Techniques and technologies for modulating intraocular pressure (IOP)

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Techniques and technologies for modulating intraocular pressure (IOP)

Glaucoma is a disease characterized by optic neuropathy defined by characteristic optic disc damage and visual field loss for which intraocular pressure (IOP) is a major modifiable risk factor. It is the second leading cause of blindness worldwide[1,2]. With the aging population, the incidence and burden of glaucoma are expected to rise to even more significant levels[3]. Lowering the IOP remains the only treatment option to control glaucoma, and prevent further damage. This can be achieved by various methods that will be discussed below.

IOP lowering drops (Table 1)

Topical eye drops are the first, and most commonly used line of treatment, for ocular hypertension and open angle glaucoma. They decrease IOP by increasing aqueous drainage and/or reducing aqueous production. Treatment regimens vary depending on the individual medications and the clinical response of each individual patient.

It is essential to establish the patient's baseline untreated maximum IOP and then to set a target IOP. This target value is generally set as the pressure at which the rate of loss of ganglion cells is the same as the age-dependent rate of cell loss[4]. Practically, the target pressure is the highest IOP with which there is no progression of clinically detectable glaucomatous optic nerve damage from the physician's perspective (i.e. no optic disc abnormality, no visual field defects) or the patient's perspective (i.e. no noticeable reduction in vision, no impact on daily activities or quality of life)[4]. Some studies aim to reduce IOP to a given value[5,6] or by a given percentage[7], regardless of patient risk factors and baseline pressure. This, however, does not take into account that the risk of nerve damage varies between patients. More recent strategies calculate target pressures based on when other parameters change[8] (e.g. reversal of disc cupping, improvement in visual fields), or the degree of nerve damage at baseline[9] and the number and severity of other non-pressure risk factors[10].

There are five main classes of anti-hypertensive eye drops, which are the prostaglandin analogues, beta-blockers, sympathomimetics (alpha agonists), carbonic anhydrase inhibitors and cholinergics (miotics), as well as combination formulas. There are also new agents emerging, with novel mechanisms of action[11]. According to the UK NICE guidelines for the diagnosis and management of glaucoma[12], generic prostaglandin inhibitors are the first-line for patients with IOP>24mmHg and/or suspected chronic open angle glaucoma (if there is a risk of visual impairment within their lifetime; if not then regular visual assessments are initially advised). For patients who cannot tolerate the first-line treatment, an alternative generic prostaglandin analogue or a beta-blocker are second-line options. If none of the above is tolerated, then third-line options are a non-generic prostaglandin analogue, sympathomimetics, carbonic anhydrase inhibitors, cholinergics, or combination treatments. Combination treatments can also be used when a single agent is unable to achieve the desired IOP reduction.

Prostaglandin analogues are the most commonly used medications for the reduction of ocular hypertension and the treatment of open-angle glaucoma[13,14]. They have a

moderate speed of therapeutic effect, but have a longer duration of effect than other anti-hypertensive agents and so only require once-daily dosing. Formulations of Latanoprost, Bimatoprost and Travoprost are available in generic form. They have an excellent systemic safety profile; however, some ocular side effects still occur[15].

Beta-blockers are the second most commonly used class of topical ocular anti-hypertensives. They were developed in the late 1970s[16,17], with timolol being approved by the FDA in 1978[18]. They have a rapid therapeutic effect, and as a result, are used as the first line in acute closed-angle glaucoma and post-operative ocular hypertension, but as a second line in chronic open angle glaucoma (or first line in patients with contraindications to prostaglandin analogues). All formulations are available in generic form; making them one of the least expensive medications for modulation of IOP. Topical beta-blockers have a better ocular side effect profile than prostaglandin analogues, however, their absorption into the general circulation, via the lacrimal drainage system and conjunctival vasculature[19], causes a variety of systemic side effects. Topical beta-blockers are therefore contraindicated in patients with asthma, chronic obstructive pulmonary disease, poorly controlled congestive cardiac failure, bradycardias, and severe peripheral arterial disease[20].

Carbonic anhydrase inhibitors are another class of topical modulators of IOP. The enzyme carbonic anhydrase catalyzes the conversion of carbon dioxide and water into carbonic acid [21]. The secretion of aqueous humor from the ciliary body epithelium is dependent on carbonic anhydrase. Carbonic anhydrase inhibitors reduce IOP by blocking this process and thereby decreasing the secretion of aqueous humor from the ciliary body into the posterior chamber[22,23]. In 1954, the oral carbonic anhydrase inhibitor Diamox (acetazolamide) was shown to markedly reduce IOP in humans[24]. Systemic acetazolamide reduces the secretion of aqueous humor by around 30%[25]. However, oral carbonic anhydrase inhibitors have a wide range of significant systemic side effects, which limits their long-term use. It was not until the mid-1990s that the first topical carbonic anhydrase inhibitor, dorzolamide hydrochloride (2%) was introduced[22]. Subsequently, Brinzolamide ophthalmic suspension (1%) was developed[26]. Carbonic anhydrase is present in the corneal endothelium. Carbonic anhydrase inhibitors have not been shown to cause any clinically significant change in corneal thickness in subjects with normal corneas, however in subjects with compromised corneas (e.g. in Fuchs' dystrophy, or after complicated cataract surgery), they can result in corneal decompensation that does not necessarily reverse after cessation of treatment[25]. All carbonic anhydrase inhibitors are contraindicated in patients with known sulphonamide allergy. Systemic and topical carbonic anhydrase inhibitors are excreted mainly via the kidneys, and so should be avoided if creatinine clearance < 30 ml/min.

Parasympathomimetics: Pilocarpine is the most commonly prescribed cholinergic; it typically reduces the IOP by 20%–30%. [27] Its mechanism of action is by increasing the uveoscleral outflow, allowing another alternative route for eyes with compromised conventional drainage pathway. It is short-acting, so commonly used before laser treatment, or surgical iridotomy, to stretch the iris and is available in two forms as drops used four times a day or as a 4% gel used once a day [28].

The final major class of medications that modulate IOP are **the alpha-adrenergic agonists**. Previously, non-selective adrenergic agonists were used for the treatment of

glaucoma or ocular hypertension; however, they have been replaced by more selective alpha-2-adrenergic agonists[29]. There are two alpha agonists licensed for use in the modulation of IOP: brimonidine tartrate (0.1%, 0.15%) and Apraclonidine hydrochloride (0.5%, 1%). They have similar efficacy and safety profiles in clinical practice[30]. There are no absolute adult contraindications to the use of topical alpha agonists for ocular hypertension[31]. Alpha agonists may be of therapeutic value in the treatment of glaucoma due to factors additional to their hypotensive effect[32]. Reports of the neuroprotective effect of brimonidine in humans have come from the Low-pressure Glaucoma Treatment Study[33]; however, more large-scale clinical trials are required to investigate these potential neuroprotective effects further.

Osmotic agents

Mannitol 20% (1.0–1.5g/Kg intravenously) and glycerol (1.0–1.5g/Kg orally) are commonly used in controlling acutely raised IOP. Careful assessment of renal and cardiac status must be done before their usage as they increase blood volume and therefore increase cardiac preload. Mannitol may also alter blood glucose levels.

