Review Article

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New trends in glaucoma risk, diagnosis & management

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Recent advances have seen a surge of new ideas and technologies to aid in the detection, treatment and further understanding of glaucoma. These technologies and advances are discussed to provide information on risk-factors, diagnosis and treatment. Glaucoma has never before seen such an advance in research and therapies coming forward in to the clinical workplace. It is an exciting time for physicians and researchers alike and over the next decade will certainly see advances in early detection, efficacious treatments and neuroprotection.

Key words Detection of apoptotic retinal cells (DARC) - glaucoma - intracocular pressure telemetry - IOP fluctuation - neuro-protection - Rho kinase inhibitors - surgical devices

Introduction

Glaucoma refers to a group of conditions characterised by typical changes to the retinal nerve fibre layer and optic nerve head resulting in reduced visual field sensitivity. Its enormous social and economic impact can be appreciated by the fact that it remains a leading cause of blindness worldwide[1]. Not surprisingly, glaucoma research is attempting to reduce this burden through improved disease detection and more effective treatments. Specific areas of focus include methodologies for earlier diagnosis, elucidating modifiable risk factors and developing better intraocular pressure (IOP) -dependant and non IOP-dependant treatments. There have been several new and exciting advances in these areas which are discussed in this review article.

Risk factors

Trans-cribrosal and CSF pressure: The lamina cribrosa provides structural and nutritional support to retinal ganglion cells (RGC) as these pass from the pre-laminar to post-laminar optic nerve[2]. As glaucoma advances, the lamina cribrosa displays marked posterior bowing in the direction of a pressure differential between IOP and the CSF [trans-cribrosal pressure differential (TCPD)][3,4]. Although we know much about IOP in glaucoma, our understanding of CSF pressure is emerging. So far, findings suggest that reduced CSF pressure, leading to a pathologically large TCPD, may contribute to glaucoma pathogenesis[8]. Recent studies indicate that CSF pressure may be a risk factor for primary open angle glaucoma (POAG). Retrospective analysis of patients undergoing lumbar puncture shows

a steady, sustained decline in CSF pressure from 55 years onwards[5,6]. Compared with those in the 45-49 yr age group, CSF pressure in 80-84 yr olds was reduced by 20.4 per cent and 33.5 per cent in 85-89 yr olds[5]. The decline in CSF pressure observed from 50 years onwards appears to mirror increasing glaucoma risk beyond this age.

The same group also reported that CSF pressure increases proportionate to body mass index (BMI)[6]. Individuals with a BMI of 35 kg/m^2 have mean CSF pressure 32.4 per cent higher than individuals with BMI of 18 kg/m^2. Working on the assumption that a low CSF pressure might be harmful due an increased TCPD, it follows that low BMI might be a risk factor for glaucoma. This is consistent with the findings in population-based studies that risk of POAG is lower with higher BMI[7]. It is also interesting given the observation that higher BMI is associated with higher mean IOP[8]. Given the positive correlation between increasing mean IOP and glaucoma risk, one would expect the reverse to be true. That this is not the case points to the potential importance of other factors including CSF pressure and the TCPD.

A retrospective analysis of CSF opening pressures in individuals undergoing lumbar puncture has shown important differences between glaucoma and control. Lower CSF pressures were documented in individuals with POAG (9.1 ± 0.77 mmHg) or NTG (normal tension glaucoma) (8.7 ± 1.16 mmHg) compared to control (11.8 ± 0.71 mmHg). Further, those with ocular hypertension had higher CSF pressure compared to age-matched control (12.6 ± 0.85 mmHg vs 10.6 ± 0.81 mmHg)[9].

The TCPD has been estimated in patients with and without glaucoma. By prospectively measuring IOP and CSF pressure, Ren *et al*[10] were able to approximate the TCPD by using the following formula:

TCPD = Intraocular pressure - Cerebrospinal fluid pressure

They examined 43 patients with open-angle glaucoma (14 NTG, 29 POAG) and 71 subjects without glaucoma.The outcome of lumbar puncture was the same as reported by Berdahl *et al*[9]: NTG and POAG were associated with lower mean CSF pressure. Further, it was shown that TCPD was significantly higher in POAG (12.5 ± 4.1) and NTG (6.6 ± 3.6) compared to control (1.4 ± 1.7).

