A systematic review of existing data on long-term lithium therapy: neuroprotective or neurotoxic?

Konstantinos N. Fountoulakis¹,², Eduard Vieta³, Constanttin Bouras², Grigorios Notaridis⁴, Panteleimon Giannakopoulos², George Kaprinis¹ and Hagop Akiskal⁴

¹ 3rd Department of Psychiatry, Aristotle University of Thessaloniki, Greece
² Department of Psychiatry, University of Geneva, Switzerland
³ Bipolar Disorders Program, Hospital Clinic, University of Barcelona, IDIBAPS, Barcelona, Spain
⁴ International Mood Center, University of California at San Diego and Veterans Administration Medical Center, San Diego, CA, USA

Abstract

Lithium is an efficacious agent for the treatment of bipolar disorder, but it is unclear to what extent its long-term use may result in neuroprotective or toxic consequences. Medline was searched with the combination of the word ‘Lithium’ plus key words that referred to every possible effect on the central nervous system. The papers were further classified into those supporting a neuroprotective effect, those in favour of a neurotoxic effect and those that were neutral. The papers were classified into research in humans, animal and in-vitro research, case reports, and review/opinion articles. Finally, the Natural Standard evidence-based validated grading rationale was used to validate the data. The Medline search returned 970 papers up to February 2006. Inspection of the abstracts supplied 214 papers for further reviewing. Eighty-nine papers supported the neuroprotective effect (6 human research, 58 animal/in vitro, 0 case reports, 25 review/opinion articles). A total of 116 papers supported the neurotoxic effect (17 human research, 23 animal/in vitro, 60 case reports, 16 review/opinion articles). Nine papers supported no hypothesis (5 human research, 3 animal/in vitro, 0 case reports, 1 review/opinion articles). Overall, the grading suggests that the data concerning the effect of lithium therapy is that of level C, that is ‘unclear or conflicting scientific evidence’ since there is conflicting evidence from uncontrolled non-randomized studies accompanied by conflicting evidence from animal and basic science studies. Although more papers are in favour of the toxic effect, the great difference in the type of papers that support either hypothesis, along with publication bias and methodological issues make conclusions difficult. Lithium remains the ‘gold standard’ for the prophylaxis of bipolar illness, however, our review suggests that there is a rare possibility of a neurotoxic effect in real-life clinical practice even in closely monitored patients with ‘therapeutic’ lithium plasma levels. It is desirable to keep lithium blood levels as low as feasible with prophylaxis.

Key words: Lithium, long-term treatment, neuroprotection, neurotoxicity.

Introduction

From a historical point of view, in 1817 Johan Arfwedson discovered a new alkali and Jons Jacob Berzelius named it ‘lithion’. Lithium (Li) (Jefferson and Greist, 2000) follows hydrogen and helium on the periodic table, and it is the third simplest element (atomic number 3, atomic weight 6.94) and the first solid one. The first time it was used in medicine was in 1843 by Alexander Ure. In 1886 Karl Lange used it for the prophylactic treatment of depression and later, in 1894 his brother, Fritz Lange, used it to treat acute depression. During that period (1880s) Li was also widely used in the form of mineral spring waters, believed to cure many ills. However, in 1898, the first toxic report appeared and by 1949 Li products had been removed from the market.
John Cade was the first to report Li’s antimanic properties in 1949 (Bech, 2006; Cade, 1970); he also reported the death of a patient from ‘lithium toxæmia’ 22 months after first taking Li. However, Mogens Schou established the effectiveness of Li for the treatment of bipolar disorder (Schou, 1997). One of the robust effects of Li therapy for bipolar disorder is a mortality-lowering and suicide-reducing effect. The recommended therapeutic Li blood levels for bipolar disorder range from 0.8 to 1.5 mEq/l. Levels of the robust effects of Li therapy for bipolar disorder is a mortality-lowering and suicide-reducing effect. The recommended therapeutic Li blood levels for bipolar disorder range from 0.8 to 1.5 mEq/l. Levels >1.2–1.5 mEq/l are potentially toxic. Maintenance levels could be lower, between 0.6 and 0.9 mEq/l. Unfortunately, it seems there is no magic serum Li concentration below which intoxication never occurs. For this reason use of the lowest blood levels compatible with prophylaxis has been suggested (Akiskal, 1999; Schou, 1997).

The prophylactic effect of Li against suicide was quickly recognized (Bech et al., 1976; Petterson, 1977). Our current knowledge about Li solidly supports its usefulness during all phases of bipolar illness, and its specific effectiveness on suicidal prevention (Baldessarini et al., 2003; Calabrese et al., 2006; Geddes et al., 2004; Goodwin et al., 2003, 2004). It is particularly impressive that in a population-based sample of 20,638 health-plan members with bipolar disorder, unadjusted rates were greater during treatment with valproate than during treatment with Li for emergency-department suicide attempt (31.3 vs. 10.8/1000 person-years, p < 0.001), suicide attempt resulting in hospitalization (10.5 vs. 4.2/1000 person-years, p < 0.001), and suicide death (1.7 vs. 0.7/1000 person-years, p = 0.04) (Goodwin et al., 2003). Such anti-suicidal effect was confirmed after a systematic review of existing data (Cipriani et al., 2005), although there is some concern that there was a misinterpretation of data (Connemann, 2006). For these reasons, Li use is strongly supported in all published treatment guidelines (Fountoulakis et al., 2005). However, its mode of action and how it exerts its therapeutic effect are not definitely known. It is certain that there is not a state of Li deficiency in humans and therefore such a deficiency cannot be the cause of bipolar disorder. It has been shown that Li acts at multiple sites inside the neuron as an inhibitor of key enzymes and it is likely that its effect depends largely on the state of activation (Corbella and Vieta, 2003; Lenox and Frazer, 2002; Wu et al., 2004).

