

## **American Academy of Ophthalmology**

**Title:** Drug-Related Adverse Effects of Clinical Importance to the Ophthalmologist  
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## **WHO CLASSIFICATION SCHEME**

Where data is available (i.e., published or submitted for publication), we have classified medications according to the World Health Organization's Causality Assessment of Suspected Adverse Reactions Guide (Edwards & Biriell). This template helps categorize medications into side effect profiles. The definitions are as follows:

- **Certain:** A clinical event, including a laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or by the presence of other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
- **Probable/Likely:** A clinical event, including a laboratory test abnormality, occurring within a reasonable time from administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possible:** A clinical event, including a laboratory test abnormality, that occurs within a reasonable time from administration of the drug, but which could also be explained by concurrent disease or the presence of other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- **Unlikely:** A clinical event, including a laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and for which the presence of other drugs, chemicals or underlying disease provides a plausible explanation.
- **Conditional/Unclassified:** A clinical event, including a laboratory test abnormality, reported as an adverse reaction but about which more data is essential for a proper assessment or for which the additional data are under examination.
- **Unassessable/Unclassifiable:** A report, suggesting an adverse reaction, which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

## **TAMUSOLIN (FLOMAX®) AND ALPHA-ADRENERGIC ANTAGONISTS (ALFUZOSIN, DOXAZOSIN, TERAZOSIN)**

**Primary Use:** These alpha-adrenergic antagonists are used to treat benign prostatic hyperplasia and hypertension.

**Clinical Concerns:** Intraoperative floppy iris syndrome (IFIS) associated with tamsulosin was first reported by Chang and Campbell in 2005. They suggest IFIS diagnosis be based on three intraoperative findings: fluttering and billowing of the flaccid iris stroma, a propensity for iris prolapse, and progressive constriction of the pupil during surgery. Additional characteristics also include poor preoperative pupil dilation and elasticity of the pupil margin.

It is hypothesized that the alpha-1A blocking effect of tamsulosin is not purely selective for the prostate as it may also selectively block the receptors in the iris dilator muscle.

Tamsulosin has a relatively long half-life, and it is possible that long-term receptor blockade could result in a type of disuse atrophy of the iris dilator smooth muscle. This may explain why some patients have permanent IFIS, even after the medication is discontinued.

Boehringer Ingelheim has subsequently changed the labeling on tamsulosin to reflect the possibility of IFIS in patients who may require cataract surgery.

**WHO Classification:** Certain

1. Floppy iris syndrome (primarily associated with tamsulosin)
2. Amblyopia
3. Blurred Vision

**Management Guidelines:** Inquire, in advance of cataract surgery whether or not a patient is taking an alpha-adrenergic inhibitor like tamsulosin (Flomax®) so the surgery can be planned accordingly. Iris retractors or other pupil expansion devices will help enlarge the pupil size throughout surgery in IFIS patients. Some ophthalmologists have suggested using Healon 5 with low aspiration parameters to maintain pupil size. Unfortunately, stopping the medicine does not always ensure IFIS will not occur.

**TOPIRAMATE (TOPAMAX®)**

**Primary Use:** Topiramate is a novel agent used to treat patients with various types of epilepsy and migraine headaches. It is used off label as a “magic” weight reduction medication and in bipolar disorder and clinical depression.

**Clinical Concerns:** Recent case reports by Banta, et al, Rhee, et al, and Sankar, et al have ballooned into almost 100 cases of a classic syndrome of acute angle closure glaucoma (Fraunfelder FW, Keates EU, Fraunfelder FT: Topiramate associated acute, bilateral, secondary angle-closure glaucoma. Ophthalmology 111(1):109-111, 2004.

In the Registry series:

- Patients range in age from 3½ - 53 years of age
- Time to onset of reaction ranges from 3 - 14 days after the start of oral therapy

**WHO Classification:**

|  |  |
|--|--|
| <p><u>Certain</u></p> <p>Acute glaucoma (mainly bilateral)</p> <p>Anterior chamber shallowing</p> <p>Ocular hyperemia</p> <p>Increased ocular pressure</p> <p>Mydriasis</p> <p>Suprachoroidal effusions</p> <p>Visual field defects – acute glaucoma</p> <p>Ocular pain</p> <p>Decreased vision</p> <p>Acute myopia (up to 6-8 diopters)</p> | <p><u>Probable/Likely</u></p> <p>Blepharospasm</p> <p>Oculogyric crisis</p> <p>Retinal bleeds</p> <p>Uveitis</p><br><p><u>Possible</u></p> <p>Scleritis</p> <p>Teratogenic effects, including ocular malformations</p> |
|--|--|

Before the syndrome was recognized, the majority of patients were treated with laser iridectomies or peripheral iridectomies, which we now know is not beneficial.

### **Guidelines for Management**

1. Patients should stop the medication
2. Hyperosmotic therapy
3. Cycloplegic
4. Topical antiglaucoma medication

### **BISPHOSPHONATES:**

**PAMIDRONATE DISODIUM (AREDIA®), ALENDRONIC ACID (FOSAMAX®), IBANDRONATE, ZOLEDRONATE (ZOMETA®), RISEDRONATE SODIUM (ACTONEL®), CLODRONATE (BONEFOS®), ETIDRONATE DISODIUM (DIDROCAL®), OLPADRONATE**

**Primary Use:** Pamidronate disodium (3-amino-1-hydroxy propylidene, disodium salt pentahydrate) inhibits bone resorption in the management of hypercalcemia of malignancy, osteolytic bone metastases of both breast cancer and multiple myeloma, and Paget's disease of the bone.

**Clinical Concerns:** This class of drug has been reported to cause anterior uveitis and nonspecific conjunctivitis. There are case reports of episcleritis, nerve palsy, ptosis, retrobulbar neuritis, and yellow vision. We previously reported a case of anterior scleritis and a case of posterior scleritis associated with pamidronate use, without rechallenge data. The most studied drug in this class, pamidronate, has caused 17 cases of unilateral scleritis and one case of bilateral scleritis. Onset is usually within 6-48 hours of intravenous drug administration. Six patients had positive rechallenge testing with the scleritis occurring after a repeat drug exposure. Other ocular side effects with positive rechallenge data, associated with pamidronate disodium use, include blurred vision, nonspecific conjunctivitis, ocular pain, bilateral anterior uveitis and episcleritis.

