

# An update on glaucoma treatment

In the UK, some form of glaucoma affects two in 100 people over the age of 40 years and five in 100 people over the age of 75 years.

Lucy Titcomb gives an overview of the condition and looks at treatment of primary open angle glaucoma

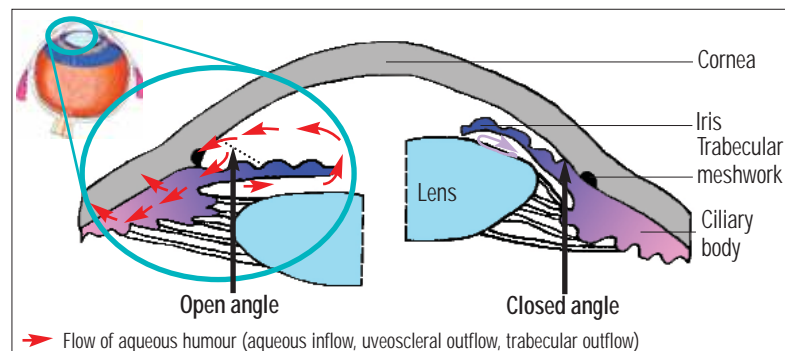


Figure 1: Cross section of the eye

Glaucoma comprises a group of eye diseases with various causes that result in optic neuropathy. The optic nerve becomes damaged, resulting in histopathological changes and loss of visual function. Glaucoma is the world's second biggest cause of blindness. The condition affects around 60 million people, of whom about 10 per cent become blind. In the UK, it accounts for 15 per cent of registered blind people, although this figure probably underestimates morbidity because many people who are eligible for registration do not appear in the statistics.<sup>1</sup>

Classification of glaucomas is usually based on cause and mechanics (see Panel 1).

## Primary open angle glaucoma

Primary open angle glaucoma (POAG), in which the angle of the anterior chamber is open (see Figure 1), is the most common type of glaucoma, with an increased prevalence in:

- People with high intraocular pressure
- People over 40 years of age
- People of black African or Caribbean origin
- People with parents or siblings who have the condition
- People with short sightedness greater than -6.00 dioptres
- People with vascular risk factors (eg, systemic hypotension [where low perfusion pressure cannot counteract the effects of raised intraocular pressure] migraine and Raynaud's phenomenon)

There is also a possible association with diabetes.

POAG is a disease of insidious onset. It is symptomless in its early stages and up to 40 per cent of useful sight can be lost before a person seeks advice. Regular eye tests are, therefore, crucial in detecting glaucoma early.

In POAG a chronic, gradual destruction of ganglion cell axons is caused by the blockage of axonal transport. This, in turn, is caused by a variety of factors — mechanical, vascular

## Panel 1: Classification of glaucoma

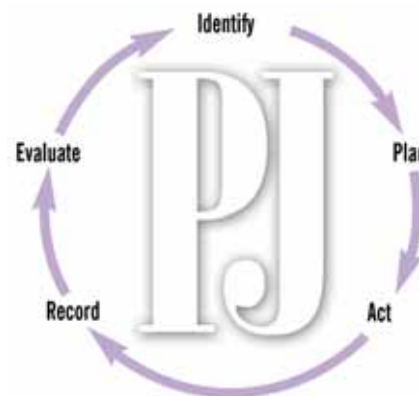
### Primary glaucomas

- Open angle (eg, high tension, normal tension)
- Closed angle (ie, primary angle closure glaucoma)

### Secondary glaucomas

- Open angle (eg, pigmentary, exfoliation syndrome, neovascular, lens-induced)
- Closed angle

Developmental glaucomas (eg, primary congenital, secondary retinopathy of prematurity)



## Identify knowledge gaps

1. Which drugs are now considered to be first-line therapy in primary open angle glaucoma?
2. Which drugs are available as combination eye drops and what are their advantages?
3. Where can people learn more about glaucoma?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record", (available at: [www.uptodate.org.uk](http://www.uptodate.org.uk)). This article relates to "common disease states" (see appendix 4 of "Plan and record").

and biochemical — and their contribution can differ between patients. Glaucoma is not simply ocular hypertension. In some patients optic nerve damage occurs at low levels of intraocular pressure (normal tension glaucoma) while others withstand elevated pressures without damage. The range of intraocular pressure follows a normal distribution pattern with a mean of 16mmHg and an upper limit for normal intraocular pressure of 21mmHg.

