Glaucoma

advances in assessment and therapy

Recent advances in diagnostic techniques have improved the early detection of glaucoma, and new medications have increased the therapeutic options for patients with this condition.

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What is glaucoma?

The term 'glaucoma' is derived from the Greek word *glaukos* meaning a blue-grey appearance. Hippocrates used the term to describe the bluish discolouration of the pupil. During the Middle Ages, glaucoma was considered a disease of the crystalline lens. By the 1700s it was recognised that the glaucomatous eye was hard, resisting the pressure exerted by the fingers. In the late 1800s the invention of the ophthalmoscope allowed the observation of the changes in the optic nerve head associated with glaucoma.

Glaucoma is now understood to be a group of diseases with characteristic optic nerve head changes and associated visual field loss, rather than a disease of 'high pressure in the eye'. Raised intraocular pressure is one of the primary risk factors for glaucoma, but not essential to the diagnosis. Conversely, patients may have ocular hypertension (raised pressure) with no evidence of glaucoma.

Glaucoma is the third leading cause of blindness worldwide, accounting for about 15% of all cases. An estimated 93 million people have primary open angle glaucoma, resulting in over 9 million cases of blindness.

In Australia, the most common form of glaucoma is primary open angle glaucoma, with a prevalence of 3%. It is more common with increasing age and in women. Angle closure glaucoma is uncommon; it is seen mostly in patients of Asian descent and in elderly, long sighted Caucasians. Patients who have symptoms of coloured rings in their eyes when looking at artificial lights and headache during the evening (often while watching television or at the movies) may have intermittent angle closure that is related to partial dilatation of the pupil.

Risk factors

The risk factors for glaucoma are summarised in the box opposite. Intraocular pressure remains strongly related to the development of glaucoma, with the risk increasing the higher the pressure.

Community screening

Nearly 50% of cases of glaucoma found in community screening studies are undiagnosed. Therefore regular examinations are critical in the management of glaucoma; the main cause of visual loss is late presentation. Community screening recommendations are summarised in Table 1. Subjects with any risk factor should be assessed by the age of 35 years. For most people an assessment is recommended by the age of 40 years.

Assessment in general practice

When assessing patients for glaucoma, ask them about their risk factors. Note especially if there is a family history of glaucoma or history of raised intraocular pressure.

A simple torchlight test is helpful to identify those at risk of developing angle closure glaucoma (Figure 1). Aim a beam of light from the temporal side of the eye in the plane of the iris. The pattern of iris illumination and shadow reflects the depth of the chamber. If the chamber is shallow the temporal iris will be illuminated and the nasal iris in shadow. Patients with a shallow chamber are at risk of angle closure. Their pupils should not be dilated, and they should be referred to an ophthalmologist for further assessment.

Examine the optic disc by direct ophthalmoscopy, preferably through a dilated pupil. The risk of developing angle closure glaucoma after pupil dilation is very low in patients who do not have a shallow anterior chamber.

Generalised optic disc cupping is one of the earliest changes to be detected in glaucoma. It can be difficult to appreciate, but a comparison of one eye with the other is useful to identify subtle changes (Figure 2).

Progressive glaucoma leads to thinning of the retinal nerve fibre layer. Nerve fibre bundle defects can sometimes be seen using the green light on the ophthalmoscope (Figure 3).

Disc margin haemorrhage (Figure 4) is an important prognostic sign for the development and progression of glaucoma. Any patient with this should be checked for systemic disease (by measuring blood pressure, full blood count, erythrocyte sedimentation rate and blood serum lipids) and referred to an ophthalmologist for a full evaluation.

Inexpensive, self-administered visual field tests, such as the Oculo-Kinetic Perimeter, can be used as a screening tool in the surgery and are more accurate than confrontation tests in assesing visual field.

