Objectives
At the conclusion of this program, participants will be able to:
1. Name the principal neurotransmitters thought to be important for eye movement control.
2. Cite side effects of medications commonly used to treat nystagmus, including gabapentin, baclofen and clonazepam, and types of nystagmus they have been shown to benefit.
3. Identify three nystagmus-causing conditions for which disease-specific therapy is available.
4. Explain the uses and limitations of prisms and optical image stabilization systems in the treatment of nystagmus.
5. Describe the benefits and risks of botulinum toxin injections and eye muscle surgery in patients with congenital and acquired nystagmus.

CME Questions
1. Of the following, which is NOT considered an important neurotransmitter for brainstem control of eye movements?
   a. Dopamine  
   b. GABA (A and B receptor subtypes)  
   c. Acetylcholine  
   d. Glutamate  
   e. Glycine

2. Gabapentin, clonazepam and baclofen have all been used to treat various forms of nystagmus. Of the following, which pair of side effects is most often experienced with these medications?
   a. Paresthesias and dysgeusia  
   b. Diarrhea and headache  
   c. Dry mouth and urinary retention  
   d. Sedation and ataxia  
   e. Itchiness and hallucinations

3-6. Match the drug (in the first column) with the type of ocular oscillation upon which it has been reported to have the most dramatic benefit (from the second column):

3. Memantine  
4. Baclofen  
5. Carbamazepine  
6. 3,4-diaminopyridine (DAP)  
   a. Downbeat nystagmus  
   b. Superior oblique myokymia  
   c. Acquired pendular nystagmus  
   d. Acquired periodic alternating nystagmus

7. Optical image stabilization systems, as developed by Rushton and colleagues, have the following disadvantages in treating nystagmus except:
   a. Reduced visual field  
   b. Nullify normal eye movements as well as nystagmus  
   c. Invariable degree of image stabilization  
   d. Inconvenience of strong spectacle and contact lenses  
   e. Magnify images

8. Patient tolerance of botulinum toxin injections for nystagmus is limited because of all of the following, except:
   a. Common side effects of anisocoria and lid retraction  
   b. Frequent incidence of diplopia and ptosis  
   c. Need for repeat injections every 3 months or so  
   d. Impairment of vestibular and tracking eye movements  
   e. Occasionally increased nystagmus in untreated eye

9. Successful application of the following newer procedure for congenital nystagmus (CN) suggests that altering the sensorimotor feedback loop between eye and brain may be an important final common pathway of positive surgical outcome in this disorder:
   a. Anderson-Kestenbaum procedure  
   b. Cüppers artificial divergence procedure  
   c. Extensive four-muscle recession  
   d. Harada-Ito operation  
   e. Simple tenotomy of the horizontal recti

Overview
Treatment should be considered for patients with symptoms like visual blurring and oscillopsia arising from persistent nystagmus. Pharmacological interventions take into account growing awareness of the chemical anatomy of the ocular motor system and may include newer agents with CNS activity. Optical approaches, including image stabilization and prisms, may be helpful for some patients. Eye muscle surgery or chemodenervation can reduce symptoms and improve visual acuity when less invasive options fail. Interested readers are referred to several other reviews on related subjects.1-6

Why Treat Nystagmus?
Much of the ocular motor system is devoted to ensuring that images of individual objects, or of the visual environment as a whole, are held stable upon the retina. The smooth pursuit system allows us to track small moving objects accurately, while the vestibular and optokinetic
systems act to keep the visual world stationary on the retina. These movements allow for optimal visual resolution and contribute to a perception of stability of ourselves or the environment. Involuntary ocular oscillation causes images to slip or jump across the retina in a manner that does not coincide with other sensory evidence of motion. Retinal image slip degrades visual acuity and causes a perception of blurring. Patients with nystagmus are variably aware of these problems. In particular, individuals with congenital nystagmus (CN) generally do not report oscillopsia and may not notice degradation of image quality, especially if they have afferent visual deficits at baseline. Patients with CN are less likely to pursue treatment than those who are more aware of symptoms. Most nystagmus patients presenting for treatment have a problem of central neural origin, usually from acquired brainstem dysfunction. Peripheral vestibular nystagmus seldom lasts for more than a week after an acute insult. It is managed chiefly with medications that relieve the accompanying nausea. Examples of central nystagmus that may persist include: acquired pendular nystagmus (such as the vertical form seen with oculopalatal myoclonus), unidirectional vertical, torsional or horizontal nystagmus, gaze-evoked nystagmus, periodic alternating nystagmus and seesaw nystagmus. Symptoms are particularly bothersome when horizontal or vertical nystagmus is present in primary position or in the slight downgaze position typically used for reading.

