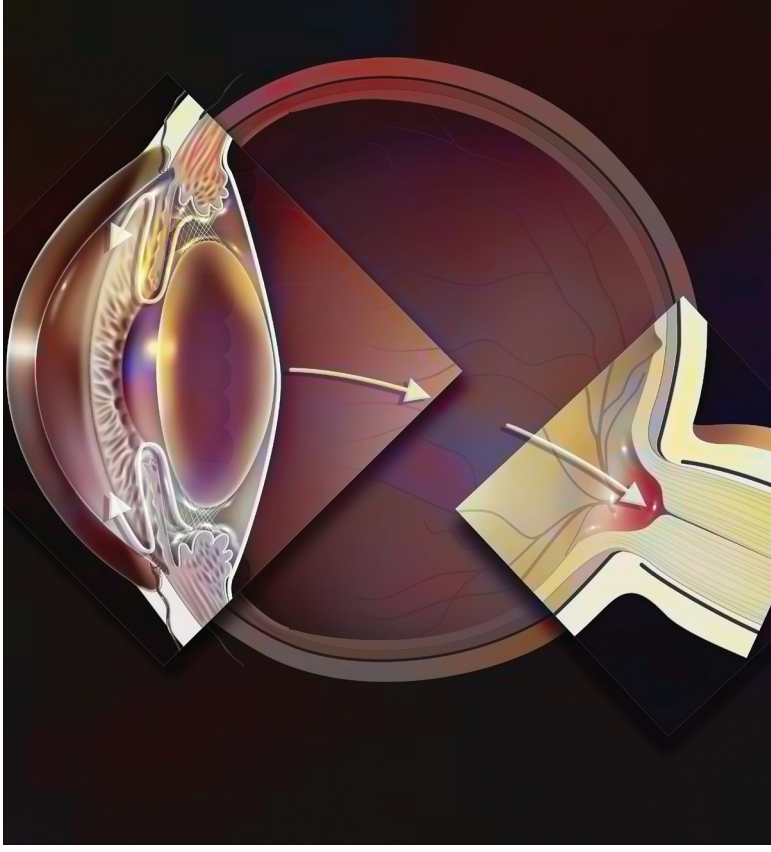
Management of open angle glaucoma

Medicines and laser



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An awareness of a patient's risk profile for glaucoma and the importance of early detection can help prevent vision loss that is irreversible once it occurs. Knowledge of the algorithms guiding glaucoma treatment options, the medications used and factors leading to nonadherence, as well as the increasing interest in laser therapy and lifestyle and nutrition interventions, can further aid disease management.

Glaucoma is a leading cause of preventable blindness worldwide and poses a growing concern due to the ageing population, as prevalence increases with age. Chronic open angle glaucoma, the most common subtype, earned the moniker 'silent thief of sight' for its asymptomatic nature until the very late stages of significant and irreversible visual field loss. Human peripheral vision is extensive (about 60 degrees nasally and superiorly, 95 degrees temporally and 75 degrees inferiorly) and essential for survival. Early visual loss requires perimetric detection. By the time open angle glaucoma becomes symptomatic, even with modern automated and sensitive visual field analysers, loss of visual field does not manifest until at least 30% of the retinal ganglion cells that comprise the optic nerve have been lost.[1-3] The consequences of this visual loss include an increased risk of falls and motor vehicle accidents and reduced quality of life. Thus, early detection and ongoing monitoring are vital for timely intervention. GPs can help to ensure this takes place and that ongoing management is maintained as, although there is no cure, the 'thief' can be stopped from causing blindness. Furthermore, as diabetes and blood pressure control increase the risk of glaucoma, optimisation of general health may play a role in management.[4,5]