The correlation between TCPD and neuro-retinal rim loss or visual field changes has also been prospectively studied[11]. Twenty two patients with high-pressure glaucoma, 13 patients with normal-pressure glaucoma, and 17 subjects with ocular hypertension underwent ophthalmic and neurological assessment including applanation tonometry, lumbar puncture and scanning laser polarimetry of the optic nerve head. Compared to rim area/visual field and IOP or CSF pressure, a moderately strong negative correlation for neuroretinal rim (r = -0.38) and moderately strong positive correlation for visual field loss (r = 0.38) was found. However, there remain several unanswered questions about the CSF pressure and glaucoma. For example, in these studies it was assumed lumbar puncture was opening pressure, and hence CSF pressure was equal to the pressure exerted by CSF around the optic nerve, but this is yet to be proven. In addition, lumbar puncture and hence CSF pressure measurement is too invasive to be used in routine. There is therefore, an unmet need for non-invasive CSF pressure telemetry.

IOP fluctuation: The lowering of IOP to prevent progression of glaucoma is now the backbone of glaucoma management and is supported by several well designed randomised controlled trials that have demonstrated that lowering the IOP reduces the rate of glaucomatous damage. These studies have included the Ocular Hypertension Treatment Study (OHTS)[12], which, showed that lowering IOP reduced the rate of glaucomatous damage as defined by field loss or optic nerve head damage or both. Treatment by lowering IOP reduced the damage in patients by 10 to 5 per cent over five years. The Collaborative Normal Tension Glaucoma Study established itself as the first randomised controlled study[13], which supported the idea that lowering IOP worked in both in POAG patients and NTG groups. In amongst these studies, there has been some interest in the idea that IOP fluctuation may play a role in disease progression even in those patients on treatment[14,15]. Two major publications, the Collaborative Initial Glaucoma Treatment Study (CIGTS) and the Advanced Glaucoma Intervention Study (AGIS) have also given weight and support to the idea that IOP fluctuation is a significant contributor to visual field progression[16,17]. Fluctuation in the IOP can be thought of as occurring at different frequencies - there is diurnal variation occurring during a single day, short term fluctuation that is occurring over days and weeks and long term fluctuation occurring over months and years. In practice, significant variation is seen over different visits or during phasing of the patient over a single day. Clearly, the inter-visit variation may be

made up of variations in diurnal, short and long-term fluctuations.

Currently IOP remains the major treatable risk factor for progressive glaucoma[15,18]. A growing body of evidence shows that not only is mean IOP reduction important but that fluctuations of IOP may play a role[15,16,22,23]. The reduction in IOP as a mean has been shown to reduce progression of visual filed loss but within this group there are still subjects with progressive field loss. The mechanism for progression despite adequate IOP reduction has been postulated to be due to IOP fluctuations and several studies have shown that fluctuations exist despite "adequate" topical IOP lowering treatment[15,19,20]. Early studies in this field include work by Bergea and colleagues[14] who identified risk factors for visual field deterioration included IOP range and peak. Similar findings in IOP standard deviation and field progression were seen by Stewart *et al*[21]. A post-event review of the AGIS data by Caprioli and Coleman[17] demonstrated using a multivariate model that IOP variation was an independent risk factor for visual field progression with an odds ratio of 1.39 per cent (95% CI, 1.09-1.79, *P*=0.009). More recently, data from the CIGTS confirmed earlier reports that IOP peak and fluctuation were both important predictors of disease progression and aggressive intervention should be adopted where these factors are seen[16]. In this study, three factors were found to be predictors of progression at the 3-9 year old follow up: high peak IOP (*P*=0.03), wide standard deviation (*P*=0.06) and a great range of IOP (*P*=<0.01).

The mechanism behind disease progression associated with IOP fluctuation, however, is not currently well understood. The fluctuation in IOP possibly causes damage through alteration in balance in homeostatic mechanisms designed to protect the retinal ganglion cell (RGC) and may lead to damage to the optic nerve head and glial tissues[24]. Alternatively, fluctuations in IOP may cause chronic remodelling of the lamina cribrosa, as seen in monkey eyes subjected to raised IOP, where there is thickening of lamellar lamellae, deformation of the lamina cribrosa and an increase in connective tissue remodelling[25]. It is likely that these changes are irreversible with less tensile strength in the remodelled state, leading to alteration in the homeostatic protective mechanisms and possible vascular compromise[24]. Other evidence for IOP fluctuation causing damage comes from systemic hypertension where raised blood pressure (BP) is known to lead to end organ damage, but, more recently there has been evidence that BP fluctuation and variability is in itself an independent risk factor for end-organ damage. This has been shown in both animal and human models and the reduction of blood pressure variability is now a core strategy in the treatment of systemic hypertension[26-29].

