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Novel therapies for open-angle glaucoma

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Abstract

Open-angle glaucoma is a multifactorial optic neuropathy characterized by progressive loss of retinal ganglion cells and their axons. It is an irreversible disease with no established cure. The only currently approved treatment is aimed at lowering intraocular pressure, the most significant risk factor known to date. However, it is now clear that there are other risk factors involved in glaucoma's pathophysiology. To achieve future improvements in glaucoma management, new approaches to therapies and novel targets must be developed. Such therapies may include new tissue targets for lowering intraocular pressure, molecules influencing ocular hemodynamics, and treatments providing neuroprotection of retinal ganglion cells. Furthermore, novel drug delivery systems are in development that may improve patient compliance, increase bioavailability, and decrease adverse side effects.

Introduction

The World Health Organization reports that glaucoma affects approximately 60 million people worldwide. Primary open-angle glaucoma, the most common form of glaucoma, was estimated to cause new blindness in approximately 8.4 million people in 2010 [1]. Primary open-angle glaucoma is characterized by a painless, progressive, and permanent loss of vision starting in the periphery and moving towards the central vision. Since the peripheral vision is affected first, patients do not typically realize any visual field deficits until substantial and permanent damage has occurred [2].

Glaucoma is a chronic optic neuropathy involving damage to the retinal ganglion cells and their axons. It is hypothesized that the retinal ganglion cells and their axons become damaged through various, specific insults [3]. However, the pathogenesis of glaucoma is still largely unknown. While the specific insults that lead to glaucomatous change are still under investigation, several risk factors (other than elevated intraocular pressure) have been explored. This has allowed for a better understanding of the disease process and for the development of novel therapies. Here, we will discuss the limitations of current therapies and potential novel therapeutic targets for both elevated intraocular pressure and non-elevated intraocular pressure glaucoma. We will also discuss new drug delivery systems with an emphasis on nanotechnology, which may advance future glaucoma management.

Increased intraocular pressure risk factors and therapies

Risk factors associated with glaucoma have been well studied, and include chronically elevated intraocular pressure, age, ethnicity, and the presence of a family history of glaucoma [2,4,5]. Lowering intraocular pressure remains the only currently approved medical course of treatment. Clinical trials have shown substantial benefits of lowering intraocular pressure in both pre-emptive treatment for patients suspected to have glaucoma and in patients with established primary open-angle glaucoma [6,7]. Conventional therapy has focused on affecting the balance of aqueous humor production and outflow, as a decrease in net aqueous humor volume results in decreased intraocular pressure. Currently, this includes

medication eye drops, laser treatment to the trabecular meshwork, or surgery. However, lowering of intraocular pressure does not prevent or stop the progression of glaucoma, signifying the importance of discovering new treatment paradigms.

New medical targets

There are currently six classes of drugs approved for clinical use to treat glaucoma: miotics, beta-blockers, alpha-agonists, epinephrine derivatives, carbonic anhydrase inhibitors, and prostaglandin analogues. They act by either decreasing aqueous humor production or by increasing aqueous outflow. Of these, prostaglandin analogs may be the only treatments that modulate the molecular changes in the aberrant trabecular meshwork system seen in glaucoma patients [8,9].

Data from the Early Manifest Glaucoma Trial (EMGT) suggest the goal of initial intraocular pressure reduction should be ≥25–30% from the patient's baseline intraocular pressure. In patients with severe glaucomatous change, aggressive treatment may be necessary, lowering intraocular pressure even further in order to salvage as much remaining vision as possible [10]. Unfortunately, not all patients reach intraocular pressure goals, despite efforts to treat with either medical monotherapy or combination medical therapy. Consequently, these points underscore the importance of discovering new therapies for glaucoma.

A number of new intraocular pressure-lowering therapies are currently in development. These include treatments that relax the tension within the trabecular meshwork (*via* effects on cell volume and shape, or by manipulating cell-cell or cell-matrix adhesions), modulate cellular contractions in the trabecular meshwork, or decrease aqueous humor production/increase uveoscleral outflow by new mechanisms. The list of therapies is substantial and includes RhoA GTPase kinase, endothelin-1, transforming growth factor-ß, connective tissue growth factor, nitric oxide, angiopoietin-like molecules, adenoside, latrunculins, cochlin, cannabinoids, melatonin, ghrelin, angiotensin II, serotonin, and forskolin [11–13]. These therapies are not yet commercially available, and, for brevity, we will only discuss cannabinoids here.

Cannabinoid receptor agonists (CRAs), including tetrahydrocannabinol (THC), have been investigated for their potential role as effective glaucoma treatments [14]. CRAs have been shown to activate multiple signal transduction cascades that lead to various effects, such as relaxation and antimigration in human ocular tissues, which likely contribute to increasing the dimensions of Schlemm's canal to lower intraocular pressure [15–18]. Lastly, CRAs may also provide neuroprotection through interaction with cannabinoid receptors within the ocular tissues [19]. The American Glaucoma Society does not recommend marijuana as a treatment for open-angle glaucoma due to its side effect profile, short duration of action, and the possibility of contributing to glaucomatous change by possibly decreasing blood supply to the optic nerve [20]. More research on CRAs must be done in order to develop a selective agonist that is both efficacious and well-tolerated.

