Expert Opinion

The pharmacological treatment of nystagmus: a review

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Nystagmus is an involuntary, to-and-fro movement of the eyes that can result in a reduction in visual acuity and oscillopsia. Mechanisms that cause nystagmus are better understood in some forms, such as acquired periodic alternating nystagmus, than in others, for example acquired pendular nystagmus, for which there is limited knowledge. Effective pharmacological treatment exists to reduce nystagmus, particularly in acquired nystagmus and, more recently, infantile nystagmus. However, as there are very few randomized controlled trials in the area, most pharmacological treatment options in nystagmus remain empirical.

Keywords: 3,4-diaminopyridine, acquired nystagmus, acquired pendular nystagmus, baclofen, downbeat nystagmus, gabapentin, infantile nystagmus, memantine, multiple sclerosis, periodic alternating nystagmus, upbeat nystagmus

Expert Opin. Pharmacother. (2009) ***10****(11):1805-1816*

1. Introduction

The involuntary, to-and-fro oscillation of the eyes in pathological nystagmus can occur in the horizontal, vertical and/or torsional plane and be further classified into a jerk or pendular waveform [1]. Nystagmus leads to reduced visual acuity due to the excessive motion of images on the retina, and also the movement of images away from the fovea [2]. As the desired target falls further from the centre of the fovea, receptor density decreases and therefore the ability to perceive detail is reduced [3]. Visual acuity also declines the faster the target moves across the fovea [4].

Three main mechanisms stabilize the line of sight (to static targets) so that the image we see is fixed and clear. The first is fixation, which has two components: i) the ability of the visual system to detect retinal drift and initiate corrective eye movements; and ii) the suppression of unwanted eye movements away from the viewed target. The second mechanism is the vestibulo-ocular reflex. Motion detectors in the inner ear generate eye movements to compensate for perturbations and provide clear vision during head movement. The final mechanism is the gaze-holding system, enabling the eyes to hold an eccentric position. A disruption in any of the three mechanisms can result in the eyes drifting away from the target and corrective fast eye movements being made, leading to nystagmus [5].

Nystagmus can be infantile or acquired in later life and it is important to differentiate between the two types. This can be achieved by considering not only the time of onset of the nystagmus, but also the waveform characteristics of the nystagmus. For those who have infantile nystagmus (IN), this can be idiopathic or secondary/associated to another eye disease, such as retinal disease, albinism, low vision or visual deprivation in early life [1]. Nystagmus can be acquired through vestibular or neurological disease. The most common causes of acquired neurological nystagmus are stroke or multiple sclerosis [6].

It is possible to differentiate between different types of nystagmus by examining the waveform. IN usually occurs in the horizontal plane and has a jerk waveform – a slow phase drift and a fast corrective phase repositioning the eye. The direction of a jerk nystagmus is described using the fast phase. In IN, the slow phase usually

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10.1517/14656560902978446 © 2009 Informa UK Ltd ISSN 1465-6566

has an increasing velocity [7]. Often, IN consists of pendular waveforms (sinusoidal movements) interrupted by regularly occurring foveating saccades. Acquired nystagmus (AN) can appear in the horizontal, vertical or torsional plane and can be of a jerk or pendular waveform [5]. AN jerk waveform presents very frequently with a decreasing slow phase velocity (**Figure 1**).

Nystagmus waveforms can be viewed in detail via eye-movement recordings. Eye movements can be documented using different methods. Electroculography, the scleral search coil and video eye-tracking devices are the most common techniques, although there are advantages and disadvantages for all methods [8]. The quality of electroculography tends to be affected by artefact but, as it is relatively non-invasive, the technique can be used in children. The scleral search coil is not usually well tolerated for more than 30 min but has the advantage of recording three-dimensional eye movements (horizontal, vertical and torsional). Most video eye-trackers record in only two dimensions; however, this head-mounted piece of equipment has no contact with the eyes and is well tolerated, even by children. Another advantage of the video eye-tracker is high-quality recordings.

Nystagmus can be quantified in terms of amplitude (size) and frequency (cycles *per se*cond). The intensity of the nystagmus can be measured by multiplying the amplitude by the frequency [9]. Nystagmus intensity can vary with eye position and often there is a position of gaze in which the oscillations are minimal. This is usually referred to as the null point. If the null point does not coincide with the primary gaze position then a head position may be adopted to reduce the nystagmus [10]. This can result in a face turn when the nystagmus is in the horizontal plane or a chin up or down position when nystagmus occurs in the vertical plane.

Nystagmus can be distressing for both those with IN and AN. Although patients with IN and AN both have reduced vision, patients with AN tend to suffer from oscillopsia (the illusion of constant movement of the surroundings) and hence may be more troubled by the condition. The constant perception of motion is extremely distressing to the patient. In fact the impact of nystagmus is significant, with visual functioning scores worse in nystagmus than that of other visual impairments such as age-related macular degeneration [11]. The occurrence of nystagmus is also higher than early estimations. Previously it was thought that the prevalence of nystagmus was 1/1000 [12]; however, more recent data has estimated the prevalence to be that of 2.4/1000, more than double the previous figures [13].

Some forms of nystagmus are better understood than others. In forms that are understood, the range of knowledge includes animal models, the neurotransmitter involved and pharmacological treatment that can be effective. In other forms there is limited knowledge [14]. There are very few randomized controlled trials in the treatment of nystagmus and most of the current considerations for pharmacological treatment of the condition rely on low-quality reports. This review discusses hypotheses for the cause and possible pharmacological treatment for AN and IN. We do not cover peripheral vestibular nystagmus because this is usually associated with vertigo and postural imbalance. The symptoms associated with this type of nystagmus are usually transitory and therefore it is not necessary to treat peripheral vestibular nystagmus as an isolated symptom [15]. Central vestibular nystagmus is addressed under acquired neurological nystagmus forms.