Pathogenesis

The pathogenesis of glaucoma is multifaceted and not completely understood, despite advances in its genetics and pathophysiology. Glaucoma is defined as characteristic visual field defects with matching optic nerve changes. The most common form of glaucoma is primary open angle glaucoma (POAG), typically associated with elevated intraocular pressure (IOP). Although high IOP is an important risk factor for POAG and contributes to optic nerve damage, it is not the condition's defining feature. Indeed, glaucoma can occur at normal IOP levels (normal tension glaucoma [NTG]) and, conversely, elevated IOP may not always lead to optic nerve damage (ocular hypertension [OHT]). Research focuses on factors such as impaired optic nerve perfusion, ocular biomechanics and mitochondrial dysfunction in the disease process. Nonetheless, lowering IOP remains the primary modifiable risk factor and the only proven means to slow disease progression; thus, it is the focus of all current treatments.

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1. RISK FACTORS FOR GLAUCOMA

Common risk factors

- Increasing age – risk increases significantly after the age of 40 years and continues to rise with each decade
- Elevated intraocular pressure
- Myopia (near-sightedness)
- Ethnicity – higher risk in patients of Afro-Caribbean, Hispanic and Asian descent
- Systemic disease (including hypertension, diabetes) and medication use (corticosteroid use)
- Thin corneas

Additional factors for consideration

- Vascular insufficiency and normal tension glaucoma risk
  - hypotension, especially nocturnal blood pressure dips; consider avoiding night time dosing of antihypertensives if such glaucoma is difficult to control
  - Raynaud's phenomenon
  - migraine
  - obstructive sleep apnoea
  - diabetes
- Underlying ocular conditions causing secondary open angle glaucoma; in these conditions the outflow drainage pathway dysfunctions due to blockage from either:
  - pigment in pigment dispersion syndrome
  - flaky dandruff-like material in pseudoexfoliation syndrome
  - inflammatory cells in uveitis glaucoma (often associated with systemic conditions such as seronegative arthropathies and sarcoidosis)
  - previous blunt ocular trauma
  - new blood vessels in the angle in response to ischaemia (e.g. as a consequence of proliferative diabetic retinopathy or retinal vein occlusion)
  - lens-induced glaucoma from leaky lens material in hypermature cataracts

Adapted from Schacknow P, Samples J. The Glaucoma Book: A Practical, Evidence-Based Approach to Patient Care. New York, NY: Springer; 2010: 399-420.

With regard to glaucoma screening, GPs have an important role in identifying high-risk patients and facilitating formal optometric assessment, including automated visual field testing and optic nerve scanning, where available. Box 1 summarises the main risk factors for glaucoma.

Glaucoma management

The goal of treatment is to prevent visual field loss that will impact a patient's quality of life in their lifetime. Patients may have a 'target IOP' set – an estimated IOP upper limit at which progression of glaucoma is unlikely to occur. This target is based on the individual's pretreatment IOP, the severity of their visual field defect and other risk factors, such as their corneal thickness, age and family history. Glaucoma can often progress despite seemingly satisfactory IOP. In such cases, the target pressure is lowered further, and treatment is escalated to achieve this. The prime criterion for whether therapy is adequate is when stability of the optic nerve structure and visual function have been achieved. Patients therefore need regular long-term monitoring with their ophthalmologist or optometrist (Table 1).

Glaucoma management has traditionally commenced with medical pharmacotherapy (eye drops), followed by laser therapy and, finally, surgical procedures. However, the patient's treatment must be individualised for their disease severity and take into account other medical, as well as social, factors. Thus, any of these three management options can be initiated at any stage of the disease, and may often be done so in combination with each other (Figure 1).

Do lifestyle factors play a role in glaucoma management?

Several important lifestyle factors can impact disease progression. Treatment compliance is the most important of these.

Certain hobbies can increase the risk of disease progression. Activities that result in a prolonged valsalva manoeuvre, strain or increased venous return to the head can lead to IOP spikes, which if sustained, may impact a patient's glaucoma. Examples include inversions during yoga, wearing tight goggles when swimming, playing brass or wind instruments, glass blowing and weightlifting. Systemic diseases, such as diabetes, hypertension and hypotension, are also risk factors for glaucoma development.