Novel therapeutics evaluated in clinical trials would need to demonstrate equivalent or superior safety and efficacy as compared to the current standards of intraocular pressure-lowering drugs. The most desirable compounds would be those that have novel modes of action or have a synergistic effect with those currently available.

Non-intraocular pressure risk factors and therapies

Reduction of intraocular pressure has failed as a concept to completely prevent or arrest glaucoma pathology as a stand-alone treatment in all patients. Some normal patients have an elevated intraocular pressure and do not experience glaucomatous change. In contrast, there is a subset of patients with normal-tension glaucoma—a type of glaucoma in which glaucomatous change occurs despite normal intraocular pressure [21]. These patients have a consistently normal intraocular pressure (8–22 mmHg), but still experience progressive vision loss [5]. Thus, it is now well established that the pathogenesis of open-angle glaucoma is not a direct consequence of increased intraocular pressure, but a combination of other factors, including vascular, genetic, anatomical, and immune factors. Of these, much attention has been placed on changes in ocular perfusion pressure and blood flow as well as factors affecting neuroprotection. The limitations of lowering intraocular pressure emphasize the need for developing molecules and therapies targeted to other mechanisms, which may be involved in the disease process.

Vasculature and hemodynamics

In recent years, researchers have confirmed that local and systemic vascular factors play a role in the pathophysiology of open-angle glaucoma. A multitude of research has indicated that alterations in ocular hemodynamics may be involved in the disease [22–28]. However, the mechanisms by which vascular impairments may translate to glaucoma progression are still unclear [29]. Some studies have examined alterations of ocular hemodynamics in relation to clinical markers of glaucoma progression, finding an association between progressive glaucoma and decreased retrobulbar vessel blood velocities [30–35].

Multiple population-based studies have shown that low ocular perfusion pressure (calculated as ⅔ mean arterial pressure minus intraocular pressure) is associated with glaucoma incidence, prevalence and progression [22,36–38]. It is hypothesized that decreased ocular blood flow may contribute to the ischemic death of retinal ganglion cells or may be a response to the decrease in metabolic demand for oxygen and nutrients secondary to retinal ganglion cell death [29,39].

It is hypothesized that vascular dysregulation is involved, at least in part, in the pathogenesis of open-angle glaucoma, particularly in normal tension glaucoma. Autoregulation is the ability of a vascular bed to maintain a relatively constant blood flow despite changes in perfusion pressure. In a non-autoregulated vascular bed, small changes in perfusion pressure may lead to fluctuations in blood flow. Studies suggest that autoregulation is abnormal in glaucoma [40–42]. The reason behind abnormal autoregulation in glaucoma is unclear; however, reduced ocular perfusion pressure past the limit of autoregulation, increased variability of ocular perfusion pressure, and dipping of nocturnal blood pressure have been identified as risk factors [43,44].

Our understanding of the relationship of ocular hemodynamics and glaucoma is still limited, which is due, in part, to the difficulty in directly measuring all relevant vascular beds which may be implicated in glaucoma. Several methods are used, but there is not currently a gold standard. In regards to treatment, increasing ocular perfusion pressure as part of glaucoma treatment will be pharmacologically challenging, as care must be taken to prevent systemic hypertension. A more feasible target may be to simply prevent the over treating of hypertension, especially in patients who undergo nocturnal intraocular pressure dipping, in order to maintain ocular perfusion pressure. Ideally, novel therapies that directly increase ocular blood flow without affecting the systemic vasculature may be developed.

Neuroprotection

A logical approach to treatment is to save retinal ganglion cells from glaucomatous injury or to repair neurons that have been damaged. It is likely that future therapies for glaucoma will not only target decreasing intraocular pressure but also include treatments to protect the neurological structures of the eye. A number of mechanisms have been proposed to explain retinal ganglion cell death in glaucoma, including ischemia, oxidative stress, excitotoxicity, defective axonal transport, trophic factor withdrawal, and neuroinflammation. Some established modalities and potential therapeutic approaches will be covered here.

Excitotoxicity is a proposed etiology or contributor to glaucoma, and it is thought to occur when dying cells release excessive amounts of neurotransmitter, such as glutamate. This may be directly or indirectly toxic to retinal ganglion cells [45]. Thus, inhibitors of glutamate, such as aminoguanidine or memantine, have been studied as neuroprotective agents, where memantine has been shown to be protective against retinal ganglion cell loss in animal models [19,46,47]. Allergan announced that its second Phase III clinical trial investigating low-dose memantine and its effect on open-angle glaucoma progression failed to show a statistically significant reduction in disease progression, despite seeing a reduction in its first Phase III trial. The company failed to adequately reproduce the preliminary results seen in the first Phase III clinical trial with high-dose memantine [48]. Allergan has continued research in this area, but the company does not seem optimistic about getting an approved agent in the market in the near future.

Brimonidine, an alpha2-adrenergic receptor agonist, may not only lower intraocular pressure but also serve an additional, separate purpose of providing neuroprotection [49]. Specifically, the 2011 Low-Pressure Glaucoma Treatment Study (LoGTS), a randomized, double-masked, multicenter clinical trial, reported that brimonidine showed a statistically significant reduction in visual field progression compared to timolol, despite a similar mean pre-treatment intraocular pressure in both groups of patients [50]. This implies that brimonidine may mitigate disease progression through a different mechanism than lowering intraocular pressure. It may be that brimonidine is neuroprotective to the retinal ganglion cells. However, a 2013 Cochrane Review of the 2011 LoGTS argues that the study results are inconclusive, due to the high risk of attrition and reporting biases when juxtaposed with the 2005 design report. As such, the review authors assert there is currently no evidence to support the idea that brimonidine is neuroprotective at this time [51]. Additional studies investigating brimonidine and other potential neuroprotective agents are, therefore, required.