The prevalent theory of Li’s mode of action concerns ions and particularly sodium–Li counter-exchange. Substitution of sodium ions by Li ones in many membrane and intracellular mechanisms is believed to stabilize various processes. On the other hand, it seems that multiple neurotransmitter systems are affected by Li. There are many sites along the signal transduction pathways that are targets for Li action [e.g. protein kinase C (PKC) isozymes, myrisoylated alanine-rich C kinase substrate (MARCKS), activated protein-1 (AP-1), adenosine monophosphate cAMP-responsive element (CRE) and more]. The inositol depletion hypothesis had also been suggested as a mechanism of action, but further studies suggested Li increases inositol 1,4,5-triphosphate (IP3) concentrations (Corbella and Vieta, 2003).

What is known about the effect of Li in the central nervous system is that it inhibits PKC and glycogen synthase kinase-3 (GSK-3), a protein kinase involved in cytoskeletal development and the regulation of phosphorylation which is involved in Alzheimer’s disease. GSK-3β phosphorylates and thereby regulates the functions of many metabolic, signalling, and structural proteins, including AP-1, cyclic AMP response element binding protein (CREB), heat shock factor-1, nuclear factor of activated T cells, Myc, β-catenin, CCAAT/enhancer binding protein, and NFκB. Moreover, Li is reported to robustly increase the levels of the cytoprotective B-cell lymphoma protein-2 (Bcl-2) in areas of rodent brain and in cultured cells. This protein has anti-apoptotic and neurotrophic effects (Lenox and Frazer, 2002).

The toxic effects of Li may affect multiple organs and systems including the central nervous, cardiovascular and gastrointestinal systems, kidneys, the thyroid, parathyroid, etc. Li may also induce adverse effects on electrolyte balance, hypothyroidism or hypercalcaemia. It may also rarely be associated with benign intracranial hypertension (pseudotumour cerebri), a myasthenia gravis-like syndrome, lowering of the seizure threshold, a Creutzfeld–Jakob-like syndrome or a neuroleptic malignant-like syndrome (Jefferson and Greist, 2000). The current study attempted to perform a systematic review of the literature in order to answer the question whether chronic Li therapy at ‘therapeutic’ levels has ultimately a neuroprotective or a neurotoxic effect. The answer to this question has obvious and profound practical implications for everyday clinical practice.

Material and method

Medline was searched (Wilczynski and Haynes, 2006) with the combination of the word: ‘Lithium’ with key words that referred to every possible effect on the central nervous system. These key words were the following: encephalopathy, brain lesion,
neurotoxicity, neuroprotective, brain atrophy, cognitive disorder, dementia. Only English-language articles were included in the present study. A large number of papers were originally identified. The first step was to read the abstract and then decide on the basis of the abstract alone whether the article was relevant to the aim of the study or not. The articles were chosen on the basis of either the abstract alone, or in cases where the abstract was not sufficiently clear, by reviewing the full text. The selection was done according to the opinion of the reader (which was one of the authors – K.N.F.) and demanded that the paper to be relevant to the aims of the study. The paper should deal with Li in humans or animals, and report adverse events at ‘therapeutic levels’ although the latter proved to be rather unreliable in some articles. The strategy was flexible, and rather ‘over-inclusive’.

The papers were classified into those supporting a neuroprotective effect, those in favour of a neurotoxic effect and those neutral. In terms of the type of paper, they were classified in (a) research on humans (b) animal and in-vitro research, (c) case reports, and (d) review/opinion articles. Papers dealing with animals and those with in-vitro methodology were classified together because a combined methodology was used in most cases. Moreover, on many occasions it was difficult to distinguish review and opinion articles.

In order to validate the level and the quality of the data, a system that would include both clinical and basic science data was necessary. The Natural Standard evidence-based validated grading rationale (available in detail online at http://www.nlm.nih.gov/medlineplus/druginfo/natural/grading.html; last accessed 2 January 2007) was used.

Results

The Medline search returned 970 papers up to February 2006 inclusive. The inspection of the abstracts produced 214 papers for further review. The number of papers in each group is shown in Table 1.

A significant number of other papers (included in the original 970) deal with the study of Li mechanism of action and provide indirect evidence for or against these theories, but are not included in the present review.

