TITLE

Glaucoma: Hot topics in Pharmacology

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GLAUCOMA: LATEST AVENUES AND ADVANCES

INTRODUCTION:

Glaucoma is a leading cause of blindness worldwide, characterised by progressive multifactorial neurodegeneration of retinal ganglion cells (RGCs) within the retinal nerve fibre layer (RNFL) and their corresponding axons within the optic nerve head (ONH).(1,2) It is projected to affect 79.6 million people worldwide by 2020, of which 11.2 million will be bilaterally blind, emphasising its personal, economic and social burden.(3) Clinically, patients suffering from the most common subtype, primary open-angle glaucoma (POAG), will classically experience the progressive loss of their peripheral visual field, which can eventual lead to complete blindness.(4) Due to the disease's asymptomatic nature, it is estimated that in the developed world only half of people affected by glaucoma are aware of their condition and that there is a subsequent ten-year delay between initial onset and diagnosis of glaucoma, by which time irreversible blindness can occur.(5,6) Glaucoma research currently aims to meet the need for optimisation of risk factors, diagnostics and therapeutic strategies in glaucoma. New avenues and advances in these fields of research are discussed in this review article.

RISK FACTORS

TRANS-CRIBROSAL AND CSF PRESSURE

It is thought that in glaucoma the lamina cribrosa (LC) is displaced posteriorly and compressed which implies an unknown force acting on the LC.(7) Since the LC forms the border between the intraocular space with a higher pressure and the retrobulbar space with a lower pressure, a pressure gradient exists across the LC which is IOP minus CSF pressure in the retrobulbar space.(8) This trans-cribrosal pressure differential (TCPD) is thought to play an important role in the pathophysiology of glaucoma as it has been found that abnormal pressure gradients can affect both orthograde and retrograde optic nerve axoplasmic flow.(9,10)

There have been several studies to investigate the link between glaucoma and CSF pressure which show that glaucoma patients tend to have lower CSF pressures. A retrospective study of patients undergoing lumbar punctures noted that patients' CSF pressures appear to decline as they age from 55 years onwards, which reflects the increased glaucoma risk beyond this age.(11) Jonas et al. found that a glaucoma group displayed a lower calculated CSF pressure and greater estimated translaminar pressure difference than a non-glaucomatous group.(12) These findings are supported by Berdahl et al who carried out a retrospective review of 31,787 medical records where it was found that

normotensive glaucoma (NTG) and POAG were associated with lower mean CSF pressure in a group of 28 patients with open-angle glaucoma than in a control group of 49 non-glaucomatous patients.(13) It was also found that TCPD was significantly higher in POAG (12.5+- 4.1) and NTG (6.6 +- 3.6) compared to control (1.4 +- 1.7) This association between TCPD and glaucoma was also noted by Ren et al. A prospective study of 52 patients found that neuroretinal rim area (correlation coefficient r = -0.38) and mean visual field defect (p = 0.008; r = 0.38) were significantly associated with increased trans-lamina cribrosa pressure difference.(14)

Whether it is TCPD, lower mean CSF pressure or a combination of both that contributes to glaucomatous changes is unclear. A recent experimental study found that reduction in CSF pressure, in monkeys that had a shunt inserted, was associated with development of optic neuropathy with reduction in neuroretinal rim area and volume, and increase in cup-to-disc area ratios.(15)

There are a number of questions regarding the link with CSF pressure and glaucoma. Both IOP and CSF pressure are dynamic and fluctuate over time and their measurements are influenced by several factors, thus the estimation of TCPD should be best calculated based on simultaneous measurements of both IOP and CSF pressure. None of the available studies did it, and they are based on two non-dependent and changing variables.(16)

Recent literature review and meta-analysis showed only five studies that reported quantitative TCPD parameters, four based on lumbar puncture and one on noninvasive two-depth transcranial Doppler device.(17) Studies based on lumbar puncture CSF pressure measurement assumed that lumbar CSF pressure was equal to the retrolaminar CSF pressure, which was never proved and even questioned in several studies.(18) An interesting discussion of this is presented elsewhere.(19) Moreover, Hayreh advocated that TCPD caused by low CSF pressure is not able to cause bowing back of the rigid and compact band of lamina cribrosa and plays a role in development of optic neuropathy.(20)

Another issue is the clinical applicability of these studies as clearly lumbar punctures are a highly invasive procedure, which cannot be used as a risk stratification tool in a clinical setting. A potential development in this regard is the possibility of non-invasive CSF pressure telemetry. There are currently various potential non-invasive methods being developed such as telemetry based on otoacoustic emissions or transcranial doppler insonation of the ophthalmic artery.(21,22) These are promising areas for non-invasive CSF telemetry, which will have wide impacting clinical applications in medicine and perhaps could provide a use in the risk stratification of glaucoma patients too.

IOP Fluctuation:

The reduction in IOP is the mainstay of glaucoma treatment and well established as an acceptable method of reducing the rate of glaucomatous optic nerve damage. The use of IOP lowering treatments has been well supported by numerous studies such as the Ocular Hypertension Treatment Study and the Collaborative Normal Tension Glaucoma Study.(23,24) Such studies have supported the theory that lowering IOP reduced the rate of visual field loss in both POAG and NTG groups. Recently there has been growing interest into the importance of IOP fluctuation in the progression of glaucomatous damage, both in terms of short term and long term fluctuations. Studies reveal that IOP tends to fluctuate throughout the day and over longer intervals however due to lack of standardisation in experimental protocols a consensus has been difficult to achieve.(25–27) Fluctuation of IOP can be short term in that it is diurnal or occurring over days and weeks; long term fluctuation is considered as occurring over months and years.