Diet and nutrition may affect the risk of glaucoma. Although there is no scientific evidence that any specific diet has a beneficial effect on glaucoma, randomised controlled trials (RCTs) are underway to investigate whether nutritional supplementation with oral nicotinamide (vitamin B3) offers neuroprotection against glaucoma progression.[6] Nonvalidated research suggests that deficiencies in vitamin B12, folate and vitamin D may be associated with NTG and its progression. Patients with NTG also often present as a particular demographic that includes having a low BMI, being vigilantly health conscious, and more likely to be taking many supplements and consuming a low-salt diet. In these patients, achieving a healthy BMI, avoiding dehydration and consuming an adequate amount of salt is recommended to avoid hypotension and low cerebrospinal fluid pressure that may worsen glaucoma.

Early data suggest that stress management and relaxation techniques, including meditation, may have a complementary role in glaucoma management.[7] An RCT showed that mindfulness-based stress reduction by meditation reduced IOP, positively affected stress biomarkers and improved quality of life of patients with POAG.[7]

Medical management

Topical therapy

Topical pharmacological therapies for glaucoma, namely eye drops, reduce IOP by increasing the outflow of aqueous humour, decreasing aqueous humour production, or both. The four main classes of glaucoma eye drops used today are prostaglandin analogues, beta blockers, carbonic anhydrase inhibitors and alpha agonists. Their doses, mechanisms of action and common side effects are summarised in Table 2.

Prostaglandin analogues are generally considered first-line treatment because of their excellent efficacy and once-a-day dosing (usually nightly). Miotics such as pilocarpine are no longer in common use

for open angle glaucoma because of their poor side effect profile. If a second agent is required, several options exist for combination formulations that optimise convenience and adherence for patients (e.g. latanoprost/timolol, bimatoprost/timolol, brinzolamide/timolol, dorzolamide/timolol, brimonidine/timolol and brinzolamide/brimonidine).

Poor treatment adherence

Strict adherence with eye drop use is critical to achieving glaucoma stability. Poor adherence is poses a significant challenges to glaucoma management, as patients do not have symptoms from the disease and drops may be poorly tolerated. Studies show nonadherence with glaucoma treatment to be as high as 60%.[8] Patients tend to use their drops more reliably in the lead up to an appointment, resulting in a falsely low IOP reading that does not reflect their usual control level. A recent study explored factors affecting glaucoma eye drop adherence in 145 patients in Australia through a questionnaire. Lower adherence rates were correlated with:[9]

- difficulty in applying drops
- a history of depression
- poor memory
- low self-reported motivation rating.

Recognising these risk factors, especially a history of mental health problems, can help identify and overcome compliance barriers. Encouraging adherence is one of the important ways GPs can contribute to the care of patients with glaucoma. Key points on how GPs can help optimise compliance are summarised in Box 2.

Eye drop intolerance

Eye drops can be poorly tolerated, leading to the exacerbation of dry eye symptoms and causing irritation, redness and, occasionally, a more severe follicular conjunctivitis. This can be a result of intolerance to the medications themselves, as well as the preservatives contained in eye drop formulations. Benzalkonium chloride is the most commonly used preservative and has toxic effects to the ocular surface.

