Eye movement disorders

# Drug treatments for eye movement disorders

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Advances in the treatment of eye movement disorders

## PATHOGENESIS OF ABNORMAL EYE MOVEMENTS AND THEIR VISUAL CONSEQUENCES

The modern rationale for the treatment of abnormal eye movements rests on current concepts of the neurobiology of ocular motility and vision.[1] In order to see clearly the details in our visual world, images must be held quite still upon the retina, especially the central, foveal part, which has the highest density of photoreceptors. In order to read, which concerns detection of high spatial frequencies, image motion should ideally be less than about 5°/s.[2] If image drift substantially exceeds this limit, visual acuity will decline and the illusion that the world is moving (oscillopsia) may be experienced. Normally, three main mechanisms hold gaze (the line of sight) steady, so that our view of the world is clear and stable.[2] The first is the vestibulo-ocular reflex, by which the motion detectors of the inner ear initiate eye movements to compensate for head perturbations, such as occur during locomotion. The second mechanism is "visual fixation," which has two components: the detection of retinal image drift and programming of corrective eye movements, and the suppression of unwanted eye movements that take the eye away from the target. The third mechanism depends on a neural network that makes it possible to hold the eyes at an eccentric position (for example, in lateral gaze). Malfunction of any of these three mechanisms may cause the eyes to drift away from the object of regard; corrective, quick phases (saccades) may then redirect the fovea towards the target. Thus a definition of nystagmus is repetitive to and fro involuntary eye movements that are initiated by slow drifts of the eye.

It is important to differentiate pathological nystagmus from physiological nystagmus. During rotation of the head and body in space, both vestibular nystagmus and optokinetic nystagmus act to reduce motion of images of the world on the retina, and so to preserve clear vision. During pathological nystagmus, however, drifts of the eyes away from the target degrade vision. In one pathological form, pendular nystagmus, the eye drifts consist of to and fro sinusoidal oscillation; this form of nystagmus is often visually disabling and presents an important therapeutic challenge.

Nystagmus is different from inappropriate saccades that intrude on steady fixation.[2] Saccades produce brief, high speed movement of images upon the retina, but this does not normally interfere with stable clear vision. Only when inappropriate saccades repeatedly misdirect the fovea will vision be impaired—for example, during reading.

We now know a good deal about the anatomical and physiological substrates for the three gaze holding mechanisms, and the neural machinery that generates saccades.[1 2] Less is known about the pharmacological substrate for eye movements, but recent findings have suggested possible treatments for abnormal eye movements.[3] However, as will be seen, success with any drug may turn out to be more complicated than originally supposed, and empirical trials have contributed as much as drug selection based on animal studies. Table 1 summarises drugs reported to suppress the more common forms of abnormal eye movements. Other types of treatment, including optical methods and botulinum toxin, are summarised elsewhere.[2] The clinical features of pathological nystagmus and saccadic abnormalities have recently been reviewed, with video examples.[4]

### Pathogenesis and treatment of vestibular forms of nystagmus

The vestibulo-ocular reflex (VOR) depends on motion detectors in the inner ear that respond to angular and linear head accelerations. The organisation of the peripheral vestibular system—with a resting neural discharge rate even with the head stationary, and reciprocal push-pull contributions from the two ears—predisposes to the development of imbalances.[2] Thus sudden loss of neural activity from one ear (a *peripheral* imbalance) will be misinterpreted as head rotation leading to vertigo and nystagmus. Imbalances of vestibular "tone" can also occur on a *central* basis, leading to downbeat, upbeat, and torsional forms of nystagmus. A third mechanism by which pathological vestibular nystagmus can arise is an *instability* in the adaptive mechanisms that normally govern the performance of the VOR; the best understood example is periodic alternating nystagmus.

#### Treatment of nystagmus caused by peripheral vestibular imbalances

Nystagmus caused by peripheral vestibular imbalance resolves spontaneously over the course of a few days because of central adaptive mechanisms.[5] Drug treatments play only a minor role, mainly to control attendant vertigo and nausea. A range of neurotransmitters has been identified within the vestibular system,[6] although drugs with antihistamine, anticholinergic, and phenothiazine properties remain the most popular (table 1). Current approaches emphasise using these "vestibular sedatives" only for 24 to 48 hours, if vertigo and nausea are severe.[5] After this time, exercises are encouraged to accelerate the brain's ability to correct the imbalance.

