

## 1.1. Lithium and downbeat nystagmus

### Introduction

Lithium (Camcolit<sup>®</sup>, Priadel<sup>®</sup> and generic) has been granted marketing authorisation in the Netherlands since 1971 and is indicated for *the treatment of the manic phase of bipolar disorders, for prophylaxis of the manic and depressive phase of bipolar disorder and for the prophylaxis of recurrent depressive episodes* [1].

Downbeat nystagmus (DBN) is the most common form of acquired involuntary ocular oscillations overriding fixation. It is characterised by slow upward drifts and fast downward phases. The most common presenting symptoms are unsteadiness of gait and vertigo. On further inquiry, patients frequently report blurred vision or oscillopsia that increases on lateral gaze. DBN is often associated with other oculomotor disorders, predominantly smooth pursuit deficits and impairment of the optokinetic reflex and visual fixation suppression of the vestibulo-ocular reflex (VOR). DBN may be caused by lesions of the vestibulocerebellum and, rarely, bilateral paramedian brainstem pathology. In a large proportion of patients, however, no anatomical lesion can be identified (so-called idiopathic DBN) [2]. The aetiology of DBN is diverse. Craniocervical malformations, cerebellar degeneration, vascular pathology, inflammatory disease, multiple sclerosis and use of or intoxication with lithium or antiepileptic drugs have, among others, been implicated [2].

### Reports

On April 2, 2010 the database of the Netherlands Pharmacovigilance Centre Lareb contained two reports concerning downbeat nystagmus is association with the use of lithium.

Table 1. Reports of downbeat nystagmus associated with the use of lithium

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 65811 F, 52	lithium 800 mg daily, bipolar affective disorder	venlafaxine	nystagmus	unknown discontinued recovered
B 91313 F, 52	lithium 1000 mg daily, psychosis	paracetamol, rizatriptan, paracetamol/ codeine	nystagmus	11.5 years dose reduction recovered

From the information in the reports it is clear that report A and B are not duplicate reports. The patients do not have the same date of birth and are from different parts of the country.

Patient A is a female aged 52 years, with downbeat nystagmus following administration of lithium carbonate 800 mg daily for bipolar affective disorder with an unknown latency. Situation occurred in a stable state of her lithium therapy for several months. Evaluation by a neurologist took place in April 2007, after almost six years of use of lithium. Nuclear magnetic resonance imaging (MRI) did not show any abnormalities. Lithium carbonate was withdrawn. The patient switched to valproic acid, after which she recovered. Concomitant medication was venlafaxine. The reporter was a specialist doctor (psychiatrist).

Patient B is a female aged 52 years, with a downbeat nystagmus following administration of lithium carbonate for psychosis diagnosed with a latency of 11.5 years after start, 11 years after perception of visual field defects. Following dose reduction from 1000 to 800 mg, the patient recovered. Concomitant medications were paracetamol, paracetamol/codeine and rizatriptan. MRI did not reveal any abnormalities, ocular causes were excluded by a consulted ophthalmologist. The reporter was a specialist doctor (neurologist).

## Other sources of information

### *SmPC*

The SmPC of lithium does not describe (downbeat) nystagmus [1,3].

### *Literature*

In the literature lithium has been associated as a cause of downbeat nystagmus, most often as a chronic effect despite normal levels [4-6], and rarely with acute overdose [6,7]. Some patients had been treated for several years with therapeutic lithium levels before the nystagmus developed [8]. There may be predisposing conditions such as hypomagnesaemia [5], cerebellar degeneration [6], or Chiari malformation (structural defects in the cerebellum) [9]. Nystagmus can resolve [5,10] or persist [6,11] after stopping lithium.

Some case reports are described below to illustrate this association.

Primary position downbeat nystagmus has been described during lithium therapy in two patients with manic-depressive illness. Withdrawal of lithium resulted in marked resolution of the nystagmus in one patient, with only minimal improvement in the second. In this latter patient, valproic acid was effective in producing marked decreases in the nystagmus and in lessening the difficulty with oscillopsia [10].

Downbeat nystagmus with extrapyramidal symptoms was reported in a 58-year-old male who had received 1200 milligrams (mg) lithium daily for 4 years. The patient was being effectively treated for a bipolar illness, with lithium levels in the range of 0.96 to 1.4 millimoles/liter (mmol/L), when downbeat nystagmus developed. It was accompanied by mild cogwheel rigidity and a tremor at rest. The admission lithium level was 1.1 mmol/L and all laboratory tests were normal or negative. Reduction of the lithium dose to 600 mg daily and the serum level to 0.45 mmol/L reduced the severity of the nystagmus. An increase in the daily lithium dose to 1200 mg resulted in recurrence of the downbeat nystagmus to the same degree as when the patient was admitted [12].

### *Databases*

Due to the limited number of reports of this association in the Lareb database, the reporting odds ratio (ROR) could not be calculated.

