

# Congenital Nystagmus: Randomized, Controlled, Double-Masked Trial of Memantine/Gabapentin

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**Objective:** Nystagmus consists of involuntary to and fro movements of the eyes. Although studies have shown that memantine and gabapentin can reduce acquired nystagmus, no drug treatment has been systematically investigated in congenital nystagmus.

**Methods:** We performed a randomized, double-masked, placebo-controlled study investigating the effects of memantine and gabapentin on congenital nystagmus over a period of 56 days. The primary outcome measure was logarithmic minimum angle of resolution (logMAR) visual acuity; the secondary outcome measures were nystagmus intensity and foveation, subjective questionnaires about visual function (VF-14) and social function. Analyses were by intention to treat.

**Results:** Forty-eight patients were included in the study. One patient in the placebo group dropped out. Patients were randomized into either a memantine group ( $n = 16$ ), gabapentin group ( $n = 16$ ), or placebo group ( $n = 15$ ). Mean visual acuity improvements showed a significant effect between treatment groups ( $F = 6.2$ ;  $p = 0.004$ , analysis of variance) with improvement in both memantine and gabapentin groups. Participants with afferent visual defects showed poorer improvements in visual acuity to medication than those with apparently normal visual systems. However, eye movement recordings showed that both nystagmus forms improved in nystagmus intensity ( $F = 7.7$ ;  $p = 0.001$ ) and foveation ( $F = 8.7$ ;  $p = 0.0007$ ). Participants subjectively reported an improvement in vision after memantine and gabapentin treatment more often than in the placebo group ( $p = 0.03$ ). However, there were no significant differences between the treatment groups with visual function (VF-14) or social function questionnaires because all groups reported improvements.

**Interpretation:** Our findings show that pharmacological agents such as memantine and gabapentin can improve visual acuity, reduce nystagmus intensity, and improve foveation in congenital nystagmus.

Ann Neurol 2007;61:130–138

Nystagmus consists largely of involuntary periodic to and fro movement of the eyes, which can be pendular or of jerk type with a slow and fast component. It is either congenital or acquired due to neurological disease.<sup>1</sup> The prevalence is estimated at 1/1,000.<sup>2</sup> The impact of nystagmus on vision is significant, with visual function scoring worse than age-related macular degeneration.<sup>3</sup> Although a few studies with pharmacological agents have been done in acquired neurological nystagmus, little research has been directed toward treatment of congenital nystagmus.

Congenital nystagmus can be idiopathic (CIN), which is most likely caused by abnormal development of areas in the brain controlling eye movements and gaze stability.<sup>4</sup> It can also be associated with albinism

and retinal diseases such as achromatopsia, blue cone monochromatism, or congenital stationary night blindness. Some evidence exists that in these diseases nystagmus is not caused by low vision but rather is intrinsic to the disease. For example, carriers of blue cone monochromatism with normal visual acuity (VA) have eye movement abnormalities.<sup>5</sup> In albinism, misrouting of the nerve fibers in the optic chiasm with more fibers crossing than in healthy individuals also indicates a neurodevelopmental abnormality. A third congenital form of nystagmus occurs with visual deprivation in early infancy, for example, by congenital cataract or optic nerve hypoplasia.

A small number of studies have shown that pharmacological treatment can reduce acquired nystagmus.

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Received Aug 4, 2006, and in revised form Oct 12. Accepted for publication Nov 24, 2006.

This article includes supplementary materials available via the Internet at <http://www.interscience.wiley.com/jpages/0364-5134/suppmat>

Published online Feb 5, 2007 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ana.21065

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The potential role of GABA in eye movement stability<sup>6-8</sup> prompted studies using baclofen<sup>9</sup> and gabapentin.<sup>9-11</sup> Gabapentin reduced acquired pendular nystagmus. Pendular nystagmus caused by multiple sclerosis improved with memantine, an agent involving effects on *N*-methyl-D-aspartate, 1-Amino-3-Hydroxy-5-Methyl-4-Isoxazole Propionic Acid (AMPA), and dopaminergic pathways.<sup>12</sup> Several other drugs have been reported to reduce acquired nystagmus but were not used in controlled studies.<sup>13-15</sup>

In contrast with acquired nystagmus, pharmacological treatment has been recently reported in only a few cases of congenital nystagmus.<sup>16,17</sup> We have reported a case of congenital nystagmus associated with corneal dystrophy where VA improved with gabapentin<sup>18</sup> and a series including seven patients with various forms of congenital nystagmus all improving with gabapentin.<sup>19</sup>

These results prompted us to investigate the effect of two drugs, gabapentin and memantine, in a placebo-controlled, double-masked study in congenital nystagmus. Our hypothesis was that memantine and gabapentin can improve VA and reduce nystagmus intensity in congenital nystagmus.

## Subjects and Methods

The study was approved by the Leicestershire Ethics Committee and all subjects gave written consent before enrollment in the study. The trial was registered on the International Standard Randomised Controlled Trial Number scheme (ISRCTN; No. 65414827).