Diagnosis

As the anatomical and functional changes from glaucoma are largely irreversible, early disease detection remains an important strategy to prevent visual impairment. This has been achieved by assessing optic nerve structure and function using optic nerve imaging and perimetry, respectively. Although fundamentally unchanged for several decades, both imaging and perimetric techniques have improved considerably. Newer strategies are emerging to complement these established techniques. These include retinal nerve fibre analysis and the detection of retinal ganglion cell apoptosis *in vivo*.

Spectral domain OCT: Optical coherence tomography (OCT) in glaucoma offers the opportunity to objectively measure the retinal nerve fibre layer and its associated change with time. It is an attractive tool in glaucoma assessment due to its ability to take non-contact, objective high-resolution measurements. Newer generation OCT scanners, referred to as spectral or Fourier domain (SD) OCT, are 200 times faster than the older time-domain (TD) OCTs, reducing patient movement artefact and increasing axial resolution. The new SD OCTs are able to achieve a resolution of 3-6 microns compared with a 10-micron resolution previously achieved with TD OCT[30].

The potential power of SD OCT in glaucoma management is enormous but is dependent on establishing structural and functional relationships. Ideally changes should be detected earlier than with the traditional gold standard of visual fields and indirect ophthalmoscopy of the optic nerve head. The changes detected should also be reproducible so that progression can be accurately monitored with time. Vizzeri *et al*[31] and Gonzalez-Garcia *et al*[32] both demonstrated that excellent reproducibility can be obtained with two different commercially available machines (Cirrus and RTVue). In addition, other investigators looking at variability and comparing spectral based technology with time based systems concluded that there was less variability in retinal nerve fibre layer measurements with the newer technology[33,34]. Like TD OCT, the newer SD OCT can obtain data in two methods - direct circular scanning and re-sampling the data of interest

from a 3-D data set. Shin *et al*[35] tested retinal nerve fibre layer (RNFL) thickness measurement reproducibility by both re-sampling and direct circular scanning using the RTVue OCT; they were able to show excellent reproducibility in both modes. Improved reproducibility of RNFL measurement by SD-OCT may enhance the ability to detect glaucoma at an earlier stage by enabling the detection of smaller changes at an earlier stage than TD-OCT previously allowed. However, due to the slow progression of glaucoma and the relative newness of this technology we must wait for longer-term studies to determine its ability to detect glaucoma at an early stage.

DARC (Detection of Apoptotic Retinal Cells): The ability to detect glaucoma at the earliest stages before field loss, where approximately 40 per cent of ganglion cells have already been lost, has been a goal in clinical glaucoma management for several decades. A new technique which utilizes the unique optical properties of the eye to directly visualize retinal ganglion cell (RGC) death may now be a realistic option and for the first time may give glaucoma physicians the opportunity to detect glaucoma earlier and monitor the response to treatment in a visual and quantifiable manner[36]. The technology relies on the unique properties of annexin V, a protein which has the ability to bind to negatively charged phospholipids in the presence of Ca^{2+} . Annexin V has the ability to identify cells undergoing apoptosis *in vivo* using both radiological and macroscopic fluorescent techniques. A technique termed "Detection of Apoptotic Retinal Cells" (DARC) has been developed which utilizes non-radioactive fluorescent labelled annexin V and high-resolution imaging to enable real-time detection of apoptosis in the RGCs[36]. Post-mortem and histological studies have previously shown apoptosis to be a feature of glaucomatous damage in eyes and the ability to detect these findings *in vivo* is a significant leap forward. DARC technology in the animal model has shown good correlation with histological findings[37]. In a rat model of ocular hypertension there was a significant correlation between the histological outcome and the DARC *in vivo* findings at 2, 3, 4, 8 and 16 wk with minimal intra- and inter-animal variability[38]. It is anticipated that DARC technology might be able to give a snapshot in time of the number of dying retinal ganglion cells - "a DARC count"[39]. In order for this data to be meaningful, large population based studies would be needed to establish the DARC count in relation to glaucoma and normal age related cell death. The technology has been demonstrated well in animal models but now must undergo phase 1 clinical trials to assess its safety and toxicology effects under the UK Medicines and Healthcare regulatory agency (MHRA) guidelines. There is a precedent for the clinical use of annexin V, it has been used previously in up to 30 clinical trials with none showing any adverse events, but as it is a modified agent with its fluorescent tag it is classed as a new drug[40]. In short, DARC may prove to be an exciting new biomarker for glaucoma which is able to give a real time *in vivo* snapshot of RGC death in glaucoma and the effect of treatment on this process.

