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# Ocular Adverse Effects Associated with Systemic Medications

## Recognition and Management

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## Abstract

This article reviews several retrospective case series and reported adverse events regarding common ocular adverse effects related to systemic therapy. It is not intended as a comprehensive summary of these well described adverse drug reactions, nor is it intended to cover the complete spectrum of all ocular adverse effects of systemic therapy. Many systemic drugs may produce ocular toxicity, including bisphosphonates, topiramate, vigabatrin, isotretinoin and other retinoids, amiodarone, ethambutol, chloroquine and hydroxychloroquine, tamoxifen, quetiapine, cyclo-oxygenase (COX)-2 inhibitors, erectile dysfunction agents and some herbal medications. For this review, the certainty of the adverse effect

profile of each medication was evaluated according to the WHO Causality Assessment Guide.

A certain relationship has been established for pamidronate and alendronate as causes of scleritis, uveitis, conjunctivitis and blurred vision. Topiramate has been established as adversely causing symptoms consistent with acute angle-closure glaucoma, typically bilateral. Vigabatrin has been shown to cause bilateral irreversible visual field defects attributed to underlying medication-induced retinal pathology. Isotretinoin should be considered in the differential diagnosis of any patient with pseudotumour cerebri. Patients taking amiodarone and hydroxychloroquine should be monitored and screened regularly for development of optic neuropathy and maculopathy, respectively. Sildenafil has been reported to cause several changes in visual perception and is a possible, not yet certain, cause of anterior ischaemic optic neuropathy. Patients taking tamoxifen should also be monitored for development of dose-dependent maculopathy and decreased colour vision. COX-2 inhibitors should be included in the differential diagnosis of reversible conjunctivitis. Several herbal medications including canthaxanthine, chamomile, datura, *Echinacea purpurea*, *Ginkgo biloba* and liquorice have also been associated with several ocular adverse effects.

It is the role of all healthcare professionals to detect, treat and educate the public about adverse reactions to medications as they are an important health problem.

The term 'side effect' usually refers to an undesired or negative effect of medication that is extraneous to the intended therapy. When the effect is negative, the term 'adverse effect' is used. Drug-induced ocular adverse effects are the second most frequent reason for claims against ophthalmologists.[1,2] This may not be surprising given that prescribing medications is the most common therapeutic service provided by physicians. According to the National Center for Health Statistics, new or continued medications are ordered or provided at 41% of visits to an ophthalmologist's office. Because serious injury can occur, drug-related adverse effects can be costly to defend, indemnify or settle.[2]

The rich blood supply and relatively small mass of the eye make it particularly susceptible to drug-induced adverse reactions. Adverse ocular reactions to drugs are diverse. Drug molecules present in the system may become selectively deposited in specific ocular tissues such as the cornea, lens and retina, causing varied symptoms of drug toxicity. Fortunately, most adverse reactions induced by systemic medications are reversible if detected early. However, if undetected, toxic effects may progress and cause irreversible ocular damage often with an associated reduction in visual function.[3,4]

For ophthalmic drugs to be effective, they must reach ocular tissue in relatively high concentrations. There are several different administration routes for ophthalmic drugs, including the topical, oral, parenteral, periocular, intracameral (intraocular administration into the anterior segment) and intravitreal routes. Topical application is the most common route of administration because it is simple, less invasive and does not involve the passage of drugs through the blood-aqueous barrier. However, some disorders require systemic drug administration to achieve adequate therapeutic levels of the drug in and around the ocular tissues.

Certain factors increase the probability of an adverse ocular reaction. One such factor is use of a medication over long periods of time, for example, in cases of arthritic and cardiovascular diseases. In some patients, it may be difficult to establish whether ocular pathology is caused by the condition being treated or by a drug used to treat the condition.

 

Patient age is also a significant factor in the prevalence of ocular drug reactions. Older patients are more likely to have used medications for protracted periods. Also, the metabolism and excretion of a drug can be affected by decreased efficiency of the kidney and liver secondary to the patient's age, or by conditions adversely affecting these organs.[3,4]

Some drug responses cannot be predicted from the drug's pharmacological mode of action. A genetic basis may underlie many of these unpredictable responses, as observed in the rapid rise in intraocular pressure reported with topical corticosteroids.[5]

The prevalence of adverse reactions is closely associated with drug dosage. Most reported ocular reactions occur when the dose is beyond the therapeutic range. It is essential that clinicians try to establish whether the ocular problem coincided with the start of drug therapy or with a change in drug dosage. A useful marker is seen when the onset of the reaction coincides with commencement of the medication, but reactions can occur at any time during or after a course of medication, and can continue for years after cessation.

We performed a MEDLINE literature search using the following keywords: 'ocular', 'visual', 'eye', 'side effects', 'adverse effects', 'medication' and 'treatment'. Some of the medication adverse effects obtained through this search are summarised below; these were selected at the authors' discretion, taking into account some of the more recent published medication adverse effects, and are not presented in any particular order. This brief review is not intended as a comprehensive summary of these well described adverse drug reactions, nor is it intended to cover the complete spectrum of all ocular adverse effects of systemic therapy. Interested readers are encouraged to refer to textbooks cited within the references.

## 1. Categorising Adverse Drug-Related Events

The WHO Causality Assessment Guide of Suspected Adverse Reactions was used to classify the reported adverse drug-related events into the following categories: certain, probable/likely, possible, unlikely, conditional/unclassified and unassessable/unclassifiable.[6] The 'certain' category includes plausible time relationship to drug administration

**Table I.** WHO definitions: causality assessment of suspected adverse reactions (reproduced from Brick,[2] with permission)

| |
|---|
| **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 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 laboratory test abnormality, with a reasonable time sequence to 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 laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear |
| **Unlikely** |
| A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations |
| **Conditional/Unclassified** |
| A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or 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 |

