American Nystagmus Network

Pharmacology Treatment for Nystagmus

Introduction

Nystagmus is often seen in an ophthalmology practice. Nystagmus prevalence in the general population is about 24 per 10,000 [Sarvananthan, 2009]. Physiologic and pathologic nystagmus present very differently. In physiologic nystagmus, the slow phases of nystagmus minimize retinal image slip. In contrast, in pathological nystagmus, the slow phases of pathologic nystagmus cause retinal image slip. Retinal image slip of greater than 5 degrees per second produces a decline in visual acuity; due to the image of the object of interest is no longer on the fovea, causing *oscillopsia*. [Thurtell, 2011, Demer, 1993] Oscillopsia is the sensation that the surrounding environment is frequently in motion when it is, in fact, stationary. Oscillopsia is usually a symptom of conditions that affect eye movement or the eye's ability to stabilize images, especially during movement. These oscillations can also cause visual symptoms, such as difficulty reading since they take the eye off-target so that the image of the object of interest no longer lies on the fovea. [Demer, 1993]

Goals of Treatment

The treatment goal is to reduce symptoms: blurred vision, reducing the speed of the slow nystagmus phases, or suppressing saccadic oscillations. Treatments that stop the eyes from moving altogether are not ideal because they cause oscillopsia during head movements (due to the loss of vestibulo-ocular reflex) and diplopia (due to the loss of vergence eye movements). Therefore, treatments that suppress the abnormal eye movements without affecting regular eye movements are preferred.

General Approach to Treatment

Treatment of nystagmus has been proposed to include medical, optical, surgical, and other miscellaneous treatments. Most treatments aim to suppress the abnormal eye movement without affecting regular eye movements. Others seek to negate the visual consequences of abnormal eye movements. Choice of treatment depends on the type of nystagmus and its characteristics. Even though some patients will benefit from one treatment approach, others will require a combination of treatments.

Table 1: Proposed Treatments for Nystagmus [Thurtell, 2010]

Treatment Approach	Examples
Medical	Gabapentin Memantine 4-aminopyridine 3,4-diaminopyridine Baclofen Clonazepam Valproate Trihexyphenidyl Benztropine Scopolamine Isoniazid Carbamazepine Barbiturates Alcohol Acetazolamide Brinzolamide (topical) Cannabis
Other (Miscellaneous)	Botulinum toxin Acupuncture Biofeedback Cutaneous stimulation

Treatment for Acquired forms of Nystagmus

Pharmacological treatments are usually the most effective for treatment acquired forms of nystagmus. Surgical, optical, and other treatments may also be beneficial. The dosing and common side effects of pharmacological treatments for acquired forms of nystagmus are summarized below.

Table 2: Drug Treatments for Acquired Nystagmus [Thurtell, 2011]

Nystagmus Type	**Treatment (dose, frequency)**	**Common Side-Effects**
Peripheral Vestibular Nystagmus	Treatment of the underlying disorder	Not applicable

Table 2: Drug Treatments for Acquired Nystagmus [Thurtell, 2011] - Continued

Nystagmus Type	**Treatment (dose, frequency)**	**Common Side-Effects**
Downbeat Nystagmus	4-aminopyridine (5-10mg, tid) 3,4-diaminopyridine (10-20mg, tid) Clonazepam (0.5-1mg, bid)	Dizziness, paresthesias, incoordination Dizziness, paresthesias, incoordination Drowsiness, dizziness, incoordination
Upbeat Nystagmus	Memantine (10mg, qid) 4-aminopyridine (5-10mg, tid) Baclofen (5-10mg, tid)	Lethargy, dizziness, headache Dizziness, paresthesias, incoordination Drowsiness, dizziness, lethargy
Torsional Nystagmus	Gabapentin (300mg, qid)	Dizziness, incoordination, drowsiness
Seesaw Nystagmus	Alcohol Clonazepam (0.5-1mg, bid) Memantine (10mg, qid)	Drowsiness, incoordination, vomiting Drowsiness, dizziness, incoordination Lethargy, dizziness, headache
Periodic Alternating Nystagmus	Baclofen (5-10mg, tid) Memantine (5-10mg, qid)	Drowsiness, dizziness, lethargy Lethargy, dizziness, headache
Acquired Pendular Nystagmus in MS	Gabapentin (300mg, qid) Memantine (10mg, qid)	Dizziness, incoordination, drowsiness Lethargy, dizziness, headache