New methods of drug delivery

Medication eye drops are currently the mainstay of open-angle glaucoma treatment and have been shown to decrease intraocular pressure and slow glaucoma progression [52]. However, these topical medications are limited by poor patient compliance, low bioavailability, and the potential for local and systemic side effects [53]. Novel platforms for drug delivery are being developed to address these problems.

Enhanced topical delivery systems such as nanoparticle-based formulas, drug-eluting contact lenses, bioadhesive

matrices, and ocular drug-eluting inserts have the potential to increase precorneal residence time, thus corneal penetration [53]. Nanoparticles offer a unique platform for drug delivery, as the modulation of particle size can enhance drug permeation across the cornea. A nanodiamond-embedded contact lens, capable of lysozyme-triggered release of timolol maleate for sustained therapy, has been recently devised where it was demonstrated that the nanoparticles could release the drug over time while maintaining the integrity of the lens [54]. Drug-eluting contact lenses have long been an area of study, and advances in hydrogel technology now allow for a 50% bioavailability [53,55]. A number of preclinical studies of drug-eluting contact lenses showed reduced intraocular pressure similar to commercial eye drops with improved bioavailability [56–58]. Bioadhesive matrix polymers can provide increased residence time, compared with gel formulations or drops when placed on the conjunctival cul-de-sac or cornea [59–61]. Matrix materials may provide controlled drug release with once-weekly or once-monthly dosing. Ocular drug-eluting inserts designed for placement in the puncta or conjunctival sac have also been well studied and are currently being studied in clinical trials (NCT00820300, NCT01915940, NCT00693485) [62].

Periocular injections and surgically implanted reservoirs allow for long-term sustained drug delivery, as well as improved targeting of the posterior segment. Injection may allow for months of drug delivery with a single dose. Surgically implanted reservoirs in the vitreous have the potential to provide the most extended drug release. These implants are available for drug delivery for other ocular diseases and are currently being studied for use in glaucoma as well (NCT00693485) [63–65].

Currently, none of these new drug delivery systems are Federal Drug Administration (FDA) approved for commercial use in glaucoma [66]. While sustained drug delivery systems are promising, it is important to consider factors affecting the risk/benefit ratio of these therapies. The primary disadvantages for these new approaches are cost and the invasiveness of the implanted devices. This is especially the case with surgically implanted reservoirs, as there is the risk of further surgery if complications arise. Other factors to consider include patient tolerability and the potential for allergy or immune response. Issues regarding drug stability, the risk of dose dumping, and toxicity are other factors that require further careful investigation [67].

Nanomedicine in glaucoma

Nanotechnology introduces a potential paradigm shift in the approach towards reduction of intraocular pressure. The improved ability to manipulate matter at the molecular level opens up unprecedented opportunities in the approach to treating glaucoma. Recent advancements may offer novel drug delivery vectors to enhance bioavailability and uptake, as well as instruments that could improve intraocular pressure-reducing surgical outcomes [68–70].

As drug delivery vectors, nanomaterials exhibit unique chemical and physical properties that, in conjunction with drug molecules, may potentially increase the availability of a pharmaceutical compound to a target site. These properties include increased rates of permeability through barriers, protection of nanoparticle-loaded drug molecules from degradation, and prolonged contact time between the drug and target tissue [68–70]. One notable study synthesized latanoprost-loaded liposomes for therapeutic evaluation of the nanomaterial in rabbit eyes. These particles were found to have a 20-fold loading efficiency as compared to that of a daily administered commercially available topical latanoprost (50 μg/mL). In animal testing, Natarajan *et al.* discovered a significantly higher mean reduction of intraocular pressure in rabbits treated with latanoprost-loaded liposomes, as compared with rabbits that were administered daily topical latanoprost eye drops over 90 days [71]. A unique feature of the design is the slow sustained release over a period of time, which may improve adherence to the medication.

Drainage devices

Besides drug delivery, nanodevices can be designed for a number of other purposes, such as to improve surgical outcomes by managing aqueous humor drainage. Researchers designed an artificial nanodrainage implant to assist the natural filtration mechanism of the trabecular meshwork [72]. A biodegradable cone-shaped plug filter that has a 44 μm diameter hole in the centre and 500 μm length was developed by Maleki *et al.* as a non-valved glaucoma drainage device [73]. These were designed to stabilize intraocular pressure after surgical operations and prevent it from dropping drastically.

The Glaukos Corporation (Laguna Hills, California) has developed a heparin-coated titanium L-shaped trabecular micro-bypass stent named the iStent®. It is designed to create a pathway from the canal of Schlemm to the anterior chamber and allow flow to circumvent the trabecular meshwork [74]. Craven *et al.* demonstrated that cataract surgery, combined with a single trabecular micro-bypass stent, resulted in a more favorable outcome than having cataract surgery alone. Arriola-Villalobos *et al.* demonstrated that the Glaukos iStent implantation combined with cataract surgery resulted in a significant intraocular pressure reduction of 3.16±3.9 mmHg

(P=0.002) after 53 months of follow-up. No adverse effects related to stent implantation were observed [75].