Downbeat nystagmus is not available as a MedDRA preferred term. On April 13, the WHO database of the Uppsala Monitoring Centre contained 44 reports of nystagmus in association with lithium which was reported disproportionately (ROR = 7.3, 95% CI 5.4 -9.8).

Under nystagmus, on April 12 the Eudravigilance database contained one additional report of downbeat nystagmus associated with lithium use, occurring in a 34-year old male. The patient developed nystagmus during a legionella pneumonia. No lithium levels were available. The reaction occurred seven years after first use of lithium.

### *Prescription data*

The number of patients using lithium in the Netherlands is shown in Table 2.

Table 2. Number of patients using lithium in the Netherlands between 2005 and 2008 [13]

Drug	2005	2006	2007	2008
Lithium	31,563	31,648	30,210	32,591

### *Mechanism*

Nystagmus and other abnormalities of the extraocular muscles are said to be caused by a direct effect of lithium on the central nervous system [14].

The mechanism of lithium-induced downbeat nystagmus (DBN) remains unclear, but the associated pathology probably affects nuclear structures in the cervicomedullary region, the area disrupted by other causes of DBN such as Chiari malformation, demyelination, and infarction [7].

## Discussion and conclusion

Lareb has received two well documented reports of downbeat nystagmus in patients treated with lithium. In the second patient the latency time is more than eleven years. It could be that the downbeat nystagmus in this patient occurred due to an increased lithium blood level. Increases in the lithium blood level can occur due to renal function disorders or hydration. Unfortunately, after follow-up from the reporter, the lithium blood level remains unknown for this case.

The association between downbeat nystagmus and lithium has been described in the literature extensively and is supported by a disproportionate number of associations in the WHO database. It should be considered to mention downbeat nystagmus to the SmPC of lithium as either an adverse reaction in section 4.8 of the SmPC or in section 4.4 'Special warnings and precautions with use'.

- It should be considered to mention downbeat nystagmus in the SmPC of lithium

## References

1. Dutch SmPC Priadel®, tabletten met gereguleerde afgifte 400 mg. (version date: 1-4-2007, access date: 2-4-2010) <http://db.cbg-meb.nl/IB-teksten/h05821.pdf>.
2. Wagner JN, Glaser M, Brandt T, Strupp M. Downbeat nystagmus: aetiology and comorbidity in 117 patients. *J Neurol Neurosurg. Psychiatry* 2008;79(6):672-7.
3. Dutch SmPC Camcolit® 400 mg. (version date: 1-11-2004, access date: 2-4-2010) <http://db.cbg-meb.nl/IB-teksten/h09013.pdf>.
4. Halmagyi GM, Rudge P, Gresty MA, Sanders MD. Downbeating nystagmus. A review of 62 cases. *Arch Neurol* 1983;40(13):777-84.
5. Coppeto JR, Monteiro ML, Lessell S, Bear L, Martinez-Maldonado M. Downbeat nystagmus. Long-term therapy with moderate-dose lithium carbonate *Arch Neurol* 1983;40(12):754-5.
6. Halmagyi GM, Lessell I, Curthoys IS, Lessell S, Hoyt WF. Lithium-induced downbeat nystagmus. *Am J Ophthalmol.* 1989;107(6):664-70.
7. Corbett JJ, Jacobson DM, Thompson HS, Hart MN, Albert DW. Downbeating nystagmus and other ocular motor defects caused by lithium toxicity. *Neurology* 1989;39(4):481-7.
8. Lee MS, Lessell S. Lithium-induced periodic alternating nystagmus. *Neurology* 2003;60(2):344
9. Monteiro ML, Sampaio CM. Lithium-induced downbeat nystagmus in a patient with Arnold-Chiari malformation. *Am J Ophthalmol.* 1993;116(5):648-9.
10. Williams DP, Troost BT, Rogers J. Lithium-induced downbeat nystagmus. *Arch Neurol* 1988;45(9):1022-3.
11. Rosenberg ML. Permanent lithium-induced downbeating nystagmus. *Arch Neurol* 1989;46(8):839
12. Gracia F, Koch J, Aziz N. Downbeat nystagmus as a side effect of lithium carbonate: case report. *J Clin Psychiatry* 1985;46(7):292-3.
13. College for Health Insurances. GIP database. (version date: 10-2-2010, access date: 10-2-2010) <http://www.gipdatabank.nl/index.asp?schermscherm=tabellenFrameSet&infoType=g&tabel=01-basis&item=J01FF>.
14. Fraunfelder FT; Fraunfelder FW. Fraunfelder FT, Fraunfelder FW, and Randall JA, editors. *Drug-Induced Ocular Side Effects*. 5th ed. Butterworth-Heinemann; 2001.

This signal has been raised on September 2010. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB [www.cbgmeb.nl/cbg/en/default.htm](http://www.cbgmeb.nl/cbg/en/default.htm) or the responsible marketing authorization holder(s).