The medical therapies for chronic glaucoma

The number of medications available to treat glaucoma is increasing. Many of the older agents are still available, so GPs need to know how the new ones fit in.

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Glaucoma is the most common cause of preventable blindness and the second most common cause of irreversible blindness in our community (after macular degeneration). The prevalence of glaucoma in Australia is about 3%. Approximately 50% of patients identified in population surveys are undiagnosed and untreated. It has been estimated that the number of patients with glaucoma will double over the next 30 years as our population ages. Risk factors found in Australian cross-sectional studies include increasing age, higher intraocular pressure, a positive family history, myopia, systemic hypertension and diabetes. Other risk factors, particularly for normal tension glaucoma, include migraine, cold intolerance and sleep apnoea.

Blindness due to glaucoma is largely preventable, especially if patients are diagnosed early. Although the visual damage is not reversible, it can usually be stabilised. This article discusses the management of chronic glaucoma, with a focus on the medical therapies that are currently available.

What is chronic glaucoma?

Chronic open angle glaucoma is an optic neuropathy resulting in damage to the head of the optic nerve and visual field loss. The exact pathological mechanism is unknown, but the primary risk factors are thought to be sensitivity of the optic nerve to raised intraocular pressure and poor optic nerve perfusion. The vision loss is gradual and progressive, and it can be extensive before being noticed by the patient (Figures 1a and b).

Clinically, the first changes occur at the optic disc and it is important that clinicians look for the characteristic sign of optic disc cupping (see Figures 2a and b). In all patients over 40 years of age with any risk factors for glaucoma, the GP should view the optic discs with an ophthalmoscope. Any patient with significant optic disc cupping or asymmetrical discs should be referred to an ophthalmologist for further screening.

Management

The aim of treatment is to preserve patients' sight while maintaining their quality of life. Studies investigating the effects of improving blood flow and neuroprotection on the natural history of the disease are being undertaken, but long term follow up is needed before we can confirm the effectiveness of these interventions. Lowering the intraocular pressure is the only scientifically proven strategy that results in stabilisation of glaucoma.

IN SUMMARY

- **Patients who are aged over 40 years should be screened for glaucoma if they have any of the following risk factors: a family history of glaucoma, myopia, systemic hypertension, or diabetes.**
- **Blindness caused by glaucoma is largely preventable. Although the visual damage is not reversible, it can usually be halted.**
- **The key strategy for treating glaucoma is lowering the intraocular pressure. Topical drug therapy is usually the first management option tried.**
- **Instructing patients in techniques to reduce the rate of systemic absorption of any topical ophthalmic drug will help to reduce the incidence of adverse events.**

Medical therapy

The mainstay of management for open angle glaucoma is to reduce the intraocular pressure. Medications achieve this by decreasing aqueous production or increasing outflow of aqueous, or both. A target pressure is set for each patient – this level will depend on the risk of progressive visual damage. Decreasing the intraocular pressure by 30 to 50% may stop progression.

GPs have an important role in ensuring that patients are taking their glaucoma medications correctly, and should explain the correct way to instil eyedrops (see the patient handout on page 25). It is also necessary to monitor for possible adverse events and interactions with other medications. Patients do not always report all their systemic drugs to the ophthalmologist, and they sometimes forget the name of a medication they are taking or do not mention starting a new one.

