REVIEW ARTICLE

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Drug-Induced Ocular Disorders

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Abstract

While beneficial therapeutically, almost all medications have untoward effects on various body tissues and functions, including the eye in which organ toxic reactions are readily detectable. Every part of the eye and all ocular functions could be affected adversely. In this review, we describe the most commonly recognized drug-induced ocular disorders, their specific clinical features, the

medications that can cause the problem, the differential diagnosis and possible mechanisms of action, as well as guidelines for the management of the adverse reactions.

The eyelids are most frequently involved in drug toxicity that commonly manifests as inflammation, hypersensitivity reaction or dermatitis. Drug-induced keratoconjunctival disorders present mainly as conjunctival hyperaemia (red eye), with or without superficial corneal involvement. Frequently, drug preservatives in topical ocular medications induce these adverse effects. Treatment of blepharospasm with Botox® may lead to drooping of the eyelids and corneal exposure. Intraoperative floppy iris syndrome is a drug-induced reaction in patients treated with tamsulosin and who undergo cataract surgery. Certain sulfa-based drugs can cause swelling of the ciliary body and lead to the development of angle-closure glaucoma. In addition, adrenergic agents, certain β_2-adrenergic agonists and anticholinergic agents may induce pupillary dilation and precipitate angle-closure glaucoma in susceptible patients. Glucocorticoids administered systemically, topically or intravitreally are known to increase intraocular pressure, which can lead to the development of open-angle glaucoma in susceptible patients. This painless form of glaucoma has also been associated with the use of the anticancer agents docetaxel and paclitaxel. The toxic effects of systemic and topically applied drugs may manifest as cloudiness of the lens. Long-term use of glucocorticoids produces a characteristic posterior subcapsular cataract and, although the opacities may remain stationary or progress, they rarely regress upon drug withdrawal. Systemic administration of phenothiazines or busulfan induce cataractous changes in the anterior or posterior cortex, respectively. Many systemic drugs reach the retina through the vascular supply. Aminoquinolines induce a characteristic bull's eye maculopathy. Phenothiazines bind to melanin granules and can cause a severe phototoxic retinopathy. Typical tamoxifen retinopathy manifests as crytalline deposits in the inner retina. Some patients treated with retinoids have decreased night vision and abnormal dark-adaptation. Patients on long-term treatment with linezolid may develop an optic neuropathy (swollen or pale optic disc), symmetric painless decrease of visual acuity and colour vision, and bilateral visual field defects. A probable link exists between amiodarone and a bilateral optic neuropathy that is very similar to nonarteritic ischaemic optic neuropathy (NAION). The most common adverse effects of cGMP-specific phosphodiesterase type 5 inhibitors (erectile dysfunction drugs) are changes in colour perception, blurry vision and increased light sensitivity; recently these drugs have been also implicated in the development of NAION. A bilateral, retrobulbar optic neuropathy that manifests as loss of visual acuity or colour vision and visual field defect is associated with the use of ethambutol. Many different kinds of medications can cause similar ocular adverse reactions. Conversely, a single medication may affect more than one ocular structure and cause multiple, clinically recognizable disorders. Clinicians should be mindful of drug-induced ocular disorders, whether or not listed in product package inserts and, if in doubt, consult with an ophthalmologist.

Although therapeutically beneficial, most medications can cause various degrees of adverse effects. Among all body organs, it is aptly stated that the eye manifests drug toxicity second only to the liver. The eye (figure 1) is considered as a microcosm of different tissues in the body; by using various optical devices, most of the structures can be examined *in vivo* directly at high magnification, thus providing a unique opportunity for clinicians to diagnose and manage manifestations of drug-induced adverse effects.

Ocular disorders occur not only from topical/local application of drugs, but also from their systemic administration. There are thousands of prescription and non-prescription drugs that can cause ocular drug toxicity.[2,3] Not being an exhaustive review of the literature, this paper is not intended to describe all the ocular adverse effects of various medications. However, we have included the classic medications that can cause ocular toxicities with significant visual consequences as well as recently discovered ocular adverse effects from drugs such as tamsulosin and linezolid. We cite specific examples of drugs that produce one or more disorders of the adnexa, keratoconjunctiva, intraocular pressure (glaucoma), lens (cataract) and uveal tract as well as vitreoretinopathies and optic neuropathy.

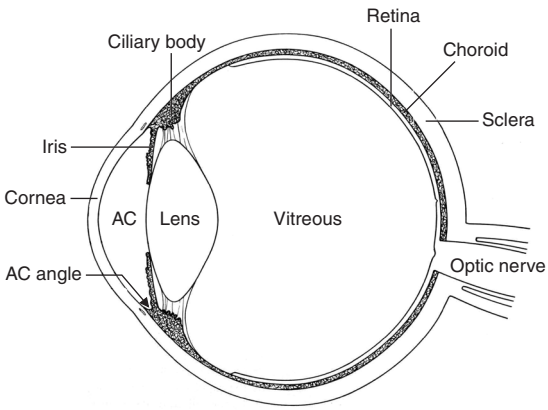

Fig. 1. Diagrammatic representation of the human eye and its main structural components. **AC** = anterior chamber. (This figure was published in Tripathi RC, Tripathi BJ.[1] The eye. In: Riddell R, editor. Pathology of drug-induced and toxic diseases. New York (NY): Churchill Livingstone, 1982: 377-456. Copyright Elsevier). Reproduced with permission.

This review is based in part on papers published in peer-reviewed, ophthalmic and non-ophthalmic scientific journals indexed by the MEDLINE database, drug product inserts, the 60th edition of the *Physicians' Desk Reference*[2] and the 2nd edition of the *Physicians' Desk Reference for Non-Prescription Drugs*.[3] Searches included various combinations of terms such as 'eye', 'eyelid', 'conjunctiva', 'cornea', 'anterior chamber', 'glaucoma', 'uvea', 'iris', 'ciliary body', 'choroid', 'lens', 'vitreous', 'retina macula', 'optic nerve', 'toxicity', 'pathology', 'physiopathology' and 'human'. Selected articles in *Drug-Induced Ocular Side Effects*[4] were also searched. Citations were included at the authors' discretion. The last literature search was conducted in June 2007.

1. Drug-Induced Eyelid and Keratoconjunctival Disorders

The eyelids (figure 2) are composed of skin (the thinnest in the body), specialized dermal appendages, muscles, fibrous tissue and mucous membrane of the conjunctiva.[5] The lids are among the eye structures that are most frequently involved in drug toxicity and related injuries.[1] Inflammation of the eyelid is synonymous with dermatitis or eczema. Erythema multiforme is an acute, self-limiting dermatosis with the multiform lesions of macules, papules and bullae. These hypersensitivity reactions may involve skin only (erythema multiforme minor) or, in its most severe form that starts suddenly with high fever and prostration, as a predominantly bullous eruption of the skin and mucous membranes (erythema multiforme major or Stevens-Johnson syndrome). The list of medications that can cause erythema multiforme is long and includes paracetamol (acetaminophen), amiodarone, allopurinol, ampicillin, captopril, cefazolin, clindamycin, doxycycline, isoniazid, phenobarbital, penicillin, sulfadiazine, sulfonamides and vancomycin.[4]

The primary ocular presentation in Stevens-Johnson syndrome may occur as a mucopurulent conjunctivitis or pseudomembrane formation. Late complications result from cicatrization that leads to conjunctival shrinkage, trichiasis (misdirection of

