

## SHORT REPORT

## Gabapentin but not vigabatrin is effective in the treatment of acquired nystagmus in multiple sclerosis: how valid is the GABAergic hypothesis?

F Bandini, E Castello, L Mazzella, G L Mancardi, C Solaro

### Abstract

**Acquired nystagmus occurs frequently in patients with multiple sclerosis and is often the cause of illusory motion of the environment (oscillopsia), and blurring of vision. Based primarily on the beneficial effect of gabapentin on acquired pendular nystagmus (APN), a GABAergic mechanism in controlling nystagmus has been hypothesised. If increasing GABA concentrations in the CNS are critical for the treatment of nystagmus, then a selective GABAergic drug should be highly successful. However, as gabapentin is not a selective GABAergic agent, vigabatrin, a “pure” GABAergic medication, and gabapentin, were compared in a single blind cross over trial in eight patients with definite multiple sclerosis.**

**Patients were randomly assigned to begin with gabapentin (1200 mg daily) or vigabatrin (2000 mg daily). Neuro-ophthalmological and electro-oculographic (EOG) evaluations were performed four and three times, respectively. Treatment efficacy was based on improving visual acuity and EOG indices (amplitude or frequency of nystagmus, or both) by at least 50% of pretreatment values. Three out of eight patients dropped out due to adverse effects.**

**In the remaining five patients gabapentin improved symptomatic pendular or gaze evoked jerk nystagmus in four. Three patients decided to continue gabapentin therapy. Importantly, vigabatrin proved useful in only one out of five patients, suggesting that gabapentin effectiveness may be related to additional non-GABAergic mechanisms of action. Interaction with cerebral glutamate transmission by inhibition of NMDA receptor might be an alternative hypothesis for the therapeutic action of gabapentin.**

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**Keywords:** gabapentin; vigabatrin; acquired nystagmus; multiple sclerosis

Different types of nystagmus can occur in patients with multiple sclerosis and are often the

cause of illusory motion of the environment, called oscillopsia, and blurring of vision. Gaze evoked nystagmus may impair vision during eccentric gaze holding, while the more distressing acquired pendular nystagmus (APN) can affect vision while looking straight ahead. The current pharmacological management of nystagmus includes anticholinergic drugs, baclofen, sodium or potassium channel blocking drugs, clonazepam, and other antiepileptic drugs (for a review see Büttner and Fuhry<sup>1</sup>) Unfortunately, most of these agents have proved to be irregularly effective and capable of inducing intolerable adverse effects. New drugs are thus needed. Recent reports indicate memantine in multiple sclerosis<sup>2</sup> and gabapentin in other diseases<sup>3</sup> as effective treatments for acquired pendular nystagmus. Based on the these findings, a GABAergic mechanism for the control of APN has been hypothesised.<sup>3</sup> However, gabapentin is not a selective GABAergic drug, having several other molecular mechanisms of action.<sup>4</sup> This finding prompted us to compare gabapentin and a “pure” GABAergic drug vigabatrin as treatment for symptomatic nystagmus (either pendular or gaze evoked jerk nystagmus) in a group of patients with multiple sclerosis. If an increase in GABA concentrations in CSF was crucial in reducing acquired nystagmus, then vigabatrin would be expected to show considerable therapeutic properties. Although safety issues have recently been raised about extended use of vigabatrin, especially concerning the occurrence of visual field defects,<sup>5</sup> we considered a 21 day trial as harmless for our patients. This work has been published in part in abstract form.<sup>6</sup>

### Methods

Eight patients with clinically definite multiple sclerosis,<sup>7</sup> followed up as outpatients at the Multiple Sclerosis Centre of the Department of Neurological Sciences and Vision, University of Genoa, were initially enrolled in this single blind cross over trial. Three patients dropped out of the study due to the occurrence of adverse effects (two patients experienced dizziness with vigabatrin and one patient severe nausea due to gabapentin). Thus, the final group consisted of five patients, two men and three women, two with relapsing-remitting

Department of  
Neurological Sciences  
and Vision, University  
of Genoa, via De Toni  
5, 16132 Genoa, Italy  
F Bandini  
L Mazzella  
G L Mancardi  
C Solaro

ENT Division, Head  
and Neck Department,  
S Martino Hospital,  
Genoa, Italy  
E Castello

Correspondence to:  
Dr F Bandini  
fbandini@neurologia.unige.it

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Table 1 Clinical features of patients with multiple sclerosis (MS) at the study entry