Risk factors for glaucoma

- Raised intraocular pressure
- Increasing age
- Afro–Caribbean descent
- Ocular trauma
- Past or present use of corticosteroids (topical, inhaled or systemic)
- Family history of glaucoma
- Myopia
- Diabetes
- Hypertension
- Migraine

New diagnostic techniques

Visual field testing

The retina contains two main groups of retinal ganglion cells:

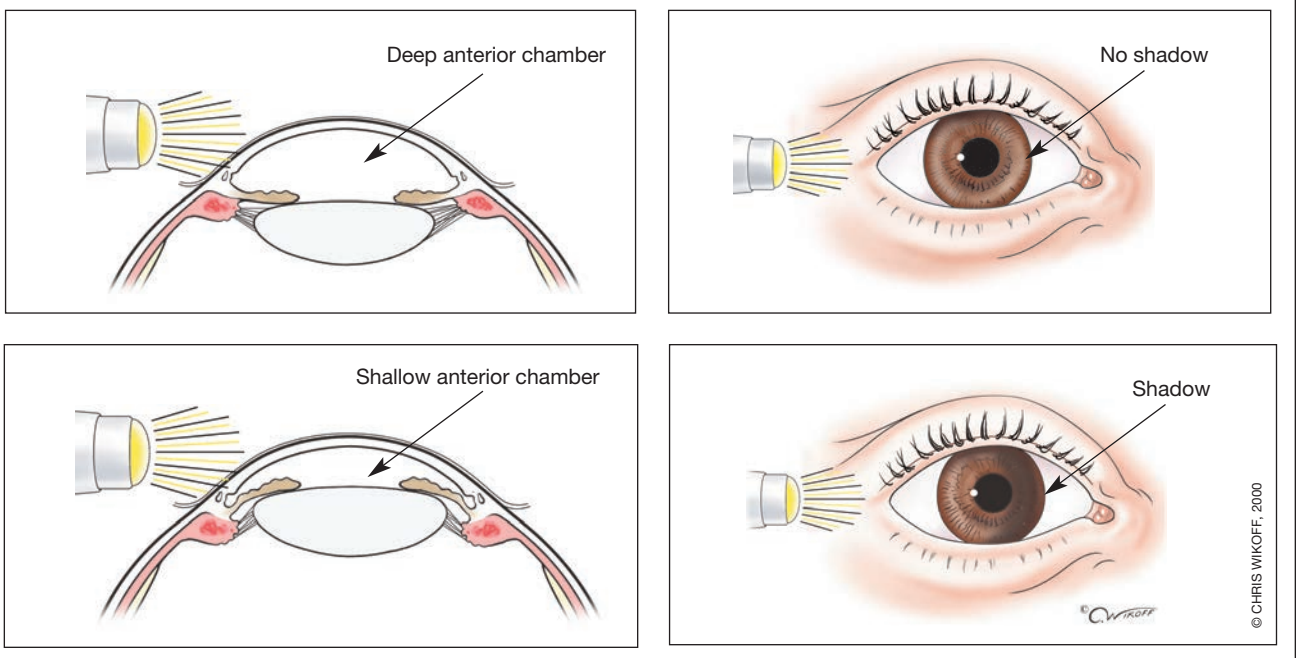
- small or P-cells (comprising 85% of the

IN SUMMARY

- New diagnostic techniques, including computerised perimetry and nerve fibre analyses, have been developed to detect glaucoma at an earlier stage; their accuracy is being evaluated.
- Several new classes of drugs have been released increasing the therapeutic options for glaucoma, including selective α_2-adrenergic agonists, prostaglandin analogues and topical carbonic anhydrase inhibitors.
- Glaucoma research has moved away from drugs that protect the optic nerve by reducing intraocular pressure and is now focusing on pressure-independent agents.
- Poor compliance with glaucoma medication remains a major problem; GPs have an important role in reinforcing the treating ophthalmologist's advice and helping to improve compliance.

continued

The torchlight test



Figures 1a to d. The torchlight test used to estimate anterior chamber depth. A light beam should be aimed from the temporal side of the eye in the plane of the iris. The pattern of iris illumination and shadow reflects the depth of the chamber. If the chamber is deep (a, top left) most of the iris will be illuminated (b, top right). If the chamber is shallow (c, bottom left) the temporal iris will be illuminated and the nasal iris in shadow (d, bottom right).

ganglion cells)
- large or M-cells (15%).

Each subgroup has a special visual function – for example, sensitivity to motion, pattern discrimination, flicker and colour vision. The progressive loss of optic nerve fibres affects different aspects of visual function. Damage to the larger retinal cells is recognised as the earliest sign of glaucomatous optic neuropathy.

Table 1. Community screening recommendations

Age (years)	Screening frequency	
	No risk factors	Risk factors
35–50	Every 3–5 years	Every 2 years
Over 50	Every 2 years	Every year

Automated perimetry remains the mainstay of assessing visual function. New computerised perimeters (such as Humphrey, Octopus and Frequency-Doubling Perimeters) test the different visual functions with higher diagnostic sensitivity, thus identifying glaucoma at an earlier stage.