**Table II.** Classification of adverse ocular effects associated with medication usage

| Medication | Certain | Probable | Possible |
|---|---|---|---|
| Pamidronate | Blurred vision<br>Pain<br>Photophobia<br>Ocular irritation<br>Nonspecific conjunctivitis<br>Anterior uveitis (rare posterior)<br>Anterior scleritis (rare posterior)<br>Episcleritis | Periocular, lid, and/or orbital oedema | Diplopia<br>Visual hallucinations<br>Yellow vision<br>Retrobulbar neuritis<br>Cranial nerve palsy |
| Alendronate | Blurred vision<br>Pain<br>Conjunctivitis<br>Uveitis<br>Scleritis | Diplopia | Glaucoma |
| Risedronate | No effects | Conjunctivitis<br>Pain<br>Scleritis<br>Uveitis<br>Blurred vision | Diplopia<br>Papilloedema<br>Episcleritis |
| Etidronate | Blurred vision | Conjunctivitis | Diplopia |
| Topiramate | Acute glaucoma (mainly bilateral)<br>Anterior chamber shallowing<br>Increased ocular pressure<br>Mydriasis<br>Suprachoroidal effusions | Blepharospasm<br>Oculogyric crisis<br>Retinal bleeds<br>Uveitis | Scleritis<br>Teratogenic effects, including ocular malformations |
| Isotretinoin | Abnormal meibomian gland secretion<br>Blepharoconjunctivitis<br>Corneal opacities<br>Decreased dark adaptation<br>Decreased tolerance for contact lens wear<br>Decreased vision<br>Increased tear osmolarity<br>Keratitis<br>Meibomian gland atrophy<br>Myopia<br>Ocular sicca<br>Ocular discomfort<br>Photophobia<br>Pseudotumour cerebri<br>Teratogenic ocular abnormalities | Decreased colour vision<br>Permanent loss of dark adaptation | Corneal ulcers<br>Diplopia<br>Eyelid oedema<br>Optic neuritis<br>Idiopathic intracranial hypertension with optic disc oedema<br>Permanent sicca-like syndrome<br>Subconjunctival haemorrhage |
| Amiodarone | Aggravated sicca (drug in tears)<br>Blepharoconjunctivitis<br>Bright lights<br>Coloured haloes around lights<br>Corneal microdeposits<br>Glare<br>Hazy vision<br>Photosensitivity<br>Periocular skin pigmentation<br>Thyroid eye disease<br>Visual sensations | Anterior subcapsular lens opacities<br>Corneal ulceration<br>Loss of eyelashes or eyebrows<br>Non-arteritic ischaemic optic neuropathy<br>Pseudotumour cerebri | Autoimmune reaction (dry mouth, dry eyes, peripheral neuropathy and pneumonitis) |

*Continued next page*

**Table II.** Contd

| Medication | Certain | Probable | Possible |
|---|---|---|---|
| Sildenafil | Changes in colour perception<br>coloured tinge<br>decreased colour vision<br>dark colours appear darker<br>Blurred vision<br>central haze<br>transitory decreased vision<br>Changes in light perception<br>increased perception of brightness<br>flashing lights, especially when blinking<br>ERG changes<br>Conjunctival hyperaemia<br>Ocular pain<br>Photophobia | No effects | Mydriasis (emotional effect?)<br>Retinal vascular accidents (secondary to exertion?)<br>Subconjunctival haemorrhage<br>Anterior ischaemic optic neuropathy |
| Tamoxifen | Corneal opacities<br>Retinal opacities, degeneration, pigmentary changes, haemorrhage<br>Loss of visual acuity | No effects | No effects |
| COX-2 inhibitors | Conjunctivitis<br>Blurred vision | No effects | No effects |
| Nicotinic acid | No effects | Cystoid macular oedema | Decreased vision, dry eyes, discoloration of the eyelids, eyelid oedema,<br>Proptosis<br>Loss of eyebrows and eyelashes, and superficial punctate keratitis |
| Canthaxanthine | Crystalline retinopathy | No effects | No effects |
| Chamomile | Allergic conjunctivitis | No effects | No effects |
| Datura | Mydriasis | No effects | No effects |
| *Echinacea purpurea* | No effects | Conjunctivitis | No effects |
| *Ginkgo biloba* | No effects | No effects | Spontaneous hyphema<br>Retinal haemorrhage |
| Liquorice | No effects | No effects | Vasospasm, visual loss associated with migraine-like symptoms |
| Vitamin A | Intracranial hypertension (when taken in large doses) | No effects | No effects |

**COX** = cyclo-oxygenase; **ERG** = electroretinogram.

and inability to explain the adverse effect by concurrent disease or other drugs or chemicals. Dechallenge data are necessary and rechallenge should be positive. 'Probable' is the same as 'certain' without positive rechallenge data. 'Possible' is an adverse event in a reasonable time sequence to administration of the drug, but could also be explained by concurrent disease or other drugs or chemicals. Positive dechallenge data are lacking or unclear in this category (table I).

## 2. Medications and Adverse Effects

### 2.1 Bisphosphonates

Bisphosphonates inhibit bone resorption by binding to hydroxyapatite crystals and inhibiting their dissolution.[7] Different bisphosphonates vary greatly in their efficacy and their adverse-effect profiles depending on the structure of the individual drug. These medications are associated with ocular adverse effects that are mainly inflammatory, i.e. conjunctivitis, uveitis and episcleritis.[8,9] Recent studies

have proved that pamidronate can cause scleritis.[10,11]

Pamidronate disodium, an intravenous bisphosphate, has been reported to cause anterior uveitis and nonspecific conjunctivitis.[9-12] Its most striking association is that of being the first medication reported to cause scleritis.[10] Case reports have also associated pamidronate with episcleritis,[13] nerve palsy,[14] ptosis[14] and retrobulbar neuritis[15] (table II).

Pamidronate bears a 'certain' relationship to uveitis, conjunctivitis, episcleritis and scleritis when taken at standard doses between 30 and 90mg intravenously. The onset of ocular signs and symptoms was usually noted within 48 hours.

Alendronate is an oral bisphosphonate widely prescribed for the treatment and prevention of osteoporosis, in particular postmenopausal osteoporosis, and for the treatment of Paget's disease of the bone.[16] This bisphosphonate has been associated with a 'certain' relationship to blurred vision, ocular pain, conjunctivitis, uveitis and scleritis when taken in dosages ranging from 5 to 40mg daily (table II). Onset of ocular signs and symptoms was noted an average of 2 days to 2 weeks (range 1 day to 1 year) after starting therapy[11] (table II).

Risedronate is taken orally and is indicated in the treatment of Paget's disease of the bone.[16] The data are not sufficiently complete to classify any ocular adverse effect as 'certain'. However, there are positive rechallenge data on a single report of scleritis associated with this medication, which indicates there could be a cause and effect relationship.[10]

Etidronate is an oral medication indicated in the treatment of symptomatic Paget's disease, or for heterotopic ossification in hip replacement and spinal cord injury patients. This medication has been associated with conjunctivitis and blurred vision[11] (table II).

