

The medical management of glaucoma

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Abstract

Glaucoma is one of the leading causes of blindness worldwide. The main characteristic features include optic disc cupping, visual field loss, and in most instances a raised intraocular pressure. Primary open angle glaucoma accounts for nearly two thirds of all cases, while angle closure glaucoma contributes the majority of the remainder. Screening for glaucoma is not cost-effective, and diagnosis of the primary open angle type is usually an incidental finding during ophthalmological examination. Various treatment options, including medical and surgical interventions are accessible in the management of glaucoma. This article contains a brief description on the pathophysiology and focuses on the pharmacological options available in the treatment of glaucoma.

Keywords: Glaucoma, prostaglandin analogs, carbonic anhydrase inhibitors, beta antagonists, alpha 2 adrenergic agonists, cholinergic agonists

Introduction

Glaucoma is a mixed group of eye disorders sharing common features which typically includes optic disc cupping and visual field loss, thereby more accurately defined as an optic neuropathy. Optic nerve damage results in progressive retinal ganglionic cell loss and irreversible blindness, if not treated.¹ Traditionally, glaucoma has been characterized by the existence of raised intraocular pressure (IOP), however nerve damage may occur in the presence of values within the statistically normal range between

8–21 mmHg. Glaucomatous disc and field changes in the absence of elevated pressure constitutes normal or low tension glaucoma (LTG).² Similarly, conditions exceeding the upper limit of 21 mmHg may not be associated with signs of visual field loss or optic disc damage and comprises ocular hypertension.³ In addition to optic neuropathy, the two main types of glaucoma (open angle and closed angle) are described on the appearance of the drainage system within the eye, including associated increase in the IOP (Figure 1).

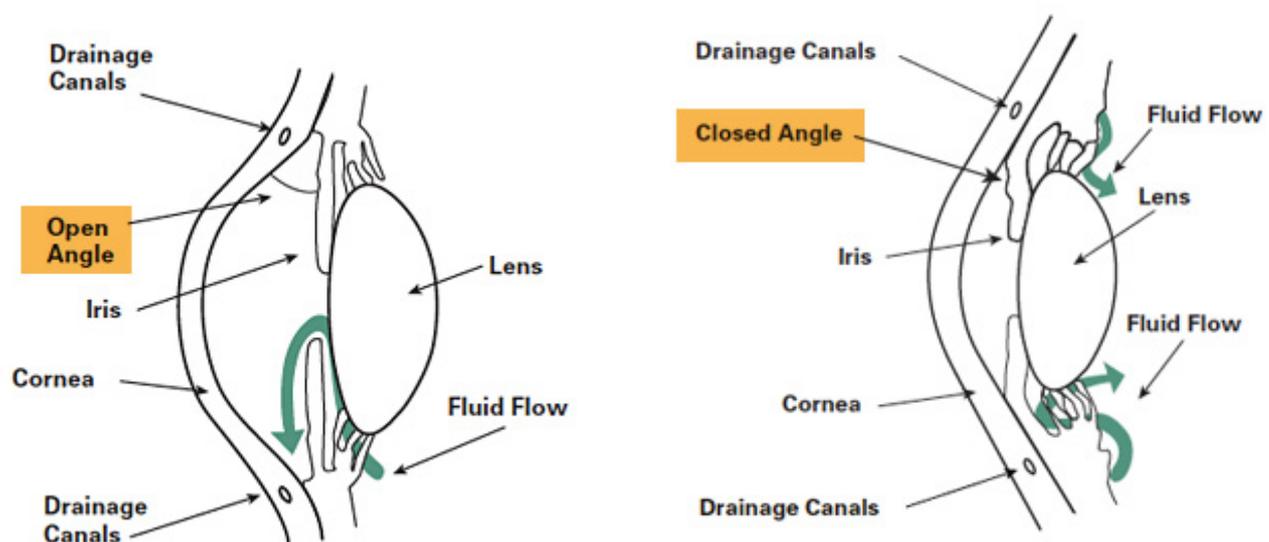


Figure 1. Difference between open angle glaucoma and closed angle glaucoma in relation to the drainage systems within the anterior chamber of the eye. [Images reprinted with permission from the Glaucoma Research Foundation, <http://www.glaucoma.org/>]

Both types can be further divided into primary versus secondary, and congenital versus acquired. Glaucoma has a global prevalence of 3.54% in those aged between 40 and 80 years, and is the second leading cause of irreversible blindness, only superseded by cataracts. Open angle glaucoma is the highest in Africa (4.2%), while closed angle glaucoma is more prevalent in Asia (1.09%).⁴