### **WHO Classification:**

#### Certain

Blurred vision  
Ocular irritation  
Nonspecific conjunctivitis  
Pain  
Epiphoria  
Photophobia  
Anterior uveitis (rare – posterior)  
Anterior scleritis (rare – posterior)  
Episcleritis

#### Probable

Periocular, lid and/or orbital edema

#### Possible

Retrobulbar neuritis  
Yellow vision  
Diplopia  
Cranial nerve palsy  
Ptosis  
Visual hallucinations

**Guidelines for Management:** This is the only class of drug proven to cause scleritis. Bisphosphonates can cause vision-threatening diseases. The seriousness of these conditions may dictate discontinuation of the drug in some uveitis cases and, in this series, all cases of scleritis. Further guidelines are as follows:

1. If persistent decrease in vision or ocular pain occurs, the patient should see an ophthalmologist.
2. Nonspecific conjunctivitis seldom requires treatment, and usually decreases in intensity or may be absent on subsequent pamidronate injections. In rare instances, a non-steroidal anti-inflammatory eye drop may be needed.
3. Bilateral anterior uveitis or, rarely, posterior or bilateral uveitis may occur and can vary markedly in severity. Many cases require intensive topical ocular or systemic medication. In some instances, the drug may need to be discontinued for the uveitis to resolve.
4. Episcleritis may require topical ocular medication; however, pamidronate may be continued.
5. In this series, for the scleritis to resolve, even on full medical therapy, the intravenous pamidronate had to be discontinued.

### **ETHAMBUTOL (MYAMBUTOL®)**

**Primary Use:** Indicated in the treatment of pulmonary tuberculosis.

**Clinical Concerns:** From 822 spontaneously reported adverse ocular reactions due to ethambutol received at the National Registry of Drug-Induced Ocular Side Effects (Portland, Oregon) and the World Health Organization (Uppsala, Sweden), there are 55 case reports of optic neuropathy (24 male, 31 female). Average dose was 1032 mg/day (weight of subjects unavailable but this would be in the targeted therapeutic range of approximately 15mg/kg assuming an average weight of 70 kg or 155 lbs) with an average duration of therapy until development of optic neuropathy of 235 days. The literature describes a dose-related incidence of ocular side effects with development of optic neuropathy in 50% of patients at a dose of 60-100 mg/kg/day, 5-6% at 25 mg/kg/day, and 1% with dosages at or below 15 mg/kg/day.

Ethambutol optic neuropathy is usually retrobulbar and bilateral, though sometimes asymmetric. Ethambutol toxicity may affect only the small caliber papillo-macular bundle axons, which are hard to visualize, and optic atrophy will not develop for months after the fibers are lost. This means objective findings on the fundus exam are frequently unrecognized. Optic neuropathy may occur, on average, at 2-5 months after starting therapy. The earliest ophthalmologic findings in toxic optic neuropathy from ethambutol may be loss of visual acuity, color vision loss or

central scotomas. Ethambutol also has an affinity for the optic chiasm with bitemporal visual field defects manifesting with toxicity.

The pathophysiology underlying ethambutol optic neuropathy remains unclear. However, one possible explanation is that ethambutol chelates copper in the retinal ganglion cells and their fibers in the optic nerve. The metabolite of ethambutol, ethylenediiminodibutyric acid, is a strong chelator of copper. Copper is required as a cofactor for cytochrome c oxidase, a key enzyme in the electron transport chain and cellular oxidative metabolism within mitochondria. It is possible that ethambutol decreases the levels of copper available for cytochrome c oxidase, and therefore the required energy for axonal transport around the optic nerve. In essence, mitochondrial insufficiency in the optic nerve fibers may underlie the impairment of axonal transport in the optic nerve and lead to optic neuropathy.

**Management Guidelines:** Ophthalmic examinations are recommended by the PDR every month for doses of ethambutol greater than 15mg/kg/day. No official standard of care exists regarding how often to see patients and which tests to perform in dosages less than 15 mg/kg/day. We recommend the following:

1. Obtain informed consent prior to assuming care for patients taking ethambutol explaining that optic neuropathy can occur at any dose despite regular ophthalmic exams and that the vision loss can be severe and irreversible.
2. Obtain a baseline exam to include a visual field test, color vision test, dilated fundus and optic nerve exam, and visual acuity.
3. If any visual symptoms occur, patients should discontinue the medication and see an ophthalmologist.
4. Frequency of examination is monthly for doses greater than 15mg/kg/day (PDR), however, monthly exams at lower doses may be necessary for patients at increased risk for toxicity:
  - Diabetes mellitus
  - Chronic renal failure
  - Alcoholism
  - Elderly
  - Children
  - Other ocular defects
  - Ethambutol-induced peripheral neuropathy
  - Dose greater than 15mg/kg/day

Consider discontinuation of ethambutol after any signs of loss of visual acuity, color vision, or for a visual field defect

Consider optical coherence tomography or contrast sensitivity testing as these tests could pick up early ethambutol toxicity not detected with the baseline exam. Optical coherence tomography (OCT) may be the future for following toxic optic neuropathies as subtle retinal nerve fiber layer (NFL) swellings can be visualized with the acute insult and NFL thinning can be visualized from chronic toxicity.

## **SILDENAFIL (VIAGRA®), TADALAFIL (CIALIS®), VARDENAFIL (LEVITRA®)**

**Primary Use:** Management of erectile dysfunction.

**Clinical Concerns:** Sildenafil (Viagra®) has been studied far more extensively than the two more recently released agents. In pre-marketing clinical trials, tadalafil and vardenafil have about the same type and incidence of visual side effects as sildenafil. In our opinion, to date there is no proof of any permanent damage from any of these agents on the visual system. Vascular effects may be rarely associated, but one cannot distinguish a drug side effect from increased physical exertion with increased blood pressure and pulse rate, which may occur with sexual activity.