TABLE 1. PATIENT FOLLOW UP MONITORING RECOMMENDATIONS

Glaucoma stage	Management recommendation	Recommenced monitoring intervals
Early stable glaucoma	Serial assessment by an ophthalmologist or alternating ophthalmologist and optometrist, depending on patient choice and specialist availability	6- to 12-monthly
Moderate stable glaucoma	Serial assessment and management by an ophthalmologist, in collaboration with an optometrist	6-monthly
Advanced glaucoma	Must be managed by an ophthalmologist	At the ophthalmologist's discretion: generally, at least three to four times a year
Unstable glaucoma	Needs referral to an ophthalmologist as soon as possible	To be managed by an ophthalmologist until deemed stable again
Acutely raised intraocular pressure	• Medical emergency • Needs immediate referral to an ophthalmologist • Emergency medical treatment can be initiated by a qualified optometrist or GP as transfer is arranged	Definitive management by an ophthalmologist

Adapted from The Royal Australian and New Zealand College of Ophthalmologists RANZCO. Clinical practice guidelines for the collaborative care of glaucoma Patients and suspects by ophthalmologists and optometrists in Australia. RANZCO; Sydney, 2019. Available online at: https://ranzco.edu/wp-content/uploads/2018/11/Guidelines-for-the-Collaborative-Care-of-Glaucoma-Patients.pdf (accessed October 2023).

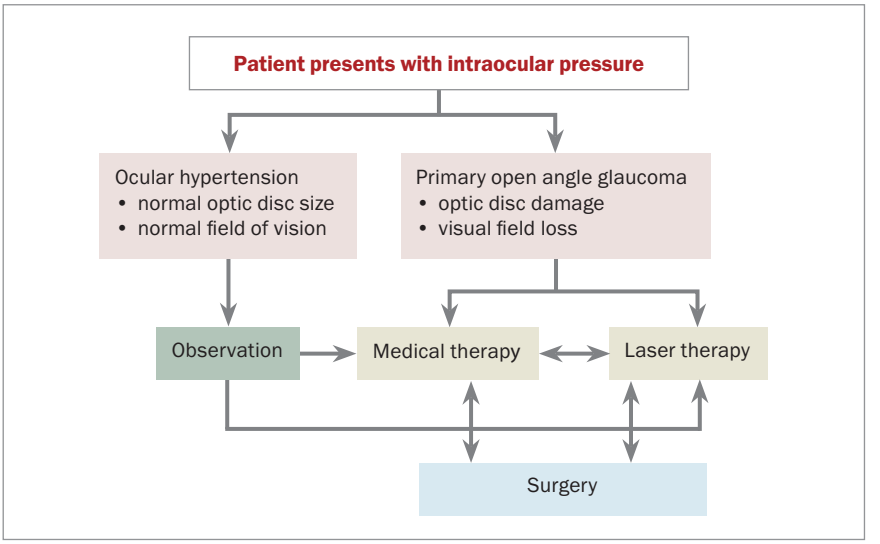

Figure 1. A simple management algorithm for patients presenting with intraocular pressure (IOP). After determining the underlying cause of the IOP, patients may be managed at any stage of disease with medical therapy, laser therapy or surgery, or a combination of these. The double-ended arrows represent interchangeable treatment options.

TABLE 2. EYE DROP MEDICATIONS FOR GLAUCOMA

Medication class	Generic names	Mechanism of action	Dosing (duration of action)	Common side effects	
				Local	Systemic
Prostaglandin analogues	• Bimatoprost • Latanoprost • Travoprost • Tafluprost	Increases uveoscleral outflow	Instilled once daily (every 24 to 36 hours)	• Conjunctival hyperaemia • Hyperpigmentation • Overgrowth of eye lashes, iris and lid skin • Can exacerbate intraocular inflammation (uveitis, macular oedema) and occasionally cause orbital inflammation and orbital fat loss	Nil significant
Beta blockers	• Betaxolol • Timolol	Suppresses aqueous inflow	Instilled once or twice daily (every 12 to 24 hours)	Allergic blepharoconjunctivitis (uncommon)	• Can induce bronchospasm, bradycardia and hypotension • Contraindicated in asthma, COPD, bradycardia • Use with caution in older people • Can cause depression, mood swings and erectile dysfunction
Carbonic anhydrase inhibitors	• Brinzolamide • Dorzolamide	Supresses aqueous inflow	Instilled twice to three times daily (every 8 hours)	Commonly stings on administration, but generally well tolerated	Sulfonamide allergies are a relative contraindication
Alpha agonists	• Apraclonidine • Brimonidine	Suppresses aqueous inflow and increases uveoscleral (unconventional) outflow	Instilled twice to three times daily (every 8 to 12 hours)	• Possibly the least tolerated, with high rates of hyperaemia and allergic blepharoconjunctivitis (up to 15% for brimonidine, 30% for apraclonidine) • Can exacerbate intraocular inflammation	• Dry mouth and headaches • Can interact with tricyclic acid and monoamine oxidase inhibitor antidepressants • Central nervous system depression, including apnoea and hypotension in children