Is Quantitative Ocular Motor Assessment Helpful?
In my view, oculographic measurement is helpful, but seldom pivotal, in treating patients with pathological nystagmus. Most of the time, careful clinical observation is sufficient to classify an ocular oscillation to decide, for example, whether the abnormal movement is true nystagmus with a smooth component, or whether it is purely saccadic, and to describe how it behaves at different gaze positions and distances. As a much less expensive alternative to oculography, video recording is beneficial not only for careful dissection of nystagmus at one’s leisure, away from the chaotic environment of the clinic, but for permanent documentation as well.

Since treatment should be based largely on relief of symptoms, the patient’s subjective reports should be weighted heavily in making therapeutic decisions. Placebo effects and wishful thinking must be taken into account. Objective assessment of improvement may be sought by evaluating central visual functions that are degraded by retinal image slip, such as visual acuity and high-frequency contrast sensitivity. These measurements are less sensitive to torsional oscillation than to horizontal or vertical eye movements that defoveate images. Having said all of this, oculography, particularly with a search coil system, can be essential in characterizing a subtle disorder, particularly when movements are of small amplitude and in more than one plane. Quantitative analysis is also indispensable if treatment decisions hinge on moderate improvement that may not be perceptible to the patient or clinician.

Why Isn’t Pharmacological Therapy of Nystagmus Straightforward?
Ideally, all pathological nystagmus could be attributed to abnormalities of a single neurotransmitter subsystem, manipulation of which would remedy the problem. Unfortunately, the chemical anatomy of the ocular motor system is complex, with the same neurotransmitters sometimes having opposing actions at different sites. As a result, nystagmus is often resistant to currently available neuroactive drugs. Acquired periodic alternating nystagmus (PAN) is one exception. It is linked chiefly to dysfunction of the GABAA system and it responds well to modification of that system with baclofen (see Table 1). In many cases, nystagmus responds partially to drugs that act upon different neurotransmitter subsystems. An analogy might be drawn with treatment of Parkinson’s disease, primarily a disorder of dopaminergic pathways, compared to dystonias like blepharospasm that generally show no more than modest responses to manipulation with cholinergic, GABAergic or dopaminergic drugs. Adding to the difficulty in choosing drug treatments is the fact that persistent central nystagmus often results from conditions like multiple sclerosis and hereditary degeneration, in which precise anatomical and chemical localization is not possible.

Neurotransmitters strongly linked to the ocular motor system include GABA, an inhibitory neurotransmitter that is thought to play an important role in vestibular velocity storage and gaze-holding, and acetylcholine and glutamate, which provide excitatory activity in the vestibular system. Pharmacological agents with activity upon GABAa, GABAb, muscarinic and nicotinic (cholinergic), and NMDA (glutamatergic) receptors have been shown to modify central nystagmus in humans. Like GABA, glycine serves as an inhibitory transmitter within the vestibular system; it is also the key neurotransmitter used by omnipause neurons, which restrain unwanted saccades. Dopamine, norepinephrine and serotonin appear to be less important for brainstem ocular motor function, although they may play a role in cerebral eye movement control.

What Drugs Are Particularly Useful In Treating Ocular Oscillations?
All of the following are off-label uses; no drug has been FDA-approved for treatment of ocular oscillations (see Table 2).

