**Title:**

**JOURNAL CLUB: NYSTAGMUS AND SACCADIC INTRUSIONS**

**Learning Objectives:**

1. To list the goals of treatment for nystagmus and saccadic intrusions.
2. To identify potential weaknesses in clinical trials for nystagmus treatment.
3. To list potential treatments for downbeat, acquired pendular, and congenital forms of nystagmus on the basis of recent clinical trials.

**CME Questions:**

1. Which of the following is least likely to require medical treatment?
   - a) Downbeat nystagmus
   - b) Acquired pendular nystagmus
   - c) Periodic alternating nystagmus
   - d) Oculopalatal tremor
   - e) Square-wave jerks

2. Which of the following medications is most likely to suppress downbeat nystagmus?
   - a) Baclofen
   - b) Memantine
   - c) Gabapentin
   - d) 4-aminopyridine
   - e) Carbamazepine

3. Which of the following medications is most likely to suppress acquired pendular nystagmus?
   - a) Baclofen
   - b) Memantine
   - c) Valproate
   - d) 4-aminopyridine
   - e) Carbamazepine

**Keywords (Max 5):**

1. Nystagmus
2. Saccadic intrusions
3. Oscillopsia

**Introduction/Abstract** *(Please see instructions for formatting details):*
Nystagmus is common, with a prevalence of approximately 24 per 10,000 in the general population.1 Because of the associated visual symptoms and negative impact on quality of life,2 many patients with nystagmus request treatment. Unlike physiologic nystagmus (e.g., during head movements), where slow phase drifts minimize retinal image slip, the slow phase drifts of pathologic nystagmus cause retinal image slip. When retinal image slip from pathologic slow phase drifts is greater than about 5 degrees per second, it can produce blurred vision, because the image of the object of interest no longer lies on the fovea, and illusory motion of the visual environment (oscillopsia).3 Saccadic intrusions also cause visual symptoms, such as difficulty reading, as they consist of inappropriate saccadic eye movements that take the image of the object of interest off the fovea.3

Body (Please see instructions for formatting details):

GOALS OF TREATMENT AND GENERAL TREATMENT APPROACHES

Goals of Treatment
The primary goal of treatment is to reduce the patient’s visual symptoms by reducing the speed of nystagmus slow phases or frequency of inappropriate saccades. Treatments that stop the eyes from moving altogether (e.g., BOTOX® injections into the extraocular muscles or retrobulbar space) are not ideal, because they also impair physiologic eye movements (e.g., vestibulo-ocular reflex and vergence).4 Consequently, treatments that suppress the slow phase drifts or inappropriate saccades without affecting physiologic eye movements are preferred.4 Note that some types of nystagmus (e.g., gaze-evoked nystagmus) and saccadic intrusion (e.g., square-wave jerks) do not usually give rise to visual symptoms and, thus, do not require specific treatment.3

General Approaches to Treatment
Many treatments for nystagmus and saccadic intrusions have been proposed, including medical, optical, and surgical treatments, but few have been evaluated in prospective, masked, and controlled clinical trials.3-5 Commonly prescribed drug treatments and their doses are listed in Table 1.5 The aim of this journal club session is to review the results of recent trials evaluating treatments for nystagmus and saccadic intrusions.