Novel agents are under experimental investigation and may be introduced into clinical practice in the future. Rho kinase (ROCK) is an enzyme expressed in many tissues [34]. It is thought that excess rho kinase activity contributes to cerebral[35] and coronary[36] vasospasm and hypertension[37]. In the early 2000s, Rho kinase inhibitors emerged as a potential new treatment for glaucoma[38]. Ripasudil hydrochloride hydrate (Glanatec ophthalmic solution 0.4%) is a rho kinase inhibitor that was developed and approved for use in the treatment of glaucoma in Japan in 2014[39]. It is administered on a twice-daily regimen[40]. Other Rho Kinase inhibitors are currently being tested[41,42]. All rho kinase inhibitors currently in clinical trials have so far shown promising safety profiles[11].

Similar to other chronic asymptomatic diseases, adherence to eye drop treatment tends to be relatively poor among patients with glaucoma[43]. Only an estimated 60-70% of prescribed eye drop doses are taken by patients with glaucoma[43]. Reasons for poor compliance and adherence to treatment are varied and complex.

Various combination medications are available as an alternative for managing patients whose IOP does not respond to a single agent. Fixed-combination PGA/timolol preparations have been shown to be more effective at reducing IOP than PGA therapy alone[44]. Other fixed combinations are available, which help in improving compliance.

Currently, the use of preservatives in ocular hypotensive formulations is widespread. This most obvious advantage that preservatives confer is a longer shelf-life[45]. Increasingly, the focus is switching to the development of entirely preservative-free formulations. Several prostaglandin analogues, timolol, dorzolamide and several combination agents are now available in preservative-free formulations. Surveys have demonstrated that glaucoma patients on preservative-free drops have fewer symptoms and signs of ocular surface disease, compared to those on preservative-containing drops. Furthermore, the survey found that most of the adverse signs and symptoms induced by preserved drops were reversed after the withdrawal of the preservative-containing agent. [46] However, other studies have demonstrated little or no corneal

damage resulting from a range of concentrations of Benzalkonium chloride (BAK) one of the most common preservatives used in eye drops,[45] and meta-analyses have shown that in patients taking twice the daily dose of BAK, there is no significant increase in corneal staining compared to those on half the dose[47]. Regarding the economic considerations of preservative and preservative-free drops, there have been no studies performed to directly compare the cost-effectiveness of individual medications in their BAK-preserved and preservative-free formulations[45].

The past decade has seen increasing evidence that ocular hypertension, although a feature of many cases of glaucoma is not the primary pathology in the disease, and that neurodegeneration is the fundamental pathological process of glaucomatous disease [48]. Furthermore, studies have demonstrated the similarity between the mechanism of cell death in glaucoma and neurodegenerative diseases such as Alzheimer's Disease [92,93] and Parkinson's Disease[51]. As a result, neuroprotection has become a significant focus of research into both the mechanisms behind glaucoma and new medications[52]. As mentioned previously, brimonidine has also been shown to have a neuroprotective effect[33,53]. Another area of research in neuroprotection in glaucoma is that of glutamate-induced excitotoxicity. Although the results of some studies have been called into question and generated some controversy, glutamate release in the retina has been suggested as one mechanism of retinal ganglion cell death in glaucoma[54–57]. Memantine is the only current glutamate inhibitor in clinical use and has promising neuroprotective effects in acute and chronic animal models of glaucoma[55–58].

Lasers in the reduction of IOP (Table 2)

Lasers can be used in managing glaucoma to lower IOP by increasing aqueous outflow or reducing inflow. The nature of laser delivery can be varied in terms of power, wavelength, treatment area or duration. Laser treatments in glaucoma also vary in the longevity of their action, with some treatments lasting a few years, while others deliver permanent effects. In some cases, the use of laser can be considered a primary treatment, whereas laser procedures also play an essential role in refractory glaucoma.

Increasing outflow: Laser Trabeculoplasty

By directly targeting the trabecular meshwork (TM), aqueous drainage from the eye can be increased in order to lower IOP,[59] even if the mechanisms behind this are not fully understood. Such techniques include argon laser trabeculoplasty (ALT) and the newer selective laser trabeculoplasty (SLT)[60]. ALT is a non-selective treatment proven to be efficacious when compared to topical timolol therapy by the Glaucoma Laser Trial[61]. SLT is a technique described in 1995[62] that selectively targets pigmented TM through which trabecular filtration is thought to occur,[63] while having considerably less effect on the neighbouring non-pigmented cells and structures with lower optical absorption properties[64].

The efficacy of SLT in open-angle glaucoma has been shown to equal that of topical therapies both in terms of percentage IOP reduction and lowering IOP into the 'normal range'[65,66] and has therefore been proposed as a primary treatment [67] eliminating eyedrop adherence issues and the subsequent local and systemic side effects that may occur. One study reported success rates of 63% of early glaucoma patients and in 59%

of advanced patients[68] (success=IOP less than 21mmHg or a greater than 20% IOP reduction) demonstrating the little effect of disease duration or severity on IOP-lowering potential. Peak IOP and IOP fluctuation have also been reported beneficiaries of SLT treatment[69]. As to whether the treatment effect is dose-dependent, the comparison between 180-degree and 360-degree treatments show greater efficacy where a larger proportion of the TM has been treated[70–73] and reduction in inter-visit variability in the 360-degree group[74]. 'Crossover' effects describing enduring IOP reduction in untreated contralateral eyes have been reported[75] and refuted,[76] with contrasting explanations given including increased adherence to drops after laser procedures, or migration of activated macrophages. Whether or not this is an actual biological effect, this has led to the exclusion of other eyes in many of the studies. Another curiosity of SLT efficacy is the observation of additional benefit to those patients who are not using prostaglandin analogue topical therapy[77,78]. However, a larger prospective study refuted this finding, reporting similar efficacy regardless of prostaglandin use[79].

In primary angle closure, a smaller body of evidence suggests SLT may provide an alternative treatment option in order to lower IOP. This can be affected by the obstruction of the trabecular meshwork due to apposition or secondary causes, limiting both access and visualization with laser, and efficacy due to secondary changes seen to occur in the TM microstructure[80,81]. Therefore, eyes with visible or partially visible TM on gonioscopy after peripheral iridotomy have been examined to gauge its efficacy. Studies investigating IOP-lowering in eyes with a patent peripheral iridotomy have reported results of up to 41% mean reduction in IOP[82]. Another group have reported a 4mmHg mean reduction equal to that produced by topical travoprost 0.004% at 6-month follow-up[83]. Importantly for the quality of life, a further study reported a reduction of eyedrop medications with SLT in PACG, with 67% of their patients achieving a minimum of 3mmHg IOP-lowering[84]. In pseudoexfoliation (PXF) syndrome where there is blockage of the trabecular meshwork and Schlemm's canal by exfoliative dandruff-like material, a limited amount of short term studies have reported similar outcomes to those amongst POAG patients,[85,86] as well as when using ALT[87].

SLT has been shown to be non-inferior to ALT by way of meta-analyses[65,88] with the added advantages of being a repeatable treatment. Failure rates two years after therapy have been quoted at around 50%[89] therefore warranting further or repeat treatments. In comparison to ALT where the success rate has been quoted to be around 33% for repeat procedures,[90] SLT fares better in terms of success rates between 36-67% using similar benchmarks[91–94] and time-to-failure analysis[95]. As to the magnitude of the effect of repeated treatments, results are varied with both equal[96] and diminished[95] responses being reported. Tolerability of both SLT and ALT also seems to be equitable, with no significant differences found in rates of anterior chamber flare and IOP spikes between SLT and ALT, although numerically higher in the latter[88].