## Primary angle closure glaucoma

Primary angle closure glaucoma (PACG), in which the angle of the anterior chamber is closed by the peripheral part of the iris (see Figure 1), results in a rapid increase of intraocular pressure and must be treated rapidly to avoid blindness. It is more common in people of east Asian, Alaskan or Inuit origin, females and people with long sightedness. PACG can be precipitated by factors that dilate the pupil, such as decreased light intensity and drugs. It is a medical emergency, requiring intravenous administration of ocular hypotensives and laser or surgical resolution.

## Secondary glaucomas

The treatment of secondary glaucomas involves the removal or control of the underlying cause in addition to reducing intraocular

## Panel 2: Antiglaucoma agents

Class	Drug	Presentation(s)	Dose frequency
Prostaglandin analogues	Latanoprost	Eye drops 0.005%	<i>od</i> (in the evening)
	Travoprost	Eye drops 0.004%	<i>od</i> (in the evening)
Prostamides	Bimatoprost	Eye drops 0.03%	<i>od</i> (in the evening)
Beta-blockers	Betaxolol	Eye drops suspension 0.25%*	<i>bd</i>
		Eye drops solution 0.5%	
	Carteolol	Eye drops 1%, 2%	<i>bd</i>
	Levobunolol	Eye drops 0.5%*	<i>od</i> or <i>bd</i>
	Metipranolol	Single dose eye drops 0.1%	<i>bd</i>
	Timolol	Eye gel 0.1%	<i>od</i> (in the morning)
		Eye drops 0.25%*, 0.5%*	<i>bd</i>
		Gel-forming eye drops solution 0.25%, 0.5%	<i>od</i> (in the morning)
Sympathomimetics	Apraclonidine	Eye drops 0.5%	<i>tds</i>
	Brimonidine	Eye drops 0.2%	<i>bd</i>
	Dipivefrin	Eye drops 0.1%	<i>bd</i>
Carbonic anhydrase inhibitors	Acetazolamide	Tablets 250mg	250mg up to <i>qds</i>
		Modified release capsules 250mg	250–500mg <i>od</i>
	Brinzolamide	Eye drops 1%	<i>bd</i> or <i>tds</i>
	Dorzolamide	Eye drops 2%*	<i>tds</i> but <i>bd</i> if used with beta-blockers
Parasympathomimetics	Pilocarpine	Eye drops 0.5%, 1%, 2%*, 3% 4%	<i>tds</i> or <i>qds</i>
		Ophthalmic gel 4%	<i>od</i> (at bedtime)

\* Also available in single dose form

pressure. For example, patients with an increase in intraocular pressure associated with topical corticosteroids would require a change in prescription. This article, however, concentrates on the diagnosis and treatment of primary open angle glaucoma.

### Diagnosis

As part of a routine eye test the optometrist measures intraocular pressure typically using a non-contact (air puff) tonometer, assesses the appearance of the optic nerve head with an ophthalmoscope and measures the visual field with perimetry. If the pressure is above the normal range, if there is a marked difference in readings between the two eyes, if there are signs of optic nerve damage, if there is an increased ratio of the depression in the centre of the optic nerve head (cup) to the whole optic nerve disc or if there is an abnormality in the visual field, the patient will be referred to an ophthalmologist.

The ophthalmologist will perform a comprehensive ophthalmic assessment, which in-

cludes examining the eyes at a slit lamp biomicroscope, noting the appearance of the conjunctiva, cornea, iris, anterior chamber and lens, assessing the angle of the anterior chamber, evaluating the optic nerve head with ophthalmoscopy, laser imaging technology or optical coherence tomography, measuring intraocular pressure with applanation tonometry and examining the visual field with perimetry. If there are signs of optic neuropathy at raised or normal intraocular pressure, a diagnosis of high or normal tension POAG, respectively, is made. A target intraocular pressure is defined and appropriate therapy is instituted.

If there is a raised intraocular pressure without signs of optic nerve damage, a diagnosis of ocular hypertension is made and unless the patient shows signs of other intraocular damage warranting initiation of therapy, he or she will be reviewed regularly.