Ocular side effects are common, dosage dependent and thus far have all been fully reversible. Reported side effects include changes in color perception (objects have colored tinges, usually blue or blue/green, though they may also be pink or yellow; diminished color vision on the Farnsworth-Munsell 100 Hue Test; and dark colors may appear darker). Patients have also reported blurred vision, sometimes with central haze and transitory decreased vision. These agents may cause changes in light perception, increased perception of brightness and/or a sensation of seeing flashing lights, especially when blinking.

While Sildenafil has been reported to cause ERG changes, Cordell et al in a 15 center 6 month trial of daily use of either Sildenafil or Tadalafil verse a placebo found no abnormal ERG or any other retinal function parameters. This drug may cause hyperemia and subconjunctival hemorrhages. Some patients report ocular pain and photophobia. There have also been reports of mydriasis, although this is probably not drug-related.

The above ocular side effects are dose-dependent with all three drugs, but with sildenafil occur at the following incidences:

|       |        |
|-------|--------|
| 50mg  | 3%     |
| 100mg | 10%    |
| 200mg | 40-50% |

Incidence is the same for all ages, and the incidence and severity of reported ocular side effects is directly proportional to blood drug levels. The side effects based on dosage with sildenafil start 15-30 minutes after ingestion of the drug, and usually peak 60 minutes after ingestion.

### **WHO Classification:**

#### Certain:

Changes in color perception

Objects have colored tinges—usually blue or blue-green, may be pink or yellow

Decreased color vision

Dark colors appear darker

Blurred vision

Central haze



Transitory decreased vision  
 Changes in light perception  
   Increased perception of brightness  
   Flashing lights, especially when blinking  
 Conjunctival hyperemia  
 Ocular pain  
 Photophobia

Possible:

Subconjunctival hemorrhage  
 Anterior ischemic optic neuropathy  
 Macular edema  
 Ocular rosacea

Conditional/Unclassified:

Mydriasis (emotional effect?)  
 Retinal vascular accidents (secondary to exertion?)

Sildenafil has recently become a controversial drug due to the media spotlight on the risk of NAION. To date, the literature contains 14 case reports, including a single report of positive rechallenge (recurrence of NAION when drug therapy was restarted). Spontaneous reporting systems record 86 cases of visual disturbances associated with sildenafil therapy. From this poorly documented data, the association between sildenafil and NAION is “possible” according to WHO criteria requiring that a clinical event occur within a reasonable time from drug administration. There is no well-researched explanation as to how sildenafil therapy could cause NAION. Over 27 million men have used sildenafil. Most are vasculopathic and fall into an age group in which they are already at risk for NAION.

There are four published cases of macular edema (Allibhai et al 2004, Quiram et al 2005) and another seven in the National Registry (Fraunfelder and Fraunfelder 2007). Four of these cases have positive rechallenge of serous macular edema associated with erectile dysfunction drugs at normal or elevated dosages. Included are cases of chronic macular edema, which would not resolve until the drug was stopped. While these data are suggestive, the nature of non-drug-induced serous macular edema is recurrent and transitory. Further data are necessary.

Ioannides et al reported 10 men on erectile dysfunction agents who developed full blow acne rosacea. While ocular rosacea was not mentioned in this dermatologic study, this side effect should be considered.

**Management Guidelines:** We feel that the only patients who should not take phosphodiesterase type 5 inhibitors (sildenafil, vardenafil, and tadalafil) are those who have previously suffered NAION in one eye or anyone who experiences transitory visual loss while on these medications. These patients may be more prone to developing NAION in the same or fellow eye if sildenafil or other medicines in this class are ingested. Also, the subset of patients who take phosphodiesterase type 5 inhibitors may have the highest risk of developing NAION, independent of an adverse effect, but this is not proven.

## **HERBAL MEDICINES AND NUTRITIONAL SUPPLEMENTS**

**Primary Use:** These agents are used to treat a variety of systemic and ocular conditions.

**Clinical Concerns:** Alternative therapies for human disease have an enormous presence in the United States health care system, and their popularity appears to be increasing. In a 1990 survey of 1539 adults, 33.8% of respondents used herbal medicines or nutritional supplements. By 1997, the number had increased to 42.1%, with most people paying the cost out-of-pocket. In February 2004 the WHO emphasized the importance of this \$60 billion industry by publishing guidelines on the use of herbal medicine. Included are recommendations on cultivating, collecting, classification, quality control, storage, labeling and distribution.

Prescription drugs and over-the-counter, non-prescription drugs are monitored by the Food and Drug Administration (FDA) because they are sold for a specific indication and are marketed over state lines. By contrast, herbal medicines and nutritional supplements are not marketed to treat specific diseases, are exempt from the interstate commerce law and fall under the purview of the Dietary Supplement and Health Education Act of 1994. No efficacy or safety has to be proven to sell these agents, of which there are 700 botanicals and 1,000 nutritional products. In addition, there are no official standards governing the production of alternative therapies in the United States, and the potency and purity of these products are subject to substantial variation. For example, ginseng (*Panax ginseng*) was evaluated by the American Botanical Council in 2001. This group found that only 52% of products marketed as containing ginseng actually contained any of this botanical.

From 263 spontaneous reports received at the National Registry and from an additional 60 case reports in the literature, canthaxanthine, *chamomile*, *datura*, *Echinacea purpurea*, *ginkgo biloba*, *licorice*, niacin and vitamin A are all associated with clinically significant ocular side effects.

### **WHO Classification:**

#### Canthaxanthine

Certain: Crystalline retinopathy

#### Chamomile

Certain: Allergic conjunctivitis

#### Datura

Certain: Mydriasis

#### Echinacea purpurea

Probable: Conjunctivitis

#### Ginkgo biloba

Possible: Spontaneous hyphema, retinal hemorrhage

#### Licorice

Possible: Vasospasm, visual loss associated with migraine-like symptoms

#### Niacin

Probable: Cystoid macular edema

Possible: Decreased vision, dry eyes, discoloration of the eyelids, eyelid edema, proptosis, loss of eyebrows and eyelashes, and superficial punctate keratitis

#### Vitamin A

Certain: Intracranial hypertension when taken in large doses

**Guidelines for Management:** Herbal medicines and nutritional supplements are being used by a large segment of the population, many times without strong evidence on efficacy or safety. Fortunately, if the clinician recognizes an ocular or systemic side effect from one of these agents, the symptoms are usually reversible. Clinicians should remain vigilant in recognizing adverse ocular reactions as well as inquiring whether these alternative treatments are being used as patients frequently do not disclose this information to their physicians.

