Clinical Ophthalmology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Current primary open-angle glaucoma treatments and future directions

This article was published in the following Dove Press journal:
Clinical Ophthalmology
19 October 2012
Number of times this article has been viewed

Gabriel Beidoe
Shaker A Mousa

Pharmaceutical Research Institute at Albany College of Pharmacy and Health Sciences, Rensselaer, NY, USA

Abstract: Primary open-angle glaucoma (POAG) is a leading cause of blindness with no known cure. Management of the disease focuses on lowering intraocular pressure (IOP) with current classes of drugs like prostaglandin analogs, beta-blockers, alpha-agonists, and carbonic anhydrase inhibitors. These treatments have not helped all patients. Some patients continue to experience deterioration in the optic nerve even though their IOPs are within the normal range. New views have surfaced about other pathophysiological processes (such as oxidative stress, vascular dysfunction, and retinal cell apoptosis) being involved in POAG progression, and adjunctive treatments with drugs like memantine, bis(7)-tacrine, nimodipine, and mirtogenol are advocated. This review examines the current and proposed treatments for POAG. Some of the proposed drugs (bis(7)-tacrine, nimodipine, vitamin E, and others) have shown good promise, mostly as monotherapy in various clinical trials. It is recommended that both the current and proposed drugs be put through further robust trials in concurrent administration and evaluated.

Keywords: bis(7)-tacrine, betaxolol, memantine, mirtogenol, POAG, timolol, travoprost

Introduction

Glaucoma is the second most prevalent eye condition, after cataracts,[1,2] known to cause blindness worldwide. About 66.8 million people worldwide are afflicted with glaucoma.[3] An estimated 4.4 million Americans have glaucoma, and over 120,000 of these people are rendered blind as a result.[4] The actual etiology of the condition remains unknown.[2,5] There is no known cure.

Glaucoma consists of many eye disorders, such as congenital glaucoma, secondary glaucoma, primary angle closure glaucoma (PACG), normal tension glaucoma (NTG), pigmentary glaucoma, and primary open-angle glaucoma (POAG). These disorders destroy the optic nerve, which sends visual information to the brain, leading to blindness.[1,6] POAG accounts for around 70% of the total glaucoma cases worldwide.[5,7] Normal tension glaucoma is a variation of POAG, but NTG is associated with normal intraocular pressure (IOP). Some experts believe a lack of adequate perfusion to the optic nerve is the cause of NTG.[6] In POAG, there is a malfunction in the ocular drainage system, resulting in the accumulation of aqueous fluid. This increases the IOP, which impinges incessantly on and damages the optic nerves.

Management of POAG has focused on reducing the IOP.[8,9] The American Academy of Ophthalmology recommends that in treating POAG, the target IOP should be a 25% reduction of the baseline or untreated IOP and that it should be subsequently managed on an individual basis.[10] To put things in perspective, normal IOP is around 15.5 mmHg, NTG is associated with an IOP of <21 mmHg, and POAG patients have

Correspondence: Shaker A Mousa
Pharmaceutical Research Institute at Albany College of Pharmacy and Health Sciences, 1 Discovery Drive (Room 238), Rensselaer, New York 12144, USA
Tel +1 518 694 7397
Fax +1 518 694 7567
Email shaker.mousa@acphs.edu

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/OPTH.S32933

an abnormally high IOP. With an IOP of >30 mmHg, the potential for vision loss is 40 times greater compared to an IOP of 15 mmHg.[6]

Managing just IOP is not effective in all patients,[9,11,12] especially in the 20%–30% of POAG patients, ie, NTG patients, whose optic nerve degeneration is thought to be independent of IOP.[5,13] These patients continue to experience optic nerve damage although their IOPs are within normal range.[14] This observation has resulted in the view that other pathological processes are involved in the progression of POAG.[2,15,16] Many experiments have shown an association between POAG and disease progressing processes like oxidative stress, protein misfolding, excitotoxicity, vascular dysregulation, and immune dysregulation.[2,15,16] These same processes have been observed in some neurodegenerative disorders like Alzheimer's disease and Parkinson's.[2,15,16] It is thought that simultaneously stopping these pathological processes will stem POAG progression. This review will present current and proposed medications in order to ascertain their usefulness in managing POAG.

Methodology

A literature search was conducted using PubMed and ClinicalTrials.gov with keywords such as primary open angle glaucoma, memantine, bis(7)-tacrine, and neuroprotection. Information from other sources, such as the Glaucoma Research Foundation, National Eye Institute, National Glaucoma Research, and Dipiro's pharmacotherapy text was also used to give an expanded picture of this disease state and its treatments.[4,5,17]

Primary open-angle glaucoma risk factors and pathophysiology

Risk factors for primary open-angle glaucoma include: age >60 years, genetic predisposition, certain eye characteristics (such as a pupillary defect, thin cornea, myopia), low educational status, smoking, African descent, and visual problems (such as ocular hypertension, larger horizontal or vertical cup disc ratio, greater Humphrey visual field pattern deviation, asymmetries in the visual field, and IOP).[4]

The human eye is made up of two fluid-filled chambers surrounding the lens; the aqueous and the vitreous humors. In the vitreous chamber, which is in close proximity to the optic nerves, the fluid does not drain. In the anterior chamber, fluid is continuously produced by the epithelium of the ciliary body and continuously drains at an equivalent rate. This fluid nourishes and cleanses the eye and mainly exits through the trabecular meshwork (TM), or another pathway that is insensitive to eye pressure, the uveoscleral outflow pathway. Fluids in both the vitreous and anterior chambers maintain IOP to prevent the eye from collapsing. In POAG, the rate of fluid production in the aqueous humor is not impaired; however, the outflow becomes impeded by the narrowing of the meshwork pores. This results in the generation of excessive IOP in the anterior chamber that is relayed via the vitreous humor onto the optic nerve. The pressure points damage the optic nerve. This is analogous to a hinged door closing and squeezing in on one's fingers.