Hong et al studied 688 eyes in patients with POAG or chronic primary angle closure glaucoma (PACG) who had undergone phacoemulsification after trabeculectomy. After 3 years of follow-up, patients with POAG and an IOP SD greater than 2 mm Hg had a significantly worse mean visual field (VF) deviation than did patients with an IOP SD of 2 mm Hg or less. Hence they concluded that reduced postoperative IOP fluctuation was statistically associated with a slower progression of VF damage.(28) Similar conclusions could be drawn from a cohort from the Advanced Glaucoma Intervention Study, which included 509 eyes with refractory OAG not well controlled with medication. It was found that for each 1 mm Hg increase in IOP fluctuation, the odds of VF progression increased by about 30%. In fact when regression analyses were repeated in eyes with and without a history of cataract extraction, IOP fluctuation was the only variable to be consistently associated with VF progression.(29) The Collaborative Initial Glaucoma Treatment Study also reinforced the finding that IOP peak and fluctuation were important predictors of disease progression at 3-9 years follow up.(30) High peak IOP, wide standard deviation and a large range of IOP were all linked to disease progression.

With regards to diurnal variation most studies of repeated IOP measurements throughout the day have determined that values tend to peak early in the morning and decline over the course of the day.(31–34) Gonzalez et al carried out an analysis of daytime IOP curves from 149 patients with OHT found that 64 % of eyes that had a difference of more than 5 mm Hg between the peak and trough IOP in their diurnal curve eventually had VF defects within 4 years.(35)

Whilst the link between IOP fluctuation and disease progression is gaining increasing evidence the mechanism underlying this is still not well understood. It is postulated that IOP fluctuation may affect homeostatic mechanisms that protect retinal ganglion cells which in turn may lead to optic

nerve head and glial tissue damage.(36) Another theory is the chronic remodelling of LC as a result of fluctuation IOP leading to irreversible changes and a reduced tensile strength.(37)

SMOKING

A new controversial risk factor being investigated in glaucoma patients is cigarette smoking. There have been studies to suggest an association between smoking and POAG and also studies to counter this argument. The Blue Mountain Eye Study suggested a moderate positive association between smoking and increased IOP.(38) Fan et al found a significant association (Odds Ratio 10.8) between current smoking and POAG in thirty-two patients. These finding have been supported by other older case-control studies which also found associations with current smoking and POAG.(39,40) Whereas other studies have found an association with past smoking and POAG.(41,42) Renard et al found in 339 cases of POAG was associated with higher frequency of heavy smoking (40 pack-years or more, OR = 3.93).

In the meta-analysis including 7 reports, 4 cross-sectional and 3 case-control studies the odds ratio for POAG for current and former smokers was 1.37 and 1.03 respectively.(43) It was also shown that smoking might be associated with increased risk of early-onset POAG, (44) and that smoking has also a negative impact on POAG surgery.(45) Although smoking and alcohol consumption together influence glaucoma progression, it is more influenced by smoking than by alcohol consumption.(46) It was reported that smoking increases the expression of IL-6, as well as caspase-3 and PARP-1 in the aqueous humor and in plasma of POAG women aged 40–90 years.(47)

Interestingly, in Chinese cohort smoking was significantly correlated with decreased central corneal thickness (CCT).(48) Although mechanism for decreased corneal thickness in POAG smokers remains unclear, it was suggested more attention should be paid to CCT measurement to estimate correct target IOP. On the other hand, several studies reported little or no evidence for any relation between smoking and POAG (49–51) and the recent study did not confirm the influence of chronic tobacco smoking on IOP.(52) Smokers and nonsmokers did not vary significantly in the prevalence of open-angle glaucoma and angle-closure glaucoma in adult Chinese population,(53) and in Los Angeles Latino population.(54) The prospective longitudinal study of 527 Caucasian POAG cases and 1539 Caucasian controls has shown that the association between cigarette smoking and arterial hypertension in relation to POAG depends on nitric oxide synthase 3 isoform single nucleotide polymorphism.(55)

Most studies that have been carried out did not categorize the number of cigarettes smoked. In the limited papers where this has been done, there appears to be a dose–response relationship. In a prospective cohort study by Wise et al. in 32,570 participants found that heavy smokers (≥20 pack years) were more than twice as likely to have POAG, in the group under 50 years of age.(56)

The association with smoking and glaucoma is contentious and has been poorly investigated with very few high quality studies and not much risk stratification based on pack years. This is surprising considering the extent to which smoking has been investigated as a risk factor in most other medical fields. The evidence exploring the association of smoking in general with POAG is limited, however clinicians should consider the potential relationship with heavy smoking. More in-depth studies which take a detailed smoking history are most certainly required.(57)

VASCULAR RISK FACTORS

Vascular dysregulation was shown to be important risk factor for GON.(58) Primary vascular dysregulation, the term introduced by Flammer, described otherwise healthy subjects that show abnormal regulation in response to temperature changes and mechanical or emotional stress.(59) Low OPP was shown to be a risk factor for the prevalence, incidence and progression of glaucoma in large epidemiological studies.(60)

