The Balancing Act of Glaucoma

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Background

Glaucoma is considered the leading cause of irreversible blindness in the world, and second leading cause of blindness worldwide next to cataracts (1). Currently almost half a million people in Canada, nearly 3 million people in the United States, and over 60 million people worldwide have glaucoma (2). The condition is especially common in those of African heritage, being 4 times more prevalent than in those of Caucasians (3), as well as being up to 10 times greater risk of progression in blacks compared to whites (4). Asians have been shown to have greater risk of narrow angle glaucoma than other ethnicities (5). Due to the often slow and painless damage to the retinal nerve fiber layer, at least half of those with glaucoma are unaware that they have the condition. Some studies have shown no symptomatology or visual field loss when half or more of the approximately 1.2 million retinal nerve fibers are lost (6-9). There are several types of glaucoma, divided broadly into primary (originating on its own) and secondary (originating from another pathological source) forms, and open and closed angle forms (Table 1). The most common type is primary open angle glaucoma (POAG).

Table 1. Glaucoma types, categorized within primary or secondary, and open or closed angle forms.

	OPEN-ANGLE	CLOSED ANGLE
PRIMARY	Primary open angle glaucoma (POAG)	Primary angle closure glaucoma (PACG) -acute, subacute, intermittent, chronic
	Primary congenital/infantile glaucoma	Plateau iris glaucoma
	Juvenile onset open angle glaucoma (JOAG)	Pupillary block glaucoma
	Normotensive glaucoma (NTG)*	Iatrogenic (surgery-induced) glaucoma
SECONDARY	Pigmentary/Pigment dispersion glaucoma	Malignant/aqueous misdirection/ciliary block glaucoma
	Pseudoexfoliation glaucoma	Iridocorneal endothelial (ICE) glaucoma
	Uveitic/inflammatory glaucoma	Anterior chamber cleavage (ACC) glaucoma
	Traumatic/angle recession glaucoma	Shallow anterior chamber/dysgeneses
	Posner-Schlossman syndrome/ glaucomatocyclitic crisis glaucoma	High hyperopia
	Steroid-induced glaucoma	Medication-induced angle closure glaucoma (i.e. mydriatics)

Regardless of the type of glaucoma, the commonality is gradual retinal nerve fiber layer (RNFL) loss and accompanying neuroretinal rim thinning of the optic nerve. This results in the characteristic thinning of the optic disc rim (typically starting inferiorly, then superiorly, temporally, and finally nasally) with exposure of the lamina cribrosa. Other signs, such as rim notching, bayoneting of retinal vessels over the neruoretinal rim, laminate striae, alpha and beta peripapillary atrophy, and (in the case of normotensive glaucoma) splinter or Drance hemorrhages off the optic disc may present to the optometrist or ophthalmologist. Pallor of the disc is not as common in glaucoma as in other neuropathies such as chronic optic neuritis, toxic neuropathy, and ischemic neuropathies (10).

Various instruments are currently useful for identifying and monitoring glaucoma and glaucoma progression (Table 2). The clinician should have these instruments available for managing patients with glaucoma.

Table 2. Recommended instruments for managing patients with glaucoma

Tonometer	High plus biomicroscopy lens
Visual field analyzer	Biomicroscope
Retinal camera	Gonioscopy lens
Retinal nerve fiber analyzer	Blood pressure/pulse device
Pachymeter	

There are more additional tests available in helping diagnose and manage glaucoma, including genetic testing. Other less-common tests are the Ocular Response Analyzer (Reichert, Corp.; New York, USA) which measures corneal hysteresis, corneal deformation analyzers such as the Corvis ST, ocular pulse analyzers, which look at the vascular flow rhythm and amplitude, electrophysiological testing such as the electroretinogram (ERG) and visualevoked potential (VEP), various unique stimulus visual field tests such as frequency-doubling technology (FDT) perimetry, and other advanced retinal imaging technology (i.e. multispectral imaging, retinal Doppler flowimetry, etc.) under current investigation.

