

# Pharmacotherapy of vestibular and ocular motor disorders, including nystagmus

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**Abstract** We review current pharmacological treatments for peripheral and central vestibular disorders, and ocular motor disorders that impair vision, especially pathological nystagmus. The prerequisites for successful pharmacotherapy of vertigo, dizziness, and abnormal eye movements are the “4 D’s”: correct diagnosis, correct drug, appropriate dosage, and sufficient duration. There are seven groups of drugs (the “7 A’s”) that can be used: antiemetics; anti-inflammatory, anti-Ménière’s, and anti-migrainous medications; anti-depressants, anti-convulsants, and aminopyridines. A recovery from acute vestibular neuritis can be promoted by treatment with oral corticosteroids. Betahistine may reduce the frequency of attacks of Ménière’s disease. The aminopyridines constitute a novel treatment approach for downbeat and upbeat nystagmus, as well as episodic ataxia type 2 (EA 2); these drugs may restore

normal “pacemaker” activity to the Purkinje cells that govern vestibular and cerebellar nuclei. A limited number of trials indicate that baclofen improves periodic alternating nystagmus, and that gabapentin and memantine improve acquired pendular and infantile (congenital) nystagmus. Preliminary reports suggest suppression of square-wave saccadic intrusions by memantine, and ocular flutter by beta-blockers. Thus, although progress has been made in the treatment of vestibular neuritis, some forms of pathological nystagmus, and EA 2, controlled, masked trials are still needed to evaluate treatments for many vestibular and ocular motor disorders, including betahistine for Ménière’s disease, oxcarbazepine for vestibular paroxysmia, or metoprolol for vestibular migraine.

**Keywords** Vertigo · Dizziness · Vestibular neuritis · Ménière’s disease · Vestibular paroxysmia · Vestibular migraine · Episodic ataxia type 2 · Downbeat nystagmus · Upbeat nystagmus · Pendular nystagmus · Periodic alternating nystagmus · Infantile nystagmus · Square-wave saccadic intrusion · Ocular flutter · Opsoclonus

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## Introduction

Vertigo and dizziness arise from many multisensory and sensorimotor syndromes of various etiologies and pathogenesises, which are best elucidated using an interdisciplinary approach. After headache, vertigo is one of the most frequent presenting symptoms to physicians in many disciplines, with a life-time prevalence of almost 30% [1]. Here, we first review current pharmacological treatments for common peripheral and central vestibular disorders (for description of other therapies, see reviews [2, 3]). Second, we focus on those ocular oscillations that impair vision and

may give rise to illusory motion of the visual environment (oscillopsia). In particular, the pathophysiology, topographic diagnosis, and current pharmacological treatment of downbeat nystagmus (DBN), upbeat nystagmus (UBN), acquired pendular nystagmus (APN), and saccadic oscillations that impair vision (for description of other therapies, see reviews [4–7]) are discussed.

### Rationale for pharmacotherapy of vertigo, dizziness, and ocular motor disorders impairing vision

The prerequisites for successful pharmacological treatment of vertigo, dizziness, ocular motor disorders, and pathological nystagmus are the “4 D’s”: correct diagnosis, correct drug, appropriate dosage, and sufficient duration. First, a correct *diagnosis*—easily made in most patients on the basis of the patient history and clinical examination, and without laboratory investigations; second, the correct *drug*—only a few have been proven in controlled trials to be effective; third, an appropriate *dosage*—often the initial dose is too low or too high, so that the treatment is either ineffective or not well tolerated; and fourth, a sufficient *duration*—often drugs are either given for too long, such as antivertiginous agents (e.g., dimenhydrinate), which delay central compensation and may cause drug dependence, or not long enough, such as in Ménière’s disease or vestibular migraine, which require long-term treatment [8].

Depending on their etiology, vestibular disorders can be treated with drugs, physical therapy, psychotherapeutic measures, or rarely surgery. Before commencing treatment, the patient should be informed that the prognosis is generally good for two reasons: (a) vertigo often takes a favorable natural course, since peripheral vestibular function improves or central vestibular compensation of the vestibular tone imbalance takes place; and (b) most forms can be successfully treated (mainly with drugs or physiotherapy). Several drugs are now available for the specific treatment of certain vestibular and ocular motor disorders.

### Peripheral vestibular disorders

Three typical forms of peripheral vestibular dysfunction can be identified based on their characteristic symptoms and signs: (1) acute or subacute unilateral vestibular failure (usually acute vestibular neuritis), characterized by rotational vertigo, oscillopsia, and a tendency to fall toward the affected ear; (2) bilateral peripheral vestibular failure (bilateral vestibulopathy), characterized by instability of gait and posture, and oscillopsia induced by head movements; and (3) paroxysmal peripheral vestibular stimulation or inhibition, characterized by attacks of vertigo and

oscillopsia, occurring, for instance, in benign paroxysmal positioning vertigo, Ménière’s disease, and vestibular paroxysmia.

### Acute vestibular neuritis

After benign paroxysmal positioning vertigo, vestibular neuritis is the second most common cause of peripheral vestibular vertigo. It accounts for 7% of patients presenting to outpatient clinics that specialize in the treatment of dizziness [2] and has an incidence of 3.5 per 100,000 population [9]. The key symptoms and signs of vestibular neuritis include the following: an acute onset of sustained, rotational vertigo; horizontal spontaneous nystagmus, with a torsional component, beating toward the unaffected ear; postural imbalance with positive Romberg’s sign (i.e., falls toward the side of the affected ear when the eyes are closed); and nausea and vomiting. Caloric testing usually shows ipsilateral vestibular paresis or paralysis. Evidence suggests that vestibular neuritis is caused by reactivation of a latent Herpes simplex virus type 1 (HSV-1) infection. Thus, using the polymerase chain reaction, HSV-1 DNA has been detected on autopsy in about two of three human vestibular ganglia [10–14]. This, as well as the expression of CD8-positive T-lymphocytes, cytokines, and chemokines, indicates that the vestibular ganglia are latently infected with HSV-1 [15].

In a prospective, randomized, double-masked, two-by-two factorial trial, 141 patients with acute vestibular neuritis were randomly assigned to receive treatment with placebo, methylprednisolone (100 mg/day, doses tapered by 20 mg every fourth day), valacyclovir (1 g tid for 7 days), or methylprednisolone plus valacyclovir [16]. Vestibular function was determined by caloric irrigation, with the use of the standard vestibular paresis formula, to measure the extent of unilateral caloric paresis [17], within 3 days of the onset of symptoms and 12 months afterwards. The mean improvement in peripheral vestibular function at the 12-month follow-up was 39.6% in the placebo group, 62.4% in the methylprednisolone group, 36.0% in the valacyclovir group, and 59.2% in the methylprednisolone plus valacyclovir group. Analysis of variance showed that methylprednisolone had a significant effect, but valacyclovir did not. Therefore, this study showed that methylprednisolone alone significantly improves the recovery of peripheral vestibular function in patients with vestibular neuritis, whereas valacyclovir is not effective. However, future studies employing more detailed testing of vestibular function might yet define a therapeutic role for valacyclovir. All in all, this inexpensive and well-tolerated therapy can be recommended as the drug treatment of choice for vestibular neuritis and should be considered in combination with other treatments that have been shown to

improve vestibular compensation, such as vestibular exercises [18–20].