Neuroprotective

Research on human subjects

Li may increase the glycine and choline levels of red blood cells in geriatric patients (Pomara et al., 1983), have an effect on the formation of β-amyloid precursor protein derivatives and tau proteins (Clarke et al., 1993), antagonize vinca alkaloid neurotoxicity (which induces peripheral neuropathy and muscle damage) (Petrini et al., 1999) and increase total brain N-acetyl-aspartate (NAA – a putative marker of neuronal viability and function) levels after 4 wk of therapy in all brain regions (Moore et al., 2000a). These authors reported that after 4 wk of Li treatment in bipolar patients grey-matter volume was increased by 3% on average, which is an impressive rate, also of note is that this finding was present in 8 out of 10 of the patients studied (Moore et al., 2000b). The authors attribute their findings rather to a true neurotrophic effect of Li rather than to cell swelling, or changes in magnetic resonance imaging contrast associated with Li treatment. However, after such an impressive and robust finding, one would expect a burst of replication studies, however, these never materialized. In another study which was cross-sectional, Bayer and colleagues reported that older bipolar patients had a larger left hippocampus in comparison to controls and this, according to the authors could be related to previous Li therapy but not valproate (Beyer et al., 2004). It is peculiar why this effect is exerted unilaterally only in the left hemisphere and the confounding role of the clinical subtype that led to a preferential treatment with Li vs. valproate cannot be excluded.

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Li-treated rats showed less deficits than untreated cholinergic excitotoxic lesioned animals on both behaviour and biochemistry of the lesioned cortex (Arendt et al., 1999; Pascual and Gonzalez, 1995). This may be supportive of a protective action for Li against excitatory amino-acid neurotoxicity. In accord with this, Li pretreatment at therapeutic concentrations for 7 d prevents the neurotoxic effect of NMDA receptor activation by fully attenuating NMDA-mediated cytoplasmic vacuolization (Bown et al., 2003; Ma and Zhang, 2003; Nonaka and Chuang, 1998), and specifically of glutamate (Chalecka-Franszak and Chuang, 1999; Chen et al., 2003; Kopnisky et al., 2003; Shao et al., 2005) and p53 (Chen and Chuang, 1999; Lu et al., 1999) induced effects and apoptosis. This is possibly done through the enhancement of the brain-derived neurotrophic factor (BDNF) expression/secretion, leading to the activation of TrkB receptor (Hashimoto et al., 2002b). Moreover, at clinically relevant plasma concentrations, Li treatment is reported to inhibit apoptosis induced by many factors such as trophic factor withdrawal (Jin et al., 2005), amyloid β-peptide (Aβ) (Alvarez et al., 1999; De Ferrari et al., 2003; Ghribi et al., 2003; Phiel et al., 2003; Su et al., 2004), β-amyloid peptide-(1-42) (Wei et al., 2000), etoposide- and camptothecin-induced apoptosis (Beurel et al., 2004), aluminium-induced translocation of cytochrome c (Ghribi et al., 2002; Savory et al., 2003), quinolinic acid (Senatorov et al., 2004), thapsigargin-induced stress on the endoplasmic reticulum (Chuang et al., 2002), colchicine (Jorda et al., 2004, 2005), C2-ceramide (66% protection may be due to inhibition of NMDA receptors or GSK-3β (Centeno et al., 1998; Mora et al., 2002a,b), potassium ionophore valinomycin application (Li and El-Mallah, 2000), low potassium (K+) (Mora et al., 1999, 2002a; Nonaka et al., 1998), ouabain (Hennion et al., 2002), phentoyin and carbamazepine (Nonaka et al., 1998) as well as from ageing of the cultures (Kang et al., 2003; Nonaka et al., 1998) but not osmotic stress-induced caspase activation and apoptosis, although it reduces phosphorylation at the Tau-1 epitope (Stooktoff and Johnson, 2001). Li, applied in cultured neurons, may also reverse the stress-induced (after immobilization of the living animal) impairment of long-term potentiation (Perez et al., 2003).

It has also been reported that Li may up-regulate Bcl-2 and Bcl-X(L) down-regulate Bax, abolish caspase-3 activity and reduce DNA damage, and this regulatory effect on the apoptosis-controlling proteins occurs in both the mitochondria and endoplasmic reticulum (Bush and Hyson, 2006; Chen et al., 1999; Chen and Chuang, 1999; Chuang et al., 2002; Ghribi et al., 2002; Kopnisky et al., 2003; Senatorov et al., 2004; Wei et al., 2000, 2001; Youdim and Arraf, 2004). It also increases phosphorylated CREB levels (Kopnisky et al., 2003). It may also increase neuronal metabolism (Wilot et al., 2004) and nerve growth factor (NGF) concentrations in the frontal cortex (+23.2%), hippocampus (+72%), amygdala (+74%) and limbic forebrain (+46.7%) (Hellweg et al., 2002).

Li treatment may reduce mossy fibre sprouting caused by pilocarpine-induced limbic epilepsy (Cadotte et al., 2003) and prophylactic treatment with Li may prevent the onset/progression of HIV-associated cognitive impairments (Everall et al., 2002) by avoiding neuronal loss. On the other hand, increased neurogenesis (close to a 25% increase in the dentate gyrus) is reported in the adult rodent hippocampus (Chen et al., 2000). Moreover, it may activate the extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) in the primary cortical neurons, thus exerting neuroprotective effects (Di Daniel et al., 2005).

The relationship of Li effect to dosage and duration of administration was shown in a study on cultured cerebellar granule neurons (CGNs). A 3-h treatment (short-term) was ineffective; pretreatment for 3–5 d (long-term) protected (CGNs) against β-bungarotoxin-induced neurotoxicity, but longer treatment for 6–7 or a higher concentration of Li led not only to loss of the neuroprotective effect but also to a neurotoxic effect (Tseng and Lin-Shiau, 2002).