Management of POAG

Current treatments

Regardless of the form of POAG, current treatment is the same.[9] This treatment comprises incisional surgery, laser surgery, and medication. All these treatments aim to relieve the pressure on the optic nerve either by slowing the rate of aqueous humor production or by increasing the rate of excess aqueous humor drainage. There is an array of medications to lower the IOP in POAG, which are divided into five major classes: prostaglandin analogs, beta blockers, diuretics, cholinergic agonists (parasympthomimetics), and alpha agonists.[18] The various mechanisms of action, efficacies, and side effect profiles of these medications differ among patients, as shown in Table 1.

Monotherapy

In general, monotherapy is the first treatment approach. It increases compliance and decreases systemic and topical adverse reactions, especially if the drug in question is used or applied once daily.[27] If the drug is not efficacious or tolerable, it should be changed.

A single-agent drug like latanoprost is able to reduce the IOP by greater than 30% from baseline in patients with IOPs of 20–24 mmHg, but IOP reductions are even higher in baseline IOPs that are >24 mmHg.[28] The IOP reduction with latanoprost and the rest of the prostaglandin analogs (PGAs) is not across-the-board. In one study, latanoprost decreased IOP by 30% in only 10% of patients.[29] This implies that some patients cannot meet the American Academy of Ophthalmology initial IOP reduction target of 25% of the baseline IOP on latanoprost alone. Latanoprost, as well as beta blockers, are thought to be potent drugs,[27,30] and one study found no significant differences between beta blockers and PGAs.[31] Consequently, all could be used as first-line monotherapy agents, including other PGAs like bimatoprost or travoprost.[27]

Table 1 Current treatment drugs for POAG[19–26]

Drug class	Drug and daily frequency	Route	Mechanism of action	Side effects in class
Prostaglandin analogs	Latanoprost 1x Travoprost 1x Unoprostone 2x Bimatoprost 1x	Topical	Increased trabecular drainage	Eye lash thickening, eye lid darkening, eye staining
Beta blockers	Betaxolol 2x (selective) Carteolol 2x Timolol 1–2x Levobunolol 1–2x	Topical	Decreased aqueous fluid production	Eye irritation, hyperemia, blurred vision, impaired lung function
Diuretics (carbonic anhydrase inhibitors)	Brinzolamide 3x Dorzolamide 3x Acetazolamide 2–4x Methazolamide 2–3x	Topical Oral	Decreased aqueous fluid production via HCO_3^- unavailability	Blurred vision, bitter taste, acidosis, hepatic necrosis
Cholinomimetics	Carbachol 3x Pilocarpine 3–4x Physostigmine 1–4x	Topical DOG Plastic film	Open the TM by contraction of ciliary muscle forces	Night blindness, blurred vision, burning eye sensation
Alpha agonists (selective)	Epinephrine 1–2x Dipivefrin 2x	Topical	Increased trabecular flow	Tremor Palpitation
Alpha agonists (non-selective)	Brimonidine[a] 3x Apraclonidine[b] 3x	Topical	Reduced aqueous production and increased uveoscleral flow	Hyperemia, allergic conjunctivitis, itching, lacrimation

Notes: [a]Brimonidine has a dual mechanism of action; [b]apraclonidine only reduces aqueous production.
Abbreviations: POAG, primary open-angle glaucoma; DOG, drops, ointment, gel.

Brimonidine was found to be as efficacious as timolol, if not better, in reducing IOP. Topical brimonidine and not timolol should be considered a first-line treatment in patients with hypertension and glaucoma who are on concurrent systemic beta blockers.[24] Betaxolol, which is supposed to be an improvement on timolol, does not seem to be. Both betaxolol and timolol impair lung function and betaxolol even raises IOP.[23] In another study involving three beta-blockers, carteolol, betaxolol, and timolol, each administered as a monotherapy, it was found that these medications did not adequately treat over 50% of enrolled patients' eyes during the 7 years of the study, and additional medications were added within the time of the study. Betaxolol, a beta-1 selective, had more side effects than carteolol, a non-selective beta blocker, and in some cases, betaxolol took up to 12 months longer to equal the IOP lowering abilities of carteolol or timolol.[32]

Cholinergic drugs like pilocarpine are the ones that come close to targeting the TM, although indirectly. They should be excellent for treating PACG because they open up the drainage angle by removing the blockage caused by the covering iris. The cholinergics cause the ciliary muscle to contract, and in doing so, open up the drainage pores in the meshwork. This unique mechanism of action causes contraction of the ciliary muscle and relaxing of the lens, resulting in a more spherical lens shape. This shape is only good for seeing near objects. Cholinergic drugs, by virtue of their mechanism of action, have an additive effect in enhancing myopia in glaucoma patients, which presents as night blindness and blurred vision,[33] both of which pose a safety risk. It has also been established that myopia is a risk factor for POAG,[34,35] and most glaucoma patients are myopic.

