# Neuro-ophthalmologic side-effects of systemic medications

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**Purpose of review**
Systemic medications may cause side-effects manifesting primarily as neuro-ophthalmologic problems. It is paramount for the physician to be updated on both well recognized and novel associations between drugs and their potential adverse reactions.

**Recent findings**
There is a growing list of medications that can cause pupil dilation, pupil constriction, dyschromatopsia, worsening of ocular myasthenia gravis, posterior reversible leukoencephalopathy syndrome, pseudotumor cerebri, disturbances in eye movements, accommodation problems, or optic neuropathy. This is partly due to the increasing number of drugs available in each class, but also to the increased recognition of neuro-ophthalmological disorders.

**Summary**
This review discusses neuro-ophthalmological problems and the medications that may precipitate them.

**Keywords**
medication, neuro-ophthalmologic, ocular, ophthalmic, ophthalmologic, side-effects, toxicity

## INTRODUCTION

Our modern healthcare system encourages physicians to frequently review and reconcile the patient medication list. Electronic medical records have made this task more manageable, but physicians are doubling their efforts to remain updated on medication side-effects and adverse reactions.

Ocular side-effects may occur due to prescription, homeopathic, or herbal medications [1–3]. Neither the prescribing physician nor the patient may be aware of these potential complications. Furthermore, the Food and Drug Administration-approved product labeling information for many medications is broad and generic; 'blurry vision' is an ubiquitous side-effect that provides little guidance for the physician.

This article aims to provide an updated review of ocular side-effects of systemic medications specifically relevant in neuro-ophthalmology. Examples of visual side-effects other than those particular to neuro-ophthalmology are summarized in Table 1 [4,5,6▪–9▪,10,11].

Reported medication side-effects must be interpreted with perspective. For example, the ophthalmic effects of some medications are undeniable and obvious, such as atropine causing mydriasis. Others have very strong evidence and the pathophysiology is clear, such as worsening of myasthenic weakness after botulinum toxin injection. However, verification for some purported medication–side-effect relationships has not been made. For example, evidence is not conclusive that β-blockers worsen myasthenia gravis, or that phosphodiesterase type five (PDE-5) inhibitors cause ischemic optic neuropathy, despite conventional belief that these effects are proven. Furthermore, other medications have been associated with an adverse ophthalmologic event based only on one or several case descriptions. Some of these reports were released prior to MRI, and have not been reconfirmed, yet persist in tables and lists. Thus, for any medication–side-effect relationship, it is important to consider the strength of evidence and pathophysiological reasoning.

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**Curr Opin Ophthalmol** 2013, 24:540–549

DOI:10.1097/01.icu.0000434557.30065.a7

## KEY POINTS

- Many prescription, over-the-counter, and recreational drugs can potentially cause ocular side-effects, some of which particularly induce, worsen, or mimic neuro-ophthalmological disorders.
- Abnormal pupil responses or anisocoria should prompt a thorough review of medications, as well as all topically applied substances that may have contacted the area around the eye.
- Accomodation problems are a common cause of blurry vision for which no organic cause is otherwise found. Many medications have cholinergic properties that may exacerbate this problem.
- Some medications are purported to cause side-effects based on rare case reports or nonrandomized trials. Such associations should be recognized as possible, but confirmatory studies should be encouraged so that the true incidence of associations is known.

In this article, we have attempted to create tables that include the most well established medication–side-effect relationships, highlighting reports published over the past 12 months.

## MEDICATIONS THAT MAY AFFECT THE PUPIL

Medications that increase pupil size could result in bilaterally symmetric pupil dilation or unilateral mydriasis. The latter situation may mimic an acute incipient compressive third nerve palsy and often prompts emergent evaluation. Unilateral mydriasis usually results from effects of medication directly contacting the ocular surface. This can occur from mydriatic drops whose primary function is to produce pupillary dilatation, or it can occur as an unintended side-effect of other medications. We have seen unilateral eye dilation in the intensive care setting due to aerosolized respiratory therapies containing ipratropium and albuterol asymmetrically escaping the facemask or ventilator equipment [12]. If it contacts the eye, transdermal scopolamine can also cause unilateral mydriasis due to its anticholinergic properties. Scopolamine has been reported to cause unilateral pupil dilation when used as an antiemetic in patients taking chemotherapy [13] and for prevention of postoperative nausea after plastic and reconstructive surgery [14▪], highlighting the increased recognition of this side-effect.