Ivantus (Irvine, California) has developed the Hydrus, which is an "intracanalicular scaffold" that is constructed from nitinol and positioned within Schlemm's canal. The implant increases outflow by bypassing the trabecular meshwork. The Hydrus implantation plus cataract surgery was compared to a Hydrus-only implantation over six months. The mean intraocular pressure of the Hydrus/cataract group decreased from 21.1 to 15.6 mmHg, and the medication used decreased from 2.1 to 0.4 medications per patient. While some side effects resolved within a week, three cases of mild hyphema and two cases of iris damage were noted in the study [76].

SOLX Inc. (Waltham, Massachusetts) developed the Gold Shunt Device that makes a pathway from the anterior chamber to the suprachoroidal space, rather than to the canal of Schlemm, as in traditional shunts. One study showed a decrease in mean intraocular pressure of 9.2 mmHg from 27.6 mmHg baseline one day after surgery and stabilized to 18.2 mmHg at 52 weeks. Furthermore, patients needed less glaucoma medication, which decreased from 2.55 medications at baseline to 1.16 at 52 weeks [77].

Intraocular pressure sensors

Tracking intraocular pressure is a critical component for providing excellent glaucoma care. The current gold standard for measuring intraocular pressure is Goldmann Applanation Tonometry (GAT). However, there are a lot of issues with using GAT to accurately measure intraocular pressure. First, GAT's ability to yield accurate results relies on the eye being perfectly spherical and the cornea being an elastic, thin membrane—both of which are not true. Second, other biomechanical properties of the globe, such as central cornea thickness and scleral rigidity, affect GAT measurements and vary between patients. Third, and most importantly, GAT provides only one datum point at one particular time [78]. Many studies show that intraocular pressure is not static throughout the day, but, instead, has a circadian rhythm [79,80].

One key benefit of using a 24 hour intraocular pressure monitor is the ability to observe nocturnal pressure levels, which are different in primary open-angle glaucoma versus normal patients [79]. This information helps us to diagnose primary open-angle glaucoma sooner, to detect and prevent primary open-angle glaucoma progression, to better understand how current and future medications affect intraocular pressure rhythms, to improve patient understanding and adherence, and to learn how lifestyle factors may influence primary open-angle glaucoma [78]. Nanodevices may provide an opportunity to develop innovative extra- and intraocular sensors to continuously measure intraocular pressure. Fortunately, a few new devices have been engineered in order to do this.

Extraocular intraocular pressure sensors

One such product is the SENSIMED Triggerfish®, which has been approved for use in Europe, but has not yet been FDA approved in the United States [81]. This device is a comfortable soft disposable silicone contact lens that allows for ambulatory telemetric monitoring of intraocular pressure over a 24 hour period [80,82]. The contact lens detects circumferential changes in the corneoscleral region of the eye. Since the changes in this region are directly correlated to changes in intraocular pressure, the estimated intraocular pressure can be indirectly calculated. Information is then sent wirelessly to an antenna attached near the patient's ipsilateral eye. Using Bluetooth technology, the data may be sent to a computer for data analysis [83]. The problems we see with the Triggerfish® are the cost (as the contact lenses are not designed for long-term use), and the bulkiness of the peri-orbital antenna and recorder.

Intraocular pressure sensors

GAT, air puff tonometry, and even the Triggerfish® rely on indirect methods for measuring intraocular pressure. Ideally, we would be able to directly measure intraocular pressure as it would provide researchers and clinicians with a tool to reliably and accurately assess the true intraocular pressure without having to correct for ocular biomechanical differences between patients. Chen and colleagues have developed an intraocular pressure sensor involving a Bourdon tube and a protective membrane that does not require an external energy source, making routine replacement less of an issue [84]. While this model would require invasive surgery, this sensor could provide direct intraocular pressure measurements, and independent biomechanical properties, multiple times throughout the day [69]. LaunchPoint Technologies, Inc. (Santa Barbara, California) and a group of engineers at the University of Washington are currently developing separate, feasible intraocular pressure sensors that will be either injected into the vitreous of the eye or attached to an intraocular lens [85,86]. We look forward to seeing how these technologies will change clinical practice.

While more studies are required to further elucidate potential adverse effects due to nanoparticles and human studies are needed before nanomedicine can be implemented into the clinic, nanomedicine promises to deeply impact our approach to treating glaucoma.

Conclusion

Glaucoma is a devastating disease that affects millions of people worldwide. As researchers and clinicians uncover more about glaucoma and its pathogenesis, more therapeutic targets will be identified and refined. Therapies focusing on neuroprotection and vascular function may provide novel additions or alternatives to traditional intraocular pressure-lowering methods. Consequently, clinicians may soon have an increased number of therapeutic options to choose from, along with potentially more effective treatments. Great caution must be applied to any shift away from established therapies towards novel treatments in disease management. While the FDA has not recently approved any new medication classes for glaucoma therapy, researchers have made great strides in both identifying potential treatment targets and creating novel medication delivery systems that may benefit persons affected by glaucoma in the future.