Quality of life and cost-benefit ratios are both endpoints that are conceivably favored with SLT in comparison to continuing topical therapy. Results so far have reported SLT becoming the cheaper treatment when compared to generic latanoprost in the second year of treatment[97,98]. This effect is seen sooner in comparison to combination therapy, even when two-yearly SLT is factored in. Cost analyses and

quality of life are currently being studied in large prospective studies comparing SLT treatment with topical therapy[99,100] with results yet to be published.

Micropulse laser trabeculoplasty (MLT) is a variant of SLT using a micropulse laser. First described in 2005,[101] MLT is administered using a mirrored lens to deliver pulses of laser treatment 300 μs in duration. When efficacy is compared to SLT, the IOP outcomes are similar. One prospective head-to-head study randomised 69 patients to either 360-degree SLT or MLT. Similar proportions of patients achieved success criteria in both groups, with no significant differences in IOP throughout the yearlong follow-up period. Patients reported less discomfort in the MLT group, but MLT was also associated with a trend towards higher IOPs at all time points (non-statistically significant)[102].

Reducing inflow: Cyclophotocoagulation

Destruction of the ciliary body in order to reduce aqueous production has traditionally been reserved as a last-resort treatment in eyes with advanced disease, owing to the poor side effect profile of early techniques such as cyclodiathermy and cyclocryotherapy including phthisis, uveitis, pain and reduction in vision[103–105]. With time, the technique has adopted new lasers and approaches to improve its safety and tolerability. Transscleral cyclophotocoagulation (TSCPC) is now most commonly applied using a semiconductor diode laser in the near infrared spectrum (810nm) while localizing the ciliary body using scleral transillumination[106]. While still reserved as a treatment for advanced refractory cases, it is a useful tool in achieving substantial IOP lowering effects of more than 15mmHg[107–109] with rates of hypotony, usually defined as chronic IOP less than 5mmHg, quoted at being between 1%-9.5%, especially in patients with neovascular glaucoma and high starting pressures[107,109–112]. This risk is reportedly reduced by using lower energy especially in these high-risk groups[110,113,114] and in those patients where treatment sessions are restricted to under 80J[115]. However, no clear linear relationship between power and rates of hypotony have been seen, except in cases of neovascular glaucoma[110].

An endoscopic variant of cyclophotocoagulation (ECP) has also been developed via a limbal or pars plana approach, first described in 1992[116]. ECP also uses an 810nm diode laser in common with the trans-scleral variant, combined with a xenon light source,[117] a helium-neon laser aiming beam, and an endoscope offering a 110-160 degree field of view. The procedure is usually carried out under subtenon or intracameral anaesthesia with viscoelastic inflating the ciliary sulcus to maximise visualisation of the ciliary processes.

The efficacy of ECP has been compared to non-ECP techniques including TSCPC, cyclocryotherapy and tube surgery in refractory cases[118,119]. A meta-analysis compared six controlled trials (n=429), reporting no significant difference in IOP outcomes between ECP and non-ECP techniques. The average IOP lowering rate amongst ECP was quoted as ranging between 28.8%-49.3%. ECP is now commonly similarly combined with phacoemulsification to minimally invasive glaucoma surgery (MIGS)[120]. As a primary procedure in glaucoma, studies of combined procedures have demonstrated an IOP reduction of 47% lasting a minimum of two years, accompanied by a significant reduction in eyedrop burden[121].

A large-scale report on 5,824 ECP outcomes reported rates of complications including IOP spikes (14.5%), haemorrhage (3.8%), vision loss of more than 2 lines (1.03%), substantial choroidal effusions (0.38%) and retinal detachments (0.27%)[122]. The complication profile of combined phacoemulsification-ECP procedures was also quite similar, including IOP spikes (14.4%), fibrinous uveitis (7.06%), cystoid macular oedema (4.34%), transient hypotony (2.17%), iris bombé (1.08%). It is thought the increased tissue specificity and visible endpoint of the ECP procedure that spares the choroidal circulation and ciliary muscles and allows more accurate quantification of the treatment delivered may be largely protective against post-operative hypotony found in the trans-scleral variant[123]. Mean IOP, the number of drops and visual acuity have all been reported as improved, at 1 year in a retrospective review[124], with 2-year success rates (defined as IOP≤21mmHg) reported at 74%-82% in a different study[119,125]. Although longer-term data are scanty, such results may encourage wider uptake of this procedure as a second-line or primary treatment option, given the favorable safety outcomes.

Micropulse transscleral cyclophotocoagulation (MP-TSCPC) is another variant of cyclophotocoagulation described in 2010[126]. Comparing efficacy between techniques is limited by the definition of 'success' and variations in follow-up duration and frequency. However, in the original MP-TSCPC 2010 case series, mean IOP reduction was quoted as 16% at 18 months with a 'success' rate of 72.7% (IOP 6-21 or 30% reduction in IOP at last follow-up visit)[126]. Another larger randomized study comparing MP-TSCPC with continuous wave TSCPC reported a 45% reduction in mean IOP at 18 months in both groups, including multiple treatments which were required in 46% of eyes in the MP-TSCPC group and 58% of eyes in the continuous wave group[127]. Furthermore, no difference in eyedrop requirements was found between the two groups after both MP-TSCPC and continuous wave TSCPC. Other studies have reported very similar rates[128,129]. In terms of complications, most reports favour MP-TSCPC, with no hypotony observed with MP-TSCPC in several studies[126,127,130]. One study reported 46% of eyes after MP-TSCPC having ongoing anterior chamber inflammation 3 months after the procedure[128]. However, the incidence of this complication is still reportedly reduced in MP-TSCPC (4% vs 30%) when compared with continuous wave TSCPC[127]. As with all types of cyclophotocoagulation, further studies are needed to extensively stratify patients according to energy and glaucoma type to definitively decide which factors are more predictive of poor outcomes.

Surgery for lowering the IOP (Table 3)

When all non-surgical therapies have been exhausted glaucoma filtration surgeries, trabeculectomy (trab) and tube shunts, are the most common second-line therapy[131].

Trabeculectomy

First described in 1968 by Cairns and Watson, trabeculectomy remains the gold-standard surgery[132] and is the most widely performed[133] followed closely by tube shunt procedures[131].

Traditional trabeculectomy has been associated with vision-threatening complications

such as hypotony (early) and endophthalmitis (early, late). Long-term complications such as bleb leak or failure due to fibrosis of the subconjunctival tissue around the bleb and scleral flap can also happen[131,134]. Patients at high risk for trabeculectomy failure may be younger, African ethnic origin[135], previous ocular surgeries such as cataracts, pre-operative IOP greater than 20mmHg[134], uveitic glaucoma, aphakic, pseudoexfoliation, advanced visual field (VF) loss at time of surgery or prolonged exposure to eye drops[136–138]. Scarring (fibrosis) is the primary cause of postoperative failure and can arise during the first weeks to months following surgery. Fibrosis occurs at the site of the new conduit or the scleral flap[139] resulting in reduced aqueous humor outflow in the filtration path potentially leading to uncontrolled IOPs.

Multiple studies have cited a higher risk of cataracts 5 to 11 years after trabeculectomy with and without anti-fibrotic use. [140–143] The Collaborative Initial Glaucoma Treatment (CIGTS) study found that patients who underwent initial trabeculectomy were at higher risk of cataract extraction compared to medicated patients during the first 5 years after treatment, however after 5 years, the risk did not continue to differ significantly[144]. The Advanced Glaucoma Intervention Study (AGIS) described a similar finding with a 78% increased risk of developing cataracts after initial trabeculectomy[142].