Unilateral eye dilation should also prompt questioning for over-the-counter medication use. One report described a patient who was evaluated in the emergency department for acute unilateral mydriasis. She was found to be using a hemorrhoidal cream to decrease puffiness around her eyes. The cream contained phenylephrine 0.25% [15].

Either prescription or illicit drugs can cause bilateral pupil dilation, and are listed in Table 2. Bilateral pupil dilation is a classic sign of anticholinergic toxicity, which also produces confusion, flushing, dry skin, fever, tachycardia, bowel stasis, myoclonus, and urinary retention. Both prescription and herbal medicines can result in anticholinergic toxicity. Pupillary mydriasis is the most common clinical feature when anticholinergic poisoning is caused by Chinese herbal medicines [16▪].

Conversely, some drugs have the potential to cause pupil constriction. Organophosphates, used as pesticides and nerve agents, are the prototypical miotic agents due to their cholinergic effects. Medications that cause miosis are not as likely to cause anisocoria, but may result in bilaterally miotic pupils (Table 3 [17]).

## MEDICATIONS THAT MAY CAUSE DYSCHROMATOPSIA

Certain medications can cause afferent visual problems, including abnormally tinted vision. Blue tinting, called cyanopsia, can occur after cataract extraction, but is also a rare dose-related side-effect of sildenafil [18].

Xanthopsia, yellow vision tinting, can be caused by cataracts, and also by digitalis (digoxin) toxicity. Vincent Van Gogh, whose paintings are often tempered with a yellow hue, always painted his physician, Dr Paul-Ferdinand Gachet, holding a foxglove plant (*Digitalis purpurea*). This situation has led to the theory that Van Gogh was being over-treated with the herb, and thus suffering from digitalis poisoning.

In addition to dyschromatopsia, *Digitalis* can also cause photopsias [19] and decreased visual acuity. These effects do not necessarily indicate drug toxicity, as they can occur at normal serum levels [20]. Symptoms can resolve after drug discontinuation.

## MEDICATIONS THAT MAY WORSEN DIPLOPIA OR PTOSIS IN NEUROMUSCULAR JUNCTION DISORDERS

Most patients with a disorder of the neuromuscular junction such as myasthenia gravis will eventually be prescribed a medication associated with worsening of their disease. Some of these medications are always contraindicated in myasthenia and others

**Table 1. Ocular side-effects of systemic medications, categorized by location.**

| Location | Possible ocular side-effect | Medication class | Notes |
|---|---|---|---|
| Eyelid | Erythema multiforme with lid edema and thickening, conjunctival congestion, and mucous membrane inflammation | Antibiotics (e.g., sulfonamides, doxycycline) [4]; HAART [5]; analgesics; NSAIDS; anticonvulsants | Stevens–Johnson syndrome is the most severe manifestation of erythema multiforme, and is more likely to show ocular involvement than other forms |
| Uvea | Acute angle closure glaucoma | Adrenergic agents, anticholinergics (e.g., tricyclic antidepressants), sulfa-based drugs (e.g., topiramate) | The relationship of topiramate and glaucoma appears to be associated with new users of the medication rather than chronic users [6▪] |
| Uvea | Intraoperative floppy iris syndrome | Alpha1-adrenergic receptor antagonists (e.g., tamsulosin) | Usually reported as a complication of cataract surgery |
| Uvea | Open angle glaucoma, caused by changes in the trabecular cells resulting in ocular hypertension | Corticosteroids | Dose, duration, and site of administration affect incidence. Neither high dose intravenous steroids for multiple sclerosis, nor short-term inhaled corticosteroids resulted in increased chance of progression to glaucoma [7▪,8▪] |
| Lens | Increased cataract formation | Corticosteroids, neuroleptics (e.g., thorazine). | Light therapy to treat psoriasis may require eye protection to avoid the possibility of cataract formation. |
| Retina | Maculopathy | Aminoquinolines (e.g., chloroquine, hydroxychloroquine) | The AAO has produced guidelines regarding screening for hydroxychloroquine retinopathy; these guidelines have resulted in higher cost but no improvement in maculopathy detection [9▪] |
| Retina | Macular edema | Fingolimod | More likely to occur in patients with a past history of uveitis or diabetes mellitus; fingolimod-associated macular edema is dose related and may improve upon cessation of therapy [10] |
| Retina | Photoreceptor dysfunction | Vigabatrin | Based on a prospective, ongoing cohort study, the reported incidence of visual field constriction associated with vigabatrin may actually be a phenomenon seen with epilepsy and other AEDs, and not restricted only to vigabatrin [11] |

Medication side-effects primarily causing neuro-ophthalmologic manifestations are not included in this table, and are discussed in detail below. This table is not inclusive, but includes a representation of the spectrum of diseases encountered in practice. AAO, American Academy of Ophthalmology; AED, antiepileptic drug; HAART, highly active antiretroviral therapy.