The Barbados Eye Studies reported that baseline vascular risk factors, including decreased systolic blood pressure and decreased systolic, diastolic, and mean ocular perfusion pressure, can influence the risk of POAG.(61) Specifically, low ocular perfusion pressure doubled the risk of glaucoma in that population. The Early Manifest Glaucoma Trial reported that baseline predictors of progression of open-angle glaucoma include decreased ocular systolic perfusion pressure, a history of cardiovascular disease, and decreased systolic blood pressure.(61) The Thessaloniki Eye Study showed that a diastolic blood pressure of less than 90 mm Hg due to antihypertensive treatment is associated with increased optic-nerve cupping and a decreased rim area of the optic disk in subjects without glaucoma.(62) The Proyecto VER Study (63) and the Egna-Neumarkt Study (64) reported that patients with diastolic perfusion pressure as low as 45-50 mmHg had 3-4.5 times risk of developing glaucoma compared to those with diastolic perfusion pressure of 65 mmHg. Interestingly, vascular factors were shown to play significant roles in the pathogenesis of many neurodegenerative diseases, including Alzheimer's disease and amyotrophic lateral sclerosis.(65,66)

LIGHT TOXICITY AS A RISK FACTOR

It was also proposed by Osborne and collaborators that visual light might be a factor for explaining why retinal ganglion cells might be particularly susceptible in mitochondrial diseases and glaucoma.(67) They showed that mitochondrial failure occurs when the disease is initiated and also as a secondary event, exacerbated when the cells are nutritionally deprived.(68) Moreover, they suggested that patients with glaucoma might benefit from reducing the intensity of light entering the eye.

Diagnosis and Monitoring

Glaucoma remains a disease whose effects are largely irreversible even when using the latest therapeutic interventions, therefore early disease detection remains the main approach by which ophthalmologists prevent visual impairment. Currently the two main strategies used in a clinical setting to assess the structure and function of the optic nerve are optic nerve imaging and perimetry respectively. In addition to these established techniques further strategies have emerged which offer promising prospects for early diagnosis and better monitoring in glaucoma.

Optical Coherence Tomography (OCT)

OCT provides a significant role in aiding diagnosis in glaucoma. It delivers an accurate measurement of the retinal nerve fibre layer (RNFL) thickness which can then be used to make a quantifiable assessment of glaucomatous structural loss (69). OCT's ability to produce high resolution images in a non-invasive manner makes it particularly attractive as a diagnostic tool in glaucoma.

Traditionally Time Domain OCT (TD-OCT) has been used to aid diagnosis but this has since been usurped by a newer generation technology, Spectral Doman OCT (SD-OCT) (70). SD-OCT provides up to 200 times faster scanning speeds compared to TD-OCT, this is of particular importance in minimising movement artefact due to involuntary movements of the eye. Furthermore the faster scanning speeds in conjunction with the higher density sampling provided by SD-OCT allow better visualisation of pathophysiological features of the retina (71,72). Also SD-OCT has better axial resolution compared to TD-OCT, with SD-OCT (3-6 μm) shown to improve axial resolution by two-three times as compared to TD-OCT (10 μm) (69). Ensuring that results are reproducible is important in maintaining an accurate diagnosis of glaucoma, studies that looked specifically at the reproducibility of both modalities found that a key measure of glaucoma, the sectorial RNFL thickness had significantly less variability in the SD-OCT group as compared to TD-OCT (73,74). Additionally different SD-OCT devices (Cirrus and RTVue OCT) have shown consistently good reproducibility (75,76). Encouragingly SD-OCT has shown to be better at sectorial measurement

which is of particular importance as glaucomatous damage typically presents as a localised defect in its earlier stages before spreading.

As described previously glaucomatous damage manifests as a structural and functional decay of the optic disc, OCT provides an assessment of structural damage with visual field assessment functional loss. *Horn et al* was able to demonstrate a correlation between structural damage viewed by OCT and functional loss as visual field defects, of note a strong correlation was seen in the peripapillary areas of the retina (77). Furthermore the study used another modality to assess structural damage, scanning laser polarimetry (SLP) and found that SD-OCT showed better associations between perimetric defect and corresponding RNFL loss than SLP (77). However another study comparing TD-OCT and SD-OCT found there to be no significant difference in the strength of structural-functional relationship between the two devices (73).

It is hoped that as the SD-OCT technique improves it will be capable of diagnosing glaucoma before gold standard perimetry and optic nerve head assessment. So far studies have shown SD-OCT provides improved reproducibility as compared to TD-OCT therefore improving SD-OCT's ability to detect smaller changes earlier, ensuring earlier diagnosis. However due to the slow progression of the disease and the technologies recent emergence, there are no long term studies demonstrating SD-OCT's ability to detect glaucoma in its early stages. Furthermore studies have shown readout variability between SD-OCT devices as each companies inbuilt software systems define the outer retinal border at different levels (78). For example Cirrus HD OCT delineates the outer retinal border as the level of interdigitation between outer segments and retinal pigment epithelium (RPE) whilst the Heidelberg Spectralis defines it as level of the RPE- Bruch's membrane complex (79). Therefore a study comparing the readouts of the two SD-OCT systems found that the significant difference in values produced was due to software used rather than the devices themselves (78).