2. Acquired nystagmus

2.1 Acquired pendular nystagmus

Acquired pendular nystagmus (APN) is a sinusoidal movement that can occur in the horizontal or vertical plane and that often has both horizontal and vertical components. The oscillations may be conjugate or disconjugate and, in some cases, monocular. This form of nystagmus occurs in many conditions, the most common being disorders of central myelin (often multiple sclerosis) and vascular disease (syndrome of oculopalatal myoclonus) [16]. These two main causes result in APN that differs in clinical features. In association with demyelinating disease typically the amplitude has been described as being greater in the eye with the poorer vision, frequency is 2 – 8 Hz and intranuclear ophthalmoplegia is commonly associated. For APN related to the syndrome of oculopalatal tremor, the oscillation may be vertical or disconjugate vertical/torsional, frequency is 1 – 3 Hz and may be synchronized with movements of the palate and other branchial muscles [5].

It is likely that different pathophysiologies are involved in each form of APN. One hypothesis for APN in demyelinating disease suggests that in patients with APN the oscillations arise in the neural integrator for eye movement – the gaze-holding mechanism that allows the eye to be held steady at an eccentric position [17]. The nucleus prepositus hypoglossi and medial vestibular nucleus region are known to play a part in the neural integrator function, which may be affected by a motor feedback signal from cell groups of the paramedian tracts to the cerebellar flocculus [18]. On magnetic resonance imaging, patients with multiple sclerosis often show lesions that may affect the paramedian cell groups. It is therefore proposed that APN arises from an unstable neural integrator which causes the oscillations [19]. Microinjections of agents of agonist or antagonist action at receptors for gamma-aminobutyric acid (GABA), glutamate and kainite in the region of the nucleus prepositus hypoglossi and medial vestibular nucleus in monkeys caused gaze-evoked nystagmus with centripetal eye drifts. Injections of the GABA-A agonist, muscimol, close to the centre of the medial vestibular nucleus caused drift away from the central position with increasing velocity waveforms, suggesting an unstable neural integrator [20]. Similar effects were also observed in cats [21]. It has been postulated that the use of GABAergic agents may suppress APN as the increased gain of feedback may be equal to the decrease in inhibition by the cerebellum [14].

For APN that is related to oculopalatal tremor, the main pathological finding is hypertrophic olivary degeneration. It

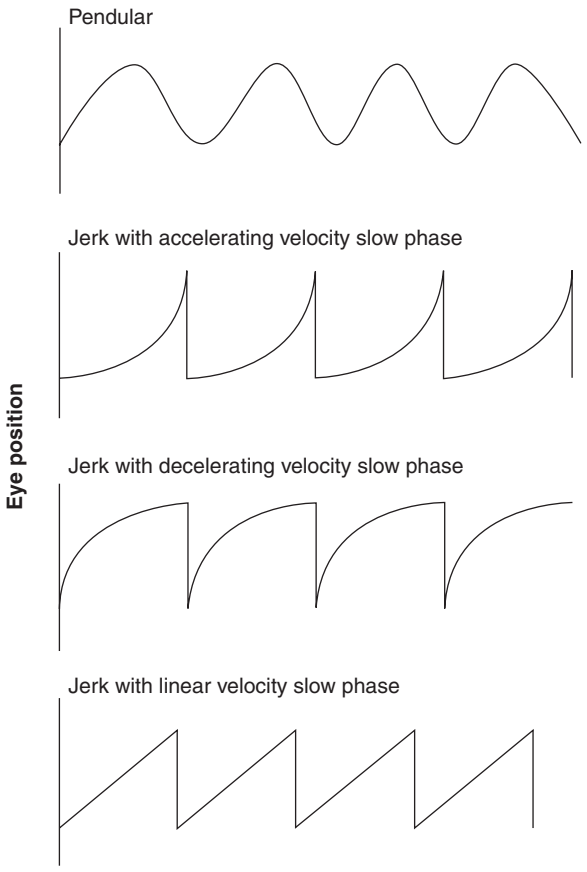

Figure 1. Nystagmus waveforms can be used to differentiate between types of nystagmus. Pendular nystagmus, jerk nystagmus with an accelerating slow-phase, jerk nystagmus with a decelerating slow and a linear slow-phase nystagmus.

has been suggested that responsibility for the syndrome may lie with a disruption of connections between the dentate nucleus and the contralateral inferior olivary nucleus [5]. One hypothesis is that deafferentation of the inferior olive gives rise to modification of connexion junctions between adjacent neurons leading to abnormal oscillatory neural activity [22].

Older studies suggest that the anticholinergic drug trihexyphenidyl was successful in the treatment of APN, hypothesizing that the disturbance of cholinergic mechanisms may play a part in the pathophysiology of APN [23,24]. However, in a later report of one of the few randomized, controlled trials of the treatment of nystagmus, only one of six patients showed an improvement in visual acuity while taking trihexyphenidyl [25]. Also, only a minor suppression of nystagmus was noted and intolerable side effects resulted in only a few of the original patients completing the trial.

The anticholinergic drug scopolamine has also been found useful in reducing APN and improving visual acuity [26]. The use of isoniazid has also been reported, with significant reduction of APN oscillations; however, it is unclear upon where this drug acts [27]. Suppression of APN has also been noted, in one patient, after smoking cannabis but not with nabilone tablets or capsules containing cannabis oil [28].