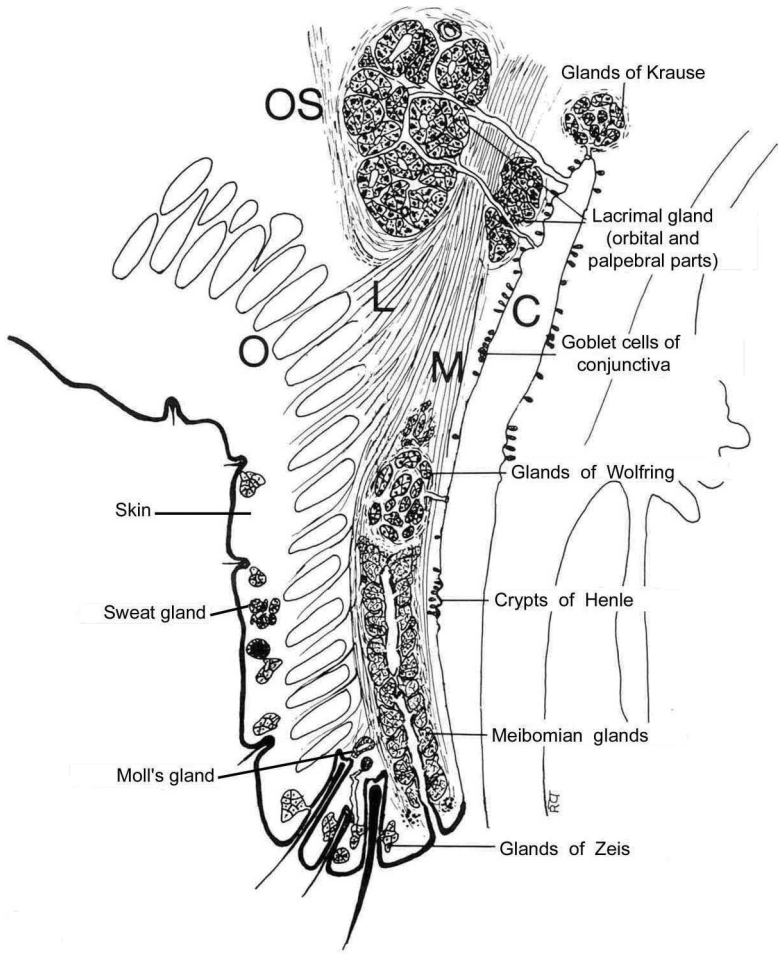

Fig. 2. Diagrammatic representation of main components of human upper eyelid in a vertical cross-section. **C** = conjunctival cul-de-sac; **L** = levator muscle; **M** = smooth muscle of Müller; **O** = orbicularis oculi muscle; **OS** = orbital septum. (This figure was published in Tripathi RC, Tripathi BJ.[1] The eye. In: Riddell R, editor. Pathology of drug-induced and toxic diseases. New York (NY): Churchill Livingstone, 1982: 377-456. Copyright Elsevier). Reproduced with permission.

eyelashes) and mucin tear deficiency (dry eye). Treatment is discontinuation of the offending medication and supportive therapy that includes oral corticosteroids, artificial tears and ointments to provide lubrication of the ocular surface and antibacterials to prevent ocular infection. Late eyelid sequelae can be corrected surgically when the disease is quiescent.

Many drugs used topically and systemically can cause keratoconjunctival disorders that manifest mainly as conjunctival hyperaemia (red eye) with or without superficial corneal epithelialopathy. Drug preservatives, especially benzalkonium chloride and thiomersal, also contribute to the development of these adverse effects.[6,7] Benzalkonium chloride causes cytotoxicity by inducing P2X7 cell death receptor activation that is associated with oxidative stress and apoptosis.[8] Keratoconjunctival disorders can be transient but prolonged use of the drug, especially for the treatment of dry eye or glaucoma, may induce varying degrees of lid puffiness, dry eye syndrome, as well as papillary eruptions or follicular

formations in the bulbar/palbepral conjunctiva (figure 3 and figure 4). Frequently, patients complain of a gritty or burning sensation and have a watery discharge. Vascular and tissue liberation of biogenic amines are often the cause of these tissue reactions. Usually the signs and symptoms subside on withdrawal of the stimulus and/or with the use of antagonist and/or blocking agents. A new formulation of antiglaucoma medication (travoprost without benzalkonium chloride) has been shown to be equivalent in efficacy and safety to the original formulation[9] and may prove to be of benefit in reducing benzalkonium chloride-induced ocular surface changes in patients with glaucoma. Systemic administration of morphine and opium have also been implicated in causing keratoconjunctivitis.[4]

Botulinum toxin type A (Botox® [1]) is a purified neurotoxin complex that is used primarily to treat blepharospasm, hemifacial spasms and Meige's syndrome, as well as strabismus and various neuromuscular disorders of the head and neck. Ocular adverse effects after Botox® treatment of blepharospasm and hemifacial spasm include ptosis (drooping eyelids) and reduced blinking that leads to exposure of the cornea, persistent corneal epithelial defect and corneal ulceration.[4] Vigorous treatment of any corneal exposure with lubricating eyedrops, ointment, therapeutic soft contact lenses or closure of the eye by patching or tarsorraphy is important to prevent serious eye damage.

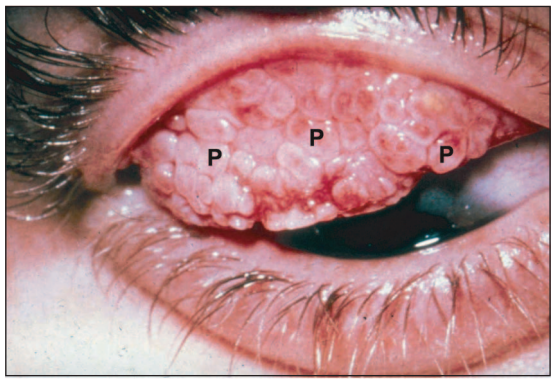

Fig. 3. Giant papillary eruptions (P) in the palpebral conjunctiva of an everted upper eyelid attributable to use of thiomersal in contact lens solution. (This figure was published in Tripathi RC, Tripathi BJ.[1] The eye. In: Riddell R, editor. Pathology of drug-induced and toxic diseases. New York (NY): Churchill Livingstone, 1982: 377-456. Copyright Elsevier). Reproduced with permission.

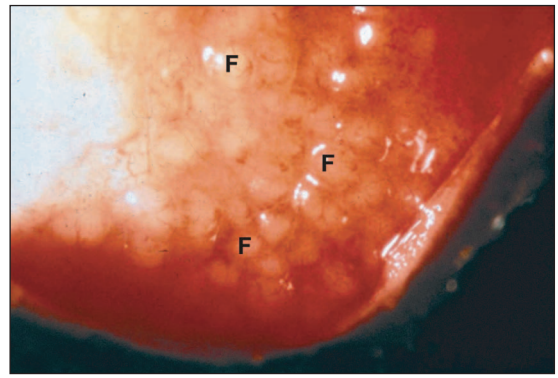

Fig. 4. Gross appearance of the formation of follicles (F) in the palpebral conjunctiva of a retracted lower eyelid attributable to prolonged use of eyedrops containing the preservative, benzalkonium chloride. (This figure was published in Tripathi RC, Tripathi BJ.[1] The eye. In: Riddell R, editor. Pathology of drug-induced and toxic diseases. New York (NY): Churchill Livingstone, 1982: 377-456. Copyright Elsevier). Reproduced with permission.