Abbreviations

CRA, Cannabinoid receptor agonists; FDA, Federal Drug Administration; GAT, Goldmann Applanation Tonometry; LoGTS, Low-Pressure Glaucoma Treatment Study.

Disclosures

The authors declare that they have no disclosures.

References

1. **Glaucoma is second leading cause of blindness globally.** World Health Organization; 2011. [http://www.who.int/bulletin/volumes/82/11/feature1104/en/]
2. Weinreb RN, Khaw PT: **Primary open-angle glaucoma.** *Lancet* 2004, **363:**1711-20.
3. Cherecheanu AP, Garhofer G, Schmidl D, Werkmeister R, Schmetterer L: **Ocular perfusion pressure and ocular blood flow in glaucoma.** *Curr Opin Pharmacol* 2013, **13:**36-42.
4. Czudowska MA, Ramdas WD, Wolfs RC, Hofman A, De Jong PT, Vingerling JR, Jansonius NM: **Incidence of glaucomatous visual field loss: a ten-year follow-up from the Rotterdam Study.** *Ophthalmology* 2010, **117:**1705-12.
5. Tielsch JM, Katz J, Singh K, Quigley HA, Gottsch JD, Javitt J, Sommer A: **A population-based evaluation of glaucoma screening: the Baltimore Eye Survey.** *Am J Epidemiol* 1991, **134:**1102-10.
6. **Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Collaborative Normal-Tension Glaucoma Study Group.** *Am J Ophthalmol* 1998, **126:**487-97.
7. Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP, Parrish RK, 2nd, Wilson MR, Gordon MO: **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:**701-13; discussion 829-730.
8. Weinreb RN, Lindsey JD: **Metalloproteinase gene transcription in human ciliary muscle cells with latanoprost.** *Invest Ophthalmol Vis Sci* 2002, **43:**716-22.
9. Weinreb RN, Toris CB, Gabelt BT, Lindsey JD, Kaufman PL: **Effects of prostaglandins on the aqueous humor outflow pathways.** *Surv Ophthalmol* 2002, **47(Suppl 1):**S53-64.
10. Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M: **Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial.** *Arch Ophthalmol* 2002, **120:**1268-79.

F1000Prime RECOMMENDED

11. Kaufman PL, Rasmussen CA: **Advances in glaucoma treatment and management: outflow drugs.** *Invest Ophthalmol Vis Sci* 2012, **53:**2495-500.
12. Rocha-Sousa A, Rodrigues-Araujo J, Gouveia P, Barbosa-Breda J, Azevedo-Pinto S, Pereira-Silva P, Leite-Moreira A: **New therapeutic targets for intraocular pressure lowering.** *ISRN Ophthalmol* 2013, **2013:**261386.
13. Zhang M, Maddala R, Rao PV: **Novel molecular insights into RhoA GTPase-induced resistance to aqueous humor outflow through the trabecular meshwork.** *Am J Physiol Cell Physiol* 2008, **295:**C1057-70.
14. Kaufman PL: **Marijuana and glaucoma.** *Arch Ophthalmol* 1998, **116:**1512-3.
15. Porcella A, Maxia C, Gessa GL, Pani L: **The synthetic cannabinoid WIN55212-2 decreases the intraocular pressure in human glaucoma resistant to conventional therapies.** *Eur J Neurosci* 2001, **13:**409-12.
16. Ramer R, Hinz B: **Cyclooxygenase-2 and tissue inhibitor of matrix metalloproteinases-1 confer the antimigratory effect of cannabinoids on human trabecular meshwork cells.** *Biochem Pharmacol* 2010, **80:**846-57.
17. Stamer WD, Golightly SF, Hosohata Y, Ryan EP, Porter AC, Varga E, Noecker RJ, Felder CC, Yamamura HI: **Cannabinoid CB(1) receptor expression, activation and detection of endogenous ligand in trabecular meshwork and ciliary process tissues.** *Eur J Pharmacol* 2001, **431:**277-86.
18. Stumpff F, Boxberger M, Krauss A, Rosenthal R, Meissner S, Choritz L, Wiederholt M, Thieme H: **Stimulation of cannabinoid (CB1) and prostanoid (EP2) receptors opens BKCa channels and relaxes ocular trabecular meshwork.** *Exp Eye Res* 2005, **80:**697-708.
19. Nucci C, Bari M, Spano A, Corasaniti M, Bagetta G, Maccarrone M, Morrone LA: **Potential roles of (endo)cannabinoids in the treatment of glaucoma: from intraocular pressure control to neuroprotection.** *Prog Brain Res* 2008, **173:**451-64.
20. Jampel H: **American glaucoma society position statement: marijuana and the treatment of glaucoma.** *J Glaucoma* 2010, **19:**75-6.
21. Cedrone C, Mancino R, Cerulli A, Cesareo M, Nucci C: **Epidemiology of primary glaucoma: prevalence, incidence, and blinding effects.** *Prog Brain Res* 2008, **173:**3-14.
22. Bonomi L, Marchini G, Marraffa M, Bernardi P, Morbio R, Varotto A: **Vascular risk factors for primary open angle glaucoma: the Egna-Neumarkt Study.** *Ophthalmology* 2000, **107:**1287-93.
23. Harris A, Kagemann L, Ehrlich R, Rospigliosi C, Moore D, Siesky B: **Measuring and interpreting ocular blood flow and metabolism in glaucoma.** *Can J Ophthalmol* 2008, **43:**328-36.
24. Harris A, Rechtman E, Siesky B, Jonescu-Cuypers C, McCranor L, Garzozi HJ: **The role of optic nerve blood flow in the pathogenesis of glaucoma.** *Ophthalmol Clin North Am* 2005, **18:**345-53, v.
25. Hayreh SS: **Blood flow in the optic nerve head and factors that may influence it.** *Prog Retin Eye Res* 2001, **20:**595-624.
26. Hulsman CA, Vingerling JR, Hofman A, Witteman JC, de Jong PT: **Blood pressure, arterial stiffness, and open-angle glaucoma: the Rotterdam study.** *Arch Ophthalmol* 2007, **125:**805-12.
27. Leske MC, Heijl A, Hyman L, Bengtsson B, Dong L, Yang Z: **Predictors of long-term progression in the early manifest glaucoma trial.** *Ophthalmology* 2007, **114:**1965-72.
28. Moore D, Harris A, Wudunn D, Kheradiya N, Siesky B: **Dysfunctional regulation of ocular blood flow: A risk factor for glaucoma?** *Clin Ophthalmol* 2008, **2:**849-61.