Combination therapy

Monotherapy may not be enough to produce the much-needed drop in IOP for some patients, and so combining drugs is the next alternative. If a monotherapy drug is only partially efficacious, other drugs with differing mechanisms can be added. To make it easier on patients and to improve compliance, different drugs have been formulated together in what are termed combination drugs, such as the two available in the US, Cosopt® (timolol and dorzolamide) and Combigan® (timolol and brimonidine), and others available in Europe, DuoTrav® (travoprost and timolol) and Xalacom® (latanoprost and timolol).

In a randomized, double-masked study, fixed combinations of latanoprost and timolol significantly lowered IOP levels by more than 30% in 73.5% of patients compared to latanoprost alone (57.5% of patients) and timolol alone (32.8% of patients).[36,37] Combinations of timolol 0.5% with either dorzolamide 2% or brinzolamide 1% were studied with respect to retrobulbar hemodynamics and IOP.[38] Each combination significantly reduced IOP; the timolol/dorzolamide combination lowered IOP by 4.3 mmHg (95% confidence intervals [CI]: –4.5 to –4.2 mmHg), and the timolol/brinzolamide combination lowered IOP by

4.2 mmHg (95% CI: –4.4 to –4.2 mmHg). The timolol/dorzolamide combination significantly decreased the resistivity index in the ophthalmic artery, short posterior ciliary arteries, and central retinal artery by 0.02 units ($P < 0.001$), allowing enhanced retrobulbar blood flow.[38] A similar study with a combination of betaxolol and pilocarpine to assess IOP reductions and safety resulted in severe side effects ranging from blurred vision to headaches – so much so that 10%–15% of the patients on the pilocarpine or its combination with betaxolol had to be terminated from further participation in the study.[33] Overall though, the combination medications have higher IOP reductions of at least 2 mmHg more than individual agents like betaxolol or pilocarpine.[33] It should be noted that not all combination therapies resulted in significant decreases in IOP. A study trying to assess the additive hypotensive effects of dorzolamide and a morning bimatoprost dose in POAG saw no significant IOP reductions on adding dorzolamide (mean IOP 12.8 ± 2.9 mmHg after bimatoprost monotherapy versus 12.2 ± 2.6 mmHg following the addition of dorzolamide), although vascular resistance in the ophthalmic artery decreased following the combination treatment.[30] There was also no significant reduction in IOP compared to baseline in a double-masked study with travoprost on one hand versus a timolol/latanoprost combination on the other.[20]

In NTG, or in other POAG cases where significant IOP reductions were achieved, it was difficult to obtain further IOP reductions even with combination drugs.[28,39] This is indicated by the findings of several studies where dorzolamide was added to either a PGA or a beta blocker.[40,41] Since PGAs have been found to be efficacious,[42,43] a new open-label, randomized control trial was conducted to verify if a double PGA (bimatoprost and latanoprost) could prove more efficacious than the individual drugs; however, the mean IOP increased by 1.8 mmHg ($P = 0.006$) when compared with the baseline. The IOP returned to baseline when the bimatoprost was discontinued.[44] Some medications like apraclonidine and pilocarpine are mostly used to control IOP increases associated with ocular surgeries like cataract removal and trabeculoplasty.[45] Epinephrine is rarely used even topically because of cardiovascular side effects.[22]

The combination of surgery and medications in one study (Collaborative Initial Glaucoma Treatment Study) showed dramatically reduced IOP (15 mmHg versus 17.2 mmHg) over a 2 to 9 year follow-up.[8] These results showed a significant reversal of cupping in the surgical group compared to the medication group, but cup reversal did not mean reversal of optic nerve degeneration or improved visual function.[46]

Future treatments

Increased IOP has always been the premise upon which POAG treatment decisions are made. Evidence is mounting that increased IOP is not the only culprit causing POAG progression. Some patients continue to have optic nerve deterioration. They suffer from optic nerve ischemia, hemorrhage, and apoptosis of retinal ganglion cells.[5] These symptoms are believed to be fuelled by local autoimmune disorders, oxidative stress, overstimulation of NMDA glutamate receptors, and mitochondrial dysfunction.[47] Therefore, the IOP-lowering approach will not sufficiently manage POAG in those individuals. Additional therapy is needed, and if proposed drugs in clinical trials are found to be efficacious, then these will be adjunct to the current therapy. Memantine, bis(7)-tacrine, mirtogenol, vitamin E, N-acetylcysteine, glutathione, forskolin, rutin, vitamins B1 and B2, erythropoietin, marijuana, and nimodipine have all been proposed (Table 2).