IOP telemetry: The evidence in support of peak IOP and IOP fluctuation points to the importance of targeted IOP strategies. This is particularly so given evidence that the timing and type of current IOP lowering therapies can effect IOP fluctuation in different ways[41-43]. The ability to identify individual differences might allow treatment to be tailored to individuals and perhaps lead to lower rates of progression.

Our ability to identify patients requiring targeted treatment is improving. An example is the development of a telemetric strain gauge contact lens (Sensimed Triggerfish)[44]. The device comprises a disposable silicone contact lens with an embedded micro-electromechanical system and a thin microfabricated platinum titanium strain gauge that measures the changes in corneal curvature. It is based on the assumption that a correlation exists between IOP and corneal curvature, with an IOP variation of 1 mm Hg produces a change of central corneal curvature radius of approximately 3 microns. Measurements are taken every 5 min for a duration of 30 sec, giving a total of 288 measurements (each of which is a mean of 300 readings) over a 24 h period. The results obtained are presented in an arbitrary unit and not millimetres of mercury[45]. Using 24 h tracing, there has been identifiction of individual circadian IOP patterns[45]. The evidence available is anecdotal at present but the device may open new vistas in redefining optimal IOP control following glaucoma therapy. The future of this technology relies on translating the arbitary electrical signal produced by the contact lens strain gauge into a meaningful intraocular pressure and this is the current focus of studies. There is also the pardigm shift that will inevitably come with this type of technology where physicians may be faced with hundreds of IOP readings over a 24 h period where previously they were aquainted with a single Goldman applanation

tonometry (GAT) reading[45]. Although these devices do have some potential it remains to be seen how these fair with large scale clinical trials to validate their use.

Other devices for continuous IOP monitoring are under development and the initial results appear encouraging. It remains to be seen whether any of these developments lead to a tolerable, cost-effective and accurate device with clinical applications.

Treatment

Advances in glaucoma treatment are desperately needed. This is because proven medical and surgical therapies are limited in their capacity to stop glaucoma progression. Both work by reducing IOP, a risk factor for glaucoma but not necessarily the sole cause for disease progression. Very low IOP will not guard against glaucoma progression in all patients, presumably due to the influence of other risk factors. Further, very low IOP in itself may cause sight threatening ocular complications. This is most often seen following glaucoma surgery such as trabeculectomy where very low IOP, sometimes unintentional, can be achieved.

Recent exciting developments in glaucoma management hope to, in part, address these concerns. These include the development of a new class of IOP lowering medications (Rho-kinase inhibitors), newer and safer techniques for surgically reducing IOP and the development of non-IOP dependant therapies such as neuroprotection.

Rho kinase inhibitors: The Rho family is a group of guanosine triphosphotases (GTPases) which, have a central role in cellular processes including actin cytoskeleton activity and cell contraction and motility (actin-myosin related)[46]. Rho associated coiled coil-forming protein kinase (ROCK) is a downstream effector of Rho in the Rho-dependant signal pathway. Therefore, ROCK inhibitors may enhance aqueous drainage by acting on the actin cytoskeleton and cellular motility in the trabecular meshwork, schlemms canal and ciliary muscle[47-49]. This new class of ocular antihypertensives may lower IOP by decreasing resistance to aqueous outflow by cellular relaxation in the trabecular meshwork and schlemms canal specifically by decreasing myosin light-chain phosphorylation[50,51]. Due to the diversity of protein kinase activity despite their relative similarity of structural binding sites it offers a significant challenge to develop a class of drug that is ROCK specific in activity without having additional effect on other pathways[52,53]. There are several ROCK inhibitors in clinical trials for glaucoma and ocular hypertension including AR-12286 (phase 2, Aerie pharmaceuticals) and K 115 (phase 2, Kowa pharmaceuticals)[46]. Aerie pharmaceuticals have reported that AR-12286 reduced IOP to 4.4 mmHg to a maximum of 6.8 mmHg in a twice-daily dosing regime of 0.25 per cent with the only side effect reported being trace to moderate hyperaemia[54]. Although AR-12286 which originates from the aminoisoquinoline amide series is a relatively selective agent, its long-term tolerability and safety in humans is as yet unknown[46].