### **HYDROXYCHLOROQUINE/CHLOROQUINE (PLAQUENIL®)**

**Primary Use:** Hydroxychloroquine is used for the treatment of rheumatoid arthritis and lupus erythematosus, dermatologic conditions, and various inflammatory disorders. Chloroquine is no longer available except for malaria treatment and is primarily used in the military.

**Clinical Concerns:** From published reports, approximately one million patients have used hydroxychloroquine or chloroquine, yet only 20 cases of toxicity have been reported in the low dose range (<6.5mg/kg.day). In addition, all of these cases occurred after 5 years of treatment. Still, retinal toxicity can be devastating and guidelines need to be available for screening. It should be emphasized that the recommendations that follow are aimed at detection and not prevention, as stopping the drug is the only way to prevent possible side effects and this is not an option for some patients. Specific clinical concerns are addressed below:

Hydroxychloroquine crystals have been found in the tear film, which may aggravate sicca or be bothersome to contact lens wearers. If hydroxychloroquine is found to have caused skin, eyelid, corneal or hair changes, the clinician should suspect retinal changes.

#### **Maculopathy**

Maculopathy must be bilateral and reproducible by Amsler grid and visual field testing. Transient or unilateral defects are not sufficient reasons to implicate the drug, and are not necessarily an indication to stop therapy.

A recent preliminary paper by Shroyer, et al., suggests that individuals with an ABCR mutation (Stargardt's disease) may be predisposed to develop retinal toxicity when exposed to chloroquine/hydroxychloroquine.

**Management Guidelines:** The goal in managing patients on hydroxychloroquine is to find early changes, i.e., relative scotomas. Disease in patients with early paracentral relative scotomas seldom advances when the drug is discontinued. Later findings include retinal changes, color vision loss, absolute scotoma or decreased vision. Even if the drug is stopped, once these changes occur they are irreversible, and many patients may continue to lose some vision and/or peripheral fields.

To date, there is no data to show that hydroxychloroquine toxicity worsens pre-existing macular degeneration. However, the best course in today's litigious environment may make informed consent and explanation of risk/benefit ratios necessary on an individual basis. Document in the patient's chart that you have explained that, in very rare instances, significant loss of vision can

occur after only a few years of therapy, and that he or she may need to be examined if any visual abnormality occurs.

Patients at greatest risk are those on hydroxychloroquine for longer than 5 years and those with renal or liver disease (this drug is metabolized via the kidney and liver, and thus damage to these organs may increase levels of hydroxychloroquine in the blood). Elderly, thin patients may also be overdosed, as may obese patients. Dosing regimens are based on body weight, but hydroxychloroquine is primarily absorbed by cellular tissue. Since adipose tissue is relatively acellular, obese patients may be overdosed.

How best to follow patients on hydroxychloroquine was summarized in an article in the July 2002 issue of *Ophthalmology*. These recommendations follow the overall guidelines of the American Academy of Ophthalmology for seeing patients. Patients aged 20-29, one examination; ages 30-39, two examinations; 40-64, every 2 to 4 years, and patients aged 65 and over should be seen every 1 to 2 years.

#### *Baseline Examination*

Within the first year after starting this drug, patients should have a complete, dilated ophthalmic examination, including the informed consent mentioned above, warning of possible permanent visual problems in rare instances. This baseline exam should include visual acuity, Amsler grids (with instructions for monthly home use), and optional color vision testing (preferably including the blue-yellow axis, such as the pseudo-isochromatic plates for color by American Optical Corporation). If macular abnormalities are evident, it would be ideal to obtain fundus photographs. If any progressive ocular abnormality is suspected, consider a baseline Humphrey 10-2 or other automated perimetry. Multifocal ERG is optional.

#### *Follow-up Examinations*

For patients who are not obese, frail, elderly or extremely thin, are without significant renal or hepatic disease or macular disease of any type, and who are younger than 40, another complete exam is unnecessary for 2-4 years. Patients should be seen sooner if they experience any persistent visual symptoms or if their dosage exceeds 6.5 mg/kg.

Patients between 40 and 64 years:

Same as above, with follow-up every 2-4 years

Age 64 and older:

Same as above, with more frequent follow-up (every 1-2 years)

Annual eye examinations should be considered if patients have been on hydrochloroxyquine therapy for longer than 5 years, if they are obese, or lean and small (especially in the case of elderly patients), or if they have progressive macular disease of any type, significant renal or liver disease, or their dosage exceeds 6.5 mg/kg.

#### *Follow-up Examination Procedures*

Repeat baseline examination.

Fundus photography if any macular abnormality noted

Consider fluorescein angiography only in the presence of suspicious pigmentary changes  
 Automated central visual fields (optional)  
 Multifocal ERG (selected cases)

For patients taking chloroquine, perform the tests listed above. See patients at least annually if dosage is less than 3.0 mg/kg of ideal body weight. See every 6 months if dosage is greater than 3.0 mg/kg body weight, or if patients are short, obese, or have renal and/or liver impairment.

## **FLUOROQUINOLONES**

**Primary Use:** Fluoroquinolones interfere with DNA replication by inhibiting the bacterial DNA gyrase or the topoisomerase IV enzymes, thereby inhibiting DNA replication and transcription. This class of antibiotic is considered broad spectrum and is associated with specific side-effects not seen in other classes of antibiotics.

**Clinical Concerns:** Tendinitis and tendon rupture are unique to this type of antibiotic and the risk is increased with age over 60 years, renal failure, organ transplantation, or therapy with systemic anti-inflammatory steroids. Tendinitis can occur without any risk factors after taking fluoroquinolones and can also occur many months after therapy. Peripheral neuropathy has been reported rarely with fluoroquinolone therapy and diplopia is mentioned as having been noticed in pre-marketing trials in the package inserts.