Animal experiments have shown that central vestibular compensation can be improved by several agents. A placebo-controlled clinical trial to evaluate the effects of betahistine on central vestibular compensation was started recently (BETAVEST, EudraCT No. 2009-013702-14).

In summary, the pharmacological treatment of choice for acute vestibular neuritis is corticosteroids beginning within 3 days of symptom onset (e.g., methylprednisolone 100 mg orally per day, followed by progressive tapering of the dose).

### Ménière's disease

Ménière's disease is characterized by recurrent spontaneous attacks of vertigo, fluctuating hearing loss, tinnitus, and aural fullness. Its incidence varies between 7.5 per 100,000 and 160 per 100,000 persons (for review, see [21]). Endolymphatic hydrops is assumed to be the pathological basis of Ménière's disease and is thought to arise due to either excessive production or inadequate absorption of endolymph. The increased endolymphatic pressure causes periodic rupturing of, or leakage from, the membrane separating the endolymphatic from the perilymphatic space (by the opening of nonselective, stretch-activated ion channels [22]). Therefore, aims of treatment include reducing the production and increasing the absorption of endolymph. The clinical aims of treatment are to stop vertigo attacks, reduce or abolish tinnitus, and preserve or even reverse hearing loss. Most treatment studies have focused on reducing the attacks of vertigo, which are the severest symptom of Ménière's disease.

Many treatments have been proposed for Ménière's disease, but almost none have been demonstrated to be effective in controlled trials. Procedures to destroy the lateral semicircular canal and vestibule have been proposed since 1904. The first endolymphatic sac decompression was performed in 1926; this method is still used at some centers, despite lack of demonstration of its effectiveness [23]. Restricted salt and fluid intake and the use of diuretics were first proposed in 1934. Salt restriction and diuretics are still recommended, although there is no evidence for their efficacy [24, 25]. Vestibulotoxic drugs, such as aminoglycosides, have been used since 1948; intratympanic injections of these agents have been performed since 1956 [26]. It is remarkable that, despite the high incidence of Ménière's disease and the large number of treatment studies published in recent decades, only a few prospective, placebo-controlled, double-masked treatment trials have been performed. Moreover, there are significant differences in the treatment options offered in Europe and the US. In the US, low-salt diet, diuretics, and intratympanic injection

of gentamicin and corticosteroids are preferred. In Europe, betahistine is often used, whereas it is not approved for use in the US. A national survey of UK otolaryngologists on the treatment of Ménière's disease revealed that 94% used betahistine, 71% salt restriction, 63% diuretics, 52% sac decompression, and approximately 50% insertion of an ear tube [26]. Local gentamicin instillation has become more popular since its introduction in the UK 10 years ago; approximately two-thirds of British otolaryngologists now use this method [26].

### *Intratympanic injections of gentamicin*

Several studies have been published on the use of intratympanic gentamicin for the treatment of unilateral Ménière's disease. Initially, the strategy was to give multiple intratympanic injections of gentamicin until patients developed vestibular hypofunction, resulting in a reduced frequency of vertigo attacks, but a high rate of sensorineural hearing loss (approximately 50%). Subsequently, this approach was changed in two ways, especially after a delayed onset of ototoxicity was demonstrated [27]: (1) single instillations at fixed intervals of several days or weeks; or (2) single-shot injections with follow-up. For the latter regimen, a prospective, uncontrolled study of 57 patients with a follow-up time of 2–4 years showed that the vertigo attacks could be controlled in 95% of patients [28]. Fifty-three percent of patients needed only one gentamicin injection, while 32% needed two or three injections. A recent meta-analysis of 15 trials on gentamicin injection, including a total of 627 patients, showed that complete vertigo control was achieved in about 75% of patients and complete or substantial control obtained in about 93% [29]. The success rate was not affected by the gentamicin treatment regimen, i.e., fixed versus titrated. In addition, hearing level and word recognition was not adversely affected, regardless of treatment regimen. However, the authors pointed out that the level of evidence was inadequate due to the relatively poor study designs: none of the trials were double-masked or had a masked prospective control. Nonetheless, there is good evidence that the beneficial effect of gentamicin is due to vestibular hair cell damage [30]. A complete ablation of function, however, is probably not necessary in order to control the vertigo attacks [31]; titration to the first sign of hypofunction (e.g., spontaneous nystagmus or positive head-impulse test) is sufficient.

### *Intratympanic injections of corticosteroids*

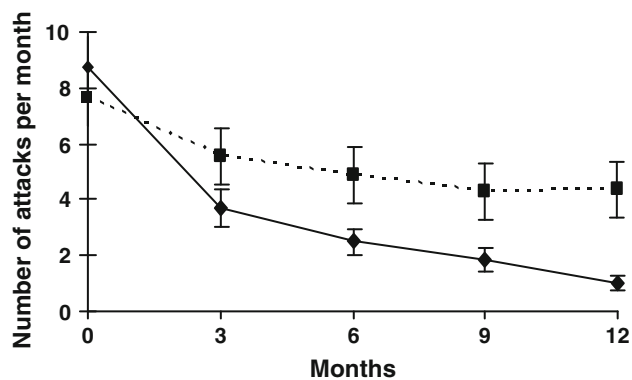
In a retrospective chart review, the effects of intratympanic injections of dexamethasone were evaluated in 34 patients with Ménière's disease [32]. After a single course of

weekly injections of 10 mg/ml dexamethasone for 1 month, only 24% of patients reported vertigo control. Another 24% responded to a repeat series of injections. Overall, control of vertigo was achieved in approximately 50% of patients with one or more courses of intratympanic dexamethasone. The safety of intratympanic dexamethasone was evaluated using transient evoked otoacoustic emissions: no change was found in 26 patients after five 4-mg injections of dexamethasone [33].

### Betahistine

In Europe, betahistine is often used, mainly on the basis of a study by Meyer [34] and more recent meta-analyses [35, 36]. Betahistine is an H<sub>1</sub>-agonist and H<sub>3</sub>-antagonist. It improves the labyrinthine microcirculation by acting on the precapillary sphincters of the stria vascularis [37]. There is evidence that it reduces the production and increases the absorption of endolymph. In an open trial of betahistine dihydrochloride in 112 patients with Ménière's disease, it was shown that high-dose (48 mg tid) and long-term treatment (12 months) were more effective than low-dose (16–24 mg tid) and short-term treatment (Fig. 1) [38]. These findings are the basis for an ongoing prospective, randomized, double-masked dose-finding study, comparing placebo with 16 mg tid and 48 mg tid of betahistine dihydrochloride.

In summary, the pharmacological treatment of choice for Ménière's disease is betahistine dihydrochloride, with a dosage of at least 48 mg tid for at least 6–12 months [38].



**Fig. 1** Effects of betahistine dihydrochloride [low dosage (filled square, dotted line): 16 or 24 mg tid versus high dosage (filled diamond, solid line): 48 mg tid] on the frequency of attacks of vertigo in 112 Ménière's disease patients. The mean number of attacks/month ( $\pm$ SEM) during the 3 months preceding treatment (month 0) is indicated, as well as the number/month during therapy (month 3, 6, 9, 12). After 12 months, the mean (median) number of attacks dropped from 7.6 (4.5) to 4.4 (2.0) ( $p < 0.0001$ ) in the low-dosage group, and from 8.8 (5.5) to 1.0 (0.0) ( $p < 0.0001$ ) in the high-dosage group. The number of attacks after 12 months was significantly lower in the high-dosage group than in the low-dosage group ( $p_{12M} = 0.0002$ ) (from [38])

Alternatively, in unilateral Ménière's disease, gentamicin can be administered transtympanically (20–40 mg/injection) at intervals of 4–8 weeks, depending on efficacy.