### Participants and Procedures

The study was performed at the Leicester Royal Infirmary. Forty-eight subjects with congenital nystagmus were enrolled between September 2004 and October 2005. Eligible for inclusion were adult subjects (>18 years of age) with congenital nystagmus. We excluded subjects if they were unable or unwilling to give written informed consent, if they had any neurological disorder other than nystagmus, if they had prior exposure to gabapentin or memantine, if they were pregnant

or breast-feeding, or if they had any other disease that prevented them from participating in the study. Demographics, diagnosis, and baseline VA of patients are listed in Table 1.

The trial profile is shown in Figure 1. Before enrollment in the study, patients had an ophthalmological examination (preenrollment assessment) including logarithmic minimum angle of resolution (logMAR) VA measuring the VA first with both eyes open, then with the right eye and the left eye with three different charts (modified Early Treatment Diabetic Retinopathy Study (EDTRS) with Sloan letters; Lighthouse Low Vision Products, New York, NY) used in random order. VA was measured using the preferred head position so each participant could use his or her position of gaze where the nystagmus is quietest (null point). Slit lamp examination, fundus examination, subjective refraction, and eye movement recordings were also performed. All patients underwent electroretinograms and visual-evoked potentials (according to International Society for Clinical Electrophysiology of Vision [ISCEV] standards)<sup>20</sup> to determine whether they had any retinal abnormalities or abnormal crossing signs in visual-evoked potentials, which indicate albinism. Participants in whom no pathology other than nystagmus was found were classified as having CIN (*n* = 21); all other participants were classified as having secondary nystagmus (SN) (*n* = 27). No participants suffered from periodic alternating nystagmus (evident from eye movement recordings). Participants were also asked to fill in the Visual Function 14 (VF-14)<sup>21</sup> questionnaire containing 14 questions about the ability to perform frequently used visual tasks and a social function questionnaire (SFQ), which we have developed for people with nystagmus<sup>3</sup> and which consists of 21 questions.

### Eye Movement Recordings

An infrared video pupil tracker with head movement compensation (EyeLink eye tracker; SensoMotoric Instruments GmbH, Berlin, Germany) was used to record horizontal and vertical right and left gaze positions at a sample rate of 250Hz. The eye tracker has a resolution of 0.005 degree and noise level of less than 0.01 degree RMS (root mean square). The horizontal and vertical range of the eye cameras was  $\pm 30$  and  $\pm 20$  degrees, respectively. The subject sat at a distance of 1.2m from a rear projection screen with visual stimuli generated using a VisLab projection system

Table 1. Demographics, Diagnostics, and Baseline Logarithmic Minimum Angle of Resolution Visual Acuity

Characteristics	Memantine Group		Gabapentin Group		Placebo Group	
	Idiopathic	Secondary	Idiopathic	Secondary	Idiopathic	Secondary
<i>n</i>	6	10	8	8	6	9
Sex, M:F	3:3	8:2	5:3	5:2	4:2	7:2
Mean age $\pm$ SD, yr	44.0 $\pm$ 8.2	37.8 $\pm$ 13.4	41.0 $\pm$ 7.6	35.1 $\pm$ 10	37.7 $\pm$ 12.9	43.8 $\pm$ 12.9
Diagnosis		6 albinism; 2 achromatopsia; 1 optic atrophy; 1 optic nerve hypoplasia		7 albinism; 1 achromatopsia		6 albinism; 1 achromatopsia; 1 optic atrophy; 1 congenital cataracts
Mean VA better Eye $\pm$ SD	0.47 $\pm$ 0.14	0.66 $\pm$ 0.27	0.29 $\pm$ 0.16	0.57 $\pm$ 0.21	0.28 $\pm$ 0.09	0.67 $\pm$ 0.18
Mean VA worse eye $\pm$ SD	0.70 $\pm$ 0.33	0.85 $\pm$ 0.23	0.40 $\pm$ 0.17	0.67 $\pm$ 0.22	0.34 $\pm$ 0.14	0.79 $\pm$ 0.23
Mean VA both eyes $\pm$ SD	0.44 $\pm$ 0.17	0.65 $\pm$ 0.27	0.24 $\pm$ 0.12	0.55 $\pm$ 0.18	0.28 $\pm$ 0.22	0.61 $\pm$ 0.16

VA = visual acuity; SD = standard deviation.

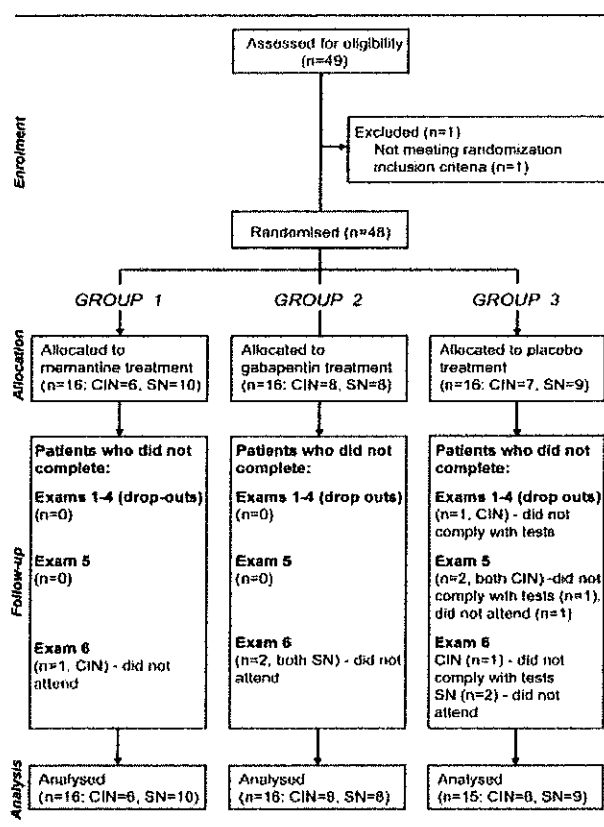


Fig 1. Trial profile. CIN = congenital idiopathic nystagmus; SN = secondary nystagmus.