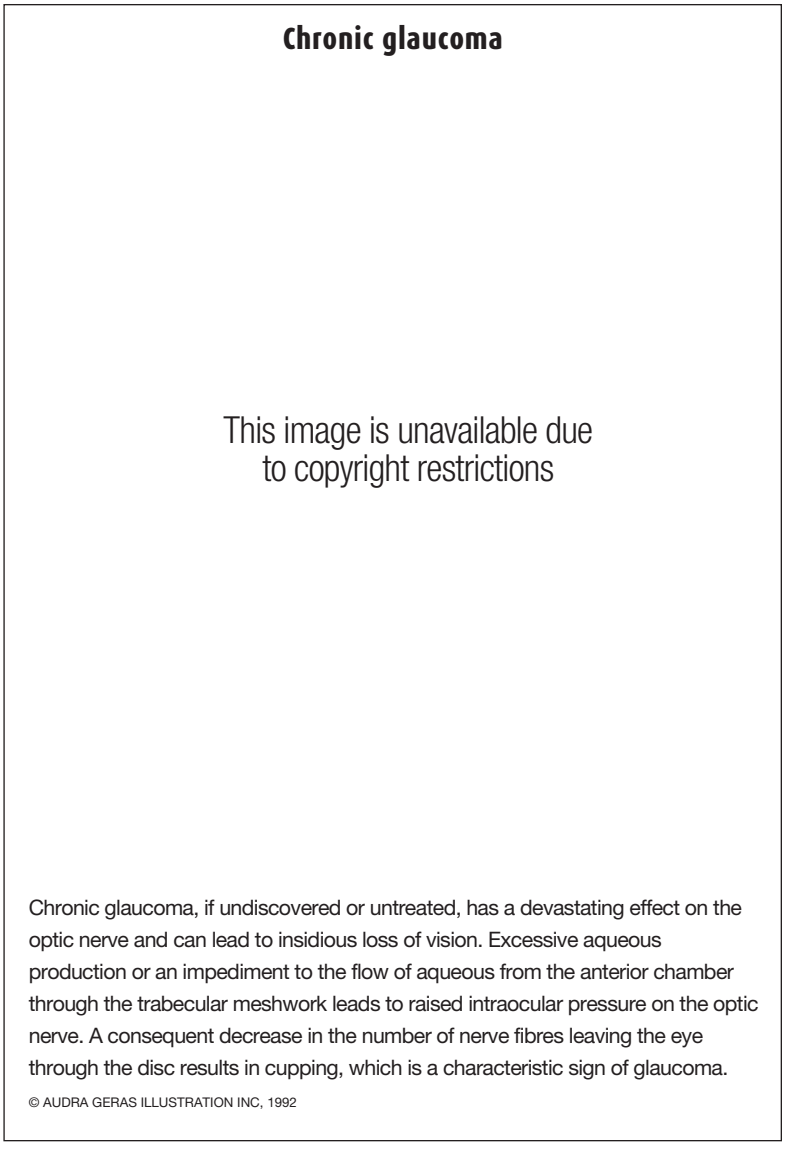
Laser treatment

If medical therapy does not lower intraocular pressure sufficiently to stop progression of glaucomatous damage, laser trabeculoplasty can be performed as an adjunctive therapy. It has a 75% success rate in lowering intraocular pressure, and 50% of patients gain benefit for up to five years.

Surgery

If medical and laser treatments fail, incisional glaucoma drainage surgery can be performed. Together with use of an antifibrotic agent, 5-fluorouracil (Fluorouracil Injection BP) or mitomycin C (Mitomycin C Kyowa), this procedure can achieve a long term success rate of up to 90%.

Chronic glaucoma



Chronic glaucoma, if undiscovered or untreated, has a devastating effect on the optic nerve and can lead to insidious loss of vision. Excessive aqueous production or an impediment to the flow of aqueous from the anterior chamber through the trabecular meshwork leads to raised intraocular pressure on the optic nerve. A consequent decrease in the number of nerve fibres leaving the eye through the disc results in cupping, which is a characteristic sign of glaucoma.

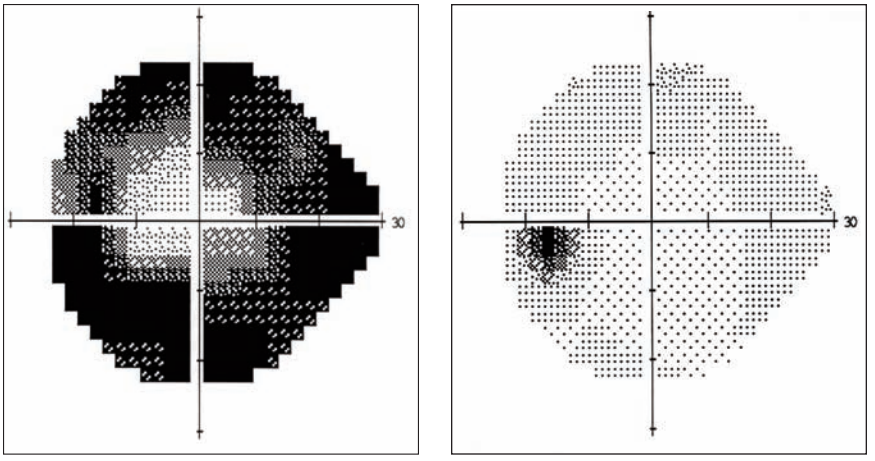
The 'traditional' medications for glaucoma

The traditional medications used to treat glaucoma include topical β-blockers, miotics and adrenergics, as well as systemic carbonic anhydrase inhibitors. These are summarised in Table 1.