Memantine and bis(7)-tacrine

Some studies have drawn a link between Alzheimer's disease, Parkinson's, and POAG. The commonality between these conditions is the excessive production of glutamate or its accumulation resulting in excitotoxicity through overstimulation of the NMDA receptors. This results in retina ischemia.[56,57] Memantine is known to selectively and uncompetitively block the NMDA receptor. An analysis of the composition of vitreous fluid of humans with POAG and monkeys with POAG indicated elevated levels of glutamate.[58] In a study to assess the toxicity of glutamate and its antagonist (memantine) on retinal ganglion cells, three groups of rats were dosed for 3 months: group 1 with low dose intravitreally injected glutamate; group 2 with an intravitreally injected combination of glutamate and memantine; and group 3, a control group, intravitreally injected with a vehicle free of glutamate but with or without memantine.[57] There were considerable increases in endogenous glutamate from 5–12 to 26–34 μM. Also, the sustained, increased concentrations of glutamate killed 42% of the retinal ganglion cells. However, the memantine treatment alone neither killed the ganglion cells nor caused an increase in the number of ganglia. When memantine was administered alongside glutamate, it exhibited a partial neuroprotective effect. The baseline number of ganglion cells per eye (that also doubled as a control count)

Table 2 Future drugs for POAG[48–55]

Drug class	Drug	Route	Purported mechanism of action	Clinical trial phase
NMDA receptor antagonist	Memantine Bis(7)-Tacrine	Oral	Prevents excitotoxicity and apoptosis	C PCT
Antioxidants	N-acetylcysteine Vitamin E	Topical	Mops up ROS	None
Antioxidant, anti-inflammatory, and antimicrobial Forskolin (terpenes)	Forskolin (flavonoid) Rutin and vitamins B1 and B2	Oral	Forskolin ↓ IOP by ↑ cAMP All maintain retinal nerve fiber layers	C
Antioxidant	Forskolin, Rutin, vitamin B plus PGA or beta-blocker	Oral	Maintain retinal nerve fiber layers ↓ IOP	NYR
Cannabinoids	Δ-1-THC Δ-9-THC Marijuana	IV/oral Oral	Improves TM outflow	NR
Food additives and herbs	Vitamin, mineral, and medical herbs–Marijuana	Oral	Reverse neuropathy	I and II but T
Mirtogenol (Flavonoid)	Pycnogenol Mirtoselect	Oral	Increases ocular blood flow	None
Hematopoietic agent	Erythropoietin	Intraperitoneally	Neuroprotection via increased survival of RGC	PCT
Calcium channel blocker	Nimodipine	Oral	Neuroprotective effects on neurons undergoing apoptosis and necrosis	NR

Abbreviations: POAG, primary open-angle glaucoma; NR, not registered; T, terminated; C, completed; NYR, not yet recruiting; PCT, preclinical trial; ROS, radical oxygen species.

was 96,000 ± 8500 to 56,000 ± 9600 ($P < 0.001$) in the glutamate-treated eye, but decreased to 83,000 ± 4900 in both glutamate and memantine-treated eyes.[57] Subsequent studies with memantine have shown mixed results,[56,59] and results from completed phase III studies that were randomized, double-masked, placebo-controlled clinical trials with memantine were negative.[60] However, a new agent, bis(7)-tacrine, also an NMDA receptor antagonist, was noted to be a more potent neuroprotective agent than memantine in a comparison in a study on retinal ganglion cells.[56]

Mirtogenol

Studies have looked into the possibility of increasing blood supply to the optical nerves to avert ischemia. Mirtogenol, a food supplement, has been considered for use as a prophylactic measure. In a study by Steigerwalt et al, IOP and ocular blood flow through the central retinal, ophthalmic, and posterior ciliary arteries were measured in two groups of human subjects with elevated IOPs (22 to 26 mmHg) but without glaucoma, and not receiving any treatment for elevated IOP. The control group (n = 18) was untreated, and the treated group (n = 20) was given daily mirtogenol for 6 months. In the mitrogenol-treated group, there were significant increases in blood flow as measured by color Doppler imaging compared to the control group, and after 3 months there was a statistically significant lowering of IOP (22.0 ± 2.6) in the treated group compared to the control group (24.5 ± 2.3 mmHg; $P < 0.05$). At 6 months, there was no significant further lowering of IOP in the treated group, and there was no effect in the controls.[48]

Vitamin E, N-acetylcysteine, and other antioxidants

Researchers have looked into whether oxidative stress is a contributing factor in POAG progression. In a study using surgically removed and cultured TM tissue from both POAG and non-POAG patients, tissue analysis revealed higher concentrations of radical oxygen reactive species (RORS), a decreased change in membrane potential, and 30% lower ATP production in the POAG TM when compared to the non-POAG TM.[49] After the addition of mitochondrial complex I inhibitor (rotenone), there was a significant spike in the production of RORS in the POAG TM but little to no increase in RORS production in the non-POAG TM, even at higher rotenone concentrations ($P < 0.05$). A decrease in membrane potential is known to cause apoptosis, and in this experiment, the POAG TM showed a 7.29-fold decline in membrane potential at baseline, then a further 7.89-fold reduction after rotenone treatment, compared to an insignificant decline in the non-POAG TM as measured with flow cytometry using a fluorescence indicator. Apoptosis is also directly proportional to the amount of lactate dehydrogenase (LDH) released. The rotenone-treated POAG TM showed a 5.53-fold LDH increase, and only a 1.35-fold LDH increase in the non-POAG TM as measured with an LDH assay kit. When the TM

tissues (POAG, or rotenone-treated POAG) were pretreated with the antioxidants vitamin E or N-acetylcysteine, there were reductions in the RORS levels (7-fold to 2.5-fold with vitamin E for POAG, 7-fold to 2.4-fold with N-acetylcysteine for POAG, 20-fold to about 6.5-fold with either vitamin E or N-acetylcysteine for rotenone-treated POAG TM). There was no change in non-POAG TM when pretreated with either vitamin E or N-acetylcysteine.[49]