29. Caprioli J, Coleman AL: **Blood pressure, perfusion pressure, and glaucoma.** *Am J Ophthalmol* 2010, **149:**704-12.

30. Galassi F, Sodi A, Ucci F, Renieri G, Pieri B, Baccini M: **Ocular hemodynamics and glaucoma prognosis: a color Doppler imaging study.** *Arch Ophthalmol* 2003, **121:**1711-15.

31. Hesse RJ: **The relationship between progression of visual field defects and retrobulbar circulation in patients with glaucoma.** *Am J Ophthalmol* 1998, **125:**566-7.

32. Satilmis M, Orgul S, Doubler B, Flammer J: **Rate of progression of glaucoma correlates with retrobulbar circulation and intraocular pressure.** *Am J Ophthalmol* 2003, **135:**664-9.

33. Schumann J, Orgul S, Gugleta K, Dubler B, Flammer J: **Interocular difference in progression of glaucoma correlates with interocular differences in retrobulbar circulation.** *Am J Ophthalmol* 2000, **129:**728-33.

34. Yamazaki Y, Drance SM: **The relationship between progression of visual field defects and retrobulbar circulation in patients with glaucoma.** *Am J Ophthalmol* 1997, **124:**287-95.

35. Zeitz O, Galambos P, Wagenfeld L, Wiermann A, Wlodarsch P, Praga R, Matthiessen ET, Richard G, Klemm M: **Glaucoma progression is associated with decreased blood flow velocities in the short posterior ciliary artery.** *Br J Ophthalmol* 2006, **90:**1245-8.

36. Leske MC, Wu SY, Nemesure B, Hennis A: **Incident open-angle glaucoma and blood pressure.** *Arch Ophthalmol* 2002, **120:**954-9.

37. Quigley HA, West SK, Rodriguez J, Munoz B, Klein R, Snyder R: **The prevalence of glaucoma in a population-based study of Hispanic subjects: Proyecto VER.** *Arch Ophthalmol* 2001, **119:**1819-26.

38. Tielsch JM, Katz J, Sommer A, Quigley HA, Javitt JC: **Hypertension, perfusion pressure, and primary open-angle glaucoma. A population-based assessment.** *Arch Ophthalmol* 1995, **113:**216-21.

39. Osborne NN, Melena J, Chidlow G, Wood JP: **A hypothesis to explain ganglion cell death caused by vascular insults at the optic nerve head: possible implication for the treatment of glaucoma.** *Br J Ophthalmol* 2001, **85:**1252-9.

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40. Fuchsjager-Mayrl G, Wally B, Georgopoulos M, Rainer G, Kircher K, Buehl W, Amoako-Mensah T, Eichler HG, Vass C, Schmetterer L: **Ocular blood flow and systemic blood pressure in patients with primary open-angle glaucoma and ocular hypertension.** *Invest Ophthalmol Vis Sci* 2004, **45:**834-9.

41. Garhofer G, Fuchsjager-Mayrl G, Vass C, Pemp B, Hommer A, Schmetterer L: **Retrobulbar blood flow velocities in open angle glaucoma and their association with mean arterial blood pressure.** *Invest Ophthalmol Vis Sci* 2010, **51:**6652-7.

42. Gherghel D, Orgul S, Gugleta K, Gekkieva M, Flammer J: **Relationship between ocular perfusion pressure and retrobulbar blood flow in patients with glaucoma with progressive damage.** *Am J Ophthalmol* 2000, **130:**597-605.

43. Choi J, Kim KH, Jeong J, Cho HS, Lee CH, Kook MS: **Circadian fluctuation of mean ocular perfusion pressure is a consistent risk factor for normal-tension glaucoma.** *Invest Ophthalmol Vis Sci* 2007, **48:**104-11.

F1000Prime RECOMMENDED

44. Sung KR, Lee S, Park SB, Choi J, Kim ST, Yun SC, Kang SY, Cho JW, Kook MS: **Twenty-four hour ocular perfusion pressure fluctuation and risk of normal-tension glaucoma progression.** *Invest Ophthalmol Vis Sci* 2009, **50:**5266-74.