### Vestibular paroxysmia

Vestibular paroxysmia is characterized by short attacks of vertigo that last for seconds to minutes, and may occur many times a day. The attacks are usually spontaneous, but are occasionally triggered by head-turns or hyperventilation. Like trigeminal neuralgia, hemifacial spasm, and superior oblique myokymia, it is assumed that vascular compression of the 8th cranial nerve is the cause of vestibular paroxysmia [39]. In a recent study, neurovascular compression was found in 95% of patients and hyperventilation caused attacks or nystagmus in about 70% of patients examined [40]. Despite these new findings, this entity remains difficult to diagnose.

As demonstrated in an open trial [40], a low dose of carbamazepine (200–600 mg/day) or oxcarbazepine (300–900 mg/day) often gives prompt relief and, thus, may help to establish the diagnosis. In patients who are unable to tolerate these medications, phenytoin, valproic acid, or acetazolamide may be effective, although there are no trial data to confirm their efficacy. Currently, a prospective, placebo-controlled, double-masked trial with oxcarbazepine is being performed.

### Central vestibular disorders

#### Vestibular migraine

Vestibular migraine is increasingly regarded as the most common central cause of recurrent attacks of vertigo. Characteristic features include recurrent attacks of various combinations of vertigo, ataxia of stance and gait, photophobia and phonophobia, and other brainstem symptoms, accompanied or followed by head pressure, pain, nausea, or vomiting [41, 42]. Treatment is the same as for migraine with aura: beta-blockers (metoprolol or propranolol), valproic acid, or topiramate for at least 3–6 months. Several treatment trials have been performed in patients with vestibular migraine. Tricyclic antidepressants in combination with diet gave a good response (>95%) in a noncontrolled trial on 81 patients [43]. For zolmitriptan, the response rate in acute attacks was 38 versus 22% for placebo in a study on 19 patients [44]. Another open trial on 10 patients demonstrated that lamotrigine (100 mg/day as a single dose) had a significant effect on the occurrence of headache and a more marked effect on vertigo [45]. The treatment options have been summarized in a retrospective study [46]. At present, only standard treatments for migraine with

aura can be recommended for vestibular migraine [47]. A placebo-controlled, multicenter trial to evaluate the efficacy of metoprolol on the frequency of attacks in vestibular migraine has been initiated (PROVEMIG EudraCT No. 2009-013701-34).

In summary, the pharmacotherapy of vestibular migraine has not yet been evaluated with state-of-the-art clinical trials. Consequently, only drugs that are effective for treating migraine with and without aura can currently be recommended. For the therapy of acute attacks, aspirin and an antiemetic could be offered, whereas metoprolol (100 mg/day), topiramate (50–100 mg/day), or valproic acid (300–900 mg/day) could be offered for prophylaxis.

### Episodic ataxia type 2

Episodic ataxia type 2 (EA 2) is characterized by recurrent attacks of ataxia, often provoked by stress or exercise, which last for several hours to days [48–50]. Clinical findings between attacks include signs of central ocular motor and vestibular dysfunction, in particular downbeat nystagmus. Patients with EA 2 can often be successfully treated with acetazolamide [51]; patients with other inherited forms of episodic ataxia might also respond to acetazolamide. Genetically, EA 2 is an autosomal dominant disorder caused by mutations in the calcium channel gene *CACNA1A* [52], which encodes the  $Ca_{V2.1}$  subunit of the so-called PQ-type calcium channel, which is strongly expressed in Purkinje cells. The functional changes induced by the PQ-type calcium channel mutation, which result in a reduced calcium current, are thought to decrease the inhibitory effect of Purkinje cells. This results in disinhibition of the deep cerebellar nuclei and, thus, ataxia, as well as disinhibition of vestibular nuclei neurons receiving anterior semicircular canal pathways, leading to downbeat nystagmus. As aminopyridines (potassium channel blockers) improve downbeat nystagmus (see below), their effects on the frequency of attacks in EA 2 were also evaluated [53]. In three patients with EA 2 who no longer responded to standard treatment with acetazolamide (two with proven mutations of the *CACNA1A* gene), 4-aminopyridine (5 mg tid) prevented attacks. Attacks recurred after the treatment was stopped, and reintroduction of the treatment stopped the attacks (mean follow-up time was greater than 12 months). Based on the above-mentioned open trial, a placebo-controlled cross-over trial has been performed, showing that 4-aminopyridine reduces the frequency of attacks and improves quality of life in EA 2 (paper submitted).

Originally, it was assumed that the effects of 4-aminopyridine were due to increased inhibition by Purkinje cells, a hypothesis supported by animal experiments [54]. However, recent studies on a mouse model of EA 2 show that

therapeutic concentrations of 4-aminopyridine restore the diminished precision of pacemaking in affected Purkinje cells, by prolonging the action potential and increasing the action potential after-hyperpolarization [55]. The clinical findings are supported by an animal study on the calcium channel mutant tottering mouse; aminopyridines reduced the frequency of attacks in the mouse by increasing the threshold for attack initiation, without altering the character of the attacks [56].

In summary, acetazolamide remains the pharmacological treatment of choice for episodic ataxia type 2; a dosage between 250 and 1,000 mg/day is usually effective, although higher doses may be required. Acetazolamide may cause kidney stones, requiring patient counseling of this risk. Alternatively, 4-aminopyridine can be used with a dosage of 5–10 mg tid.

### Pathological nystagmus and saccadic intrusions

Nystagmus can be defined as a repetitive, to-and-fro movement of the eyes that is initiated by a slow phase. Nystagmus is common with a prevalence of around 0.1% [57], and often produces visual symptoms, such as blurred vision or illusory motion of the visual environment (oscillopsia) [4]. Common forms of acquired nystagmus include gaze-evoked, downbeat, and upbeat nystagmus, and pendular nystagmus associated with either multiple sclerosis or the syndrome of oculopalatal tremor (OPT). Reviewing therapies for nystagmus: downbeat and upbeat nystagmus may respond to aminopyridines, acquired pendular nystagmus to gabapentin and memantine, and periodic alternating nystagmus to baclofen. Infantile (congenital) forms of nystagmus often do not give rise to visual symptoms, especially when the patient has well-developed foveation periods that provide stable, clear “snapshots” of the world. Those patients with visual symptoms from infantile nystagmus may benefit from memantine, gabapentin, surgical, or optical therapies [7]. To date, several clinical trials have been performed to evaluate some pharmacological treatments for nystagmus, but further trials are necessary to confirm the efficacy of many other proposed treatments.

Gaze-evoked nystagmus is probably the most common form of acquired nystagmus encountered in clinical practice, occurring in individuals taking a range of drugs, including anticonvulsants, benzodiazepines, and ethanol, as well as in patients with cerebellar disease [4]. However, it rarely causes visual symptoms, because it is absent when the eyes are close to center position, and rarely requires specific treatment. Thus, gaze-evoked nystagmus will not be considered further in this review. In the following sections, the pathophysiology and treatment of other common

and clinically relevant forms of nystagmus are discussed. The frequencies of other forms of nystagmus and saccadic intrusions, as seen in a specialist neurological dizziness unit, are summarized in Table 1 [58]. However, according to one epidemiological study, the most frequent form is acquired pendular nystagmus, due to its high prevalence in multiple sclerosis patients [59]. Pharmacological treatments are generally the most successful means of therapy for acquired forms of nystagmus; alternative treatment approaches for nystagmus, such as optical devices and surgery, are reviewed elsewhere [7]. The characteristics, pathogenesis, and treatment of downbeat, upbeat, acquired pendular, periodic alternating, and infantile (congenital) forms of nystagmus are summarized in Table 2.