(Sensomotoric Instruments GmbH) and Hitachi CP-X958 LCD video projector (resolution: 1024 × 768; Hitachi, Chula Vista, CA). A chin rest was used to maintain a fixed head position.

The eye movement task consisted of participants following a fixation target (1-degree diameter) moving every 8 seconds horizontally (except for two volunteers with vertical nystagmus following a similar vertically moving target) from −24 to +24 degrees in 3-degree steps (see Fig 4B). An initial calibration of the data was performed off-line using fixations of a 3 × 3 grid (±20 degrees wide and ±15 degrees high). The calibration was then corrected for non-linearity using the main visual task by fitting forth order polynomials to mean positions measured during foveation of each of the 3-degree steps from −24 to +24 degrees (see Fig 4C). Care was taken not to include data where fixation switched from one eye to the other in alternating strabismus, or where volunteers struggled to maintain fixation at the most eccentric positions.

A program was written to analyze the nystagmus waveforms, using all available 2- to 5-second blocks of data (mean, 3.5 seconds; standard deviation, 0.78 second) in which the volunteer was “fixating” the target. At each location, the intensity of the nystagmus (amplitude × frequency) and the expanded Nystagmus Acuity Function (NAFX) were calculated as an estimate of foveation (developed by L.F. Dell’Osso, full details are given online at: [www.wmlab.org](http://www.wmlab.org)).

In brief, the NAFX is performed by gradually increasing position and velocity thresholds until foveation periods are seen during each cycle. The NAFX function estimates VA from the mean foveation duration and standard deviations of position and velocity data during the foveation. The mean intensity and NAFX in the null region were estimated from the values ±6 degrees eccentricity about the minimum intensity value (see Fig 4D). Mean intensity was also estimated across all locations (from −24 to +24 degrees) where the volunteers were successfully fixating the target. Data from the eye with better VA were used for analysis, or in patients with strabismus, from the predominantly fixing eye.

### Randomization

After the initial examination before the study, participants were randomly assigned to memantine, gabapentin, or placebo treatment.

The Pharmacy Production Unit of the Royal Hallamshire Hospital prepared blocks of drug packages for six patients to allow subrandomization of patients according to the diagnosis of CIN or SN. Each block contained two packages for participants with memantine capsules, two with gabapentin capsules, and two with placebo capsules. The order of the packages was random and unknown to the examiners and participants. Randomization was performed by the pharmacy using a random number sequence in blocks of three (Scientific Tables, Documenta Geigy). Because we enrolled more participants with SN than CIN, four blocks of six packages were used for SN patients, three blocks of six packages for CIN patients, and one block of six packages for the remaining patients (three CIN and three SN patients). Each time six patients were recruited, a new block of six drug packages was ordered from the pharmacy and patients were allocated in order of their recruitment to the following number of drug packages.

The Pharmacy Production Unit of the Royal Hallamshire Hospital encapsulated memantine (5mg), gabapentin (300mg), and placebo (microcrystalline cellulose [Avicel, DHP Ltd supplies]) in identical gelatin capsules and packaged them sealed in plastic bottles with a 5-week supply. After the initial visit before enrollment, participants came for another six visits. The first examination was before treatment. Then participants received an increasing amount of capsules (number of capsules equal in the three treatment groups) over a 35-day period and maintained the same dosage for an additional 21 days (Table 2). Memantine was increased up to a dosage of 40mg because previous studies in acquired nystagmus have shown that some patients required more than the licensed dosage (20mg) to reduce their nystagmus. Gabapentin was prescribed up to 2,400mg.<sup>12</sup> If patients did not tolerate a drug dosage, they were asked to call one of the investigators and discuss side effects, and if necessary, they were asked to reduce the dosage to the last well-tolerated dose. Patients had further examinations 2 weeks (on 20mg or 4 capsules memantine, 1,200mg or 4 capsules gabapentin, and 4 capsules placebo), 5 weeks, and 8 weeks (on 40mg or 8 capsules memantine, 2,400mg or 8 capsules gabapentin, and 8 capsules placebo) after the beginning of the study. Patients came for