2. Drug-Induced Uveal Tract Disorders

The iris, together with the ciliary body and choroid, constitutes the uveal tract (figure 1).[5] The bulk of the ciliary body is formed by smooth muscle fibres arranged meridionally, radially and circumferentially. The bilayered ciliary epithelium is smooth posteriorly and markedly convoluted anteriorly (the ciliary processes). On the posterior aspect of the iris, the nonpigmented epithelium of the ciliary body continues as a pigmented layer, and forms the myoepithelium of the dilator pupillae muscle of the iris. The smooth muscle sphincter pupillae is located within the iris stroma around the pupil.

2.1 α_1-Adrenergic Receptor Antagonists

α_1-Adrenergic receptor antagonists (α_1-blockers) competitively inhibit the sympathetic autonomic nervous system, which results in relaxation of the smooth muscles in the neck of the bladder and prostatic urethra,[10,11] as well as in the iris.[12] These

1 The use of trade names is for product identification purposes only and does not imply endorsement.

medications are prescribed widely for the treatment of benign prostate hypertrophy to improve urinary outflow and associated symptoms. Tamsulosin was the first α_1A subtype-selective blocker to be approved in the US for the treatment of benign prostate hypertrophy and is currently the most commonly prescribed medication for this condition.[13,14] Recently, a newly recognized intraoperative floppy iris syndrome has been reported in patients treated with tamsulosin and undergoing cataract surgery.[15] Intraoperative floppy iris syndrome has three distinctive features: a flaccid iris stroma that undulates and billows in response to ordinary intraocular fluid currents; a propensity for the floppy iris stroma to prolapse toward the surgical incision despite proper wound construction; and progressive intraoperative pupil constriction even with standard preoperative pharmacological measures to prevent this from happening.[15] Tamsulosin does not seem to affect vision or eye health. If the eye surgeon is made aware of its use by the patient before cataract surgery, modified surgical techniques can be used with excellent results.[16] It is important to note the possibility that intraoperative floppy iris syndrome may occur several years after a patient has stopped using tamsulosin or similar drugs. This syndrome can also occur with other non-specific α_1-blockers.

2.2 Sulfa-Based Drugs

Certain sulfa-based drugs (e.g. topiramate) can cause swelling of the ciliary body, which causes angle-closure glaucoma to manifest or be precipitated (see section 3.2.3).

3. Drug-Induced Glaucoma

Glaucoma, historically considered as a raised intraocular pressure disease, is currently defined as a

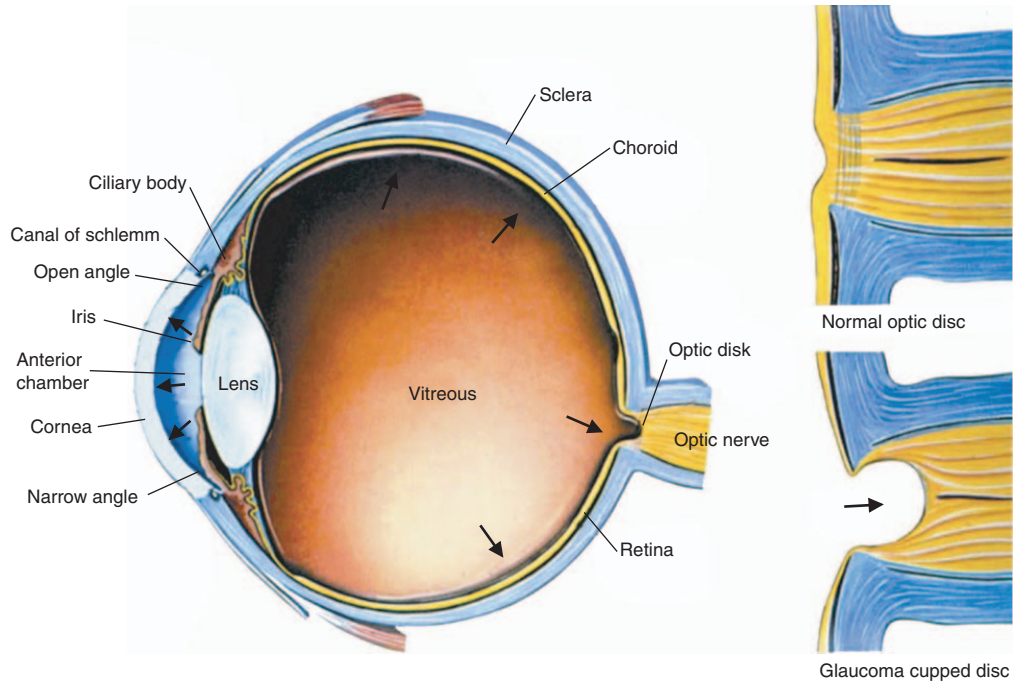

Fig. 5. Diagrammatic representation of the human eye depicting structural alterations in glaucomatous disease. The anterior chamber contains aqueous humor that originates from the ciliary body. Obstruction in the drainage pathway of the aqueous humor results in an increase in intraocular pressure (shown by arrows) and manifests as excavation or cupping of the optic disc characteristic of glaucomatous optic neuropathy (see bottom right; for comparison, a normal optic cup is depicted at top right). The diagram also illustrates the difference between open and narrow angle of the anterior chamber; hence, the terminology open-angle and closed-angle glaucoma (reproduced from Tripathi et al.,[17] with permission).

heterogeneous group of diseases that have in common a characteristic optic neuropathy with associated visual field loss for which elevated intraocular pressure is one of the primary risk factors.[17] There are no ideal schemes to classify glaucoma but in practice, glaucoma is broadly categorized as primary (aetiology unknown) or secondary (aetiology known). All glaucomas are further classified according to the status of the angle of the anterior chamber (i.e. the proximity of the root of the iris to the corneoscleral junction) as either open or closed (figure 5). Thus, adult onset glaucoma may occur with an open-angle (primary or secondary) or with a closed angle (acute or angle closure glaucoma). However, it is recognized that all glaucomas are secondary to some abnormalities, whether currently identified or not. Drug-induced glaucomas are secondary glaucomas because they are brought about by the use of specific systemic or topical medications. Detailed information on this subject can be found in a previous review article.[17]

3.1 Drug-Induced Open-Angle Glaucoma

Patients develop increased intraocular pressure, optic neuropathy and visual field defects associated with the use of several medications. There is usually no eye pain, redness or acute vision loss and ocular examination, with few exceptions, shows a normal appearance of the angle of the anterior chamber.