**Table 2. Drug classes and medications that can cause pupil dilation**

| Medication class | Examples | Notes |
|---|---|---|
| Anticholinergics | Atropine, scopolamine, ipratropium | Atropine eye drops may dilate the pupil up to a full week |
| Serotonin reuptake inhibitors | SSRIs, SNRIs, MAOs | Serotonin syndrome, a toxic overconsumption of serotonergic medications, is potentially fatal. It manifests as pupil dilation, mental status changes, hyperthermia, tachycardia, tremors, and diaphoresis |
| Adrenergics | Amphetamines, cocaine | Police officers are trained to identify pupillary dilatation as a possible sign of illicit drug use. Pupil size greater than 6 mm in direct light is recognized as abnormal |
| Serotonergics | LSD, psilocybin, mescaline, MDMA | 'Molly' is the colloquial street name for purified MDMA (ecstasy) and is rising in popularity. A toxic overdose similar to serotonin syndrome, associated with dilated pupils, can occur |

LSD, lysergic acid diethylamide; MAOs, monoamine oxidase inhibitors; MDMA, 3,4-methylenedioxy-N-methylamphetamine; SNRIs, serotonin and norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

**Table 3. Drugs (both legal and illicit) that result in pupil constriction**

| Class | Examples | Notes |
|---|---|---|
| Opioids | Morphine, fentanyl, heroin, tramadol | One study used pupillometry to evaluate the effects of tramadol on pupil size. While 70% of subjects developed pupillary constriction, 30% had mydriasis [17]. |
| Neuroleptics | Haloperidol, quetiapine | The combination of constricted pupils and confusion in a patient taking antipsychotics suggests neuroleptic overdose. |
| Serotonin receptor antagonist and reuptake inhibitors | Trazodone | Although trazodone also has some anticholinergic activity, and can cause side effects such as headaches, orthostatic dizziness, and dry mouth, its alpha-adrenergic blockade properties probably result in the pupil miosis. |
| Noradrenergic serotonergic antidepressants | Mirtazapine | Pupil constriction has been reported as a feature of mirtazapine overdose. |
| Cholinergics | Pyridostigmine | Anticholinesterase properties result in contraction of the pupillary sphincter as well as impaired accommodation. |

LSD, lysergic acid diethylamide; MAOs, monoamine oxidase inhibitors; MDMA, 3,4-methylenedioxy-*N*-methylamphetamine; SNRIs, serotonin and norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

are to be given only in extreme circumstances. However, some medications have caused worsening only in very rare cases, and can still be used with caution.

There are three types of potential medication interactions in patients with myasthenia. One group of medications may actually precipitate an iatrogenic myasthenia-like syndrome. These are listed in Table 4 [21,22▪]. A second class of medications may worsen existing myasthenia gravis by exacerbating pathophysiological dysfunction in the neuromuscular junction (Table 5 [23▪,24–28]). A third group of medications may cause fatigue, asthenia, or malaise, and result in generalized weakness. Examples of this third group are narcotics, benzodiazepines, and β-blockers. As these medications are commonly prescribed, the physician must consider the relative risk–benefit ratio for each individual case.

## MEDICATIONS THAT MAY INDUCE POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

Posterior reversible encephalopathy syndrome (PRES) is a recognized cause of cortical visual loss and visual field defects, and is accompanied by mental status changes and seizures. PRES has myriad causes, including hypertensive crisis and eclampsia, but toxic response to medication is another.

Medications reported to induce PRES [29▪–31▪,32,33▪,34–38] are summarized in Table 6 [39▪–42▪], highlighting those first described within the past year.