#### Treatment of nystagmus caused by central vestibular imbalances

It has been possible to identify several mechanisms leading to downbeat nystagmus, and to develop animal models.[2] For example, the vestibular cerebellum is known to govern, by inhibitory pathways, the central projections of the anterior canals (which generate upward eye movements) but not central projections of the posterior canals (which generate downward eye movements).[2] Thus vestibular cerebellar lesions, such as the Chiari malformation, will remove inhibition from anterior canal projections, causing the eyes to drift up (and leading to downbeat nystagmus). Projections from the cerebellar cortex to the vestibular nuclei use the transmitter γ-aminobutyric acid (GABA). Thus GABAergic agents might be expected to suppress downbeat nystagmus. Similar considerations apply to upbeat nystagmus, which can in some cases be related to lesions that selectively affect central projections of the anterior versus the posterior canals.[2] In other cases of upbeat nystagmus, involvement of medullary structures important in the gaze holding mechanism, discussed below, may be required.

Clonazepam is reported to reduce downbeat nystagmus from a variety of causes.[7 8] The $GABA_B$ agonist baclofen is reported to reduce downbeat nystagmus and associated oscillopsia.[9] However, a double blind comparison of baclofen and gabapentin showed that neither drug produced consistent improvement, and in some patients the nystagmus was made worse.[10] The cholinergic drug physostigmine (an acetylcholine esterase inhibitor), given intravenously,



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**Table 1** Summary of current drug treatments for nystagmus*

| | |
|---|---|
| **Vestibular forms of nystagmus** | |
| Peripheral imbalance | Diphenhydramine, promethazine, prochlorperazine, ondansetron for relief of attendant vertigo and nausea; resume activities as soon as able |
| Central imbalance | |
| • *Downbeat nystagmus* | Clonazepam, baclofen, trihexyphenidyl; acetazolamide (for nystagmus associated with episodic ataxia type II) |
| • *Upbeat nystagmus* | Baclofen |
| Central instability | |
| • *Periodic alternating nystagmus* | Baclofen |
| **Nystagmus associated with visual system disorder** | |
| • *Seesaw nystagmus* | Baclofen, clonazepam, alcohol, gabapentin |
| **Nystagmus from disorders of the gaze holding mechanism** | |
| • *Acquired pendular nystagmus* | In association with disease of central myelin: gabapentin, memantine, clonazepam, trihexyphenidyl, scopolamine; cannabis, alcohol<br>As part of the syndrome of oculopalatal tremor ("myoclonus"): gabapentin, valproate trihexyphenidyl |
| **Saccadic intrusions and oscillations** | |
| • *Square wave jerks* | Methylphenidate |
| • *Opsoclonus and ocular flutter* | Clonazepam, popranolol, gabapentin, corticosteroids, intravenous immunoglobulin, plasma exchange |
| **Miscellaneous abnormal movements** | |
| • *Superior oblique myokymia* | Gabapentin, carbamazepine, popranolol |
| • *Ocular neuromyotonia* | Carbamazepine |

*For details see refs 2 and 3.

causes worsening of downbeat nystagmus.[9] Conversely, the anticholinergic drug scopolamine reduces downbeat nystagmus when given intravenously,[11] but oral anticholinergic agents such as trihexyphenidyl[12] produce only a modest improvement which is offset by substantial side effects. Thus at present the drug treatment of downbeat nystagmus is unsatisfactory.

Upbeat nystagmus is occasionally suppressed by clonazepam,[9] but it often resolves spontaneously over a few months. Torsional nystagmus is rare, and there are few data available on its treatment. Nystagmus in familial episodic vertigo and ataxia type 2 is often downbeat and responds to acetazolamide and calcium channel blockers.[13]

### Treatment of nystagmus caused by instability of vestibular mechanisms

Periodic alternating nystagmus (PAN) is a horizontal jerk nystagmus that reverses direction approximately every two minutes.[2] This uncommon form of acquired nystagmus occurs with lesions affecting the nodulus and uvula of the cerebellum—either experimental or clinical. PAN probably arises from an abnormality affecting a form of "memory" for persistent vestibular stimuli referred to as "velocity storage." The nodulus and uvula appear to govern velocity storage, and when these structures are lesioned, velocity storage is prolonged. Adaptive mechanisms that attempt to hold velocity storage in check cause an oscillating vestibular imbalance, manifest as PAN. Baclofen is effective treatment in most cases of acquired PAN.[14] (A congenital form of PAN, which probably has a different pathogenesis, usually does not respond to baclofen.) The initial suggestion was that baclofen worked as treatment for PAN because it is a $GABA_B$ agonist and so compensated for loss of inhibitory inputs from the cerebellum.[2 14] However, baclofen also has other effects that may be more important with oral administration, such as effects on glutamate.[3]

### Pathogenesis and treatment of nystagmus caused by disorders of visual fixation

Disorders of the anterior visual pathways that degrade vision often cause nystagmus. This is probably a result of two separate mechanisms: deprivation of motion vision information that can be used to programme eye movements to compensate for drifts of the eyes away from the target; and loss of visual signals that are essential for "calibration" of the normal ocular motor responses. Thus retinal disorders such as Leber's congenital amaurosis cause continuous nystagmus from birth.[2]

Occasionally, nystagmus and ocular drifts cause oscillopsia even when there is residual vision, and gabapentin may help some of these patients with pendular nystagmus (personal observations). Optic nerve demyelination in multiple sclerosis may be associated with acquired pendular nystagmus, but it remains uncertain whether loss of visual input is the main reason for this visually disabling oscillation, which is discussed further below.