Due to the multiple reports of diplopia associated with fluoroquinolone therapy received at the National Registry of Drug-Induced Ocular Side Effects (Casey Eye Institute, Oregon Health and Science University, Portland, Oregon) an association between fluoroquinolones and diplopia was investigated.

There are multiple fluoroquinolones which have been marketed in the United States (US) and included in this database study are moxifloxacin, ciprofloxacin, norfloxacin, ofloxacin, gatifloxacin, and levofloxacin. None of these medications were administered as eye drops and gatifloxacin has subsequently been removed from the US market with the exception of the ophthalmic solution.

We found 171 case reports of diplopia associated with fluoroquinolones in the National Registry. There were 75 case reports associated with ciprofloxacin, 40 with ofloxacin, 20 with levofloxacin, 16 with moxifloxacin, 11 with norfloxacin, and 9 with gatifloxacin. Patients included 76 men and 91 women. In 4 case reports, gender was not specified. The median age was 51.6 years (range 6-95 years). Dosage varied between the different fluoroquinolone drugs; average dose was within the range recommended in the package insert for each drug. The median dosages were as follows: ciprofloxacin 500mg daily (range 250-750), ofloxacin 600mg daily (range 400-800mg), levofloxacin 500mg daily (range 250-750mg daily), moxifloxacin 400mg daily (400mg only dose reported), norfloxacin 800mg daily (800mg only dose reported), and gatifloxacin 400mg daily (400mg only dose reported). Seventeen subjects also had concomitant tendinitis, 49 patients were 60 years or older, 1 patient had renal cysts, and 4 were taking systemic anti-inflammatory steroids.

The median time from the start of fluoroquinolone therapy to the appearance of diplopia was 9.6 days (range 1 day to 5 months) from 86 case reports where the time to onset of diplopia after

starting the fluoroquinolone was reported. There were 53 reports of positive dechallenge and 5 positive rechallenge case reports (Table 2).

**WHO Classification:**

Certain: allergic reaction or precipitates in cornea from topical ocular administration

Probable: Diplopia, exacerbation of myasthenia gravis

Possible: Uveitis

Unclassifiable: optic neuropathy, intracranial hypertension

**Management Guidelines:** It is unknown how fluoroquinolone therapy could cause diplopia. Therapy with this class of medication has been reported to cause tendinitis and tendon rupture in 0.14% to 0.4% of patients without other risk factors. It has not been suggested before that extraocular muscle tendons could be affected by fluoroquinolones as achilles, quadriceps, peroneus brevis, extensor pollicis longus, biceps and rotator cuff tendons are the most commonly reported. Still, extraocular muscle tendons are attached to skeletal muscles and could be affected in much the same way as other skeletal muscle tendons.

In 53 instances when the drug was reportedly withdrawn, the diplopia resolved. There is also a possible mechanism for these ADRs: localized tendinitis in the extraocular muscles. Perhaps most compelling are the 5 positive rechallenge case reports.

**HMG-COA REDUCTASE INHIBITORS (STATINS)**

**Primary Use:** The medications known as 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors (statins) are a class of hypolipidemic drugs used to lower cholesterol levels in patients at risk of cardiovascular disease (Table 1). The enzyme HMG-CoA reductase is inhibited, thereby preventing the rate-limiting step in the mevalonate pathway of cholesterol synthesis. Clinical trials have documented the efficacy of statins in preventing coronary heart disease, cerebrovascular accidents, and death from hypercholesterolemia-related disease. Although side effects are rare, myopathies are a well-known adverse reaction to statin therapy.

**Clinical Concerns:** The myopathy most often associated with statin therapy affects skeletal muscle and, to date, there is a single published case report of a myopathy of the skeletal musculature around the eye, a case of unilateral blepharoptosis (ptosis), presumably due to levator palpebrae superioris myositis in a patient taking 10 mg of atorvastatin daily.<sup>3</sup> When atorvastatin was discontinued, the ptosis resolved within 4 days and did not reoccur.

Due to the multiple reports of diplopia and ptosis associated with statin therapy received at the National Registry of Drug-Induced Ocular Side Effects (Casey Eye Institute, Oregon Health and Sciences University, Portland, Oregon) an association between statins and adverse events of this type was investigated.

We found 256 case reports of diplopia, ptosis, or ophthalmoplegia associated with statins in the spontaneous reporting databases. Patients included 143 men and 91 women. In 22 case reports, gender was not specified. The average age was 64.5 +/- 10 years (range 34-89 years). Dosage varied between the different statin drugs; average dose was within the range recommended in the package insert for each statin. The mean dosages were as follows: atorvastatin 22.6mg +/- 17.5mg daily (range 10-80mg daily), cerivastatin (discontinued and no dosages reported), fluvastatin 43.3mg +/- 18mg daily (range 20-80mg daily), lovastatin 25mg +/-

14mg daily (range 10-40mg daily), pravastatin 26mg +/-14mg daily (range 10-40mg daily), rosuvastatin 10mg +/- 0.0mg daily (range, 10mg only dosages reported ), and simvastatin 22.2mg +/- 18.9mg daily (range 5-80mg daily). A total of 108 patients were taking no other medications except the statin. The other 148 patients were taking concurrent medications that included high blood pressure medications such as beta-blockers, diuretics, and calcium-channel blockers. Seven of these patients were taking a second statin drug and 5 were taking gemfibrozil. Women frequently were taking estrogen replacement therapy, and many patients took an aspirin daily. Nine patients had diabetes mellitus and 91 had hypertension.

The average time from the start of statin therapy to the appearance of the ADR was 8.3 months +/- 1.5 months (range 1 day to 84 months). A total of 23 case reports described total ophthalmoplegia. Ptosis was reported alone 20 times and in conjunction with diplopia 13 times. There were 62 reports of positive dechallenge and 14 positive rechallenge case reports (Table 2).