In another study, a link was made between a vitamin E-deficient diet and increased retinal ganglion cell death in an induced glaucoma rat model, where rats' IOPs were surgically elevated. Three rat groups were observed; the groups were fed on standard chow feed, vitamin E-enriched chow, or vitamin E-deficient chow. The average retinal numbers of ganglion cells were 79.6%, 78.6%, and 71.3% of controls, respectively, at the end of the study. The vitamin-E deficient group had significantly higher lipid peroxidation as measured by colorimetric measurement in isolated retinas (14.42 ± 0.25 μM; $P = 0.016$ in 3 days; 10.46 ± 0.11 μM; $P = 0.042$, in 5 weeks) compared to the standard chow group (11.37 ± 0.31 μM in 3 days; 8.95 ± 0.16 μM in 5 weeks). Accordingly, the study suggested that higher retinal ganglion cell death in the vitamin E-deficient chow feed group could be related to increased lipid peroxidation levels.[61]

The antioxidants (forskolin, rutin, and vitamins B1 and B2) were actually administered to POAG patients in a bid to replenish their depleting reserves, but results on their efficacy are not yet reported.[50–52]

The depletion of the antioxidant glutathione by buthionine sulfoximine in mice was linked to apoptosis of retinal ganglion cells.[62] A new study is ongoing and will determine if glutathione is also low systemically in POAG patients.[63]

Erythropoietin

Erythropoietin has been found to have neuroprotective effects. This was observed in a DBJ/2J mouse model of POAG, where erythropoietin was administered at doses between 3000 and 12,000 U/kg, and prevented the loss of retinal ganglion cells. This was similar to the effects of memantine. However, untreated DBJ/2J control animals had a loss of retinal ganglion cells.[53]

Marijuana

Marijuana has been noted to reduce IOP by increasing aqueous drainage through the uveoscleral outflow pathway. In a case report involving one patient, it acted as a last-line therapy for two reasons: the patient was clearly intolerant of other medications, and other medications were not efficacious enough. Smoking marijuana cigarettes combined with the ingestion of 1 or 2 marijuana cookies reduced IOP from 30 mmHg to 15 mmHg.[54]

In a randomized, double-masked, placebo-controlled study, it was noted that sublingual administration of canabidiol did not reduce IOP. However, a sublingual administration of delta-9-tetrahydrocannabinol (Δ-9-THC) did reduce IOP over placebo although for only 4 hours (23.5 mmHg versus 27.3 mmHg; $P = 0.026$). The route of administration clearly mattered because topically applied Δ-9-THC did not work.[55] Depending on the strength, the Δ-9-THC will require multiple dosing. It is premature to advocate for this treatment until a larger randomized, blinded trial has been conducted.

Nimodipine

Vascular dysregulation has been implicated in POAG. One theory is that ischemia of the retina is caused by lack of adequate blood supply due to the squeeze experienced by the blood vessels serving the optic nerve and the retina as a result of the high IOP. This squeeze can also cause blood vessels to burst, resulting in hemorrhage. Calcium channel blockers are known to relieve the pressure on the blood vessels. In a study involving the use of oral nimodipine, it was found to indirectly improve color sensitivity by increasing blood flow to the optic nerve head in NTG patients[64] and improve the visual field[65] compared to the placebo group. Oral nimodipine was used because it has a high lipid coefficient and is able to cross the blood–brain barrier.[63] Other calcium channel blockers (flunarizine and nifedipine) gave mixed results.[66,67]

Conclusion

POAG medications aim to increase the drainage of excess aqueous humor, mostly through uveoscleral outflow, and to a lesser extent, the TM. In other words, these medications do not adequately target the TM, which presents the most surface area for drainage. It is for this reason that no one medication is able to reduce the IOP by more than 25% across the board. Consequently, patients will have to use a myriad of medications to control POAG and compliance becomes a problem. Monotherapy is not usually the answer and other drugs should be added or other approaches considered. One cannot use two PGAs together; using them together will cause an increase in IOP. If using one PGA does not work, it is necessary to first switch between drugs in the same class. The maximum timeframe for using beta blockers as monotherapy should be 1 year, after which, combination therapy or another approach

for reducing IOP should be used. Betaxolol should be used as a last-line beta blocker.

Apart from the cholinergic drugs, no drug class comes close to effectively targeting the TM. Thus, patients use multiple drugs, and the risks of side effects and low compliance are real. It may be cost effective if more research is targeted at TM-opening drugs. Cholinergic drugs come close to fulfilling this requirement, but their side effects do not make them attractive and it is recommended that they be used as a last line or that they are better used for PACG.