Li pretreatment but not treatment may reduce apomorphine-induced behaviour (Gruenthal, 1984). Chronic Li treatment may prevent stress-induced alterations in the morphology and function of neurons (decrease in dendritic length, increase in glial glutamate transporter 1 mRNA expression and the phosphorylation of cAMP-response element binding in the hippocampus) (Wood and Young, 2004).

Li inhibits GSK-3β and thus ameliorates platelet-activating factor (PAF) (Maggirwar et al., 1999) and trophic factor withdrawal induced neuronal apoptosis (Jin et al., 2005), tau phosphorylation (Hong et al., 1997; Munoz-Montano et al., 1997; Perez et al., 2003), staurosporine-induced activation of caspase-3 (Bijur et al., 2000), Aβ peptide production (Phiel et al., 2003), etoposide- and camptothecin-induced apoptosis (Beurel et al., 2004), and may even protect against HIV encephalitis (Dou et al., 2005).

Li may be useful in the treatment of brain ischaemia (Cimarosti et al., 2001), since it is reported to reduce...
the infarct volume in the rat model of middle cerebral artery occlusion reperfusion (Ren et al., 2003) by as much as 56% (Nonaka and Chuang, 1998) and decrease the neurological deficits (Xu et al., 2003) possibly through a pathway involving the NMDA receptors (Nonaka and Chuang, 1998).

Case reports

There were no case reports to review.

Reviews

Review papers suggest that Li robustly protects cultured rat brain neurons from glutamate excitotoxicity mediated by NMDA receptors, possibly by reducing the level of NR2B phosphorylation at Tyr1472 and thus Ca$^{2+}$ influx. It also may involve decreased expression of pro-apoptotic proteins (p53 and Bax), enhanced expression of the cytoprotective protein Bcl-2, and activation of the cell survival kinase Akt. This neuroprotection effect against glutamate excitotoxicity is long-lasting, requires long-term pretreatment and occurs at therapeutic concentrations (Bauer et al., 2003; Chuang, 2004, 2005; Chuang et al., 2002; Hashimoto et al., 2002a; Jope, 1999; Lagace and Eisch, 2003; Chuang, 2004; Gray et al., 2003; Harvey et al., 2002; Hongisto et al., 2003; Manji et al., 1999, 2000a,b; Rowe and Chuang, 2004). Its inhibition of GSK-3β supports cell survival since GSK-3β facilitates apoptosis (Alvarez et al., 2002; Bauer et al., 2003; Gould and Manji, 2002; Grimes and Jope, 2001; Harvey et al., 2002; Hongisto et al., 2003; Jope, 1999; Jope and Bijur, 2002; Li et al., 2002a; Manji et al., 1999). After chronic Li administration, a robust elevation in the levels of the cytoprotective protein Bcl-2 mainly in the frontal cortex, hippocampus, and striatum is observed (Chuang, 2004; Gray et al., 2003; Manji and Moore, 2001; Manji and Duman, 2001; Manji et al., 1999, 2000a,b; Rowe and Chuang, 2004; Wada et al., 2005). Review papers suggest that Li remains the only medication demonstrated to markedly increase Bcl-2 levels in several brain areas (Manji et al., 2000a; Wada et al., 2005). Further, Li adjusts signalling activities regulating second messengers, transcription factors, and gene expression (Jope, 1999; Li et al., 2002b), as well as neurotrophic factors and various anti-apoptotic and cell survival pathways (e.g. CREB, BDNF, and MAP kinases) (Bauer et al., 2003; Chuang, 2004; Gray et al., 2003; Harvey et al., 2002; Ledoux, 2003; Manji and Duman, 2001; Manji et al., 2000b; Rowe and Chuang, 2004; Sassi and Soares, 2001; Wada et al., 2005). It also exerts effects on components of the Wnt signalling pathway (Gould and Manji, 2002) while its chronic administration modulates expression of several genes (Manji and Moore, 2001). It may also improve defence against viral infections, specifically DNA viruses (Harvey et al., 2002) and damage by ischaemia (Wada et al., 2005).

A list of the substances through which Li may act and produce a neuroprotective effect are shown in Table 2.

Neurotoxic

Research articles

As much as 30–40% of Li-treated patients may show reversible abnormal generalized slowing and paroxysmal diffuse delta activity in the clinical EEG (James and Reilly, 1971; Struve, 1987). Moreover, a slowing of motor and sensory nerve conduction velocities and prolonged central neural conduction times obtained from somatosensory and brainstem auditory-evoked potentials is reported (Chang et al., 1990). Such changes seem to correlate with the duration of Li therapy (Eisenstat et al., 1989). It seems that chronic maintenance treatment with Li affects the peripheral nerves as well, even if the impairment is rarely such as to warrant discontinuation of treatment. However, it has been suggested that monitoring of conduction velocities could be a useful method for the early detection of a possible Li neurotoxicity (Faravelli et al., 1999).