Patient No	Age	Sex	MS duration (y)	MS course	EDSS	Previous optic neuritis	Nystagmus type	
1	31	M	5	RR	3.5	Right eye	APN + RJN	RE>LE
2	43	F	14	CP	6	Bilateral	APN	RE>LE
3	39	F	8	RR	4.5	Right eye	APN + R/LJN	RE=LE
4	47	F	8	CP	5	None	APN + LJN	LE>RE
5	55	M	21	CP	6.5	Bilateral	APN + RJN	RE>LE

RR=Relapsing-remitting; CP=chronic-progressive; APN=acquired pendular nystagmus; RJN=right jerk nystagmus; LJN=left jerk nystagmus; R/LJN=right and left jerk nystagmus; RE=right eye; LE=left eye.

multiple sclerosis and three with chronic progressive multiple sclerosis. The mean age was 36.5 (range 24–55) years and the mean disease duration was 10.5 (range 5–21) years. At study entry, mean EDSS score was 5.5. All patients experienced a stable, symptomatic, horizontal nystagmus causing oscillopsia, or blurred vision, or both. One (patient 2) had APN with a mild suppression (and a slight improvement in visual acuity) by fixation of a near target. Four patients presented with APN plus gaze evoked jerk nystagmus. No previous symptomatic treatment had been attempted. Clinical details are shown in table 1.

Patients were randomly given either gabapentin or vigabatrin (both available commercially in Italy) at an increasing dosage to 1200 mg/day and 2000 mg /day, respectively, for 21 days. A lapse of 2 weeks between the two treatments served as a wash out period. Both the treating physician and the patients were aware of the nature of the medications. Gabapentin was given at an initial dose of 300 mg daily. After 3 days, dosage was increased to 300 mg twice daily. After 7 days the dosage was titrated to 1200 mg. The dose of vigabatrin was initially 500 mg daily, then was increased to 500 mg twice daily after 3 days, to reach a maximum dosage (2000 mg) after 7 days. No concomitant medications were allowed. All patients provided informed consent to participate.

Four neuro-ophthalmological examinations were performed: (1) before starting therapy (T0); (2) after 3 weeks of treatment (T1); (3) after a 2 week wash out (T2); (4) at the end of the second treatment period (3 weeks) (T3). The examination included an assessment of nystagmus with description of eye movement

and a short video recording, and measurement of monocular and binocular visual acuity (decimal values) at near (Parinaud card) and far (Snellen card) distances, in the primary position and in eccentric horizontal gaze.

A DC electroculography (EOG) recording (Nicolet-Nystar) was performed at T0, T1, and T3. Silver-silver chloride electrodes were attached to the inner and outer canthi of the eyes to record horizontal eye movements. Calibration was done before and during the recording session. We recorded nystagmus with or without fixation in the primary position (looking straight ahead) and in eccentric horizontal gaze, horizontal random saccades (6 degrees–32 degrees) and horizontal smooth pursuit movements (0.4, 0.2, and 0.1 Hz and 16 degree amplitude). The EOG amplifier allowed automatic measurements of mean amplitude (degrees) and frequency (Hz) of oscillations from 1 minute recording sessions. Latency, accuracy, and velocity of horizontal saccades and smooth pursuit gain were automatically measured as well. Both neuro-ophthalmological and EOG assessors were blinded to the nature of the drugs.

The efficacy of treatment was determined using three indices: (1) subjective report of decreased oscillopsia; (2) improvement of visual acuity of at least 50% from baseline values; (3) cessation of nystagmus or reduction in either amplitude or frequency of oscillations by at least 50% from baseline values.

## Results

Table 2 provides a summary of effects of both drugs in each patient. Gabapentin proved effective in four out of five patients tested

Table 2 Amplitude and frequency of nystagmus and visual acuity (near and far) values in patients with multiple sclerosis (MS) before and during GBP and VGB treatment