To maximise the benefits of trabeculectomy while minimising the risk of adverse events, several variations and modifications of the procedure have been developed[145–147]. The Moorfield's Safer Surgery System was developed as a simplified method using minimal materials, providing a more efficient, consistent and effective approach[139]. This method comprised of 'best practices' includes cordoning off surgery to the superior half of the globe to reduce inflammation and endophthalmitis, using a corneal traction suture to reduce the risk of haematoma and performing a fornix-based conjunctival flap to achieve a more diffuse bleb[148].

Antimetabolites

Antimetabolites such as 5-fluorouracil (5-FU) and mitomycin-C (MMC) were developed to inhibit fibrosis and are routinely administered either topically to the sclera at the site of the future ostomy or pre-operatively injected into the sub-tenon space and patients at higher risk of trabeculectomy failure may require higher concentrations or more extended exposure[131]. However, due to fibroblast cell inhibition, the conjunctiva covering the sclera may become thin, leading to a greater outflow of aqueous humor or the drug may have a toxic effect on the epithelium and reduce production of aqueous humor, both resulting in hypotony. Over time, holes may form in the conjunctiva permitting bacteria into the eye resulting in endophthalmitis[149]. Several systematic reviews and meta-analyses have explored the use of anti-metabolites paired with trabeculectomy during and post procedure[149,150]. A Cochrane systematic review and meta-analysis of 11 RCTs (n=698 patients) assessed the effects of intraoperative MMC compared to placebo in three groups of patients (patients at high risk of trab failure patients with no previous surgical intervention, and patients who underwent trab with cataract surgery) at 12 months[149]. Mean IOP was significantly reduced in MMC compared to placebo in the three groups of patients measured. When comparing the efficacy of IOP lowering power of MMC to 5-FU, one systematic review (11 trials, n=687 eyes) reported patients treated with MMC demonstrated lower IOP, however, the quality of evidence

was low due to high risk of selection bias and findings being inconsistent [151]. Green et al. (12 trials, n=1319 patients) assessed the effects of 5-FU administered intra and postoperatively at 12 months demonstrating results favoring 5-FU to placebo in patients with high risk of failure and primary trabeculectomy groups, yet no significant difference between 5-FU and controls in the combined surgery group[152]. Additionally, postoperative 5-FU in primary trabeculectomy reduced IOP greater than intraoperative administration

Anti-inflammatories

Anti-inflammatories such as corticosteroids and non-steroidal anti-inflammatories (NSAIDs) have also been used to reduce the production of inflammatory mediators in the inflammatory phase of wound healing[153]. However, corticosteroids have been associated with an increased risk of cataracts and increasing IOP after surgery. NSAIDs have not been associated with these risks, yet there is more evidence pointing to lower the effectiveness of NSAIDs compared to corticosteroids[154]. In a three-armed RCT, Breusegem et al. investigated the preoperative use of self-administered topical ketorolac versus fluorometholone versus placebo eye drops; results indicated that anti-inflammatories, notably steroids, may be an effective additive at decreasing the incidence of bleb failure leading to more stable IOPs[155].

Comparing steroids to placebo, Starita et al. reported that patients (n=52 eyes) who used topical prednisolone 1% for 3 weeks postoperatively had significantly lower IOP at 20 weeks follow-up[156]. When comparing postoperative topical steroids to combined topical and 50mg oral prednisolone, Azuara-Blanco et al. reported no statistically significant difference in IOP between the groups in 35 patients at 12 months[157].

Anti-VEGF

More recently, anti-vascular endothelial growth factor (anti-VEGF) drugs have been employed as a potential wound modulator. VEGF, a signal protein that stimulates the formation of new blood vessels (angiogenesis), is present during the proliferative phase, so it is thought that inhibiting this factor would reduce scar formation[158,159]. Bevacizumab has been injected via the subconjunctival route after needling revision[160,161] and preoperatively injected intravitreally resulting in functioning blebs and stable IOPs at 6 months[162,163]. Although promising initial results, more studies are needed with larger sample sizes, control arms and longer follow-up time to confirm long-term safety and efficacy[153].

Releasable sutures

To prevent hypotony, a technique using releasable sutures to close the scleral flap that can be removed to allow greater outflow of aqueous humor was developed[164]. A meta-analysis synthesizing results from 6 RCTs (n=296 eyes) comparing trabeculectomy with and without releasable sutures reported trabeculectomies with releasable sutures were associated with greater efficacy of lowering IOP compared to without releasable sutures[165]. However, the various studies reported inconsistent rates of complications and small sample sizes hampering the ability to draw strong conclusions for clinical practice.

Tubes

In cases where trabeculectomy fails or will likely fail, tube shunts may be indicated [166]. The non-valved Molteno implant was the first commercially available tube implant; however, currently, the most commonly used shunts are the valved Ahmed implant and non-valved Baerveldt implant[167]. Valved shunts limit the flow of aqueous humor in the outgoing direction, thus theoretically preventing hypotony; however, antiglaucomatous eye drops are still required for many patients with the Ahmed valve.

Most evidence points to comparable efficacy of both Baerveldt and Ahmed shunts with a lean towards better IOP control and fewer side effects with the Baerveldt[167,168]. A Cochrane systematic review of RCTs by Tseng et al. compared the different tubes. One trial (n=57) comparing Ahmed to Molteno found higher mean IOP in the Ahmed group at 24 months. Similarly, two trials (combined n=464) compared the Ahmed to the Baerveldt implant, and both found a higher mean IOP in the Ahmed group at 12 months follow-up[167]. One of these studies, the Ahmed Versus Baerveldt (AVB) trial continued to demonstrate superior ($P<0.001$) mean IOP reduction in the Baerveldt group (13.2±4.7mmHg) compared to the Ahmed group (15.8±5.2mmHg) at 5 years. However, the Baerveldt shunt resulted in more serious early complications[168]. Finally, a systematic review of 5 systematic reviews including patients with various types of glaucoma including POAG, closed-angle, neovascular, uveitic and congenital, observed moderate evidence that Baerveldt achieves a greater IOP reduction compared to Ahmed and requires fewer re-interventions[169]. These results suggest that the Baerveldt implant could be more effective at moderating IOP compared to the Ahmed, yet is associated with a higher risk of complications.

Trabs vs tubes

Multiple studies have compared trabeculectomies versus various tubes with comparable IOP reduction between the two therapies. A systematic review of 6 controlled trials comparing the Ahmed valve implant to trabeculectomy reported that Ahmed was comparable to trabeculectomy in IOP reduction, yet Ahmed was associated with a lower frequency of adverse events[170]. Two RCTs comparing the Baerveldt to trabeculectomy yielded similar results; however, Baerveldt required significantly more antiglaucomatous medication and had a higher complication rate[171]. This similarity carried over time in the Tube Versus Trabeculectomy (TVT) study (n=212 eyes) which demonstrated comparable mean IOPs between Baerveldt (14.4±6.9mmHg) and trabeculectomy (12.6±5.9mmHg) groups ($p=0.12$) and a similar need for antiglaucomatous medication at 5 years follow-up[172]. However, in this study, an essential inclusion criterion was that all study eyes must have either undergone previous cataract extraction with intraocular lens implantation, trabeculectomy or both, therefore not all trabeculectomies were primary trabs, which could explain the lack of significant difference between the two groups[173]. To clarify this relationship, the Primary Tube Versus Trabeculectomy (PTVT) study reported a statistically significantly lower mean IOP in primary trabeculectomy (12.4±4.4mmHg) compared to Baerveldt (13.8±4.1mmHg) at one year ($p=0.01$)[174].