Specific kinematic abnormalities show that chronic treatment with Li salts is associated with an impairment of fast single-joint movements’ cerebellar control even in the absence of clear signs of toxicity (Setta et al., 1998). Abnormal involuntary movements during long-term Li treatment are reported in 8% of patients at baseline and in 16% after 7 yr. They seem to be age-dependent and high 12-h Li levels may constitute an important risk factor, along with female gender, early onset of affective illness, low body weight and the occurrence of dementia among first-degree relatives (Axelson and Nilsson, 1991). Tardive dyskinesia is reported to affect 22.5% of bipolar patients, with age and Li therapy acting as risk factors (Dinan and Kohen, 1989).

The reports to the Spontaneous Reporting System database of the United States Food and Drug Administration suggest that Li level and taking Li+haloperidol (but not haloperidol dosage) were significant factors in the development of adverse events. Other neuroleptics did not show similar effects, and other factors like age, sex, etc. were not statistically significant (Goldman, 1996a). The spectrum of neuroleptic malignant syndrome (NMS) symptoms and signs was prevalent in this database, especially altered consciousness, hypertonia/rigidity...
and tremor. Nearly 30% of registered cases met criteria for a full NMS diagnosis (Goldman, 1996b). Although these two previous reports do not suggest a role of neuroleptic dosage, other authors report contrary results, i.e. the dosage of the neuroleptic administered, and not the serum Li level or Li dose, predicts which patients will become neurotoxic (Miller and Menninger, 1987a,b). Others report that adding a neuroleptic is the crucial factor leading to Li toxicity in more than half of patients even at normal plasma Li levels (Miller et al., 1986). One factor that might be important is the type of neuroleptic in combination with its dosage, since another study reports that 50% of patients receiving the haloperidol + Li combination showed abnormal EEG recordings (photoparoxysmal and photomyoclonic responses) while no such abnormal findings were observed in patients treated with other neuroleptic–Li combinations (Saran et al., 1989). Another study, after searching the UK General Practice Research Database reported higher rates of Alzheimer’s disease in Li-treated patients in comparison to the rest (Dunn et al., 2005).

There is sufficient evidence to support the notion that Li toxicity occurs primarily in the context of chronic therapeutic administration (‘chronic poisoning’), rather than in the context of an overdose. The strongest risk factors are nephrogenic diabetes insipidus, aged >50 yr and thyroid dysfunction (Oakley et al., 2001), in addition to neuroleptic (mainly haloperidol) co-administration. Why this should happen even at ‘therapeutic’ plasma levels is obscure. One possible explanation is that Li plasma levels are not a perfect way to monitor treatment. Some authors propose that Li ‘plasma level–red blood cell level’ ratio is a better correlate of Li neurotoxicity, even when the plasma Li levels are within the therapeutic range. Moreover, an increase in the intra-erythrocyte sodium–potassium ratio was observed in toxic patients in comparison to non-toxic patients (Elizur et al., 1982).

### Animal studies/ in-vitro studies

Phenothiazines increase Li influx in red cells and the distribution ratio in vitro (Pandey et al., 1979), and this observation may help in understanding the clinical reports of an increased toxicity of Li when administered with antipsychotics.

Pretreatment with Li sensitizes the brain to cholinergic seizures induced by Soman, a potent acetylcholinesterase inhibitor (Pazdernik and Emerson, 2001). Furthermore, Li has been used along with pilocarpine in the development of an animal model for temporal lobe epilepsy. Administration of pilocarpine
(30 mg/kg s.c.) to rats pretreated with LiCl (3 mEq/kg i.p.) produces a state of status epilepticus in animals within half an hour. The phenomenon can be blocked by atropine, scopolamine and the GABAergic agents GABA, sodium valproate, baclofen and clonazepam when given prior to pilocarpine, but not when administered 30 min after pilocarpine administration (George and Kulkarni, 1996). This model of epilepsy leads to early brain damage and atrophy (Persinger et al., 1998; Roch et al., 2002). Various studies investigated the protective effect that many agents may have on such a model, like tacrine (Bagetta et al., 2002), ketamine hydrochloride (Cook, 1999; Fujikawa, 1995; Santi et al., 2001), topiramate (Rigoulot et al., 2004), low long-term caffeine consumption (Rigoulot et al., 2003), MK-801 (Walton and Treiman, 1991), diazepam and pentobarbital (Du et al., 1995). However, some drug combinations considered protective may have the opposite result at least under specific conditions. Thus, administration of tacrine in rats pretreated with Li causes seizures and hippocampal damage possibly by enhancing the expression of cyclooxygenase type 2 (COX-2) enzyme protein in the dorsal hippocampus and elevate brain PGE2 content during the preconvulsive period (Paoletti et al., 1998).

Li is reported to reduce the activity of calcium/calmodulin-dependent protein kinase II (CaM kinase II), which is an enzyme with a pivotal role in synaptic plasticity and cognitive functions. On the contrary, antidepressants significantly increased the kinase activity in presynaptic vesicles of the frontal/prefrontal cortex while haloperidol induced no change (Celano et al., 2003). LiCl at two different doses (1 mEq/kg and 2 mEq/kg – equivalent to human therapeutic dosages) was reported not to inhibit muricidal behaviour in rats, and at the higher dose caused neurotoxicity in six of 11 rats. The same behaviour was blocked by imipramine (Rush and Mendels, 1975).