Table 2. Drug Dosage, Examination Dates, and Side Effects

Day	Memantine Group (n = 16)	Gabapentin Group (n = 16)	Placebo Group (n = 15)	Number of Capsules (AM, lunch, PM)
1 <sup>a</sup>				
1-5	10mg	600mg	2 capsules	2 (1, 0, 1)
6-10	15mg	900mg	3 capsules	3 (1, 1, 1)
11-15	20mg	1,200mg	4 capsules	4 (2, 1, 1)
15 <sup>a</sup>				
16-20	25mg	1,500mg	5 capsules	5 (2, 2, 1)
21-25	30mg	1,800mg	6 capsules	6 (2, 2, 2)
26-30	35mg	2,100mg	7 capsules	7 (3, 2, 2)
31-35	40mg	2,400mg	8 capsules	8 (3, 3, 2)
35 <sup>a</sup>				
36-56	40mg	2,400mg	8 capsules	8 (3, 3, 2)
56 <sup>a</sup>				
≈75 <sup>a</sup>				
Reduced dosages and side effects				
Reduced dosage	30mg (n = 3), 25mg (n = 1), 20mg (n = 1), 15mg (n = 1)	2,100 mg (n = 1)	None	
Capsules taken, %	92.4	90.8	99.1	
Side effects	Dizzy, tired, sleepless, light-headed, nauseated, headaches, shaky, weak, drowsy <sup>b</sup>	Dizzy, tired, sleepless, light-headed, nauseated, forgetful, headaches, shaky, depressed <sup>b</sup>	Dizzy, tired, light-headed, nauseated, headaches <sup>c</sup>	

<sup>a</sup>Patients underwent examinations on days 1, 15, 35, 56, and ≈75.

<sup>b</sup>n = 9.

<sup>c</sup>n = 5.

additional visits 14 days and 2 to 3 months after they stopped drug intake. Participants and examiners were masked to the treatment of each participant until the end of the study.

At each visit, best-corrected VA was measured, eye movement recordings were performed (methods as described for initial examination), and patients filled in the questionnaires (question about subjective improvement of vision and nystagmus after treatment, VF-14, SFQ). The primary outcome measure was the change in logMAR VA between examinations 1 and 4 with both eyes open. Secondary outcome measures were change from examination 1 to 4 in foveation (measured using the NAFX), mean percentage changes in nystagmus intensity in the null region and across all positions from -24 to +24 degrees, and change in VF-14 and SFQ questionnaires after the 56 days of treatment. On visit 4, the participants were also asked whether they had subjective improvement in vision and nystagmus. They were asked whether their vision and nystagmus changed with treatment and could answer "yes" or "no." If they answered yes, they were asked whether their vision and nystagmus got worse or better and to grade it in three categories: (1) a little, (2) moderately, or (3) a great deal.

After the trial, participants were given the possibility to continue memantine or gabapentin prescribed in a clinical setting.

#### Statistical Analysis

The power calculation was based on our previous data (see Shery and colleagues<sup>19</sup>) in seven patients with congenital nys-

tagmus (two with CIN, five with SN). The mean improvement in logMAR VA under gabapentin treatment was 0.14, with the standard deviation of the improvements being 0.14. Fifteen subjects in each group would be required for a statistical power of 80%. To account for possible dropouts, we aimed to include 48 participants.

An "intention-to-treat" analysis was used with improvement in vision between visits 1 and 4 as the primary outcome measure and change in nystagmus intensity and foveation (NAFX) between visits 1 and 4 as a secondary measure. The general linear model was used to statistically compare groups, with respect to improvement in VA, nystagmus intensity, NAFX, and questionnaire responses, introducing treatment group and type of nystagmus as fixed effects. A Bonferroni correction was introduced to perform pairwise post hoc comparisons between the treatment groups. Because missing data occurred for only one participant, mean substitution using patients in the same treatment group and with the same type of nystagmus was used to predict the missing outcome values. A crosstab Pearson's  $\chi^2$  test was used to compare subjective responses concerning whether the patients thought that their vision or nystagmus had improved.

For graphical presentation of data, a regression method was used to predict missing data for visits 5 and 6.

#### Results

Of the 48 patients enrolled, 47 completed the first 4 examinations, 46 completed the first 5 examinations, and 43 completed all 6 examinations (see Fig 1). One

patient with CIN, assigned to the placebo group, dropped out after the initial examination because she developed anxiety when wearing trial frames and eye movement recording equipment. The tolerability of the drug was good, and there were no serious adverse side effect. In the memantine group, 9 of 16 patients had side effects (patients described being dizzy, tired, sleepless, light-headed, nauseated, headaches, shaky, weak, and drowsy), and 6 patients reduced the dosage. In the gabapentin group, there were also 9 of 16 patients with side effects (patients felt dizzy, tired, sleepless, light-headed, nauseated, forgetful, headaches, shaky, and depressed), and 2 participants had to reduce the dosage. In the placebo group, 5 of 15 subjects had side effects (consisting of dizziness, tiredness, light-headedness, nausea, and headaches), but none had to reduce the number of capsules taken (see Table 2 for details). On the reduced dosage, participants had no or only slight well-tolerated side effects such as tiredness.

Figure 2 shows mean VA of the three treatment groups at examinations 1 to 6 for patients with CIN and SN. In the memantine and gabapentin groups, there was an increase in VA between examinations 1 and 4 for CIN. When the drug was stopped after examination 4, the VA deteriorated after 2 weeks (examination 5) and returned to values similar to pre-treatment at examination 6 after 2 to 3 months. For participants with SN, the increase of VA was small.