Patient No	Baseline				GBP				VGB			
	Nystagmus		Visual acuity		Nystagmus		Visual acuity		Nystagmus		Visual acuity	
	Amplitude (degrees)	Frequency (Hz)	Near	Far	Amplitude (degrees)	Frequency (Hz)	Near	Far	Amplitude (degrees)	Frequency (Hz)	Near	Far
1	3	4–5	0.4–0.6	0.4–0.4	0.5–1*	2*	0.8*–0.8	0.8*–0.8*	3	4	0.4–0.5	0.4–0.4
	3	4–5	0.1–0.1	0.1–0.2	1*	2*	0.4*–0.5*	0.4*–0.6*	3	4	0.1–0.1	0.1–0.2
2	3	4	0.2–0.5	0.1–0.4	2	4	0.2–0.4	0.1–0.3	3	4	0.2–0.4	0.1–0.3
3	3	3.5	0.6–0.6	0.6–0.6	1*	1.5*	0.7–0.8	0.8–0.7	3	3.5	0.8–0.8	0.7–0.8
	3–4	4	0.4–0.4	0.5–0.4	1–2*	1.5*	0.7*–0.7*	0.7–0.7*	3	3	0.5–0.4	0.5–0.5
4	5–6	2–3	0.6–0.6	0.8–0.8	1*	2	0.5–0.6	0.8–0.8	1*	3	0.5–0.5	0.8–0.8
	5	2	0.2–0.1	0.3–0.1	2*	2	0.4*–0.4*	0.6*–0.4*	2*	3	0.4–0.4*	0.5–0.4*
5	3	5–6	0.5–0.6	0.5–0.5	1*	4–5	0.8*–0.8	0.8*–0.8*	3	4–5	0.5–0.6	0.5–0.6
	3	5	0.3–0.3	0.4–0.4	1*	5	0.5*–0.5*	0.6*–0.6*	3	4	0.3–0.4	0.3–0.4

The first row shows values obtained in straight ahead fixation, and the second row shows values in eccentric gaze; the first column refers to the right eye, the second to the left eye. The asterisks show significant differences from the baseline condition (improvement by at least 50% in visual acuity or EOG parameters).

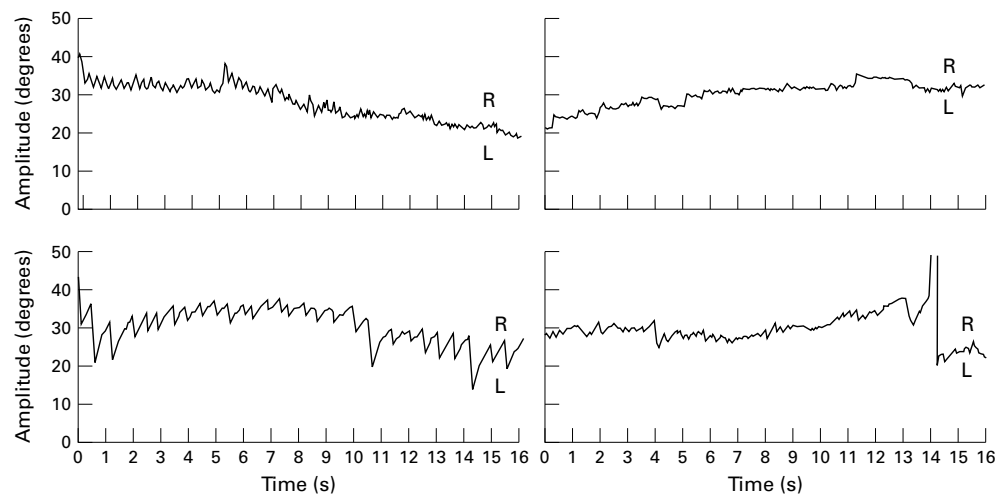


Figure 1 Two monocular DC-EOG recordings (open right eye) before (left) and during gabapentin treatment (right) for patient 1 (upper traces) and patient 4 (lower traces). Gabapentin induced a clear reduction of nystagmus amplitude and frequency in both patients. R = Rightward eye rotation; L = leftward eye rotation.

(80%). It improved visual acuity in straight ahead viewing in two patients, and in eccentric gaze in four patients; this was the same for near and far viewing. Amplitude of EOG oscillations was reduced in four patients, and frequency in two patients. Figure 1 shows two examples of nystagmus reduction (patients 1 and 4). Vigabatrin was effective in only one out of five patients (patient 4) (20%), affected by APN plus left gaze evoked nystagmus. Both drugs were ineffective in patient 2, with APN, who showed no change either in oscillopsia/visual acuity or EOG indices.

Two out of three patients (3 and 4), with pretreatment oscillopsia, reported a subjective improvement in illusory motion during gabapentin treatment. Patient 4, who responded well to both drugs, reported a reduction of oscillopsia also with vigabatrin. Patients 1, 3, and 4 decided to continue taking gabapentin.

Horizontal saccades and smooth pursuit measure values were unaffected by both drugs.