Nerve fibre layer analysers

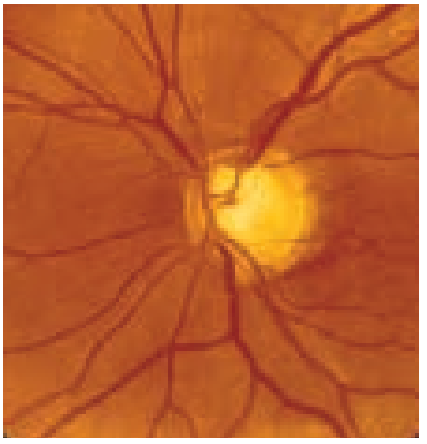
Up to 40% of optic nerve fibres are lost before visual field changes become evident. New techniques have been developed, therefore, to assess the retinal nerve fibre layer and the function of the optic nerve. These include:
- scanning laser polarimetry
- confocal scanning laser ophthalmoscopy
- optical coherence tomography.

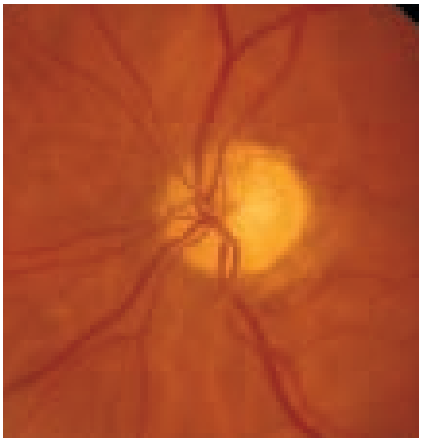
The precise role of these new instruments, particularly their accuracy in detecting early glaucoma, is still being evaluated.

Medical treatment

A major problem with the medical treatment of patients with glaucoma is poor compliance. As there is no immediate symptomatic improvement and many patients require multiple agents, compliance can be as low as 30%. Education is critical to ensure patients understand the nature of their disease and the need for sustained control of intraocular pressure. Community groups, such as Glaucoma Australia (tel: 1800 500 880; website: http://www.glaucoma.org.au), provide valuable education and support.

Patients must understand that glaucoma is diagnosed by optic disc and visual field changes, but that treatment is directed towards lowering intraocular pressure.





Figures 2a and b. Optic disc cupping. A comparison of one eye with the other is useful to identify subtle changes. The disc in figure a (left) is more cupped than that in figure b (right).

The GP's role

GPs have a critical role in reinforcing the treating ophthalmologist's advice. By asking patients about their treatment, the GP can help to prevent many compliance problems. Common mistakes made by patients are:

- failing to take their medications regularly
- using excessive doses
- instilling drops ineffectively.

Patients should be encouraged to instil their eye drops regularly to ensure 24-hour intraocular pressure control. Reminding them to close their eye gently for at least three minute after instilling the drops and occluding the puncta by pressing on the closed inner eyelids will minimise systemic absorption of the medication.

Home nursing visits or instillation devices may be needed if patients are unable to instil their drops correctly.

If patients are prescribed new systemic medications, potential interactions with glaucoma medications should be considered.

Existing glaucoma medications

For many years, β-blockers, pilocarpine, topical adrenergic agents, and systemic acetazolamide (Diamox) have been the mainstays of medical therapy for primary open angle glaucoma, and they are still widely used.

Beta blockers

Beta blockers may be prescribed as a morning only dose to minimise the risk of nocturnal systemic hypotension, which has been implicated in some studies as a possible cause of optic nerve head ischaemia. They are contraindicated in patients with asthma and heart block and may cause lethargy and loss of libido. Betaxolol (Betoptic, Betoquin) is a cardioselective β-blocker with fewer pulmonary complications.

An altered blood lipid and high density lipoprotein cholesterol profile is an important potential side effect of β-blockers and needs to be monitored in patients with other risk factors for ischaemic heart disease.

