



Ophthalmology Update

Richmond Eye Associates, P.C.

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Ophthalmic topics of interest to the medical physician

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Special points of interest:

- Smoking marijuana is impractical as a treatment for glaucoma.
- Allopurinol use has been associated with risk of cataract extraction.
- A Fourth Cranial Nerve Palsy is a common cause of vertical diplopia.
- There is reduced recurrence of herpetic eye disease with oral Acyclovir.

Medical Marijuana: Is Glaucoma a Valid Indication?

Several states have passed laws allowing marijuana smoking for certain medical indications. As of 11/3/98, these states included Alaska, Arizona, Nevada, Oregon, and Washington. Generally, the medical use of marijuana is allowed only with certain conditions, including AIDS, epilepsy, glaucoma, and multiple sclerosis, and a physician's prescription is not required. Instead a physician statement can protect the patient from prosecution.

In glaucoma, intraocular pressure is felt to play a significant role in the progressive deterioration in the optic nerve. Cannabinoids have been found to lower intraocular pressure in humans in a dose-related fashion, but with a consistently short duration of action. Both marijuana and its active ingredient D⁹-THC lower the intraocular pressure in about 65% of humans, whether inhaled or taken orally. In normal subjects, the intraocular pressure fell 25%, and in patients with open angle glaucoma, the pressure fell 30%. However, the duration of action was only 3 to 4 hours, by which time the eye pressure returned to pre-smoking levels.

Topical (eyedrop) application of D⁹-THC in humans is unacceptable due to significant ocular irritation.

Since glaucoma is a 24 hour a day disease, marijuana would have to be smoked 8 to 10 times a day to consistently control intraocular pressure, given its short duration of action. Clearly, compliance would be a major problem, especially with glaucoma being a largely asymptomatic disease until it is very advanced. Intermittent use of marijuana would not allow continuous control of intraocular pressure, allowing visual loss to occur.

"In order to control glaucoma, 8 to 10 marijuana cigarettes a day, or over 3000 per year, would have to be smoked."

Other side effects of marijuana smoking include orthostatic hypotension, elevated pulse rate, emphysema-like lung

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Ocular Complications of Allopurinol and Amiodarone

1. ALLOPURINOL

Allopurinol is a commonly used drug for the treatment of chronic gout and hyper-uricemia. While treatment with allopurinol is generally well tolerated, a recent study¹ published in the journal *Ophthalmology* has demonstrated an association between long-term

administration of allupurinol and increased risk of cataract extraction in elderly patients. In this Canadian study, a 10% random sample from their health insurance plan database identified 3677 cases of cataract extraction who met other eligibility requirements from 1987 – 1994. Of these cases, 89 patients had

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Ocular Complications, continued from page 1

been exposed to allopurinol with an average observation time of 6.4 years. 21,686 controls were identified. The risk of cataract extraction was associated with increasing age, female gender, hypertension, diabetes, glaucoma, and steroid use. Of patients exposed to allopurinol, there was no increase in risk with up to 3 years of use. However, with over 3 years of use, there was an increased risk of cataract extraction with an odds ratio of 1.53, and a cumulative dose over 400 grams with an odds ratio of 1.82. Patients who were "new" users of allopurinol (no use until after their first year in the database) showed a higher risk, with an odds ratio of 2.34 with 3 years of use, and 3.29 with 400 grams cumulative.

Another study has demonstrated allopurinol to be present in extracted cataractous lenses by phosphorescence spectroscopy.

2. Amiodarone

Amiodarone² is an antiarrhythmic agent used in patients with recurrent ventricular tachycardia or fibrillation. It has been associated with pulmonary fibrosis and commonly with

corneal and lens deposits. The corneal deposits are visible by slit lamp, and appear as verticillata, similar to findings with chloroquine therapy, and in Fabry's disease. Up to 40% of patients may see colored halos around lights at night related to this, but visual loss is rare.

Bilateral and unilateral ischemic optic neuropathy have been reported in users of amiodarone. In most of these cases, visual loss is permanent, and may be severe. Typical visual field defects of ischemic neuropathy have also been observed. Patients taking amiodarone commonly have other medical problems which may also lead to ischemic optic neuropathy, such as diabetes and hypertension, and thus a causal relationship has not been proven. Discontinuation of the drug has not generally lead to visual improvement in these cases, and may not be warranted except in cases of severe bilateral visual loss. In any case of sudden visual loss, prompt ophthalmic consultation is recommended to identify other treatable causes.