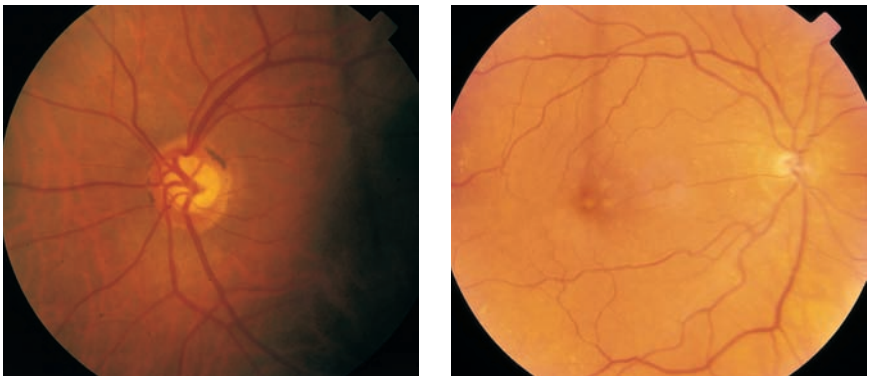
Beta blockers

Beta blockers remain the most commonly prescribed antiglaucoma drugs. Timolol (Optimol, Tenopt, Timoptol, Timoptol-XE) and levobunolol (Betagan), two nonselective β-blockers, inhibit the rate of aqueous production by about 40% – this reduces intraocular pressure by 20 to 25%. Betaxolol (Betoptic, Betoptic S; Betoquin), a selective β_1-blocker, reduces intraocular pressure by only 15 to 20%. Timolol or levobunolol can be instilled once daily (this has equal effect to twice daily dosing for most patients); betaxolol is needed twice daily.

With longer term use of timolol or levobunolol, tachyphylaxis is not uncommon and intraocular pressure slowly rises. Withdrawing the drug for a few months (i.e. taking a 'drug holiday') often re-establishes its efficacy. Ocular adverse reactions include corneal anaesthesia and a reversible dry eye syndrome. The incidence of burning or stinging following instillation of timolol or levobunolol



Figures 1a and b. Visual field testing. Shading represents visual field loss. a (left). Advanced visual field loss and tunnel vision in glaucoma. b (right). A normal visual field, shown for comparison purposes. The dark area located temporally corresponds with the normal blind spot.



Figures 2a and b. a (left). Cupping of the optic disc in glaucoma. b (right). Normal optic disc cupping, shown for comparison purposes (note lower magnification in Figure 2b).

is lower (6 to 9%) than with betaxolol (30%). About 3% of patients may develop allergic blepharoconjunctivitis.

The main problem with timolol or levobunolol is the potential for systemic adverse effects. These are the same as the adverse effects of oral β-blockers – the most important are bronchoconstriction, bradyarrhythmias, masking of hypo - glycaemia, depression, impotence and an increase in falls in the elderly. As betaxolol is relatively selective for β_1-receptors, it should pose less respiratory risk; its pharmacokinetic properties (higher plasma binding and larger volume of distribution) also make it less likely to provoke other systemic effects.

Miotics

The use of miotics for chronic open angle glaucoma is decreasing – these agents are pilocarpine and carbachol (Isopto Carbachol). These parasympathomimetic drugs cause constriction of the ciliary muscle, exerting a physical tug on the trabecular meshwork and thereby increasing aqueous outflow.

The concurrent constriction of the sphincter pupillae causes uncosmetic miosis as a side effect which dims vision, especially in older patients with cataract. Retinal detachment has been reported. In addition, the miosis resulting from years of use can create technical problems during cataract surgery. Another side effect is browache, a frequent symptom at the start of therapy that usually decreases after a few weeks. Spasm of accommodation with fluctuating myopia can be particularly troublesome to young patients. In addition, the need to instil these agents up to four times daily is inconvenient for most patients and makes compliance very difficult.

Adrenergic agonists

Dipivefrine (Propine) is the only non-selective adrenergic agonist still available. This is a prodrug that is converted to adrenaline after absorption into the eye. Dipivefrine is seldom used now because of its relatively weak tendency to reduce intraocular pressure, frequent conjunctival hyperaemia and allergic blepharoconjunctivitis. It has an additive effect to pilocarpine, carbachol and carbonic anhydrase inhibitors and may be partially additive to β-blockers.

Systemic carbonic anhydrase inhibitors

The only systemic carbonic anhydrase inhibitor now available in Australia is acetazolamide (Diamox). It is still the most potent ocular hypotensive medication available, and can reduce intraocular pressure by 40 to 60%.