The improvement in vision in logMAR VA was 0.15 ( $\pm 0.18$ ), 0.09 ( $\pm 0.05$ ), and 0.04 ( $\pm 0.03$ ) for CIN and 0.05 ( $\pm 0.04$ ), 0.04 ( $\pm 0.07$ ), and  $-0.03$  ( $\pm 0.05$ ) for SN in the memantine, gabapentin, and placebo groups, respectively (Fig 3A). Both treatment groups ( $F = 6.2$ ;  $p = 0.004$ ) and type of nystagmus ( $F = 10.1$ ;  $p = 0.002$ ) had a statistically significant

effect on improvement in logMAR VA. Pairwise post hoc comparisons showed that the effect of the treatment group was mainly due to differences between memantine and placebo groups ( $p = 0.003$ ) with a nonsignificant difference between gabapentin and placebo groups ( $p = 0.11$ ). The difference between gabapentin and memantine groups was not significant ( $p = 0.55$ ). By chance, the starting VA of the memantine group was higher than the gabapentin group. Consequently, when VAs are expressed as percentage improvement, both memantine and gabapentin show similar effects (see Fig 3C); percentage improvement in VA was 22.2% ( $\pm 8.5\%$ ), 24.5% ( $\pm 7.2\%$ ) and 8.6% ( $\pm 3.2\%$ ) for CIN, and 5.8% ( $\pm 1.8\%$ ), 6.7% ( $\pm 4.5\%$ ), and  $-5.3\%$  ( $\pm 2.2\%$ ) for SN in the memantine, gabapentin, and placebo groups, respectively. When expressed in this way, there was also a significant effect due to the treatment groups ( $F = 5.2$ ;  $p = 0.009$ ) and to type of nystagmus ( $F = 17.4$ ;  $p = 0.0001$ ). Pairwise post hoc comparisons showed that both memantine ( $p = 0.04$ ) and gabapentin ( $p = 0.01$ ) groups had significantly higher percentage improvement in VA than the placebo group. There was no significant difference between memantine and gabapentin groups ( $p = 0.99$ ).

In Figure 4A, original recordings of eye movements are shown for patients in each treatment group at examinations 1 and 4. The change in nystagmus from  $-24$  to  $+24$  degrees is represented in Figure 4B. Figure 4C indicates that all three examples could fixate the targets during foveation reasonably accurately. Figure 4D shows the change in intensity between the first and fourth examination from  $-24$  to  $+24$  degrees, with the hatched area indicating the null region estimate.

The Supplementary Figure shows video recordings of eye movements of a patient before memantine ad-

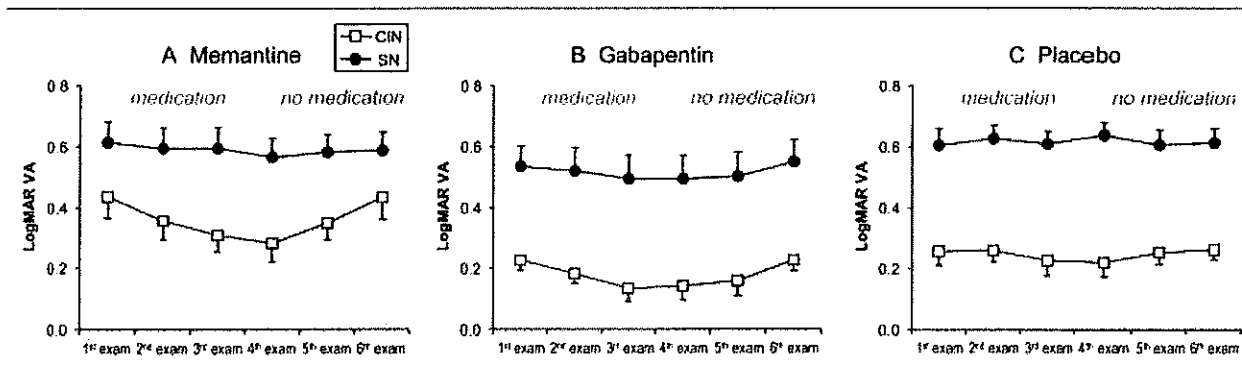
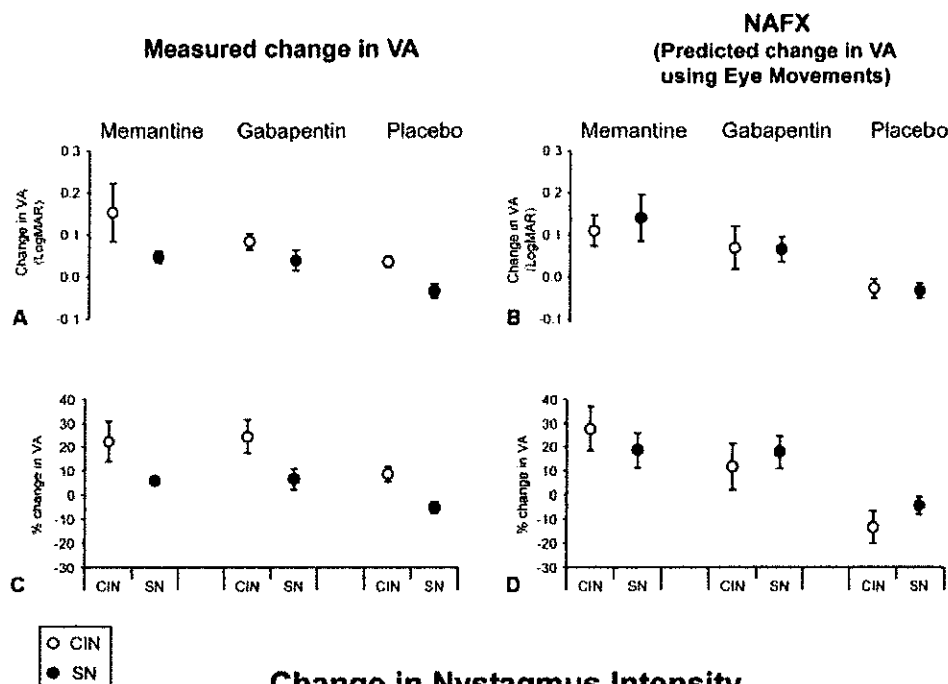