In patients taking atorvastatin, we found 55 case reports of diplopia, 5 cases of ptosis, 3 cases of diplopia with ptosis, and 3 cases of ophthalmoplegia. Patients taking cerivastatin had 15 cases of diplopia, 1 case of ptosis, 1 case of diplopia with ptosis and 1 case of ophthalmoplegia. In patients taking fluvastatin, we found 8 case reports of diplopia and 2 cases of ophthalmoplegia. For lovastatin, we found 34 case reports of diplopia, 2 cases of ptosis, 2 cases of diplopia with ptosis, and 6 cases of ophthalmoplegia. In patients taking pravastatin, there were 38 reported cases of diplopia, 4 cases of ptosis, 4 cases of diplopia with ptosis, and 5 cases of ophthalmoplegia. Patients taking rosuvastatin had 5 cases of diplopia and one case of ptosis. For simvastatin, we found 59 cases of diplopia, 7 cases of ptosis, 3 cases of diplopia with ptosis, and 6 cases of ophthalmoplegia.

### **WHO Classification:**

Possible: Diplopia, ptosis, ophthalmoplegia, exacerbate myasthenia gravis, cataracts

**Management Guidelines:** There is a known mechanism for these ADRs: localized myositis in the extraocular muscles or levator palpebrae superioris muscles. Systemic myopathy is an ADR commonly associated with statin therapy. Perhaps most compelling are the positive rechallenge case reports.

Myositis due to statin therapy is estimated to occur in approximately 0.1% of patients and this increases to 0.5%-2.5% if gemfibrozil is administered at the same time. It is possible that a localized myositis occurred in the extraocular muscles or the levator muscles on and around the eye, leading to the ADRs reported here. In the single published case report of ptosis related to statin therapy, magnetic resonance imaging (MRI) showed an enlarged right levator muscle. Enhanced with gadolinium, these images suggest myositis.

From the data presented, it appears that statin-associated diplopia, ptosis, and ophthalmoplegia are completely reversible on discontinuation of the statin as evidenced by the 62 positive dechallenge case reports. It is possible that toxicity results from many months of therapy, but the data, so far, is inconclusive. The reversibility of the ADR coincides with the published medical literature on statin-associated myopathy and with the single case report from the ophthalmic literature.

### **HEPATITIS B VACCINE**

**Primary Use:** Hepatitis B vaccine was approved by the FDA in November 1981 and is currently recommended in the prevention of hepatitis B for all children aged 0-18 years. In addition, the vaccine is recommended for some adults such as homosexual men, subjects incarcerated for long periods of time, and for health care workers. The dosage is usually administered in 2 or 3 separate vaccinations. There are currently two recombinant vaccines (Recombivax HB<sup>®</sup> and Engerix-B<sup>®</sup>) used in the United States. There are additional products licensed in the U.S. that contain these vaccines in combination with other vaccines.

**Clinical Concerns:** There are multiple case reports of uveitis occurring in association with vaccines. These include Bacillus Calmette-Guerin (BCG) vaccine, diphtheria, tetanus, and pertussis (DPT) vaccines, influenza vaccine, measles, mumps, and rubella vaccines (MMR), varicella vaccine, and smallpox vaccine. To date, there is a single case report of uveitis occurring after hepatitis B vaccine.

Thirty-two case reports of uveitis occurring after hepatitis B vaccine were reported to the National Registry. The average age was 29 years (1-57 years old) with 8 male and 24 female. The average number of days until uveitis was reported after vaccination was 3 days (1-15 days). The uveitis was reported to occur after the first vaccination in 15 subjects, after the second vaccination in 3 subjects, after the third vaccination in 3 subjects and duration of time to occurrence of uveitis was not reported in 9 subjects. One patient had recurrent uveitis after both the second and third booster.<sup>7</sup> One subject had recurrent uveitis after the first and second vaccination. Three subjects also received typhoid vaccine during the same time period as the hepatitis B vaccine and boosters.

Twenty-four of 32 patients (75%) developed systemic illness with symptoms consistent with influenza like illness, fever, arthralgia, arthritis and other eye findings, such as retinopathy. From the spontaneous reports, it appears all subjects recovered, although the treatment for the uveitis was not reported.

**WHO Classification:**

Possible: uveitis

**Management Guidelines:** The potential mechanism for development of uveitis in patients who receive hepatitis B vaccines could be related to a delayed type hypersensitivity reaction. In many infectious and systemic diseases, the deposition of immune complexes with subsequent complement activation is a major pathogenic mechanism for the development of uveitis. From the case series presented here, the average of 3 days after antigen exposure until the development of uveitis may argue in favor of an immune complex deposition mechanism. Although there is debate that uveitis occurs due to hepatitis B infection, there is evidence that immune complex deposition diseases like glomerulonephritis and cryoglobulinemia occur during chronic hepatitis B infection. As suggested by Fried et al, it is possible the surface antigen of the vaccine and the hepatitis B antibodies of the immune response after vaccination formed immune complexes which initiated the ocular response of uveitis. Hence, the surface antigen of the hepatitis virus could be responsible for the development of uveitis both after vaccination and with hepatitis B surface antigen during the course of hepatitis B infection. There have been case reports of uveitis in hepatitis B infections.



## **NATIONAL REGISTRY OF DRUG-INDUCED OCULAR SIDE EFFECTS**

The objectives of the Registry are:

- To establish a national center where reports of possible drug-induced ocular side effects can be accumulated
- To add to this database the spontaneous reporting data of possible drug-induced ocular side effects collected from the Food and Drug Administration (FDA) (Rockville, Md) and the World Health Organization (WHO) (Uppsala, Sweden)
- To compile the data in the world literature on reports of possible drug-induced ocular side effects in humans
- To publish some of this data every 4 to 5 years in book form
- To make available this data to physicians who feel their patients may have a possible drug-induced ocular side effect

You can contact us to help you with a suspected drug reaction, to access data in the Registry, or to report a case. When sending data, it would be ideal to include the following information: name of drug, dosage, length of time on drug, suspected reaction, what happened if the drug was stopped, if rechallenged, and concomitant drugs. The name and address of the person reporting the case is optional, but encouraged.