3.1.1 Corticosteroids

Glucocorticoids are used for their anti-inflammatory properties. All exogenous glucocorticoids (applied topically to the eye and the periocular tissues, injected into the vitreous cavity, or administered intravenously, in pill form or as an inhalant) are known to cause increased intraocular pressure, which leads to glaucoma.[17-20] The elevated intraocular pressure is due to increased resistance to outflow of aqueous humor because of structural and functional changes in the outflow pathway induced by glucocorticoids.[17,18]

Clinically, corticosteroid-induced glaucoma presents similar to primary open-angle glaucoma with elevated intraocular pressure, open angles and ultimately cupped optic discs and visual-field defects. The time frame when ocular hypertension begins and the degree of intraocular pressure elevation depend on the specific drug, the dosage, the frequency and route of administration and susceptibility of the individual patient. Physicians should be cognizant of the ocular adverse effects of corticosteroids and refer patients at risk or when in doubt for ophthalmic examination. If the intraocular pressure increases, corticosteroids should be tapered as soon as possible. A correlation exists between the length of corticosteroid treatment and the time it takes to lower the eye pressure. NSAIDs such as flurbiprofen, ketorolac and diclofenac, which are topical eyedrops and do not seem to raise intraocular pressure markedly, can be used in some instances.[17] If the corticosteroid treatment cannot be discontinued, or the intraocular pressure does not decrease after discontinuation of the corticosteroids, medical and surgical treatments should be instituted.[17]

3.1.2 Anti-Neoplastic Agents: Docetaxel and Paclitaxel

Docetaxel and paclitaxel belong to a new generation of anticancer agents used in the treatment of a variety of neoplastic diseases, primarily in the advanced stages. The mechanism by which these medications cause or exacerbate glaucomatous disease is unknown. There is a report of a patient who developed a classical clinical picture of open-angle glaucoma in both eyes after receiving docetaxel, and the disease recurred on follow-up treatment of the metastases with paclitaxel.[21]

3.2 Drug-Induced Angle-Closure Glaucoma

Acute angle-closure glaucoma has a sudden onset with severely increased intraocular pressure, eye pain, redness and cloudy vision. Eye examination reveals a closed anterior chamber angle (figure 5). It is one of the most painful conditions of the body. Several drugs can precipitate angle-closure glaucoma by narrowing the angle of the anterior chamber, by pupillary dilation and/or forward movement of the iris/lens diaphragm (pupillary block glaucoma), and by swelling of the ciliary body epithelium, lens or vitreous body.[17] The exact mechanism of drug-induced angle-closure glaucoma is not specified in

the product literature and most inserts simply list the general term 'glaucoma' as a contraindication, or 'can cause glaucoma' without specifying the type of glaucoma. Such statements are often confusing to both clinicians and patients.

The risk factors for acute angle-closure glaucoma include race (high prevalence in Inuit Eskimos, Asians and Hispanics), advanced age, narrow angle and/or shallow depth of the anterior chamber, female sex, hyperopia (far-sightedness) and family history.[17,22] A simple oblique penlight illumination test can help identify the patients who are at risk.[23] In patients with a shallow anterior chamber, the iris is convex as it bows forward over the lens. Under these conditions, the nasal iris is seen in shadow when a light is directed from the opposite (temporal) side. As the convexity of the iris increases, so do the shallowness of the anterior chamber and the shaded nasal aspect of the iris. However, this method is not always reliable in determining the risk of angle closure.[24] When in doubt, the patient should be referred to an ophthalmologist for definitive evaluation at the slit-lamp biomicroscope and by using a goniolens (gonioscopy).

3.2.1 Adrenergic Agonists

Adrenaline (epinephrine) is utilized commonly for the treatment of ventricular fibrillation, allergic reactions and anaphylactic shock, and ephedrine is used in the treatment of nasal congestion as well as for anaesthesia-related hypotension. These medications induce pupillary dilation, which can precipitate an attack of acute angle-closure glaucoma in susceptible patients.[17] Salbutamol is a β_2-specific adrenergic agonist used as an inhalant for bronchodilation in patients with asthma or chronic obstructive pulmonary disease (COPD). It can be absorbed through the cornea and conjunctiva, causing pupillary dilation, which can lead to angle-closure glaucoma in susceptible patients.[25] This adverse effect can be prevented by using properly fitted masks and handheld nebulizers that could decrease ocular absorption. Protective eyewear offers additional preventive benefit.

3.2.2 Anticholinergics

Ipratropium bromide is used in combination with salbutamol as a bronchodilator in patients with COPD. The anticholinergic action induces pupillary dilation, which can cause acute angle-closure glaucoma in susceptible patients.[26,27] Antidepressants, such as fluoxetine, paroxetine, fluvoxamine and venlafaxine, as well as histamine H_2 receptor antagonists, such as cimetidine and ranitidine, which are used in the treatment of gastroesophageal reflux disease and duodenal ulcers, have a weak anticholinergic effect but can cause pupillary dilation and angle-closure glaucoma in susceptible patients.[28]

3.2.3 Sulfa-Based Drugs

Topiramate is a novel sulfamate-substituted monosaccharide agent used in the treatment of various types of epilepsy, migraine headaches, depression and neuropathic pain. As with other sulfa-based drugs, an allergic reaction induces swelling of the ciliary body and forward displacement of the lens-iris diaphragm, which cause shallowing of the anterior chamber angle and acute angle-closure glaucoma.[29-32] There are >100 such cases reported in the literature, and acute elevation of intraocular pressure usually occurred within the first 2 weeks of starting topiramate therapy.[32] The most common presenting symptom is blurred vision. Treatment guidelines include discontinuation of the sulfa-containing drug and medical management to decrease intraocular pressure. Laser iridotomies or peripheral iridectomies are of no benefit.[32]

4. Drug-Induced Cataract

The crystalline lens is a biconvex, transparent structure located behind the iris; it is composed of a lens capsule, cortex and nucleus.[5] The lens increases in size throughout life because new cells are constantly added to the cortex. The toxic effects of medications manifest as cloudiness of the lens in different anatomical locations, which to a great extent may be determined by the route of drug administration.[1] For example, equatorial changes are more common with systemically administered drugs that cross the blood-aqueous barrier, whereas centrally located anterior lens changes are more com-

mon with topically administered drugs.[1] Posterior subcapsular and cortical changes occur more often as a result of diffusion of noxious substances from the posterior chamber by crossing the blood-aqueous barrier, uveal inflammation and through disturbance of the vitreous humor.[1]

4.1 Glucocorticoids

Long-term use of corticosteroids can produce posterior subcapsular cataracts (figure 6). Cataract formation has been reported to occur following various routes of corticosteroid administration including systemic, topical use around the eyelids, inhalants and nasal sprays. The incidence of drug-induced cataract is related to the dosage and duration of corticosteroid administration. Although individual susceptibility to corticosteroid-induced cataracts appears to vary, they occur in both children and adults.[33] The opacity begins at the posterior pole as refractile or multicoloured (polychromatic) dots or layers. The posterior subcapsular cataract that develops is characteristic of corticosteroid toxicity; however, the cataractous changes that gradually spread toward the equator in a subcapsular fashion cannot be differentiated from complicated cataract, radiation cataract, cataract associated with other ocular disease (retinitis pigmentosa) and senile cataract.[1] The lens opacities may progress or remain stationary, but rarely regress upon withdrawal of the corticosteroids.[1]

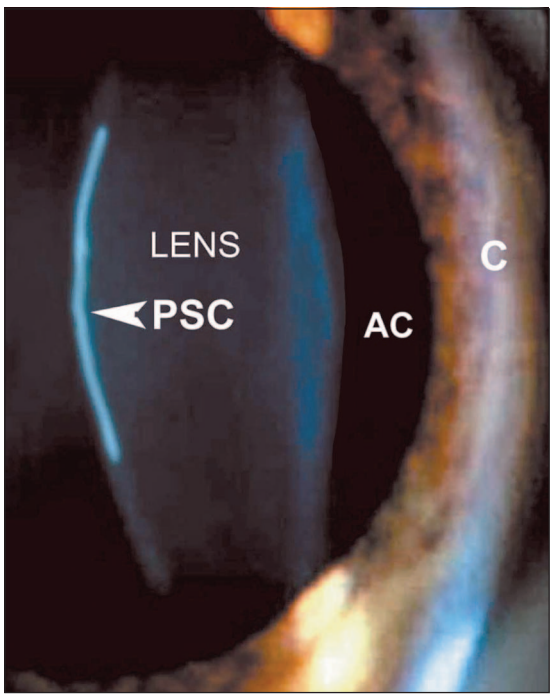

Fig. 6. Slit-lamp biomicroscopic appearance of posterior subcapsular cataract (PSC) in a patient receiving long-term systemic glucocorticoid therapy. **AC** = anterior chamber; **C** = cornea.