### Treatment of POAG

Glaucomatous damage that has already occurred is not reversible so the aim of treatment is to achieve an intraocular pressure that will not result in any further damage to the optic nerve head. Initial treatment is generally pharmacological and the ophthalmologist has a wide range of topical medicines from which to choose (see Panel 2). All of these lower intraocular pressure by reducing the inflow of aqueous fluid or increasing aqueous outflow, with some of the agents reducing pressure by more than one mechanism.

**First-line monotherapy** Unless the ophthalmologist decides the target pressure cannot be attained with a single agent, first-line monotherapy is instituted. This will normally be a prostaglandin analogue, a prostamide (bimatoprost) or a beta-blocker.

**Prostaglandin analogues and bimatoprost** The prostaglandin analogues latanoprost and travoprost and the prostamide bimatoprost are the most powerful topical ocular hypotensive agents currently available, lowering intraocular pressure by 25 to 30 per cent.<sup>2</sup> Latanoprost and travoprost increase aqueous outflow through the uveoscleral route while bimatoprost increases outflow through both trabecular and uveoscleral routes. In a recent meta-analysis,<sup>3</sup> the authors concluded that travoprost and bimatoprost may have greater efficacy than latanoprost in lowering intraocular pressure in ocular hypertension or glaucoma.

All these agents are well tolerated systemically but can cause eye redness (hyperaemia), permanent changes in iris pigmentation and an increase in length, number and pigmentation of the eyelashes, which is reversed on stopping treatment. Pigmentation of the periocular skin can occur but is rare. Cystoid macular oedema, a painless disorder in which multiple cyst-like areas of fluid appear in the macula and cause retinal swelling or oedema, is a possible side effect in patients following cataract extraction.

Reactivation of herpes simplex keratitis has been reported with latanoprost and bi-

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matoprost so these products are contraindicated in patients with a history of herpes keratitis. Prostaglandin analogues and bimatoprost products are also contraindicated in pregnant and breastfeeding women and in patients allergic to ingredients, such as the preservative benzalkonium chloride, of which there is a particularly high concentration (0.02 per cent) in latanoprost drops.

**Beta-blockers** Following the introduction of timolol in the late 1970s, beta-blockers became the drugs of first choice to treat glaucoma (until they were sidelined by the prostaglandin analogues and prostamides). The five beta-blockers on the UK market vary in their pharmacological properties and the formulations in which they are available (see Panel 2), but all lower intraocular pressure by reducing aqueous inflow by beta-blockade in the ciliary epithelium.

While the non-selective beta-blockers reduce pressure by 25 per cent, administration of the only selective beta-blocker, betaxolol, results in less of a reduction. Timolol, the gold standard in this group and the most widely used, is available in several formulations and is the beta-blocker present with other antiglaucoma agents in combination products (see below). Gel-forming solutions allow once daily dosage.

Levobunolol has a longer duration of action than timolol, allowing once daily administration. Metipranolol, now only available in a preservative-free product, has a higher incidence of periocular dermatitis than other beta-blockers and is rarely used.

Carteolol possesses intrinsic sympathomimetic activity, which makes it the beta-blocker of choice in patients with dyslipidaemia (beta-blockers without intrinsic sympathomimetic activity can decrease high density lipoprotein and raise triglyceride levels). It also has the lowest lipophilicity of the topical beta-blockers so it is worth trying carteolol in patients who experience adverse central nervous system effects with other beta-blockers.

Betaxolol blocks  $\beta_1$ - in preference to  $\beta_2$ -receptors but this is cardioselectivity and not cardioselectivity and, like the other beta-blockers, it is contraindicated in patients with asthma or chronic obstructive pulmonary disease. The 0.25 per cent suspension produces the same effect as the 0.5 per cent solution because, in the former, betaxolol is suspended in slow release particles.

Although the amount of a beta-blocker in an eye drop is low compared with that in oral products, eye drop administration avoids the first pass metabolism and systemic side effects of beta-blockade are possible. These include bradycardia, hypotension, bronchospasm, cold extremities and impotence, and central nervous system effects, such as headache, ataxia, weakness, lethargy, insomnia and nightmares. Beta-blockers are, therefore, also contraindicated in patients with sinus bradycardia, second- and third-degree atrioventricular block or overt cardiac failure.