Chiasmal lesions are associated with *seesaw nystagmus*, which consists of elevation and intorsion of one eye and synchronous depression and extorsion of the other eye in the first half cycle, followed by change in direction during the next half cycle.[2] Seesaw nystagmus may arise because crossing visual inputs (from the temporal visual field) are no longer available to "calibrate" ocular responses to head roll. Individual patients with seesaw nystagmus have been reported to benefit from clonazepam and alcohol.[7 15 16]

### Pathogenesis and treatment of nystagmus caused by disorders of the gaze holding mechanism

In order for us to be able to hold the eyes steadily at an eccentric position (for example, turned into right lateral gaze), the brain must programme a tonic contraction of the extraocular muscles, otherwise the orbital tissue would pull back the eyes towards the centre.[2] This gaze holding mechanism (sometimes called the neural integrator for eye movements) depends on several component structures that, together, constitute a network of neurones. For horizontal gaze, key structures are the medial vestibular nucleus and adjacent nucleus prepositus hypoglossi (MVN-NPH). For vertical gaze, a key structure is the interstitial nucleus of Cajal (INC). Both are probably governed by a brain stem–cerebellar circuit that includes the cell groups of the paramedian tracts, which are spread throughout the brain stem, and receive a "copy" of all premotor eye movement commands.[17] The paramedian tract cell groups project to the vestibular cerebellum which, in turn, projects back to the MVN-NPH and to the INC. In patients with multiple sclerosis and



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acquired pendular nystagmus, magnetic resonance imaging often shows lesions that may be affecting the paramedian tract cell groups.[18]

Experimental inactivation of the MVN-NPH by discrete injections of muscimol, which increases normal GABA inhibition and thereby decreases neuronal activity, disrupts horizontal gaze holding, causing severe gaze evoked nystagmus.[19 20] Local injection of NMDA (N-methyl-D-aspartate) agonists and antagonists into this region also causes gaze evoked nystagmus.[20] Pharmacological inactivation of the INC with muscimol produces failure of eccentric vertical and torsional gaze holding.[21] Pharmacological inactivation of the paramedian tract cell groups also results in failure of gaze holding,[22] as do surgical lesions of the vestibular cerebellum.[2] How can these data be used to select drug treatment for abnormal eye movements?

Gaze evoked nystagmus is seldom visually disabling unless severe, because patients' eye drifts are minor when the eyes are close to central position. On the other hand, instability of the neural network could cause nystagmus either with drifts away from the centre position (reported with cerebellar disorders) or, conceivably, acquired pendular nystagmus. This latter idea—that acquired pendular nystagmus arises from an instability in the gaze holding mechanism—has gained some experimental support,[23] and has prompted trials of drugs with effects on GABAergic and glutamate receptors. Nonetheless, more than one mechanism is probably responsible for acquired pendular nystagmus, and we discuss it separately below.

### Treatments for acquired pendular nystagmus

Acquired pendular nystagmus is encountered in at least three clinical settings: first, in association with disorders of central myelin such as multiple sclerosis, toluene addiction, and a range of congenital disorders of myelin formation; second, as part of the syndrome of oculopalatal tremor ("myoclonus"), which typically develops months after a brain stem stroke, and is associated with synchronised movements of the palate and other branchial muscles (hypertrophic olivary degeneration is also a feature); and third, as a feature of Whipple's disease affecting the nervous system, when the nystagmus is usually convergent–divergent and associated with movements of the masticatory muscles (oculomasticatory myorhythmia).[2] It seems likely that different mechanisms underlie each form.

The most effective treatments for acquired pendular nystagmus in association with disorders of central myelin are gabapentin[10] and memantine.[24] In one double blind study comparing gabapentin with baclofen in a group of 15 patients, nystagmus decreased and visual acuity improved significantly with gabapentin, but not with baclofen.[10] Other drugs with presumed GABAergic effects, such as clonazepam and valproate, also help some patients.[7] These clinical observations, combined with the effects of pharmacological inactivation on the gaze holding mechanism noted above, led to a "GABAergic hypothesis" for acquired pendular nystagmus.[10] However, the more purely GABAergic drug vigabatrin is ineffective as a treatment.[25] Furthermore, memantine—a drug with NMDA blocking, AMPA (α-amino-3-hydroxy-5-methyl-4-isoxalone-propionic acid) receptor modulation, and dopaminergic action—is also effective for acquired pendular nystagmus in multiple sclerosis.[24] Thus it seems that suppression of this form of nystagmus probably occurs through glutamate blocking mechanisms (a property that gabapentin possesses). Gabapentin is also effective in some patients with oculopalatal tremor.[10] It is generally well tolerated but can make ataxia worse. Some patients do not respond at all to gabapentin, but many do obtain some relief from their visual symptoms.