### Downbeat nystagmus (DBN)

Downbeat nystagmus (DBN) is a common form of acquired nystagmus (Table 1) [58] that is characterized by slow upward drifts with downward quick phases. Patients frequently report blurred vision or oscillopsia, which increases on lateral gaze, as well as associated unsteadiness of gait and postural imbalance [58]. DBN is usually most prominent on lateral and downward gaze. DBN is often influenced by convergence, sometimes with suppression [4, 60, 61], and is often associated with other ocular motor, cerebellar, and vestibular signs, including impairment of smooth pursuit, optokinetic nystagmus, and visual suppression of the vestibulo-ocular reflex (VOR) [4, 62–66].

DBN has been associated with many disorders [4, 62, 64–67]. In a recent study, 117 patients were reviewed to establish whether analysis of a large sample and improved diagnostic testing would reduce the number of cases with

**Table 1** Frequency of infantile (congenital) and/or acquired ocular oscillations in 4,854 consecutive patients who were seen in a neurological dizziness unit; patients with pure gaze-evoked nystagmus were not included

Type of nystagmus/ocular oscillation	Number
Downbeat nystagmus	101
Upbeat nystagmus	54
Central positional nystagmus	26
Pendular nystagmus	15
Infantile (congenital) nystagmus	12
Pure torsional nystagmus	12
Seesaw nystagmus	8
Ocular flutter	8
Square wave jerks	7
Opsoclonus	1
Periodic alternating nystagmus	1

Downbeat nystagmus was the most frequent fixation nystagmus (from [58])

“idiopathic” DBN in favor of specific diagnoses [58]. In 62% ( $n = 72$ ) of patients, an etiology was identified (“secondary” DBN); common causes included cerebellar degeneration demonstrated by CT or MRI ( $n = 23$ ) and cerebellar ischemia ( $n = 10$ ). In the remaining 38% ( $n = 45$ ), no cause was found; thus, “idiopathic” DBN remains common. Substantial proportions of patients with both idiopathic and secondary DBN have associated bilateral vestibulopathy, polyneuropathy, or cerebellar ataxia, sometimes without cerebellar abnormalities on MRI.

Three main pathophysiological mechanisms have been proposed for DBN: (1) a tone imbalance of the central vestibular pathways subserving vertical eye movements [60, 62, 68, 69], including the otolithic pathways, such that DBN is often gravity dependent [70, 71]; (2) an imbalance of vertical smooth-pursuit tone causing spontaneous upward drift [72]; and (3) a mismatch in the three-dimensional neural coordinate system for vertical saccade generation due to a defect of the neural velocity-to-position integrator for gaze holding [64]. Bilateral ablation of the cerebellar flocculus and paraflocculus in monkeys produces DBN and a gaze-holding deficit [73], as well as impaired smooth pursuit, adaptation of the horizontal VOR [74, 75], and visual suppression of the VOR [76]. Marti et al. [77] proposed that the distribution of the on-directions of vertical gaze-velocity Purkinje cells in the flocculus is inherently asymmetrical; these cells are predominantly activated with ipsilateral and downward gaze velocities, whereas only ~10% of them show on-directions for upward gaze velocities [78]. With functional magnetic resonance imaging (fMRI) and 18F-fluorodeoxyglucose positron emission tomography, it was shown that patients with DBN have diminished activation and metabolism in the flocculi (Fig. 2) [79, 80], supporting the view that a functional deficiency of the flocculi causes not only a defect in downward pursuit, but also DBN [77]. Recent studies using voxel-based morphometry have demonstrated atrophy in areas of the cerebellum related to ocular motor function in patients with DBN [79, 81].

Since the inhibitory influence of GABAergic Purkinje cells was assumed to be impaired in DBN, several agents that act via GABA have been investigated. Clonazepam, a GABA<sub>A</sub> agonist, improved DBN (dosage 0.5 mg tid–1 mg bid) in two uncontrolled studies [82, 83]. Baclofen, a GABA<sub>B</sub> agonist, was thought to reduce DBN [84], but a double-masked cross-over trial showed that only 1 of 6 patients with DBN responded [85]. Gabapentin, now known to be an alpha-2-delta calcium channel antagonist, only suppressed DBN in 1 of 6 patients in the same clinical trial [85].

On the basis of the assumed pathophysiological mechanism of DBN, the effects of 3,4-diaminopyridine (3,4-DAP) were evaluated in a randomized, controlled, cross-

**Table 2** Summary of the clinical features, pathophysiology, etiology, site of lesion, and current treatment options for common forms of central nystagmus

