

### **A review of clinical trials of lithium in neurology**

*Yung CY: Pharmacol Biochem Behav. 1984;21 Suppl 1:57-64.*

Abstract: 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.

### **Focus on therapy of hypnic headache**

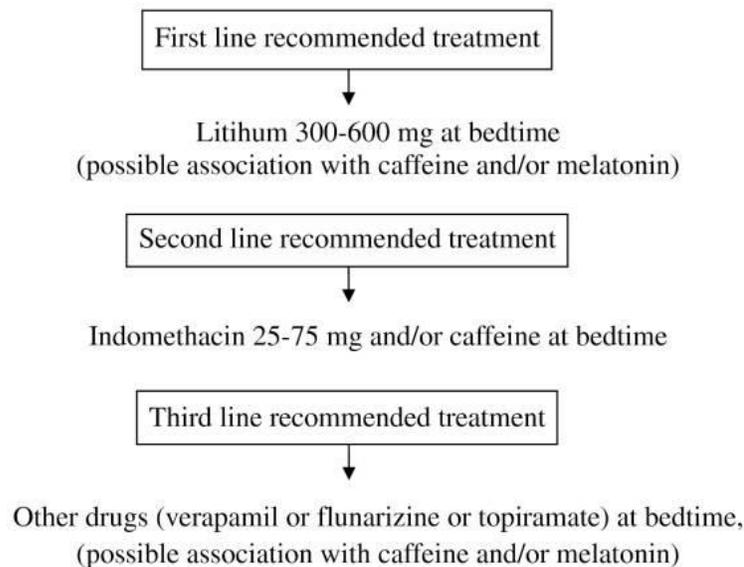
*Lisotto C, Rossi P, Tassorelli C, Ferrante E, Nappi G: J Headache Pain. 2010 Aug;11(4):349-54. Epub 2010 Jun 29.*

Source: Headache Centre, Department of Neuroscience, S. Vito al Tagliamento Hospital, Pordenone, Italy.

Abstract: Hypnic headache (HH) is a primary headache disorder, which occurs exclusively during sleep and usually begins after 50 years of age. There are no controlled trials for the treatment of HH. We reviewed all the available papers, including 119 cases published in literature up to date, reporting the efficacy of the medications used to treat HH. Acute treatment is not recommended, since no drug proved to be clearly effective and also because the intensity and the duration of the attacks do not require the intake of a medication in most cases. As for prevention, a wide variety of medications were reported to be of benefit in HH. The drugs that were found to be effective in at least five cases are: lithium, indomethacin, caffeine and flunarizine.

Lithium was the most extensively studied compound and demonstrated to be an efficacious treatment in 32 cases. Unfortunately, despite its efficacy, significant adverse effects and poor tolerability are not rare, mainly in elderly patients. Many patients reported a good response to indomethacin, but some could not tolerate it. Caffeine and melatonin treatments did not yield robust evidence to recommend their use as single preventive agents. Nevertheless, their association with lithium or indomethacin seems to produce an additional therapeutic efficacy. A course of lithium should be tried first, followed 3-4 months later by tapering. If headache recurs during tapering, a longer duration of therapy may be needed. If lithium treatment does not provide a significant response, indomethacin can be commenced as second-line approach. If these treatments prove to be ineffective or poorly tolerated, other agents, such as caffeine and melatonin, can be administered.

#### Suggested flowchart for the treatment of Hypnic Headache



#### The Neuroprotective Disease-Modifying Potential of Psychotropics in Parkinson's Disease

*Edward C. Lauterbach, Leonardo F. Fontenelle, Antonio L. Teixeira: Parkinsons Dis. 2012; 2012: 753548.*

Abstract: Neuroprotective treatments in Parkinson's disease (PD) have remained elusive. Psychotropics are commonly prescribed in PD without regard to their pathobiological effects. The authors investigated the effects of psychotropics on pathobiological proteins,

proteasomal activity, mitochondrial functions, apoptosis, neuroinflammation, trophic factors, stem cells, and neurogenesis. Only findings replicated in at least 2 studies were considered for these actions. Additionally, PD-related gene transcription, animal model, and human neuroprotective clinical trial data were reviewed.

Results indicate that, from a PD pathobiology perspective, the safest drugs (i.e., drugs least likely to promote cellular neurodegenerative mechanisms balanced against their likelihood of promoting neuroprotective mechanisms) include pramipexole, valproate, lithium, desipramine, escitalopram, and dextromethorphan.

Fluoxetine favorably affects transcription of multiple genes (e.g., MAPT, GBA, CCDC62, HIP1R), although it and desipramine reduced MPTP mouse survival.

Haloperidol is best avoided.

The most promising neuroprotective investigative priorities will involve disease-modifying trials of the safest agents alone or in combination to capture salutary effects on H3 histone deacetylase, gene transcription, glycogen synthase kinase-3,  $\alpha$ -synuclein, reactive oxygen species (ROS), reactive nitrogen species (RNS), apoptosis, inflammation, and trophic factors including GDNF and BDNF.

### **Lithium: a switch from LTD- to LTP-like plasticity in human cortex**

*Voytovych H, Kriváneková L, Ziemann U: Neuropharmacology. 2012 Aug;63(2):274-9. Epub 2012 Apr 5.*

Source: Department of Neurology, Goethe-University Frankfurt, Schleusenweg 2-16, D-60528 Frankfurt am Main, Germany.