Detection of Apoptotic Retinal Cells (DARC)

Currently the detection of glaucoma is limited by the late presentation of visual field loss symptoms which predominately occur in the later stages of disease. This delay limits the efficacy of therapeutic interventions. It is thought that by the time patients develop visual field loss approximately 40 percent of RGCs have been lost through apoptosis (12) with previous post-mortem and histological studies corroborating these findings. The realisation that the early diagnosis of glaucoma can be effective in slowing down disease progression has meant that recent research has focused on identifying early diagnostic markers. The apoptosis of RGCs is one of the first stages that occur in glaucoma (13,14) thereby showing great promise as a prospective early diagnostic tool.

DARC technology has the potential to directly visualise these apoptosing RGC's thereby providing early diagnosis and the ability to accurately monitor the efficacy of treatment. Annexin V plays a pivotal role in DARC technology due to its ability to bind to negatively charged phospholipids in the presence of Ca^{2+} thereby enabling it to identify cells of interest undergoing apoptosis *in vivo*. By using a combination of non-radioactive fluorescently labelled annexin V and high resolution imaging, DARC is able to detect RGC apoptosis in real- time (15). The fluorescently labelled Annexin V is administered intravitreally (13), the annexin V-bound fluorophore is then excited using a 488 nm wavelength argon laser. The fluorescence light emission is then detected by a photodetector system with a 521-nm cut-off filter, finally the retina is imaged with a confocal laser scanning ophthalmoscope (16).

DARC technology has been used in animal models of glaucoma such as the OHT where it has successfully shown a good correlation with well recognised histological endpoints (17). Furthermore DARC has been used to evaluate neuroprotective strategies in animal models of glaucoma which include amyloid-beta targeting therapy (18), glutamate modulation (19) and topical Coenzyme Q10 (18). It is envisaged that DARC can provide a snapshot of the number of dying RGC's at one time point thus giving a "DARC count" (20).

So far the technology has been demonstrated in multiple animal models of neurodegenerative disease with the results of phase 1 clinical trials assessing safety and toxicology due to be published later this year. In conclusion DARC provides an exciting biomarker of real-time *in vivo* RGC death for glaucoma and potentially for other neurodegenerative diseases as well.

Intraocular Pressure (IOP) Telemetry

Growing evidence suggests that peak IOP and IOP fluctuation can vary markedly in individuals with glaucoma, this is of particular importance as the timing and type of treatment effects fluctuation in different ways (21,22). Therefore technologies that are able to detect these variations have great potential to provide ophthalmologists with the required information to tailor treatments to suit each individual's type of glaucomatous disease and so slow the rate of progression.

Continuous IOP measurement is required to detect IOP fluctuations; this has led to the development of modern technologies that can accurately measure continuous IOP through implantable sensors. One of the first implantable sensors was developed by Svedberg (91) who incorporated an IOP sensor into the implanted artificial intraocular lens (IOL) during cataract extraction. IOP measurements were collected by an external detector assimilated into devices such as glasses. To date this technology has only been reported *in vitro* with plans for *in vivo* studies (91). Further to this *in vivo* animal studies incorporating modern microchip technology into intraocular lenses implanted

into enucleated rabbit and porcine eyes produced similar IOP readings to those collected using standard pneumotonometry *in vitro* and *in vivo*. A miniaturized electronic capacitive pressure sensor was incorporated into a single microchip with readings detected by an external device using magnetic high-frequency transmission. This technology was limited by the size of the device as it was too large to fit within the capsular bag for long-term implantation (92). Although both technologies have not translated into human studies, these technologies provide an advantage for glaucoma patients requiring cataract extraction by reducing the need for multiple procedures and so reducing the risk of post-operative endophthalmitis.

A different method of continuous IOP measurement involves the insertion of an unpowered parylene pressure tube sensor into the anterior chamber (AC). The thin walled tube undergoes angular deformation in response to IOP changes which can be detected by physicians or by the patient themselves using stereoscopes or magnifying equipment (93,94). The main advantages of this technology are its biocompatibility and low running costs as no electronic transmission is required to detect IOP values. However nocturnal readings cannot be taken when the patient is asleep as the AC needs to be visualised, furthermore patients already with peripheral field loss may have difficulty seeing the deformations. At present the technology is undergoing *in vitro* testing to assess effectiveness and tolerability in the AC.

One device that has been used in human clinical trials developed by Implandata GmbH uses a capacitive sensor to allow continuous IOP monitoring. The lens can be implanted either in the capsular bag or the sulcus between the capsular bag and iris and is encompassed by a biocompatible silicone material allowing long term implantation (95). The attached external reader can collect up to 3,000 measurements over a period of a month allowing continuous IOP measurement. *In vivo* animal studies have shown tolerability of the IOL and good correlation between IOP measurement and IOP values acquired by cannulation manometry (95).