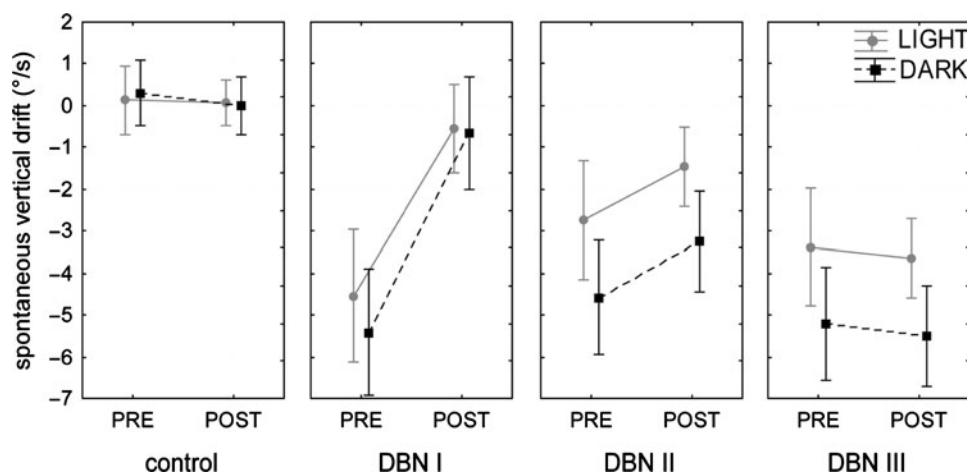
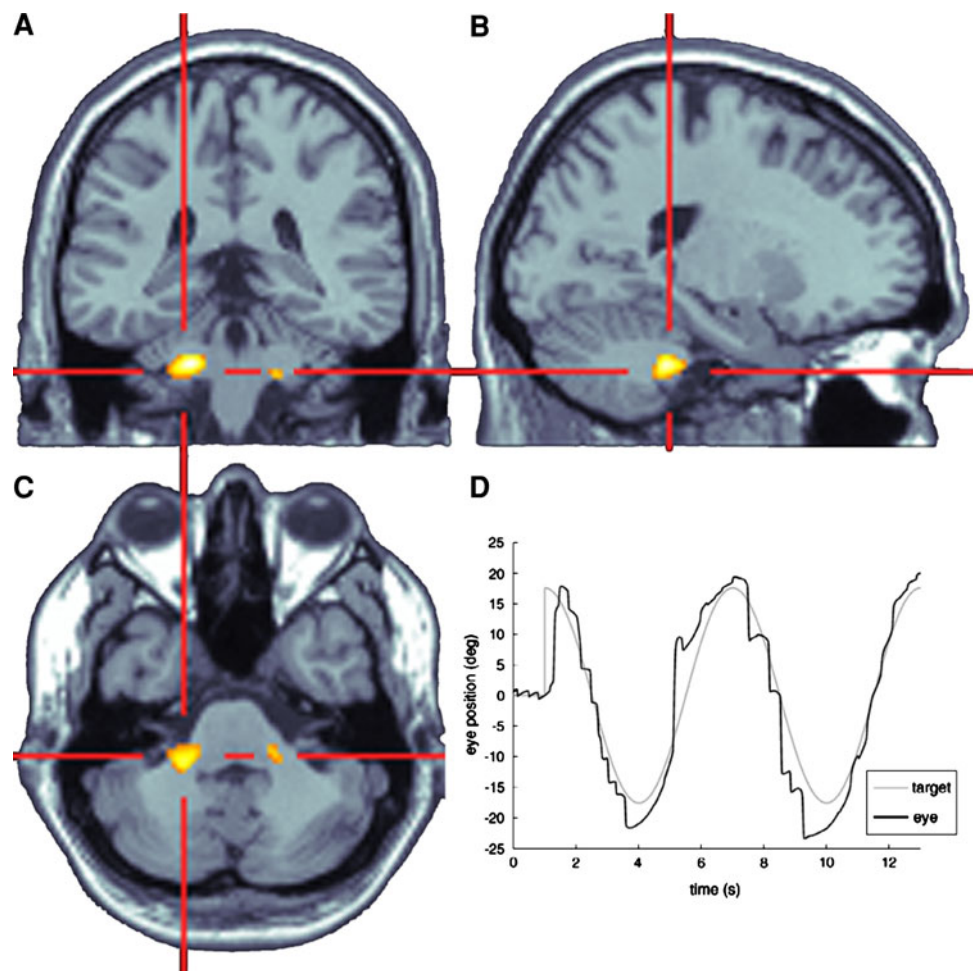
	Downbeat nystagmus (DBN)	Upbeat nystagmus (UBN)	Acquired pendular nystagmus (APN)	Periodic alternating nystagmus (PAN)	Infantile (congenital) nystagmus
Direction of nystagmus (quick phase)	Downward, may be diagonal with lateral gaze	Upward	Mainly horizontal, may have vertical and/or torsional components	Horizontal	Mainly horizontal; may have torsional and small vertical components
Waveform (slow phase)	Jerk, constant, increasing, or decreasing slow-phase velocity	Jerk, constant, increasing, or decreasing slow-phase velocity	Pendular, sinusoidal slow-phase	Jerk, mostly constant slow-phase velocity	Accelerating slow-phases; foveation periods when the eye is transiently still
Special features	Increased intensity during lateral and downward gaze; sometimes influenced by convergence	Increased intensity during upward gaze; may convert to DBN on convergence	Associated with other oscillations (e.g., palate) and with hypertrophic degeneration of the inferior olive	Changes direction every 90–120 s	Null zone, in which nystagmus is minimal; often suppressed with convergence
Sites of lesion	Cerebellum (bilateral floccular hypofunction); rarely lower brainstem lesions	Medial medulla, ponto-mesencephalic junction, rarely cerebellum	Pontomedullary, probably affecting components of neural integrator for gaze holding	Cerebellum (nodulus, uvula)	Uncertain; some cases are associated with afferent visual system anomalies
Etiology	Cerebellar tumors, degenerations, Chiari malformations, and stroke; idiopathic; often associated with bilateral vestibulopathy and neuropathy	Brainstem or cerebellar stroke and tumors; Wernicke’s encephalopathy	Multiple sclerosis, oculopalatal tremor due to brainstem or cerebellar stroke involving Guillain-Mollaret triangle	Cerebellar degeneration, cranio-cervical anomalies, multiple sclerosis, cerebellar tumors and stroke	Uncertain; may be associated with afferent visual system anomalies; hereditary in some patients (e.g., FRMD7 mutations)
Treatment	4-Aminopyridine (5–10 mg tid), 3,4-diaminopyridine (10–20 mg tid), baclofen (5 mg tid) clonazepam (0.5 mg tid)	Often transient, treatment often not necessary; baclofen (5–10 mg tid) 4-aminopyridine (5–10 mg tid)	Memantine (10 mg qid) gabapentin (300 mg qid)	Baclofen (5–10 mg tid)	Gabapentin (300 mg qid) memantine (10 mg qid)

over trial involving 17 patients with DBN due to cerebellar degeneration, infarction, Chiari malformation, or unknown etiology [86]. The mean peak slow-phase velocity of DBN was measured before and 30 min after ingestion of 20 mg of 3,4-DAP or oral placebo. 3,4-DAP reduced the mean peak slow-phase velocity from 7.2 deg/s before treatment to 3.1 deg/s 30 min after ingestion ( $p < 0.001$ ). The mean peak slow-phase velocity was decreased by more than 50% in 10 of 17 patients. Except for transient perioral or digital paresthesia (3 patients) and nausea and headache (1 patient), no other significant side-effects were reported. The authors demonstrated that the single dose of 3,4-DAP significantly improved DBN and visual acuity, and also reduced oscillopsia. It must be kept in mind that only 50% of all patients with DBN respond to this treatment, mainly those without focal lesions of the cerebellum or brainstem [86]. These findings were supported by a more recent trial assessing the effect of 3,4-DAP on DBN in patients with cerebellar degeneration [87]. An effect of 3,4-DAP on the

gravity dependence of DBN is also reported [88] and those taking 3,4-DAP often report improved balance [89]. It is thought that aminopyridines might increase the activity and excitability of Purkinje cells [54], thereby restoring the physiological inhibitory influence of the vestibulo-cerebellum on the vestibular nuclei. More recent animal studies have demonstrated that therapeutic concentrations of 4-aminopyridine restore the diminished precision of pace-making in Purkinje cells [55].

The underlying mechanism of action of 4-AP in DBN was also investigated in two studies using the magnetic search-coil technique to make precise measurements of eye movements [90, 91]. The major findings of these studies were as follows: (1) 4-AP not only improved DBN, but also improved smooth pursuit [90]; (2) 4-AP improved fixation by restoring gaze-holding ability and neural integrator function; and (3) 4-AP may work best when DBN is associated with cerebellar atrophy (Fig. 3) [91]. If DBN is caused by a focal structural lesion, 4-AP does not improve

**Fig. 2** Activation of the flocculus (*red*) demonstrated, using fMRI, in controls vs patients for the contrast “smooth pursuit in the downward direction” (SMDOWN)—“fixation of a target in the middle of the display” (FIXMID). Results obtained by region of interest group analysis are superimposed onto orthogonal sections (**a** coronal plane, **b** sagittal plane, **c** axial plane) at Montreal Neurological Institute coordinates  $xyz = -20, -36, -40$ , through a standard brain template ( $p < 0.01$ ). **d** Original recording (search-coil) of vertical pursuit (0.1667 Hz, amplitude  $\pm 18^\circ$ ), which demonstrates relatively normal upward pursuit and impaired downward pursuit in a patient with DBN (from [79])