Pathophysiology of glaucoma

Aqueous humour (a transparent, low protein containing fluid) is continuously secreted by the ciliary epithelium providing structural support to the lens. This watery fluid is present in both the anterior and posterior chambers of the eye and drains through a sieve-like trabecular meshwork located in the angle between the cornea and the iris. Final drainage out of the eye occurs via the canal of Schlemm into the episcleral vein or intrascleral venous plexus terminating in the ocular veins.⁵

Open angle glaucoma

In open angle glaucoma, the trabecular meshwork undergoes morphological changes over time, resulting in progressive impairment of drainage although it remains anatomically open. (Figure 1) Open angle glaucoma most often affects both eyes, but asymmetric involvement is not uncommon. Primary open angle glaucoma (POAG) is the most common type and accounts for 74% of all glaucoma cases. It is estimated that 57.5 million people (3.05%) worldwide suffer from POAG.⁴ Prevalence among Black populations is the highest, with 2.1% at age 40 and 12.2% at age 80 being reported. The incidence in Asian populations (0.8% at age 40 and 4.3% at age 80), and Caucasians (0.4% at 40 years and 5.3% at 80 years) suggests an ethno-genetic disease pattern.⁶ Although the exact cause of POAG remains unknown, more than fifty risk factors and secondary causes have been identified. Some of these include diabetes mellitus, migraine headache, cardiovascular disease, asthma or COPD (inhaled anticholinergics and glucocorticosteroids), myopia, advanced age and a family history of first-degree relatives with the same condition.^{7,8} Disease progression leads to the formation of scar tissue between the iris and trabecular meshwork and will ultimately result in closing off the anterior chamber. The consequent rise in IOP is transmitted to the optic disc and is eventually responsible for atrophy and nerve fiber damage. Owing to the slow progression of the disease, POAG remains asymptomatic until central vision is affected. It does not present with headache, eye pain or loss of visual acuity. Diagnosis is usually incidental during routine fundusoscopic or optometry examinations. A cup : disc ratio of 0.6 (glaucomatous cupping), and central corneal thickness in the presence of risk factors is suggestive of glaucoma, and requires ophthalmological referral (Figure 2). The progression from POAG to Chronic Angle-Closure Glaucoma (CACG), requires lifelong treatment.⁹

Official general population screening policies do not exist and are not cost-effective. Measuring IOP has a sensitivity of only 47.1%, implying that nearly half of patients with POAG will have IOP below 22 mmHg. However, patients with risk factors are encouraged to undergo annual ophthalmological examinations and additional IOP measurements.¹⁰

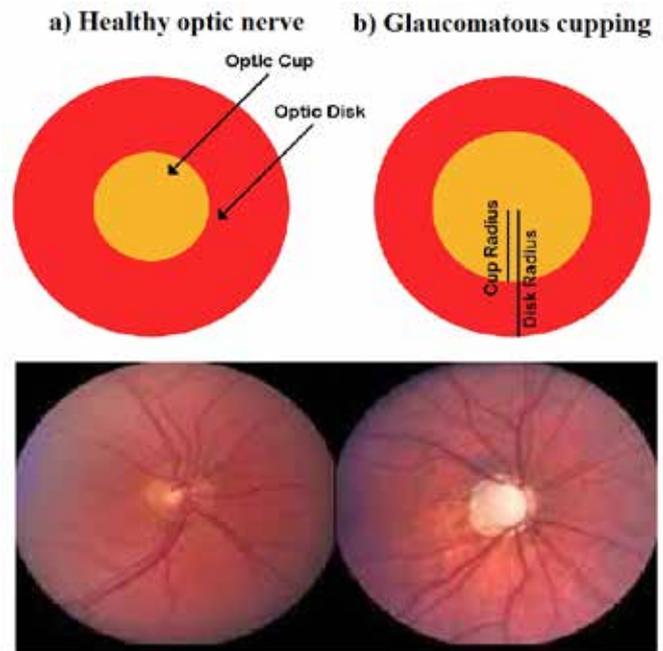


Figure 2. Normal optic disc (a) vs glaucomatous cupping (b) [Images adapted with permission from the Glaucoma Research Foundation, <http://www.glaucoma.org/>]