Reports can be mailed to: National Registry of Drug-Induced Ocular Side Effects  
Casey Eye Institute  
3375 SW Terwilliger Blvd.  
Portland, OR 97239-4197

or faxed: (503) 494-4286  
or sent to our website [www.eyedrugregistry.com](http://www.eyedrugregistry.com)

The next edition of Drug-Induced Ocular Side Effects will be entitled Clinical Ocular Toxicology. It will include updates on the information in its predecessors and will also include an expanded section covering the basics of ocular toxicology.

### **References:**

#### **Overview Books:**

- Fraunfelder FT, Fraunfelder FW, Chambers WA. Clinical Ocular Toxicology. Saunders/Elsevier 2008
- Fraunfelder FT, Fraunfelder FW, Randall JA, eds. Drug-Induced Ocular Side Effects. 6th ed. Elsevier, 2007.

Grant WM, Schuman JS, eds. Toxicology of the Eye. 4th ed. Springfield, Mass: Charles C. Thomas; 1993.

### **Journal Articles:**

#### **WHO Articles**

International drug monitoring: the role of national centers. Geneva, Switzerland: World Health Organization (WHO); 1972. The WHO Technical Report Series No. 498.  
Edwards IR, Biriell C. Harmonisation in pharmacovigilance. *Drug Safety* 1995;10:93-102.

#### **Tamsulosin and alpha-adrenergic antagonists**

Arshinoff, S.A.: Modified sst-usst for tamsulosin-associated intraocular floppy-iris syndrome. *J. Cataract Refract. Surg.* 32:559-561, 2006.  
Boehringer Ingelheim. Important safety on Intraoperative floppy iris syndrome (IFIS). Internet Document: 14 Oct 2005. available from <http://www.hc-sc.gc.ca>.  
Chang, D.F., and Campbell, J.R.: Intraoperative floppy iris syndrome associated with tamsulosin. *J. Cataract Refract. Surg.* 31:664-673, 2005.  
Kershner, R.M.: Intraoperative floppy iris syndrome associated with tamsulosin. *J. Cataract Refract. Surg.* 31:2239-2241, 2005.  
Lawrentschuk, N., and Blysm, G.W.: Intraoperative 'floppy iris' syndrome and its relationship to tamsulosin: a urologist's guide. *BJU Int.* 97:2-4, 2006.  
Nguyen, D.Q., Sebastian, R.T., and Philip, J.: Intraoperative floppy iris syndrome associated with tamsulosin. *BJU Int.* 97:197, 2006.  
Osher, R.H.: Association between IFIS and flomax. *J. Cataract Refract. Surg.* 32:547, 2006.  
Parssinen, O.: The use of tamsulosin and iris hypotony during cataract surgery. *Acta Ophthalmol. Scand.* 83:624-626, 2005.  
Schwinn, D.A., and Afshari, N.A.: Alpha 1-adrenergic antagonists and floppy iris syndrome: tip of the iceberg? *Ophthalmology.* 112:2059-2060, 2005.

#### **Topiramate**

Banta JT, Hoffman K, Budenz DL, Ceballos E, Greenfield DS. Presumed topiramate-induced bilateral acute angle-closure glaucoma. *Am J Ophthalmol* 2001;132:112-114.  
Fraunfelder FW, Fraunfelder FT, Keates EU. Topiramate-associated acute, bilateral, secondary angle-closure glaucoma. *Ophthalmology* 2004; 111:109-111.  
Rhee DJ, Goldberg MJ, Parrish RK. Bilateral angle closure glaucoma and ciliary body swelling from topiramate. *Arch Ophthalmol* 2001;119:1721-1722.  
Sankar PS, Pasquale LR, Grosskreutz CL. Uveal effusion and secondary angle-closure glaucoma associated with topiramate use. *Arch Ophthalmol* 2001;119:1210-1211.

## Bisphosphonates

- De S, Meyer P, Crisp AJ. Pamidronate and uveitis (letter to the editor). *Br J Hematol* 1995;34:479.
- Fraunfelder FW, Fraunfelder FT, Jensvold B. Scleritis and other side effects associated with pamidronate disodium. *Am J Ophthalmol* 2003;135:219-222.
- Fraunfelder FW, Fraunfelder FT. Bisphosphonates and ocular side effects. *N Engl J Med* 2003;348:1187-8.
- Macarol V, Fraunfelder FT. Pamidronate disodium and possible ocular adverse drug reactions. *Am J Ophthalmol* 1994;118:220-224.
- Siris ES. Bisphosphonates and iritis. *Lancet* 1993;341:436-437.
- Stewart, GO, Stuckey BG, Ward LC, et al. Iritis following intravenous pamidronate. *Aust NZ J Med* 1996;26:414-415.

## Ethambutol

- Fraunfelder FW, Sadun AA, Wood T. Update on ethambutol optic neuropathy. *Expert Opin Drug Saf.* 2006 Sep;5(5):615-8. Review.

## Erectile Dysfunction Drugs

- Allibhai, Z.A., et al: Central serous chorioretinopathy in a patient taking sildenafil citrate. *Ophthalmic Surg. Lasers Imaging* 2004; 35:165-167.
- Egan RA, Pomeranz H. Transient ischemic attack and stroke associated with sildenafil (Viagra®) use. *Neurology* 2002;59:293.
- Fraunfelder FW, Fraunfelder FT. Scientific challenges in postmarketing surveillance of ocular adverse drug reactions. *AM J Ophthalmol* 143: 145-149, 2007.
- Fraunfelder FT, Laties A. Visual side effects possibly associated with sildenafil (Viagra®). *J Toxicol Cut Ocular Toxicol* 2000;19:21-25.
- Fraunfelder FW, Pomeranz H, Egan, RA. Non-arteritic ischemic optic neuropathy and sildenafil. *Arch Ophthalmol* 2006; 124:733-4.
- Pomeranz HD, Smith KH, Hart WM Jr., Egan RA. Sildenafil-associated nonarteritic anterior ischemic optic neuropathy. *Ophthalmology* 2002;109:584-587.

## Herbal Medicines and Nutritional Supplements

- Blumenthal M, Busse WR, Goldberg A, et al. In Blumenthal M, Busse WR, Godlberg A, et al., eds. The Complete German Commission E Monographs Therapeutic Guide to Herbal Medicines. Austin, Texas, American Botanical Council, 1998-685.
- Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. *JAMA* 1998; 289:1569-1575.
- Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the Unites States—prevalence, costs, and patterns of usage. *N Engl J Med* 1993;328:246-520.