Gabapentin (Neurontin) is approved by the FDA as an adjunctive drug for seizures and, more recently, for
treatment of post-herpetic neuralgia. In a multi-center, controlled trial, Averbuch-Heller and colleagues demonstrated significant quantitative improvement with gabapentin in most patients with pendular nystagmus. Baclofen produced much less benefit in this group. Patients with downbeat nystagmus had variable effects, with occasional benefit from either drug. Although its structure resembles GABA, the mechanism of action of gabapentin is not entirely clear. Bandini et al. compared the effects of gabapentin and vigabatrin, a drug thought to work strictly through GABAergic mechanisms, on acquired pendular nystagmus with or without gaze-evoked nystagmus in five multiple sclerosis patients. Gabapentin produced quantifiable improvement in four of five patients, while vigabatrin only helped one patient. The authors suggested that the effect of gabapentin upon nystagmus may be glutamatergic rather than GABAergic. The main side effects of gabapentin are sedation and ataxia; the latter may pose a particular problem in patients with acquired nystagmus, most of whom have some cerebellar dysfunction at baseline.

**Baclofen (Lioresal)** is thought to work chiefly as a GABA$_A$ agonist and is approved for use in spasticity. Halmagyi and colleagues demonstrated abolition of acquired PAN in two patients on baclofen 30 mg/day, but not in a patient with congenital PAN. Lack of response to baclofen in congenital PAN has been characteristic. Dieterich et al. gave baclofen 15 mg/day to patients with upbeat or downbeat nystagmus, documenting significant quantitative improvement in four of five cases. As above, Averbuch-Heller and colleagues demonstrated modest benefits of baclofen (30 mg/day) in patients with pendular and downbeat nystagmus. Increased GABAergic activity within the velocity storage system explains the effect of baclofen in PAN, while enhanced cerebellar inhibition of brainstem vestibular signals may account for its benefit in acquired vertical nystagmus. Side effects of baclofen include drowsiness and fatigue.

**Clonazepam (Klonopin)** is a longer-acting benzodiazepine that is FDA-approved for generalized seizures and panic disorder. Like other drugs in this group, it has GABA$_A$ agonist properties. Currie and Matsuo reported significant improvement in most patients with downbeat and pendular nystagmus after a single 1-2 mg dose of this agent, and symptomatic relief for up to three years on clonazepam 1-2 mg/day. Young and Huang described enduring symptomatic and oculographic improvement in five patients with idiopathic downbeat nystagmus, using clonazepam 1 mg bid. Cochin and colleagues reported a single patient with post-traumatic see-saw nystagmus whose ocular oscillation was eliminated by clonazepam; nystagmus did not recur even after the drug was discontinued. The most common side effects of benzodiazepines are sedation and ataxia.

**Acetazolamide (Diamox)** is well known to neuroophthalmologists as a carbonic anhydrase inhibitor used in treating glaucoma and idiopathic intracranial hypertension. It has been found useful in a range of ion channel disorders, one of which is the autosomal dominant episodic ataxia type 2 (EA2). Patients with EA2 present with paroxysms of gait and limb ataxia, vertigo and cerebellar eye movement disturbances including gaze-evoked, rebound and downbeat nystagmus. Attacks may last hours to days and often evolve into progressive interictal cerebellar dysfunction. In almost all patients with EA2, acetazolamide reduces the frequency and severity of attacks. Acetazolamide can also reduce symptoms in patients with spinocerebellar ataxia type 6 (SCA6), which is characterized by downbeat nystagmus and associated with mutations on the same calcium channel gene as EA2. In patients who are intolerant of acetazolamide, methazolamide (Neptazane), dichlorphenamide (Daranide) or topiramate (Topamax), an anticonvulsant with weak carbonic anhydrase activity, can be tried. These drugs should be considered for patients with episodes of dizziness and balance disturbance, especially if typical features of cerebellar eye movement dysfunction can be established. Carbonic anhydrase inhibitors can cause paresthesias, dysgeusia and, rarely, kidney stones.