Fig 2. Logarithmic minimum angle of resolution visual acuity (logMAR VA; mean and standard error of the mean [SEM]) for participants treated with memantine (A), gabapentin (B), and placebo (C) before drug administration (Examination 1) and 2 (Examination 2), 5 (Examination 3), and 8 weeks (Examination 4) after drug administration, and 2 weeks (Examination 5) and 2 to 3 months (Examination 6) after the drug was stopped. CIN = congenital idiopathic nystagmus (open squares); SN = secondary nystagmus (closed circles).

## Change in Visual Acuity



## Change in Nystagmus Intensity

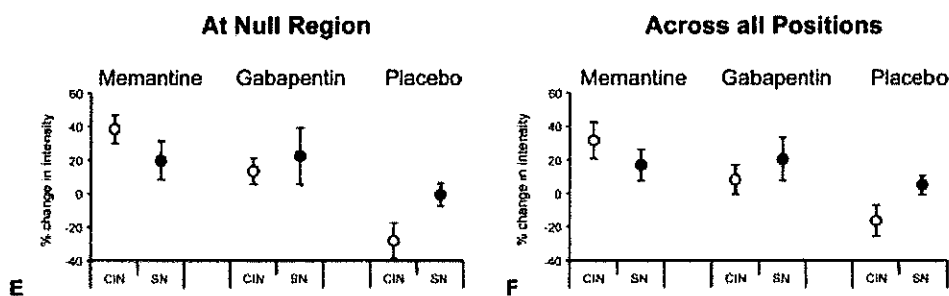


Fig 3. Absolute change (mean and standard error of the mean) in (A) measured logarithmic minimum angle of resolution (logMAR) visual acuity (VA), (B) predicted change in logMAR from eye movement recordings (using Nystagmus Acuity Function [NAFX]), (C) percentage change in measured logMAR VA, and (D) percentage change in predicted logMAR VA from eye movement recordings. The change measured was before and after 56 days of treatment with memantine or gabapentin for patients with congenital idiopathic nystagmus (CIN; open circles) and secondary nystagmus (SN; solid circles). (E, F) Mean percentage change of nystagmus intensity (E) in the null region and (F) across all points measured from  $-24$  to  $24$  degrees over the same time period.

ministration. After 30mg memantine intake, the nystagmus of this patient clearly decreased.

Using the NAFX (predicted changes in VA using eye movement recordings) to estimate foveation, we noted that VA improved similarly in CIN and SN groups, for all three treatment groups, in contrast with actual VA, where CIN improved much more than SN (compare Figs 3A and 3B). Thus, treatment group had a statistically significant effect on the NAFX ( $F = 7.8$ ;  $p = 0.001$ ), whereas type of nystagmus did not ( $F = 0.02$ ;  $p = 0.89$ ). Pairwise post hoc comparisons showed that

both memantine ( $p = 0.001$ ) and gabapentin ( $p = 0.02$ ) groups had significantly higher percentage improvement in NAFX than the placebo group. There was no significant difference between memantine and gabapentin groups ( $p = 0.99$ ).

Figures 3E and 3F show the change in intensity at the null region and across all positions tested, respectively. The effect of the medications influences nystagmus intensity in a similar way at the null region and across all other positions. These patterns also bear resemblance to the percentage change in NAFX VA (see