Clodronate is used in Europe and Canada for tumour-induced bone disease.[7] It has not been approved by the US FDA. This medication is also used by some to prolong survival in breast cancer patients. Although some studies indicate there are fewer metastases with clodronate therapy, there is no evidence of prolonged survival in patients taking clodronate.[17] Reports of clodronate-induced uveitis have a 'probable' association and blurred vision is classified as having a 'possible' association[18] (table II).

Pamidronate is the first medication ever reported to cause scleritis. Bisphosphonates are high molecular weight drugs that have been described as potentially causing immune complex formation and possibly being secreted by the lacrimal gland, thus causing transient irritation to mucus membranes.[3] Pamidronate stimulates the production of a distinct subgroup of T cells to inhibit bone resorption. As analogues of pyrophosphate, they can activate receptors in T cells leading to cytokine release.[18,19] This may contribute to an immunological reaction in patients who develop uveitis and/or scleritis. Some authors have contended that the nitrogen-containing bisphosphonates (alendronate, pamidronate, risedronate) are more likely to cause uveitis.[20-23] Nitrogen-containing bisphosphonates are known to cause transient pyrexia, a flu-like syndrome and serological changes resembling a typical acute phase response.[3,18,19] The cytokines released with this acute phase response could act as adjuvants in an immune reaction with the uvea of the eye as the target organ.

However, a non-nitrogen-containing bisphosphonate, clodronate, has also been reported as inducing uveitis.[18] Still, there are many more reports of uveitis associated with nitrogen-containing bisphosphonates than there are for the bisphosphonates that do not contain nitrogen (etidronate, clodronate, tiludronate).

In summary, bisphosphonates are associated with ocular inflammation. Ocular pain, photophobia, blurred vision, periorbital changes and glaucoma can be due to uveitis, scleritis and other types of ocular inflammation. Ocular inflammation, especially scleritis and uveitis, is of the greatest concern in the eye care of patients taking bisphosphonates. Scleritis causes a severe deep eye pain, and can lead to structural damage of the globe and loss of vision. Patients typically present with a piercing ocular pain that is worse at night and awakens them from sleep. The sclera assumes a violaceous hue in natural sunlight and scleral vessels become inflamed and can

have a crisscross pattern. Scleral oedema develops acutely and scleral thinning can occur, along with vision loss, if necrotising scleritis persists or inflammation is left unchecked. Ocular complications from scleritis can include keratitis, cataract, uveitis and glaucoma.[12,24]

In uveitis associated with bisphosphonate therapy, the early symptoms may be mild or severe, depending on which part of the uvea is affected and on the amount of inflammation. Anterior uveitis usually has the most dramatic symptoms, typically presenting with severe pain in the eye, redness of the conjunctiva, sensitivity to bright light and a decrease in vision. The examiner may see prominent blood vessels on the conjunctiva near the edge of the iris, white blood cells floating in the aqueous humour and deposits of white blood cells on the inside surface of the cornea. Intermediate uveitis is typically painless. Vision may be decreased and the patient may see floaters (irregular floating black spots). Posterior uveitis typically produces decreased vision with or without floaters. There may also be retinal detachment and inflammation of the optic nerve (symptoms include loss of vision, which may vary from a small blind spot to total blindness). Diffuse uveitis may produce any or all of these symptoms. Uveitis can rapidly damage the eye and can produce long-term, vision-threatening complications, such as swelling of the macula, glaucoma and cataracts. Those affected may have only one episode or periodic recurrences over months to years.

Suggestions for treatment of bisphosphonate-induced ocular adverse effects are as follows. If there is a persistent decrease in vision or if ocular pain occurs, examination by an ophthalmologist is necessary. Nonspecific conjunctivitis seldom requires treatment and usually decreases in intensity or may be absent on subsequent treatments. In rare instances, a nonsteroidal anti-inflammatory eye drop may be needed. More than one ocular adverse effect can occur at the same time, i.e. episcleritis with uveitis. Bilateral anterior uveitis or, rarely, posterior or bilateral uveitis may occur and can vary markedly in severity. Many patients require intensive topical ocular or systemic medication. In some instances, the drug may need to be discontinued for uveitis to resolve. Episcleritis may require topical ocular medication; however, the bisphosphonate may be continued. In all patients studied by Fraunfelder et al.,[11] the bisphosphonate had to be discontinued for the scleritis to resolve, even on full medical therapy.

## 2.2 Antiepileptic Drugs

### *2.2.1 Topiramate*

Topiramate, a sulfamate-substituted monosaccharide, is structurally unrelated to any other antiepileptic drug (AED). This AED is also used in the management of migraine, depression and neuropathic pain. Off label, it has gained popularity as a weight reduction agent, to treat migraine headaches and to treat bipolar disorder.

Topiramate has been associated with acute angle-closure glaucoma. Findings associated with topiramate-associated acute, bilateral, secondary angle-closure glaucoma syndrome include blurred vision, conjunctival hyperaemia, corneal oedema, shallow anterior chamber, cataracts, pupil changes, elevated intraocular pressure, visual field defects and blindness. Topiramate has also been associated with causing bilateral myopia, bilateral suprachoroidal effusions, blepharospasm, myokymia, nystagmus and diplopia. Scleritis has also been reported.[25]

Topiramate-associated visual adverse effects and their WHO classifications are listed in table II. The entity described as topiramate-associated acute, bilateral, secondary angle-closure glaucoma[26,27] can present in the same manner as an acute angle closure glaucoma attack. All the findings of acute glaucoma, such as ocular pain, headache, nausea and vomiting, pupillary changes, hyperaemia, corneal oedema, cataracts, retinal and vascular accidents, visual field defects and blindness have been reported.[25] In most patients, this is a bilateral process. If not recognised as a drug-related event, this condition can easily be confused with acute, pupillary block, narrow angle glaucoma for which a peripheral iridectomy is indicated. However, if the drug is stopped and medical management instituted, pressure may return to normal in hours to days without the need for an iridectomy. The acute pressure elevation usually occurs

within the first 2 weeks after starting topiramate therapy, but it has been reported within hours after doubling the dose. If pressure elevation goes untreated, serious outcomes are possible, including blindness.