**Anticholinergic medications** like scopolamine (Transderm Scop), benztropine (Cogentin) and trihexyphenidyl (Artane) may have modest effects upon nystagmus. Using intravenous muscarinic blocking agents, Barton and colleagues showed quantitative improvement in seven patients with pendular or downbeat nystagmus, with scopolamine having a greater effect than benztropine. Other groups, using oral or transdermal delivery of these agents, have failed to demonstrate significant or consistent benefit, however. Leigh et al. had little success with maintenance therapy on oral trihexyphenidyl; of 10 treated patients, only six tolerated the drug long enough to complete the study. Of these six patients, only one showed improvement. The authors also evaluated the effects of tridihexethyl, a muscarinic antagonist that does not cross the blood-brain barrier; this drug showed benefit for nystagmus in some patients, implying a peripheral mechanism of action. Starck and colleagues tried scopolamine for acquired pendular nystagmus, demonstrating mild improvement in only two of eight patients. Kim et al. reported a similar experience, demonstrating no consistent benefit of transdermal scopolamine in an unmasked, quantitative trial in seven patients with acquired nystagmus. Side effects of anticholinergic medications include dry mouth, urinary retention, blurred vision and sedation.
Memantine (Namenda) has just been approved by the FDA for treatment of moderate to severe Alzheimer’s disease. It has been in use in Europe for over 20 years for Alzheimer’s and Parkinson’s diseases and has also been tested in AIDS dementia, glaucoma and neuropathic pain. Memantine is an NMDA receptor antagonist that blocks excitatory glutamatergic pathways. In a study of 14 patients with acquired pendular nystagmus associated with multiple sclerosis, Stack and colleagues20 identified dramatic benefit with no significant adverse reactions. Doses used for Alzheimer’s disease range from 5 mg qd to 10 mg bid. Adverse effects include dizziness, headache, constipation and confusion.

3,4-Diaminopyridine (DAP) has been used for years in the treatment of Lambert-Eaton myasthenic syndrome (LEMS). It acts as a potassium channel blocker and works in LEMS by potentiating release of acetylcholine from peripheral presynaptic nicotinic vesicles. It has also been shown to increase Purkinje cell activity in vitro. Strupp and colleagues22 used quantitative, placebo-controlled analysis in 17 patients with downbeat nystagmus (DBN) from a variety of causes, showing that nystagmus slow phase velocities were reduced by over 50% in most patients after a single 20 mg dose of DAP. Ten patients reported sustained symptomatic improvement, with less oscillopsia or better gait stability, over one month after initiating treatment with DAP 10-20 mg tid. Presumably, DAP worked in these cases by increasing the inhibitory influence of the vestibulocerebellum upon the upward VOR. Side effects were fairly minor and included paresthesias, nausea and headache. In LEMS patients, doses of 5-25 mg tid-qid are used. Doses toward the upper end of this range may induce seizures. In the US, DAP is only available on a compassionate use/ investigational basis (Jacobs Pharmacueticals, Princeton, NJ, 609-921-7447).

4-aminopyridine (4-AP) is a similar compound that may penetrate the blood-brain barrier better, have a longer half-life, and be better tolerated than DAP.23 Trials of 4-AP in downbeat nystagmus are underway (John Leigh, personal communication).

Ethanol has been associated with anecdotal improvement in single cases of seesaw nystagmus24 and acquired pendular nystagmus.25 Carisoprodol (Soma) also reduced symptoms in the patient reported by Lepore.25 Smoking marijuana, but not taking cannabis pills, helped one patient with pendular nystagmus associated with multiple sclerosis.26 Stimulants such as dextromethorphan (Dexedrine) and diethylpropionate (Tenuate) have shown benefit in anecdotal cases of CN.27,28 A patient with acquired pendular nystagmus in oculopatalal myoclonus benefited from using valproic acid (Depakene).29 Finally, Traccis and colleagues30 reported on the use of isoniazid (INH) 800-1000 mg/day in three patients with acquired pendular nystagmus from multiple sclerosis; two of three experienced abolition of nystagmus and relief of oscillopsia.

What Are Some Forms of Nystagmus For Which Specific Therapies Are Helpful?