Glaucoma was traditionally defined as a disease of elevated eye pressure, leading to specific optic nerve damage and visual field loss. Currently, eye pressure has been removed from the definition, as patients with normal untreated eye pressure (typically between 10-21mmHg) can have glaucoma. However, the primary goal of treatment for glaucoma at the time of this presentation is still to lower the intraocular pressure, by medicinal, laser, and/or incisional surgical means. Neuroprotection and gene therapy for glaucoma are being actively researched and may likely serve as future treatment modalities (11).

Pathophysiology

There is still debate as to the specific process by which glaucoma occurs. Many types of glaucoma appear to have polygenic (involving both genes and environment) and multifactorial elements (including complex inheritance and genetic patterns) in development and progression. Three classic theories are 1) direct mechanical damage to the retinal nerve fibers, affecting internal organelles and axoplasmic flow, 2) ischemia of the optic nerve due to reduced blood flow to the optic nerve, and 3) apoptosis, or 'programmed cell death', which may have a genetic propensity (12).

The ciliary body produces aqueous via the non-pigmented ciliary epithelium, a single cell layer that borders the ciliary body and posterior iris with the anterior vitreal face. This cell layer has within the cell membrane the enzyme carbonic anhydrase (CA), which produces the aqueous (13). Roughly 80 percent of the aqueous flows from the ciliary body into the posterior chamber (behind the iris but in front of the anterior vitreous face), through the pupil, and out through the trabecular meshwork and Schlemm's canal to the venous system. The other 20 percent leave the eye through the uveo-scleral

tissue (14). If one considers the eye a 'closed sink', the 'tap' would be the ciliary body, the 'drain' would be the trabecular meshwork, and the 'overflow hole' would be the uveo-scleral tissue. Several types of open-angle glaucoma show a disruption in this sink – usually a dysfunction at the 'drain' (trabecular meshwork). Closed-angle glaucoma shows a definite problem in outflow due to direct or indirect blockage of the trabecular meshwork.

Recent efforts in genetic testing have shown a strong link to mutations in cells of the trabecular meshwork, leading researchers to link glaucoma to reduced aqueous outflow (15). Direct ocular tissue, blood, or saliva samples can be analyzed, and mutations confirmed using established gene sequencing methods. Currently there are at least 15 genetic tests to help confirm various types of glaucoma. More notable ones are the MYOC gene for POAG, the OPTN, TBK1, and OPA1 genes for NTG (OPTA1 causes primary optic atrophy, which shares features with NTG), and the CYP1B1 and LTBP2 genes for congenital glaucoma. As sensitivity and specificity of these and other genetic tests increase over the years, application towards targeted gene therapy may become more viable in the future (16).

Several risk factors for glaucoma should be identified. A key risk factor is the patient being of black race, as there is a much higher chance of glaucoma as well as progression of glaucoma. Aside from rare congenital glaucoma (where large and sometimes hazy corneas are noted in the infant) and juvenile forms of glaucoma, typically patients over 40 years of age are at higher risk for glaucoma than younger patients. Family history of glaucoma is variable, but a greater risk is usually present if the patient's siblings have been diagnosed with glaucoma. Vascular disease may also be a relative risk factor; patients with diabetes, hypertension, hyperlipidemia, Reynaud's Syndrome, or other systemic vascular disease should be looked at more closely. Retinal vascular disease (i.e., vascular occlusion) may increase the risk. Smokers and those who drink in excess may also be factors to consider. Steroid medications (topical or systemic) are known to increase IOP in 'steroid responders' (patients who have in increase in ocular pressure and/or posterior subcapsular cataracts with corticosteroid use), another risk (17).

Once a comprehensive case history and battery of pertinent tests is run, a patient may be considered to have low to no risk of glaucoma, risk factors for glaucoma, ocular hypertension (traditionally considered above 21mmHg uncorrected by pachymetry), glaucoma suspicion (based on IOP, visual field, and/or other objective tests), or glaucoma (the specific type of glaucoma determined by the

case history and tests performed). Often repeat testing is needed to help confirm or rule-out the diagnosis. Table 3 lists the indications to initiate treatment.