## MEDICATIONS THAT MAY INDUCE PSEUDOTUMOR CEREBRI

Pseudotumor cerebri can be precipitated by certain medications. In these cases, it can be called

**Table 4. Medications that can precipitate a myasthenia gravis-like clinical picture**

| Class | Examples | Indication | Notes |
|---|---|---|---|
| Chelators, reducing agents | D-Penicillamine, tiopronin | Autoimmune disease, cystinuria | In most cases, AchR antibodies are associated with the onset of a myasthenia-like syndrome, but the relatively rare anti-MUSK antibody has also appeared after penicillamine treatment, and resolved after discontinuation of the medication [21] |
| Interferon | Interferon-α, interferon-β | Hepatitis C | Treatment of hepatitis C may include triple therapy with pegylated interferon, ribavirin, and a protease inhibitor. The induction of myasthenia gravis has been reported as a complication of this combination [22▪] |

AchR, acetylcholine receptor; MUSK, muscle-specific kinase.

**Table 5. Medications that can worsen preexisting myasthenia gravis**

| Class | Drug | Notes |
|---|---|---|
| Botulinum | OnabotulinumtoxinA | Botulinum has been reported to unmask myasthenia gravis [23▪], and generally contraindicated in myasthenia gravis |
| Anesthetics and neuromuscular blockers | Isoflurane, succinylcholine | Use of epidural anesthesia or decreased dose of anesthetic medications, and access to mechanical ventilation are several goals in management of myasthenic patients [24] |
| Antibiotics | Telithromycin, aminoglycosides (e.g., gentamicin, tobramycin, streptomycin); bacitracin, polymyxin, colistin, vancomycin, clindamycin, macrolides (e.g., erythromycin, azithromycin), fluoroquinolones (e.g., ciprofloxacin, gatifloxacin), many others. | Telithromycin is the antibiotic considered absolutely contraindicated in myasthenia gravis. Almost all classes of antibiotics have been associated with worsening of myasthenia gravis to some extent, with aminoglycosides being the most well established. Clindamycin, vancomycin, and the polypeptides are also considered relatively high risk. Lower risk antibiotics include the fluoroquinolones [25], macrolides, and cyclins. There is little risk with sulfa antibiotics or penicillins |
| Quinines | Quinine, quinidine | Quinine therapy is used in regions of malaria. In patients with myasthenia, other treatment options like artesunate have been used as malaria therapy in myasthenic patients with malaria to avoid worsening with quinine [26] |
| β-Blockers | Labetolol, propranolol, atenolol, others. | The common use of these medications results in questions of their safety in the patients with myasthenia. Although increased fatigue is common, true weakness is unlikely [27]. |
| Calcium channel blockers | Amlodipine, nifedipine, nicardipine, others | Rare, but severe cases of both cardiogenic and respiratory decompensation have occurred in patients with myasthenia who received even one dose of calcium channel blocker. |
| HMG-CoA reductase inhibitors | Atorvastatin, pravastatin, rosuvastatin, others | Another ubiquitous medication, statins can be used in patients with myasthenia gravis when indicated [28]. Because statins can either potentially worsen myasthenia gravis or cause a statin myopathy, it is necessary to perform more extensive evaluation for a patient with myasthenia on statins who weakens. |
| Antiepileptics | Phenytoin, gabapentin, carbamazepine, barbiturates, ethosuximide | There are case reports of both phenytoin and gabapentin causing a worsening of myasthenia, but in general the overall risk of worsening in myasthenia gravis due to AEDs is relatively small. Phenytoin should probably be avoided in myasthenia gravis. |
| Ophthalmologic drops | β-Blockers (e.g., timolol, betaxolol), ecothiophate, acetazolamide, proparacaine/tropicamide, | Mostly case reports. These drops are not contraindicated, but an increase in symptoms in a myasthenic should prompt questioning of use. |
| Magnesium | Parenteral or oral formulations | Relatively high doses of magnesium are given for preeclampsia, and myasthenia gravis may worsen or first manifest in this situation. |
| Psychiatric medications | Lithium, tricyclics, phenothiazines (e.g., chlorpromazine). | The myasthenic effect may occur with nontoxic levels of medication and improve with lowering of the doses. |

AED, antiepileptic drug; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-CoA, reductase inhibitors.

secondary intracranial hypertension, as opposed to idiopathic intracranial hypertension (IIH). Recent use of medications listed in Table 7 [43▪,44] should be sought out in patients presenting with pseudotumor. Some tables listing medications that cause pseudotumor include other medications include amiodarone, cyclosporine, mycophenolate, and phenytoin. However, there are no good test–retest studies confirming that these relationships exist [45]. Cases of cyclosporine-induced IIH may