The proposed new drugs have shown good promise. Even though some are still in the preclinical phases, it is recommended that more attention is accorded these drugs to enhance an all-round attack on POAG.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Monemi S, Spaeth G, DaSilva A, et al. Identification of a novel adult-onset primary open-angle glaucoma (POAG) gene on 5q22.1. *Hum Mol Genet*. 2005;14(6):725–733.
2. Tamura H, Kawakami H, Kanamoto T, et al. High frequency of open-angle glaucoma in Japanese patients with Alzheimer's disease. *J Neurol Sci*. 2006;246(1–2):79–83.
3. Vyas P, Naik U, Gangaiah JB. Efficacy of bimatoprost 0.03% in reducing intraocular pressure in patients with 360 degrees synechial angle-closure glaucoma: a preliminary study. *Indian J Ophthalmol*. 2011;59(1):13–16.
4. NEI. Glaucoma and Optic Neuropathies Program. [Web page] Bethesda, MD: National Eye Institute; 2009 [updated 2009]. Available from: http://www.nei.nih.gov/strategicplanning/nationalplan1.pdf. Accessed March 3, 2011.
5. Dipiro J, Talbert RL, Yee GC, Wells BG, Posey LM, editors. *Pharmacotherapy: A Pathophysiologic Approach*. 7th ed. New York, NY: McGraw Hill; 2009.
6. Heiting G, Haddrill M. Glaucoma: Types, Symptoms, Diagnosis and Treatment [updated Dec, 2011]; Available from: http://www.allaboutvision.com/conditions/glaucoma.htm#typesofglaucoma. Accessed June 6, 2012.
7. Park BC, Tibudan M, Samaraweera M, Shen X, Yue BY. Interaction between two glaucoma genes, optineurin and myocilin. *Genes Cells*. 2007;12(8):969–979.
8. Musch DC, Gillespie BW, Niziol LM, Cashwell LF, Lichter PR. Factors associated with intraocular pressure before and during 9 years of treatment in the Collaborative Initial Glaucoma Treatment Study. *Ophthalmology*. 2008;115(6):927–933.
9. Heijl A, Leske MC, Bengtsson B, Hyman L, Hussein M. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol*. 2002;120(10):1268–1279.
10. AAO. American Academy of Ophthalmology Glaucoma Panel, Primary Open Angle Glaucoma. [Web page] San Francisco, CA: AAO PPP Glaucoma Panel, Hoskins Center for Quality Eye Care; 2010; Available from: http://www.aao.org/ppp. Accessed March 3, 2011.
11. Lichter PR, Musch DC, Gillespie BW, Guire KE, Janz NK, Wren PA, et al. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. *Ophthalmology*. 2001;108(11):1943–1953.
12. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002;120(6):701–713.
13. Sommer A, Tielsch JM, Katz J, et al. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. *Arch Ophthalmol*. 1991;109(8):1090–1095.
14. Gogate P, Deshpande R, Chelerkar V, Deshpande S, Deshpande M. Is glaucoma blindness a disease of deprivation and ignorance? A case-control study for late presentation of glaucoma in India. *Indian J Ophthalmol*. 2011;59(1):29–35.
15. Bayer AU, Keller ON, Ferrari F, Maag KP. Association of glaucoma with neurodegenerative diseases with apoptotic cell death: Alzheimer's disease and Parkinson's disease. *Am J Ophthalmol*. 2002;133(1):135–137.
16. Bayer AU, Ferrari F, Erb C. High occurrence rate of glaucoma among patients with Alzheimer's disease. *Eur Neurol*. 2002;47(3):165–168.
17. GRF. Glaucoma Research Foundation. [Website] San Francisco: Glaucoma Research Foundation; [updated May 1, 2009]; Available from: http://www.glaucoma.org/learn/diagnostic_test.php. Accessed February 25, 2011.
18. Narayanaswamy A, Neog A, Baskaran M, et al. A randomized, crossover, open label pilot study to evaluate the efficacy and safety of Xalatan in comparison with generic Latanoprost (Latoprost) in subjects with primary open angle glaucoma or ocular hypertension. *Indian J Ophthalmol*. 2007;55(2):127–131.
19. Katzung BG. *Basic and Clinical Pharmacology*. 7th ed. Norwalk, CT: Appleton and Lange; 1997.
20. Franks WA, Renard JP, Cunliffe IA, Rojanapongpun P. A 6-week, double-masked, parallel-group study of the efficacy and safety of travoprost 0.004% compared with latanoprost 0:005%/timolol 0.5% in patients with primary open-angle glaucoma or ocular hypertension. *Clin Ther*. 2006;28(3):332–339.
21. Blondeau P, Rousseau JA. Allergic reactions to brimonidine in patients treated for glaucoma. *Can J Ophthalmol*. 2002;37(1):21–26.
22. Kerr CR, Hass I, Drance SM, Walters MB, Schulzer M. Cardiovascular effects of epinephrine and dipivalyl epinephrine applied topically to the eye in patients with glaucoma. *Br J Ophthalmol*. 1982;66(2):109–114.
23. Diggory P, Cassels-Brown A, Vail A, Hillman JS. Randomised, controlled trial of spirometric changes in elderly people receiving timolol or betaxolol as initial treatment for glaucoma. *Br J Ophthalmol*. 1998;82(2):146–149.
24. Schuman JS. Effects of systemic beta-blocker therapy on the efficacy and safety of topical brimonidine and timolol. Brimonidine Study Groups 1 and 2. *Ophthalmology*. 2000;107(6):1171–1177.
25. ClinicalPharmacology. Drug Monographs. [Web database]: Clinical Pharmacology; [updated 2009–2010]; Available from: http://www.clinicalpharmacology-ip.com/default.aspx. Accessed March 3, 2011.
26. Micromedex. Drug Monograph. [Web database]: Micromedex; [updated 2011]; Available from: http://www.thomsonhc.com. Accessed March 3, 2011.
27. Kammer JA, Katzman B, Ackerman SL, Hollander DA. Efficacy and tolerability of bimatoprost versus travoprost in patients previously on latanoprost: a 3-month, randomised, masked-evaluator, multicentre study. *Br J Ophthalmol*. 2010;94(1):74–79.
28. Denis P, Baudouin C, Bron A, et al. First-line latanoprost therapy in ocular hypertension or open-angle glaucoma patients: a 3-month efficacy analysis stratified by initial intraocular pressure. *BMC Ophthalmol*. 2010;10:4.
29. Ang A, Reddy MA, Shepstone L, Broadway DC. Long term effect of latanoprost on intraocular pressure in normal tension glaucoma. *Br J Ophthalmol*. 2004;88(5):630–634.