Table 1: Drug treatments for acquired nystagmus5

<table>
<thead>
<tr>
<th>Nystagmus Type</th>
<th>Treatment (dose, frequency)</th>
<th>Common Side-Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Vestibular Nystagmus</td>
<td>Treatment of underlying vestibular disorder</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Downbeat Nystagmus</td>
<td>4-aminopyridine (5-10mg, tid-qid)</td>
<td>Dizziness, paresthesias, incoordination</td>
</tr>
<tr>
<td></td>
<td>3,4-diaminopyridine (10-20mg, tid)</td>
<td>Dizziness, paresthesias, incoordination</td>
</tr>
<tr>
<td></td>
<td>Clonazepam (0.5-1mg, bid)</td>
<td>Drowsiness, dizziness, incoordination</td>
</tr>
<tr>
<td>Upbeat Nystagmus</td>
<td>Memantine (10mg, qid)</td>
<td>Lethargy, dizziness, headache</td>
</tr>
<tr>
<td></td>
<td>4-aminopyridine (5-10mg, tid-qid)</td>
<td>Dizziness, paresthesias, incoordination</td>
</tr>
<tr>
<td></td>
<td>Baclofen (5-10mg, tid)</td>
<td>Drowsiness, dizziness, incoordination</td>
</tr>
<tr>
<td>Torsional Nystagmus</td>
<td>Gabapentin (300mg, qid)</td>
<td>Dizziness, incoordination, drowsiness</td>
</tr>
<tr>
<td>Seesaw Nystagmus</td>
<td>Alcohol</td>
<td>Drowsiness, incoordination, vomiting</td>
</tr>
<tr>
<td></td>
<td>Clonazepam (0.5-1mg, bid)</td>
<td>Drowsiness, dizziness, incoordination</td>
</tr>
<tr>
<td></td>
<td>Memantine (10mg, qid)</td>
<td>Lethargy, dizziness, headache</td>
</tr>
<tr>
<td>Periodic Alternating Nystagmus</td>
<td>Baclofen (5-10mg, tid)</td>
<td>Drowsiness, dizziness, incoordination, incoordination, Lethargy, dizziness, headache</td>
</tr>
<tr>
<td></td>
<td>Memantine (5-10mg, qid)</td>
<td>Lethargy, dizziness, incoordination, incoordination, Lethargy, dizziness, headache</td>
</tr>
<tr>
<td>Acquired Pendular Nystagmus in MS</td>
<td>Gabapentin (300mg, qid)</td>
<td>Dizziness, incoordination, incoordination, incoordination, Lethargy, dizziness, headache</td>
</tr>
<tr>
<td></td>
<td>Memantine (10mg, qid)</td>
<td>Lethargy, dizziness, incoordination, incoordination, Lethargy, dizziness, headache</td>
</tr>
<tr>
<td>Acquired Pendular Nystagmus in OPT</td>
<td>Gabapentin (300mg, qid)</td>
<td>Dizziness, incoordination, incoordination, incoordination, Lethargy, dizziness, headache</td>
</tr>
<tr>
<td></td>
<td>Memantine (10mg, qid)</td>
<td>Lethargy, dizziness, incoordination, incoordination, Lethargy, dizziness, headache</td>
</tr>
<tr>
<td></td>
<td>Baclofen (5-20mg, tid)</td>
<td>Dizziness, incoordination, incoordination, incoordination, Lethargy, dizziness, headache</td>
</tr>
</tbody>
</table>

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

POTENTIAL PITFALLS IN INTERPRETATION OF TREATMENT TRIALS

Although the primary goal of treatment is to reduce patient’s visual symptoms, most trials use eye movement recordings as well as measures of visual function (e.g., visual acuity) to quantify any treatment effect. Factors that need to be considered in the interpretation of treatment trials for nystagmus and saccadic intrusions include the following:

1. Subject numbers: many trials include only a small number of subjects, because of the rarity of many forms of nystagmus and saccadic intrusions. Few multi-center trials have been completed, because the required eye movement recording equipment is not readily available and recording conditions can be difficult to standardize.
2. Calibration of eye movement recording system: the eye movement recording system often requires an *in vivo* calibration, where the patient looks toward a visual target at a known angle away from the central fixation point, such that the signal that is recorded by the system can be appropriately scaled. Since steady fixation is often not possible during the calibration in a patient who has nystagmus or saccadic oscillations, the accuracy of the findings becomes less certain. Consequently, eye movement recording systems that do not require *in vivo* calibration, such as the magnetic search coil system, are preferred. In the case of the magnetic search coil system, the search coil is calibrated *in vitro* (e.g., on a gimbal device) before the search coil is placed on the eye and an *in vivo* calibration is not required.

3. Resolution of eye movement recording system: an adequate sampling rate (ideally greater than 250 Hz) is required to accurately calculate the amplitude and speed of eye movements. Eye movement recording systems with sampling rates less than 100 Hz are inadequate for quantification of slow phases or saccades. Inadequate sampling rate can also result in aliasing, where high-frequency components of the data are inappropriately interpreted as being lower-frequency components. An adequate spatial resolution (e.g., less than 0.5 degrees) is also desirable.