**Table 6. Medications that have been reported to induce posterior reversible encephalopathy syndrome**

| Medication | Examples | Notes |
|---|---|---|
| Immunosuppressants | Cyclosporine A, tacrolimus (FK 506), sirolimus, corticosteroids | This is the most common drug class associated with PRES |
| Cytotoxic chemotherapeutic agents | Cisplatin, oxaliplatin, carboplatin, gemcitabine, cytarabine, tiazofurin, methotrexate, vincristine, L-asparaginase, oxaliplatin/5-fluoracil/leucovorin [39▪] | Oxaliplatin/5-FU/leucovorin is also known as FOLFOX 5 therapy and is the most recently reported of this class |
| Antiangiogenics | Bevacizumab, sunitinib, sorafenib, pazopanib [40▪] | Pazopanib is used as treatment for metastatic renal cell cancer. |
| Monoclonal antibodies | Rituximab, infliximab, anti-disialganglioside (anti-GD2) monoclonal antibody immunotherapy [41▪]. | Anti-GD2 MoAb is used as a therapy for high-risk neuroblastoma. |
| Others | GCSF, antiretrovirals, linezolid, erythropoietin, carbamazepine, interferon-α, ciprofloxacin [42▪] | Myriad case reports exist regarding a drug-induced PRES reaction. Correlation does not necessarily represent causation in all cases |

GCSF, granulocyte colony-stimulating factor; PRES, posterior reversible encephalopathy syndrome.

represent PRES (see above). We found only one case report of phenytoin-related pseudotumor. The same is true for other medications (e.g., indomethacin, danazol), which appear in lists due to single cases reported many years ago. Tamoxifen is one such example, but a Medline search for 'Tamoxifen' and 'pseudotumor cerebri' or 'idiopathic intracranial hypertension' yielded no results. These examples highlight the need for continued re-examination and evaluation of the evidence.

## MEDICATIONS THAT MAY CAUSE A DISTURBANCE IN EYE MOVEMENTS

Medication side-effects may manifest as efferent visual problems [46]. Often, these ocular side-effects are not isolated, rather part of widespread neurologic dysfunction suggesting medication toxicity. At times, the cause–effect relationship is fairly obvious, such as onabotulinum causing increased ptosis, after extraocular muscle (EOM) injections [47]. Other effects may be subtle, and patients have difficulty describing the problem. Eye movement recordings measuring velocity and gain may be helpful. Table 8 [48,49▪,50–54] lists eye movement abnormalities and the medications that can cause them.

Oculogyric crisis is a dystonic syndrome causing involuntary sustained deviation (usually upwards) of the eyes, mutism, mydriasis, neck dystonia, and agitation. The reaction may mimic encephalitis or seizure. When caused by medication, it is due to an extrapyramidal reaction

**Table 7. Medications that may induce pseudotumor cerebri**

| Class | Examples | Notes |
|---|---|---|
| Vitamin A derivatives | Retinoids, isotretinoin (used to treat acne) | The pathophysiology behind vitamin A and IIH is complex, as revealed by the fact that in pediatric pseudotumor, low serum vitamin A levels can also be present [43▪] |
| Cycline antibiotics | Tetracycline, doxycycline, minocycline | Simple withdrawal of the offending agent may not be satisfactory, and ancillary treatments, sometimes aggressive, may be required |
| Corticosteroid use or withdrawal | Female hormonal contraception or hormone therapy | The fact that either use or withdrawal of steroids can precipitate IIH suggests that the neuroendocrine axis is dysfunctional in pseudotumor, and this complex relationship is not yet fully understood |
| Human growth hormone | Also known as somatotropin | HGH-associated IIH may occur in the absence of headache, obesity, or other common associations of the idiopathic variety, making close surveillance of patients on HGH necessary [44] |

HGH, human growth hormone; IIH, idiopathic intracranial hypertension.

from postsynaptic receptor blockade. Opsoclonus describes the rapid disorganized fast eye movements that can occur due to encephalitis or as a paraneoplastic reaction, and has no intersaccadic latency interval. Presence of either of these ocular motor disorders requires an evaluation of possible medication-related causes.