Acute myopia up to 8.75 diopters may occur in a matter of hours after starting topiramate use, but may take weeks to fully resolve on or off medication. Sulfa-containing medications, such as topiramate, are known to cause transient myopia. Lenticular swelling, forward rotation of the lens-iris diaphragm, ciliary body swelling causing increased curvature of the lens surfaces, and spasm of accommodation have all been proposed as the mechanism behind this occurrence.[3,25,28-31]

The management of topiramate-related acute pressure elevation requires stopping the drug in consultation with the prescribing physician, since decreasing the dosage as little as 50mg may exacerbate pre-existing systemic conditions. Instituting maximal medical therapy, including oral and topical aqueous suppressants, is indicated. Laser iridotomy or peripheral iridectomy may not be beneficial if the glaucoma is only associated with topiramate therapy, but would be considered adequate in the setting of angle closure if one is not certain that it is completely medication-induced. Topical miotics are probably contraindicated, as these could precipitate a relative pupillary block that would exacerbate the condition.

#### 2.2.2 Vigabatrin and Tiagabine

Vigabatrin is a selective, enzyme-activated, irreversible GABA aminotransferase inhibitor.[32] It is a custom-made AED that is particularly useful in the management of drug-resistant partial seizures and infantile spasms, especially those secondary to tuberous sclerosis.[33-36] The antiepileptic effect is presumably mediated by elevation of GABA levels of the brain caused by inhibition of GABA metabolism.[36]

Initially, only relatively minor adverse effects were attributed to vigabatrin use.[37] It was first introduced into clinical practice in the UK on a trial basis in the mid 1980s and granted licence in 1989. The FDA has not approved its use in the US. Over the last decade, the marked efficacy of this medication and its low toxic effects prompted widespread use in Europe. The manufacturers of vigabatrin (Hoechst Marion Roussel) had received 28 reports of visual field abnormalities worldwide by January 1997 in an estimated 140 000 patients treated.[38] This information appears to have not been released during that time. Since 1997, numerous reports have appeared of visual field abnormalities in adults and children treated with this AED. In most documented cases, the visual field defect seems to be a specific, bilateral, symmetrical and irreversible peripheral constriction.[38-40] The fact that most patients are asymptomatic with normal visual acuity may have contributed to the late recognition of these visual field defects that apparently occur in more than 30% of patients but were initially estimated to affect fewer than 0.1%.[41-44]

The site of toxicity is proposed to be the retina, where GABA is an important modulatory neurotransmitter. Vigabatrin increases GABA levels by inhibiting the GABA transaminase enzyme. GABA is an inhibitory neurotransmitter in bipolar cells and some amacrine cells and may have a role in the modulation of phototransduction from the retinal photoreceptor cells to the ganglion cells.[45] Systemic vigabatrin has been shown to cross the blood-retinal barrier and can be detected immunocytochemically in the retina.[46] Vigabatrin causes white matter microvacuolation and intramyelinic oedema in the brains of rodents and dogs but not in monkeys and humans.[47] It also has been shown to cause accumulation of GABA in the retinal Muller cells.[48] How an increase in retinal GABA levels may produce visual field constriction is not clear, but the lower density of ganglion cells in the peripheral retina or a toxic effect on the retinal Muller cells has been suggested as being possibly related.[49] Thus far, the understanding of the role played by GABA in retinal transmission is not sufficient to allow for a mechanistic explanation of the adverse effects of vigabatrin.

There is no consensus regarding screening visual field examinations for patients taking vigabatrin.[49] The incidence, higher than previously estimated, of

this complication, particularly in asymptomatic patients, suggests that screening visual field examinations may be necessary. Daneshvar et al.[49] have recommended visual field examinations covering the peripheral 60° of the visual field for all patients taking vigabatrin, before or soon after starting treatment and at regular intervals thereafter. Any reproducible visual field constriction not present at the baseline examination may be associated with vigabatrin. The decisions on continuing treatment in these patients must be individualised based on a benefit-risk assessment.

Tiagabine has a mechanism of action that resembles that of vigabatrin. Thus, suspicions have been presented that tiagabine might produce similar changes in visual function to those associated with vigabatrin.[50] However, findings have not been replicated and several studies have found normal visual function in patients treated with tiagabine. Although no significant association with visual field changes or acuities has yet been found with tiagabine, cases of deteriorating colour vision have been reported.[51-53]

### 2.3 Isotretinoin and Other Retinoids

Retinoids are used to treat severe recalcitrant nodular acne, acne vulgaris and severe recalcitrant psoriasis, and to induce remission of leukaemia. Ocular adverse effects are dose related and probably the most frequent adverse reactions of these drugs. Isotretinoin-related ocular adverse effects are listed with their WHO classifications in table II.

The retinoid family includes vitamin A and synthetic derivatives such as isotretinoin, etretinate and retinoin. Isotretinoin, the most widely prescribed retinoid, has been associated with a 'certain' WHO classification for inducing intracranial hypertension (IH) due to positive rechallenge data, a characteristic pattern of rapid IH onset after exposure, and the fact that this agent is a degradative product of all-*trans* retinoic acid (tretinoin), a known contributor to IH.[54-60] Vitamin A has been well documented as a cause of IH, and other retinoids such as tretinoin can cause IH.[61-63] The incidence of IH in patients taking tretinoin has been quoted as 9%.[64] Tretinoin, acitretin and etretinate have been reported as having a 'probable' causal relationship to IH.[59]

The mechanism of how retinoids cause IH has been postulated as being through a common pathway.[61] It is possible that high doses of this class of drug induce a secretion of cerebrospinal fluid and alter the lipid constituents of the arachnoid villi. This may then disrupt the normal transport systems and impede the absorption of cerebrospinal fluid at the arachnoid villi.[64]

Isotretinoin has been shown to be secreted in tears by the lacrimal gland and has been associated with causing meibomian gland dysfunction and thus causing eye and contact lens discomfort, dry eye complaints, blepharoconjunctivitis, transient blurring of vision and acute transient refractive changes.[3]

For patients receiving retinoids, we suggest the following management guidelines. In patients on retinoid therapies who develop otherwise unexplained headaches or blurred vision, a prompt ophthalmology consultation to rule out papilloedema should be performed. Periodic ophthalmology examinations should also be completed to rule out papilloedema even in asymptomatic patients on retinoid therapy for 6 months or more because IH can develop without symptoms. Concomitant use of tetracyclines or vitamin A should be avoided, as they may potentiate the development of IH.[65,66]