Table 2: Drug Treatments for Acquired Nystagmus [Thurtell, 2011] - Continued

Nystagmus Type	Treatment (dose, frequency)	Common Side-Effects
Acquired Pendular Nystagmus in OPT	Gabapentin (300mg, qid) Memantine (10mg, qid) Trihexyphenidyl (5-20mg, tid)	Dizziness, incoordination, drowsiness Lethargy, dizziness, headache Dry mouth, blurred vision, dizziness

Abbreviations: bid, twice daily; MS, multiple sclerosis; OPT, oculopalatal tremor; qid, four times daily; tid, three times daily

Peripheral Vestibular Nystagmus

Nystagmus is seen in patients with peripheral vestibular diseases, such as vestibular neuritis, Ménière's disease, and benign paroxysmal positional vertigo. Associated vertigo, nausea, and vomiting are often more distressing to the patient than the nystagmus's visual symptoms, intermittent. Because of this, the patient is best managed with treatments addressing the underlying disorder. [Strupp, 2011]

Downbeat Nystagmus

Downbeat nystagmus is common and often causes disabling visual symptoms, such as vertical oscillopsia. Many affected patients seek treatment. At present, aminopyridines are the first-line treatment for downbeat nystagmus. In those who do not respond, a trial of clonazepam could be considered. Surgeries, including tenotomy and reattachment, can be regarded as treating severe, intractable oscillopsia in patients with downbeat nystagmus, either alone or in combination with medical therapy [Tomsak, 2008]. Still, clinical trials are yet to be performed.

Upbeat Nystagmus

Upbeat nystagmus can produce vertical oscillopsia, but the nystagmus resolves spontaneously; long-term treatment is only required if it is persistent. There have been very few clinical trials evaluating proposed treatments. A trial of memantine, 4-aminopyridine, or baclofen could be considered in patients with visual symptoms from persistent upbeat nystagmus.

Torsional Nystagmus

Torsional nystagmus can cause disabling oscillopsia. While further studies are required to identify medications that suppress torsional nystagmus, a trial of gabapentin could be considered in patients with visual symptoms from persistent torsional nystagmus.

Seesaw Nystagmus

Acquired seesaw nystagmus is rarely encountered but can give rise to disabling oscillopsia. Treatment with clonazepam, gabapentin, or memantine may be considered in patients with visual symptoms from persistent seesaw nystagmus.

Periodic Alternating Nystagmus

Patients with acquired periodic alternating nystagmus often complain of oscillopsia. At present, baclofen is considered first-line treatment for acquired periodic alternating nystagmus, while memantine could be tried in those patients who do not respond to baclofen.

Acquired Pendular Nystagmus in Multiple Sclerosis

Acquired pendular nystagmus (APN) can occur in patients with multiple sclerosis (MS) and causes disabling visual symptoms. The hypothesis that it arises due to instability of the oculomotor neural integrator led to the testing of drugs thought to have effects on GABA- and glutamate-mediated mechanisms. There is a potential role for combining drug therapies, such as gabapentin and memantine, but no clinical trials have been conducted. Surgeries, including tenotomy and reattachment, might help to suppress APN in patients with severe, intractable oscillopsia [Tomsak, 2008] but should not be routinely recommended as clinical trials are yet to be performed.

Acquired Pendular Nystagmus in Oculopalatal Tremor

The nystagmus of oculopalatal tremor (OPT) often causes severe, intractable oscillopsia. Although the nystagmus of OPT is often more refractory to treatment with gabapentin and memantine than is APN due to MS, a trial of therapy is worthwhile. There is a potential role for combined drug therapies, such as gabapentin and memantine, or surgical treatment, such as tenotomy and reattachment. Still, these treatment approaches have not been evaluated in clinical trials.