## MEDICATIONS THAT MAY CAUSE ACCOMMODATION DEFECTS

Although not a neuro-ophthalmologic disorder *per se*, we have had frequent neuro-ophthalmology consultations for unexplained visual disturbance in which the diagnosis was medication-induced accommodation defect. For this reason, we are including a short discussion of this problem.

Medications with anticholinergic effects are given for a wide variety of conditions, including glaucoma, Parkinson's disease, bladder incontinence, and chronic obstructive pulmonary disease. These agents exert their antagonist effects through a competitive blockade of receptors to the neurotransmitter acetylcholine. Cholinergic receptors are categorized as muscarinic or nicotinic based on their response to naturally occurring parasympathomimetic products. Muscarinic receptors (subtypes 1–5) are located in the bladder, gastrointestinal tract, eye, heart, brain, and salivary glands [55]. Binding of these receptors opposes the endogenous parasympathetic effects of acetylcholine in the central and peripheral nervous system, allowing for their pharmacologic effect.

The presence of muscarinic receptors on the ocular surface implicates cholinergic regulation in the pathogenesis or treatment for a number of ocular conditions [56]. We have already listed anticholinergics as exacerbating narrow angle glaucoma and discussed anticholinergics and pupil constriction. In addition to these effects is the potential disturbance of accommodation [57]. Just as muscarinic receptors located on the sphincter pupillae muscle are stimulated by the parasympathetic nervous system to contract smooth muscle and decrease the amount of light entering the eye, parasympathetic stimulation of muscarinic receptors on the ciliary muscle causes contraction of the smooth muscle, allowing for the lens to become more spherical and refractory to light. This accommodation allows the eye to view objects at varying distances. Paralysis of the ciliary muscle, referred to as cycloplegia, and subsequent loss of accommodation, are the ocular side-effects caused by muscarinic antagonists.

**Table 8. Eye movement abnormalities and medications that can cause them**

| Eye movement abnormality | Associated medications | Notes |
|---|---|---|
| Decreased saccadic velocity | Benzodiazepines, carbamazepine, gabapentin, barbiturates, haloperidol, amphetamines, nitrous oxide, risperidone | Not all antiepileptic medications induce ocular motor side-effects with the same frequency. The newer antiepileptic pregabalin appears to induce less saccadic dysfunction than carbamazepine [48] |
| Impaired smooth pursuits | Benzodiazepines, phenytoin, carbamazepine, barbiturates, lithium, narcotics, chloral hydrate, nitrous oxide | Smooth pursuits may be impaired even by therapeutic doses of these medications, and this deficit does not necessarily represent toxicity |
| Internuclear ophthalmoplegia | Tricyclics, barbiturates, phenothiazines, lithium, narcotics, beta-blockers, tacrolimus | Would likely be a sign of severe toxicity and associated with other features including coma |
| Gaze palsy | Tricyclics, phenytoin, carbamazepine, barbiturates, lithium, baclofen, valproate [49▪] | Usually a feature of toxicity |
| Opsoclonus | Diphenhydramine [50], tricyclics, lithium, cyclosporin A. | |
| Nystagmus | Antiepileptics, lithium. | Many different types of nystagmus (upbeat, downbeat, positional, gaze evoked) can occur from AEDs, and may be a sign of toxicity. |
| Convergence spasm | Phenytoin | A single case report from 1980 is the only listing from a PubMed search of 'Convergence spasm' and 'phenytoin' or 'dilantin' [51] |
| Oculogyric crisis | Carbamazepine, phenothiazines, lithium, lamotrigine [52], metoclopramide [53], cefixime [54]. | First generation neuroleptics are more likely to induce a crisis compared with second or third generation. Intravenous benztropine is a proposed treatment for an attack |

AEDs, antiepileptic drugs.