Within the past few years, intravitreal injection of triamcinolone has been used frequently for the treatment of macular oedema associated with retinal vein occlusion or diabetes mellitus, as well as idiopathic, proliferative and neovascular intraocular diseases, proliferative diabetic retinopathy and exudative age-related macular degeneration.[34,35] While the treatment is beneficial in improving vision in these patients, significant adverse effects need to be considered. In addition to a possible rise in intraocular pressure and associated development of glaucoma (see section 3.1.1), cataracts eventually develop in nearly all patients who receive an intravitreal injection of triamcinolone.[36]

4.2 Phenothiazines

Phenothiazines are a group of psychotropic medications used in the treatment of depressive, involutional, senile or organic psychoses and various forms of schizophrenia. Chlorpromazine and thioridazine are the most common phenothiazines involved in cataract formation and this adverse effect is dose and drug dependent. Systemic administration of these medications leads to accumulation of fine, white to yellowish-brown granules in the anterior cortex just beneath the capsule in the area of the pupillary aperture.[4] With time, the granules become arranged in a stellate pattern and develop into true anterior polar cataract.[4]

4.3 Alkylating Agents: Busulfan

Busulfan is an alkylating agent used in the palliative treatment of chronic granulocytic leukaemia and other blood dyscrasias. Systemic administration of this anticancer agent causes a posterior subcapsu-

lar lens opacity.[5] There are often scattered punctate cortical opacities and/or a polychromatic sheen to the posterior lens capsule.[4] Animal studies suggest that the cataractous changes may be related to interference of the drug with nucleic acid production during mitosis of the lens epithelium.[37]

Irrespective of the drug that induces cataractous changes, surgical removal of the lens is the treatment to regain vision.

5. Drug-Induced Retinal Abnormalities

The retina (figure 1) is derived from neuroectoderm and it represents an extension of the brain in the eye. This thin, delicate layer of stratified nervous tissue is composed of the retinal pigment epithelium and the sensory retina.[5] Noxious substances reach the retina mainly through the vascular supply, and many systemic drugs are implicated in causing retinopathy.

5.1 Aminoquinolines

Aminoquinolines such as chloroquine and hydroxychloroquine are used in the treatment of malaria, extraintestinal amoebiasis, rheumatoid arthritis and lupus erythematosus. Ocular toxic effects are related to duration of medication use, total dose and patient age.[38] The greatest risk for overdosing is in obese patients. Other groups of patients who are susceptible to toxic changes include small, thin, elderly patients in whom the base dosage is excessive, and those with renal disease.[4,39] Toxic maculopathy is usually reversible only in its earliest phases, thus early detection of toxic reaction is very important;[4,38] however, no accepted, standardized method exists for this purpose.

Guidelines for following patients in whom long-term treatment is anticipated include a baseline ophthalmic examination to determine visual acuity, colour vision, central visual fields, ophthalmoscopy, electroretinography and chronological fundus photography.[4,39,40] Follow-up examination is recommended every 6–12 months as long as the patient is taking these drugs. Maculopathy must be bilateral and detectable by Amsler grid and visual field testing to implicate this class of medications. The bull's eye maculopathy (figure 7) is a typical, advanced retinopathy caused by aminoquinolines-induced ocular toxicity,[4,38,41-43] although a number of other entities, which include cone and cone-rod dystrophy, Stargardt disease (fundus flavimaculatus), age-related macular degeneration and chronic macular hole, can cause a similar clinical picture.[44] Recommendations on screening for chloroquine and hydroxychloroquine retinal toxicity have been published by the American Academy of Ophthalmology.[45]

5.2 Phenothiazines

Phenothiazines including chlorpromazine and thioridazine are antipsychotic agents and are concentrated in uveal tissue and retinal pigment epithelium by binding to melanin granules. A phototoxic process has been postulated to be involved in both the increased ocular pigment deposits and the retinal degeneration.[4] Chlorpromazine used in high-dose therapy commonly results in abnormal pigmentation of the eyelids, interpalpebral conjunctiva, cornea and anterior lens capsule.[4] Cataract may develop as described in the section on drug-induced cataract, but pigmentary retinopathy from this medication is rare. In contrast, thioridazine causes severe retinopathy that can develop within a few weeks or months of high-dose utilization.[4,47,48] Initially, pa-

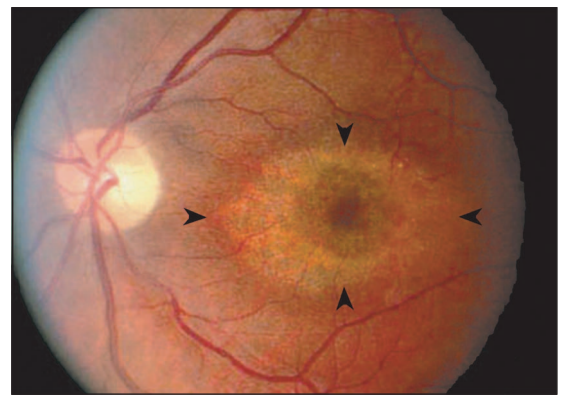

Fig. 7. Fundus appearance of 'bull's eye' maculopathy (arrows) of the retina in a 35-year-old woman treated for 15 years with hydroxychloroquine for systemic lupus erythematosus and prior to discontinuation of therapy for 7 years (courtesy of the University of Michigan Department of Ophthalmology and Visual Sciences).[46]

tients complain of blurry vision, and the fundus shows coarse retinal pigment stippling in the posterior pole. Over a few months, the retinopathy evolves to widespread but patchy atrophy of the pigment epithelium with characteristic areas of hypo- and hyperpigmentation. Symptoms include loss of visual field and night vision.