4. Control of head and fixation position: many forms of nystagmus vary depending on head orientation relative to gravity, eye-in-head position, and vergence angle. Ideally, the head should be immobilized in a consistent position during the recording sessions, with the eye movement recording taken with the patient looking toward a fixation target at a set distance from the patient and at a set location in the visual field. In congenital forms of nystagmus that have a null point or null zone, the eye movements should be recorded in a variety of gaze positions, so that the location and breath of the null zone can be determined.

5. Visual symptoms may not correlate with nystagmus speed or intensity: in congenital forms of nystagmus, visual symptoms will often correlate better with the frequency and duration of “foveation” periods than with slow phase speed. Thus, quantification of the frequency and duration of “foveation” periods might be preferred over quantification of the slow phase speed or other measures of nystagmus intensity.

6. Other relevant outcome measures may not be reported: ability to function, quality of life, and cosmetic aspects are often not considered as outcome measures in nystagmus treatment trials, yet may be relevant to the patient’s concerns and goals for treatment.2

**DOWNBEAT NYSTAGMUS**

Downbeat nystagmus causes vertical oscillopsia and affected patients frequently seek treatment. The aminopyridines (3,4-diaminopyridine and 4-aminopyridine; K+ channel blockers) can suppress downbeat nystagmus;6,7 4-aminopyridine is thought to be more effective due to better central nervous system penetration.8 Three recent clinical trials merit discussion.


**ABSTRACT:** *Objective:* The effects of 4-aminopyridine (4-AP) on downbeat nystagmus (DBN) were analysed in terms of slow-phase velocity (SPV), stance, locomotion, visual acuity (VA), patient satisfaction and side effects using standardised questionnaires. *Methods:* Twenty-seven patients with DBN received 5 mg 4-AP four times a day or placebo for 3 days and 10 mg 4-AP four times a day or placebo for 4 days. Recordings were done before the first, 60 min after the first and 60 min after the last drug administration. *Results:* SPV decreased from 2.42 deg/s at baseline to 1.38 deg/s with 5 mg 4-AP and to 2.03 deg/s with 10 mg 4-AP (p<0.05; post hoc: 5 mg 4-AP: p=0.04). The rate of responders was 57%. Increasing age correlated with a 4-AP-related decrease in SPV (p<0.05). Patients improved in the ‘get-up-and-go test’ with 4-AP (p<0.001; post hoc: 5 mg: p=0.025; 10 mg: p<0.001). Tandem-walk time (both p<0.01) and tandem-walk error (4-AP: p=0.054; placebo: p=0.059) improved under 4-AP and placebo. Posturography showed that some patients improved with the 5 mg 4-AP dose, particularly older patients. Near VA increased from 0.59 at baseline to 0.66 with 5 mg 4-AP (p<0.05). Patients with idiopathic DBN had the greatest benefit from 4-AP. There were no differences between 4-AP and placebo regarding patient satisfaction and side effects. *Conclusions:* 4-AP reduced SPV of DBN, improved near VA and some locomotor parameters. 4-AP is a useful medication for DBN syndrome, older patients in particular benefit from the effects of 5 mg 4-AP on nystagmus and postural stability.
COMMENT: The study confirms, in a larger number of patients and with a more rigorous study design, that the slow phase velocity of downbeat nystagmus can be significantly decreased in some patients with 4-aminopyridine. As suggested by prior studies, those with idiopathic downbeat nystagmus responded better than those with other causes for their nystagmus. Older patients tended to respond better than younger patients. Some patients also showed improvement in postural and locomotion parameters. Side effects were similar to those reported with placebo. For unclear reasons, use of a higher dose (10 mg) of 4-aminopyridine did not result in an amplified treatment effect.