Closed angle glaucoma

With closed angle glaucoma, a primary hypermetropic anatomical defect (such as weakened ciliary muscles, naturally small eyes, narrow angle or thick lens) in the absence of an identifiable secondary cause, results in the pupil compressing the drainage canal between the iris and cornea. Compression and narrowing of the canal reduces or obstructs the outflow of aqueous humour in passing through the pupil, therefore accumulating in the anterior chamber (Figure 1).¹¹ Primary angle closure glaucoma (PACG) is less common than POAG and accounts for approximately a third of all cases, with a global incidence of 0.5%.⁴ Symptoms of closed angle glaucoma depend on the degree of angle closure and in some instances may resolve spontaneously; in which case it may become chronic. In established disease, vision loss is severe and permanent. Secondary causes of angle-closure glaucoma include masses or hemorrhage in the posterior segment of the eyeball or the presence of a fibrovascular membrane (neovascular glaucoma) over the anterior chamber angle. Risk factors for angle closure glaucoma include older age (> 60 years), female gender, Asian ethnicity, hyperopia and a positive family history.¹¹ Attacks occur more frequently at night when diminished light cause mydriasis and narrowing of the angle.¹² Unexpected closure (acute angle closure glaucoma, AACG) of the anterior chamber angle due to pupillary block may result in a sudden rise in IOP. It constitutes a medical emergency, since permanent blindness and irreversible damage to the optic nerve may occur. Acute attacks are characterized by intermittent symptoms such as severe eye pain, nausea and vomiting, loss of vision, halos around lights, unilateral red tearing eye, oval shaped non-reactive pupil, a cloudy cornea and the loss of red reflex (Figure 3).

In addition, it is estimated that prescribed, or over-the-counter pharmacological agents are responsible for at least 30% of acute

angle closure glaucoma.¹³ These include antihistamines, cholinergic and anticholinergic agents, adrenergic agents, antidepressants, sulphonamides, anticoagulants and glucocorticosteroids. Table 1 below summarises the mechanism responsible for causing AACG.



Figure 3. Acute angle closure glaucoma showing oval shaped pupil, corneal haziness and loss of red reflex [Image available from <https://en.wikipedia.org/wiki/Glaucoma>]

Treatment goals

The goal in treating POAG is to establish and maintain the intraocular pressure at a range where visual field loss will have the least negative impact on the patient's perceived visual disability. "Various studies have shown that visual field loss in glaucoma has been associated with a significant decrease in a person's vision-related quality of life. This is evident in activities requiring optimal vision, such as dark adaptation, avoiding unintentional bumping into objects and outdoor mobility.^{14,15} Determining the target intraocular pressure needs to be individualised for each patient, since the measured pressure at diagnosis could be within the normal range of 8 to 21 mmHg in 30–50% of patients.¹⁶ Aiming for pressures within these ranges will contribute towards optic nerve damage and further progression. It is generally accepted that patients with early disease benefit from a reduction of at least 20% in the baseline value. A reduction of 30% is recommended in individuals with more advanced features of POAG.¹⁷ Target IOP should continuously be re-calculated during monitoring and follow-up assessment of visual fields and disc and nerve fiber examinations. Reducing the IOP, however, does not guarantee that progression will not transpire. The choice of therapy depends on the relative risks and benefits of available modalities, which include pharmacological treatment, laser therapy or incisional surgery. Factors such as cost, dosing, patient's age, the presence of comorbidities (asthma or

Table 1. Drugs associated with precipitating acute angle closure glaucoma (AACG)

Drug class	Mechanism
Histamine 1 and 2 receptor antagonists	
Brompheniramine Chlorpheniramine Dexchlorpheniramine Dimethindene Pheniramine Triprolidine	Antihistamines used in treatment of allergic disease, GORD and peptic ulcer disease have weak anticholinergic effects which may induce mydriasis.
Cimetidine Ranitidine	
Cholinergic agents	
Pilocarpine	Indicated for use in acute closed angle glaucoma by increasing uveoscleral outflow, but in rare instances may also cause an acute attack due to anterior movement of iris resulting in complete miotic-induced angle closure.
Anticholinergic agents	
Tropicamide Atropine Homatropine Cyclopentolate	Anticholinergics are used to induce pupil dilatation and relaxation of ciliary muscle during fundus examination. The long acting anticholinergic action frequently induces acute attacks.
Ipratropium	50% of patients with pre-existing glaucoma nebulized with ipratropium develop acute attacks due to corneal diffusion of nebulized solution.
Adrenergic agents	
Phenylephrine Apraclonidine Ephedrine Adrenaline Amphetamines	α_1 adrenergic agents cause mydriasis and individuals with shallow anterior chambers are more at risk to develop acute attack. Occurs with local (eye), nasal, systemic administration.
Salbutamol Albuterol Terbutaline	Absorption through cornea via face-mask escape during nebulization Nebulized β adrenergic agents for bronchospasm increases IOP and induce transient angle closure. This is exacerbated if combined with ipratropium. Stimulation of β_2 receptors in ciliary body promotes aqueous humour secretion.