After 7-d Li treatment, at low concentrations Li elicited an increase in the number and thickness of connecting nerve fibres, and the size of neuronal aggregates; at high concentrations it induced a severe deterioration of cell morphology, which ultimately resulted in neuronal death. Similar changes were observed concerning the carbachol and the muscarinic receptor-induced phosphoinositide turnover (Gao et al., 1993). In addition, LiCl inhibits the NGF-induced neuronal differentiation of rat PC12 pheochromocytoma cells (Harada et al., 1996). These findings may mean that the neurotrophic effect described by other studies may in fact be quite problematic. Moreover, a reduced nerve fibre area in the Li-treated animals was found in rats after 30 wk of Li administration at therapeutic levels (Licht et al., 1997). The effects of Li on [Ca\[^{2+}\]]\text{c}\text{a} and neuronal death seem to depend on the developmental stage of neurons and the growth conditions to which they are subjected, as well as the treatment duration (Yao et al., 1999).

Four weeks of Li administration increases 34% the expression of astrocyte cell marker, glial fibrillary acidic protein (GFAP) in rats and this is consistent with the finding of the same research group that reported mild gliosis in the hippocampal CA1 area and the dentate gyrus which was associated with a change in the orientation of astrocytic processes. In control animals astrocyte processes were mainly orientated perpendicularly to the striatum pyramidal, whereas in treated animals the cells were predominantly stellar in appearance (Rocha et al., 1998; Rocha and Rodnight, 1994).

Rats given Li in their drinking water for 4 wk after the 6-hydroxydopamine injection showed a greatly attenuated recovery of sensorimotor functions after unilateral damage to the mesotelencephalic dopaminergic projection, compared to brain-damaged rats drinking unadulterated water (Kozlowski et al., 1983).

Case reports

There are several case reports suggesting that Li may exert neurotoxicity at normal therapeutic or even subtherapeutic levels (Bell et al., 1993; Evans and Garner, 1979; Gallinat et al., 2000; Ghadirian and Lehmann, 1980; Hay and Simpson, 1982; Kumar et al., 1999; Lang and Davis, 2002; Mosovich, 1993; Prettyman, 1994; Strayhorn and Nash, 1977; Thornton and Pray, 1975; West and Meltzer, 1979), especially when combined with haloperidol (Sandyk and Hurwitz, 1983). Ageing and intracranial pathology may constitute an additional risk factor for Li neurotoxicity at therapeutic serum levels (Flint, 1993; Kemperman et al., 1989) and neurotoxicity is observed in elderly patients despite ‘therapeutic’ doses of antidepressant and Li (Austin et al., 1990). Li-induced delirium has been reported in geriatric patients with ‘therapeutic’ serum Li levels (Brown and Rosen, 1992).

After the addition of neuroleptics, extrapyramidal symptoms (Addonizio, 1985; Arya, 1996; Muthane et al., 2000; Normann et al., 1998) or delirium may appear (Normann et al., 1998). Akathisia is reported also without concomitant antipsychotic therapy (Price and Giannini, 1986). Tardive dyskinesia-like syndrome is reported after Li monotherapy (Beitman, 1978; Sternbach and Jordan, 1990) or in combination...
with carbamazepine (Lazarus, 1994) or haloperidol (Spring and Frankel, 1981). Choreoathetosis (Reed et al., 1989) and tardive dystonia are also reported (Chakrabarti and Chand, 2002).

Combination treatment may increase the likelihood of Li neurotoxicity. This includes carbamazepine at therapeutic doses (Chaudhry and Waters, 1983) and neuroleptics (Fetzer et al., 1981; Prakash et al., 1982a,b) especially haloperidol (Hellwig et al., 1996; Keitner and Rahman, 1984; Mann et al., 1983), thioridazine (Cantor, 1986; Spring, 1979), chlorpromazine (Yassa, 1986), clozapine (Lee and Yang, 1999) olanzapine (Swartz, 2001), and loxapine (Fuller and Sajatovic, 1989).

NMS (Gabuzda and Frankenburg, 1987; Lambreva et al., 2005) with tardive dyskinesia (Spring and Frankel, 1981) is reported with a combination of haloperidol and Li (Akpaffiong, 1992) and amitriptyline and Li (Fava and Galizia, 1995), or Li alone (with cerebellar degeneration) (Naramoto et al., 1993). The combination with antipsychotics can be associated with epileptic seizures (Addy et al., 1986).

Creutzfeldt–Jakob-like syndrome has also been reported with Li therapy (Casanova et al., 1996; Kemperman and Notermans, 1989; Primavera et al., 1989; Smith and Kocen, 1988) which may be reversible when caused by the concomitant use of l-dopa (Broussolle et al., 1989). This syndrome is seen also after combination treatment with nortriptyline (Finelli, 1992) l-mepromazine, and phenobarbitone (Kikyo and Furukawa, 1999). Other syndromes reported are an irreversible cerebellar syndrome (Verdoux and Bourgeois, 1990), a sixth cranial nerve palsy (Slonim and McLarty, 1985) and asterixis (Stewart and Williams, 2000).

Secondary neurotoxic effects include Wernicke's encephalopathy following Li-induced diarrhoea (Epstein, 1989) and Li-induced nephrogenic diabetes insipidus (Meinardi and Donders, 1997).

There is one small study of the report of five patients who developed toxic effects on low doses of Li and were successfully treated with linoleic acid in the forms of safflower oil, in an effort to increase dihomogammalinolenic acid (DGLA) which is blocked by Li and leads to the inhibition of prostaglandin synthesis (PG) EI by blocking the mobilization of DGLA (Lieb, 1980).