The finding that GABA plays a role in the mechanisms by which gaze is held steady prompted a randomized, controlled trial using two GABAergic drugs, gabapentin and baclofen [29]. In the 15 patients with APN, there was a significant improvement in visual acuity and reduction in eye movement while taking a relatively small dose of 900 mg per day gabapentin, but no significant changes with 30 mg per day baclofen. Half of the APN subjects who reported oscillopsia before gabapentin treatment noticed a decrease in illusory motion after medication. Further case reports confirmed the viability of gabapentin as a treatment for APN [30,31]. Gabapentin was also shown to be effective in APN when compared in a cross over trial with vigabatrin, another GABAergic drug [32]. All of the five patients who completed the trial showed improvement of APN during the gabapentin regime. Vigabatrin proved useful in only one patient. Gabapentin is not a selective GABAergic drug and has other mechanisms of action, whereas vigabatrin is a pure GABAergic agent. As vigabatrin, a pure GABAergic drug, did not reduce nystagmus, this suggests that the success of gabapentin may be attributed to one of its additional non-GABAergic mechanisms. Gabapentin also has an antiglutaminergic action by inhibition of the NMDA receptor and this was offered by the authors as an alternative hypothesis for the usefulness of gabapentin as a therapy for APN.

Consistent with this hypothesis is the effect of memantine, another NMDA receptor antagonist. In 11 patients with APN, the oscillations ceased when 15 – 60 mg memantine were administered [33]. Nystagmus amplitude decreased significantly with 30 mg memantine per day in all patients, and with a dosage of 40 mg per day a complete cessation of APN was reported (**Figure 2**). Five of the patients also benefited from an improvement in visual acuity of at least 50% in one eye.

Treatment for APN should be commenced with up to 2400 mg gabapentin per day in three divided doses. If this does not improve the nystagmus, 20 – 40 mg of memantine per day divided into two or three doses is advised.

2.2 Downbeat nystagmus

Downbeat nystagmus (DBN) is usually present in mid-position and tends to be exacerbated on downgaze and lateral gaze. Downbeat nystagmus most commonly occurs in cerebellar degeneration, Chiari malformation and drug intoxication [34]. A possible hypothesis with regard to the mechanism of DBN is based on the firing rates of vertical gaze-velocity cerebellar Purkinje cells in the flocculus and paraflocculus in primates. The Purkinje cells fire more rapidly for downward smooth-pursuit eye movements than they do for upward [35]. Impaired downward smooth-pursuit, resulting in DBN, could be due to a lesion of these Purkinje cells. In support of this hypothesis is the presence of DBN in monkeys after ablation of the cerebellar flocculus and paraflocculus [36].

Further studies in humans support the hypothesis that the cerebellar flocculus and paraflocculus play a role in DBN [37].

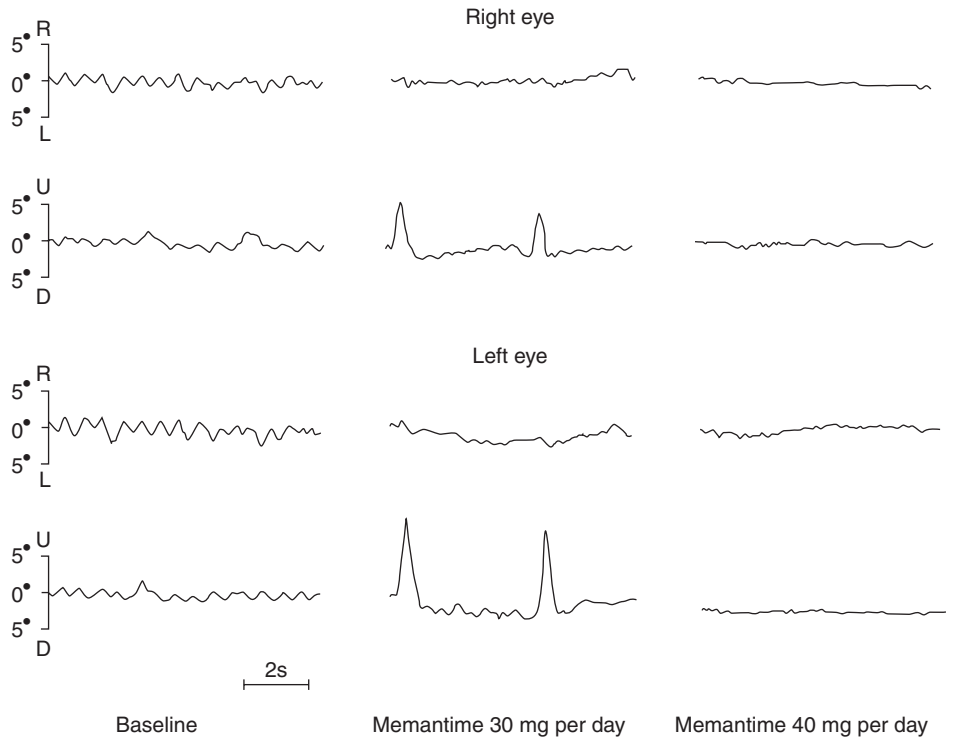

Figure 2. Eye movement recordings of one patient with acquired pendular nystagmus (APN) acquired due to multiple sclerosis. Vertical and horizontal eye movement traces before and after memantine. Reduction in amplitude after 30 mg per day memantine and further decrease in amplitude when memantine was increased to 40 mg per day.

Positron emission tomography (PET) scans of a patient with DBN showed reduced cerebral glucose metabolism, bilaterally, in the region of the cerebellar tonsil and flocculus/paraflocculus as compared to a normal database of the whole brain [38]. Evaluation of floccular activity with fMRI in four patients with DBN while performing vertical smooth pursuit eye movements showed significantly reduced activity of both floccular lobes during downward pursuit compared to controls [39]. Furthermore, computational model simulation of the effect of extensive loss of floccular Purkinje cells resulted in ocular motor features that are typically associated with DBN [40].