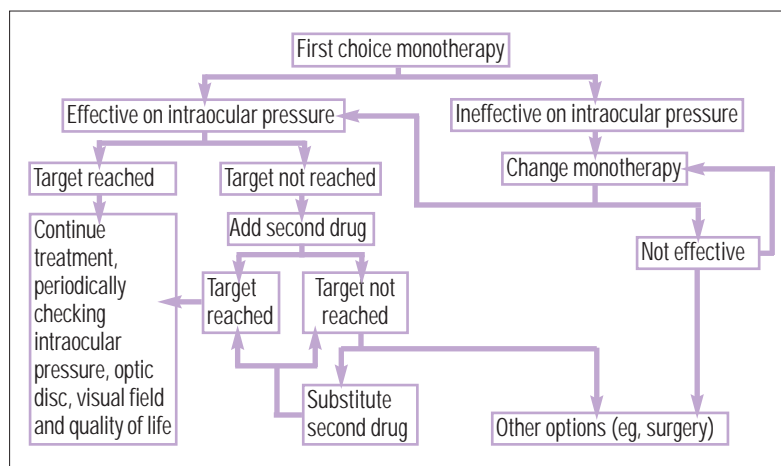


Figure 2: Guidelines for treating primary open angle glaucoma

**Second-line therapy** If first-line therapies are contraindicated, ineffective or not tolerated, a sympathomimetic or carbonic anhydrase inhibitor can be used.

**Sympathomimetics** The original non-selective sympathomimetic eye drop, adrenaline, has been discontinued but its pro-drug, dipivefrin, remains available. However, while better tolerated than its parent drug, dipivefrin is rarely used today and its place in therapy has been taken by the  $\alpha_2$ -selective agents apraclonidine and brimonidine. These drugs lower intraocular pressure by 20 to 25 per cent by reducing aqueous inflow. Brimonidine also increases aqueous outflow by the uveoscleral route.

The most commonly reported side effects are oral dryness, conjunctival redness and allergic conjunctivitis, which may be delayed in onset. Brimonidine is more selective for the  $\alpha_2$ -receptors than apraclonidine so  $\alpha_1$ -mediated side effects, such as mydriasis and lid retraction, are more likely with apraclonidine. Although neither drug is licensed for use in children under 12 years old, if a selective sympathomimetic is indicated, off-label use of apraclonidine is preferred over brimonidine, which passes through the blood-brain barrier, giving rise to side effects associated with central nervous system depression.<sup>4</sup>

**Carbonic anhydrase inhibitors** For many years, the only carbonic anhydrase inhibitor (CAI) used in the treatment of glaucoma was the non-selective drug acetazolamide, which was administered systemically. The topical CAIs, dorzolamide and brinzolamide, selectively inhibit carbonic anhydrase II, which is the predominant isoenzyme in the eye, and lower intraocular pressure by 15 to 20 per cent through reducing aqueous inflow. Both drugs cause taste disturbance, which can be reduced by punctal occlusion — keeping the eye closed and pressing a finger against the corner closest to the nose for one minute reduces the passage of eye drops into the nasopharynx. Punctal occlusion also reduces systemic absorption of eye drops.

Other common side effects of CAIs include headache, local irritation and blurred vision. Nausea and fatigue, side effects

### Panel 3: Advantages of combination products

- Less washout may increase efficacy
- Lower preservative load
- Improved compliance
- Possibly lower incidence of side effects
- Lower prescription charge

commonly associated with systemic CAIs, appear to be more common than with dorzolamide than with brinzolamide. Oral acetazolamide is now rarely used for the long-term control of intraocular pressure.

**Parasympathomimetics** Pilocarpine is now the only parasympathomimetic available commercially. Its dosing frequency (four times a day) and troublesome ocular side effects of miosis and myopia have relegated it to a drug of last resort in the treatment of the open angle glaucomas. Where it is still used for POAG the long-acting gel, instilled at bedtime, is preferred.

**Prescribing** The aim of treatment is to achieve an intraocular pressure that will prevent further damage to the eye. In general, this means reducing pressure by at least 20 per cent from that at which damage occurred or, in advanced glaucoma, to reduce pressure to below 18mmHg. If the first choice monotherapy is ineffective or if therapy is not tolerated, another topical agent can be initiated as monotherapy. On the other hand, if the agent is well tolerated but a sub-optimal reduction occurs adjunctive therapy can be initiated (see Figure 2, p221). Choice of therapy must take quality of life, cost and compliance into account. Generally, if more than two topical medicines are required to control intraocular pressure, other forms of therapy (eg, surgery) should be considered.