Non-penetrating glaucoma surgery (NPGS)

Examples of these procedures are deep sclerectomy and viscocanalostomy procedures. Several randomised controlled trials (RCTs) suggested an improved safety profile, but

there is still no consensus about their efficacy when compared to trabeculectomy [175–180].

Deep sclerectomy (DS):
A prospective study by Dahan et al. that included 43 eyes and followed patients for 30 months, reported a 50% mean drop in IOP, with success rates of 61.4% at 21 months, 36.6% at 24 months, and 18.9% at 30 months [181].
Antimetabolites and implants use are suggested to improve the success rate[182,183]. However, the evidence is inconclusive as some comparative studies did not report a significant difference regarding success rates[182,184,185]. 5FU and MMC have been both used in studies to assess their effect in improving the success rate [184–186].

Viscocanalostomy
It aims to improve aqueous drainage by injecting high viscosity sodium hyaluronate into Schlemm's canal [187].
Several studies demonstrated the improved safety profile of augmented viscocanalostomy in comparison to MMC augmented trabeculectomy, but failed to prove similar efficacy between the two procedures [175–179,188,189].

Express shunt (Alcon Laboratories, Inc., Fort Worth, TX)
Several randomized trials have compared EX-PRESS to trabeculectomy [190–193]; however, only one study (n=78 patients) reported statistically significant long-term IOP reduction with EX-PRESS[194,195]. Compared to trabeculectomy (50.0%), EX-PRESS (76.9%) provided better (*P*=0.0193) IOP control, meaning patients required fewer antiglaucomatous medications and surgical interventions[194], especially in the first 3 years, however, the difference in IOP control did not remain significant at 5 years follow-up[195].

Minimally invasive glaucoma surgery (MIGS) and IOP (Tables 4,5)

Minimally invasive glaucoma surgeries (MIGS) are perceived as less traumatic surgical interventions for patients with mild to moderate glaucoma, for those seeking less dependence on drop treatment, or are intolerant to standard medical therapy[196]. The commonly accepted definition is that MIGS are procedures in which implantation of a surgical device with the intention of lowering IOP is performed, this is achieved via an outflow mechanism with either an ab interno or ab externo approach, minimal trauma with very little or no scleral dissection, minimal or no conjunctival manipulation, good safety profile and rapid recovery[197].
MIGS devices can be trabecular, suprachoroidal and subconjunctival interventions[197], that can be performed with cataract surgery or as a stand-alone procedure[198].

TRABECULAR MESHWORK BYPASS STENTS
These include iStent, iStent inject, and Hydrus, They allow the flow of aqueous from the anterior chamber to Schlemm's canal, but have the limitation that the IOP cannot fall below the episcleral vien pressure.

iStent

The iStent Study Group[199], is an RCT conducted by Carven et al., which compared cataract surgery to cataract surgery and one iStent. In the iStent study arm, IOP was <21mmHg with no medications in 61% of patients at 24 months, compared to 50% in the cataract only group, which was statistically significant (P=0.036). There was a statistically significant mean decrease in medications in the combined group, compared to the cataract surgery group at 12 months, that continued to appear at 24 months, but was no longer statistically significant.

The use of iStent for advanced cases has been studied by Neuhann, including cases with previous drainage procedures and follow up of 36 month[200]. In the analysis of the cohorts, the mean IOP was 15.4±2.2mmHg in eyes that had no previous intervention, with 13% were on IOP medications, compared to 14.2±2.3mmHg mean IOP in cases that had previous surgery, with 44% of the eyes were on IOP medications. Lower IOP threshold was needed in eye with prior glaucoma surgery. In the group with no previous glaucoma surgery, there was a 34% reduction in mean IOP and 93% reduction in the mean number of medications.

Using multiple implants as a stand-alone procedure was studied by Katz et al., and was shown to enhance the IOP reduction, with further reduction in IOP with additional stents (p=0.001). The mean unmedicated IOP was found to be 15.9±0.9mmHg, 14.1±1.0mmHg, and 12.2±1.1mmHg with one, two, and three stents respectively at 18 months of follow-up [201]. This was the motivation behind the development of a second-generation iStent, the iStent Inject, which consists of two preloaded stents

Istent inject was studied by Voskanyan et al. showing that implantation of this device resulted in IOP ≤18mmHg in 66%, and 81% of cases without medications, and with medications respectively, at 12 months, with an encouraging safety profile[202].

Hydrus

An RCT conducted by Pfeiffer et al. that followed 100 eyes for 24 months had compared cataract surgery alone versus combined cataract surgery and Hydrus stent and had shown a significant increase in cases reached 20% reduction in diurnal IOP in the combined surgery group (80% in combined group vs. 46% in cataract only group) (p=0.0008). It also showed a significant lower IOP (p=0.0093), and a significantly less number of patients on IOP medications (p=0.0008) in the combined surgery group [203]. In terms of safety, both groups showed a similar safety profile. Focal peripheral anterior synechiae developed in six (12%) patients, and commonly situated near the inlet of the device, however, it did not affect the efficacy of the device.

SUPRACHOROIDAL IMPLANTS

This includes CyPass, iStent supra, and the SOLX Gold micro shunt.

No published data were found on the iStent supra (ab interno) and the SOLX Gold micro shunt (ab externo) at the time of this review.

The CyPass

Several studies had assessed CyPass efficacy and safety profile, whether implanted during cataract surgery or as a separate procedure.

Combined CyPass insertion and cataract extraction with IOL implantation (CE/IOL)

The COMPASS Trial considered as the primary study to assess CyPass efficacy and safety profile, it is an RCT that compared CE/IOL+CyPass to CE/ IOL alone in 505 eyes, with 2 years of follow-up[204]. IOP showed a reduction of 7.4mmHg and 5.4mmHg in the microstent arm, and the control arm respectively ($p<0.001$). 85% eyes of the stent arm remained drop-free at 24 months. It also demonstrated an excellent safety profile with no vision-threatening adverse events in the CyPass group at 24 months.

In early September, Alcon announced the voluntary global market withdrawal of the CyPass micro stent due to concerns of progressive endothelial cell loss (ECL), due to results from the COMPASS-XT trial which is 3 years extension of Alcon's 2 years COMPASS trial, showing a significant ECL (>30%) in the combined group versus the control group[205].

Other smaller scale studies that looked into the efficacy and possible complications of cypass+CE/IOL includes the multicentre prospective study conducted by Hoeh et al. which included 57 uncontrolled POAG patients and 41 controlled POAG patients undergoing CyPass+CE/IOL and showed good safety profile. It demonstrated a statistically significant reduction in mean IOP and medications with 37% reduction in IOP and 50% reduction in medications in the uncontrolled group at 6 months. While the IOP remained controlled below 21mmHg, there was 71.4% reduction in medications ($p<0.001$) in the controlled group [206]. No series adverse events were found, with transient hypotony being the commonest to occur.

Höh et al. studied the efficacy and safety of combined CyPass+CE/IOL in 136 eyes including controlled, and controlled cohorts. Patients were followed for 2 years [207]. No sight-threatening adverse events were seen in any of the remaining 82 subjects at the end of the study, with transient hypotony (15.4%) and micro stent obstruction (8.8%) being considered the most common complications seen. Further glaucoma surgery was needed in fifteen eyes (11%). The mean IOP in the uncontrolled group (n=23) was found significantly lower ($p<0.0001$) at months 6, 12, and 24. A statistically significant reduction of the mean IOP from baseline was seen at months 6 ($p=0.0188$) and 12 ($p=0.0356$) in the controlled group (n=59). The mean decrease of IOP medications from baseline was found statistically significant in both groups at all points of the study.