Downbeat nystagmus (DBN) can be caused by a variety of degenerative and structural conditions affecting the cerebellum. Chiari malformation is a well-established cause of DBN and other cerebellar eye movement disorders.31,32 Special care should be taken to analyze the position of the cerebellar tonsils on MRI, since mild downward displacement may cause symptoms, yet be easily missed.33 Corrective surgery through suboccipital craniectomy often alleviates symptoms.31-33

Focal epilepsy is a rare cause of episodic nystagmus, but it should be kept in mind, since it occasionally presents without alteration of consciousness, visual hallucinations, or other evidence of seizure activity. Horizontal nystagmus beating away from the side of the seizure focus is typical, with most cases arising from a posterior hemispheric focus.34,35 Unique variants include ictal periodic alternating nystagmus,36 monocular nystagmus37 and nystagmus with skew deviation.38 Epileptic nystagmus usually responds to anticonvulsants.

Successful reports of symptomatic treatment for saccadic intrusions, including square wave jerks, ocular flutter and opsoclonus, are rare, although a basis in neurotransmitter dysfunction has been suggested by several observations. For example, excessive square wave jerks can be produced when normal individuals are subjected to catecholamine depletion with metyrosine39 and were reported in a patient on a monoamine oxidase inhibitor after a single dose of L-tryptophan, the precursor of serotonin.40 Fukazawa and colleagues41 reported improvement of macrosaccadic oscillations and macrosquare wave jerks with clonazepam, diazepam and phenobarbital. This therapeutic effect may have reflected selective GABA_A activation rather than generalized CNS depression, since other sedative drugs did not have the same benefit. In a patient with post-traumatic saccadic intrusions and a relative null-point above primary position, Weissberg et al.42 effected improvement with yoked vertical prisms. A wide range of disease-specific treatments have been at least partly successful for paraneoplastic and idiopathic or parainfectious opsoclonus-myoclonus syndrome, including tumor removal, plasmapheresis, intravenous immunoglobulin, and steroids.43

Superior oblique myokymia (SOM) comprises episodic, irregular activation of the superior oblique muscle on one side. Patients complain of intermittent vertical or torsional diplopia, often with monocular oscillopsia referable to the affected eye. These symptoms correspond to tonic or arrhythmic clonic movements that do not comprise true nystagmus. Symptoms can remit for
long intervals spontaneously or after treatment, only to recur months later. Although SOM was once thought to be largely benign, an increasing number of reports have linked the disorder with structural lesions near the trochlear nerve exit zone from the midbrain, including tumor and arteriovenous malformation. It has been suggested that most cryptogenic cases of SOM are actually caused by microvascular compression. Neurosurgery has been undertaken to decompress the affected nerve; in two patients operated upon by one group, SOM was eliminated, with one patient suffering persistent trochlear nerve palsy. In most cases, SOM responds at least initially to medication, including anticonvulsants like carbamazepine and gabapentin or topical beta-blockers. In refractory or persistent cases, superior oblique tenectomy and transposition of the superior oblique tendon by the Harada-Ito procedure have been successful. These eye muscle procedures may be safer than microvascular decompression through craniotomy.

**Vitamin E deficiency** arises from longstanding defects in the absorption or transport of fat-soluble vitamins, from conditions including abetalipoproteinemia, cholestatic liver disease, intestinal malabsorption, and isolated genetic dysfunction of tocopherol transfer proteins. Neurological manifestations include ataxia, proprioceptive loss and areflexia. Patients may develop atypical pigmentary retinopathy. Regardless of the underlying cause, advanced vitamin E deficiency produces a very characteristic, symmetrical pattern of ocular motility disturbance that superficially resembles WEBINO (wall-eyed bilateral internuclear ophthalmoplegia) syndrome. Patients are exotropic and have limited adduction, but demonstrate slower abducting saccades than adducting saccades and have dissociated nystagmus that is worse in the adducting eye. This condition improves after parenteral vitamin E supplementation.

**Wernicke’s encephalopathy** should be considered in any patient with nystagmus who is at risk for nutritional deficiency. Ethanol abuse is the most easily recognized cause of vitamin E deficiency, but subtler causes may elude initial consideration, such as intestinal malabsorption (for example, after bariatric surgery) and protracted vomiting (for example, in hyperemesis gravidarum). Nystagmus may take many forms in Wernicke’s encephalopathy, with upbeat and gaze-avoided nystagmus the most common. Empiric therapy with parenteral thiamine is inexpensive and effective.

