Three classes of medication have been implicated in causing or worsening existing ophthalmological conditions, including alpha-blockers such as tamsulosin, PDE5-inhibitors such as sildenafil, and anticholinergics, including oxybutynin. Some associations have been purely theoretical, others based on case reports with no suggestion of a mechanism. The maxim ‘prescribe with caution’ may be sound advice from a medico-legal point of view, but it is not a practical guide for clinicians keen to minimise harm to their patients. This article discusses each class in turn, presenting the evidence in the literature to date, and summarises the recommendations for their use with regards to their ophthalmological side-effects.

ALPHA-BLOCKERS AND FLOPPY IRIS SYNDROME

Alpha-blockers are widely prescribed in the UK. It is estimated that in the age group 70–79 around 46% of men describe having classical lower urinary tract symptoms (LUTS), and with drug treatment being first line for these symptoms a significant proportion of these patients will be prescribed an alpha-blocker. Highly selective alpha-blockers such as tamsulosin have been found to have a relatively low side-effect profile, with only around 5% of patients experiencing symptoms of dizziness, although there are varying reports on the incidence of retrograde ejaculation.

Another common complaint associated with advancing age is the development
widely from 37.9% to 100%.3,5–9 IFIS has been reported to be between 0.6 and 3.7%, reports on the incidence of IFIS of IFIS in the general population has been found to be associated with other conditions such as diabetes, hypertension, and cardiovascular disease.

IFIS is a triad of progressive intraoperative pupillary constriction, iris prolapse and a flaccid, unpredictable iris. The first suggestion of an association between alpha-blockers and IFIS came from Chang and Campbell who reported that 96% of their cohort who developed IFIS were, or had been, on tamsulosin.3 Other alpha-blockers were not implicated in this study.

The proposed mechanism for IFIS with alpha-blockers is through the blockade of the alpha-1 receptors, specifically alpha-1a receptors, which are found both in the prostate and in the iris. In the eye the dilator muscles of the iris are under sympathetic control, mediated by these alpha-1 receptors, while the radial constrictor muscles are under parasympathetic control. It is thought that drugs like tamsulosin block the alpha-receptors responsible for pupil dilatation, thereby resulting in unopposed parasympathetic action with a constricted pupil and an unstable and ‘floppy’ iris. Other alpha-blockers have varying selectivity for this receptor subtype, which may explain the variation in the incidence of IFIS with different alpha-blockers.

The time taken for tamsulosin to affect the iris is also disputed. Chang et al suggested that it would only occur after a minimum of 2 weeks of taking the drug.2 Others have found detectable effects on iris dilatation intraoperatively after only 2 days of taking tamsulosin.14 Chang et al also carried out a study where they stopped tamsulosin 1–8 weeks prior to surgery and found no significant difference in the severity of IFIS.15

The recommendations for alpha-blockers in relation to cataract surgery are listed in Box 1.

**Box 1. Recommendations on the use of alpha-blockers in relation to cataract surgery**

- Anyone not currently on alpha-blockers should not commence these until after cataract surgery
- If an alpha-blocker has already been started and the risk of urinary retention is low, patients can stop taking tamsulosin at least 2 weeks in advance of surgery with the involvement of the ophthalmologist
- If the patient is at significant risk of retention it is advisable to continue the tamsulosin and inform the ophthalmologist

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sudden, unilateral, complete or partial loss of vision, usually on waking. Few patients become permanently blind and 42% of patients improve markedly within 6 months, although 12% of patients develop worsening visual impairment and 15% of patients find their other eye becomes involved within 5 years.17,18 There are no clinically effective treatments for this condition.

It is thought that NAION develops in patients with already ‘crowded’ optic disks, where a large number of nerve fibres are packed into a small space. This, combined with existing cardiovascular risk factors, reduces flow to the optic nerve, particularly at night when arterial hypoperfusion is most likely to occur.

PDE5-inhibitors have been developed specifically to increase arterial flow to end-organs due to their vasodilatory action. Despite this apparently contradictory mechanism there have been suggestions from a number of small studies that PDE5-inhibitors increase the risk of NAION. McGwin et al reported that in a case-control series of 76 patients there was a statistically significant difference only if the patient had suffered a previous myocardial infarction.19 Other reports have been from case studies alone.

PDE5-inhibitors, such as sildenafil, are very commonly used drugs for erectile dysfunction, and they are used particularly in patients with existing cardiovascular disease. This means that there is significant overlap between patients using PDE5-inhibitors and those experiencing NAION.