TREATMENT:

Despite the complex nature of glaucoma pathogenesis, current clinical practice only offers IOP-lowering therapies. The landmark glaucoma trials, including the Ocular Hypertension Treatment Study (OHTS), the Early Manifest Glaucoma Trial (EMGT), the Advanced Glaucoma Intervention Study (AGIS) and the Collaborative Normal Tension Glaucoma Study (CNTGS), have demonstrated that lowering IOP in most glaucoma patients is beneficial.(96–101) Indeed, it is the most important modifiable risk factor for glaucoma. However it has been observed that IOP level is not proportional to disease progression and that disease progression can still occur in patients with drug controlled IOP and in patients with an IOP less than 21 mmHg.(97,99) These patients are categorised as having

NTG, which consists of up to one half of sufferers of POAG.(102) There is therefore an urgent need to develop therapeutic targets independent of IOP. This has led to an interest in the role of novel neuroprotective agents in the treatment of glaucoma. The value of neuroprotective agents is that they have the potential to diminish the final common pathway of glaucoma pathogenesis, RGC apoptosis, which may itself be caused by a range of aetiologies. Therefore, they may be either used alone or in tandem with other therapeutic agents.

Current glaucoma treatment includes pharmacological agents, of which there are five main classes (cholinergic, B-blockers, alpha-blockers, prostaglandin analogues and carbonic anhydrase inhibitors), laser therapy and surgery. However, in over half of patients with ocular hypertension or glaucoma, monotherapy fails to maintain target IOP.(103) New, effective IOP-lowering medications are thus sought, as summarised in TABLE 1.

Table 1: New drugs in development for glaucoma

New drug classes	**Examples**
RHO inhibitors	AMA0076(104), AR-13324(104), K-115(104)
Neurotrophic agents	CNTF(105), BDNF(105), NGF(105)
Glutamate antagonists	Memantine(106)
Alpha-2 adrenergic agonists	Brimonidine(107)
Calcium channel blockers	Nimodipine(108), nilvadipine(109), brovincamine(109)
Antioxidants	Coenzyme Q10(110,111)
Anti-inflammatory	Anti-TNFα(112)
Increasing ocular blood flow	Betaxolol(113)
Other	Caffeine(113), antihypertensives(113), gingko biloba extract(113)

RHO KINASE INHIBITORS:

The Rho family is a group of small guanosine-triphosphatase (GTP) binding proteins (RhoA, RhoB and RhoC), which regulate cell shape, motility, proliferation and apoptosis throughout the body through their effects upon actin-myosin.(114,115) The discovery of Rho kinase expression in trabecular meshwork, ciliary muscle cells and optic nerve head has led to their considerable interest in glaucoma research.(116) Furthermore, work has demonstrated higher levels of RhoA in glaucomatous optic nerve heads compared to age-matched controls.(98)

In the Rho-dependent signal transduction pathway, Rho is activated upon binding to GTP, which further stimulates downstream effector Rho associated coiled coil-forming protein kinases (ROCK1 and ROCK2) to polymerize actin. ROCK activation leads to phosphorylation of myosin light chain

(MLCK) and LIM kinases. MLCK induces actin fibre contractility and LIM kinases increase cell migration, together obstructing aqueous humour outflow.(117–119) Thus, ROCK inhibitors can enhance aqueous humour drainage by inhibiting MLCK and LIM phosphorylation and thereby inhibiting the contractility and cellular motility within the trabecular meshwork, Schlemm's canal and ciliary muscle.(120–122) Research into ROCK inhibitors that can affect cellular cytoskeleton and motility of the components of the conventional outflow pathway has led to a potential new ocular antihypertensive class.

Y-27632 was the first ROCK specific inhibitor discovered.(123) Multiple studies since have demonstrated that ROCK inhibitors can lead to a reduction in IOP.(111–113) A significant challenge is identifying ROCK-specific inhibitors, which do not affect other protein kinases; chronic glaucoma usage could otherwise lead to a profound side effect profile. There have been several clinical trials for glaucoma investigating ROCK inhibitors. Hyperaemia is also one of the main reasons why this drug class has not progressed through clinical trials..(104)

Current ROCK specific inhibitors in clinical trials include:

1. AMA0076 caused altered cellular behaviour in human trabecular meshwork cells, reducing aqueous outflow resistance and thereby reducing IOP in ocular normotensive and hypertensive rabbits without significant adverse effects.(126) Phase 2 study was completed in January 2015; results are awaited. (https://clinicaltrials.gov/show/NCT02136940)
2. AR-13324 is currently in Phase 3 Clinical Study (https://clinicaltrials.gov/show/NCT02207621). AR-13324 is a "dual-action" ROCK inhibitor shown to both reduce aqueous humour inflow, as well as increase the facility of aqueous outflow. Phase 2 clinical trials showed that AR-13324 topical administration once daily led to an IOP reduction of 5.7mmHg.(127) It has also been combined with latanoprost to form a "triple-action" glaucoma drop PG324.(128) Phase 2 clinical trials completed in January 2016 and showed PG324 lowered IOP by 1.9 and 2.6mmHg compared to latanoprost and AR-13324 respectively alone after once daily usage for 28 days.(110)
3. K-115 (ripasudil): Oral administration of K-115 ROCK inhibitor in mice led to delayed RGC death, demonstrating its therapeutic potential in glaucoma. Evidence suggests its mechanism is by modulation of the conventional aqueous outflow route, leading to aqueous outflow via the trabecular meshwork.(110–112) Administration of K-115 as monotherapy over 52 weeks in a large multicenter prospective study including 388 patients with glaucoma, OHT or exfoliation glaucoma revealed an IOP-lowering effect, with a mean IOP reduction of -2.6 and -3.7 at trough and peak respectively.(132) Furthermore, additive IOP-lowering effects were seen when used in conjunction with prostaglandin analogues or beta-blockers. Side effects included a mild self-resolving

conjunctival hyperaemia in 74.6% of patients. The phase 3 study showed similar IOP-reduction effects after only 8 weeks of treatment when used with latanoprost or timolol.(94) Recent work has shown the effects of K-115 on trabecular meshwork and schlemms canal cells *in vitro*.(96) Work has shown that K-115 inhibits both ROCK1 and ROCK2 more potently than other Rho-kinase inhibitors.(97)