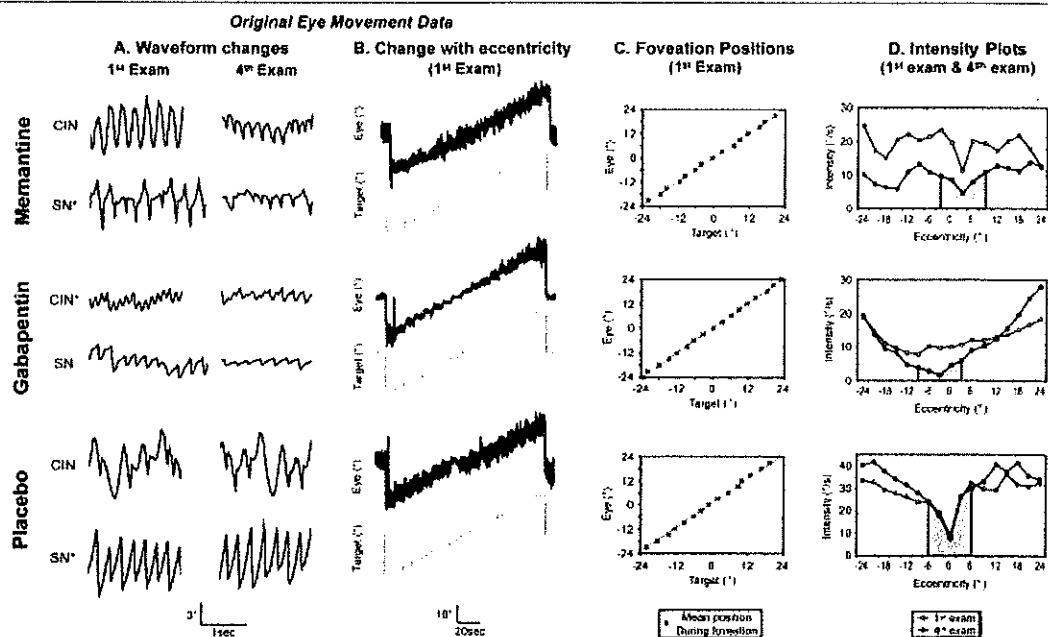


Fig 4. (A) Original horizontal eye movement recordings of the right and left eye of (first row) a patient with congenital idiopathic nystagmus (CIN) and (second row) a patient with secondary nystagmus (SN) associated with albinism before and during memantine treatment; (third row) a patient with CIN and (fourth row) a patient with SN associated with achromatopsia before and during gabapentin treatment; (fifth row) a patient with SN and (sixth row) a patient with SN associated with albinism before and during placebo treatment at examinations 1 and 4. Eye movements to the right are represented by an upward deflection, and eye movements to the left by a downward deflection. Asterisks indicate participants also shown in B, C, and D. (B) The change in nystagmus for a patient in each treatment group when following a fixation target moving horizontally from  $-24$  to  $+24$  degrees in 3-degree steps. (C) The mean eye position measured during foveation (X; determined using Nystagmus Acuity Function [NAFX]) is shown for the same three patients for each target position. These plots were used for the following functions: (i) to correct nonlinear data (by fitting a fourth order polynomial), (ii) to identify changes in the fixing eye in the case of alternating strabismus, and (iii) to identify when patients could not maintain fixation in the most eccentric gaze positions. (D) Change in nystagmus intensity is plotted for the first (open circles) and fourth (solid circles) examinations from  $-24$  to  $+24$  degrees. The hatched areas indicate the area used to measure mean intensity and NAFX at the null point for examinations 1 and 4 (ie,  $\pm 6$  degrees around the minimum intensity).

Fig 3D). Consequently, the treatment group had a statistically significant effect in all three cases ( $F = 7.7$ ,  $p = 0.001$  for percentage change in intensity at null region;  $F = 4.7$ ,  $p = 0.02$  across all positions;  $F = 8.8$ ,  $p = 0.0007$  for percentage change in NAFX), whereas type of nystagmus did not ( $F = 0.41$ ,  $p = 0.52$  for percentage change in intensity at null region;  $F = 0.59$ ,  $p = 0.45$  across all positions;  $F = 0.02$ ,  $p = 0.88$  for percentage change in NAFX).

Pairwise post hoc comparisons suggest that memantine may have a more potent effect than gabapentin on percentage change in nystagmus intensity (memantine vs placebo:  $p = 0.001$  at null region and  $p = 0.02$  across all positions; gabapentin vs placebo:  $p = 0.01$  at null region and  $p = 0.14$  across all positions) and NAFX (memantine vs placebo:  $p = 0.0008$ ; gabapentin vs placebo:  $p = 0.009$ ), although there was no significant difference between the two

groups (memantine vs gabapentin:  $p \geq 0.95$  for all measures).

At visit 4, 10 patients reported a subjective improvement in vision on memantine treatment (6 "a little," 2 "moderately," 2 "a great deal"), 9 patients reported an improvement in vision on gabapentin treatment (3 "a little," 5 "moderately," 1 "a great deal"), and in the placebo group, 1 patient reported they improved "a little" and one patient reported they deteriorated "moderately." The differences among the groups were significant ( $p = 0.03$ , crosstab Pearson's  $\chi^2$  test). Seven patients reported a subjective improvement in nystagmus on memantine treatment (4 "a little," 1 "moderately," 2 "a great deal"), 6 patients reported an improvement in vision on gabapentin treatment (1 "a little," 2 "moderately," 3 "a great deal"), and in the placebo group, 1 patient reported

they improved "a little." These differences were not significant ( $p = 0.17$ ).