Table 3. Indications for Glaucoma Treatment

Established glaucoma
Glaucoma one eye, ocular hypertension other eye
Ocular hypertension one or both eyes
Intraocular Pressure (IOP) level
Rising IOP
Risk factors & suspect ocular hypertension
One eye, suspect ocular hypertension
IOP > 21 with history of retinal vein occlusion

Current Treatment Options for Glaucoma

Medical therapy is presently the most common initial intervention to lower IOP. There are many drugs available for initial therapy, and medication choice may be influenced by potential cost, side effects, dosing schedules, and the degree of pressure lowering needed (see Table 4 for an overview of options available). If target IOP is not achieved by one medication, then either switching or adding medications should be considered depending on whether the individual patient has responded to the first medication (the first medication should not be kept in the regimen if there is no response in IOP lowering). Prostaglandin analogs are the most frequently prescribed initial eye drops for lowering IOP in patients with glaucoma because they are most efficacious, well-tolerated, and instilled once daily.(18) They are also relatively safe.Some common side effects are, redness, itching, dryness, pigmentary changes, and blurred vision.

They are, therefore, often considered as initial medical therapy unless other considerations, such as contraindications, cost, side effects, intolerance, or patient refusal preclude this. Other agents include beta-blockers, alpha2 adrenergic agonists, parasympathomimetic, and topical and oral carbonic anhydrase inhibitors.

To determine the effectiveness of topical therapy, it is necessary to distinguish between the therapeutic impact of an agent on IOP and ordinary background spontaneous fluctuations of IOP. Though monocular trials have been recommended in the past to determine whether a topical ocular hypotensive agent is effective, recent studies have shown that such trials are not good predictors of long-term efficacy. A monocular trial is defined as the initiation of treatment in only one eye, followed by a comparison of the relative change in IOP in both eyes at follow-up visits to account for spontaneous fluctuations in IOP. However, the trial may not work because the two eyes of an individual may respond differently to the same medication, asymmetric spontaneous fluctuations in IOP may occur, and monocular topical agents may have a contralateral effect. A better way to assess IOP-lowering response is to compare the effect in one eye with multiple baseline measurements in the same eye, but the number of necessary baseline measurements will vary among patients. (24)

If a single medication is effective in lowering IOP but the target pressure is not reached, combination therapy or switching to an alternative therapy may be appropriate. Similarly, if a drug fails to reduce IOP sufficiently despite good adherence to therapy, it can be replaced with an alternative agent until effective medical treatment, whether alone or in combination, is established.

Adequate treatment of glaucoma requires a high level of adherence to therapy. Frequently this is not achieved, and studies indicate relatively poor adherence to therapy. Multiple dosing requirements or side effects (such as depression, exercise intolerance, and impotence that might occur with topical beta-blockers) may impact adherence to therapy. Even with instruction, free medication, once-daily administration, use of a dosing aid, and electronic monitoring of adherence, nearly 45% of patients in one study took fewer than 75% of their prescribed doses. (25) Fixed combinations of two medications may improve patient adherence by reducing the number of drops required for therapy. Instilling eye drops correctly is difficult for many patients, and their ability to do so may worsen with aging, comorbidities, and as glaucoma progresses. Repeated instruction and counseling about proper techniques for using medication, including waiting at least 5 minutes between multiple drop regimens as well as a clearly written medication regimen and follow-up telephone calls or smart phone reminders may improve adherence to therapy.(26) At each examination, medication dosage and frequency of use should be recorded. Reviewing the time medication was taken may be useful to help patients link eye-drop administration to activities of daily living and to be sure patients are actually using their eye drops. Adherence to the therapeutic regimen and recommendations for therapeutic alternatives or diagnostic

procedures should be discussed. (good quality, strong recommendation) (27) Cost may be a factor in adherence, especially when multiple medications are used. Patient education through oral, written, and online information and informed participation in treatment decisions may improve adherence and overall effectiveness of glaucoma management. Adherence is also handicapped when patients run out of medication before they are permitted to refill their prescription. However, patients with Medicare insurance may refill their medication after they have completed at least 70% of the month, or approximately 21 days of therapy.