### 2.4 Ethambutol and Isoniazid

Ethambutol is still considered a primary therapy against *Mycobacterium tuberculosis* and has synergistic actions when combined with other agents.[67] It can cause a multitude of dose- and time-dependent ocular adverse effects including colour vision changes, visual field defects and, of most importance, unilateral or bilateral optic neuritis which can continue to progress for 1–2 months after the drug is discontinued.[68] The Physicians' Desk Reference (PDR) discusses the possibility of optic neuropathy and attempts to provide guidelines for clinicians to screen for optic nerve toxicity.[16] However, it remains unclear what tests should be performed and how often. The literature describes a dose-related

incidence of ocular adverse 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 ≤15 mg/kg/day.[3]

Ethambutol optic neuropathy is usually bilateral and can be asymmetric. Ethambutol toxicity may affect only the small calibre papillomacular bundle axons, and optic atrophy will not develop until months after the fibres are lost. This means objective findings on the fundus exam are frequently absent. The literature suggests that optic neuropathy may occur, on average, 2–8 months after starting therapy. The earliest ophthalmological findings in toxic optic neuropathy from ethambutol may be loss of visual acuity, colour vision loss or central scotomas. Ethambutol also has an affinity for the optic chiasm with bitemporal visual field defects manifesting with toxicity.[3,69]

Isoniazid is frequently prescribed concurrently with ethambutol for tuberculosis owing to multiple cases of drug resistance to single-agent therapy. Isoniazid also has been associated with optic neuropathy, and differentiating toxicity due to ethambutol versus isoniazid can be challenging.[70,71] In general, the toxicity from isoniazid is less frequent, less severe and is usually reversible.[3] When in doubt, it may be necessary to undertake dechallenge with isoniazid and/or ethambutol after consultation with the primary care physician.

The pathophysiology underlying ethambutol optic neuropathy remains unclear. However, one possible explanation is that ethambutol chelates copper in the retinal ganglion cells and their fibres in the optic nerve. Ethylenediiminodibutyric acid, a metabolite of ethambutol, 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 also decreases the required energy for axonal transport around the optic nerve.[72,73] Thus, mitochondrial insufficiency in the optic nerve fibres may underlie the impairment of axonal transport in the optic nerve and lead to optic neuropathy.

The US PDR recommends monthly ophthalmic examinations for patients taking doses of ethambutol >15 mg/kg/day.[16] No official standard of care exists regarding how often to see patients and which tests to perform for those taking >15 mg/kg/day. Outside the US, especially in some developing countries, monthly exams are not practical and would create a large burden for eye care providers. Because of medicolegal concerns, ophthalmologists in the US should use the PDR as a guideline, as the package insert published in the PDR was agreed upon by the FDA and industry alike.

The authors of this article recommend obtaining 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 vision loss can be severe and irreversible. A baseline examination should be performed including visual acuity, visual field and colour vision testing, and a dilated fundus and optic nerve exam. If any visual symptoms occur, the medication should be discontinued and the patient seen by an ophthalmologist. Frequency of examinations should be monthly for dosages >15 mg/kg/day (PDR); however, monthly exams at lower doses may be necessary for patients at increased risk for toxicity, such as those with diabetes mellitus, chronic renal failure or alcoholism, and for the elderly, children and those with other ocular pathologies or ethambutol-induced peripheral neuropathy. Discontinuation of ethambutol should be considered after any signs of loss of visual acuity or colour vision or for a visual field defect. Optical coherence tomography or contrast sensitivity testing should also be considered in these patients, as these tests could pick up early ethambutol toxicity not detected with the baseline exam.

### 2.5 Amiodarone

Amiodarone is a well known benzofuran derivative that is used in the treatment of various cardiac arrhythmias. Its half-life ranges from 26 to 160 days.[3] Ocular adverse effects produced by this drug

are common and are time- and dose-dependent. Because of this, ophthalmic examinations should be conducted for a baseline and every 6–12 months, or more frequently depending on findings. The cornea is the most commonly affected ocular structure, with superficial punctuate opacities occurring in 69–100% of patients receiving amiodarone. There is often a loss of eyelashes or eyebrows along with eyelid and periocular tissue photosensitivity. Furthermore, the conjunctiva may develop yellow-brown deposits. Lenticular changes can include anterior, subcapsular, small, yellow-white punctuate opacities and cortical changes.[3] One of the most severe adverse effects of amiodarone use is optic neuropathy.

Amiodarone-associated optic neuropathy has been reported to have an incidence of 1.79%.[74] The expected incidence of nonarteritic ischaemic optic neuropathy in the general population aged ≥50 years is 0.3%.[74]

Macaluso et al.[75] characterised amiodarone-associated optic neuropathy as having an insidious onset, slow progression, bilateral visual loss and protracted disc swelling that stabilised within months of discontinuing the medication. Because patients taking amiodarone often have severe vascular disease, the incidence of nonarteritic anterior ischaemic optic neuropathy (NAION) in these patients is probably higher than that of the age-matched population. At present there are no reported cases of amiodarone neuropathy causing vision of no light perception. Macaluso and colleagues proposed that the insidious onset, bilateral pathology, less severe visual loss (20/20 to 20/200 in amiodarone-induced versus 20/20 to no light perception in NAION) and slower improvement of optic disc oedema of amiodarone-induced optic neuropathy compared with that of acute NAION helps the ophthalmologist in differentiating these two causes of decreased vision associated with optic disc oedema. The WHO classification of other established visual adverse effects related to this medication are listed in table II.

The cause of amiodarone-induced optic neuropathy is unknown, but this condition may be due to a drug-induced lipid storage disease (primary lipidosis) in optic nerve axons.[76] There is a selective accumulation of intracytoplasmic lamellar inclusions in large optic nerve axons, and this may decrease axoplasmic flow biochemically or mechanically. Many of these patients may already have a compromised optic nerve secondary to vascular disease, and the amiodarone deposition in the axons further impedes neural function, causing vision loss. The result is optic nerve head oedema, which can persist as long as transport is compromised. Resultant optic nerve head oedema may persist as long as transport is inhibited, i.e. as long as several months following discontinuation of amiodarone, which, as noted earlier in this section, has a half-life of up to 160 days.

Since it may be impossible to distinguish NAION from amiodarone-induced optic neuropathy in many patients, those who experience any visual disturbance should see an ophthalmologist promptly. Patients should have a baseline ophthalmic exam and may be seen every 6 months for monitoring, although this is controversial. If optic neuropathy is suspected, discontinuation of the drug in consultation with the patient's cardiologist at the first signs of optic nerve involvement must be considered unless the ophthalmologist is very confident of the diagnosis of NAION.