**Whipple disease** is caused by the organism *Tropheryma whippelii* and generally presents with diarrhea, weight loss, and arthropathy. Neurological manifestations include vertical gaze paresis, dementia and myoclonus. Although seen in the minority of cases, oculomasticatory myorhythmia with slow convergent-divergent ocular oscillations, is pathognomonic of Whipple disease of the nervous system. A parenteral third-generation cephalosporin or penicillin plus streptomycin is typically needed when there is neurological involvement; intravenous medication should be followed by long term treatment with oral trimethoprim-sulfamethoxazole.

**What Is the Role of Optical Devices?** Rushton and Cox developed a purely optical approach to the chief problems of oscillopsia and image blurring that arise from nystagmus. **Optical image stabilization** calls for fitting of a strong minus (up to −58.00 diopters) contact lens combined with a strong plus (up to +32.00 diopters) spherical spectacle lens. In essence, the spectacle lens moves the focal point forward from the retina to the center of ocular rotation, where the image remains stationary independent of any eye movement. The contact lens then refocuses the image on the retina without nullifying the image stabilizing property of the spectacle lens. Various degrees of optical image stabilization can be obtained by changing the spherical powers of the spectacle and contact lenses; investigations in patients have used between 20 and 90%. The degree of desired stabilization varies between patients, in part because of central adaptation to spontaneous eye movement; this is particularly true in patients with CN, who may paradoxically notice oscillopsia for the first time in their lives when images are artificially stabilized. Patients with acquired downbeat nystagmus can experience an inversion in the direction of perceived motion as 100% image stabilization is approached.

**Optical image stabilization** would seem to be an ideal solution to nystagmus symptoms, but there are a number of problems that limit patient acceptance. The lens system magnifies images and reduces the field of vision. The high-power contact lenses are cumbersome and hard to manipulate for patients with motor problems, although discomfort from the hard lenses used in initial studies can be lessened with smaller gas permeable units, increasing patient acceptance. Most disturbing to patients is the fact that the optical system, by design, acts to neutralize the effects of eye movements, including normal functions like smooth pursuit, vergence and the VOR. The eyes thus cannot compensate fully for head or image movement, and patients may develop oscillopsia and blur when they move their heads or when objects move in relation to them. Practical application of optical image stabilization is limited to times when subjects are viewing a relatively motionless visual target with their heads fixed, using one eye (for example, classroom lectures or reading). **Prisms** may be useful for patients in whom nystagmus is significantly damped by convergence or divergence or, less often, in patients with an eccentric null position of minimal nystagmus. Bilateral base-out prisms have been used effectively in CN patients whose nystagmus...
dampens with convergence,69,70 and occasionally in patients with acquired nystagmus.30,60 A protocol suggested by Dell’Osso69 calls for bilateral 7 diopter base-out prisms, combined with −1.00 diopter spheres to account for the induced accommodation. Conjugate prisms can be used to shift a relative null position toward center. Many CN patients seem comfortable with the horizontal head turn they have developed over the years and may not benefit. Conjugate vertical prisms may be helpful in patients with acquired nystagmus when they have a vertical null position and would otherwise have to pitch their head forward or backward to optimize vision.