Antidepressants	
Imipramine Amitriptylene Clomipramine	Tricyclic antidepressants (TCA) have higher incidence of anticholinergic side effects responsible for increase IOP in acute attacks.
Paroxetine Venlafaxine Fluvoxamine Citalopram Escitalopram	Selective serotonin reuptake inhibitors less incidence compared to TCAs. Mydriasis as result of increased serotonin causing supraciliary effusion.
Sulphonamides	
Acetazolamide Hydrochlorothiazide Cotrimoxazole Topiramate	Acetazolamide mainly used in acute closed angle emergencies, but may also be used in chronic open angle glaucoma. In rare cases, chronic administration may precipitate acute angle closure. Mechanism relates to ciliary body edema causing relaxation of zonules allowing the lens to thicken and become displaced.
Anticoagulants	
Enoxaparin Heparin Warfarin	Rare secondary cause of acute attack. Increased IOP as a result of overtreatment leading to vitreous, choroidal or subretinal hemorrhage.
Glucocorticosteroids	
Dexamethasone Prednisolone Fluoromethalone Hydrocortisone	Elevated IOP due to increased outflow resistance which is facilitated by upregulation of glucocorticoid receptors on the trabecular meshwork cells. Dexamethasone and prednisolone raises IOP more compared to others. Fluoromethalone least likely towards IOP elevation.
Triamcinolone	Increased expression and deposition of matrix proteins and crystals causing physical obstruction.

COPD), pregnancy, adherence to treatment and the degree of optic disc damage should be considered in choosing an appropriate treatment regimen.¹⁸

In treating AACG, the primary goal is to make the correct diagnosis to prevent permanent loss of vision. This is achieved by rapid lowering of the IOP and reversal of the angle closure. Empiric treatment with topical and systemic aqueous humour suppressants (β blockers and acetazolamide) reduces the IOP, followed by pilocarpine to reverse the pupil block. In the absence of available trials comparing medical options for treatment of AACG, the initial management usually consists of administering one drop of 0.5% timolol, 1% apraclonidine and 2% pilocarpine one minute apart. This is followed by intravenous acetazolamide or mannitol. Eye pressure should be checked every hour until specialist ophthalmological care can be provided.¹⁹

Pharmacological management

Pharmacological management is the most common initial intervention in lowering the IOP, although laser trabeculoplasty and surgery are frequently used to slow the disease progression.¹⁹ Surgical treatment has no advantage over pharmacological management in visual field protection, however surgical interventions attain target IOP in 46% of cases compared to 35% in those being treated medically.²⁰

Several agents are available and the primary choice of drug depends on the degree of pressure lowering which needs to be achieved. It is recommended to initiate treatment on one type of medication. If an inadequate response in lowering the IOP is observed, the dose may be adjusted, or a second agent may be added. If the first agent fails to demonstrate any measureable clinical response, it should be removed from the regimen and be replaced with an

alternative drug.²¹ Pharmacological agents used to lower the IOP include prostaglandin analogs, carbonic anhydrase inhibitors, α_2 adrenergic agonists, cholinergic agonists, β blockers and hyperosmotic agents. Adequate treatment of glaucoma requires a high level of adherence. It is estimated that 45% of patients will default on chronic treatment, if they are not appropriately followed up and counselled regarding dosage instructions and possible side effects.²² Table 2 below summarises the currently available drugs in South Africa used to lower intraocular pressure.

Prostaglandin receptor analogs

Latanoprost, travoprost and bimatoprost are prostaglandin F_2 agonists, which increases the uveoscleral outflow of aqueous humour. It is considered the most potent group of topical ocular hypotensive agents currently available and may lower baseline IOP by 25–35%.²³ There are few associated systemic side effects and mostly relates to headaches. In addition, latanoprost may cause joint/muscle pain and flu-like symptoms. Local adverse effects include blurred vision, conjunctival hyperaemia, eye discomfort, permanent iridial pigmentation, macular edema and thickening of the eyelashes.²⁴