CyPass stand-alone implantation

García-Feijoo et al. followed 60 eyes that underwent stand-alone CyPass implantation for 1 year, and included eyes with OAG and uncontrolled IOP (>21mmHg) on topical therapy [208]. IOP showed a 34.7% reduction, IOP medications were reduced from 2.2±1.1 medications to 1.4±1.3 medications at 12 months. Most common adverse events included IOP spikes to >30mmHg that lasted beyond 1 month in 11% of cases; cataract progression, that was seen in 12.2% of the cases at 12 months; hyphaema that

occurred in 6% and resolved by the first month. In eyes that were indicated to secondary glaucoma surgical intervention, further glaucoma surgery was successfully avoided in 83% of eyes.

A study was being conducted to assess the safety and effectiveness of the use of visco-assisted CyPass Micro-Stent implantation for the lowering of intraocular pressure in subjects who have open angle glaucoma (Viscopass). It describes injecting 60 µL of an ophthalmic viscosurgical device (OVD) at the end of the lumen. However, no published results were found.

SUBCONJUNCTIVAL FILTRATION

They are similar to traditional trabeculectomy and aqueous shunt surgery, hence requiring subconjunctival MMC injection pre-insertion to optimize bleb function and survival.

XEN implant

It is an ab interno porcine gelatin stent, which was shown that it does not get occluded, and does not cause a tissue reaction in the eye [209] and is implanted via a clear corneal incision, avoiding conjunctival dissection.

One of the earliest studies investigating Cataract surgery combined with the insertion of a XEN implant (the 63 or 140 model) without using MMC, demonstrated a significant reduction in IOP with a qualified success of 85.3% and a complete success rate off medications of 47.1% [210].

In another study implanting XEN 140 model + MMC as a stand-alone procedure (n=49 eyes) and including cases with previously failed trabeculectomy, Sheybani et al. demonstrated a 36.4% reduction in IOP from baseline at 12 months, with 40% complete success, while 89% qualified success [211]. No serious adverse events were found in the study.

Bleb needling remains the most common complication of Xen implant, with 44.1% reported to require bleb needling with MMC or surgical revision in a recent study, this; however, did not affect success rate at 12 months [212]. This compares to a 14% needling rate in the trabeculectomy arm of the Primary Tube Versus Trabeculectomy Study. Postoperative loss of IOP control due to subconjunctival fibrosis is more common in Xen stent compared to trab despite less conjunctical dissection[174].

InnFocus

It is an ab externo drainage device, which resembles the trabeculectomy in the steps of surgery, and is considered more invasive than other MIGS. In a study, which included combined and stand-alone cases of micro shunt and MMC, 80% had IOP ≤14mmHg at 3 years. At 3 years, the mean IOP was 10.7±1.5mmHg; with 95 % qualified success

rate and a reduction in medications from 2.6±0.9 to 0.8±1.2[213]. Transient hypotony and choroidal effusion were the most frequent adverse effects, and they spontaneously resolved. No long-term serious adverse events were reported.

Summary:

Glaucoma is a disease characterized by optic neuropathy defined by characteristic optic disc damage and visual field loss for which intraocular pressure (IOP) is a major modifiable risk factor. Lowering the IOP remains the mainstay treatment to stop the progression of glaucoma. Different modalities can be used to achieve this including IOP lowering medications, laser, and surgeries. Nowadays, minimally invasive glaucoma surgeries and newer lasers are becoming more popular due to their safety profile, and their efficacy, allowing the patients to be less dependent on life long medications and substituting more invasive procedures as trabeculectomy, and shunt operations. This review will go through the different ways used to lower the IOP, and the newest techniques, and modalities used to achieve this.

Keywords:

Intraocular pressure, neuroprotective, laser trabeculoplasty, cyclophotocoagulation, trabeculectomy, shunt procedure, non-penetrating glaucoma procedures, minimally invasive glaucoma procedures.

Expert Commentary:

Lowering the intraocular pressure remains the mainstay treatment for glaucoma, with increasing evidence of neuroprotection rather than decreasing the intraocular pressure, which is of particular importance in normal tension glaucoma, and in cases that continue to progress despite achieving target intraocular pressure. The use of preservative-free agents and combinations can help increase compliance with drops.
Laser procedures continue to gain popularity as being a non-invasive, safe, and effective way to control the intraocular pressure, with the newer laser (Selective laser trabeculoplasty, micropulse cyclophotocoagulation, endoscopic cyclophotocoagulation) developed that can be used as the first line of treatment, with minimal damage that allows repeated treatments. Some can be done with cataract surgery (endoscopic cyclophotocoagulation), mimicking minimally invasive glaucoma procedures.
Surgical intervention remains the gold standard for refractory cases, including trabeculectomy, and shunt procedures, with the introduction of non-penetrating glaucoma procedures which allows for less side effect profile.
The use of antimetabolites, anti-inflammatories and antivascular endothelial growth factors allows for better success rate.
Minimally invasive glaucoma procedures are considered the newest modality to control the intraocular pressure, which can be done alone or with cataract surgery. Various devices are described, which shows promising success, and good safety profile, but larger randomized control trials are needed with longer follow-up.

Five-year view:

The authors of this review believe that in five-years time lasers and minimally invasive glaucoma procedures will replace eye drops, and surgeries like trabeculectomy, and shunt procedures.
New minimally invasive glaucoma devices will emerge, and the existing ones will have better success and safety profile.
Neuroprotective medications will gain more popularity, in preventing ganglion cell death in high-risk individuals.

Key issues:

- Intraocular pressure lowering drops remains the first line of treatment of newly diagnosed glaucoma patient
- Preservative-free agents and combination medications are gaining popularity
- Neuroprotective drugs are a new group of medications, which shows some hope.
- Selective laser trabeculoplasty is a safe alternative as a first line treatment in cases of open-angle closure, which shows good efficacy and safety.
- Endoscopic cyclophotocoagulation is an option to decrease the intraocular pressure, which can be combined with cataract surgery.
- Trabeculectomy and shunt procedures remain the mainstay for refractory glaucoma cases.
- Minimally invasive glaucoma procedures are a popular alternative to control the intraocular pressure, and decrease drop dependence.

References:

[1] Quigley HA. Number of people with glaucoma worldwide. Br. J. Ophthalmol. [Internet]. 1996 [cited 2018 Nov 4];80:389–393. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8695555.

[2] Quigley HA, Vitale S. Models of open-angle glaucoma prevalence and incidence in the United States. Invest. Ophthalmol. Vis. Sci. [Internet]. 1997 [cited 2018 Nov 4];38:83–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9008633.

[3] Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br. J. Ophthalmol. [Internet]. 2006 [cited 2018 Nov 4];90:262–267. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16488940.

[4] Jampel HD. Target Pressure in Glaucoma Therapy. J. Glaucoma. 1997. p. 133–136.

[5] Fluorouracil T, Surgery F, Group S. Fluorouracil Filtering Surgery Study One-Year Follow-up. Am. J. Ophthalmol. 2018;186:xxxiii–xlii.

[6] Glaucoma Laser Trial Research Group. The Glaucoma Laser Trial (GLT) and Glaucoma Laser Trial Follow-up Study: 7. Results. Am. J. Ophthalmol. 1995;120:718–731.

[7] Gordon MO, Beiser JA, Brandt JD, et al. The Ocular Hypertension Treatment Study. 2002;120.