What About Botulinum Toxin?
A number of authors have treated patients by pharmacologically immobilizing eye muscles with retrolubar or selective intramuscular injections of botulinum toxin. Helveston and Pogrebnjak71 used 25 unit retrolubar injections of botulinum toxin A and documented improved vision for 5-13 weeks in two patients with acquired nystagmus, with no side effects. Leigh and colleagues72 injected botulinum toxin into the horizontal recti of two patients with acquired pendular nystagmus. Predictably, this abolished horizontal nystagmus, leading to an improvement in visual acuity, but did not alter nystagmus in other planes. The same group used retrolubar injections of 10-25 units of botulinum toxin A in three patients with acquired pendular nystagmus.73 Nystagmus was significantly reduced in all three planes during the 2-3 months of drug effect, but diplopia, ptosis and eye irritation limited patient tolerance. In the latter two studies, no patient chose to repeat the treatment. Repka et al.74 treated six patients (9 eyes) with 25-30 units of retrolubar botulinum toxin A, and reported reduced nystagmus amplitude and improved visual acuity in all patients. Benefits usually lasted no more than eight weeks, but two patients with oculopalatal myoclonus experienced improvement for up to six months. Lennerstrand and colleagues75 reported on their experience with botulinum toxin in a variety of conditions, including acquired pendular nystagmus treated chiefly with intramuscular injections. They cited an 18% overall incidence of ptosis or vertical strabismus, and suggested using botulinum toxin therapy as a predictor of the response to surgery. Ophthalmoparesis from botulinum toxin injections reduces useful eye movements like the VOR and may cause patients to develop maladaptive responses, including increased nystagmus in the untreated eye.72 Long term tolerance of nystagmus treatment with botulinum toxin is limited by the various side effects noted above and by the cumulative risk of serial injections over many years.

When Is Surgery Recommended?
Eye muscle surgery may be useful when other modes of treatment have failed. Surgery has the longest track record in CN, dating back over 50 years. The Anderson-Kestenbaum procedure is used in patients whose nystagmus demonstrates an eccentric null position, a gaze point at which the oscillation is minimal. The idea is to artificially move the null position closer to the orbital center by relocating the attachments of the desired muscles, usually the horizontal recti. In addition to shifting the null position, this procedure can expand it and can even dampen nystagmus in eccentric positions.76,77 In the artificial divergence procedure devised by Cüppers, muscle attachments are moved to increase convergence activation in patients whose nystagmus dampens at near. The artificial divergence procedure alone (2 muscles) or in combination with Anderson-Kestenbaum surgery (3 muscles) may be more effective than the Anderson-Kestenbaum procedure alone (4 muscles).72 In patients without either a null region or significant improvement with convergence, extensive resections of the four horizontal recti have been used to reduce involuntary eye movement.78,79 Ductional amplitudes are usually preserved and visual acuity and nystagmus intensity are improved in most, but not all, patients receiving this procedure. Ocular misalignment, sometimes requiring a second operation, is an occasional complication.

More recently, less aggressive surgery has been applied to CN.80 Hertle and colleagues81 reported the results of simple tenotomy of the 4 horizontal recti in 10 patients with CN and various baseline afferent deficits. The authors performed tenotomy of the desired muscles, reattaching them at their original insertions, and quantified afferent function and eye movements one year post-operatively; 9 of 10 patients showed sustained benefits. Despite clinical improvement, the waveforms of CN are changed little by this approach.82 Successes with tenotomy suggest that altering the sensorimotor feedback loop at the level of the eye muscle tendons modulates CN. This may be a large part of the mechanism of improvement with more aggressive operations.

Much less has been written on the surgical treatment of acquired nystagmus than on CN. Buckley and Elston83 performed extensive surgery on the vertical recti of two patients with acquired pendular vertical nystagmus from oculopalatal myoclonus. This produced partial reduction in nystagmus, but limited vertical gaze. Campos and colleagues84 performed vertical Anderson-Kestenbaum surgery on four patients with acquired vertical nystagmus and anomalous compensatory head positions, reporting prolonged improvement in all. A combined pharmacological (gabapentin) and surgical (vertical Anderson-Kestenbaum) approach was helpful in one multiple sclerosis patient with acquired horizontal-vertical nystag-
mus. The four-muscle tenotomy procedure pioneered by Dell’Osso and Hertle has been applied to a multiple sclerosis patient with horizontal pendular nystagmus, who was simultaneously treated for acquired exotropia; the operation improved nystagmus and visual acuity, implying that feedback loops might be active in acquired nystagmus, as in CN (Lou Dell’Osso, personal communication).

What Other Treatments Have Been Tried for Nystagmus?