In these five patients both drugs were well tolerated. Adverse effects were limited to only two patients and were characterised by a mild decrease in daytime alertness in one patient (with gabapentin) and mild nausea in the second (with gabapentin). Increasing the doses of both drugs resulted in higher plasma concentrations within the dosage range. However, a clear relation between dosage and plasma concentration was not detected.

### Discussion

Within the limits of a single blind trial, our results in a selected multiple sclerosis population confirm previous reports of gabapentin efficacy in relieving symptomatic nystagmus.<sup>3</sup> Gabapentin can thus be considered as a promising agent for the treatment of symptomatic nystagmus in patients with multiple sclerosis, both gaze evoked and pendular nystagmus. Although these two types of eye oscillation reflect different pathogenetic mechanisms, both seemed to respond well to gabapentin.

The main result of our study, however, is that vigabatrin was ineffective in improving oscillopsia or blurred vision and in reducing nystagmus;

only one patient (4) benefited from vigabatrin (and from gabapentin as well). Vigabatrin is a structural analogue of GABA, with a well known “pure” mechanism of action—that is, an irreversible inhibition of GABA transaminase. This, in turn, produces an increase in GABA concentrations in CNS. Caution is obviously needed to draw any conclusion from a study on only five patients. However, lack of therapeutic success with a selective GABAergic drug such as vigabatrin raises some considerations. Firstly, GABA seems to be just one, and probably not the most important, neurotransmitter involved in coordinating conjugate ocular movements, at least in the horizontal plane. Many other neurotransmitters—such as excitatory aminoacids, acetylcholine, and glycine—have been identified in the ocular motor system and are likely relevant in controlling visual fixation.<sup>1</sup> Secondly, the beneficial action of gabapentin on nystagmus may be exerted through a non-GABAergic mechanism. Gabapentin is a relatively novel antiepileptic drug recently found to be effective for several neurological symptoms including paroxysmal symptoms in patients with multiple sclerosis.<sup>8</sup> Several putative mechanisms of action have been identified for gabapentin. Among them, voltage dependent block of voltage sensitive sodium ( $\text{Na}^+$ ) channels, attenuation of voltage sensitive calcium ( $\text{Ca}^{2+}$ ) channels, and antiglutamatergic activity at the NMDA site.<sup>4</sup> The molecular mechanisms underlying pathological nystagmus are very complex and, whereas the pathophysiology of eccentric gaze holding impairment is well established, little is known about the neuropharmacology of APN.<sup>3</sup> It is tempting to speculate that the multiple pharmacological actions of gabapentin might explain its role in controlling different types of eye oscillation. In particular, a glutamate antagonist effect through inhibition of NMDA receptor at different neuroanatomical sites (decrease of excitatory input either to the motor neurons or to the Purkinje cells?) might be responsible for the therapeutic action. The reported beneficial effect on APN by memantine,<sup>2</sup> another non-

competitive NMDA receptor antagonist, is consistent with this hypothesis.

- 1 Büttner U, Fuhry L. Drug therapy of nystagmus and saccadic intrusions. *Adv Otorhinolaryngol* 1999;55:195-227.
- 2 Starck M, Albrecht H, Pollmann W, et al. Drug therapy for acquired pendular nystagmus in multiple sclerosis. *J Neurol* 1997;244:9-16.
- 3 Averbuch-Heller L, Tusa RJ, Fuhry L, et al. A double-blind controlled study of gabapentin and baclofen as treatment for acquired nystagmus. *Ann Neurol* 1997;41:818-25.
- 4 White HS. Comparative anticonvulsant and mechanistic profile of the established and newer antiepileptic drugs. *Epilepsia* 1999;(suppl 5):S2-10.
- 5 Hardus P, Verduin WM, Postma G, et al. Concentric contraction of the visual field in patients with temporal lobe epilepsy and its association with the use of Vigabatrin medication. *Epilepsia* 2000;41:581-7.
- 6 Bandini F, Castello E, Mazzella L, et al. Gabapentin and vigabatrin as treatment for symptomatic nystagmus in multiple sclerosis: a single-blind crossover trial. *Neurology* 1999;52:A29;S12.001.
- 7 Poser CM, Paty DW, Scheinberg LC, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983;33:227-31.
- 8 Solaro C, Lunardi GL, Capello E, et al. An open-label trial of gabapentin treatment of paroxysmal symptoms in multiple sclerosis patients. *Neurology* 1998;51:609-11.

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