**Table 9. Medications with anticholinergic properties that may cause accommodation problems**

| Class | Examples | Clinical utility |
|---|---|---|
| Antidepressants | Amitriptyline, imipramine, paroxetine, fluoxetine, fluvoxamine citalopram, escitalopram | Major depression, bed wetting, OCD, fibromyalgia, generalized anxiety disorder, panic disorder, bulimia |
| Monoamine oxidase inhibitors | Phenelzine sulfate, tranylcypromine sulfate | Atypical depression, anxiety, hypochondriasis |
| Neuroleptics | Perphenazine, trifluoperazine, fluphenazine | Schizophrenia, psychosis, acute mania |
| Antihistamines | Diphenhydramine, dimenhydrinate, chlorpheniramine, promethazine, cimetidine, ranitidine | Allergy, motion sickness, sleep aid, peptic ulcer disease |
| Anti-Parkinson's | Trihexyphenidyl, orphenadrine, benztropine | Parkinson's disease |
| Antimuscarinics | Atropine, scopolamine, homatropine, tropicamide, oxybutynin, glycopyrrolate | Induction of mydriasis, overactive bladder, reduction of airway secretions |
| Parasympatholytics | Nebulized ipratropium bromide, salbutamol, tiotropium bromide | COPD, asthma |
| Cardiac agents | Disopyramide phosphate, diltiazem, nifedipine | |
| Anesthetic agents | succinylcholine, ketamine | |

COPD, chronic obstructive pulmonary disease; OCD, obsessive compulsive disorder.

**Table 10. Medications associated with optic neuropathy**

| Class | Examples | Notes |
|---|---|---|
| PDE-5 inhibitors | Vardenafil, sildenafil, tadalafil | Despite numerous case reports suggesting causation, there are no confirmed relationships between AION and PDE-5 inhibitors to suggest AION occurs at a higher proportion than in the general population [59–61]. An open label crossover study is currently underway to further define a causal link (clinicaltrials.gov identifier: NCT00867815) |
| Antiarrhythmics | Amiodarone | Average drug use of 9 months prior to symptoms. Thirty three percent of patients are asymptomatic. Disc edema occurs in 85%. Fifty eight percent improve after drug cessation. Twenty percent remain <20/200 [62]. |
| Antibiotics | Linezolid | The risk ratio of blindness in linezolid is higher than in other antibiotics [63], and this risk is seen in children as well as adults [64] |
| Anti-TB drugs | Isoniazid, ethambutol | Retinal ganglion cells appear to be the site of toxicity in ethambutol-associated optic neuropathy [65▪] |
| Disulfiram | | Rare dose-related reports of optic neuritis in patients treated with disulfiram |
| Immunosuppressants | Cyclosporin, tacrolimus | Tacrolimus or cyclosporin-induced optic neuropathy can occur with or without toxic levels. Discontinuation of the drug if possible may lead to improvement [66] |
| Chemotherapeutics | Cisplatin, carboplatin, vincristine | The infrequency of reports makes it difficult to state whether there is a true relationship, or by what pathophysiology it would occur [67,68] |
| Tamoxifen | | Case reports of tamoxifen causing optic neuropathy are supported by the finding that the action of tamoxifen on the optic nerve head results in subclinical swelling and possible increased crowding [69] |
| Antitumor necrosis factor therapy | Etanercept, infliximab, adalimumab | Similar to the PDE-5 inhibitors, there have been numerous case reports over the last several years denoting a relationship between TNF-α therapy and optic neuritis. Even so, causation much be interpreted with caution, as some analyses suggest that the risk is no greater than in nonusers [70▪▪▪] |

AION, anterior ischemic optic neuropathy; PDE-5, phosphodiesterase type 5; TB, tuberculosis; TNF, tumor necrosis factor.

Adverse ophthalmologic effects can be induced by a number of different classes of anticholinergic medications due to the ubiquitous distribution of muscarinic receptors in the body. Atropine, the prototype anticholinergic medication, is used to reduce motility in the gastrointestinal tract and to reduce respiratory secretions as pretreatment in anesthesia. In addition to classic antimuscarinic agents, other classes of drugs such as antihistamines, cimetidine, theophylline, and digoxin may have anticholinergic effects. Table 9 lists medications that can precipitate visual disturbance due to loss of accommodation.

## MEDICATIONS THAT MAY CAUSE OPTIC NEUROPATHY

The optic nerve is a potential site for functional disruption due to drug side-effects [58]. An outline of these medications is listed in Table 10 [59–64, 65▪,66–69,70▪▪].

## CONCLUSION

Medication use is based on a risk–benefit profile. Because new medications are constantly being developed within classes, and novel medication classes are themselves being created, the physician should remain updated on potential adverse reactions and side-effects. A critical evaluation of the strength of evidence linking a medication to its purported adverse reaction helps establish the most appropriate risk–benefit profile for each individual.

### Acknowledgements

*The authors wish to thank Mrs Lynn Bannon for organizational assistance.*

### Conflicts of interest

*There are no conflicts of interest.*

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

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