Abbreviation: COPD = chronic obstructive pulmonary disease.
Adapted from Denniston AKO, Murray PI (eds). Oxford Handbook of Ophthalmology (4th edn). Oxford University Press; Oxford, 2018.

For mild adverse reactions, conservative measures are recommended, such as switching to preservative-free formulations, using regular lubricant artificial tears and treating any coexisting blepharitis. If the reaction is severe, identifying and stopping the culprit drop is essential; alternative drops can be trialled and selective laser trabeculoplasty (SLT) should be considered instead.

Although it can be tempting to consider a course of weak topical corticosteroids to treat the inflammatory component of dry eye, these should be used with caution in patients with glaucoma and only under the guidance of an ophthalmologist because of the high prevalence of corticosteroid-induced IOP spikes (known as a steroid response) that occur in one of 10 patients, which can be detrimental to glaucoma progression.

Glaucoma can be associated with dry eye syndrome, and aggressive treatment may improve both IOP control and quality of life. Treatment may include the use of topical immunomodulatory agents, such as ciclosporin or lifitegrast, and treatment options, such as trying to reduce reliance on topical treatment by the use of SLT.

Oral therapy

Acetazolamide is an oral agent that is extremely effective at lowering IOP but is poorly tolerated and can cause paraesthesia in the fingers, toes and around

2. HOW CAN CLINICIANS OPTIMISE PATIENT ADHERENCE TO EYE DROPS?

- Ask patients how often they are forgetting their drops and about their hit and miss rate
- Educate patients about the natural history of glaucoma and importance of strict adherence. Refer patients to community support groups or online resources, such Glaucoma Australia (https://glaucoma.org.au)
- Revise drop administration technique (Figure 2), including punctal occlusion and leaving at least a few minutes between different eye drops so the first is not washed out by the second
- Explore barriers to administering drops. For instance, older patients with arthritic hands can find it difficult to squeeze eye drop bottles effectively; eye drop dispensing aids can be obtained for free through Glaucoma Australia or purchased from local pharmacies (Figure 3)
- Simplify medication regimen by considering combination formulations

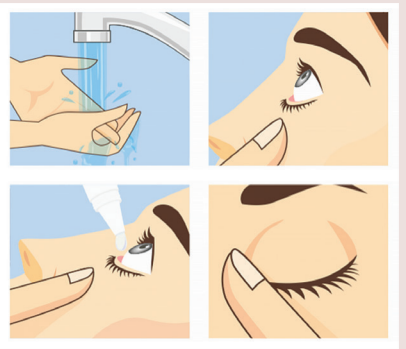

Figure 2. Drop administration technique and punctal occlusion. Wash hands thoroughly before applying drops (top left). With head tilted back, gently pull down the lower eyelid (top, right). Holding the eye drop bottle upside down with the other hand, aim to place the drop on the lower lid pocket (bottom left). Once the drop is placed, apply gentle pressure over the drainage canal with the fingertip for at least two minutes to stop the eye drops from draining down to the nose and throat (bottom, right). Repeat process for the other eye if needed. If multiple eye drops are needed, leave at least five minutes between drops.

Reproduced with permission from Glaucoma Australia. Patient handout on eye drops. Available online at: https://glaucoma.org.au/sites/default/files/2020-08/GA_11299_2019_Eye-Drop_8pp-DL_Roll-Fold_FA-Online.pdf (accessed October 2023).