Table 4 IOP-lowering medications, efficacy, and mechanism of action.

Medication Class	Compound	IOP reduction (%)	Mechanism of action			
			Increases uveoscleral outflow	Increases trabecular outflow	Decreases aqueous production	Decreases episcleral venous pressure
Prostaglandin analogues	bimatoprost, latanoprost, tafluprost, travoprost	25–35	Yes	No	No	No
β-Blockers (i) Nonselective	timolol, levobonolol, carteolol, metipranolol	20–25	No	No	Yes	No
(ii) *β*1-Selective	betaxolol	20	No	No	Yes	No
Carbonic anhydrase inhibitors (i) *Topical*	dorzolamide, brinzolamide	20	No	No	Yes	No

Medication Class	Compound	IOP reduction (%)	Mechanism of action			
			Increases uveoscleral outflow	Increases trabecular outflow	Decreases aqueous production	Decreases episcleral venous pressure
(ii) *Systemic*	acetazolamide, methazolamide, dichlorphenamide	30–40	No	No	Yes	No
Adrenergic agonists (i) α-2 Selective	brimonidine, apraclonidine	20–25	Yes	No	Yes	No
(ii) Nonselective	dipivefrin, epinephrine	15–20	Yes	No	Yes	No
Parasympathomimetics	pilocarpine, echothiophate	20–25	No	Yes	No	No
Novel IOP-lowering medications						
Rho-kinase inhibitors	netarsudil	16–21	No	Yes	Yes	Yes
Nitric oxide-donating prostaglandin analogue	latanoprostene bunod	32–34	Yes	Yes	No	No
FC rho-kinase inhibitor/latanoprost	netarsudil/latanoprost	30–36	Yes	Yes	Yes	Yes

Surgical or Advanced Treatment Options

When a patient does not reach goal pressure with topical medical management the cliinician may decide to advance to surgical means. There are a number of surgical interventions that exist that present various levels of risk, benefit and efficacy for various patients. Enclosed in table 5 is a review of trabeculectomy, canaloplasty, minimally invasive glaucoma surgery (MIGS), trabecular laser, various glaucoma drainage devices, and cyclodestructive options and their various success and complication rates.

Table 5. Various Surgical methods and success rates. (28)

Procedure	Short-Term Success (1 year)	Long-Term Success (>3 years; qualified or complete, with varying IOP endpoints)	Success Without Follow-Up Interventions	Success Without Use of Antimetabolites	Chance of Uncomplicated Procedure
Trabeculectomy[1-5]	+++	+ 40–71%	−−	−−	−
Canaloplasty[6-10]	+++	++ 36–78%	++	+++	++
MIGS[12-21]	+++	+ insufficient data	++	++	++
Trabecular laser[22-24]	++	− 32–44%	+	+++	++
Glaucoma drainage devices[25-31]	+++	+ 8–50%	−	−	−
Cyclodestructive[32-36]	++	+/− little data	+	+++	+/−

Scale: −−− = very poor; +++ = very good

The Newest Frontier in Glaucoma Management

There exist many issues with current medical therapy in glaucoma. Adherence to the prescribed eye drop, adverse events with the medicine itself, diurnal control of the pressure once the medicine is applied, and lastly cost or accessibility.

The newest frontier in glaucoma treatment is in advancing delivery mechanisms to apply current therapeutics in a safer long-lasting way. The perceived benefits of drug delivery devices include reduced

cost to patients, increased compliance, and fewer ocular side effects. Challenges include achieving efficacy over an extended delivery period and uncertainty regarding patient acceptance of the devices.

A study published in 2018 aimed to assess patients' acceptance of six potential drug delivery approaches. (19) For this study, 199 patients filled out a questionnaire, and investigators calculated their acceptance rates. The acceptance rates, in descending order, were as follows:

- triple combination eye drop, 85%
- microdose eye spray, 54%
- drug-eluting periocular ring insert, 43%
- injectable subconjunctival drug insert, 32%
- drug-eluting contact lens, 31%
- injectable anterior chamber implant, 30%

Patients who had more significant glaucoma or had undergone invasive glaucoma surgery were more likely to consider alternative options to traditional eye drops. (19)

The FDA recently cleared one new glaucoma drug delivery device and one or more new devices in development may be available in the near future.