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45. Ullian EM, Barkis WB, Chen S, Diamond JS, Barres BA: **Invulnerability of retinal ganglion cells to NMDA excitotoxicity.** *Mol Cell Neurosci* 2004, **26:**544-57.

46. Hare W, WoldeMussie E, Lai R, Ton H, Ruiz G, Feldmann B, Wijono M, Chun T, Wheeler L: **Efficacy and safety of memantine, an NMDA-type open-channel blocker, for reduction of retinal injury associated with experimental glaucoma in rat and monkey.** *Surv Ophthalmol* 2001, **45(Suppl 3):**S284-9; discussion S295-86.

47. Pang IH, Johnson EC, Jia L, Cepurna WO, Shepard AR, Hellberg MR, Clark AF, Morrison JC: **Evaluation of inducible nitric oxide synthase in glaucomatous optic neuropathy and pressure-induced optic nerve damage.** *Invest Ophthalmol Vis Sci* 2005, **46:**1313-21.

48. **Memantine Update: Allergan Reports Fourth Quarterly Operating Results.** [http://agn.client.shareholder.com/earningsreleasedetail.cfm?ReleaseID=290764]

49. Foxton RH, Finkelstein A, Vijay S, Dahlmann-Noor A, Khaw PT, Morgan JE, Shima DT, Ng YS: **VEGF-A is necessary and sufficient for retinal neuroprotection in models of experimental glaucoma.** *Am J Pathol* 2013, **182:**1379-90.

F1000Prime RECOMMENDED

50. Krupin T, Liebmann JM, Greenfield DS, Ritch R, Gardiner S: **A randomized trial of brimonidine versus timolol in preserving visual function: results from the Low-Pressure Glaucoma Treatment Study.** *Am J Ophthalmol* 2011, **151:**671-81.

F1000Prime RECOMMENDED

51. Sena DF, Lindsley K: **Neuroprotection for treatment of glaucoma in adults.** *Cochrane Database Syst Rev* 2013, **2:**Cd006539.

F1000Prime RECOMMENDED

52. van der Valk R, Webers CA, Schouten JS, Zeegers MP, Hendrikse F, Prins MH: **Intraocular pressure-lowering effects of all commonly used glaucoma drugs: a meta-analysis of randomized clinical trials.** *Ophthalmology* 2005, **112:**1177-85.

53. Peng CC, Burke MT, Carbia BE, Plummer C, Chauhan A: **Extended drug delivery by contact lenses for glaucoma therapy.** *J Control Release* 2012, **162:**152-8.

54. Kim HJ, Zhang K, Moore L, Ho D: **Diamond nanogel-embedded contact lenses mediate lysozyme-dependent therapeutic release.** *ACS Nano* 2014, **8:**2998-3005.

F1000Prime RECOMMENDED

55. Li CC, Chauhan A: **Modeling ophthalmic drug delivery by soaked contact lenses.** *Ind Eng Chem Res* 2006, **45:**3718-34.

56. Ciolino JB, Stefanescu CF, Ross AE, Salvador-Culla B, Cortez P, Ford EM, Wymbs KA, Sprague SL, Mascoop DR, Rudina SS, Trauger SA, Cade F, Kohane DS: **In vivo performance of a drug-eluting contact lens to treat glaucoma for a month.** *Biomaterials* 2014, **35:**432-9.

F1000Prime RECOMMENDED

57. Jung HJ, Abou-Jaoude M, Carbia BE, Plummer C, Chauhan A: **Glaucoma therapy by extended release of timolol from nanoparticle loaded silicone-hydrogel contact lenses.** *J Control Release* 2013, **165:**82-9.

F1000Prime RECOMMENDED

58. Peng CC, Ben-Shlomo A, Mackay EO, Plummer CE, Chauhan A: **Drug delivery by contact lens in spontaneously glaucomatous dogs.** *Curr Eye Res* 2012, **37:**204-11.

F1000Prime RECOMMENDED

59. Fulgencio Gde O, Viana FA, Ribeiro RR, Yoshida MI, Faraco AG, Cunha-Junior Ada S: **New mucoadhesive chitosan film for ophthalmic drug delivery of timolol maleate: in vivo evaluation.** *J Ocul Pharmacol Ther* 2012, **28:**350-8.

60. Huang SF, Chen JL, Yeh MK, Chiang CH: **Physicochemical properties and in vivo assessment of timolol-loaded poly (D,L-lactide-co-glycolide) films for long-term intraocular pressure lowering effects.** *J Ocul Pharmacol Ther* 2005, **21:**445-53.

61. Kashiwagi K, Ito K, Haniuda H, Ohtsubo S, Takeoka S: **Development of latanoprost-loaded biodegradable nanosheet as a new drug delivery system for glaucoma.** *Invest Ophthalmol Vis Sci* 2013, **54:**5629-37.

62. Macoul KL, Pavan-Langston D: **Pilocarpine ocusert system for sustained control of ocular hypertension.** *Arch Ophthalmol* 1975, **93:**587-90.

63. Haller JA, Bandello F, Belfort R, Jr., Blumenkranz MS, Gillies M, Heier J, Loewenstein A, Yoon YH, Jacques ML, Jiao J, Li XY, Whitcup SM: OZURDEX GENEVA Study Group: **Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion.** *Ophthalmology* 2010, **117:**1134-46.e1133.