Early reports of the treatment of DBN suggest that GABAergic drugs may be useful. A single dose of 2 mg of the GABAergic drug clonazepam eliminated DBN in six of ten patients in primary position and seven of ten patients in downgaze; improvements in visual acuity and oscillopsia were also noted [41]. However, 2 mg clonazepam is a large dose and can be associated with significant side effects. In this study, patients suffered from sedative effects and were not allowed to drive for 8 h after taking the 2-mg dose. Clonazepam has also been deemed successful in treating acquired idiopathic DBN, but not in those with DBN attributed to cerebellar degeneration [42]. It is possible that the ability of clonazepam to enhance GABA activity may reduce DBN by compensating for the loss of inhibitory input from the cerebellum to ocular premotor neurons. Baclofen, another drug with GABAergic properties, prescribed at 15 mg per day, reduced DBN in two patients [43]. The possible mechanism of baclofen will be discussed later in periodic alternating nystagmus.

More recently, a randomized controlled trial has reported that the potassium-channel blocker 3,4-diaminopyridine (3,4-DAP) is effective in DBN [44]. Seventeen patients with DBN due to cerebellar atrophy, infarction, Chiari malformation and idiopathic aetiology were included in the trial. Patients were evaluated after 20 mg of 3,4-DAP was ingested orally. At maximum effect, 12 of the included patients had a 40% reduction in eye movements and ten reported less oscillopsia (**Figure 3**). The patients with DBN due to cerebellar infarctions only showed a minor reduction. Nine patients continued with the drug and showed ongoing benefit with only minor side effects such as nausea and headache. Cerebellar Purkinje cells inhibit the vestibular nucleus mediating upward but not downward eye movements [14,45,46]. Therefore, impaired cerebellar function would cause an upward drift of the eyes with a rapid corrective downward eye movement causing DBN. As Purkinje cerebellar cells are rich in potassium channels, increasing the discharge of these neurons will enhance Purkinje cell activity, which will in turn restore the inhibitory

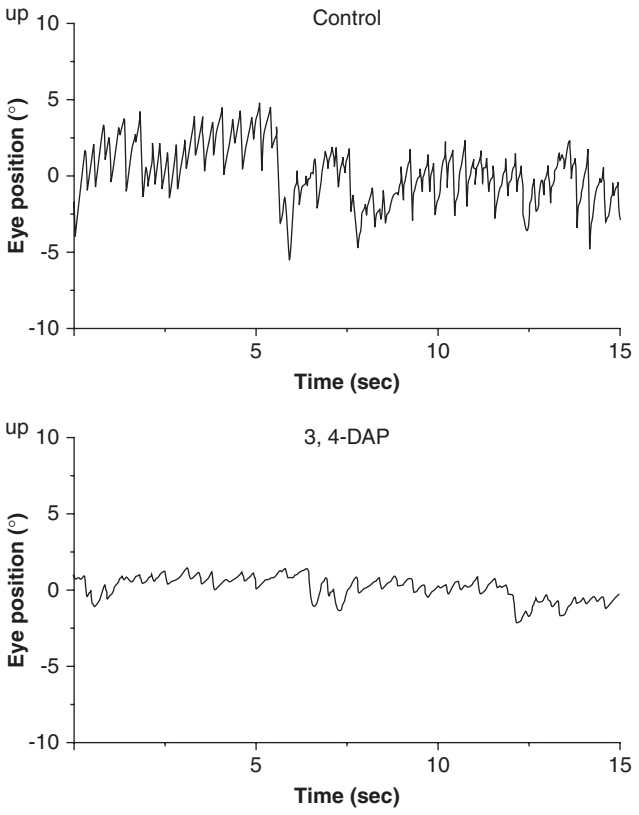

Figure 3. Vertical eye movement recording before (upper image) and 30 min after (lower image) ingestion of 3,4-diaminopyridine (3,4-DAP) showing decrease in nystagmus amplitude and frequency.

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influence of the cerebellum on vertical eye movements to a normal level [47].

Studies administering potassium channel blocker 4-aminopyridine (4-AP) have also been reported to increase Purkinje cell excitability in the cerebellar flocculi and dampen DBN [48]. A trial of 15 patients with DBN due to cerebellar atrophy of an idiopathic nature or due to other aetiologies, reports that 12 patients showed a decrease of DBN in straight ahead gaze after 10 mg 4-AP; this was particularly true for those with cerebellar atrophy [49]. 4-AP was also effective in reducing vertical and horizontal gaze-evoked drift regardless of the aetiology of DBN and may therefore also be a promising treatment for those with a dominant gaze-evoked component of nystagmus.

A trial with clonazepam may reduce DBN. However, if this is not successful, treatment with 10 – 20 mg 3,4-DAP per day in four divided doses should be administered. 4-AP prescribed at 10 mg three times a day may also be of benefit and patients may also suffer from fewer side effects than with 3,4-DAP.

2.3 Upbeat nystagmus

Upbeat nystagmus (UN) occurs infrequently. UN that occurs in the primary position is a vertical nystagmus, in which the fast phase beats upwards, and is usually increased on upgaze. However, unlike DBN, primary-position UN does not usually increase on lateral gaze [50]. Primary-position UN is most commonly reported with stroke, Wernicke's encephalopathy, multiple sclerosis and tumours of the medulla, cerebellum or midbrain, and should be differentiated from UN that is evoked in upgaze. UN that is gaze-evoked in upward gaze occurs in ocular motor disorders such as myasthenia gravis, general gaze-holding failure and also in some normal subjects [5].

