15)	Li vs prednisone and methylsergide 87% of patients had >75% improvements with Li 41% of patients improved with methylsergide 50% of patients improved with prednisone
Mathew	1978	[45]	(31)	Chronic and episode CH had 80% and 84% improvement, respectively
Medina *et al*	1978	[55]	(12)	Improved Additional 5 patients with muscle contraction headache had no improvement
Peatfield	1981	[63]	(31)	14 cases were markedly improved and 10 showed lesser improvement

All trials were open noncontrolled studies

LITHIUM TRIALS IN EPILEPSY

The effects of Li following acute administration on EEG are. increased amplitude, generalized slowing with increased theta and delta wave and decreased alpha activity [28,69] These changes remain during treatment with additional changes as paroxysmal dysrhythmia, potentiation and disorganization of background rhythm. For other changes in sleep EEG, see section on sleep disorders

Based on only 4 reports in the literature, there is no evidence yet to suggest that Li possesses therapeutic value in treatment of epilepsy. The use of Li in epilepsy requires great caution [85] This is due to Li evoked changes in EEG, and the possibility of aggravating a pre-existing temporal lobe epilepsy with EEG deterioration [35], and the observation of a predisposition of patients with pre-existing EGG abnormality (unilateral spiking) to neurotoxicity of Li On the other hand, there were 2 reports (n=10 to 11) of the use of Li salts in seizure patients resulting in a reduction in seizures and aggressive behavior [22,57]

LITHIUM TRIALS IN DISORDERS OF SLEEP

Lithium increases slow wave (delta), decreases the duration of rapid eye movement (REM) sleep without REM rebound on Li withdrawal and increases REM latency without changes in total sleep time [28]. As Li stabilizes the affective disorder, the sleep deficit also improves. There is one case report suggesting a prophylatic action of Li in periodic hypersomnolence, Kleine-Levin-Critchley syndrome [33] Also, 3 case reports on 3 patient's somnolence and episodes of hypersomia were prevented by Li [1, 30, 59]. Further investigation is needed to substantiate these findings

MENIERE'S DISEASE

Thompsen's first report on Li trial in Meniere's disease was an open trial (n=30) with good results, but a subsequent double-blind cross over study (n=21) showed there were no differences between placebo and Li [82,83] There was a Li response in an additional case of Meniere's disease concommitant with manic-depressive illness [43] There is no evidence at present to show the effectiveness of Li in Meniere's disease

One case with periodic hypokalemic paralysis has been subjected to Li treatment, however, with no improvement [60]

In conclusion, most of the clinical trials of Li in neurological disorders represent uncontrolled (open studies) and case reports Designed and double-blind studies, e.g , in Huntington's chorea, tardive dyskinesia and migraine headaches invariably showed negative results The findings on combinations of Li and amitriptyline in tardive dyskinesia and Li and neuroleptic in Huntington's chorea are encouraging One double-blind study on cluster headaches showed Li to be effective to prevent recurrent attacks. Another double-blind study showed Li to be beneficial in the "on-off" phenomenon of parkinsonism Moreover, patients with hypomanic mood disorders due to organic brain disorders secondary to brain injury or drugs showed best response to Li therapy Lithium is also found to be effective in cluster headaches and the cyclic form of migraine On the other hand, migraine patients tend to react adversely with intensification of symptoms Lack of clinical response to Li treatment was found in epilepsy, especially temporal lope epilepsy, Meniere's disease and periodic hypokalemic paralysis

One needs to bear in mind the fact that Li has not been approved for use in any of these neurological conditions Patient's consent and additional clinical monitoring of Li side effects and other potential complications should be considered

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