- Fraunfelder FW. Ocular side effects associated with herbal medicines and nutritional supplements. *Am J Ophthalmol* 2004;138:639-647.
- Physicians' Desk Reference for Nutritional Supplements*. Montvale, NJ: Medical Economics Co., Inc., 2001:575.
- Physicians' Desk Reference for Herbal Medicines*. 2nd ed. Montvale, NJ: Medical Economics Co., Inc., 2000:858.
- WHO Guidelines On Good Agricultural and Collection Practices for Medicinal Plants*. Geneva, Switzerland: World Health Organization; 2004.

### **Hydroxychloroquine**

- Beebe WE, Abbott RL, Fung WE. Hydroxychloroquine crystals in the tear film of a patient with rheumatoid arthritis. *Am J Ophthalmol* 1986;101:377-378.
- Easterbrook M. Detection and prevention of maculopathy associated with antimalarial agents. *International Ophth Clinics* 1999;39:49-57.
- Easterbrook M. Is corneal deposition of antimalarial any indication of retinal toxicity? *Can J Ophthalmol* 1990;25:249-251.
- Shroyer NF, Lewis RA, Lupski JR. Analysis of the ABCR (ABCA4) gene in 4-aminoquinoline retinopathy: Is retinal toxicity by chloroquine and hydroxychloroquine related to Stargardt disease? *Am J Ophthalmol* 2001;131:761-766.

### **Fluoroquinolones**

- Cano-Parra J, Dia-Llopis M. Drug induced uveitis. *Arch Soc Esp Oftalmol* 2005;80:137-49.
- Fraunfelder FW, Fraunfelder FT. Diplopia and fluoroquinolones. *Ophthalmology* July, 2009.
- Fraunfelder FT, Fraunfelder FW, Chambers WA. Clinical Ocular Toxicology. Philadelphia, PA. Saunders Elsevier; 2008.
- Moore B, Safani M, Keesey J. Possible exacerbation of myasthenia gravis by ciprofloxacin. Case report. *Lancet* 1988;1:882.
- Motolese E, d'Aniello B, Addabbo G. Toxic optic neuropathy after administration of quinolone derivative. *Boll Oculist* 1990;69:1011-13.
- Winrow AP, Supramaniam G. Benign intracranial hypertension after ciprofloxacin administration. *Arch Dis Child* 1990;65:1165-66.
- Muzi F, Gravanta G, Tati E, Tati G. Fluoroquinolones-induced tendinitis and tendon rupture in kidney transplant recipients: 2 cases and a review of the literature. *Transplant Proc* 2007;39:1673-75.

### **HMG-CoA Reductase Inhibitors (Statins)**

- Ertas FS, Ertas N M, Gulec S, et al. Unrecognized side effect of statin treatment: unilateral blepharoptosis. *Ophthal Plast Reconstr Surg* 2006;22:222-4.

- Fraunfelder FW, Richards AB. Diplopia, blepharoptosis, and ophthalmoplegia and 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitor use. *Ophthalmology*. 2008 Dec;115(12):2282-5.
- Fraunfelder FW. Ocular hemorrhage possibly the result of HMG-CoA reductase inhibitors. *J Ocul Pharmacol Ther* 2004;20:179-182.
- Hamilton-Craig I. Statin-associated myopathy. *Med J Aust* 2001;175:486-9.
- Phillips PS, Haas RH, Bannykh S, et al. Statin-associated myopathy with normal creatine kinase levels. *Ann Intern Med* 2002;137:581-5.
- Soininen K, Niemi M, Kikki E, et al. Muscle symptoms associated with statins: a series of twenty patients. *Basic Clin Pharmacol Toxicol* 2006;98:51-4.

### **Hepatitis B Vaccine**

- Dolinova L. Bilateral uveoretinoneuritis after vaccination with Ditepe (diphtheria, tetanus, and pertussis vaccine). *Cs Oftal* 30:114, 1974.
- Esmaeli-Gutstein B, Winkelman JZ. Uveitis associated with varicella virus vaccine. *Am J Ophthalmol* 127(6):733-734, 1999.
- Farthing CF, Howard RS, Thin RN. Papillitis and hepatitis B. *Br Med J* 292:1712, 1986.
- Fried M, Conen D, Conzelmann M, Steinemann E. Uveitis after hepatitis B vaccination. *Lancet* 12;2: 631-632, 1987.
- Islam SMM, El-Sheikh HF, Tabbara KF. Anterior uveitis following combined vaccination for measles mumps and rubella (MMR): a report of two cases. *Acta Ophthalmol Scand* 78: 590-592, 2000.
- Knopf HL. Recurrent uveitis after influenza vaccination. *Ann Ophthalmol* 23(6): 213-214, 1991.
- Lee SF, Butler R, Chansue E, et al. Vaccinia keratouveitis manifesting as a masquerade syndrome. *Am J Ophthalmol* 117: 480-487, 1994.
- London WT. Hepatitis B virus and antigen-antibody complex disease. *N Engl J Med* 26:1528-1529, 1977.
- Moret Ch, Meier P, Rotman S, Lepori M, Lamy O. Fever of unknown origin with granulomatous hepatitis, uveitis and acute renal failure. *Praxis* 12:94(1-2):25-30, 2005.
- Murray PI, Prasad J, Rahi AH. Status of hepatitis B virus in the aetiology of uveitis in Great Britain. *Br J Ophthalmol* 67(10):685-687, 1983.

### **National Registry**

- Fraunfelder FT. National Registry of Drug-Induced Ocular Side Effects: Monitoring for Drug Safety. W. H. Inman, ed. London, MTP Press;1985:363-369.
- Fraunfelder FW, Fraunfelder FT. Ocular side effects recently identified by the national registry of drug-induced ocular side effects. *Ophthalmology* 2004;111:1275-1279.
- Fraunfelder FW. Ocular adverse drug reactions and the National Registry of Drug-Induced Ocular Side Effects. *Insight* 2004;XXIX:7-11.