Aside from causing a reduction in IOP, ROCK inhibitors have also been demonstrated to use other mechanisms in glaucoma treatment; (i) increasing ocular blood flow, (ii) retinal ganglion cell survival and axon regeneration, (iii) anti-fibrotic and anti-scarring agent in glaucoma filtering surgery and (iv) inhibit corneal endothelial cell dysfunction.(133)

NEUROPROTECTIVE AGENTS:

Research over the last decade has demonstrated good evidence that neuroprotective therapy is effective in glaucoma, which has been well outlined in recent reviews.(105,134) Neuroprotection is the preservation of structure and function or neuronal tissue. In glaucoma, it has the potential to promote cell survival and reduce degeneration of optic nerve structure and function in those patients showing glaucomatous changes. Whilst the pathogenesis of glaucoma is complex, several pathways are implicated, including ischaemia, oxidative stress, neurotropic growth factor deprivation, glutamate excitotoxicity, autoimmunity, calcium toxicity and mechanical compression. Neuroprotective agents aim to reduce glaucoma progression by targeting these pathways, thereby increasing retinal ganglion cell and optic nerve head function.

The Low Pressure Glaucoma Treatment Study (LoGTS) was the first study to demonstrate that neuroprotective therapies have potential as glaucoma therapeutics. LoGTS was a randomized double-masked multi-centre clinical trial, comparing visual field progression in NTG treated with either the alpha α_2 adrenergic agonist brimonidine or timolol.(135,136) Brimonidine has been shown to have neuroprotective effects in *in vitro* and animal studies.(137,138) Results showed that 9.1% of brimonidine-treated patients experienced field progression compared to 39.2% of timolol-treated patients, whilst mean IOP decreased equivocally in both groups. This suggests that brimonidine may be having a beneficial effect on visual function independently of IOP.

However, several issues may have contributed to inaccuracy of this finding. Firstly, there was a higher drop-out rate of patients from the brimonidine-treated cohort due to drop-allergy. This group may have removed a field progressing subset of patients. Secondly, there may have been diurnal IOP variation between the two cohorts of patients. Thirdly, the apparent neuroprotective effect of brimonidine could in fact have reflected faster field progression in the timolol-treated group.(136)

Memantine is the best-known NMDA antagonist and is approved for usage in Alzheimer's Disease. Animal glaucoma models suggested that memantine is protective against retinal ganglion cells.(106) Despite promising pre-clinical findings, results from a clinical study of memantine usage in glaucoma in 2010 were unfortunately never published.

Calcium channel blockers (CCBs) also have a good evidence base for therapeutic usage in glaucoma.(139) Oral nimodipine in normotensive glaucoma patients led to improved colour sensitivity and visual feeds compared to placebo, by vasodilation and subsequent increased ocular blood flow to the optic disc. (108,140) Other CCBs including nilvadipine and brovincamine have also shown to have visual benefit in glaucoma patients and *in vitro* work has demonstrated neuroprotective effects of CCBs on RGCs undergoing apoptosis and necrosis.(109)

Other promising treatment strategies which are further from clinical usage but have shown to be neuroprotective in animal models of glaucoma, include neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) and ciliary neurotrophic factor (CNTF).(141) A CNTF-secreting device (NT-501) has entered clinical trials, where it is surgically implanted into the pars plana of glaucoma patients, allowing the drug to diffuse out.(105) Initial results have shown this is a safe device and possible efficacy. Some of the 11 patients displayed no progression in the implanted eye, when the fellow eye deteriorated. Nerve growth factor (NGF) is another promising neurotrophic factor studied in glaucoma treatment. In a small scale recently reported trial, NGF eye drops were administered topically and after three months of treatment, there was significantly less RGC apoptosis, improved optic nerve function, improved visual fields and visual acuity compared to untreated controls.(142)

Oxidative stress suppression is also a promising avenue of glaucoma treatment. Coenzyme Q10 is a potent anti-oxidant that has been shown to be beneficial in neurodegenerative diseases, Parkinson's Disease and Huntington's Disease.(111) Recent evidence has also shown retinal benefits when used with Vitamin E in glaucoma patients.(110)

Activation of the immune system may play an important role in glaucoma progression. A key pro-inflammatory cytokine TNF-α is secreted by defective glial cells and leads to subsequent RGC apoptosis. The anti-TNF-α blocker etanercept has been effectively used in patients for clinical indications including juvenile arthritis, rheumatoid arthritis and ankylosing spondylitis.(112) A recent study using intraperitoneally injected etanercept in a glaucoma rat model led to reduced axonal degeneration and RGC loss.(112) Further animal work and clinical studies will need to elucidate its full therapeutic potential in glaucoma.