**Reviews/opinion papers**

The acronym SILENT (syndrome of irreversible Li-effectuated neurotoxicity) has been coined recently to denote persisting cerebellar dysfunction mainly on the basis of 55 cases reported so far (Adityanjee, 1989).

A systematic review of Li neurotoxicity at normal therapeutic doses or concentrations revealed the publication of 41 relevant cases (14 were males, and 21 females were aged < 65 yr and 6 females were aged ≥ 65 yr). These authors concluded that drug interaction effect is an important factor, because more than half of these patients received at least one neuroleptic in addition to Li treatment, 22% also received an antidepressant, 22% a carbamazepine and 17% an anxiolytic. The problem with this conclusion is that the respective percentages of the general population of bipolar patients are not known (Emilien and Maloteaux, 1996).

Other reviews report remarks on Li encephalopathy (Smith et al., 2003) with manifestations from the cerebellum (Adityanjee et al., 2005) and gliosis of the hippocampus in rats (Harrison, 1999). There are several ‘opinion’ papers arguing in favour of the toxicity hypothesis. All summarize in a non-systematic way case reports, biochemical and related data (Ban, 1978; Buchanan, 1978; Foti and Pies, 1986; Gelenberg, 1980; Johnson, 1976; Keltner, 1997; Koehler and Mirandolle, 1988; Mani et al., 1996; Perenyi et al., 1984; Sheean, 1991; Wright and Jarrett, 1991).

Various conditions attributed to Li neurotoxicity even with normal Li plasma levels are shown in Table 3.

**Neutral**

**Research studies**

In a prospective study of an estimated 9792 in-patients of a large Chinese psychiatric hospital, 12 patients developed NMS. The authors did not find any relationship between concurrent Li use and NMS (Deng et al., 1990). Similar results were reported by others (Kessel et al., 1992). A retrospective study of 2422 elderly new users of Li vs. 2918 elderly new users of valproate over an 8-yr period did not reveal any difference between groups in terms of delirium manifestation (Shulman et al., 2005). A cross-sectional study aimed at identifying predictors of tardive dyskinesia in a group of 180 psychiatric outpatients on neuroleptic medications found no relationship of the development of tardive dyskinesia and use of Li (Morgenstern et al., 1987).

Other authors dispute the proposed mechanism through which Li could exert a protective effect. More specifically they reported that Li administration in healthy individuals did not produce any differences in N-acetyl-aspartate, phosphocreatine + creatine,
glycerophosphocholine + phosphocholine (or choline-containing molecules), and myo-inositol absolute levels or ratios in the dorsolateral prefrontal cortex (Brambilla et al., 2004).

Animal/in-vitro studies

It has been reported that although application of Li inhibited GSK-3β, it failed to overcome PreSenilin-1 (PS-1)-mediated inhibition of β-catenin signalling, thus it is unlikely that Li could interfere with the role of PS-1 in Alzheimer’s disease (Palacino et al., 2001). Moreover, there are studies of Li + haloperidol in rats that did not produce any significant findings (Licht et al., 1994, 2003), but it seems that the same animal data eventually produced some evidence in favour of the toxic hypothesis (Licht et al., 1997).

Reviews/opinion

One review article concludes that many studies failed to demonstrate Li-induced memory deficits and that it is likely that subjective complaints of memory impairment were correlated with depression (Ananth et al., 1987).

Validation of data

Both the data in favour of the neuroprotective effect and those in favour of the neurotoxic effect when taken separately are of level B according to the Natural Standard evidence-based validated grading rationale, while those in favour of a neutral (no effect) are of level C. Taken together, the conclusion is that the data concerning the effect of Li therapy is that of level C, that is ‘unclear or conflicting scientific evidence’ since there is conflicting evidence from uncontrolled non-randomized studies accompanied by conflicting evidence from animal and basic science studies.

Discussion

The current review study attempted to systematically search the literature in order to answer a clinically important question, whether long-term Li treatment is neuroprotective or neurotoxic for patients. A large number of papers were identified (n = 970) and scanned. There were no randomized controlled trials (RCTs). There were only case series, cohort studies, non-randomized clinical studies, case reports, animal and basic science studies. Only a fraction of these (n = 214) were studied in depth. Most papers were in favour of the toxic effect in comparison to those in favour of the protective effect (116 vs. 89). The most important finding is the large discrepancy in the quality of papers supporting either hypothesis. No case report supports the protective effect, and this is understandable and expected, because of methodological and publication bias issues. What is impressive is the domination of animal/in-vitro studies in favour of the protective hypothesis (58 vs. 23) which is in line with review/opinion papers (25 vs. 16). However, human research papers have the opposite orientation (6 vs. 17). We submit that the body of literature above constitutes an impressive discrepancy between basic and clinical research and practice. As mentioned earlier,
the classification of the data suggests that the evidence is of level C, that is ‘unclear or conflicting’.

However, beyond this classification, there are also more fundamental problems and this difference is not only a matter of discipline or approach. It is also the result of different questions being asked.