All groups reported improvements using the VF-14 questionnaire with scores ( $\pm$  standard deviation) changing from 37.1 ( $\pm 16.2\%$ ) to 27.9% ( $\pm 15.8\%$ ) with memantine, 23.9 ( $\pm 18.4\%$ ) to 17.5% ( $\pm 17.4\%$ ) with gabapentin, and 34.0% ( $\pm 20.4\%$ ) to 28.4% ( $\pm 23.0\%$ ) in the placebo group (for VF-14, 0% = can perform all 14 visual tasks, 100% = can perform none of the 14 visual tasks). All groups also reported improvements in the SFQ with scores ( $\pm$  standard deviation) changing from 70.9 ( $\pm 16.0\%$ ) to 76.5% ( $\pm 13.0\%$ ) with memantine, 72.9 ( $\pm 16.4\%$ ) to 80.5% ( $\pm 14.1\%$ ) with gabapentin, and 67.5 ( $\pm 14.6\%$ ) to 74.3% ( $\pm 12.7\%$ ) in the placebo group (for SFQ, 100% = best social function score, 0% = worst social function score). There were no significant differences between the treatment groups with respect to VF-14 ( $p = 0.50$ ) and SFQ ( $p = 0.95$ ) scores because all groups reported improvements in visual and social function.

Thirteen study participants opted to continue to take memantine (up to 9 months) and 13 to continue with gabapentin (up to 10 months) after the study. The effect on VA and nystagmus was similar to the effect during the study and was maintained as long as the drugs were taken.

### Discussion

Our findings support the hypothesis that memantine and gabapentin are effective in treatment of congenital nystagmus. We have shown significant improvement in VA, nystagmus intensity, and foveation in patients with congenital nystagmus with memantine and gabapentin treatment. Although VA improved significantly in patients with CIN, there was only a slight effect in SN, which did not reach statistical significance. This is likely to be caused by the organic ocular disease causing afferent deficits such as non-functioning cones in achromatopsia, foveal hypoplasia in albinism, optic nerve atrophy or hypoplasia, and possible amblyopia in the patient with congenital cataract. Although the central VA did not improve significantly in SN, predicted VA using the eye movement recordings (NAFX) improved by approximately the same amount in SN and CIN. Patients with SN reported subjective improvement in vision with memantine and gabapentin and also choose to continue with treatment after the study. This might be due to improvement in peripheral vision as opposed to vision in the central retina.

Interestingly, the question whether vision changed subjectively discriminated well between treatment with either memantine or gabapentin and placebo as significantly more participants taking memantine or gabapentin indicated that their vision improved more

than those taking placebo. However, the VF-14 and SFQ showed a significant improvement after memantine and gabapentin treatment, as well as after placebo treatment. This highlights the fact that participation in a study and treatment, even with placebo, may by itself improve the subjective visual function, well-being, and social interaction of people with nystagmus.

Memantine preferentially blocks excessive glutamatergic activity, and its mechanisms of action involve effects on *N*-methyl-D-aspartate, AMPA, and dopaminergic pathways.<sup>22</sup> Gabapentin is thought to act by binding to the  $\alpha 2$  delta subunit of voltage-dependent calcium channels.<sup>23</sup> The mechanism by which these drugs suppress nystagmus are currently unclear. The recent discovery of FRMD7, a novel gene mutated in X-linked CIN, may lead to the elucidation of the mechanisms of nystagmus and the beneficial effects of these drugs.<sup>24</sup>

The tolerability of these drugs was good and there were no serious adverse reactions. Side effects were most commonly mild consisting mostly of dizziness, tiredness, and sleeplessness and did not require discontinuation.

We had to reduce the dosage in 6 of 15 patients receiving memantine compared with 2 of 16 patients receiving gabapentin. This can be explained by the fact that we used memantine at a higher dosage than routinely used (licensed up to 20mg), because in previous studies, patients with acquired nystagmus required doses larger than 20 mg.<sup>12</sup> However, with individualized reduced dosage, all patients tolerated treatment well. In our study, the VA improved on increasing dosage up to 35 days of treatment for memantine and gabapentin and continued to improve on a constant dosage during the further 21 days. Similarly, the reduction in VA was not immediate and there was still some effect of the drugs 3 weeks after drug cessation.

Patients who opted to continue with gabapentin or memantine after the study had a sustained effect as long as they took the drugs (up to 9–10 months). This indicates that the effect of memantine and gabapentin is sustained at least for several months.

We show for the first time in a controlled study that it is possible to treat congenital nystagmus pharmacologically. In the patients examined in our trial, we could not find a difference between the effect of memantine or gabapentin. Additional trials are needed to investigate whether memantine or gabapentin is better for individual patients and to analyze the optimal dosage and duration of effect of these drugs.



This study was supported by the Nystagmus Network, UK (I.G.); the University Hospitals of Leicester (RM17006, RM17007, I.G.); and the Ulverscroft Foundation (01-03, F.P., I.G.).

R.J.M. was involved in recruiting subjects, examinations, coordination of study, eye movement recordings analysis, and preparation of figures. F.A.P. was involved in the study design, eye movement recordings analysis, statistical analysis, and write up. S.T. conducted ophthalmological examinations, was medical advisor for participants, and was involved in study design. C.D. performed electrophysiological examinations. I.G. had the overall responsibility for the study and was involved in study design, patient examinations, and write up of the study.

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