**Fig. 3** Spontaneous vertical drift: vertical drift in control subjects and DBN patients due to cerebellar atrophy (DBN I), unknown etiology (DBN II), or other etiologies (DBN III) before (PRE) and after (POST) administration of 4-aminopyridine (4-AP) (gray circles

target visible, *black squares* target blanked). DBN was reduced most in DBN I and to a lesser extent in DBN II following treatment. Similar effects were observed when the target is blanked. *Error bars* indicate the 95% confidence intervals (from [91])

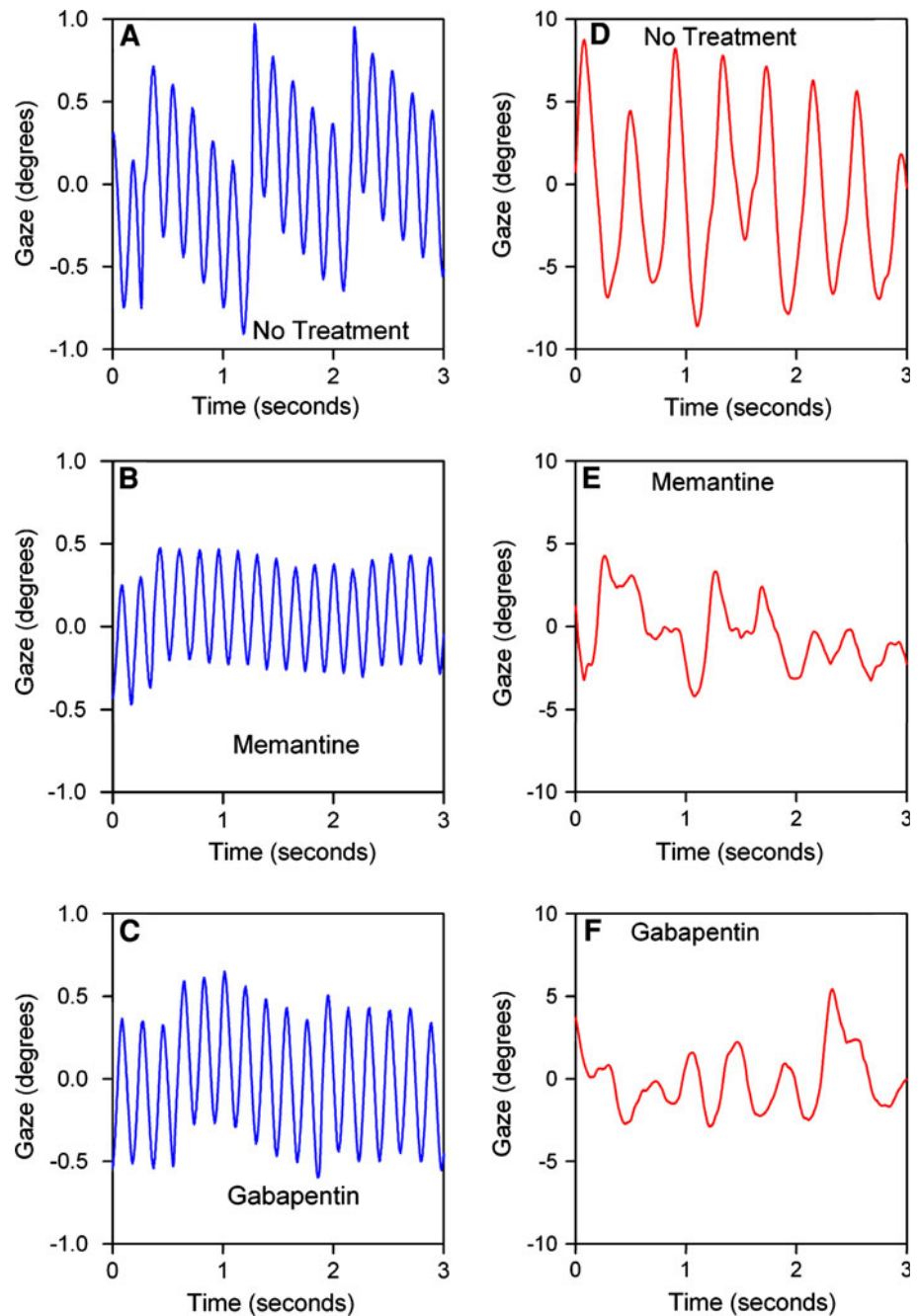
DBN in most cases. A PET study showed that 4-AP increases metabolic activity in the flocculus in parallel with reducing DBN [80]. The findings of these studies support the hypotheses for both the pathophysiological mechanism

underlying DBN and the means by which aminopyridines might reduce it.

Based on recent studies, treatment of DBN with 4-AP (5–10 mg tid) or 3,4-DAP (10–20 mg tid) is recommended.



**Fig. 4** Examples of the vertical components of acquired pendular nystagmus in association with MS (a–c) and OPT (d–f). Representative records are shown when the patients were taking no treatment for their nystagmus (top panels), memantine 40 mg/day (middle panels), or gabapentin 1,200 mg/day (bottom panels). Compare the lower-amplitude oscillations at one frequency (5.6 Hz) in the patient with MS versus the larger-amplitude oscillations at lower, variable frequencies in the patient with OPT. Both drugs (especially memantine) reduce the amplitude of the oscillations in the MS patient without changing their frequency and also suppress a superimposed upbeat nystagmus. Both drugs (especially gabapentin) reduce the oscillations of OPT, which then show more cycle-to-cycle variation



Side-effects, more common with 3,4-DAP, include seizures, if high dosages are given, and cardiac arrhythmias. Thus, every patient should have an ECG before and 30 min after ingestion of the drug to confirm that they do not develop prolongation of the corrected QT-interval. The effects of the sustained-release form of 4-AP are yet to be evaluated.

**Upbeat nystagmus**

Upbeat nystagmus (UBN) present with the eyes in central position is reported to be next most common form of

acquired nystagmus after DBN. UBN usually increases with upgaze and is associated with impaired vertical pursuit [4]. Convergence may suppress UBN or convert it to DBN. UBN is most often caused by brainstem lesions involving the ponto-mesencephalic junction and medulla; it is sometimes associated with cerebellar disease. Lesions in the pathways mediating upward eye movements, from the vestibular and perihypoglossal nuclei, via the ventral tegmental tract and brachium conjunctivum, to the ocular motor nuclei, might result in the pathological slow downward drift of the eyes seen in UBN [4, 61, 92].

Other hypotheses suggest that UBN is caused by an imbalance of vertical VOR tone or a mismatch in the neural coordinate systems of saccade generation and velocity-to-position integration. Affected patients with ponto-mesencephalic brainstem lesions often have associated unilateral or bilateral internuclear ophthalmoplegia, indicating involvement of the medial longitudinal fasciculus. The main diseases associated with UBN include multiple sclerosis, brainstem stroke or tumor, Wernicke's encephalopathy, cerebellar degeneration, and drug intoxications thought to be causing dysfunction of the cerebellum [4].