Agents with cholinergic effects are less effective as treatment for acquired pendular nystagmus. Although intravenous scopolamine may suppress the oscillations,[11] neither transdermal scopolamine or oral agents such as trihexyphenidyl benefit more than the occasional patient.[12 26] Recently, smoking cannabis (but not taking oral preparations) was reported to help one patient with multiple sclerosis,[27] a finding that opens up new possibilities for developing treatments, provided social constraints allow this.

## TREATMENT OF SACCADIC INTRUSIONS AND OSCILLATIONS

Several types of inappropriate saccadic movements may intrude upon steady fixation.[2] Square wave jerks occur in healthy subjects, but are the prominent finding in progressive supranuclear palsy and some spinocerebellar atrophies. They are small conjugate saccades, ranging from 0.5° to 5.0° in size, which take the eye away from the fixation position and then return it there after a period of about 200 ms. They seldom interfere with vision, even if they are frequent, although it has been suggested that reading performance may be improved if they are suppressed using methylphenidate.[28] Macrosaccadic oscillations consist of horizontal saccades that occur in bursts, building up and then decreasing in amplitude, with intersaccadic intervals of about 200 ms. These oscillations are usually induced by a gaze shift and are a sign of midline cerebellar disease (affecting the fastigial nucleus).[2] There is currently no effective drug treatment.

Both of these oscillations are distinct from saccadic oscillations without an intersaccadic interval, which typically occur at a frequency of 15–30 Hz. When the latter occur only in the horizontal plane, they are called ocular flutter; when they have horizontal, vertical, and torsional components, they are called opsoclonus.[2] Flutter and opsoclonus occur in four main clinical settings: parainfectious brain stem encephalitis (including multiple sclerosis), paraneoplastic syndromes, metabolic-toxic states, or idiopathic.

Recovery of opsoclonus associated with brain stem encephalitis may be speeded by intravenous immunoglobulin.[29] In opsoclonus associated with cancer, treatment of the tumour itself often does not ameliorate the neurological syndrome. In children with neural crest tumours, opsoclonus may respond to corticosteroids, intravenous immunoglobulin, or chemotherapy.[30] Plasmapheresis and intravenous immunoglobulins sometimes proved effective in adults. Symptomatic treatment of the saccadic oscillations is unsatisfactory, although propranolol, verapamil, clonazepam, and gabapentin have been reported to suppress them in individual patients.[2 31]

## TREATMENT OF MISCELLANEOUS OTHER ABNORMAL EYE MOVEMENTS THAT DISRUPT VISION

Patients suffering from *superior oblique myokymia* complain of brief recurrent episodes of monocular blurring of vision, or tremulous sensations in one eye.[2] The attacks consists of monocular spasms of small torsional–vertical rotations that can sometimes be detected by looking for the movement of a conjunctival vessel, as the patient announces the onset of symptoms. They are more easily detected during examination with an ophthalmoscope. The condition is usually benign and might be triggered by mild damage to the trochlear nerve with regeneration. Most, but not all, patients are helped by carbamazepine, propranolol, or gabapentin.[32]

*Ocular neuromyotonia* is characterised by episodes of diplopia that are usually precipitated by holding the eyes in eccentric gaze, often sustained adduction.[33] These episodes are caused by involuntary, sometimes painful, contraction of one or more muscles innervated by one oculomotor nerve. Most reported patients have undergone previous radiation treatment to the parasellar region. The mechanism responsible for ocular neuromyotonia is unknown, but ephaptic neural transmission has been suggest.



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Carbamazepine may prove effective treatment.[33]

## SUMMARY

Drug treatments now exist for some forms of acquired nystagmus and other abnormal eye movements that disrupt clear vision. Although some patients obtain substantial improvement of visual symptoms from drug treatment, many others do not. Better understanding of the molecular basis of eye movements is likely to indicate new pharmacological approaches. Anecdotal reports of agents that quell abnormal eye movements have provided useful suggestions for drug treatments, but require systematic follow up. To date, published studies of masked controlled trials of drug treatments for abnormal eye movements are few in number. Both basic scientists and clinical neurologists can contribute to advancement in this field.

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