Microdose Latanoprost

A microdose formulation of latanoprost is in development. This mode of delivery has the advantages of using 75% less drug and preservative than topical application and still getting 88% of the drug to the target tissue and achieving IOP lowering of 29%. (20) Patients still need to administer the medication, so compliance concerns are greater with this approach than with other drug delivery devices that are placed inside the eye or on the eye in other ways. An ongoing phase 3 study is assessing microdose latanoprost in chronic angle-closure glaucoma, open-angle glaucoma, and ocular hypertension.

Bimatoprost Ring

Currently under investigation, the bimatoprost ring—a topical ocular insert administered by a physician—is designed to release prostaglandin for up to 6 months per administration. The ring, made in multiple sizes, is a soft, flexible insert that rests circumferentially in the fornices on top of the conjunctiva. (21) A phase 2 clinical trial in 130 patients compared a ring containing 13 mg of bimatoprost versus timolol maleate instilled twice daily. (21) The ocular insert achieved IOP lowering of 4 mm Hg to 6 mm Hg

with a retention rate of 89%. Patients assessed the ring's comfort with a 90% acceptance rate at 6 months. (21)

Punctal Plugs

Punctal plugs are used on a daily basis to manage ocular surface disease. Two intracanalicular drug inserts are undergoing clinical evaluation in the United States.

OTX-TP is a resorbable intracanalicular insert that can deliver travoprost to the ocular surface for up to 90 days without preservatives. In a phase 3 clinical trial, the insert lowered IOP by between 3.27 mm Hg and 5.27 mm Hg in patients with primary open-angle glaucoma or ocular hypertension.

An L-shaped punctal plug with a latanoprost core is designed to create a unidirectional flow into the tear film to reduce systemic absorption of the drug. A phase 2 clinical trial showed a 20% reduction in IOP at 3 months with 92% retention. (22)

Subconjunctival Implants

A biodegradable implant that can be placed in the subconjunctival space at the slit lamp is undergoing phase 1 and 2 clinical trials. The 3 mm by 0.3 mm implant releases latanoprost over a period of 12 months.

Intracameral Implants

In March 2020 the FDA approved the biodegradable bimatoprost sustained-release intracameral implant 10 mcg for intracameral administration to treat open angle glaucoma or ocular hypertension. The implant is injected into the anterior chamber and typically resides in the inferior angle, where it elutes bimatoprost in a sustained manner.

The FDA approval is based on results from the two 20-month phase 3 ARTEMIS studies evaluating 1,122 patients on the efficacy and safety of the implant versus twice daily topical timolol drops in patients with open-angle glaucoma or ocular hypertension. In the two phase 3 ARTEMIS studies, the implant reduced IOP by approximately 30% from baseline over the 12-week primary efficacy period, meeting the predefined criteria for noninferiority to the study comparator. (23)

The travoprost intraocular implant is a travoprost-eluting device that is placed into the trabecular meshwork. Preliminary efficacy data from a phase 2 study showed an average IOP reduction through month 12 ranging from 7.9 mm Hg to 8.5 mm Hg with both slow- and fast-elusion devices. This represented a 32% to 33% reduction in IOP from baseline.

Contact Lenses

Contact lenses that elute medication have been considered as a route to achieve long-term delivery of glaucoma drugs. Comfort, compliance with wearing the lens, optical characteristics of the lens, ocular surface disease concerns, and replacement schedules are among the challenges that have been encountered in preclinical and clinical trials.

An approved contact lens combined with a patented drug-eluting process and approved drugs is currently being studied to treat a variety of diseases, including glaucoma. The device uses vitamin E nano-barriers to extend drug release. In a small phase 1 clinical trial, patients received the drug-containing lens for a 2-day dosing period. A reduction of IOP was observed over 9 days after the lens was removed. (24) A phase Ib study and phase 2 study are planned for 2021.

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