Recent work has also demonstrated the potential of caffeine to both reduce IOP when administered orally in ocular hypertensive rodent models, as well as diminish RGC loss.(143) This suggests a potential therapeutic role of caffeine and adenosine receptor antagonists in glaucoma. Oral administration of losartan also led to reduced RGC loss in mouse models of glaucoma.(144)

SURGERY:

Table 2: New surgical developments

Surgical Procedure	**Example**
Increasing trabecular outflow by bypassing TM	Trabectome(145), iStent(146), Hydrus(147), GATT(148)
Increasing uveoscleral outflow via suprachoroidal pathways	CyPass(149), iStent supra(150), SOLX Gold microshunt(151)
Reducing aqueous production from ciliary body	EyeOP1(152)
Creating a subconjunctival drainage pathway	Xen45(150), ExPress(153)

Newer surgical devices are IOP–lowering therapies that aim to be less invasive than trabeculectomy surgery (TABLE 2). Techniques that are quick and easy to use, have minimal tissue instrumentation and feature a low complication rate and short recovery profile are more likely to be successfully established within the clinical setting.

The subconjunctival space is the traditional outflow pathway used in glaucoma surgery. Xen45 (Allergan) is the most promising glaucoma micro-implant.(154) It is a 45nm-wide, 6mm-long collagen-derived gelatin and glutaraldehyde tube, which is injected via an ab interno approach, to form a pathway from the anterior chamber to the subconjunctival space. Upon hydration, it becomes flexible so can conform to surrounding tissues, reducing the risk of erosion. While there is minimal published data on the Xen45 in partulcular, the Xen63 and Xen140 demonstrated an IOP reduction from 22.4 ±4.2mmHg to 15.4 ±3.0mmHg 12 months post-operatively.(154) Furthermore, the number of medication classes reduced from 2.5 ±1.4 to 0.9 ±1.0. No adverse events have been reported so far. Xen45 is currently undergoing phase 4 clinical trials.

The EX-PRESS glaucoma filtration device is a stainless steel drainage tube, which shunts aqueous humour from the anterior chamber to the subconjunctival space. It is designed to enable stable filtration, reducing the risks of hypotony post-trabeculectomy. Additionally, it replaces the need for sclerectomy or iridectomy. Two meta-analyses have shown that the EX-PRESS device lowers IOP comparatively to trabeculectomy surgery and is associated with similar operative success and visual

outcomes.(155,156) Recent work has also demonstrated that the EX-PRESS device is associated with fewer post-operative complications of hyphaema and post-operative inflammation than trabeculectomy surgery.(153)

The Ologen implant is a biodegradable collagen matrix implant which is inserted beneath the conjunctiva following trabeculectomy. It aims to reduce fibrosis and helps in organisation of the subconjunctival scar formation. Recently published five-year follow up data has demonstrated that Ologen implant is as efficacious as MMC in terms of bleb-complication rate.(157)

The Trabectome is an electrical device that ablates the trabecular meshwork via gonioscopy surgery, thus lowering resistance to aqueous outflow. IOP outcomes have been equivalent to trabeculectomy surgery, with the main complication being intraoperative hyphaema in up to 100% of cases.(109) A recent review and meta-analysis of Trabectome outcomes illustrated that it reduces IOP by 31% and has an overall average success rate of 66% after two years.(158)

The Glaukos iStent is a titanium implant which may be inserted into Schlemm's canal through the trabecular meshwork. It allows IOP reduction and reduced additional pharmacological medications when combined with phacoemulsification surgery. A prospective trial of 99 patients followed up over 12 months demonstrated an a reduction in preoperative medication burden in 86.9% of open angle glaucoma patients when two iStent injects were implanted, with no significant side effects or complications.(146) These second generation iStents have been found to be more effective at IOP reduction than the original iStent, due to the ease of inserting multiple stents at one time.

Another promising Schlemm's canal stent is the Hydrus, which is currently in clinical trials. This 8-mm long stent is made from nitinol, a mixture of nickel and titanium, which confers optimal elasticity and biocompatibility to open up the drainage canal, lowering IOP. A prospective randomised controlled trial consisting of 100 patients randomised to treatments of either Hydrus stent with cataract surgery or cataract surgery alone in reducing IOP. The proportion of patients after 24 months using no antihypertensive medications was significantly higher in those co-treated with Hydrus stent and cataract surgery (73 vs 38%; p=0.0008).(147) Further studies are currently ongoing, comparing the Hydrus stent to the iStent.(Clinicaltrials.gov) (NCT02024464)

Suprachoroidal stents are designed to provide a direct drainage route from the anterior chamber to the suprachoroidal space. The CyPass micro-shunt is a 6mm shunt also designed for usage during cataract surgery.(149) It is inserted into the suprachoroidal space and allows aqueous flow via the uveoscleral pathway. As it is inserted via the *ab interno* route, it preserves the conjunctiva. Whilst unassociated with major side effects or complications, the most frequent adverse effect included

transient hypotony. The iStent supra is another stent very similar to the CyPass, which drains directly into the suprachoroidal space. Although results are unpublished, early results appear to be promising.(159)

The SOLX Gold shunt is an *ab externo* device composed of two rectangular-shaped gold plates with channels within its body. It is placed within the anterior chamber, with its posterior end in the suprachoroidal space, so as to allow aqueous flow across it. It may be adjusted post-operatively to affect flow, by targeting laser onto windows within its remaining channels. Success rates in clinical trials have demonstrated this device to be equivocal with usage of the Ahmed valve.(151) However, further work will need to demonstrate safety and efficacy.