30. Stankiewicz A, Wierzbowska J, Siemiatkowska A, et al. The additive effect of dorzolamide hydrochloride (Trusopt) and a morning dose of bimatoprost (Lumigan) on intraocular pressure and retrobulbar blood flow in patients with primary open-angle glaucoma. *Br J Ophthalmol*. 2010;94(10):1307–1311.
31. Mansberger SL, Hughes BA, Gordon MO, et al. comparison of initial intraocular pressure response with topical β-adrenergic antagonists and prostaglandin analogues in African American and White individuals in the Ocular Hypertension Treatment Study. *Arch Ophthalmol*. 2007;125(4):454–459.
32. Watson PG, Barnett MF, Parker V, Haybittle J. A 7 year prospective comparative study of three topical beta blockers in the management of primary open angle glaucoma. *Br J Ophthalmol*. 2001;85(8):962–968.
33. Robin AL. Ocular hypotensive efficacy and safety of a combined formulation of betaxolol and pilocarpine. *Trans Am Ophthalmol Soc*. 1996;94:89–101; discussion 101–103.
34. Suzuki Y, Iwase A, Araie M, et al. Risk factors for open-angle glaucoma in a Japanese population: the Tajimi Study. *Ophthalmology*. 2006;113(9):1613–1617.
35. Mitchell P, Hourihan F, Sandbach J, Wang JJ. The relationship between glaucoma and myopia: the Blue Mountains Eye Study. *Ophthalmology*. 1999;106(10):2010–2015.
36. Higginbotham EJ, Olander KW, Kim EE, Grunden JW, Kwok KK, Tressler CS. Fixed combination of latanoprost and timolol vs individual components for primary open-angle glaucoma or ocular hypertension: a randomized, double-masked study. *Arch Ophthalmol*. 2010;128(2):165–172.
37. Sellem E, Rouland JF, Baudouin C, et al. Predictors of additional intraocular pressure reduction in patients changed to latanoprost/timolol fixed combination. *BMC Ophthalmol*. 2010;10:10.
38. Martinez A, Sanchez-Salorio M. A comparison of the long-term effects of dorzolamide 2% and brinzolamide 1%, each added to timolol 0.5%, on retrobulbar hemodynamics and intraocular pressure in open-angle glaucoma patients. *J Ocul Pharmacol Ther*. 2009;25(3):239–248.
39. Nakamoto K, Yasuda N. Effect of concomitant use of latanoprost and brinzolamide on 24-hour variation of IOP in normal-tension glaucoma. *J Glaucoma*. 2007;16(4):352–357.
40. Kimal Arici M, Topalkara A, Guler C. Additive effect of latanoprost and dorzolamide in patients with elevated intraocular pressure. *Int Ophthalmol*. 1998;22(1):37–42.
41. Maruyama K, Shirato S. Additive effect of dorzolamide or carteolol to latanoprost in primary open-angle glaucoma: a prospective randomized crossover trial. *J Glaucoma*. 2006;15(4):341–345.
42. Higginbotham EJ, Schuman JS, Goldberg I, et al. One-year, randomized study comparing bimatoprost and timolol in glaucoma and ocular hypertension. *Arch Ophthalmol*. 2002;120(10):1286–1293.
43. Rhee DJ, Peace JH, Mallick S, Landry TA, Bergamini MV. A study of the safety and efficacy of travoprost 0.004%/timolol 0.5% ophthalmic solution compared to latanoprost 0.005% and timolol 0.5% dosed concomitantly in patients with open-angle glaucoma or ocular hypertension. *Clin Ophthalmol*. 2008;2(2):313–319.
44. Doi LM, Melo LA Jr, Prata JA Jr. Effects of the combination of bimatoprost and latanoprost on intraocular pressure in primary open angle glaucoma: a randomised clinical trial. *Br J Ophthalmol*. 2005;89(5):547–549.
45. Dapling RB, Cunliffe IA, Longstaff S. Influence of apraclonidine and pilocarpine alone and in combination on post laser trabeculoplasty pressure rise. *Br J Ophthalmol*. 1994;78(1):30–32.
46. Parrish RK, Feuer WJ, Schiffman JC, Lichter PR, Musch DC. Five-year follow-up optic disc findings of the Collaborative Initial Glaucoma Treatment Study. *Am J Ophthalmol*. 2009;147(4):717–724. e711.
47. Cheung W, Guo L, Cordeiro MF. Neuroprotection in glaucoma: drug-based approaches. *Optom Vis Sci*. 2008;85(6):406–416.
48. Steigerwalt RD, Gianni B, Paolo M, Bombardelli E, Burki C, Schonlau F. Effects of Mirtogenol on ocular blood flow and intraocular hypertension in asymptomatic subjects. *Mol Vis*. 2008;14:1288–1292.
49. He Y, Leung KW, Zhang YH, et al. Mitochondrial complex I defect induces ROS release and degeneration in trabecular meshwork cells of POAG patients: protection by antioxidants. *Invest Ophthalmol Vis Sci*. 2008;49(4):1447–1458.