### 2.6 Hydroxychloroquine

This aminoquinoline is used in the treatment of malaria and extraintestinal amoebiasis. Hydroxychloroquine is also used for the treatment of rheumatoid arthritis and lupus erythematosus, dermatological conditions and various inflammatory disorders.

Ocular adverse effects can be numerous, including an enhanced Hudson-Stahli line, whorl-like corneal depositions (cornea verticillata), transient oedema, decreased sensitivity, retina parafoveal granularity of the retinal pigment epithelium (early in the disease), bull's-eye appearance of the macula (late in the disease), attenuation of the vascular tree, peripheral fine granular pigmentary changes, prominent choroidal pattern filling defects in late phase of

fluorescein angiography, and other angiography changes.[3]

Though the side effects of hydroxychloroquine are numerous, the most adverse are mainly dose-related, seen today usually in overdose situations, obese patients or extremely thin individuals. The most serious of these effects is a form of retinal toxicity known as hydroxychloroquine bull's-eye maculopathy. This name stems from the characteristic ring-like or bull's-eye pattern of retinal pigment epithelium atrophy and hyperfluorescence on fluorescein angiography. The mechanism of this toxicity is not well understood but it seems to be related to the affinity for this medication for melanin within the retinal pigment epithelium. Patients may have abnormal sensory testing responses and distorted colour vision (late phase of disorder) with a yellow, green or blue tinge to objects and coloured haloes around lights. This maculopathy is bilateral and reproducible by Amsler grid and visual field testing.

Corneal deposits are also a characteristic finding in patients taking this medication. Vortex keratopathy or cornea verticillata is not specific to hydroxychloroquine but a finding of several 'amphophilic' drugs that can form complexes with cellular phospholipids, which cannot be metabolised by lysosomal phospholipases and, thus, are visible clinically as deposits in the superficial cornea.[3] This medication also has been found to be excreted in the tear film and can aggravate dry eye along with possibly decreasing contact lens tolerance.

For patients taking antimalarial drugs, the American Academy of Ophthalmology (2002) recommends baseline dilated fundus exams and testing the central visual field by Amsler grid or a central 10-degree radius visual field using automated field testing (Humphrey 10-2 or similar).[77] Ideally, these tests should be done before starting the antimalarial mediations (or at the latest within 1 year after starting the medications). Low-risk patients are considered to be those taking <6.5 mg/kg/day for less than 5 years. These patients should have a follow-up examination every 5 years. Higher-risk patients, such as those taking >6.5 mg/kg/day for more than 5 years, should be examined more frequently. Risk factors such as being aged >60 years and having a high body fat level, concomitant kidney or liver disease, and/or concomitant retinal disease also justify more frequent examinations.[19] A recent preliminary paper by Shroyer et al.[78] suggests that individuals with an ABCR mutation (Stargadt's disease) may also be predisposed to develop retinal toxicity when exposed to chloroquine/hydroxychloroquine.

The goal of these recommendations is to find early changes, i.e. relative scotomas, and is aimed at detection and not prevention, as discontinuation of the drug is the only way to prevent possible adverse effects and this is not an option for some patients. Early paracentral relative scotomas seldom advance when the drug is discontinued. Later findings include retinal changes, colour vision loss, absolute scotoma or decreased vision. Even if the drug is stopped, once these occur, changes are irreversible, and many patients may continue to lose some vision and/or peripheral fields.

How to best follow patients on hydroxychloroquine was summarised in an article by Marmor et al.[77] These recommendations, although not universally adopted, follow the overall guidelines of the American Academy of Ophthalmology for examining patients. Patients aged 20–29 years should have one examination; 30–39, two examinations; 40–64, an examination every 2–4 years; and those ≥65 an examination every 1–2 years.

To summarise these recommendations, the baseline examination should be performed within the first year after starting this drug. Patients should have a complete, dilated ophthalmic examination, including the informed consent mentioned earlier in this section, warning of possible permanent visual problems in rare instances. This baseline examination should include visual acuity testing, Amsler grid testing (with instructions for monthly home use), and optional colour vision testing (preferably including the blue-yellow axis, such as the pseudoisochromatic plates for colour [American Optical Corporation]). If macular abnormalities are evident, it would be ideal to obtain fundus photographs. If any progressive ocular abnormality is suspected, a baseline Humphrey 10-2 visual field or other auto-

mated perimetry concentrated on the central visual field should be considered. Multifocal electroretinogram (ERG) is optional.

Additional complete follow-up examinations may be done at 2- to 4-year intervals, in patients younger than 40 years who are not deemed high risk. High-risk patients are those who are obese, extremely thin, frail, elderly or have significant renal or hepatic disease or macular disease of any type. Patients should be seen sooner if they experience any persistent visual symptoms, if they do not meet the above criteria, or if their dosage exceeds 6.5 mg/kg.

For patients aged 40–64 years, follow-up every 2–4 years is adequate as long as the above high-risk criteria are not met. Patients aged ≥64 years should be followed more closely, with follow-up every 1–2 years. Annual eye examinations should be considered if patients have been on hydroxychloroquine therapy for longer than 5 years. Annual examinations are also appropriate for patients considered high risk or whose dosage exceeds 6.5 mg/kg. Follow-up exams should include repeat baseline examination and fundus photography if any macular abnormalities are noted. Fluorescein angiography should be considered in the presence of suspicious pigmentary changes. Automated central visual fields are optional. Multifocal ERG is helpful in selected patients.

Patients taking chloroquine should undergo the same tests mentioned above for baseline and follow-up exams, as described above. Patients should be seen at least annually if dosage is <3.0 mg/kg of ideal bodyweight or every 6 months if dosage is >3.0 mg/kg bodyweight. Patients who are short, obese or have renal and/or liver impairment should also be seen every 6 months.

### 2.7 Erectile Dysfunction Agents

Sildenafil, vardenafil and longer-acting tadalafil are selective inhibitors of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5). In the treatment of erectile dysfunction, inhibition of PDE5, which is responsible for the degradation of cGMP in the corpus cavernosum, leads to increasing levels of cGMP, which causes smooth muscles in the corpus cavernosum to relax, allowing blood inflow. This medication is known to cause changes in colour perception as well as blurred vision. These agents may cause changes in light perception, increased perception of brightness and/or a sensation of seeing flashing lights, especially when blinking.[79] Sildenafil has also been shown to cause ERG changes. Ocular adverse effects are uncommon, dosage dependent and thus far have all been fully reversible. The WHO classification for these medications is listed in table II.