1. Garbe E., et al: Exposure to allopurinol and the risk of cataract extraction in elderly patients. *Arch Ophthalmol* 116:1652-1656, 1998.
2. Mantyarvi, M., et al: Ocular side effects of amiodarone. Survey of

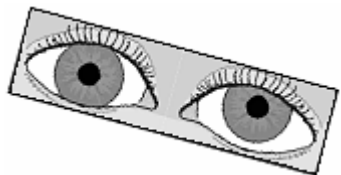
Clinical Pearl: Evaluation of Vertical Diplopia



CN 4 Palsy: Left eye slightly elevated gazing straight



CN 4 Palsy: Left eye poorly depresses in adduction



Left CN 4 Palsy: Left eye more elevated in left head tilt

The symptom of vertical diplopia, or vertical double vision, has a differential diagnosis list including neuro-ophthalmic, orbital, and medical etiologies:

- Fourth Cranial Nerve Palsy
- Third Cranial Nerve Palsy
- Thyroid Related Orbitopathy
- Myasthenia Gravis
- Orbital Blowout Fracture
- Orbital inflammatory disease or tumor

Of the above diagnoses, a Fourth Cranial Nerve palsy may be the most likely cause of an isolated symptom of vertical diplopia. The Fourth Cranial nerve innervates the ipsilateral superior oblique muscle, which is primarily involved in the torsional position of the eye (keeping the eye level with head tilting). This muscle also depresses the eye when intumed. Thus, patients with a Fourth

Cranial Nerve Palsy often present with vertical diplopia in downgaze (such as with reading), and they may complain of tilted vision. They may adopt a head position that avoids diplopia:



(Left CN 4 Palsy)

Typically, tilting the head away from the paretic side, and turning the face away from the paretic side avoids diplopia. The diagrams at left show possible findings of a left Fourth Cranial Nerve Palsy. Possible causes include:

- Head trauma, possibly minor
- Microvascular infarct of nerve
- Rarely tumor or aneurysm

There may be an association with HTN, diabetes, and possibly Temporal Arteritis.

Other causes of vertical diplopia have

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Photodynamic Therapy: A Potential Breakthrough Treatment for Macular Degeneration

Age-related macular degeneration is the leading cause of irreversible severe visual loss in Caucasians over the age of 50 in the United States. It is estimated that 2.2% of persons over the age of 65 are legally blind (vision 20/200 or worse) due to this condition. In this condition, areas of atrophy (drusen) develop in the retinal pigment epithelium underlying the retina. This in itself can progress and lead to visual

“Photodynamic Therapy may provide a treatment option for thousands of patients with macular degeneration.”

loss due to the resultant retinal dysfunction. This is often referred to as the “dry” form of macular degeneration.

In some cases, an abnormal vessel will grow beneath the retina leading to rapid loss of vision with hemorrhage, subretinal scarring, and distortion of vision. This is known as a subretinal neovascular membrane, or the “wet” form of macular degeneration.

Conventional laser ablation of these membranes can help in some cases to preserve vision, but the condition tends to be recurrent, and the laser treatment itself can leave large scotomas near the central vision. Membranes growing beneath the fovea, or those otherwise not meeting criteria for treatment, lead to progressive visual loss.

Photodynamic Therapy is a new treatment for subretinal

neovascular membranes being developed by QLT Photo-Therapeutics and CIBA Vision. In this treatment, Visudyne (a photosensitizing drug) is injected I.V., and it accumulates selectively in the abnormal subretinal vessels. Shortly thereafter, a light of a specific wavelength is shined upon the retinal area to treat, for 83 seconds. This activates the drug and selectively destroys the abnormal vessels, leaving the overlying retina intact

An ongoing randomized clinical trial has shown favorable results after 1 year of data. 61.4% of patients in the treatment group had improved or stabilized vision, compared to 45.9% in the placebo group ($p=0.0002$). Patients needed, on average, about 3 treatment sessions over the 1 year period. Adverse reactions were minimal, with only 2% experiencing generalized photosensitivity for a few days. It is not known, at this point, how much treatment would be necessary to fully treat the condition. Untreated neovascular macular degeneration tends to show less visual loss in the first year than in the subsequent 2 years, so the effectiveness of treatment may increase significantly as the study proceeds.