ABSTRACT: We investigated the effects of dalfampridine, the sustained-release form of 4-aminopyridine, on slow phase velocity (SPV) and visual acuity (VA) in patients with downbeat nystagmus (DBN) and the side effects of the drug. In this proof-of-principle observational study, ten patients received dalfampridine 10 mg bid for 2 weeks. Recordings were conducted at baseline, 180 min after first administration, after 2 weeks of treatment and after 4 weeks of wash-out. Mean SPV decreased from a baseline of 2.12 deg/s ± 1.72 (mean ± SD) to 0.51 deg/s ± 1.00 180 min after first administration of dalfampridine 10 mg and to 0.89 deg/s ± 0.75 after 2 weeks of treatment with dalfampridine (p < 0.05; post hoc both: p < 0.05). After a wash-out period of 1 week, mean SPV increased to 2.30 deg/s ± 1.6 (p < 0.05; post hoc both: p < 0.05). The VA significantly improved during treatment with dalfampridine. Also, 50% of patients did not report any side effects. The most common reported side effects were abdominal discomfort and dizziness. Dalfampridine is an effective treatment for DBN in terms of SPV. It was well-tolerated in all patients.

COMMENT: The study demonstrates that the sustained-release form of 4-aminopyridine (i.e., Ampyra® in the United States) can significantly decrease the slow phase velocity of downbeat nystagmus and improve visual acuity. The magnitude of the improvement was greater than reported in previous studies using 4-aminopyridine. The study has several shortcomings, however. It was neither masked nor placebo-controlled. Furthermore, only patients with idiopathic downbeat nystagmus and cerebellar degenerations were studied, so it is unclear if those with downbeat nystagmus from other etiologies might respond.


ABSTRACT: Objective: Downbeat nystagmus (DBN) is the most frequent form of acquired persisting fixation nystagmus with different symptoms such as unsteadiness of gait, postural instability, and blurred vision with reduced visual acuity (VA) and oscillopsia. However, different symptomatic therapeutic principles are required, such as 3,4-diaminopyridine and 4-aminopyridine, that effectively suppress DBN. Chlorzoxazone (CHZ) is a nonselective activator of small conductance calcium-activated potassium (SK) channels that modifies the activity of cerebellar Purkinje cells. We evaluated the effects of this agent on DBN in an observational proof-of-concept pilot study. Methods: Ten patients received CHZ 500 mg 3 times a day for 1 or 2 weeks. Slow-phase velocity of DBN, VA, postural sway, and the drug’s side effects were evaluated. Recordings were conducted at baseline, 90 minutes after first administration, and after 1 or 2 weeks. Results: Mean slow-phase velocity significantly decreased from a baseline of 2.74°/s ± 2.00 to 2.29°/s ± 2.12 (mean ± SD) 90 minutes after first administration and to 2.04°/s ± 2.24 (p < 0.001; post hoc both p = 0.024) after long-term treatment. VA significantly increased and postural sway in posturography showed a tendency to decrease on medication. Fifty percent of patients did not report any side effects. The most common reported side effect was abdominal discomfort and dizziness. Conclusions: The treatment with the SK-channel activator CHZ is a potentially new therapeutic agent for the symptomatic treatment of DBN. Classification of Evidence: This study provides Class IV evidence that CHZ 500 mg 3 times a day may improve eye movements and visual fixation in patients with DBN.

COMMENT: The study demonstrates that chlorzoxazone (traditionally used as a muscle relaxant) can significantly decrease the slow phase velocity of downbeat nystagmus, but the treatment effect was not as substantial as for 4-aminopyridine. Half of the patients did not report side effects. The study has several shortcomings. Firstly, a reversal of the treatment effect was not confirmed following a “wash out” period. Secondly, the study was not masked or placebo-controlled. Lastly, only patients with idiopathic downbeat nystagmus and cerebellar degenerations were included.
ACQUIRED PENDULAR NYSTAGMUS

Acquired pendular nystagmus (e.g., due to multiple sclerosis or with oculopalatal tremor) causes intractable oscillopsia and affected patients often seek treatment. Gabapentin and memantine appear to be effective treatments for acquired pendular nystagmus in the setting of multiple sclerosis, but most trials have used a video-based eye movement recording system rather than the magnetic search coil system.12-14 One recent clinical trial merits discussion.