Basic research responds to questions about specific biochemical effects of Li, and the final clinically relevant conclusion is often typically hypothetical. Research studies concerning the protective theory on human subjects are few and provide only indirect evidence on the supposed neuroprotective effect of Li, generally by showing that a substance with protective properties is enhanced, or a toxic one is inhibited. Further, when basic research studies mention prolonged administration of Li, they never extend beyond several weeks or a few months. In clinical terms this is considered as short-term, because patients need to receive Li for years in order to obtain maximum benefit. The difference remains even after correcting for the shorter life-cycle laboratory animals have in comparison to humans.

On the contrary, clinical studies tend to over-report adverse events (especially with case reports), and it is likely that many patients may suffer from high or poorly controlled Li levels in spite of therapeutic plasma levels which are not considered to be adequate for monitoring. Concomitant antipsychotic medication is another confounding variable while the pattern and importance of antipsychotic prescription is not yet well understood (Mortimer et al., 2005) especially in patients with comorbid somatic disorders (Bocchetta, 2003; McLaren and Marangell, 2004). Red blood cell Li levels seem to reflect toxicity, control of mania, and symptom suppression of tardive dyskinesia better than plasma Li levels alone (Ereshefsky et al., 1979). Thus, clinical studies, although providing answers closer to the real-world, suffer from a significant publication bias.

Another important point is that it is probable that Li effects largely depend on the activation level of the cell (Lenox and Frazer, 2002; Silverstone et al., 2005), this means that observations on healthy controls and laboratory animals or cell cultures (which can be largely considered as being ‘normal’) can not be generalized and carried over to bipolar patients.

However, even though it is difficult to arrive at a single confident summary, there are several specific considerations on the basis of our exhaustive review.

(1) Li could be beneficial for the short-term treatment of several acute insults such as those resulting from toxic agents or ischaemia. The problem is that in order to have this beneficial effect, in most cases, one needs Li pretreatment, whereas these insults are difficult to predict.

(2) Li is an agent which is cumbersome to monitor and even when all guidelines are followed, the clinician can never be sure that patients are always safe. This is because most patients receive a neuroleptic along with Li, which seems to increase the risk for adverse events.

(3) The frequency of Li encephalopathy signs and symptoms although close to 30% (when alterations in EEG are included) is nonetheless unimpressive since most cases do not pose clinical problems.

(4) The respective figure for tardive dyskinesia (>20%) is similar to that reported for typical antipsychotics. Therefore, the contribution of Li monotherapy to such dyskinesia appears negligible.

(5) The limited data available do not imply any clinically protective effect against any disease other than bipolar disorder for which Li remains the ‘gold standard’. Li has an established and well-documented effectiveness in the treatment of bipolar disorder as well as in the prevention of suicidality. Successful treatment of bipolar patients with Li may prove to be neuroprotective since it prevents the progression of the illness to a more malignant form with greater disability.

(6) Any treatment decision involves a balance between benefits and potential side-effects, and although we acknowledge the clinical importance of Li, the neurotoxicity risks might have been underestimated due to the difficulties related to long-term follow-up (Goodwin and Vieta, 2005).

The foregoing considerations suggest the clinical wisdom of keeping blood levels as low as feasible with prophylaxis. This is in line with recommendations made on the basis of research conducted by Schou (1997), and the mood clinic experience of the senior author (Akiskal, 1999).

**Conclusion**

Li remains unique and the gold standard in the treatment of bipolar illness. It is incredible that a simple element can have such an impact on the treatment of a major psychiatric illness. Clearly, there is no doubt concerning its prophylaxis against manic-depressive illness. However, our review points to the need for a closer monitoring of patients under Li treatment; plasma levels may be an inadequate method to safely monitor the drug and other more sophisticated methods should be developed, tested and applied.
However, above all, the clinician should examine the patient for early signs and symptoms of neurotoxicity even when no apparent reason exists. Two more problems should be considered. First, Li has virtually no commercial value. This may hamper research and Li could some day be unavailable just because of this. Second, the training of residents in the use of Li is deteriorating quickly. In some countries it has already completely vanished, and this makes it impossible to safeguard its proper use and monitoring. A special focus on Li training should be included in all residency training programmes. Finally, more basic research data as well as clinical data concerning combination therapy is needed. Our current knowledge concerns mainly monotherapy strategies and some combinations of two agents, but this is far removed from the real-world clinical practice where monotherapy is the exception and the average patient receives a minimum of two agents.

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References


Chen G, Zeng WZ, Yuan PX, Huang LD, Jiang YM, Zhao ZH, Manji HK (1999). The mood-stabilizing agents lithium and valproate robustly increase the levels of the neuroprotective protein bcl-2 in the CNS. *Journal of Neurochemistry* 72, 879–882.


Chuang DM (2004). Neuroprotective and neurotrophic actions of the mood stabilizer lithium: can it be used to treat neurodegenerative diseases? *Critical Reviews in Neurobiology* 16, 83–90.

Review of existing data on long-term lithium therapy


Gallinat J, Boetsch T, Padberg F, Hampel H, Hermann WM, Hegerl U (2000). Is the EEG helpful in diagnosing...


Manji HK, Moore GJ, Chen G (1999). Lithium at 50: have the neuroprotective effects of this unique cation been overlooked? *Biological Psychiatry* 46, 929–940.


or sodium valproate. *Annals of General Hospital Psychiatry* 3, 13.