These ocular adverse effects are dose dependent with all three drugs. The incidence with sildenafil use has been quoted to be 3% in those taking 50mg, 10% with 100mg and 40–50% in those taking 200mg.[80,81] The incidence is the same for all ages, and the incidence and severity of reported ocular adverse effects is directly proportional to blood drug concentrations. The adverse effects based on dosage start 15–30 minutes after ingestion of the drug and usually peak 60 minutes after ingestion.[81]

Sildenafil can be used safely in patients with glaucoma and macular degeneration. Postmarketing surveillance of sildenafil, vardenafil and tadalafil has produced several reports associating these medications as possible culprits for anterior ischaemic optic neuropathy in several patients. So far there are no data which confirm a ‘certain’ relationship between ischaemic optic neuropathy and erectile dysfunction medications. Present evidence from postmarketing surveillance suggests visual adverse effects, due to this class of medication, are benign and transitory. From these 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.[79]

We feel that the only patients who should not take PDE5 inhibitors are those who have previously experienced NAION in one eye. 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.

### 2.8 Tamoxifen

Tamoxifen is an antiestrogen agent primarily used in the treatment of estrogen-receptor positive breast cancer, ovarian cancer, pancreatic cancer and malignant melanoma. The standard dosage is ≤20 mg/day and the ocular adverse event incidence levels are about 1–2%. Dose-dependent ocular adverse effects include corneal opacities (whorl-like subepithelial calcium map-dot changes), and retinal or macular yellow or white refractile opacities, oedema, degeneration, pigmentary changes and haemorrhages.[3]

Tamoxifen retinopathy most commonly occurs after more than 1 year of therapy when a total of >100g of the drug has been taken. The retinopathy can include cystoid macular oedema, punctuate macular retinal pigment epithelial changes, parafoveal haemorrhages and peripheral retinal pigment epithelium changes. Refractile bodies located in the inner retina histologically may be the products of axonal degeneration. Visual acuity loss and the retinal lesions do not appear to regress in chronic form of tamoxifen toxicity if the drug is discontinued unless cystoid macular oedema or haemorrhages are the cause of vision loss.

An acute form of toxicity has been described but is not well defined and usually occurs within a few weeks after therapy is instituted. Symptoms include vision loss, retinal oedema, retinal haemorrhage and optic disc swelling. This was thought to result from tamoxifen estrogenic activity, which may cause venous thromboembolism. However, Gorin et al.[82,83] confirmed the risk of tamoxifen in the development of posterior subcapsular cataracts, but found minimal effects of this drug on retinal small vessel occlusive disease, with no more a risk factor than hypertension or glaucoma.

We offer the following recommended guidelines. Baseline ophthalmic examination within the first year of starting tamoxifen, which should include slit lamp biomicroscopy of the anterior and posterior segments in combination with a handheld indirect or contact lens should be performed. Baseline colour vision testing is important. In keeping with the American Academy of Ophthalmology's current recommendations, in healthy adults, a complete eye examination at least every 2 years should be completed. More frequent examinations should be carried out if ocular symptoms occur. The discovery of a limited number of intraretinal crystals in the absence of macular oedema or visual impairment does not seem to warrant discontinuation of the drug. Consultation with the oncologist is essential if significant ocular findings occur. Presence of age-related maculopathy is not a contraindication to the use of tamoxifen. However, informed consent may be advisable in our litigious society. Presence of posterior subcapsular cataracts is not an indication to stop the drug, since the condition usually progresses even if the drug is discontinued. Significant colour loss may be a valid reason to consider discontinuing the drug. Gorin et al. recommend considering discontinuing the drug for 3 months (in patients on prophylactic therapy) and retesting.[82,83] If colour vision returns to normal, then restart the drug and retest in 3 months. If, at any time, there is no rebound from stopping the drug, or continued progression, then it may be necessary to consult an oncologist and reevaluate the benefit-risk.

### 2.9 Cyclo-Oxygenase-2 Inhibitors

Cyclo-oxygenase (COX)-2 inhibitors are indicated in the treatment of osteoarthritis, rheumatoid arthritis, acute pain and dysmenorrhoea through selective blockade of COS-2 receptors. The anti-inflammatory activity appears to be effective with fewer gastrointestinal adverse effects than older NSAIDs.

Selective COX-2 inhibitors include rofecoxib, celecoxib, valdecoxib, lumiracoxib, nimesulide and etodolac. With these medications, blurred vision and conjunctivitis appear to be identified most frequently as adverse effects associated with COX-2 inhibitors, especially for rofecoxib and celecoxib, the two most widely prescribed medications in this class[84] (table II).

Coulter et al.[85] propose a possible mechanism behind the blurred vision some patients experience when receiving COX-2 inhibitors. Inhibition of synthesis of prostaglandins and other related compounds that control retinal blood flow could lead to visual changes. The vascular endothelium of retinal blood vessels produces compounds such as prostacyclin, thromboxane $A_2$ and prostaglandin $H_2$. Both COX-1 and COX-2 mediate synthesis of prostacyclin. Inhibition of either COX-1 or COX-2 may alter the COX pathway and in turn alter regulation of retinal blood flow with potential changes in vision.[86] Other NSAIDs have been reported to cause blurred vision consistent with this theory.[87,88]

In the case of selective COX-2 inhibitors, another mechanism may contribute to the blurred vision some patients experience. Four of the six COX-2 inhibitors are sulfonamides: celecoxib, rofecoxib, valdecoxib and nimesulide. Sulfonamide medications are known to cause blurred vision through what is thought to be transient myopia. The mechanism is not fully understood but could include lenticular swelling, forward rotation of the lens-iris diaphragm, ciliary body swelling causing increased curvature of the lens surfaces, and spasm of accommodation.[25,87-89] The sulfonamide property of these COX-2 inhibitors could contribute to some cases of blurred vision. Curiously, the two non-sulfur-containing selective COX-2 inhibitors do not have the bulk of data to support a 'certain' association with blurred vision including a paucity of positive rechallenge reports.

Conjunctivitis also has a 'certain' association with some COX-2 inhibitors. This may not be unusual, as many medications are secreted in the tears. It is possible these medications are secreted in the tears as well, leading to transient inflammation of the conjunctiva which resolves upon discontinuation of the drug. Many examples of this exist, such as irritative conjunctivitis from oral diazepam or oral isotretinoin.[3,55,90]

Discontinuation of therapy leads to resolution without long-term sequelae. In every instance studied, the ocular adverse effect resolved within 72 hours of discontinuation of COX-2 inhibitor.