ABSTRACT: We conducted a masked, crossover, therapeutic trial of gabapentin (1,200mg/day) versus memantine (40 mg/day) for acquired nystagmus in 10 patients (aged 28-61 years; 7 female; 3 multiple sclerosis [MS]; 6 post-stroke; 1 post-traumatic). Nystagmus was pendular in 6 patients (4 oculopalatal tremor; 2 MS) and jerk upbeat, hemi-seesaw, torsional, or upbeat-diagonal in each of the others. For the group, both drugs reduced median eye speed (p < 0.001), gabapentin by 32.8% and memantine by 27.8%, and improved visual acuity (p < 0.05). Each patient improved with 1 or both drugs. Side effects included unsteadiness with gabapentin and lethargy with memantine. Both drugs should be considered as treatment for acquired forms of nystagmus.

COMMENT: Using the magnetic search coil technique, the study shows that both gabapentin and memantine reduce slow phase speed and improve visual acuity in patients with acquired pendular nystagmus due to multiple sclerosis or with oculopalatal tremor. However, the response was idiosyncratic, with some patients showing dramatic improvement to one or both drugs and others showing only mild improvement. Only a small number of patients were included and, thus, larger studies are required to define factors that predict a response to treatment.

CONGENITAL FORMS OF NYSTAGMUS

Some patients with congenital forms of nystagmus do not have visual symptoms and most do not report oscillopsia. Asymptomatic patients do not require treatment for the nystagmus, but it may be requested due to concerns about the cosmetic appearance of the nystagmus.2 Some patients might have impaired vision due to associated afferent visual system anomalies (e.g., optic nerve or foveal hypoplasia), such that suppression of the nystagmus does not produce a significant improvement in vision. However, those patients with visual symptoms who have an intact afferent visual system will sometimes benefit from treatments that suppress the nystagmus.3,4 Optical, surgical, and medical treatments have been proposed for the treatment of congenital forms of nystagmus, but remain controversial due to a lack of well-designed prospective masked clinical trials and difficulties with measuring treatment effect.4 One recent study merits discussion.


ABSTRACT: Purpose: To report a systematic approach to, and the visual and electrophysiological effect of, eye muscle surgery in 100 patients with infantile nystagmus syndrome (INS). Methods: Prospective, interventional case cohort analysis of clinical and eye movement data in 100 patients with INS who had virgin extraocular eye muscles operated on for nystagmus with or without combinations of strabismus and an anomalous head posture. All patients were followed at least 9 months after surgery. Outcome measures, part of an IRB approved study, included binocular visual acuity, head position, strabismic deviation, and eye movement recordings, from which waveform types and an Automated Nystagmus Acuity Function (ANAF) was calculated. Computerized parametric and non-parametric statistical analysis of data were performed using standard software on both individual and group data. Results: There were 9 consistent surgical procedures used with the most common being that for a horizontal head posture alone (22%). Age at surgery averaged 14 years with 11 months followup. Sixty-eight percent had associated eye disease (optic nerve, retinal, amblyopia, cataracts). Group means in binocular acuity, strabismic deviation, head posture, and ANAF measures from eye improved for all procedures. There were 12 (12%) reoperations without any serious surgical complications. Individual analysis revealed only age and head posture differences in outcome measures between the 9 procedures. Conclusions: Using this approach, surgery on the extraocular muscles in patients with INS results in improvements in multiple aspects of ocular motor and visual function.
The study demonstrates that strabismus surgery (including tenotomy and reattachment) can be effective in improving binocular visual acuity, strabismic deviation, head posture, and nystagmus waveform in patients with congenital forms of nystagmus, even in those with afferent visual system anomalies. However, the study highlights that the choice of procedure needs to be tailored to the individual patient. Data were obtained prospectively and in a standardized fashion, but there was no masking or control group and the eye movement recordings were obtained using a video-based eye movement recording system.

CME Answers:
1. e
2. d
3. b

References:
15. Thurtell MJ, Joshi AC, Leone AC, et al. Crossover trial of gabapentin and memantine as treatment for