The only ocular side effect of acetazolamide is transient myopia, but there are many systemic adverse effects, including:

- paraesthesia in the fingers, toes and around the mouth
- anorexia
- nausea
- abdominal cramping
- diarrhoea
- depression
- metabolic acidosis
- hypokalaemia.

As acetazolamide is related to sulfonamides, adverse reactions common to all sulfonamide derivatives may occur, including Stevens–Johnson syndrome, hepatic necrosis and aplastic anaemia. Renal stone formation is not uncommon. High dose aspirin may interact with acetazolamide causing anorexia, tachypnoea, lethargy and coma. Acetazolamide may also interact with anticoagulants and antihypertensive agents.

If a patient is commencing long term treatment with acetazolamide, a baseline complete blood count, platelet count and electrolyte levels are recommended to monitor for haematological reactions. These tests should be repeated at regular intervals during therapy.

The newer drugs for glaucoma

The newer drugs used to treat glaucoma include topical carbonic anhydrase inhibitors, α_2-agonists and lipid-receptor agonists. Features of these drugs are summarised in Table 2.

Topical carbonic anhydrase inhibitors

Two topical carbonic anhydrase inhibitors are available, dorzolamide (Trusopt) and brinzolamide (Azopt Eye Drops 1%). These agents reduce intraocular pressure by 15 to 24%, with less systemic effects than acetazolamide and reasonable surface comfort. They need to be instilled two to three times daily and are mostly useful as adjunctive drugs: when added to timolol, for example, a further 15 to 20% reduction in intraocular pressure can be achieved. A topical carbonic anhydrase inhibitor is often introduced as a third line drug. It is effective when added to timolol, brimonidine and the lipid receptor agonists.

In patients with low endothelial cell counts, topical carbonic anhydrase inhibitors may increase the amount of corneal oedema present; in healthy eyes with normal endothelial cell counts, this does not seem to be a problem. The most common ocular adverse events with dorzolamide are burning and stinging (less with brinzolamide), and eyelid oedema. Conjunctival hyperaemia and upper eyelid tarsal follicles occur in up to 20% of users. Systemic adverse reactions are rare, the most common being a transient bitter taste (reported by about 30% of patients). Topical and systemic forms of carbonic anhydrase inhibitors should not be used concurrently because known adverse reactions may be increased.

Alpha$_2$ adrenergic agonists

The two topical α_2-adrenergic selective agonists available in Australia are apraclonidine (Iopidine) and brimonidine (Alphagan Eye Drops, Enidin). Stimulation of α_2-receptors lowers intraocular pressure whereas α_1-receptor activation produces side effects such as mydriasis, eyelid retraction and vasoconstriction. These agents reduce intraocular pressure by inhibiting aqueous production and increasing the uveoscleral ('unconventional') outflow. The former mechanism is thought to be more important early in

Table 1. Traditional topical and systemic medications for glaucoma

Medication	Mechanism of action	Presentation and frequency of dosing	Duration of effect
Beta blockers *Nonselective* Timolol, levobunolol *Beta$_1$ selective* Betaxolol	Inhibit aqueous inflow	Eyedrops, instilled once or twice daily (timolol and levobunolol) or twice daily (betaxolol)	12 to 24 hours
Miotics Pilocarpine, carbachol	Enhance conventional aqueous outflow	Eyedrops, instilled twice to four times daily	4 to 12 hours
Adrenergic agonists Dipivefrine	Enhance conventional aqueous outflow; may increase uveoscleral (unconventional) outflow	Eyedrops, instilled twice daily	12 to 18 hours
Systemic carbonic anhydrase inhibitors Acetazolamide	Inhibit aqueous inflow	Oral presentation, taken as ½ to 4 tablets per day	6 to 12 hours

treatment whereas the latter is more significant during prolonged treatment.

Common adverse events of α_2-agonists include red eyes (in 11% of patients), allergic blepharoconjunctivitis (found in 25% of patients taking treatment for four years), foreign body sensation and stinging. Dry mouth, headache, fatigue and drowsiness may be experienced, particularly if the patient is instilling the drops without adequate no-blinking and punctal occlusion techniques (see the handout on page 25).

Apraclonidine

Apraclonidine is very useful in controlling an attack of angle closure glaucoma and in preventing possible spikes of intraocular pressure after anterior segment laser surgery. It often causes tachyphylaxis after three months of therapy and allergic blepharoconjunctivitis; therefore, apraclonidine is only recommended for additional short term intraocular pressure reduction, not long term therapy.