Some patients with CN have discovered that trigeminal or cervical sensory stimulation reduces their nystagmus. Examples include rubbing, vibration or electrical stimulation of the face or neck. In a similar vein, contact lenses may help CN patients beyond their optical effect, possibly by providing low-level trigeminal nerve stimulation. Cervical acupuncture may modify and reduce CN, presumably through sensory mechanisms; an enduring benefit over weeks to months is not certain. Biofeedback can produce short-term improvement in CN patients. Finally, Stahl and colleagues devised an electromechanical optical device to partly nullify the effects of acquired pendular nystagmus, while preserving physiological eye movements. Their apparatus achieved some of these aims, raising hope that further technological advances could lead to a successful prosthetic implement.

Answers to CME Questions

1. a
2. d
3. c
4. d
5. b
6. a
7. c
8. a
9. e

References


Table 1
Types of Ocular Oscillation with Established Responses to Specific Drug Therapy

<table>
<thead>
<tr>
<th>Type</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired pendular nystagmus</td>
<td>gabapentin, memantine, baclofen, clonazepam</td>
</tr>
<tr>
<td>Downbeat nystagmus</td>
<td>baclofen, clonazepam, gabapentin, DAP*</td>
</tr>
<tr>
<td>Nystagmus in episodic ataxia type 2</td>
<td>acetazolamide, other carbonic anhydrase inhibitors</td>
</tr>
<tr>
<td>Acquired periodic alternating nystagmus</td>
<td>baclofen</td>
</tr>
<tr>
<td>Superior oblique myokymia</td>
<td>carbamazepine, gabapentin, β-blockers</td>
</tr>
</tbody>
</table>

* DAP is only available on a compassionate use/investigational basis in the US

Table 2
Characteristics of Drugs Used for Nystagmus

<table>
<thead>
<tr>
<th>Agent</th>
<th>Typical Doses</th>
<th>Probable Mechanism of Action</th>
<th>Common Side Effects</th>
<th>Conditions Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>acetzolamide (Diamox)</td>
<td>125-1000 mg bid</td>
<td>carbonic anhydrase inhibitor</td>
<td>paresthesias, dysgeusia</td>
<td>episodic ataxia type 2</td>
</tr>
<tr>
<td>baclofen (Lioresal)</td>
<td>5-20 mg tid</td>
<td>GABA&lt;sub&gt;B&lt;/sub&gt; agonist</td>
<td>sedation</td>
<td>acquired PAN, downbeat nystagmus</td>
</tr>
<tr>
<td>clonazepam (Klonopin)</td>
<td>0.25-2 mg tid</td>
<td>GABA&lt;sub&gt;A&lt;/sub&gt; agonist</td>
<td>sedation, ataxia</td>
<td>downbeat nystagmus, acquired pendular nystagmus</td>
</tr>
<tr>
<td>3,4-diaminopyridine (DAP)*</td>
<td>5-25 mg tid-qid</td>
<td>K&lt;sup&gt;+&lt;/sup&gt; channel blocker</td>
<td>paresthesias, nausea</td>
<td>downbeat nystagmus</td>
</tr>
<tr>
<td>gabapentin (Neurontin)</td>
<td>300-600 mg tid</td>
<td>glutamate antagonist, ?GABA agonist</td>
<td>ataxia, sedation</td>
<td>acquired pendular nystagmus, downbeat nystagmus</td>
</tr>
<tr>
<td>memantine (Namenda)&lt;sup&gt;##&lt;/sup&gt;</td>
<td>5-10 mg bid</td>
<td>NMDA (glutamatergic) antagonist</td>
<td>dizziness, headache</td>
<td>acquired pendular nystagmus</td>
</tr>
<tr>
<td>scopolamine (Transderm Scop)</td>
<td>1.5 mg patch q3days</td>
<td>muscarinic (cholinergic) antagonist</td>
<td>sedation, dry mouth</td>
<td>acute vestibulopathy, ?acquired pendular nystagmus, downbeat nystagmus</td>
</tr>
</tbody>
</table>

*available only as investigational agent in US  ## recently FDA-approved for Alzheimer’s disease

Appendix
Abbreviations used throughout paper

ACh = acetylcholine  
DAP = 3,4-diaminopyridine  
EA2 = episodic ataxia type 2  
NMDA = N-methyl-D-aspartate  
SOM = superior oblique myokymia  
VOR = vestibulo-ocular reflex