5.3 Anti-Estrogen Agents: Tamoxifen

Tamoxifen is used widely in the treatment of breast carcinoma. Besides being implicated in inducing corneal opacities and posterior subcapsular cataracts, the drug can cause retinal changes and decreased colour vision.[49] The incidence of ocular adverse effects is dependent on dosage or accumulated dose. There appears to be two forms of retinal involvement. An acute, ill-defined form manifests as vision loss, retinal oedema, retinal haemorrhage and optic disc swelling after only a few weeks of therapy. These findings may be due to tamoxifen estrogenic activity, which may cause venous thromboembolism, but are reversible on discontinuation of the drug. Typical tamoxifen retinopathy includes small refractile or crystalline dot-like yellowish deposits in the area surrounding the macula.[4,50] These crystalline bodies are located in the inner retina and histologically may be the products of axonal degeneration.[4,50] Patients treated with tamoxifen should have a baseline eye examination, including slit-lamp biomicroscopy of the anterior and posterior segments and colour vision testing, and be followed at least every 2 years but more frequently if ocular symptoms occur.[4]

5.4 Retinoids: Isotretinoin

Isotretinoin and other retinoids are used in the treatment of cystic acne, psoriasis and various other skin disorders. Ocular adverse effects are dose related and include blepharoconjunctivitis, dry eyes and transient blurred vision.[4] Some patients have decreased night vision and abnormal dark-adaptation curves while taking the medication.[4,51] The retinal dysfunction is probably due to the competition for binding sites between retinoic acid and retinol.[4,51]

6. Drug-Induced Optic Neuropathy

The optic nerve is a conduit for the axons that carry the visual information from the retina to the brain. Approximately 1.2 million axons arranged in bundles traverse the scleral sieve known as the lamina cribrosa.[5] Excavation of this structure and atrophy of the axons produces optic disc cupping as seen in glaucoma (figure 6 and figure 8a), whereas swelling of the axons and vascular congestion, as in papilloedema, produces the appearance of a 'choked' disc (figure 8b). Ischaemia of the optic nerve and slow demyelination of axons produce a pale and atrophic appearance of the optic disc with or without significant cupping.

Optic neuropathy describes a pathological condition of the optic nerve that results from various insults, such as ischaemia, mechanical compression, nutritional deficiency, toxins and drugs. The clinical features include decreased visual acuity, decreased colour vision, afferent pupillary defect and visual field loss. Drug-induced optic neuropathy usually occurs in both eyes, simultaneously or in close proximity, and the disorder improves or resolves with discontinuation of the offending drugs.

6.1 Antimicrobial Agents: Linezolid

Linezolid belongs to a novel class of synthetic antimicrobial agents effective against Gram-positive bacteria, including vancomycin-resistant enterococci and methicillin-resistant staphylocci.[52] Although the recommended therapeutic duration is 28 days, linezolid has been used long-term for high-risk, resistant bacterial infections with an increased toxicity profile. There are currently 12 reported cases of optic neuropathy associated with extended linezolid use.[52] The duration of therapy ranged from 5 to 11 months before development of optic neuropathy.[52] Patients exhibit symmetric painless decrease of vision and colour vision, bilateral visual field defects (central or cecocentral scotomas), normal maculae, as well as normal, swollen or pale optic disc. Other known causes of optic neuropathy, such as hereditary with positive family history and nutritional deficiencies, need to be excluded. Improvement of vision after discontinuation of linezolid

supports the association of the drug with optic neuropathy. The mechanism of linezolid-induced optic neuropathy is unknown, but may be due to impairment of mitochondrial protein synthesis. Patients on long-term treatment of linezolid with visual symptoms must have an ophthalmological evaluation. If linezolid-induced optic neuropathy is suspected, the medication should be discontinued and alternative treatments undertaken.

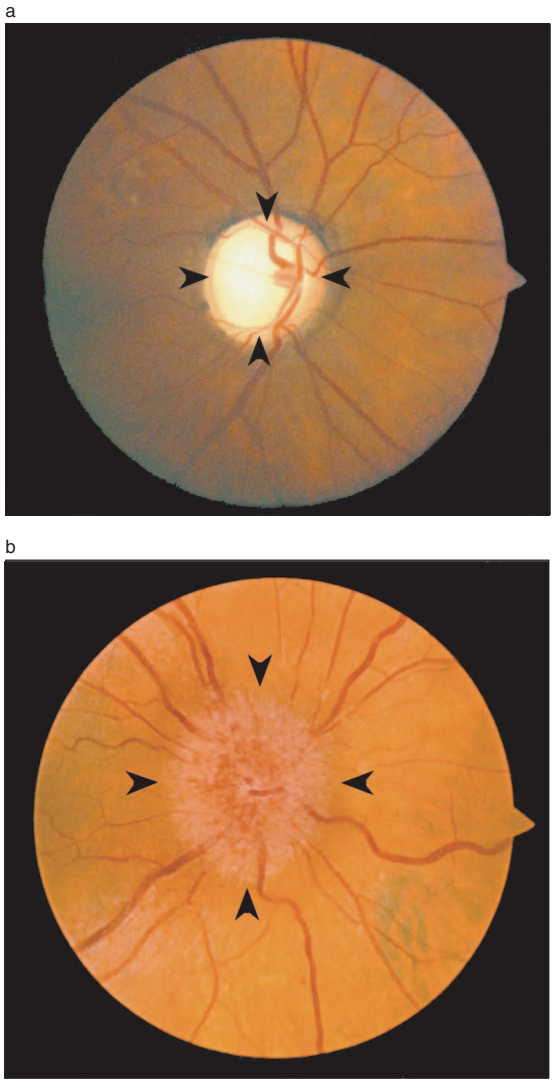

Fig. 8. (**a**) Ophthalmoscopic appearance of an advanced glaucomatous optic cup (arrows) with advanced excavation and atrophy of the optic disc, as well as nasal shift of the main blood vessels (reproduced from Tripathi et al.[17] with permission). (**b**) Ophthalmoscopic appearance of papil oedema showing fluffy disc margin (arrows) and engorged tortuous blood vessels. (This figure was published in Tripathi RC, Tripathi BJ.[1] The eye. In: Riddell R, editor. Pathology of drug-induced and toxic diseases. New York (NY): Churchill Livingstone, 1982: 377-456. Copyright Elsevier). Reproduced with permission.

6.2 Benzofuran Derivatives (Antianginal Agents): Amiodarone

Amiodarone is one of the most effective medications used in the treatment of various cardiac arrhythmias. It is clear that amidarone can cause deposits in the cornea (verticillate keratopathy), which usually does not cause significant visual impairment.[4] Although only a probable link exists between this medication and optic neuropathy, the simultaneous occurrence of optic neuropathy in both eyes and improvement or resolution on discontinuation of amiodarone, provides convincing evidence that the medication produces the optic neuropathy. Amiodarone-induced optic neuropathy is very similar to nonarteritic ischaemic optic neuropathy (NAION). The onset of visual loss in amiodarone-induced optic neuropathy is insidious (months), the degree of visual loss ranges from 20/20 to 20/200, the resolution of disc oedema takes months, and ocular involvement usually begins simultaneously within weeks of starting the medication.[53] In NAION, the onset of visual loss is rapid (days to weeks), visual acuity ranges from 20/20 to total blindness (no light perception), resolution may take only a few weeks, and rarely are the symptoms associated with amiodarone therapy.[53] The exact cause of amiodarone-induced optic neuropathy is still unknown, but the condition may be due to selective accumulation of intracytoplasmic inclusions (primary lipidosis) in the optic nerve axons, which mechanically or biochemically decrease axoplasmic flow.[4] Patients on amiodarone should have a baseline ophthalmic examination and be followed every 6 months for monitoring. An ophthalmologist should promptly examine patients who experience any visual disturbance.