Another Rho kinase inhibitor - compound K115 (an isoquinoline sulphonamide compound) has been shown in pre-clinical studies in monkeys to be efficacious, reducing the IOP by 2.3 - 4.4 mmHg versus 2.5 mmHg for Latanoprost 0.005 per cent[55]. It is currently undergoing phase 2 clinical trials in POAG and ocular hypertension patients (Kowa pharmaceuticals). Also undergoing phase 2 trials is Y-39983, as a topical application it is known as SNJ-1656 and has been evaluated in phase 1 and 2 clinical trials (Trial IDs: CRKI983A2101/NCT00515424; CRKI983A2201/NCT00846989). Interestingly it elicited different IOP responses in different animals and when tested in humans had side effects including moderate to severe hyperaemia, vascular disorders and other system problems[46,56,57]. The difference in IOP effects across different species may reflect the difference in ROCK expression or differences in anatomy, physiology and pharmacokinetics. INS117548 is another compound to undergo phase 1 tests but concerns have been raised over its safety profile in particular related to ocular burning and stinging[46].

Rho kinase inhibitors offer a potentially exciting alternative to the prostaglandin analogues but further research will be required to produce a compound with a similar IOP reduction and safety profile to the existing competition.

Surgical devices: All surgical devices aim to reduce IOP in a way that is predictable and associated with fewer side effects compared to established techniques. Current challenges faced with new devices will be applicability to glaucoma subtypes, cost and training required. Devices with multiple indications that are cheap and easy to use are likely to find a place in the treatment paradigm.

Some devices/implants aim to improve the way trabeculectomy works are as follows:

Ex-press mini shunt: a stainless steel implant used under a scleral flap similar to that used in trabeculectomy.

The theoretical advantage over standard trabeculectomy is controlled aqueous outflow in the early post-operative period resulting in less surgically induced hypotony. Studies suggest the short-term efficacy of the Ex-press mini shunt may be equal to trabeculectomy with less early hypotony but a similar complication rate overall[58-60]. Erosion and exposure of the implant within 12 months of surgery has been reported[61].

Ologen™ implant: A biodegradable lyophilized porcine collagen matrix implant used at the end of trabeculectomy to provide a scaffold for random fibroblast growth. This in turn is believed to reduce sub-conjunctival scarring severity. When inserted under the conjunctiva at the time of trabeculectomy, it acts as a spacing device. Its porous structure allows aqueous percolation through the sub-conjunctival space. Initial outcomes with Ologen™ implants in trabeculectomy were not encouraging. A prospective randomized trial of trabeculectomy with Ologen™ implant verses trabeculectomy without augmentation found no difference between groups 6 months after surgery[62]. Further, when compared with mitomycin C (MMC) augmented trabeculectomy, results are inferior[63]. Lower mean IOP was achieved in the MMC group (11.5 ± 4.1 verses 15.6 ± 2.4 mm Hg) with less IOP-lowering medication dependence. The absolute success rate in the MMC group was 100 per cent compared to 50 per cent in the Ologen™ group. This is in contrast to a more recent report that Ologen is equally effective to mitomycin C[64]. Overall, Ologen™ treated trabeculectomies achieve smaller functioning conjunctival blebs[65]. Outcomes with a 2nd generation Ologen™ implant appear to be improved[63], further results are awaited.

Some other devices aim to increase the flow of fluid from within the eye into Schlemm's canal:

Glaukos istent: A 1 x 0.3 mm titanium implant for insertion through the trabecular meshwork into Schlemm's canal. When combined with cataract surgery in open-angle glaucoma, a modest benefit in IOP reduction and reduced glaucoma medications is reported[66,67]. Impressive results have been reported in a small uncontrolled case series of secondary open-angle glaucoma[68].

Trabectome: This is an electrocautery device used during intraocular surgery to strip the trabecular meshwork, thus creating a direct communication between the anterior chamber of the eye and Schlemm's canal. It may be used alone or in combination with cataract surgery. In those undergoing Trabectome alone, mean IOP reductions of up to 40 per cent are achievable with success rates comparable to that reported after trabeculectomy[69]. Smaller yet significant IOP reduction has been reported when Trabectome is combined with phacoemulsification[70]. Eyes with secondary open-angle glaucoma may achieve better IOP reductions overall[71]. The main complication is intraoperative hyphema that may occur in up to 100 per cent of cases.

Other devices designed to facilitate aqueous flow into Schlemm's canal include the *Hydrus implant* (a nickel titanium implant inserted into Schlemm's canal) and the Stegmann canal expander (a fenestrated tube designed for insertion to Schlemm's canal).Both are still undergoing development: the outcome of clinical trials is awaited with interest.