It is hoped that Visudyne will be approved by the FDA in a timely manner so that Photodynamic Therapy will be available as a treatment option by the year 2000. Currently the only other applications of photosensitizing drugs are in oncology.

Vertical Diplopia, continued.

distinguishing hallmarks. **Thyroid related orbitopathy** presents often with a restriction of upgaze especially in abduction, due to fibrosis of the inferior rectus. Other findings of lid retraction, proptosis, conjunctival injection, periorbital soft tissue swelling, and dry eye symptoms are common. Vertical and horizontal diplopia are possible (horizontal with medial rectus fibrosis).

Left sided thyroid related orbitopathy



Myasthenia gravis is characterized by muscle weakness and fatigue. Ocular findings include a variable ptosis, often worse at the end of the day or with fatigue. Extraocular muscle dysfunction and diplopia can occur, and is highly variable. Any ocular movement pattern can be mimicked by myasthenia. Thyroid dysfunction can be associated as well.

A **Third Cranial Nerve Palsy** usually presents with unilateral ptosis, and with an eye turned out and down (due to unopposed action of the 4th and 6th cranial nerves.) The pupil may be fixed and dilated, especially with compressive etiologies (aneurysm). Microvascular ischemia spares pupillary involvement about 80% of the time. Involvement of the superior division of the nerve in the orbit may lead to an isolated paralysis of the superior rectus and ptosis.

Orbital causes of vertical diplopia include orbital floor fractures with entrapment of the inferior rectus muscle. This causes a usually painful restriction of upgaze of the eye, possibly with enophthalmos, and a history of trauma. **Orbital inflammatory syndromes** are usually characterized by painful proptosis with variable diplopia, while **orbital tumors** often cause a painless displacement of the eye with diplopia.

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- Extensive patient information, including discussion of over 80 eye conditions
- Physician section with cases and topics of interest
- Office locations, directions, insurances

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Ophthalmology Update

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Marijuana as a Glaucoma Medication

changes, and adverse cognitive effects. Hypotension may be a risk factor for glaucomatous damage, through reduced vascular perfusion of the optic nerve. Further problems with the use of marijuana as a therapeutic agent include its lack of standardization, being a plant material with varying concentrations of cannabinoids.

In summary, it would appear that further research is warranted on the use of cannabinoids in the treatment of glaucoma, but that inhaled marijuana smoke is unacceptable due to its poor duration of action and multiple adverse side effects. The exact mechanism of action of cannabinoids in the lowering of intraocular pressure is not known, and thus it is unknown how they might interact with existing glaucoma medications. Improved delivery systems, such as the development of a topical medication with a high lipid solubility, are being developed. Orally taken medications, such as Dexanabinol, which lack the euphoric side effects of marijuana smoke may be promising as a future treatment option. (From Green K., Marijuana Smoking vs Cannabinoids for Glaucoma Therapy, In: Archives of Ophthalmology, 1998;116:1433-1437.)

Brief Report: Oral Acyclovir reduces Recurrences of Herpetic Keratitis

The Herpetic Eye Disease Study Group has found that 400mg of Acyclovir taken twice daily significantly reduces the recurrence rates of Herpes Simplex viral ocular disease. Herpes keratitis is a leading cause of corneal blindness in the United States, with stromal keratitis and epithelial keratitis leading to permanent visual loss. As many as 40% of patients will experience recurrences over a 5 year period following an initial episode. Other complications of herpetic eye disease include iritis, blepharitis, and conjunctivitis.

Over a 1 year period, 19% of patients taking Acyclovir daily experienced recurrences of ocular infections, compared to 32% of those in the placebo group. There was improvement in non-ocular recurrences as well, with 19% recurring in the treatment group compared to 36% in the placebo group (primarily orofacial disease). Subsequently, during a 6 month period of non-treatment, the protective effect of the oral Acyclovir was lost.

This prophylaxis may be especially significant for patients with the more vision threatening forms of the disease. (From Acyclovir for the prevention of recurrent herpes simplex virus eye disease. N Engl J Med 339:300, 1998.)