Figure 3. Examples of eye-drop dispensing aids. Xal-Ease™ Eye drop Aid (left) and Alcon 2.5mL Eyot™ Eye drop Aid (right), both available free to patients through Glaucoma Australia and from local pharmacies.

Xal-EaseTM Eye drop Aid image reproduced with permission from Aspen Australia. Copyright Aspen Australia.

the mouth, gastrointestinal upset, altered taste, depression and malaise. It is not suitable for long-term use as it can lead to hypokalaemia, metabolic acidosis and renal impairment. Its use is, therefore, usually reserved for temporising situations, for example, in acute glaucoma or while awaiting surgical intervention. Kidney function and electrolyte levels should be monitored during use.

On the horizon

The following agents show promise in the management of glaucoma.

- Nicotinamide (vitamin B3) – has been shown to reduce glaucomatous and metabolic damage in animal models.[10,11] Promising findings in human studies support a potential neuroprotective effect, independent of IOP lowering.[12,13] Several major international RCTs are underway to determine whether its use slows glaucoma progression.[14-16]
- Implantable depot prostaglandin – a number of innovative sustained delivery platforms for glaucoma medications are under development. The bimatoprost sustained-release implant is a biodegradable, polymer-based delivery system that slowly releases the medication into the aqueous humour over a period of four to six months, with promising results shown in phase 3 studies.[17,18]
- Rho kinase inhibitors – these are a fifth class of eye drops for pressure-lowering that increase aqueous outflow via the trabecular meshwork. Introduced in Japan and gaining FDA approval in 2017, they have been recently rolled out in Europe and the UK; however, they are not yet PBS listed in Australia.

Selective laser trabeculoplasty

Laser trabeculoplasty is an alternative to topical pharmacotherapy. SLT, currently the treatment of choice for open angle glaucoma, was endorsed by the FDA in 2001 and has since been increasingly adopted as an alternative to eye drop use. It can be utilised as first-line therapy in eye drop-naïve patients, as additional therapy to existing drops when further IOP reduction is required or as a replacement for eye drops when intolerance is an issue.

The procedure

SLT is a safe, well-tolerated treatment performed in the clinic setting under topical anaesthesia. Patients may be pretreated with pilocarpine 2% eye drops if their angles are assessed as narrow for optimised visualisation. The laser is focused through a mirrored lens onto the trabecular meshwork: the drainage area in the angle between the cornea and iris. SLT uses a 532 nm frequency, double q-switched Nd:Yag laser with a 400 micrometer beam. Compared with its predecessor argon laser trabeculoplasty (ALT), SLT minimises collateral tissue damage through an ultra-short pulse duration of three nanoseconds, an order of magnitude that is 10^9 times lower than that of ALT. Thus, the laser is only absorbed by the pigmented meshwork cells and spares the adjacent non-pigmented tissue.

The procedure takes less than five minutes to perform and is well tolerated, with the main side effects being mild

3. BENEFITS OF SELECTIVE LASER TRABECULOPLASTY

- Treatment in early-stage open angle glaucoma is clinically effective for several years, with repeat treatments possible as required
- Confers good intraocular pressure control and improved quality of life for patients compared with topical treatment
- Cost-effective
- Useful in primary open angle and secondary open angle glaucomas, such as pseudoexfoliation syndrome, pigment dispersion and corticosteroid-induced and normal tension glaucomas
- As a result, it is increasingly being used as the first-line or primary treatment option

redness, discomfort and glare that resolves within a few days. Mild topical anti-inflammatory eye drops may be prescribed for up to a week after the procedure. Patients may be asked to stay for 30 minutes after the procedure for an IOP check; however, there are no post-procedure restrictions.