Carbonic anhydrase inhibitors

Acetazolamide, dorzolamide and brinzolamide are sulphonamide derivatives which reduces aqueous humour production independent to its diuretic mode of action. Acetazolamide is administered systemically in the form of oral tablets or intravenous infusion, and additionally reduces the rate of aqueous inflow up to 50%. Its usefulness is limited to the management of acute closed angle glaucoma due to unfavourable systemic side effects which may include paresthesia, nausea, diarrhoea, loss of appetite and dose related systemic acidosis. Topical application of dorzolamide

and brinzolamide demonstrates an improvement in ocular blood flow and long-term preservation of visual field. An average reduction of 15–20% in baseline IOP can be expected.²⁵ Side effects include ocular irritation, dry eyes, blurred vision, eyelid inflammation and a bitter taste.²⁶

Alpha 2 adrenergic agonists

Brimonidine is a selective α_2 receptor agonist. It initially reduces aqueous humour production followed by a subsequent increase in the uveoscleral outflow, therefore proving to be useful in preventing a rise in IOP prior to anterior segment laser surgery. Brimonidine reduces baseline IOP with approximately 20%.²⁷ Apraclonidine reduces the formation of aqueous humour but has no effect on the facilitation of outflow. It has affinity for both α_1 and α_2 adreno-receptors and are used to prevent postsurgical elevation of IOP after anterior segment laser therapy. Apraclonidine reduces baseline IOP by 30% and is additionally used as adjuvant therapy in resistant cases of glaucoma.²⁸ Systemic side effects of the alpha agonists are related to the central nervous system (headache, fatigue, insomnia, depression) and respiratory system. Caution should be taken in patients with cerebral or coronary insufficiency, postural hypotension and renal or hepatic failure. Hypersensitivity reactions, ocular irritation, eyelid edema, foreign body sensation and dry eyes are common with topical use.²⁹

Cholinergic agonists

Pilocarpine is the only available cholinergic agent in the management of acute closed-angle glaucoma registered in South Africa. Administration results in the increase in aqueous humour outflow by contraction of the ciliary muscle and constriction of the pupil. Poorly tolerated side effects, such as ciliary muscle spasm, myopia and decreased vision limits its usefulness.³⁰

Beta Blockers

Although prostaglandin receptor agonists are the most potent agents in reducing the IOP, beta blockers are regarded as the first choice in treating open angle glaucoma. Individual agents differ in their ability to lower IOP, with betaxolol achieving a 15% decrease,

compared to 20–25% with timolol and levobunolol respectively. Betaxolol is, however, more cardioselective (β_1) and therefore has fewer pulmonary side effects compared to timolol and levobunolol (which are non-selective antagonists on β_1 and β_2 receptors). The mechanism involves a reduction of aqueous humour production and does not cause miosis or accommodation disturbances compared to cholinergic agents. The most common adverse effects are ocular irritation and dry eyes. All the β blockers (including the cardioselective agents) are contraindicated in patients with asthma, COPD and bradycardia, unless alternative treatment is unavailable.³⁰

Combination agents

Several combination agents are available in the treatment of glaucoma. Most of these combinations include timolol, since β blockers are still considered first line therapy in open-angle glaucoma and ocular hypertension. Fixed-dose combination therapy is more efficacious than its individual components, but still less efficacious than its respective unfixed combinations. It provides for simplified treatment regimes and enhances compliance. Fixed dose combinations containing prostaglandins have a lower risk in causing hyperemia.³¹ Combination of timolol with dorzolamide is superior in visual field preservation compared to timolol and brinzolamide.²⁶ Combination preparations with brimonidine have less visual disturbances, taste alterations and ocular allergic reactions compared to the single ingredient product.²⁹

Cannabinoids

With the recent attention cannabis has been receiving in the management of pain and other cancer related conditions, it is important to remember the favourable effect of its active ingredient, Δ^9 -tetrahydrocannabinol (THC), in reducing ocular blood flow. Studies from the 1970s have reported a 30% reduction in the IOP by inhalation or intravenous administration of THC. The use is, however, limited owing to the cardiovascular (increased heart rate and decreased blood pressure) and neurological (tolerance and addiction) side effects. Topical application does not produce a significant clinical effect. The use of synthetic cannabinoids may provide a basis for potential future treatment strategies.³²