50. University of Roma La Sapienza. Retinal nerve fibres layers thickness study in glaucomatous patients. In: ClinicalTrials.gov [website on the Internet]. Bethesda, MD: US National Library of Medicine; 2010 [updated December 3, 2010]. Available from: http://clinicaltrials.gov/ct2/show/NCT01254006?term=NCT01254006&rank=1. NLM identifier: NCT01254006. Accessed March 3, 2011.
51. Future Products Management. Treatment of glaucomatous neuropathy with food additives. In: ClinicalTrials.gov [website on the Internet]. Bethesda, MD: US National Library of Medicine; 2005 [updated March 10, 2009]. Available from: http://clinicaltrials.gov/ct2/show/NCT00196677?term=NCT00196677&rank=1. NLM identifier: NCT00196677. Accessed March 3, 2011.
52. Sooft Italia. Effects of the oral administration of an association of forskolin with rutin and vitamins B on intraocular pressure in patients affected by primary open angle glaucoma and treated with either beta-blockers or prostaglandin eye drops. In: ClinicalTrials.gov [website on the Internet]. Bethesda, MD: US National Library of Medicine; 2009 [updated June 5, 2012]. Available from: http://clinicaltrials.gov/ct2/show/NCT00863811?term=NCT00863811.&rank=1. NLM identifier: NCT00863811. Accessed March 30, 2011.
53. Zhong L, Bradley J, Schubert W, et al. Erythropoietin promotes survival of retinal ganglion cells in DBA/2 J glaucoma mice. *Invest Ophthalmol Vis Sci*. 2007;48(3):1212–1218.
54. Zhan GL, Camras CB, Palmberg PF, Toris CB. Effects of marijuana on aqueous humor dynamics in a glaucoma patient. *J Glaucoma*. 2005;14(2):175–177.
55. Tomida I, Azuara-Blanco A, House H, Flint M, Pertwee RG, Robson PJ. Effect of sublingual application of cannabinoids on intraocular pressure: a pilot study. *J Glaucoma*. 2006;15(5):349–353.
56. Fang JH, Wang XH, Xu ZR, Jiang FG. Neuroprotective effects of bis(7)-tacrine against glutamate-induced retinal ganglion cells damage. *BMC Neurosci*. 2010;11:31.
57. Vorwerk CK, Lipton SA, Zurakowski D, Hyman BT, Sabel BA, Dreyer EB. Chronic low-dose glutamate is toxic to retinal ganglion cells. Toxicity blocked by memantine. *Invest Ophthalmol Vis Sci*. 1996;37(8):1618–1624.
58. Dreyer EB, Zurakowski D, Schumer RA, Podos SM, Lipton SA. Elevated glutamate levels in the vitreous body of humans and monkeys with glaucoma. *Arch Ophthalmol*. 1996;114(3):299–305.
59. Yucel YH, Gupta N, Zhang Q, Mizisin AP, Kalichman MW, Weinreb RN. Memantine protects neurons from shrinkage in the lateral geniculate nucleus in experimental glaucoma. *Arch Ophthalmol*. 2006;124(2):217–225.
60. Osborne NN. Recent clinical findings with memantine should not mean that the idea of neuroprotection in glaucoma is abandoned. *Acta Ophthalmol*. 2009;87(4):450–454.
61. Ko ML, Peng PH, Hsu SY, Chen CF. Dietary deficiency of vitamin E aggravates retinal ganglion cell death in experimental glaucoma of rats. *C Eye R*. 2010;35(9):842–849.
62. Roh YJ, Moon C, Kim SY, Park MH, Bae YC, Chun MH, et al. Glutathione depletion induces differential apoptosis in cells of mouse retina, in vivo. *Neurosci Lett*. 2007;417(3):266–270.
63. The Catholic University of Korea. Evaluation of systemic glutathione level in patients with normal tension glaucoma. In: ClinicalTrials.gov [website on the Internet]. Bethesda, MD: US National Library of Medicine; 2007 [updated June 14, 2010]. Available from: http://clinicaltrials.gov/ct2/show/NCT00570362?term=NCT00570362&rank=1. NLM identifier: NCT00570362. Accessed March 3, 2011.
64. Luksch A, Rainer G, Koyuncu D, et al. Effect of nimodipine on ocular blood flow and colour contrast sensitivity in patients with normal tension glaucoma. *Br J Ophthalmol*. 2005;89(1):21–25.

65. Piltz JR, Bose S, Lanchoney D. The effect of nimodipine, a centrally active calcium antagonist, on visual function and mascular blood flow in patients with normal-tension glaucoma and control subjects. *J Glaucoma*. 1998;7(5):336–342.
66. Harris A, Evans DW, Cantor LB, Martin B. Hemodynamic and visual function effects of oral nifedipine in patients with normal-tension glaucoma. *Am J Ophthalmol*. 1997;124(3):296–302.
67. Cellini M, Possati GL, Caramazza N, Profazio V, Caramazza R. The use of flunarizine in the management of low-tension glaucoma: a color Doppler study. *Acta Ophthalmol Scand Suppl*. 1997;224:57–58.