Several studies have investigated whether 90, 180 or 360 degrees of the angle need to be treated for optimal pressure reduction. Success rates were 34% in 90 degree-treated patients, 65% in 180 degree-treated patients and 82% in 360 degree-treated patients, suggesting that the whole angle should be treated for optimal success.[19]

Efficacy of SLT

The Laser in Glaucoma and Ocular Hypertension (LiGHT) trial was the first multicentre RCT to show that SLT is both clinically effective and cost saving compared with medication therapy in POAG.[20] Since then, at least eight RCTs have been performed, and a meta-analysis of 35 studies concluded that SLT results in an average IOP reduction of 20 to 30% for up to five years.[21-23] A recent 10-year follow-up study confirmed that a pressure reduction of more than 20% or an IOP below 19 mmHg was still achieved in 72% of patients at 10 years.[24]

Several studies have confirmed the use of SLT in secondary open angle glaucomas. Treatment of pseudo-exfoliation glaucoma, the most common form accounting for 25% of all open angle glaucomas worldwide, with SLT equally as successful as POAG. Other secondary open angle glaucomas, such as pigment dispersion or steroid-induced glaucoma, have equivalent pressure-lowering success with SLT but an increased risk of inflammation, discomfort or pressure spikes and, thus, patients may need treatment over two sessions. SLT is usually avoided in patients with uveitic glaucoma due to the higher risk of inflammation. In addition to an overall pressure reduction, SLT can reduce IOP fluctuations to below 3 mmHg, an important mechanism of disease progression, especially in NTG.[25]

The IOP-lowering effect of SLT does wear off over time, with a wide variability in the range of effect duration ranging from a few months to several years. In the authors' experience, most patients will have sustained pressure reduction for three to four years, although there are some reports of success from a single treatment for over eight years. With a sound safety profile, SLT is repeatable, with equal efficacy extending the duration of pressure control that can be achieved with the laser.

One of the major advantages of SLT is the benefit to the patient's quality of life through the reduction of ocular surface disease, the lack of need for daily adherence and a reduced need for surgical intervention for up to six years. Other benefits are listed in Box 3.

Conclusion

Helping patients maintain functional vision throughout their lives is one of the most powerful healthcare interventions that GPs help manage. Glaucoma vision loss is silent, gradual and irreversible. Early detection is therefore crucial and relies on awareness of patient risk factors, screening tools and recommended surveillance. Management has traditionally relied on topical IOP-lowering pharmacological therapies; however, because of high rates of nonadherence, SLT therapy is increasingly utilised. As with other ophthalmic diseases, holistic approaches to management, such as a focus on lifestyle and nutrition, may play a role in ensuring optimal vision in glaucoma. Practice points for GPs on glaucoma management are summarised in Box 4. MT

4. PRACTICE POINTS

- Chronic open angle glaucoma is an asymptomatic disease that causes progressive, irreversible visual field loss and blindness if left untreated with potentially huge impacts on quality of life.
- GPs are ideally placed to ensure early detection and ongoing monitoring occurs for timely and effective glaucoma intervention and optimising management of systemic conditions which may play a role.
- Current treatments focus on intraocular pressure (IOP) reduction, which remains the primary modifiable risk factor proven to slow disease progression.
- Eye drops are an effective treatment, with prostaglandin analogues usually first-line agents due to their efficacy and convenience.
- Poor eye drop compliance and intolerance are major challenges in glaucoma management. GPs can educate patients, explore barriers and promote proper administration techniques for optimal management.
- Selective laser trabeculoplasty offers an alternative treatment to eye drops, effectively lowering IOP with minimal side effects. It can be used as a first- or second-line option and can be safely repeated to maintain IOP-lowering effects.
- Exciting glaucoma treatment advances include the potential neuroprotective effects of nicotinamide, implantable prostaglandin delivery systems and the international adoption of topical rho kinase inhibitors.

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A list of references is included in the online version of this article (www.medicinetoday.com.au).

COMPETING INTERESTS: None.

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