Clinical Ophthalmology

Current primary open-angle glaucoma treatments and future directions

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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, known to cause blindness worldwide. About 66.8 million people worldwide are afflicted with glaucoma. An estimated 4.4 million Americans have glaucoma, and over 120,000 of these people are rendered blind as a result. The actual etiology of the condition remains unknown. 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. POAG accounts for around 70% of the total glaucoma cases worldwide. 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. 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. 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. 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
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.3 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 (parasympathomimetics), 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
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.\textsuperscript{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.\textsuperscript{25} 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.\textsuperscript{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,\textsuperscript{33} both of which pose a safety risk. It has also been established that myopia is a risk factor for POAG,\textsuperscript{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\textsuperscript{®} (timolol and dorzolamide) and Combigan\textsuperscript{®} (timolol and brimonidine), and others available in Europe, DuoTrav\textsuperscript{®} (travoprost and timolol) and Xalacom\textsuperscript{®} (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).\textsuperscript{36,37} Combinations of timolol 0.5\% with either dorzolamide 2\% or brinzolamide 1\% were studied with respect to retrobulbar hemodynamics and IOP.\textsuperscript{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 resistance 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. 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. Overall though, the combination medications have higher IOP reductions of at least 2 mmHg more than individual agents like betaxolol or pilocarpine. 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. 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.

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. This is indicated by the findings of several studies where dorzolamide was added to either a PGA or a beta blocker. Since PGAs have been found to be efficacious, 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. Some medications like apraclonidine and pilocarpine are mostly used to control IOP increases associated with ocular surgeries like cataract removal and trabeculectomy. Epinephrine is rarely used even topically because of cardiovascular side effects.

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. 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.

**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. These symptoms are believed to be fuelled by local autoimmune disorders, oxidative stress, overstimulation of NMDA glutamate receptors, and mitochondrial dysfunction. 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. 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. 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. 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®-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                    |
| Antioxidants                | N-acetylcysteine, Vitamin E               | Topical    | Mops up ROS                                                                                   | PCT                  |
| 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                             | NR                   |
| 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               | Oral or iv | 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 mirtogenol-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.55

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 patients54 and improve the visual field55 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.55 Other calcium channel blockers (flunarizine and nifedipine) gave mixed results.56,67

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.

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