It has been reported that UN decreases with the antiepileptic drug, carbamazepine [51], and that UN occasionally responds to the GABA-B agonist, baclofen [43]. Aminopyridines have also been shown be successful in the treatment of UN [48]. The potassium-channel blocker 4-AP has been reported to significantly dampen primary-position UN, relieving oscillopsia and restoring impaired upward smooth pursuit [52]. However, 4-AP had no positive effect on UN during attempted fixation in the dark. The authors postulate that 4-AP activated pathways carry visual information that could be used to aid UN suppression in the light, and propose that 4-AP helps in the activation of parallel pathways that assume the function of the lesioned structures. 4-AP might also increase the excitability of the cerebellar Purkinje cells and therefore strengthen the parallel pathway.

Treatment with 30 mg baclofen per day in three divided doses may be useful. If this does not improve UN then treatment with 4-AP should be commenced at 10 mg three times a day.

2.4 Periodic alternating nystagmus

The best understood form of AN is periodic alternating nystagmus (PAN). This is a primary-position nystagmus that periodically alternates in direction after approximately 2 min. Between each cycle there is a quiet phase of a few seconds before the nystagmus begins to beat in the opposite direction [50]. Acquired forms of PAN often occur with pathology involving the cerebellum, such as cerebellar degenerations, tumours and multiple sclerosis [5].

Experimental ablation of the nodulus and uvula of the cerebellum in monkeys was found to cause PAN when the animals were placed in the dark [53]. One function of the nodulus and uvula is to manage the time course of rotationally induced physiological nystagmus, also known as velocity storage [54]. The consequence of the ablation of the nodulus and uvula is that the duration of rotationally induced nystagmus is lengthened by increasing the time constant of velocity storage. To reverse the nystagmus a central adaptation mechanism acts and this produces PAN [55]. It has been shown that inhibitory pathways that use GABA help control to the velocity storage by the nodulus and uvula [56]. It follows that many case reports show that PAN responds well to treatment with baclofen. The first report to treat PAN with

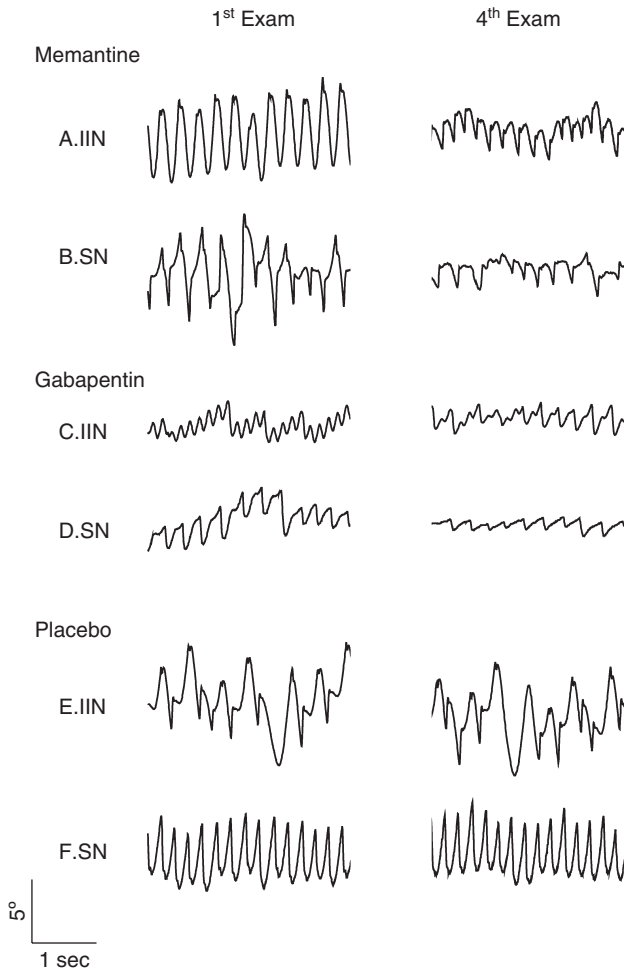

Figure 4. Change in horizontal eye movement before and after treatment for memantine, gabapentin and placebo patients in infantile idiopathic nystagmus (IIN) and secondary nystagmus (SN). Decrease in amplitude of nystagmus for memantine and gabapentin and no change in nystagmus for placebo.
Reproduced with permission from [76].

baclofen showed that a dose of 30 mg per day reduced a patient's oscillopsia and that, on examination, the nystagmus in primary position had disappeared. When the baclofen was stopped, the PAN returned [57]. Other reports have used doses of baclofen between 30 and 60 mg per day and showed improvements in terms of visual acuity, oscillopsia and eye movements [58-61]. Diazepam, 5-hydroxytryptophan, benserazide, thiocolchicoside, valproic acid and carbamazepine have been found to have no effect on PAN [62]. Gabapentin has also been reported to be of no benefit in PAN [63]. This further suggests that the success of gabapentin in APN is due to its glutaminergic properties, whereas the effects of baclofen on the vestibular cerebellum rely on GABA mechanisms. A case of PAN abolished with combination treatment of baclofen and memantine will be discussed later.

Baclofen prescribed at 30 mg per day in three divided doses is useful and commonly decreases PAN. However, congenital PAN appears to respond less so to baclofen.

3. Infantile nystagmus

Infantile nystagmus can be idiopathic or secondary to other visual deficits, such as albinism, retinal disease or loss of vision due, for example, to congenital cataracts or optic nerve hypoplasia. In IN associated with other eye disease, vision is not only affected by the excessive motion of the image on the retina caused by the nystagmus, but also by a defective visual system. In infantile idiopathic nystagmus (IIN), no underlying eye condition or neurological problems are present. It is thought that IIN is most likely caused by abnormal development of areas of the brain that control eye movement and gaze stability [64]. Patients with IIN can have a strong family history of nystagmus or can be single affected. In those with a family history of IIN it can be familial autosomal dominant or autosomal recessive, although the most frequent familial type is X-linked. A recent paper has identified the gene (*FRMD7*), which has been found to be the major cause of hereditary X-linked nystagmus. *In-situ* hybridization studies on the embryonic human brain have shown that FRMD7 is expressed in the ventricular layer of the forebrain, midbrain, cerebellum primordium, spinal cord and the developing neural retina. However, the function of FRMD7 is not yet known [65].