Abstract: Lithium, a simple cation, is the mainstay treatment of bipolar disorder. Deficient synaptic plasticity is considered one important mechanism of this disease. Lithium inhibits glycogen synthase kinase-3beta (GSK-3 $\beta$ ), which is involved in the regulation of synaptic plasticity.

In animal preparations, inhibition of GSK-3 $\beta$  by lithium up-regulated long-term potentiation (LTP) of excitatory synapses but down-regulated long-term depression (LTD). The effects of lithium on plasticity in the human brain are unexplored. We tested the effects of a single oral dose of 900 mg of lithium on LTP-/LTD-like plasticity in human motor cortex induced by established paired associative transcranial magnetic stimulation (PAS(LTP), PAS(LTD)) protocols.

We studied 10 healthy adults in a placebo-controlled double-blind randomized crossover design. PAS-induced plasticity was indexed by change in motor evoked potential amplitude recorded in a hand muscle. In the placebo session, subjects were stratified,

according to the known variability of the PAS(LTP) response, into PAS(LTP) 'LTP responders' and PAS(LTP) 'LTD responders' (n = 5 each).

Lithium did not affect the PAS(LTP)-induced LTP-like plasticity in the 'LTP responders', but switched the PAS(LTP)-induced LTD-like plasticity in the 'LTD responders' to LTP-like plasticity.

In contrast, lithium had no effect on the PAS(LTD)-induced LTD-like plasticity in the 'LTD responders'.

We provide first-time evidence that lithium significantly modulates brain stimulation induced plasticity in human cortex. The switch from LTD- to LTP-like plasticity is best explained by the inhibitory action of lithium on GSK-3 $\beta$ . This conclusion is necessarily circumstantial because GSK-3 $\beta$  activity was not directly measured. We discuss that other important plasticity-related modes actions of lithium cannot explain our findings.

## **Management of cluster headache**

*Tfelt-Hansen PC, Jensen RH: CNS Drugs. 2012 Jul 1;26(7):571-80*

Source: Danish Headache Center, Department of Neurology, University of Copenhagen, Glostrup Hospital, Glostrup, Denmark. ptha@regionh.dk

Abstract: The prevalence of cluster headache is 0.1% and cluster headache is often not diagnosed or misdiagnosed as migraine or sinusitis. In cluster headache there is often a considerable diagnostic delay - an average of 7 years in a population-based survey. Cluster headache is characterized by very severe or severe orbital or periorbital pain with a duration of 15-180 minutes. The cluster headache attacks are accompanied by characteristic associated unilateral symptoms such as tearing, nasal congestion and/or rhinorrhoea, eyelid oedema, miosis and/or ptosis. In addition, there is a sense of restlessness and agitation. Patients may have up to eight attacks per day.

Episodic cluster headache (ECH) occurs in clusters of weeks to months duration, whereas chronic cluster headache (CCH) attacks occur for more than 1 year without remissions.

Management of cluster headache is divided into acute attack treatment and prophylactic treatment. In ECH and CCH the attacks can be treated with oxygen (12 L/min) or subcutaneous sumatriptan 6 mg. For both oxygen and sumatriptan there are two randomized, placebo-controlled trials demonstrating efficacy. In both ECH and CCH, verapamil is the prophylactic drug of choice. Verapamil 360 mg/day was found to be superior to placebo in one clinical trial. In clinical practice, daily doses of 480-720 mg are mostly used. Thus, the dose of verapamil used in cluster headache treatment may be

double the dose used in cardiology, and with the higher doses the PR interval should be checked with an ECG. At the start of a cluster, transitional preventive treatment such as corticosteroids or greater occipital nerve blockade can be given.

In CCH and in long-standing clusters of ECH, lithium, methysergide, topiramate, valproic acid and ergotamine tartrate can be used as add-on prophylactic treatment. In drug-resistant CCH, neuromodulation with either occipital nerve stimulation or deep brain stimulation of the hypothalamus is an alternative treatment strategy.

For most cluster headache patients there are fairly good treatment options both for acute attacks and for prophylaxis. The big problem is the diagnosis of cluster headache as demonstrated by the diagnostic delay of 7 years. However, the relatively short-lasting attack of pain in one eye with typical associated symptoms should lead the family doctor to suspect cluster headache resulting in a referral to a neurologist or a headache centre with experience in the treatment of cluster headache.

**<http://www.sharecare.com/question/lithium-carbonate-have-label-uses>**

*Stacy Wiegman*

Lithium carbonate is approved for use to treat bipolar disorder in people 12 years of age and older. Sometimes, doctors prescribe lithium carbonate to treat conditions other than bipolar disorder. These are considered off-label uses.

Lithium carbonate may be used off-label to treat depression, Graves' disease, cluster or migraine headaches, neutropenia, agitation, and syndrome of inappropriate anti-diuretic hormone secretion, or SIADH. However, such uses are "off-label" and unapproved by the FDA for a reason -- for example, there may be too many side effects to outweigh the risks, or the effectiveness of lithium carbonate for that particular treatment hasn't yet been proven.

**[http://www.ehow.com/facts\\_5806769\\_lithium-parkinson\\_s-disease.html](http://www.ehow.com/facts_5806769_lithium-parkinson_s-disease.html)**

*J.M. Willhite*

Key Proteins: Bcl-2 is a protein that works to protect brain cells from injury. High levels of the protein glycogen synthase kinase 3b (GSK-3b) adversely affect brain cells and contribute to their deterioration.

Benefits of Lithium Treatment: Studies have demonstrated that lithium is beneficial for protecting brain cells from premature death. Lithium has been shown to increase concentrations of Bcl-2 and reduce levels of GSK-3b.