Treatment of Infantile Forms of Nystagmus

Treatment for infantile forms of nystagmus depends on the severity of visual symptoms, severity of any associated afferent visual system anomalies, and the characteristics of the nystagmus itself. [Thurtell, 2011, Thurtell, 2010] Some patients do not have visual symptoms, especially if "foveation periods" are well developed, and most do not complain of oscillopsia. [Abadi, 1999] Those with impaired vision might have so due to afferent visual system anomalies such as optic nerve or foveal hypoplasia, [Thurtell, 2011] such that suppression of the nystagmus does not produce a significant improvement in vision. However, patients with visual symptoms with intact afferent visual systems can benefit from treatments that suppress the nystagmus. [Thurtell, 2011, Thurtell, 2010]

Infantile Nystagmus Syndrome

Infantile nystagmus can be treated using optical, surgical, and medical approaches. [Thurtell, 2011, Thurtell, 2010]

Medical Treatments: Medical treatments of infantile nystagmus are less favorable since they would need to be given life-long and can cause side-effects. A randomized, controlled, double-masked trial comparing gabapentin and memantine found that the nystagmus intensity and visual acuity improved in both treatment groups. [McLean, 2007]. However, patients with afferent visual system anomalies derived only a small benefit. Recent studies have reported that infantile nystagmus might be suppressed with carbonic anhydrase inhibitors, including oral acetazolamide and topical brinzolamide. [Thurtell, 2010; Delll'Osoo, 2011] Infantile nystagmus can also be reduced after smoking cannabis. [Pradeep, 2008]

Gene Therapy: Lastly, gene therapy holds the potential to treat nystagmus associated with congenital retinal disorders. For example, in an animal model of Leber's congenital amaurosis, successful gene therapy restored vision and reduced the associated nystagmus. [Narfstrom, 2003, Acland, 2001, Jacobs, 2006, Bennicelli, 2008]

Other Infantile Forms of Nystagmus

The treatment options for other infantile forms of nystagmus are limited. Treatment for latent nystagmus (fusional maldevelopment nystagmus syndrome) consists of measures to improve vision, such as correction of refractive error and amblyopia treatment. [Thurtell, 2011; Thurtell, 2010] Spasmus nutans syndrome typically resolves spontaneously and does not require specific intervention. [Thurtell, 2011, Thurtell, 2010]

Treatment of Intractable Nystagmus

There are several treatment options for patients who do not respond to conventional approaches. Treatments to stop the eyes from moving altogether, such as botulinum toxin injections into the extraocular muscles, can also be considered in patients with intractable nystagmus. While the injections can reduce oscillopsia and improved visual acuity, patients often develop diplopia and ptosis. Furthermore, regular eye movements are impaired, and the treatment is only useful for several weeks to months, making botulinum toxin injections limited in therapeutic value. Thurtell, 2011, Thurtell, 2010]

References

1. Sarvananthan, N., Surendran, M., Roberts, E.O., et al.: The prevalence of nystagmus: the Leicestershire nystagmus survey, *Invest Ophthalmol Vis Sci* 50:5201-5206, 2009.
2. Thurtell, M.J., Leigh, R.J.: Nystagmus and saccadic intrusions, *Handb Clin Neurol* 102:333-378, 2011.
3. Demer, J.L., Amjadi, F.: Dynamic visual acuity of normal subjects during vertical optotype and head motion, *Invest Ophthalmol Vis Sci* 34:1894-1906, 1993.
4. Thurtell, M.J., Leigh, R.J.: Therapy for nystagmus, *J Neuroophthalmol* 30:361-371, 2010.