EyeOP1 is a miniature delivery device, which reduces aqueous fluid production by destroying part of the ciliary body by ultrasound. In a 12-month multi-centre prospective trial, IOP reduction of 34% was achieved and sustained by the end of the study upon EyeOP1 usage.(152) No serious adverse effects were identified.

In surgical glaucoma, gonioscopy ab-interno trabeculotomy (GATT), as described by Grover et al is an ab interno approach to a circumferential 360 degree trabeculectomy and optimises the safety profile by eliminating scleral and corneal dissection.(136) After 12 months following surgery, IOP had decreased by 11.1mmHg (SD, 6.1mmHg; 39.8% [SD 16.0%]) with 1.1 fewer glaucoma medications. Though long-term data is still needed, it is a promising technique, which is highly cost-effective.

NEW DRUG DELIVERY METHODS UNDER DEVELOPMENT

Despite the plethora of research into new and exciting glaucoma treatments, patient adherence remains a key obstacle in their benefit. Several novel delivery systems have been designed to optimise patient adherence and maximise IOP lowering potential.(160,161) These are summarised in TABLE 3.

Table 3: Drug Delivery Methods

Drug delivery method		Description
Traditional	Orally	Eg: acetazolamide. Normally for when IOP very high despite maximal topical therapy. Negatives: systemic side effects, low ocular bioavailability due to blood-retina barrier
	Topical Eye Drops and Gels	Uses: Current standard for glaucoma treatment. Gels reduce dose frequency. Negatives: <1% of drug reaches aqueous, therefore multiple daily dosing required
	Ocular inserts	Eg: Ocusert(162) Uses: Placed in inferior fornix and delivers drug over several days Negatives: may fall out, discomfort, patient education needed suited mainly for younger glaucoma patients who have manual dexterity

	Surgical implants	Eg: CNTF(163) Uses: can facilitate increased delivery of drug to target tissue for prolonged period of time Negatives: cost, invasiveness of initial and subsequent surgery
Novel	Liposomes & nanospheres	Eg: pilocarpine liposome encapsulation(164) Uses: reduce drug degradation, thereby reducing drug dosage Negatives: requires patient adherence and proper topical administration
	Contact lenses	Eg: timolol-loaded contact lenses(165,166) Uses: drug-eluting contact lenses can release medications over longer periods of time Negatives: requires long-term contact lens wear, drug may leak out of lens during storage
	Adapted surgical implants	Eg: microelectromechanical system (MEMS)(167) Uses: MEMS uses electrolysis to push re-loaded drug out of subconjunctival reservoir of device; ability to change drug size, delivery rate and re-load drug as frequently as needed in a clinic setting during routine patient visits Negatives: requires initial surgical implantation of device,
	Injectable systems	Eg: CNTF implant(161) Uses: long term release (eg 3-4 months) of drug injected in a clinic setting, both degradable and non-degradable polymers have been studied for ocular delivery Negatives: immune response to foreign body, poor targeting to retina/optic nerve
	Punctal plugs	Eg: latanoprost punctual plug delivery system (L-PPDS) Uses: inserted into tear duct to release desired drugs Negatives: patient discomfort, conjunctivitis

CONCLUSION

There are a several promising new directions of research into glaucoma risk factors, diagnostics and therapeutics, which aim to reduce the burden of this insidious disease. The results of these many ongoing clinical studies will hopefully bring a migration of these new ideas from bench to bedside.

Table 4: Abbreviations

AC	anterior chamber
AGIS	Advanced Glaucoma Intervention Study
CCB	Calcium channel blockers
CCT	central corneal thickness
CNTF	ciliary neurotrophic factor
CNTGS	Collaborative Normal Tension Glaucoma Study

CSF	cerebrospinal fluid
DARC	Detection of Apoptotic Retinal Cells
EMGT	Early Manifest Glaucoma Tria
GATT	gonioscopy ab-interno trabeculotomy
GON	glaucomatous optic neuropathy
GTP	guanosine-triphosphatase
IOL	intraocular lens
IOP	intraocular pressure
LC	lamina cribrosa
LoGTS	Low Pressure Glaucoma Treatment Study
MLCK	myosin light chain kinases
NGF	Nerve growth factor
NTG	normotensive glaucoma
OAG	open angle glaucoma
OCT	ocular coherence tomography
OHT	ocular hypertension
OHTS	Ocular Hypertension Treatment Study
ONH	optic nerve head
OPP	ocular perfusion pressure
PACG	primary angle closure glaucoma
POAG	primary open-angle glaucoma
RFNL	retinal nerve fibre layer
RGC	retinal ganglion cell
ROCK	Rho associated coiled coil-forming protein kinases
RPE	retinal pigment epithelium
SD-OCT	Spectral Doman OCT
SLP	scanning laser polarimetry
TCPD	trans-cribrosal pressure differential
TD-OCT	Time Domain OCT
VF	visual field

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