UBN usually persists for several weeks, but is not permanent in most patients. As the slow-phase velocity of UBN is initially high, many patients seek treatment for disabling oscillopsia and postural instability. GABAergic substances, such as baclofen, have been used to treat UBN, but only have a moderate effect. One uncontrolled study demonstrated a beneficial effect of baclofen (5–10 mg tid) [84]. A recent prospective, double-masked, cross-over study of gabapentin and memantine demonstrated suppression of UBN with memantine (10 mg qid) in 1 patient [121]. Two other patients with upbeat components to their nystagmus also responded to memantine [121]. In another study, 4-AP reduced the peak slow-phase velocity in the light from 8.6 to 2.0 °/s in a single patient with UBN [93]. Since 4-AP did not affect UBN in darkness, it was concluded that it reduces the downward drift in UBN by augmenting smooth pursuit commands [94]. 4-AP may strengthen these parallel pathways by increasing the excitability of cerebellar Purkinje cells [54]. In summary, most patients with UBN do not need pharmacological treatment, because the nystagmus spontaneously settles in most cases. If symptoms are severe or persistent, treatment with memantine (10 mg qid) or 4-AP (5–10 mg tid) may be effective. If these are ineffective, baclofen (5–10 mg tid) could be tried.

#### Acquired pendular nystagmus

Acquired pendular nystagmus (APN) can have horizontal, vertical, or torsional components. If the horizontal and vertical oscillatory components are in phase, the observed trajectory of the nystagmus will appear oblique, but if they are out of phase, as is usually the case, the trajectory will be elliptical or circular. The amplitude of the oscillations in each eye may differ, so that the nystagmus appears disjunctive or occasionally monocular [4]. APN occurs in two main clinical settings: (1) in association with disorders of central nervous system myelin, especially multiple sclerosis (MS); and (2) as a component of the syndrome of oculopalatal tremor (OPT), formerly known as oculopalatal myoclonus.

#### APN in multiple sclerosis (MS)

In MS, the frequency of APN typically ranges from 3–5 Hz and the oscillations are regular. Large saccades may transiently stop or “reset” the timing (phase) of the oscillations. Patients with MS who present with APN often have brainstem lesions involving the paramedian tracts [95], which relay an efference copy signal of eye position to the cerebellar flocculus [96, 97] and, thereby, contribute to gaze-holding. Although vision is often impaired in patients with MS who have APN, impaired visual feedback does not appear to be the cause [98]; it is more likely that APN arises due to instability of the neural integrator, which normally ensures steady gaze-holding [99].

Several agents have been evaluated in clinical trials of treatment for APN in MS. Anticholinergic drugs, such as trihexyphenidyl [100], have not proven effective and retrobulbar injection of botulinum toxin, evaluated in several small series of patients [7], caused side effects such as diplopia that were more troublesome to the patient than the nystagmus itself. Memantine, a noncompetitive *N*-methyl-D-aspartate receptor antagonist, was first reported as effective treatment for APN in MS in 1997 [101]. Gabapentin, which blocks the alpha-2-delta subunit of calcium channels, was also shown to be effective for this form of nystagmus [85]. These and subsequent double-masked studies have shown that both memantine and gabapentin often suppress APN in MS patients, whereas baclofen does not [85, 121, 137]. Either memantine (10 mg qid) or gabapentin (300 mg qid) may be effective in MS patients with APN (Fig. 4) [121]. The mechanism by which memantine and gabapentin suppress APN in MS remains uncertain, but current hypotheses include effects on the neural integrator, including the cell groups of the paramedian tracts, cerebellar flocculus, and medial vestibular and prepositus hypoglossi nuclei.

#### APN in OPT

Ocular oscillations are a component of the syndrome of oculopalatal tremor (OPT), with frequencies typically ranging from 2–4 Hz. APN in OPT is distinct from APN in MS, since the former has significant inter-cycle frequency variability, resulting in an irregular waveform [102]. Hypertrophic degeneration of the inferior olivary nucleus (IO), following a lesion in the “Guillain-Mollaret triangle”, is often present in patients with OPT [103, 104]. The Guillain-Mollaret triangle comprises connections between the IO and deep cerebellar relay nuclei (DCN), via climbing fiber axon collaterals in the inferior cerebellar peduncle, and between the DCN and IO, via the superior cerebellar peduncle and central tegmental tract [138]. According to the contemporary “dual-mechanism”

hypothesis, OPT is due to electrotonic coupling through enhanced connexin gap junctions between pseudohyper-trophied cells of IO. The electrotonic coupling results in synchronous firing of local patches of IO, which act as pacemakers for maladaptive learning by the cerebellar Purkinje cells [102]. Thus, the multiple frequencies and irregular waveforms of OPT are attributed to the contributions from distinct patches of IO neurons, which fire at somewhat different frequencies and trigger maladaptive cerebellar learning.

Successful drug therapy may also provide support for this dual-mechanism model for OPT, since gabapentin, memantine, and some benzodiazepines, such as clonazepam, may decrease the eye velocity of APN in OPT patients (Fig. 4) [85, 121]. The blockade of NMDA receptors in the IO, by both gabapentin and memantine, can reduce synchronization at the IO and, thus, reduce the amplitude of APN in OPT patients. Blockade of NMDA receptors in the cerebellum—at the projection of the IO to the DCN, at the projection of the climbing fibers to Purkinje cells, and pre-synaptically at Purkinje cells—decreases the output of Purkinje cells [105]. The lack of effect of baclofen on OPT is also supported by the “dual-mechanism” hypothesis. Baclofen reduces the excitability of premotor vestibular neurons via a GABAergic mechanism; according to the dual mechanism hypothesis, APN in OPT is generated by the IO and modulated by the output of the cerebellar Purkinje cells, but is not due to down-stream signal modulation by premotor neurons in the vestibular nuclei [102]. The intersubject and intrasubject variability in the effect of the drugs might also reflect different effects of the central lesions at anatomically distinct sites in the brainstem and cerebellum. Indeed, OPT patients usually show signs of more than one area of involvement in the brainstem or cerebellum [102]. From a practical point of view, we recommend using gabapentin (300 mg qid) or memantine (10 mg qid) as the drugs of choice for APN in patients with MS or OPT, although some care is required when giving memantine to MS patients, since this drug may exacerbate symptoms [117].

#### Periodic alternating nystagmus

Periodic alternating nystagmus (PAN) is a spontaneous horizontal jerk nystagmus that changes direction every 90–120 s. Affected patients complain of oscillopsia and often turn their head in the direction of the quick phases in order to bring their eyes to a position in the orbit where the slow-phase velocity is minimized, thereby reducing oscillopsia. The diagnosis is often missed if the patient is not observed for long enough to detect the reversal of the nystagmus. PAN is most often caused by cerebellar dysfunction, in particular by lesions of the more lateral

portions of the cerebellar nodulus or uvula. These lesions alter the velocity-storage mechanism in the brainstem, as has been shown in animal studies, and the oscillations are, therefore, thought to arise from disinhibition of the optokinetic–vestibular system [106]. The treatment of choice for PAN is the GABAergic drug baclofen (5–10 mg tid), which completely abolishes the nystagmus in most patients [107, 108]. Memantine may be added, if necessary [109]. However, there have been no randomized controlled trials of treatment for PAN, to date.