5. Thurtell, M.J., Rucker, J.C., Tomsak, R.L., et al.: Medical treatment of acquired nystagmus, *Expert Rev Ophthalmol* 6:307-314, 2011.
6. Strupp, M., Thurtell, M.J., Shaikh, A.G., et al.: Pharmacotherapy of vestibular and ocular motor disorders, including nystagmus, *J Neurol* 258:1207-1222, 2011.
7. Currie, J.N., Matsuo, V.: The Use of clonazepam in treating nystagmus-induced oscillopsia, *Ophthalmology* 93:924-932, 1986.
8. Tomsak, R.L., Dell'Osso, L.F., Jacobs, J.B., et al.: Eye muscle surgery for acquired forms of nystagmus. In: Leigh, R.J., Devereaux, M.W. (Eds): *Advances in Understanding Mechanisms and Treatment of Infantile Forms of Nystagmus.* New York:
9. Abadi, R.V., Whittle, J.P., Worfolk, R.: Oscillopsia and tolerance to retinal image movement in congenital nystagmus, Invest Ophthalmol Vis Sci 40:339-345, 1999.
10. Anderson, J., Lavoie, J., Merrill, K., et al.: Efficacy of spectacles in persons with albinism, *J AAPOS* 8:515-520, 2004.
11. Hertle, R.W.: Examination and refractive management of patients with nystagmus, Surv Ophthalmol 45:215-222, 2000.
12. Dell'Osso, L.F., Traccis, S., Erzurum, S.I.: Contact lenses and congenital nystagmus, *Clinical Vision Science* 3:229-232, 1988.
13. Serra, A., Dell'Osso, L.F., Jacobs, J.B., et al.: Combined gaze-angle and vergence variation in infantile nystagmus: two therapies that improve the high-visual-acuity field and methods to measure it, *Invest Ophthalmol Vis Sci* 47:2451-2460, 2006.
14. Anderson, J.R.: Causes and treatment of congenital eccentric nystagmus, *Br J Ophthalmol* 37:267-281, 1953.
15. Kestenbaum, A.: Nouvelle operation de nystagmus, *Bull Soc Ophtalmol Fr* 6:599-602, 1953.
16. Lee, I.S., Lee, J.B., Kim, H.S., et al.: Modified Kestenbaum surgery for correction of abnormal head posture in infantile nystagmus: outcome in 63 patients with graded augmentation, *Binocul Vis Strabismus Q* 15:53-58, 2000.
17. Chang, Y.H., Chang, J.H., Han, S.H., et al.: Outcome study of two standard and graduated augmented modified Kestenbaum surgery protocols for abnormal head postures in infantile nystagmus, *Binocul Vis Strabismus Q* 22:235-241, 2007.
18. Gupta, R., Sharma, P., Menon, V.: A prospective clinical evaluation of augmented Anderson procedure for idiopathic infantile nystagmus, *J AAPOS* 10:312-317, 2006.
19. Cüppers', C.: Probleme der operativen therapie des okularen nystagmus, *Klin Mbl Augenheilk* 159:145-157, 1971.
20. Sendler, S., Shallo-Hoffmann, J., Mühlendyck, H.: Die artifizielle-divergenz-operation beim kongenitale nystagmus, *Fortschr Ophthalmol* 87:85-89, 1990.
21. Hertle, R.W., Anninger, W., Yang, D., et al.: Effects of extraocular muscle surgery on 15 patients with oculo-cutaneous albinism (OCA) and infantile nystagmus syndrome (INS), *Am J Ophthalmol* 138:978-987, 2004.

22. Thurtell, M.J., Dell'Osso, L.F., Leigh, R.J., et al.: Effects of acetazolamide on infantile nystagmus syndrome waveforms: comparisons to contact lenses and convergence in a well-studied subject, *Open Ophthalmol J* 4:42-51, 2010.
23. Dell'Osso, L.F., Hertle, R.W., Leigh, R.J., et al.: Effects of topical brinzolamide on infantile nystagmus syndrome waveforms: eyedrops for nystagmus, *J Neuroophthalmol* 31:228-233, 2011.
24. Pradeep, A., Thomas, S., Roberts, E.O., et al.: Reduction of congenital nystagmus in a patient after smoking cannabis, *Strabismus* 16:29-32, 2008.
25. Narfstrom, K., Katz, M.L., Bragadottir, R., et al.: Functional and structural recovery of the retina after gene therapy in the RPE65 null mutation dog, *Invest Ophthalmol Vis Sci* 44:1663-1672, 2003.
26. Acland, G., Aguirre, G., Ray, J., et al.: Gene therapy restores vision in a canine model of childhood blindness, *Nature Genetics* 28:92-95, 2001.
27. Jacobs, J.B., Dell'Osso, L.F., Hertle, R.W., et al.: Eye movement recordings as an effectiveness indicator of gene therapy in RPE65-deficient canines: implications for the ocular motor system, *Invest Ophthalmol Vis Sci* 47:2865-2875, 2006.
28. Bennicelli, J., Wright, J.F., Komaromy, A., et al.: Reversal of blindness in animal models of leber congenital amaurosis using optimized AAV2-mediated gene transfer, *Mol Ther* 16:458-465, 2008.