**Combination therapies** Target pressures in the treatment of open angle glaucomas are lower than they were in the past and many patients will not reach these targets with monotherapy. When more than one ocular hypotensive agent is indicated, the use of a combination product has several advantages (see Panel 3, p221). Latanoprost, travoprost, bimatoprost, brimonidine and dorzolamide are all available combined with timolol. Combination products must be shown to be more effective than their components used alone and, ideally, not less effective than their components used together as separate drops (eg, the combination of two agents into one product must not reduce drug availability). Although this is not the case with all combination products, patient compliance with a single preparation has been shown to be superior to that with two separate preparations so the benefits of combination products should outweigh any concerns about a slight reduction in efficacy.

### Future drugs

New classes of antiglaucoma agents may include cannabinoids, *Ginkgo biloba*, melatonin, vasoactive peptides, calcium channel blockers and dopaminergic drugs, with research focusing on neuroprotection, neurotrophins, antioxidants, antagonism of nitric oxide and the enhancement of optic nerve head blood flow.<sup>5</sup> The drug most likely to reach the market first is memantine, an N-methyl-d-aspartate receptor antagonist that modulates the effects of pathologically elevated levels of glu-

### References

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tamate, which can lead to neuronal dysfunction. Already licensed for the treatment of moderate to severe Alzheimer's disease, memantine is under investigation for the treatment of glaucoma in a four-year, prospective, placebo-controlled, multi-institutional trial.

### The pharmacist's role

According to the Royal National Institute of Blind People (RNIB), glaucoma remains a major cause of sight loss in the UK, despite the availability of effective treatments, because people do not have regular eye tests or use their medicines correctly. Early diagnosis is the key to successful treatment so pharmacists should encourage those over 40 years old to have eye tests (which include glaucoma screening) every two years. First degree relatives of patients with glaucoma are entitled to free eye tests and should be screened annually. Once diagnosed, patients need to be monitored, so regular attendance at a glaucoma clinic is essential.

Like hypertension, glaucoma is, in its early stages, symptomless so many patients will require encouragement to use treatment. In its recent publication "Don't blame the patient!" the RNIB reported that as much as 32 per cent of patients do not pick up their repeat prescriptions and many more do not use their medicines as prescribed.<sup>6</sup> Even if patients remember to take their medicines it can be difficult for them to do so correctly. Older patients, in particular, may have problems opening or squeezing the bottle.

The RNIB says that 88 per cent of patients report never receiving instruction on the correct use of their eye drops and many leave consultations without being told that most manufacturers of glaucoma medicines provide free devices to help with the administration of eye drops. For example, Xal-ease and Eyot can be ordered from Pfizer and Alcon, respectively. Another device, Opticare, is prescribable on the NHS. Patients living alone can also be made aware that they can request district nurses to make home visits to administer eye drops.

Patients should be instructed to leave at least 10 minutes between instillation of different eye drops, with those that sting being used after the more comfortable drop to avoid washout of the second drop by reflex lacrimation. Similarly, long-acting formulations (ie, gel-forming solution) should be instilled after a simple aqueous solution.

Many support organisations offer support to patients with glaucoma, including information about glaucoma and driving, and pharmacists can signpost these.

### Signposting

- The International Glaucoma Association ([www.iga.org.uk](http://www.iga.org.uk))
- The Royal National Institute of Blind People ([www.rnib.org.uk](http://www.rnib.org.uk))
- Glaucoma specialist, a website produced by two ophthalmologists specialising in glaucoma ([www.glaucoma-specialist.com](http://www.glaucoma-specialist.com))
- The Eyecare Trust ([www.eyecare.org.uk](http://www.eyecare.org.uk))
- The Royal College of Ophthalmologists ([www.rcophth.ac.uk](http://www.rcophth.ac.uk))

### Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Target patients with primary open angle glaucoma for medicines use reviews.
2. Obtain a range of compliance aids for eye drop instillation.
3. Ask patients with glaucoma to make sure family members have regular eye tests.

### Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions: What have you learnt? How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?