#### Infantile (congenital) nystagmus

Infantile (congenital) nystagmus often develops during the first few months of life and, thus, the term infantile nystagmus is now preferred. Some cases are familial and genetically heterogeneous with autosomal dominant, autosomal recessive, and X-linked patterns of inheritance reported. Importantly, some patients with infantile nystagmus have mutations in the *FRMD7* gene [110]. Infantile nystagmus is predominantly horizontal (even in up- and downgaze) and conjugate. Furthermore, it usually increases on attempted visual fixation and with anxiety, but often suppresses with convergence. There may be a position in the orbit (the so-called neutral or “null” zone) in which the nystagmus intensity is minimal, and in which the patient prefers to hold their eyes using an appropriate head turn. The waveform of the nystagmus often changes in different gaze positions and typically shows an accelerating slow-phase profile [111]. An important signature of infantile nystagmus is the foveation period, during which the eye is momentarily still while the fovea of the retina is steadily pointed at the object of interest. Many patients with infantile nystagmus, especially those with well developed foveation periods, have no visual complaints. However, some patients may have reduced visual acuity, oscillopsia, or anomalies in head position with their nystagmus [112]. In a randomized, controlled, double-masked study, memantine (10–40 mg/day) and gabapentin (600–2,400 mg/day) decreased the intensity of infantile nystagmus and brought about a small improvement in visual acuity [113]. Those patients with infantile nystagmus who show suppression with convergence may be helped by wearing base-out prisms on their glasses. A number of surgical treatments have also been proposed for infantile nystagmus, although their role in the management of this disorder is still debated [7].

#### Other forms of nystagmus that impair vision

Seesaw nystagmus is a spontaneous nystagmus characterized by half-cycles during which one eye elevates and intorts, while the other depresses and extorts, as if pivoting

about the bridge of the nose. Pendular seesaw nystagmus consists of sinusoidal oscillations (i.e., slow phases during both nystagmus half-cycles), and is associated with large parasellar tumors causing bitemporal hemianopia and congenital optic chiasm abnormalities, such as in septo-optic dysplasia or achiasma. [114]. Pendular seesaw nystagmus may arise due to loss of crossing visual information from the temporal visual fields, thereby disrupting the calibration of eye movements compensating for roll head rotations, and leading to instability of gaze control. Pendular seesaw nystagmus can be suppressed by alcohol [115, 116] and clonazepam [118].

Hemi-seesaw nystagmus consists of slow phases during one half-cycle and quick phases during the other. It occurs with rostral midbrain lesions in the vicinity of the interstitial nucleus of Cajal (INC) [119], a structure that is responsible for the integration of vertical and torsional eye movements. Recent experimental studies in primate have indicated that lesions just posterior to the INC cause hemi-seesaw nystagmus [120]. Hemi-seesaw nystagmus may improve with memantine or gabapentin in some patients [121].

Although not clearly a form of nystagmus, superior oblique myokymia is characterized by recurrent brief episodes of monocular oscillopsia and vertical diplopia [4]. As for other brief disturbances of cranial nerve function, such as vestibular paroxysmia (discussed above), it can be relieved with carbamazepine [122] or gabapentin [123].

#### Saccadic disorders that impair vision

Square-wave saccadic jerks (SWJ), the most common saccadic oscillation encountered in clinical practice, consist of small saccades that take the eyes away from a fixation target, followed by a saccade in the opposite direction to bring the eyes back to the target, with an intersaccadic interval of typically 200 ms [4]. Small SWJ occur in healthy individuals [124]. They are also encountered in patients with cerebellar and parkinsonian diseases, especially progressive supranuclear palsy [4]. SWJ rarely degrade vision, and are not considered further here.

In contrast, ocular flutter and opsoclonus usually degrade vision, often producing oscillopsia and dizziness. Both consist of intermittent or continuous, uncalled-for, back-to-back saccades without an intersaccadic interval; the horizontal variant is known as ocular flutter, whereas the multidimensional variant is known as opsoclonus [4]. These saccadic oscillations are usually caused by paraneoplastic syndromes, post-infectious encephalitis, demyelinating diseases, or an inherited disorder (e.g., microsaccadic oscillations [125] and limb tremor). They may arise from autoimmune or cross-immune damage to cerebellar Purkinje cells, brainstem saccade generators,

constituent membrane ion channels, or possible inherited deficits in membrane properties [126, 127, 130]. Since some healthy subjects can generate saccadic oscillations, usually with a convergence effort (voluntary nystagmus or voluntary flutter) [128, 129], it has been postulated that an individual's complement of ion channel subtypes in the brainstem circuits that generate saccades might influence their ability to voluntarily generate these oscillations, as well as their dynamic characteristics. This innate ability would be under genetic influence and might explain why a relatively wide range of frequencies of saccadic oscillations are seen across normal unrelated individuals, whereas the frequency of voluntary nystagmus and saccadic oscillations is similar within families [130].

A mechanism intrinsic to the membranes of saccadic burst generators might explain the high frequency and familial dependence of saccadic oscillations [130]. According to this hypothesis, the saccadic oscillations represent unmasking of the inherent instability in the saccadic burst neuron circuit due to an imbalance between burst neuron excitability and external inhibition. It was proposed that increased excitability of the burst neurons or reduced external inhibition would result in increased amplitude of the post-inhibitory rebound (PIR)—a rebound increase in neuronal membrane discharge after sustained membrane hyperpolarization. In a neuromimetic model of the burst neurons, increased maximal conductance through pacemaker ion channels, including hyperpolarization-activated, inward-mixed, cation currents ( $I_h$ ), and low threshold calcium currents ( $I_T$ ), determined the neural excitability and the amplitude of the PIR [131]. Subsequently, it was hypothesized that increases in neural excitability and/or in PIR due to pathologically increased  $I_h$  and/or  $I_T$  reduce the effects of external inhibition, so that saccadic oscillations can emerge.

The membrane mechanism of saccadic oscillations is supported by a number of case reports on rare etiologies of saccadic oscillations or reports of successful treatment of saccadic oscillations with ion channels blockers. For example, carbamazepine, a calcium channel blocker [132], may ameliorate saccadic oscillations. Saccadic oscillations in patients abusing cocaine or with strychnine poisoning [4] could be explained by reduction in norepinephrine reuptake, causing increases in norepinephrine-induced  $I_h$  conductance [133]. Saccadic oscillations in hyperammonemic, uremic, and hyperosmolar states could be due to alterations in pH, which in turn regulates the maximal  $I_h$  conductance [134]. Organophosphate-induced opsoclonus is possibly the result of cholinergic excess causing increased activation of the fastigial nucleus, a component of a feedback loop of the brainstem saccade generator, causing hyperexcitability of the saccadic burst generators

[135]. Inherent hyperexcitability in migraineurs might explain saccadic oscillations in these patients [136].

### Conclusions and future perspectives

Considerable progress has been made over recent decades in describing the clinical characteristics of different forms of nystagmus, as well as their pathophysiology and etiology. However, the pathophysiological mechanisms underlying many forms of nystagmus are not well understood and, consequently, targeted treatments have not yet been developed. Indeed, most proposed treatments for nystagmus are yet to be validated in prospective, masked, randomized, placebo-controlled trials. Due to the rarity of many forms of nystagmus, multicenter trials are required to evaluate an adequate number of patients. Several drugs could be potentially effective (listed in alphabetical order): acetazolamide, aminopyridines, anticholinergics (benztropine, scopolamine, trihexyphenidyl), baclofen, barbiturates, benzodiazepines, cannabinoids, carbamazepine, gabapentin, lamotrigine, memantine, phenytoin, selective potassium channel blockers, selective serotonin re-uptake inhibitors, tricyclic antidepressants, topiramate, triptans, and valproic acid. Knowledge of the possible effects of these agents—most of which act specifically on certain receptors or ion channels—will also further improve our insights into the pathophysiology of the underlying disorders and how to treat them.

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