Pilocarpine

Pilocarpine is used less often than β-blockers as it is associated with focusing and night vision difficulties and pain around the eye. Retinal detachment and angle closure can also be precipitated, even after short term use. Dosage is usually four times daily; however, some patients achieve adequate pressure control with twice daily use. Combination

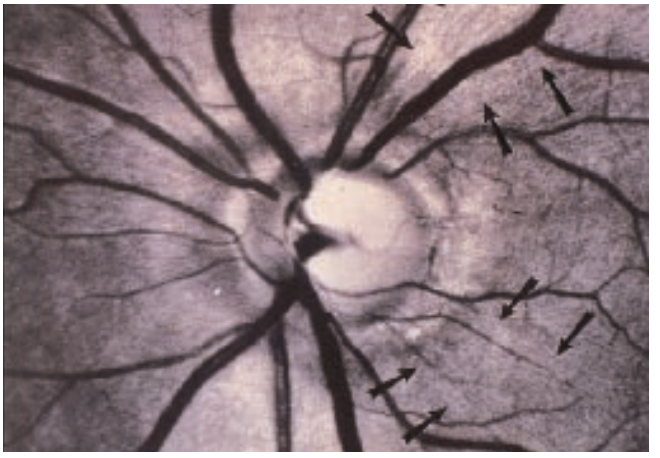


Figure 3. Retinal nerve fibre bundle defects (arrows) detected using the green light on the ophthalmoscope.

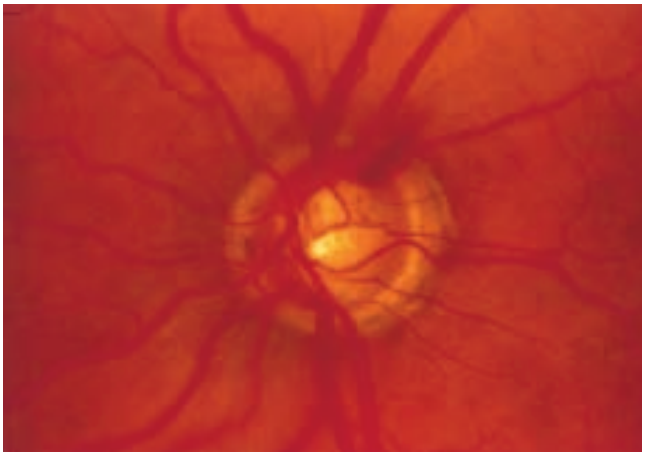


Figure 4. Disc margin haemorrhage of the left optic disc at 1 o'clock.

Table 2. New topical medications for glaucoma

Class	Generic (trade) name	Dosage	Side effects	Concerns
Selective α_2-adrenergic agonists	Apraclonidine (Iopidine) Brimonidine (Alphagan Eye Drops)	Thrice daily Twice daily	Allergic conjunctivitis, dry mouth, fatigue, abnormal taste sensation, headache, hypotension	Caution in patients taking monoamine oxidase inhibitor therapy, tricyclic antidepressants, cardiac glycosides, anithypertensive agents
Prostaglandin analogues	Latanoprost (Xalatan)	Once daily	Increased iris pigmentation, lash growth, intraocular inflammation	Long term effect of increased iris melanosomes is unknown
Topical carbonic anhydrase inhibitors	Dorzolamide (Trusopt)	Twice or thrice daily	Corneal toxicity, bitter taste following administration	Sulfonamide-related drug allergy

timolol/pilocarpine therapy (Timpilo) is available and administered twice daily.

Adrenergic agents

Adrenaline and dipivefrine (Propine) can be associated with systemic and local side effects and a poorer prognosis after glaucoma filtration surgery. They are now rarely prescribed following the release of newer agents.

Acetazolamide

Acetazolamide (Diamox) remains one of the most potent intraocular pressure-lowering agents; however, its use is limited by its significant systemic side effects. It can be used orally, intramuscularly or intravenously in acute cases (for example, in patients who have had cataract surgery or have acute angle closure glaucoma). Long term oral use is reserved for those patients whose glaucoma is not controlled by topical therapy and for whom surgery is not indicated.

New therapeutic options

In the last decade, several new classes of drugs have been released offering new therapeutic options for the treatment of glaucoma (Table 2). They include latanoprost (Xalatan), brimonidine (Alphagan Eye Drops) and dorzolamide (Trusopt).

Latanoprost

Latanoprost is the first prostaglandin to be used in the management of glaucoma. It is a prostaglandin-$F_{2\alpha}$ analogue that is as effective as timolol (Optimol, Tenopt, Timoptol).