6.3 cGMP-Specific Phosphodiesterase Type 5 Inhibitors (Erectile Dysfunction Drugs)

Sildenafil, tadalafil and vardenafil are drugs used in the treatment of erectile dysfunction. The most commonly known adverse effects from these medications are changes in colour perception, blurry vision and increased light sensitivity.[54,55] These ocular adverse effects are uncommon, dose dependent and have been fully reversible.[55] Recently, the phosphodiesterase type 5 inhibitors has been implicated in the development of NAION with >40 cases reported,[55-57] although no cause-effect relationship has been established.[57] The optic neuropathy in these patients has no distinctive features that distinguish it from spontaneously occurring NAION. The patient population who require treatment with erectile dysfunction drugs have the profile of risk factors for NAION, such as older age, hypertension and diabetes. In addition, the fact that optic neuropathy is relatively rare makes it difficult to establish a definitive association between these drugs and NAION. However, patients should stop the drugs in the event of a sudden loss of vision in one or both eyes. Patients who have previously experienced NAION in one eye may be more prone to developing NAION in the same or fellow eye if on these medications, and they should not take erectile dysfunction drugs.[57]

6.4 Antitubercular Agents: Ethambutol

Ethambutol is used in the treatment of pulmonary tuberculosis. There are >50 case reports of optic neuropathy associated with its use.[57] The incidence is dose-related, and the average duration of therapy until development of optic neuropathy is 235 days.[57] Other studies reported an incidence of 18% after 2 months on a dose of 35 mg/kg/day[58] as well as severe, bilateral visual loss of rapid onset associated with treatment using a therapeutic dose of ethambutol.[59,60] In general, at the current recommended dosage schedule, the incidence of optic neuritis is approximately 1%.[61,62] Ethambutol-induced optic neuropathy is usually retrobulbar and bilateral. The earliest ophthalmological findings may be loss of visual acuity, colour vision loss or visual field defect (central scotoma).

The pathophysiology underlying ethambutol-induced optic neuropathy is unclear. One possible explanation is that ethambutol chelates copper in the retinal ganglion cells and their axons in the optic nerve.[63] The decreased copper level affects cytochrome c oxidase activity in the mitochondria, compromising the energy supply required for axonal transport, which leads to optic neuropathy.[63]

There are no official standard of care guidelines regarding how often patients on ethambutol should have ophthalmic examinations and what tests should be performed. However, patients on the drug should be made aware that optic neuropathy as well as severe, irreversible visual loss can occur and informed consent should be obtained. A baseline eye exam including a visual field test, colour vision test, visual acuity test and fundus examination with pupillary dilation, should be performed. If any visual disturbances occur, the medication should be discontinued and ophthalmological consultation sought.

7. Conclusion

All drugs used in the treatment of ocular and systemic disorders have the potential to induce adverse effects in the eye. They can cause specific and non-specific abnormalities of various ocular structures that may manifest as blepharokeratoconjunctival disorders, glaucoma, cataract, uveal tract disorders, retinopathy and optic neuropathy. Many different kinds of medications can provoke similar adverse reactions in the eye, whereas a single medication may affect more than one ocular structure; thereby causing multiple, clinically recognizable disorders.

The extent and severity of ocular toxic adverse effects are often related to duration of treatment, dose and individual patient susceptibility. Children are as susceptible as adults to drug-induced ocular disorders. By using various optical devices, most tissues of the eye can be examined *in vivo* directly at high magnification; thus, providing clinicians with a unique opportunity to diagnose and manage drug-

induced adverse effects. Discontinuing the use of the drug could lead to resolution or reversal of the toxic manifestations, but a number of iatrogenic diseases, especially glaucoma and cataract, may be irreversible and warrant appropriate medical and/or surgical intervention to prevent or slow the loss of vision. Clinicians should be cognizant of drug-induced disorders of the eye, be watchful for their manifestation and seek consultation with an ophthalmologist when instituting therapy.

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References

1. Tripathi RC, Tripathi BJ. The eye. In: Riddell R, editor. Pathology of drug-induced and toxic diseases. New York (NY): Churchill Livingstone, 1982: 377-456
2. Physicians' desk reference. 60th ed. Montvale (NJ): Thomson Healthcare, 2006
3. PDR® for nonprescription drugs, dietary supplements and herbs. 2nd ed. Montvale (NJ): Thomson Healthcare, 2006
4. Fraunfelder FT, Fraunfelder FW. Drug-induced ocular side effects. Boston (MA): Butterworth-Heinemann, 2001
5. Bron AJ, Tripathi RC, Tripathi BJ. Wolff's anatomy of the eye and orbit. London (UK): Chapman and Hall, 1997
6. Tripathi BJ, Tripathi RC, Kolli SP. Cytotoxicity of ophthalmic preservatives on human corneal epithelium. Lens Eye Toxic Res 1992; 9 (3-4): 361-75
7. Gould HL. Solving the preservative paradox. Ophthalmology management [online]. Available from URL: http// www.ophthalmologymanagement.com [Accessed 2007 Jan 12]
8. Dutot M, Pouzaud F, Larosche I, et al. Fluoroquinolone eye drop-induced cytotoxocity: role of preservative in P2X7 cell death receptor activation and apoptosis. Invest Ophthalmol Vis Sci 2006; 47: 2812-9
9. Lewis RA, Katz GJ, Weiss MJ, et al. Travoprost 0.004% with and without benzalkonium chloride: a comparison of safety and efficacy. J Glaucoma 2007; 16 (1): 98-103
10. Lowe F. Alpha-1-adrenoceptor blockade in the treatment of benign prostatic hyperplasis. Prostate Cancer Prostatic Dis 1999; 2: 110-9
11. Thiyagarajan M. Alpha-adrenoceptor antagonists in the treatment of benign prostate hyperplasia. Pharmacology 2002; 65: 119-28
12. Nakamura S, Taniguchi T, Suzuki F, et al. Evaluation of alpha-1adrenoceptors in the rabbit iris: pharmacological characterization and expression of mRNA. Br J Pharmacol 1999; 127: 1367-74
13. Narayan P. Evans CP, Moon T. Low-term safety and efficacy of tamsulosin for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia. J Urol 2003; 170: 498-502
14. Roehrborn CG, Schwinn DA. Alpha-adrenergic receptors and their inhibitors in lower urinary tract symptoms and benign prostate hyperplasia. J Urol 2004; 171: 1029-35
15. Chang DF, Campbell JR. Intraoperative floppy iris syndrome associated with tamsulosin. J Cataract Refract Surg 2005; 31: 664-73
16. Ciccone J. ASCRS and urologists team up on Flomax [online]. Available from URL: http://www.eyeworld.org/article.php-?.sid = 3285&strict = &morphologic = &query = Ciccone%20J [Accessed 2006 Nov 14]
17. Tripathi RC, Tripathi BJ, Haggerty C. Drug-induced glaucomas. Drug Safety 2003; 26 (11): 749-67
18. Tripathi RC, Parapuram SK, Tripathi BJ, et al. Corticosteroids and glaucoma risk. Drugs Aging 1999 Dec; 15 (6): 439-50
19. Jonas JB, Kressig I, Degen R. Secondary chronic open-angle glaucoma after intravitrreal triamcinolone acetonide. Arch Ophthalmol 2003; 121: 729-30
20. Smithen LM, Ober MD, Maranan L, et al. Intravitreal triamcinolone acetonide and intraocular pressure. Am J Ophthalmol 2004; 138: 740-3
21. Fabre-Guillevin E, Tchen N, Anibali-Charpiat M-F, et al. Taxane-induced glaucoma. Lancet 1999; 354 (9185): 1181-2
22. Darkeh AK, Silverberg MA. Glaucoma, acute angle-closure [online]. Available from URL: http://www.emedicine.com/emerg/topic752.htm [Accessed 2007 Jun 8]
23. Bradford CA. Basic ophthalmology for medical students and primary care residents. 8th ed. San Francisco (CA): American Academy of Ophthalmology, 2004
24. Marsh BC, Cantor LB. The Spaeth gonioscopic grading system: assessing the configuration of the anterior chamber angle. Glaucoma Today 2005; May/Jun: 22-5
25. Rho DS. Acute angle-closure glaucoma after albuterol nebulizer treatment. Am J Ophthalmol 2000; 130 (1): 123
26. Shah P, Dhurjon L, Metcalfe T, et al. Acute angle-closure glaucoma associated with nebulised ipratropium bromide and salbutamol. BMJ 1992; 304 (6818): 40-1
27. Hall SK. Acute angle-closure glaucoma as a complication of combined beta-agonist and ipratropium bromide therapy in the emergency department. Ann Emerg Med 1994; 23 (4): 884-7
28. Dobrilla G, Felder M, Chilovi F, et al. Exacerbation of glaucoma associated with both cimetidine and ranitidine [letter]. Lancet 1982; I (8280): 1078
29. Banta JT, Hoffman K, Budenz DL, et al. Presumed topriamate-induced bilateral acute angle-closure glaucoma. Am J Ophthalmol 2001; 132 (1): 112-4
30. Rhee DJ, Goldberg MJ, Parrish RK. Bilateral angle-closure glaucoma and ciliary body swelling from topiramate. Arch Ophthalmol 2001; 119 (11): 1721-3
31. Sankar PS, Pasquale LR, Grosskreutz CL. Uveal effusion and secondary angle-closure glaucoma associated with topiramate use. Arch Ophthalmol 2001; 119: 1210-1
32. Fraunfelder FW, Fraunfelder FT, Keates EU. Topiramate-associated acute, bilateral, secondary angle-closure glaucoma. Ophthamology 2004; 111: 109-11
33. Tripathi RC, Kipp MA, Tripathi BJ, et al. Ocular toxicity of prednisone in pediatric patients with inflammatory bowel disease. Lens Eye Toxic Res 1992; 9 (3-4): 469-82
34. Jonas JB, Kreissig I, Degenring R. Intravitreal triamcinolone acetonide for the treatment of intraocular proliferative, exudative, and neovascular diseases. Prog Retin Eye Res 2005; 24 (5): 587-611
35. Jonas JB. Intravitreal triamcinolone acetonide: a change in paradigm. Ophthalmic Res 2006; 38 (4): 218-45