Infantile nystagmus is usually bilateral, conjugate, occurring in the horizontal plane and of a jerk waveform with an accelerating slow phase [7]. Waveforms in IN have been further classified into twelve subgroups, three of which are pendular, four jerk, four bidirectional jerk and one a pseudo-jerk waveform [66]. Patients with IN do not usually suffer from oscillopsia. Two hypotheses have been suggested to explain the mechanism behind the suppression of oscillopsia. The first is the 'sampling theory', by which the information from the most stable retinal images during the foveation periods can be used to establish a stable image [67]. It is suggested that only the information from the foveation period is used and the rest of the nystagmus cycle is ignored. The foveation period is a window in which the eye position is at/near the target position and the eye velocity is slow. This usually happens once per cycle of nystagmus. The second hypothesis is the 'remapping theory' whereby an efference copy signal of the nystagmus waveform is used to cancel the effects of motion [68]. This is probably the most likely theory because vision during the fast phases of the nystagmus cycle has been documented and argues against sampling. It is possible to estimate visual acuity from the foveation characteristics of nystagmus waveforms in IN and therefore make an objective assessment of potential visual acuity using an expanded nystagmus acuity function (NAFX) [69].

Although drugs have been administered for some time in AN, until recently this was not explored in IN. Early reports of treatment in infantile PAN suggest that baclofen may be

Table 1. Pharmacological treatment options for nystagmus.

Nystagmus type	Medication	Dose per day	Ref.	Sample size
APN	Gabapentin	Up to 2400 mg	[29]	15
			[30]	3
			[31]	1
			[32]	5
			[75]	11
	Memantine	20 – 40 mg	[33]	14
			[75]	3
			[57]	2
PAN	Baclofen	30 – 60 mg	[58]	2
			[59]	1
			[60]	1
			[61]	1
			[62]	1
			[63]	1
DBN	Clonazepam	2 mg	[41]	6
			[42]	7
	3,4-DAP	40-80 mg	[44]	17
	4-AP	30 mg	[49]	15
UN	Baclofen	30-60 mg	[43]	2
	4-AP	30 mg	[52]	1
IN	Gabapentin	Up to 2400 mg	[74]	1
			[75]	7
			[76]	16
	Memantine	20 – 40 mg	[76]	16

useful [70,71]. However, it has been documented that infantile PAN is often undiagnosed and as many as 9% of patients with IN have PAN [72]. More recently, smoking cannabis has been shown to reduce eye movement intensity and improve visual acuity in a patient with IIN and strabismus, particularly the latent component of nystagmus when one eye was covered [73]. Following on from the success of the use of gabapentin and memantine in AN, reports are now emerging showing benefits from these drugs in IN. A case report shows the benefit of gabapentin in IN associated with corneal opacities, improving visual acuity and dampening nystagmus [74]. A retrospective study assessing the value of gabapentin and memantine, not only in AN but also in IN, has shown promising results [75]. While two patients with IIN in this study were taking gabapentin, nystagmus amplitude was reduced and visual acuity increased by a line on the eye chart. The same benefits were noted in IN patients with other visual deficits such as the retinal disease achromatopsia. Although memantine was not prescribed to any of the IN patients in this study, it was postulated to be a strong candidate for the successful treatment of IN.

These results led to a randomized, controlled trial of gabapentin and memantine in the treatment of IN [76]. Forty-eight patients with IN were included in the study, 21 with IIN and 27 with nystagmus secondary to other visual deficits. Patients with secondary nystagmus (SN) included albinism, achromatopsia, optic atrophy, optic nerve hypoplasia and congenital cataracts. Each patient was randomized to memantine (up to 40 mg per day), gabapentin (up to 2400 mg per day) or placebo. Memantine and gabapentin both showed a positive effect in IIN and SN (**Figure 4**). Nystagmus intensity was measured across the null region and all points across the horizontal plane (–24 to 24 degrees). For both IIN and SN, the percentage change in nystagmus intensity was significant. In terms of recorded visual acuity, effects were stronger in the IIN group than the SN group. However, using the NAFX to estimate the foveation, a method to predict visual acuity using eye movement recordings, it was found that predicted visual acuity improved in both the IIN and SN groups. The tolerability of the drugs was good and only mild side effects were noted, e.g., dizziness and tiredness. None of the patients discontinued the trial and participants who opted to continue the medication after the trial had a sustained effect over more than 3 years.

Treatment for IN should commence with up to 2400 mg gabapentin per day in three divided doses. If no improvement is noted with gabapentin, then 20 – 40 mg of memantine should be prescribed.

4. Other treatments used in nystagmus

Surgical procedures are available for nystagmus. Kestenbaum procedures can be performed to correct for an abnormal head posture in a patient who has an eccentric null point. The surgery aims at moving the eyes in the orbit so that the null point is at primary position, eliminating the abnormal head posture [77,78]. The procedure is performed not only for cosmetic reasons but also to alleviate neck problems that can arise due to an abnormal head posture. There may also be improvement in visual acuity in some patients. For example, surgically correcting the head position in patients who wear glasses can enable them to view through their glasses centrally and achieve better optical correction. Early reports suggest that performing large recessions of the horizontal rectus muscles can be successful in reducing the amplitude of the nystagmus and improving visual acuity [79,80]. More recent reports assess the viability of performing the surgery without the recession or resection of the eye muscles and simply tenotomizing the four horizontal eye muscles and reattaching them in their original position. The tenotomy procedure has been reported to result in significant improvements in visual acuity and eye movement in IN, possibly by interruption of the afferent proprioceptive loop which in turn produces a dampened peripheral ocular motor response to the nystagmus