64. Schwartz SG, Flynn HW, Jr.: **Fluocinolone acetonide implantable device for diabetic retinopathy.** *Curr Pharm Biotechnol* 2011, **12:**347-51.

65. Wang J, Jiang A, Joshi M, Christoforidis J: **Drug delivery implants in the treatment of vitreous inflammation.** *Mediators Inflamm* 2013, **2013:**780634.

66. **Federal Drug Administration: Medical Devices.** [http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm312053.htm]

67. Manickavasagam D, Oyewumi MO: **Critical assessment of implantable drug delivery devices in glaucoma management.** *J Drug Deliv* 2013, **2013:**895013.

68. Diebold Y, Calonge M: **Applications of nanoparticles in ophthalmology.** *Prog Retin Eye Res* 2010, **29:**596-609.

69. Kim NJ, Harris A, Gerber A, Tobe LA, Amireskandari A, Huck A, Siesky B: **Nanotechnology and glaucoma: a review of the potential implications of glaucoma nanomedicine.** *Br J Ophthalmol* 2014, **98:**427-31.

70. Zarbin MA, Montemagno C, Leary JF, Ritch R: **Nanotechnology in ophthalmology.** *Can J Ophthalmol* 2010, **45:**457-76.

71. Natarajan JV, Ang M, Darwitan A, Chattopadhyay S, Wong TT, Venkatraman SS: **Nanomedicine for glaucoma: liposomes provide sustained release of latanoprost in the eye.** *Int J Nanomedicine* 2012, **7:**123-31.

F1000Prime RECOMMENDED

72. Pan T, Brown JD, Ziaie B: **An artificial nano-drainage implant (ANDI) for glaucoma treatment.** *Conf Proc IEEE Eng Med Biol Soc* 2006, **1:**3174-7.

F1000Prime RECOMMENDED

73. Maleki T, Chitnis G, Park JH, Cantor LB, Ziaie B: **Biodegradable microfabricated plug-filters for glaucoma drainage devices.** *IEEE Trans Biomed Eng* 2012, **59:**1507-13.

F1000Prime RECOMMENDED

74. Craven ER, Katz LJ, Wells JM, Giamporcaro JE: **Cataract surgery with trabecular micro-bypass stent implantation in patients with mild-to-moderate open-angle glaucoma and cataract: two-year follow-up.** *J Cataract Refract Surg* 2012, **38:**1339-45.

F1000Prime RECOMMENDED

75. Arriola-Villalobos P, Martinez-de-la-Casa JM, Diaz-Valle D, Fernandez-Perez C, Garcia-Sanchez J, Garcia-Feijoo J: **Combined iStent trabecular micro-bypass stent implantation and phacoemulsification for coexistent open-angle glaucoma and cataract: a long-term study.** *Br J Ophthalmol* 2012, **96:**645-9.

F1000Prime RECOMMENDED

76. Kent C: **Three Stents in the Glaucoma Pipeline.** Review of Ophthalmology; 2012. [http://www.reviewofophthalmology.com/content/t/glaucoma/c/33743/]

77. Simon G: **A Suprachoidal Gold Shunt for Glaucoma.** *European Ophthalmic Review* 2008: 42-4.

78. Mansouri K, Weinreb R: **Continuous 24-hour intraocular pressure monitoring for glaucoma–time for a paradigm change.** *Swiss Med Wkly* 2012, **142:**w13545.

79. Agnifili L, Mastropasqua R, Frezzotti P, Fasanella V, Motolese I, Pedrotti E, Iorio AD, Mattei PA, Motolese E, Mastropasqua L: **Circadian intraocular pressure patterns in healthy subjects, primary open angle and normal tension glaucoma patients with a contact lens sensor.** *Acta Ophthalmol* 2014, [Epub ahead of print].

F1000Prime RECOMMENDED

80. De Smedt S, Mermoud A, Schnyder C: **24-hour intraocular pressure fluctuation monitoring using an ocular telemetry Sensor: tolerability and functionality in healthy subjects.** *J Glaucoma* 2012, **21:**539-44.

F1000Prime RECOMMENDED

81. Gravitz L: **Glaucoma Test in a Contact Lens.** MIT Technology Review; 2010. [http://www.technologyreview.com/news/418247/glaucoma-test-in-a-contact-lens/]

82. Lorenz K, Korb C, Herzog N, Vetter JM, Elflein H, Keilani MM, Pfeiffer N: **Tolerability of 24-hour intraocular pressure monitoring of a pressure-sensitive contact lens.** *J Glaucoma* 2013, **22:**311-6.

F1000Prime RECOMMENDED

83. **SENSIMED Triggerfish® provides an automated recording of continuous ocular dimensional changes over 24 hours.** 2014. [http://www.sensimed.ch/en/sensimed-triggerfish/sensimed-triggerfish.html]

84. Chen P, Rodger D, Saati S: **Microfabricated Implantable Parylene-Based Wireless Passive Intraocular Pressure Sensors.** *J Microelectromech Syst* 2008, **17:**1342-51.

85. **Sensor in eye could track pressure changes, monitor for glaucoma.** [http://www.washington.edu/news/2014/06/16/sensor-in-eye-could-track-pressure-changes-monitor-for-glaucoma/]

86. **Intraocular Pressure Sensor.** 2014. [http://www.launchpnt.com/portfolio/biomedical/intraocular-pressure-sensor/]