[8] Jay Katz L, Spaeth G, Cantor L, et al. Reversible Optic Disk Cupping and Visual Field Improvement in Adults With Glaucoma. Am. J. Ophthalmol. 1989.

[9] Anderson DR. Glaucoma: the Damage Caused by Pressure xlvi Edward Jackson Memorial Lecture. Am. J. Ophthalmol. 1989;108:485–495.

[10] Hodapp E, Parrish RK, Anderson DR. Clinical decisions in glaucoma. Mosby; 1993.

[11] Wang SK, Chang RT. An emerging treatment option for glaucoma: Rho kinase inhibitors. Clin. Ophthalmol. 2014;8:883–890.

[12] Centre NG. Glaucoma : diagnosis and management. 2017;1–41.

[13] Golan S, Rosenfeld E, Shemesh G, et al. Original and generic latanoprost for the treatment of glaucoma and ocular hypertension: Are they really the same? Clin. Exp. Pharmacol. Physiol. 2015;42:220–224.

[14] Doucette LP, Walter MA. Prostaglandins in the eye: Function, expression, and roles in glaucoma. Ophthalmic Genet. 2017;38:108–116.

[15] Alm A, Grierson I, Shields MB. Side Effects Associated with Prostaglandin Analog Therapy. Surv. Ophthalmol. 2008;53:93–105.

[16] TJ Z, HE K. Timolol: Dose response and duration of action. Arch. Ophthalmol. 1977;95:605–607.

[17] Katz IM, Hubbard WA, Getson AJ, et al. Intraocular pressure decrease in normal volunteers following timolol ophthalmic solution. Invest. Ophthalmol. Vis. Sci. 1976;15:489.

[18] Realini T. A history of glaucoma pharmacology. Optom. Vis. Sci. 2011;88:36–38.

[19] Shields MB. Textbook of Glaucoma - 2nd Edition. 2nd ed. Baltimore: Lippincott Williams & Wilkins; 1987.

[20] BNF. BETA-ADRENOCEPTOR BLOCKERS (SYSTEMIC): Contraindications.

[21] Lindskog S. Structure and mechanism of carbonic anhydrase. Pharmacol. Ther. 1997;74:1–20.

[22] F. Sugrue M. Pharmacological and ocular hypotensive properties of topical carbonic anhydrase inhibitors. Prog. Retin. Eye Res. 2000.

[23] H Maren T. The rates of movement of Na+, Cl-, and HCO-3 from plasma to posterior chamber: effect of acetazolamide and relation to the treatment of glaucoma. Invest. Ophthalmol. 1976.

[24] Becker B. Decrease in Intraocular Pressure in Man by a Carbonic Anhydrase Inhibitor, Diamox*: A Preliminary Report. Am. J. Ophthalmol. 1954;37:13–15.

[25] Holló G. The use of topical carbonic anhydrase inhibitors in glaucoma treatment. In: Orgul S, Flamer J editors., editor. Pharmacother. glaucoma. Bern: Hans Huber

Verlag; 2000. p. 145–152.
[26] H Silver L. Brinzolamide Primary Therapy Study Group. Clinical efficacy and safety of brinzolamide (Azopt), a new topical carbonic anhydrase inhibitor for primary open-angle glaucoma and ocular hypertension. Am. J. Ophthalmol. 1998.
[27] Yoles E, Wheeler LA, Schwartz M. Alpha2-adrenoreceptor agonists are neuroprotective in a rat model of optic nerve degeneration. Invest. Ophthalmol. Vis. Sci. [Internet]. 1999 [cited 2019 Jan 15];40:65–73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9888428.
[28] Crawford K, Kaufman PL. Pilocarpine antagonizes prostaglandin F2 alpha-induced ocular hypotension in monkeys. Evidence for enhancement of Uveoscleral outflow by prostaglandin F2 alpha. Arch. Ophthalmol. (Chicago, Ill. 1960) [Internet]. 1987 [cited 2019 Jan 15];105:1112–1116. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3477218.
[29] Arthur S, Cantor LB. Update on the role of alpha-agonists in glaucoma management. Exp. Eye Res. 2011;93:271–283.
[30] Chen TC. Brimonidine 0.15% versus apraclonidine 0.5% for prevention of intraocular pressure elevation after anterior segment laser surgery. J. Cataract Refract. Surg. 2005;31:1707–1712.
[31] BNF. BNF. BRIMONIDINE TARTRATE: Side effects and contraindications.
[32] M S, LK M, AR H, et al. Experimental and clinical evidence for brimonidine as an optic nerve and retinal neuroprotective agent: An evidence-based review. Arch. Ophthalmol. 2009;127:402–406.
[33] Krupin T, Liebmann JM, Greenfield DS, et al. A Randomized Trial of Brimonidine Versus Timolol in Preserving Visual Function: Results From the Low-pressure Glaucoma Treatment Study. Am. J. Ophthalmol. [Internet]. 2011 [cited 2018 Nov 4];151:671–681. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0002939410007713.
[34] Wei L, Roberts W, Wang L, et al. Rho kinases play an obligatory role in vertebrate embryonic organogenesis. Development. 2001;128:2953–2962.
[35] Sato M, Tani E, Fujikawa H, et al. Involvement of Rho-kinase-mediated phosphorylation of myosin light chain in enhancement of cerebral vasospasm. Circ. Res. 2000;87:195–200.
[36] Masumoto A, Mohri M, Shimokawa H, et al. Suppression of coronary artery spasm by the Rho-kinase inhibitor fasudil in patients with vasospastic angina. Circulation. 2002;105:1545–1547.
[37] Masumoto A, Hirooka Y, Shimokawa H, et al. Possible involvement of Rho-kinase in the pathogenesis of hypertension in humans. Hypertens. (Dallas, Tex. 1979). 2001;38:1307–1310.
[38] P Rao V, Epstein D. Rho GTPase/Rho Kinase Inhibition as a Novel Target for the Treatment of Glaucoma. BioDrugs. 2007.
[39] Garnock-jones KP. Ripasudil : First Global Approval. 2014;2211–2215.
[40] Institute. DWT. DWTI announces the acqui- sition of marketing approval in japan for a drug for treating glaucoma and ocular hypertension, K-115 [media release].
[41] Kopczynski C, Lin C-W, deLong M, et al. IOP-lowering Efficacy And Tolerability Of AR-13324, A Dual Mechanism Kinase Inhibitor For The Treatment Of Glaucoma. Invest. Ophthalmol. Vis. Sci. 2012;53:5080.
[42] Zhang K, Zhang L, Weinreb RN. Ophthalmic drug discovery: novel targets and mechanisms for retinal diseases and glaucoma. Nat. Rev. Drug Discov. 2012;11:541.
[43] Friedman DS, Quigley HA, Gelb L, et al. Using pharmacy claims data to study adherence to glaucoma medications: Methodology and findings of the Glaucoma Adherence and Persistency Study (GAPS). Investig. Ophthalmol. Vis. Sci. 2007;48:5052–5057.
[44] Inoue K, Masumoto M, Ishida K, et al. Efficacy and Safety of Switching from

Prostaglandin Analog Therapy to Prostaglandin / Timolol Fixed Combination or Prostaglandin / Brimonidine Therapy. Open Ophthalmol. J. [Internet]. 2017 [cited 2019 Jan 9];11:156–163. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28761569.