Latanoprost lowers the intraocular pressure by increasing uveoscleral outflow of aqueous humour. One major benefit of latanoprost is its need to be administered only once daily. There appears to be a slightly better response when it is used in the evening; this is the recommended dosage time unless compliance is better with a morning dose. It is strongly additive to β-blockers, and also appears to have a paradoxical additive effect to cholinergics (which decrease uveoscleral outflow).

An interesting side effect of latanoprost is increased iris pigmentation, which usually develops in patients with hazel or mixed coloured eyes. The pigmentation is due to an increase in intracellular melanin production, and not to a proliferation of melanocytes. The changes are not reversible after ceasing treatment. There is no clinical or histological evidence of the development of iris melanoma.

Other side effects include lengthening and thickening of eyelashes, reversible iritis and cystoid macular oedema. Macular oedema has been noted in the eyes of patients with a history of complicated cataract surgery or inflammation. Most ophthalmologists would use latanoprost cautiously in patients with risk factors for intraocular inflammation.

Brimonidine

Brimonidine is a second generation α_2-adrenergic agonist. It has largely replaced apraclonidine due to the lower rate of allergy. Its effect in decreasing aqueous humour production and increasing uveoscleral outflow reduces intraocular pressure. Most patients require only twice daily dosing, but the intraocular pressure needs to be checked to ensure

adequate 24-hour control. The efficacy of brimonidine at peak drug level is similar to that of timolol, and at trough level slightly less. It appears to be additive to other glaucoma drugs, and clinical trials are currently underway to assess this response further.

Allergy is a problem with up to 10% of patients having to cease brimonidine after an episode of acute allergic conjunctivitis. Some patients may experience lethargy, dry mouth and headache. Brimonidine does not appear to affect systemic blood pressure or pulmonary function; however, it should be used cautiously in patients with significant cardiovascular disease.

Dorzolamide

Dorzolamide is a water soluble, topically applied carbonic anhydrase inhibitor. It was developed in an effort to achieve the profound intraocular pressure lowering effect of acetazolamide without the systemic side effects. Unfortunately, the pressure lowering effect is less than that of timolol, latanoprost and brimonidine, and most patients require three doses daily. Systemic side effects are minimal, but ocular irritation and a bitter taste sensation are common. Dorzolamide is a sulfonamide derivative and thus contraindicated in patients who are allergic to sulfur drugs. It is used mainly as an adjunctive agent in patients in whom surgery is not indicated.

Neuroprotection

In the last decade glaucoma research has moved away from drugs that protect the optic nerve by reducing intraocular pressure and focused on agents that are pressure-independent.

Some agents, such as calcium channel blockers and nitrates, may improve optic nerve head blood flow. Nocturnal dips in blood pressure associated with the use of systemic cardiovascular drugs may have a deleterious effect on the optic nerve head. This effect needs to be monitored carefully in patients with progressive glaucoma.

Another group of agents that block the neuronal cell death cascade (apoptosis) is being investigated.

A neuroprotective effect associated with brimonidine has been demonstrated in rats following experimental crush injuries to the optic nerve. As yet, however, there is no evidence of any neuroprotective effect in primates or humans with glaucoma.

Surgery and antimetabolites

The success rate of glaucoma filtration surgery in patients at high risk of glaucoma has been improved by the adjunctive use of antimetabolites to inhibit postoperative scarring. The healing response is the major determinant of the long term intraocular pressure after surgery, and can be profoundly dampened by 5-fluorouracil (Efudix, Fluoroplex, Fluorouracil Injection) and mitomycin C (Mitomycin C). At the clinical doses used, these drugs inhibit cell proliferation and induce cell death. This results in relatively acellular tissues that are unable to respond to healing stimuli, thereby minimising scarring. Both drugs are delivered to the subconjunctival space on soaked surgical sponges intraoperatively and via injection postoperatively. There is no evidence of systemic toxicity with the small doses used (5 mg/mL of 5-fluorouracil and 0.2 to 0.5 mg/mL of mitomycin C).

Conclusion

Glaucoma remains a common and underdiagnosed cause of visual loss in our community. New techniques have improved the detection of optic nerve damage, allowing treatment to be started earlier. GPs have an important role in referring patients with risk factors or evidence of optic disc cupping or haemorrhage, as well as in reinforcing the treatment regimen to improve compliance. MT