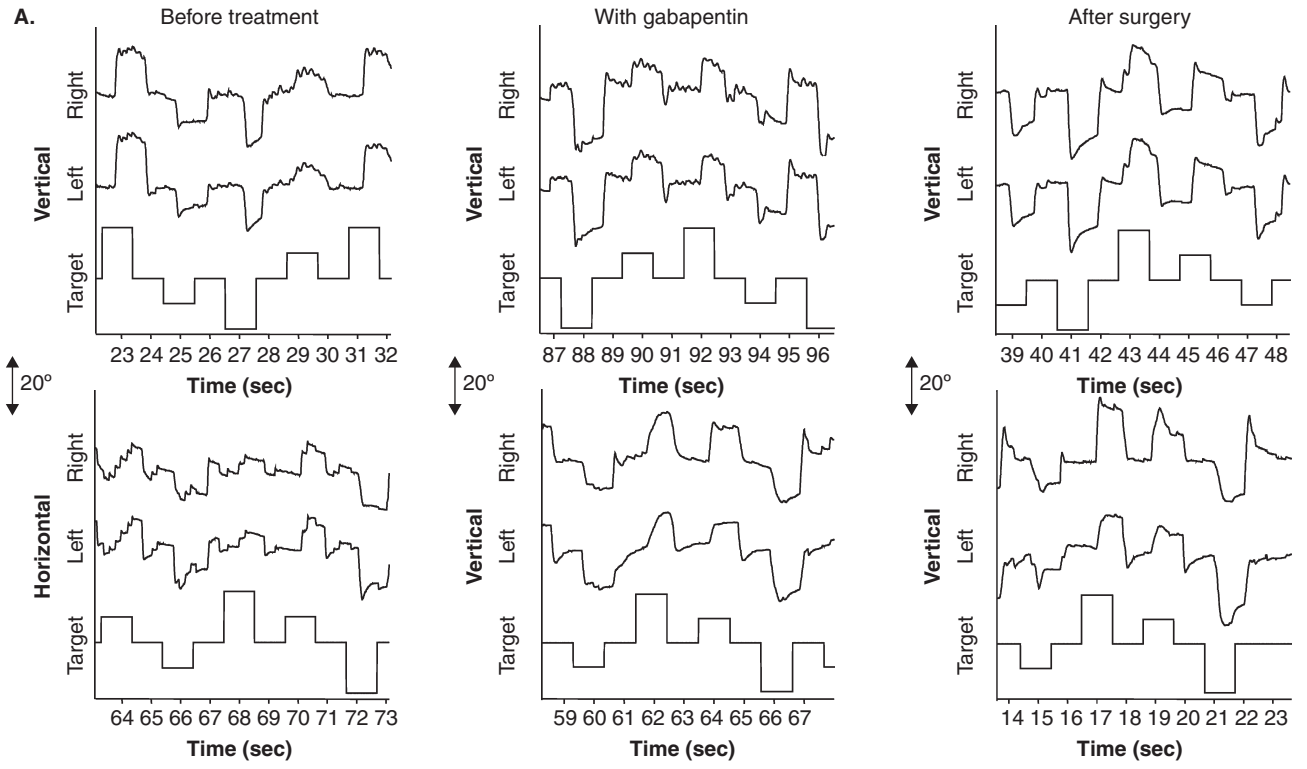

Figure 5. Eye-movement recordings. A. Eye-movement recordings in one patient with horizontal and vertical nystagmus, acquired due to multiple sclerosis, with both pendular and jerk components. Horizontal and vertical saccades (left) before treatment, (middle) after gabapentin and (right) after surgery. With gabapentin, the horizontal nystagmus is reduced whereas the vertical nystagmus remains unchanged. After surgery, the vertical nystagmus is reduced significantly.

signal [81]. Further research has considered combining tenotomy procedures with recessions of eye muscles for strabismus and Kestenbaum procedures for abnormal head postures, and has also found that this increases visual function and reduces nystagmus in both AN and IN [82].

Weakening muscles by retrobulbar injections of botulinum toxin is another approach used in the treatment of nystagmus. Studies of AN have shown that nystagmus reduces after botulinum injections, however the effects only last for approximately 6 months [83]. There are drawbacks to this type of management. Ptosis and diplopia can occur, which limits the therapeutic value and effectiveness of the treatment [84,85]. Prisms can also be used to dampen nystagmus. In some occurrences of IN, where the amplitude of nystagmus is smaller in convergence, prisms can be introduced if the patient has binocular vision. The prisms create an artificial divergence that the patient is required to overcome by converging the eyes even when looking at distance [86]. Nystagmus in multiple sclerosis can sometimes be more pronounced at near and therefore base-in prisms that reduce convergence can dampen nystagmus [87]. Audio feedback is another method that has reported to improve nystagmus. It has been proposed that if patients can hear their own eye movements they can use the feedback to control the nystagmus [88].