Sildenafil is associated with mild and transient visual changes, particularly with blue–green colour discrimination. This is thought to be due to the cross-inhibition of PDE6, which is found in the photoreceptor cells in the retina. The recommendations on prescribing of PDE5-inhibitors in relation to NAION are given in Box 2.

ANTICHOLINERGIC THERAPY AND GLAUCOMA

Anticholinergics are first-line treatments for the management of overactive bladder (OAB) and urinary urge incontinence (UUI) and work by inhibiting M3 receptors in the detrusor smooth muscle of the bladder. Anticholinergic side-effects, such as dry mouth and constipation, arise due to the interaction of these drugs with muscarinic receptors in other tissues such as the mouth and bowel.

Acute-angle closure glaucoma (AACG) is a sight-threatening condition whereby the outflow of aqueous humour from the anterior chamber of the eye is blocked, leading to a catastrophic rise in intraocular pressure and eventually infarction of the optic nerve (Figure 3). Angle closure manifests usually in patients already suffering from chronic glaucoma with narrow drainage channels, also known as ‘narrow angles’, which are at risk of suddenly being closed. Patients already being treated for glaucoma will be

**Box 2. Recommendations on use of PDE5–inhibitors and non-arteritic anterior ischaemic optic neuropathy (NAION)**

- Patients starting sildenafil should be counselled on possible transient changes in colour discrimination
- Patients with a significant cardiovascular history should also be counselled on NAION as a precaution
- Patients with pre-existing NAION in one eye should not be prescribed PDE5–inhibitors

**Figure 2. Retina of patient with non-arteritic anterior ischaemic optic neuropathy (NAION)**

**Figure 3. Pathophysiology of acute-angle closure. Pupillary dilatation can close the angle and block the outflow of aqueous humour leading to a rapid rise in intraocular pressure**
regularly followed up to assess the size of these 'angles', to establish whether they are at risk of angle closure.

One well-documented precipitating factor pushing patients from chronic glaucoma into angle closure is exposure to dark. Pupillary dilatation in these conditions leads to a further narrowing of the angle, occasionally completely blocking the outflow channels and causing a rapid rise in intraocular pressure. Treatment includes various topical eye drops to increase the outflow of aqueous humour and reduce its production, intravenous acetazolamide, and eventually surgical management with peripheral iridotomy to create a new tract for the drainage of aqueous humour.

Ophthalmologists are therefore always careful to assess the depth of the angle before administering topical dilating drops with anticholinergic activity, such as atropine, when examining the eye. It follows then that other anticholinergics could potentially also cause pupillary dilatation and therefore put patients at risk of developing AACG.

Although this mechanism sounds entirely plausible, in clinical practice this effect is extremely rare when using urological drugs. Only one case report exists of an 80-year-old lady taking oxybutynin 2.5mg twice daily who developed unilateral AACG that was successfully treated with iridotomy.

However, because of these concerns, all major trials involving anticholinergics have excluded patients with narrow angles, including the Overactive Bladder: Judging Effective Control and Treatment (OBJECT) study and the Antimuscarinic Clinical Effectiveness Trial (ACET). Not one patient in these large trials has reported AACG as an adverse event.

It is therefore extremely difficult to assess the incidence of AACG in patients taking anticholinergic drugs, as high-risk patients have generally been excluded from trials. It is worth noting that the actual reported incidence of AACG with anticholinergics still remains incredibly low. In Japan a review of 367 patients started on oxybutynin asked each patient about their glaucoma history and, where unclear, patients were sent to an ophthalmologist for clarification. Patients with open-angle glaucoma and treated, closed-angle glaucoma were started on oxybutynin with no adverse effects.

Recommendations on the use of anticholinergic drugs in glaucoma are given in Box 3.

CONCLUSION

In summary, a whole range of potential ophthalmic complications have been associated with the use of urological drugs, although causality is far from proven in each case. Perhaps the most compelling case is for tamsulosin’s effect on intraoperative behaviour of the iris, and ophthalmologists are well aware of the increased surgical complexity of these cases. In most centres, these cases will be performed by a senior surgeon. The evidence for the role of PDE5-inhibitors in NAION and anticholinergic drugs in glaucoma is far less convincing, and while a good history will help to identify the patients at risk, the actual incidence of ophthalmic side-effects is extremely low.

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REFERENCES