### 2.10 Nicotinic Acid

Nicotinic acid (niacin) taken orally has been proven in the treatment of cardiovascular and cerebrovascular disease because of its cholesterol- and triglyceride-lowering effects.[91-93] A comprehensive review of ocular adverse effects from nicotinic acid indicates a possible association with decreased vision, cystoid macular oedema, dry eyes, discoloration of the eyelids, eyelid oedema, proptosis, loss of eyebrows and eyelashes, and superficial punctate keratitis.[91] The most serious of these is cystoid macular oedema (CME). CME occurs primarily in patients receiving 3 g/day, although it has been seen in patients taking as little as 1.5 g/day. A characteristic, but not pathognomonic, petalloid hyperfluorescence without leakage is revealed by fluorescein angiography. The mechanism behind CME is unknown but the condition usually resolves within 2 weeks after stopping treatment with nicotinic acid. A possible aetiology could be a prostaglandin-induced toxic response on the Muller cells or intracellular accumulation of fluid secondary to some as yet undocumented derangement of intracellular metabolism.[93,94]

### 2.11 Herbal Medications

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 in the US. No efficacy or safety has to be proven to sell these agents, of which there are 700 botanicals and 1000 nutritional products.[16,95]

These products are of clinical importance to ophthalmologists, since many of the therapies can cause adverse effects and some interfere with prescribed medications. Approximately 40% of patients who use alternative therapies do not disclose this information to their doctor.[96]

Canthaxanthine, chamomile, datura, *Echinacea purpurea*, *Ginkgo biloba*, liquorice (licorice) and vitamin A are all associated with clinically significant ocular adverse effects[94,97] (table II).

#### 2.11.1 Canthaxanthine

This agent is used in cosmetics, as a food colouring and to produce an artificial suntan when administered orally. It is naturally occurring and is found in crustaceans and chanterelle mushrooms. When taken orally, canthaxanthine can deposit in all layers of the retina, especially the superficial layers of the macula. Clinically, the retinal findings are slowly reversible and patients are usually asymptomatic, but visual changes may be seen in static threshold perimetry, electroretinography and changes in dark adaptation.[16,98]

#### 2.11.2 Chamomile

Chamomile (*Matricaria chamomilla*) is used usually in the form of tea to treat eye disease as well as insomnia, indigestion, migraine headaches, bronchitis, fevers, colds, inflammation and burns.[95,99] There is strong evidence that this tea, when applied topically in or around the eye, can cause severe conjunctivitis. A possible mechanism for these patients' conjunctivitis could be sensitivity to the allergens present in *M. chamomilla* pollen. Because patients are using chamomile to treat their eyes, clinicians should recognise the possibility of *M. chamomilla* sensitivity in patients with what appears to be allergic conjunctivitis, especially in patients who already have an atopic history.[94]

#### 2.11.3 Datura

The dried leaves of datura are used to treat eye inflammation as well as asthma, bronchitis, influenza and coughs. The leaves contain alkaloids, in extremely varying concentrations, which are anticholinergic and parasympatholytic. Jimson weed (*Datura stramonium*) is the main member of this genus utilised for its potential therapeutic value. These botanicals have been shown to contain scopolamine and have been associated with pupillary dilation.[94]

#### 2.11.4 *Echinacea purpurea*

Echinacea is a herbal product used to treat the common cold, cough, fevers, urinary tract infections, burns and influenza.[94,100] An allergic conjunctivitis has been associated with this product. The mechanism may be due to an anaphylactic reaction.[101] There is evidence that echinacea may activate the body's autoimmune response, and the PDR suggests that its use be avoided in patients with autoimmune diseases.[16]

#### 2.11.5 *Ginkgo biloba*

*Ginkgo biloba* has been shown to act as a blood thinner and increase bleeding times.[101] Spontaneous hyphaema and retinal haemorrhages have occurred in patients taking this agent. Thus, ginkgo should be used with caution in patients who are also taking warfarin or aspirin, as the effects are additive.

#### 2.11.6 Liquorice

Liquorice (*Glycyrrhiza glabra*) root derives some of its medicinal properties from the isoflavonoid glabridin. Glabridin inhibits COX activity, and has both anti-inflammatory and antiplatelet effects. It may help patients with gastric ulcers and peptic ulcers. Ocular migraine-like visual symptoms have been reported that occur without a headache.[94] The authors of this article postulate that vasospasm of the brain, retinal and/or optic nerve blood vessels plays a role in these visual symptoms, as there is strong evidence that liquorice, through its glucocorticoid and noradrenaline effects, can cause vasospasm throughout the body.[102] Clinically, it appears that individuals need to consume large amounts of liquorice for ocular adverse effects to occur. However, caution is advised if a patient has a history of migraine headaches, as the effects could be additive.

#### 2.11.7 Vitamin A (Retinol)

Vitamin A is used primarily as an oral dietary supplement and in the treatment of vitamin A deficiency and acne. Vitamin A plays a vital role in vision and is an essential fat-soluble vitamin for many biological activities. Vitamin A deficiency can result in night blindness, xerosis of the conjunctiva and cornea, and alopecia of the eyelashes.[94] There is strong evidence that retinoids, particularly if taken in excess, can cause IH.[54,55] Physicians should be aware that large doses of vitamin A can cause IH and special caution should be exercised with patients who are taking vitamin A in addition to another type of retinoid, such as isotretinoin, as the effects could be additive in the causation of IH. This

condition resolves in the majority of patients when vitamin A is discontinued.

#### *2.11.8 Summary*

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

## 3. Conclusion

Adverse reactions to medications are an important health problem and it is the role of healthcare professionals to detect, treat and educate the public about them. Many systemic drugs may produce ocular toxicity.

Any drug in any form may cause an adverse ocular reaction if it reaches the eye. Fortunately, most ocular changes induced by drugs are reversible if detected in the early stages of toxicity, although if they are not detected early, some adverse reactions may progress to cause serious and irreversible ocular damage associated with significant loss of visual performance.

Diagnosing drug reactions requires a high index of suspicion and careful review of the patient's history, including recent use of a drug. Withdrawal of the suspected drug should result in improvement (dechallenge), and reinstitution of the drug (rechallenge) should exacerbate the patient's condition. Knowledge of drugs with potential to produce adverse ocular reactions should be updated as knowledge of these adverse outcomes arises.

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