Another approach has been to find novel pathways for fluid to leave the eye:

CyPass micro-shunt: A 6 mm tubular shunt designed for use during cataract surgery. It is inserted into the suprachoroidal space and encourages aqueous outflow via a uveoscleral pathway. A clinical trial in the USA is assessing its effectiveness. Initial results have been encouraging[72].

An alternative strategy for reducing intraocular pressure is to suppress the amount of fluid produced within it. For many years, this has been achieved with transcleral cyclophotocoagulation[73]. Newer strategies include:

EyeOP1: This device uses external ultrasound to destroy part of the ciliary body within the eye. As the ciliary body is the source of intraocular fluid production, this reduces fluid production and in turn intraocular pressure. A pilot study has shown encouraging results and a large trial in Europe is currently assessing its efficacy and safety[7].

Neuroprotection, neuromodulation and neuro-recovery: Glaucoma is a condition characterized by RGC apoptosis and therefore, is considered a type of neurodegenerative disorder. Strategies that prevent RGC apoptosis (neuroprotection), retard the way RGC apoptosis occurs (neuro-modulation) or reverse the apoptotic process (neuro-recovery) may be of great benefit in glaucoma management. The potential cellular pathways that contribute to RGC apoptosis are numerous and complex[75,76] but this presents many opportunities for therapeutic development. Several

strategies have already been investigated and many are under development.

For many years, animal studies have suggested brimonidine having neuro-protective benefits over and above its IOP lowering capability[78]. Recent findings from a human study appear to support this finding[79-81]. The "Low-tension Glaucoma Study (LoGTS)", a multi-centre randomized double-masked clinical trial compared visual field progression in glaucoma patients treated with brimonidine or timolol[80-82]. Recruited subjects had a diurnal IOP <21 mmHg in the presence of visual field and optic nerve head evidence of glaucoma. Visual field assessments were carried out every 4 months and patients were followed up for 4 years. Despite comparable IOP control over the course of followup, glaucoma progression was identified in 9.1 per cent of the brimonidine compared to 39.2 per cent of the timolol group. The results imply brimonidine conveys an ability to prevent glaucoma progression independent of the IOP lowering effect and raises the possibility of neuro-protective properties[82]. Alternative explanations for these findings exist; *(i)* was there an excessive dropout in the brimonidine group that might mask a group who would have progressed, *(ii)* there could have been different diurnal variations between the two drug groups, and *(iii)* the apparent protective effect of brimonidine could in fact reflect faster progression in the timolol group[82]. The timolol group could have a vascular compromising effect, which might lead that group to deteriorate at a faster rate compared with the brimonidine group. This theory is supported by a recent meta-analysis of betaxolol vs timolol on IOP lowering and glaucoma progression. On average, timolol reduces IOP more than betaxolol but studies consistently find more visual field progression in those treated with timolol[83].

Another medication of interest in the neuro-protection group is memantine. This compound is an N-methyl-D-aspartate (NMDA) receptor antagonist and has shown some promise in animal models but there has been less convincing evidence produced by human studies to date[77,84]. Two phase 3 trials into the safety and efficacy of memantine failed to show statistical significance for the primary endpoints[77]. It is unfortunate that these results have never been published but this finding says as much about our ability to measure apoptosis and glaucoma progression as it does about memantine efficacy in glaucoma. Perhaps the benefits of memantine were underestimated by the study design and again highlights the importance of strategies such as DARC for *in vivo* evaluation of RGC apoptosis.

Reduction of RGC apoptosis may be achieved with medications that interfere with the glutamate excitotoxic cascade including calcium channel blockers and inhibitors of glutamate release[85,77]. Brimonidine, as discussed, is an example of this. Other medication classes of interest include those that influence the way growth factors interact with RGCs (*e.g.* TNF-alpha blockers), those that enhance energy delivery to RGCs (nicotinamide) and those with neurotrophic properties (*e.g.* BDNF, NGF)[77]. All are at early stages of development and we know little about their tolerability or side effects let alone efficacy in a clinical setting. However, their development is timely given we are better equipped to quantitatively measure their benefits in terms of RGC anatomy and functionality.

Summary

Glaucoma has never before seen such an advance in research and therapies coming forward in to the clinical workplace. It is an exciting time for physicians and researchers alike and over the next decade will certainly see advances in early detection, efficacious treatments and neuroprotection.

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