Brimonidine

Brimonidine is 30 times more selective than apraclonidine for the α_2-receptor. The mean peak effect is a 24% reduction in intraocular pressure and the mean trough effect is a 15% reduction. Little, if any, tachyphylaxis has been reported after two years of treatment. Brimonidine is usually a second line agent but it may be used instead of β-blockers as a first choice, particularly in the presence of pulmonary or cardiovascular disease.

Use of monoamine oxidase inhibitors is a contraindication to the use of brimonidine. In patients taking tricyclic antidepressants, barbiturates, sedatives, β-blockers, calcium channel blockers or other systemic antihypertensive drugs, brimonidine should be used with caution.

Although the adverse effect profile of brimonidine is generally favourable, it is critically dependent on an intact blood–brain barrier. In infants and younger children, the barrier is not intact and topical brimonidine can cause profound systemic hypotension, apnoea, convulsions and cyanosis. It is absolutely contraindicated in children under the age of six years and relatively contraindicated in older children.

Lipid receptor agonists

Latanoprost (Xalatan) was the first prostaglandin analogue to become generally available and it has steadily displaced the nonselective β-blockers as first line therapy. The availability of the prostaglandin analogue travoprost (Travatan Eye Drops) and the prostamide analogue bimatoprost (Lumigan Eye Drops) has increased the number of patients who have a good chance of responding well to an agent in this class.

The lipid receptor agonists increase the outflow of aqueous fluid through the uveoscleral route. They are additive with all the other antiglaucoma drugs, with the possible exception of adrenergics and miotics, particularly in patients who have been using high concentrations of miotics for years.

For the majority of patients, one drop of a lipid receptor agonist once daily (in the evening) will lower intraocular pressure by about 30%. This allows monotherapy in many patients and has benefits in terms of compliance, convenience and overall cost. With their long duration of action, the lipid receptor agonists ensure better control of intraocular pressure throughout day and night.

If these drugs are used more frequently than once per day, intraocular pressure can increase. Many patients are

Table 2. Newer topical medications for glaucoma

Medication	Mechanism of action	Presentation and frequency of dosing	Duration of effect
Topical carbonic anhydrase inhibitors Dorzolamide, brinzolamide	Inhibit aqueous inflow	Eyedrops, instilled twice to three times daily	8 to 12 hours
Alpha$_2$ adrenergic agonists Brimonidine, apraclonidine	Inhibit aqueous inflow and increase uveoscleral (unconventional) outflow	Eyedrops, instilled twice (brimonidine) or three times daily (apraclonidine)	8 to 12 hours
Lipid receptor agonists Latanoprost, travoprost, bimatoprost	Increase uveoscleral (unconventional) outflow	Eyedrops, instilled once daily	24 to 36 hours

used to twice daily dosing from regimens of older treatments, so checking that patients are taking the correct dosage can be important. Refrigeration is recommended for latanoprost, and this may play a role in patient compliance and can be an issue in the Australian climate. Travoprost and bimatoprost do not need to be refrigerated.

Varying degrees of conjunctival hyperaemia and increased iris pigmentation were the main adverse events in all clinical trials of the lipid receptor agonists. Patients with hazel or mixed-colour irides seem to be most predisposed to a change in iris colour. The iris colour changes are irreversible but are not progressive once the drug has been withdrawn. Pigmentary changes of eyelid skin can also occur. The conjunctival hyperaemia has been found to be more frequent with travoprost and bimatoprost. Darker, thicker and longer eyelashes ('luscious lashes') are very common, and are reversible when the drug is discontinued. The ocular hypotensive effect of travoprost and bimatoprost is at least as good as that of latanoprost, and may be slightly better.

Other less common adverse effects include anterior uveitis and cystoid macular oedema in patients predisposed to these conditions; these usually resolve with drug withdrawal. There have also been reports of reactivation of herpes simplex 1 corneal lesions, but it is unclear whether these adverse effects are causally related.

Combined treatments

To improve convenience and thus compliance, there is a trend towards fixed combinations of old and new drugs. The combination of timolol and pilocarpine (Timpilo) has been with us for many years; more recently, a combination of timolol and dorzolamide (Cosopt Eye Drops) has been introduced. There is a combination of latanoprost and timolol (Xalacom Eye Drops), to be taken once daily in the morning, which is currently listed on the RPBS but not the PBS. Combinations of bimatoprost and timolol, as well as travoprost and timolol are currently undergoing trials.