Table 2. Currently available drugs in the management of glaucoma

Active ingredient / Trade name	Strength	SEP*	IOP reduction	Dose
Prostaglandin analogs				
Atana® - Actor		R151.43 (2.5 ml)		
Ocuprost® - Arrow	Latanoprost 50 µg/ml	R182.37 (3 ml)	31%	1 drop daily
Xalatan® - Pfizer		R174.02 (2.5 ml)		
Travatan® - Alcon	Travoprost 40 µg/ml	R177.55 (2.5 ml)	32%	1 drop daily
Lumigan® - Allergan	Bimatoprost 0.1 mg/ml	R182.36 (2.5 ml)	32%	1 drop daily
	Bimatoprost 0.3 mg/ml	R222.54 (3 ml)		
Carbonic anhydrase inhibitors				
Diamox® - Litha	Acetazolamide 250 mg tabs	R77.94 (30)	20% – 30%	250 mg 1–4 times daily acc to response
Azoptix® - Alcon	Brinzolamide 10 mg/ml	R171.76 (5 ml)	15% – 20%	1 drop 8–12 hourly
Glaucompress® - Actor		R120.29 (5 ml)		
Trusopt® - MSD	Dorzolamide 20 mg/ml	R150.55 (5 ml)	16% – 18%	1 drop 8 hourly

α2 adrenergic agonists				
Alphagan Purite® - Allergan	Brimonidine 1.5 mg/ml	R211.44 (5 ml)	20% – 25%	1 drop 12 hourly
Brimoct® - Actor	Brimonidine 2 mg/ml	R177.08 (5 ml)		
Iopidine® - Alcon	Apraclonidine 10 mg/ml	R3024.88 (24 x 0.25 ml units)	30% – 33%	1 drop 1 hour pre-op, 2 drops post op
	Apraclonidine 5 mg/ml	R301.49 (10 ml)		1 drop 8 hourly
Cholinergic agonists (Parasympathomimetics)				
Isopto-Carpine® - Alcon	Pilocarpine 10 mg/ml	R111.94 (15 ml)		
	Pilocarpine 20 mg/ml	R108.03 (15 ml)	20% – 25%	2 drops 6–8 hourly
	Pilocarpine 40 mg/ml	R121.14 (15 ml)		
β blockers				
Betagan® - Allergan	Levobunolol 5 mg/ml	R180.06 (7.5 ml)	20% - 25%	1 drop 12 hourly
Betoptic® - Alcon	Betaxolol 5 mg/ml	R194.96 (5 ml)	15% – 20%	1 drop 12 hourly
Loxoptic® - Actor		R148.60 (5 ml)		
Glaucosan® - Sandoz	Timolol 5 mg/ml	R67.03 (5 ml)	15% – 25%	1 drop 12 hourly
Timoptol® - MSD	Timolol 2.5 mg/ml	R97.94 (5 ml)		
	Timolol 5 mg/ml	R120.29 (5 ml)		
Combination				
Azarga® - Alcon	Brinzolamide 10 mg/ml Timolol 5 mg/ml	R188.14 (5 ml)		1 drop 12 hourly
Combigan® - Allergan	Brimonidine 2 mg/ml Timolol 5 mg/ml	R221.58 (5 ml)		1 drop 12 hourly
Cosopt® - MSD		R213.14 (5 ml)		
Glauamide-Co® - Actor	Dorzolamide 20 mg/ml Timolol 5 mg/ml	R162.70 (5 ml)		1 drop 12 hourly
Glauopt Co® - Aspen		R162.70 (5 ml)		
DuoTrav® - Alcon	Travopost 40 µg/ml Timolol 5 mg/ml	R219.03 (2.5 ml)		1 drop daily
Ganfort® - Allergan	Bimatoprost 0.3 mg/ml Timolol 5 mg/ml	R236.05 (3 ml)		1 drop daily
Co-Atana® - Alcon	Latanoprost 50 µg/ml Timolol 5 mg/ml	R180.19 (2.5 ml)		1 drop daily
Xalacom® - Pfizer		R225.25 (2.5 ml)		

* Single exit price, as listed in the *Monthly Index of Medical Specialities*. 2016;56(11)

Conclusion

General practitioners and family physicians play an important role in the diagnosis and appropriate referral of patients with suspected glaucoma. Fundoscopic examinations are quick and easy to perform and are an opportunity that present at each consultation. The early recognition of symptoms may improve outcomes and delay progression. Taking a good medical history and applying the principles of rational drug use may identify potential pharmacological causes for glaucoma. Practitioners prescribing any of the drugs known to cause acute angle glaucoma should be vigilant in patients presenting with characteristic signs or symptoms, and immediately refer them to an ophthalmologist. Patients need to be counselled on the associated adverse effects from glaucoma medication in order to improve adherence.

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