36. Cekic O, Chang S, Tseng JJ, et al. Cataract progression after intravitreal triamcinolone injection. Am J Ophthalmol 2005; 139: 993-8

37. Grimes P, von Sallmann L, Frichette A. Influence of Myleran on cell proliferation in the lens epithelium. Invest Ophthalmol 1964; 3: 566-76

38. Weiner A, Sandberg MA, Gaudio AR, et al. Hydroxychloroquine retinopathy. Am J Ophthalmol 1991; 112: 528-34

39. Roque MR, Roque BL, Foster S. Chloroquine/hydroxycholoroquine toxicity [online]. Available from URL: http://www.emedicine.com/oph/topic245.htm [Accessed 2006 Nov 21]

40. Easterbrook M. Detection and prevention of maculopathy associated with antimalarials. Int Ophthalmol Clinic 1999; 39 (2): 49-57

41. Bernstein HN. Chloroquine ocular toxicity. Surv Ophthalmol 1967; 12 (5): 415-47

42. Bernstein HN. Ocular safety of hydroxychloroquine. Ann Ophthalmol 1991; 23 (8): 292-6

43. Levy GD, Munz SJ, Paschal J. Incidence of hydroxychloroquine retinopathy in 1,207 patients in a large multicenter outpatient practice. Arthritis Rheum 1997; 40 (8): 1482-6

44. Simmons ST. 2007-2008 BCSC Section10: glaucoma. San Francisco (CA): American Academy of Ophthalmology, 2007

45. Marmor MF, Carr RE, Esterbrook M, et al. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy [online]. Available from URL: http://www.aao.org/education/statements/upload/Recommendations-on-Screening-for-Chloroquine-and-Hydroxychlorquine-Retinopathy.pdf [Accessed 2007 Jun 8]

46. The University of Michigan Kellogg Eye Center [online]. Available from URL: http://www.kellogg.umich.edu/vtm/retina_cases/48/history.html [Accessed 2007 Feb 2]

47. Tekell JL, Silva JA, Maas JA, et al. Thioridazine-induced retinopathy. Am J Psychiatry 1996; 153 (9): 1234-5

48. Shah GK, Auerbach DB, Augsburger JJ, et al. Acute thioridazine retinopathy. Arch Ophthalmol 1998; 116 (6): 826-7

49. Gorin MB, Day R, Costantino JP, et al. Long-term tamoxifen citrate use and potential ocular toxicity. Am J Ophthalmol 1998; 125: 493-50

50. Gianni L, Panzini I, Li S, et al. Ocular toxicity during adjunct chemoendocrine therapy for early breast cancer: results from international breast cancer study group trials. Cancer 2006; 106: 505-13

51. Weleber RG, Denman ST, Hanifin JM, et al. Abnormal retinal function associated with isotretinoin therapy fro acne. Arch Ophthalmol 1986; 104: 831-7

52. Rucker JC, Hamilton SR, Bardenstein D, et al. Linezolid-associated toxic optic neuropathy. Neurology 2006; 66: 595-8

53. Macaluso DC, Shults WT, Fraunfelder FT. Features of amiodarone-induced optic neuropathy. Am J Ophthalmol 1999; 127: 610-2

54. Marmor MF. Sildenafil (Viagra) and ophthalmology. Arch Ophthalmol 1999; 117: 518-9

55. Fraunfelder FW. Visual effects associated with erectile dysfunction agents. Am J Ophthalmol 2005; 140 (4): 723-4

56. Pomeranz HD, Smith KH, Hart WM, et al. Sildenafil-associated nonarteritic anterior ischemic optic neuropathy. Ophthalmology 2003; 110 (9): 1860-1

57. Fraunfelder FW, Fraunfelder FT. Drug-related adverse effects of clinical importance to the ophthalmologists [online]. Available from URL: http://piodr.sterling.net/index.cfm?.fuseaction = home.whatsnew [Accessed 2007 Jun 8]

58. Leibold JE. The ocular toxicity of ethambutol and its relation to dose. Ann NY Acad Sci 1966; 135: 904-9

59. Chatterjee VKK, Buchanan DR, Friedmann AI, et al. Ocular toxicity following ethambutol in standard dosage. Br J Dis Chest 1986; 80: 288-90

60. Smith JL. Should ethambutol be barred? J Clin Neuroopthalmol 1987; 7: 84-6

61. Barron GJ, Tepper L, Lovine G. Ocular toxicity from ethambutol. Am J Ophthalmol 1974; 77: 256-60

62. Citron KM, Thomas GO. Ocular toxicity from ethambutol. Thorax 1986; 41: 737-9

63. Kozak SF, Inderlied CB, Hsu HY, et al. The role of copper on ethambutol's antimicrobial action and implication for ethambutol-induced optic neuropathy. Diagn Microbiol Infect Dis 1998; 30 (2): 83-7

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