A general guide to which drug classes can be combined to achieve additive effects on intraocular pressure reduction is outlined in the box on page 26.

MedicineToday PATIENT HANDOUT

A guide to correctly instilling eyedrops

Your doctor will show you how to instil your eyedrops correctly. Ensure that you wash your hands beforehand, and remember that it is important that the tip of the bottle does not touch the eye. Two appropriate techniques for instilling eyedrops while keeping the tip of the bottle a safe distance from the eye are shown in Figures A and B.

Eyelid closure and punctal occlusion are helpful to decrease absorption of the drug into the body's circulation and increase ocular penetration of any topical medication, and this is described in Figure C. If you are taking more than one type of eyedrop, leave an interval of five to 10 minutes between instillations in order to avoid washing the first medication out with the next one.

The preservative used in almost all eyedrops is benzalkonium chloride, which can cause a deposit build up in soft contact lenses. If you are using soft contact lenses, remove the lenses before instilling the drops and wait for 15 minutes before reinserting the lenses.

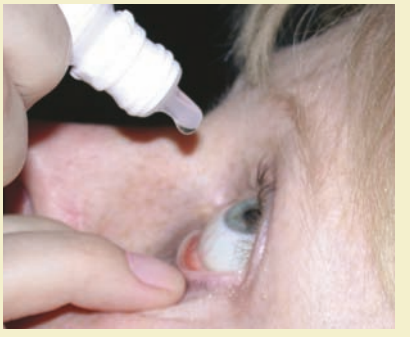


Figure A. Instillation technique 1. Use one hand to hold the lower eyelid down and rest your second hand on the first one. While not looking directly at the tip of the bottle, one drop is squeezed into the eye.

Figure B. Instillation technique 2. Rest the bottle on your forehead. Then, while looking upwards and away from the tip of the bottle, one drop is squeezed into the eye.

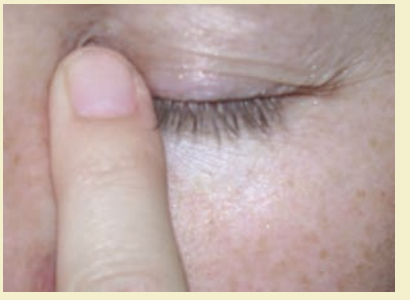


Figure C (left). Punctal occlusion. After instilling one drop into the eye, gently close the eye and apply pressure against the nose where the eyelids come together. This reduces drainage onto the nasal mucosa and absorption into the body's circulation while prolonging drug–cornea contact time and absorption into the eye.

This patient handout was prepared by Dr K. Attebo.

continued

Combining medications for glaucoma

Lowering the intraocular pressure is the only scientifically proven strategy that results in stabilisation of glaucoma. If monotherapy is not effective in reaching a patient's target intraocular pressure, additional medications may be required. The grid below shows which agents have additive effects in lowering intraocular pressure and can be used in combination.

	Beta blockers	Miotics	Adrenergic agonists	Systemic carbonic anhydrase inhibitors	Topical carbonic anhydrase inhibitors	$Alpha_2$ adrenergic agonists	Lipid receptor agonists
Beta blockers	–	Yes	Partially	Yes	Yes	Yes	Yes
Miotics	Yes	–	Yes	Yes	Yes	Yes	Not always
Adrenergic agonists	Partially	Yes	–	Yes	Yes	No	No
Systemic carbonic anhydrase inhibitors	Yes	Yes	Yes	–	No	Yes	Yes
Topical carbonic anhydrase inhibitors	Yes	Yes	Yes	No	–	Yes	Yes
$Alpha_2$ adrenergic agonists	Yes	Yes	No	Yes	Yes	–	Yes
Lipid receptor agonists	Yes	Not always	No	Yes	Yes	Yes	–

Conclusion

For most patients with chronic open angle glaucoma, medical therapy remains the first and ongoing strategy. Noncompliance is a major issue because glaucoma is a chronic, symptom-free disease that requires long term, costly treatment. Glaucoma medications are all associated with side effects and usually result in no subjective improvement to the patient. Compliance is enhanced when patients are made fully aware of the glaucomatous process.

The new drugs that reduce intraocular pressure have improved efficacy and safety margins, hopefully improving compliance. They have allowed us a greater choice for each individual patient. To exercise that choice meaningfully, we need the evidence of likely strengths and weaknesses of each of these medications, and how they interact with one another and with other drugs being used for concomitant disease. MT