5. Conclusion

The aetiology of certain forms of nystagmus, such as PAN and vertical nystagmus, is relatively well understood, whereas other forms, including IIN, are unclear. There are various pharmacological treatment options for nystagmus (**Table 1**); however, most of the evidence used for making recommendations in the treatment of nystagmus is based on case reports and few randomized, controlled trials exist. The potassium-channel blockers 3,4-DAP and 4-AP are useful in some forms of DBN, and baclofen is a valuable treatment for acquired PAN. Gabapentin and memantine improve visual acuity, dampen the eye oscillations in APN and are well-tolerated in most cases. The most recent reports are related to the treatment of IN and have shown that gabapentin and memantine are also successful in

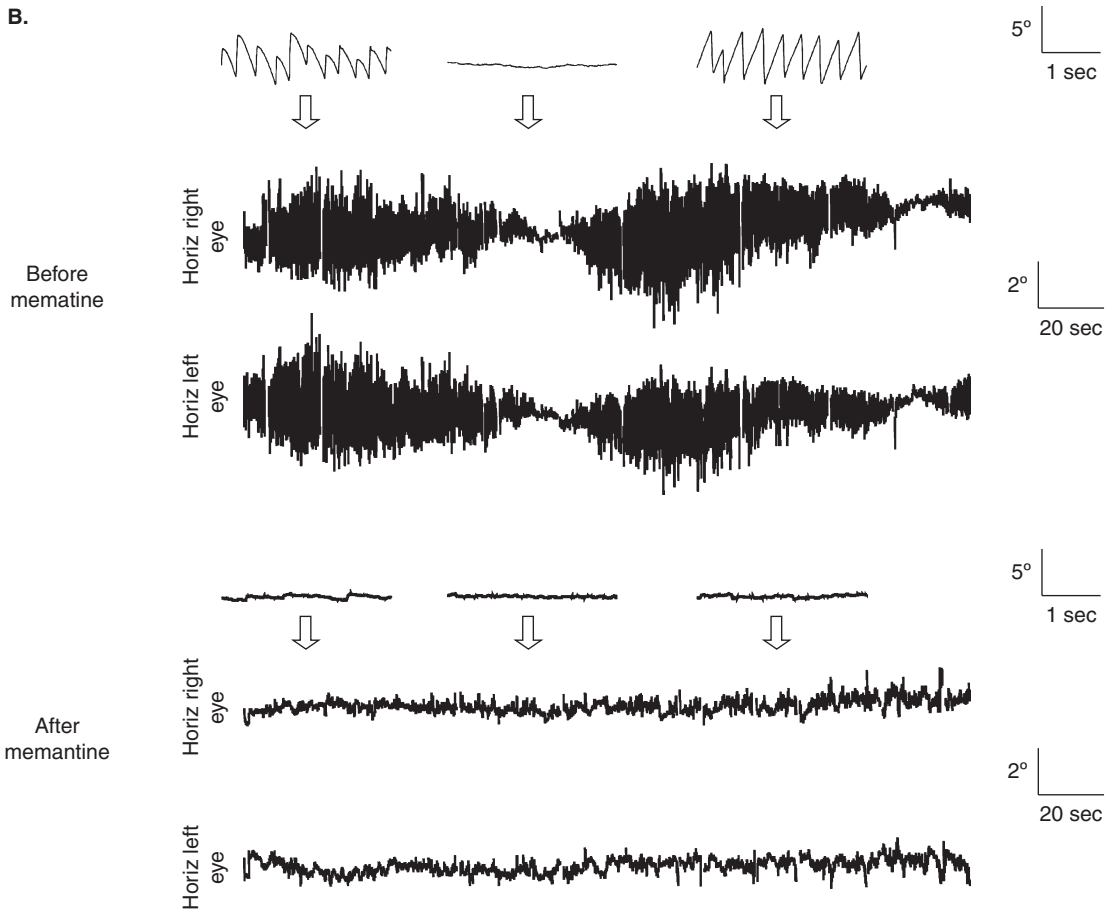

Figure 5. Eye-movement recordings (continued). B. Eye-movement recordings of acquired periodic alternating nystagmus (PAN), due to sarcoidosis, in one patient. With only baclofen (before memantine) and with baclofen and memantine (after memantine) treatment. With a combination of baclofen and memantine the nystagmus is almost abolished.
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this form of nystagmus. Additional randomized, controlled trials are required in all forms of nystagmus to enable clinicians to make decisions based on evidence and to discover which drug is the most effective for which type of nystagmus.

6. Expert opinion

Although the pathogenesis is well understood in some cases, such as PAN, knowledge is lacking in many forms of nystagmus. None the less, several successful treatments exist despite limited understanding of the mechanisms. Further research is required to gain a better understanding of the aetiology in different nystagmus forms. This will help to improve treatment options and allow us to identify why some people respond to medication more than others. The recent discovery of the *FMRD7* gene for X-linked IN may help to gain understanding of the mechanism of nystagmus.

Many of the reports on pharmacological treatment of nystagmus have no reliable, comparable measurements and the recorded outcome measures differ from study to study. For example, when change in eye movement is assessed, a standardized value of eye speed, such as intensity, should be introduced to all reports. Randomized, controlled trials are required to increase the quality of evidence and treatment trials should take into account the aetiology of nystagmus. As some forms of nystagmus are relatively rare, multi-centre studies should be introduced in these cases. The randomized, controlled trials that already exist have relatively low participation numbers.

A possibility for the future treatment of nystagmus, in our experience, lies with combination therapies. We have

previously reported a combined pharmacological and surgical case in a patient with acquired horizontal and vertical nystagmus [89]. The horizontal component responded well to gabapentin but the vertical nystagmus remained unchanged and the patient adopted a chin-up head posture to position the eyes at the null point and dampen the nystagmus. Gabapentin treatment was continued for the horizontal component and a vertical Kestenbaum procedure was performed, which eliminated the head position. Postoperatively, the oscillopsia was completely resolved and visual acuity was improved to 6/9 in both eyes from 6/36 (**Figure 5A**). We have also recently reported a case of acquired PAN that although responded to baclofen, the PAN was still extremely troublesome to the patient [90]. Combining the baclofen with memantine almost completely abolished the abnormal eye movement (**Figure 5B**). Possibly more combination approaches should be considered in an attempt to treat nystagmus.

Declaration of interest

This paper was sponsored by the Ulverscroft Foundation and the Nystagmus Network UK. The authors declare no conflicts of interest.

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