[45] Steven DW, Alaghband P, Lim KS. Preservatives in glaucoma medication. Br. J. Ophthalmol. [Internet]. 2018 [cited 2018 Nov 4];102:1497–1503. Available from: http://bjo.bmj.com/lookup/doi/10.1136/bjophthalmol-2017-311544.

[46] Pisella PJ, Pouliquen P, Baudouin C. Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. Br. J. Ophthalmol. [Internet]. 2002 [cited 2018 Nov 4];86:418–423. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11914211.

[47] Trocme S, Hwang L-J, Bean GW, et al. The role of benzalkonium chloride in the occurrence of punctate keratitis: a meta-analysis of randomized, controlled clinical trials. Ann. Pharmacother. [Internet]. 2010 [cited 2018 Nov 4];44:1914–1921. Available from: http://journals.sagepub.com/doi/10.1345/aph.1P268.

[48] Chang EE, Goldberg JL. Glaucoma 2.0: neuroprotection, neuroregeneration, neuroenhancement. Ophthalmology [Internet]. 2012 [cited 2018 Nov 4];119:979–986. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0161642011010499.

[49] Ou Y, Grossman DS, Lee PP, et al. Glaucoma, Alzheimer disease and other dementia: a longitudinal analysis. Ophthalmic Epidemiol. [Internet]. 2012 [cited 2018 Nov 4];19:285–292. Available from: http://www.tandfonline.com/doi/full/10.3109/09286586.2011.649228.

[50] Guo L, Salt TE, Luong V, et al. Targeting amyloid-beta in glaucoma treatment. Proc. Natl. Acad. Sci. U. S. A. [Internet]. 2007 [cited 2018 Nov 4];104:13444–13449. Available from: http://www.pnas.org/cgi/doi/10.1073/pnas.0703707104.

[51] Bayer AU, Keller ON, Ferrari F, et al. Association of glaucoma with neurodegenerative diseases with apoptotic cell death: Alzheimer's disease and Parkinson's disease. Am. J. Ophthalmol. [Internet]. 2002 [cited 2018 Nov 4];133:135–137. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11755850.

[52] Cheung W, Guo L, Cordeiro MF. Neuroprotection in glaucoma: drug-based approaches. Optom. Vis. Sci. [Internet]. 2008 [cited 2018 Nov 4];85:406–416. Available from: https://insights.ovid.com/crossref?an=00006324-200806000-00011.

[53] WoldeMussie E, Ruiz G, Wijono M, et al. Neuroprotection of retinal ganglion cells by brimonidine in rats with laser-induced chronic ocular hypertension. Invest. Ophthalmol. Vis. Sci. [Internet]. 2001 [cited 2018 Nov 4];42:2849–2855. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11687528.

[54] Dreyer EB, Zurakowski D, Schumer RA, et al. Elevated glutamate levels in the vitreous body of humans and monkeys with glaucoma. Arch. Ophthalmol. (Chicago, Ill. 1960) [Internet]. 1996 [cited 2018 Nov 4];114:299–305. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8600890.

[55] Guo L, Salt TE, Maass A, et al. Assessment of neuroprotective effects of glutamate modulation on glaucoma-related retinal ganglion cell apoptosis in vivo. Invest. Ophthalmol. Vis. Sci. [Internet]. 2006 [cited 2018 Nov 4];47:626–633. Available from: http://iovs.arvojournals.org/article.aspx?doi=10.1167/iovs.05-0754.

[56] WoldeMussie E, Yoles E, Schwartz M, et al. Neuroprotective effect of memantine in different retinal injury models in rats. J. Glaucoma [Internet]. 2002 [cited 2018 Nov 4];11:474–480. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12483089.

[57] Hare WA, WoldeMussie E, Weinreb RN, et al. Efficacy and safety of memantine treatment for reduction of changes associated with experimental glaucoma in monkey, II: Structural measures. Invest. Ophthalmol. Vis. Sci. [Internet]. 2004

[cited 2018 Nov 4];45:2640–2651. Available from: http://iovs.arvojournals.org/article.aspx?doi=10.1167/iovs.03-0567.

[58] Lipton SA. Possible role for memantine in protecting retinal ganglion cells from glaucomatous damage. Surv. Ophthalmol. [Internet]. 2003 [cited 2018 Nov 4];48 Suppl 1:S38-46. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12852433.

[59] Weinreb RN, Khaw PT. Primary open-angle glaucoma. Lancet (London, England) [Internet]. 2004 [cited 2018 Nov 4];363:1711–1720. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0140673604162570.

[60] Wise JB, Witter SL. Argon laser therapy for open-angle glaucoma. A pilot study. Arch. Ophthalmol. (Chicago, Ill. 1960) [Internet]. 1979 [cited 2018 Nov 4];97:319–322. Available from: http://www.ncbi.nlm.nih.gov/pubmed/575877.

[61] The Glaucoma Laser Trial (GLT). 2. Results of argon laser trabeculoplasty versus topical medicines. The Glaucoma Laser Trial Research Group. Ophthalmology [Internet]. 1990 [cited 2018 Nov 4];97:1403–1413. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2255512.

[62] Latina MA, Park C. Selective targeting of trabecular meshwork cells: in vitro studies of pulsed and CW laser interactions. Exp. Eye Res. [Internet]. 1995 [cited 2018 Nov 4];60:359–371. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7789416.

[63] Hann CR, Fautsch MP. Preferential fluid flow in the human trabecular meshwork near collector channels. Invest. Ophthalmol. Vis. Sci. [Internet]. 2009 [cited 2018 Nov 4];50:1692–1697. Available from: http://iovs.arvojournals.org/article.aspx?doi=10.1167/iovs.08-2375.

[64] Anderson RR, Parrish JA. Selective photothermolysis: precise microsurgery by selective absorption of pulsed radiation. Science [Internet]. 1983 [cited 2018 Nov 4];220:524–527. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6836297.

[65] Wong MOM, Lee JWY, Choy BNK, et al. Systematic review and meta-analysis on the efficacy of selective laser trabeculoplasty in open-angle glaucoma. Surv. Ophthalmol. [Internet]. 2015 [cited 2018 Nov 4];60:36–50. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0039625714001313.

[66] Li X, Wang W, Zhang X. Meta-analysis of selective laser trabeculoplasty versus topical medication in the treatment of open-angle glaucoma. BMC Ophthalmol. [Internet]. 2015 [cited 2018 Nov 4];15:107. Available from: http://bmcophthalmol.biomedcentral.com/articles/10.1186/s12886-015-0091-2.

[67] Melamed S, Ben Simon GJ, Levkovitch-Verbin H. Selective laser trabeculoplasty as primary treatment for open-angle glaucoma: a prospective, nonrandomized pilot study. Arch. Ophthalmol. (Chicago, Ill. 1960) [Internet]. 2003 [cited 2018 Nov 4];121:957–960. Available from: http://archopht.jamanetwork.com/article.aspx?doi=10.1001/archopht.121.7.957.

[68] Schlote T, Kynigopoulos M. Selective laser trabeculoplasty (SLT): 1-year results in early and advanced open angle glaucoma. Int. Ophthalmol. [Internet]. 2016 [cited 2018 Nov 4];36:55–61. Available from: http://link.springer.com/10.1007/s10792-015-0079-1.

[69] Kerr NM, Lew HR, Skalicky SE. Selective Laser Trabeculoplasty Reduces Intraocular Pressure Peak in Response to the Water Drinking Test. J. Glaucoma [Internet]. 2016 [cited 2018 Nov 4];25:727–731. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00061198-201609000-00004.

[70] Association for Research in Vision and Ophthalmology. SA, McGlynn RH, George MK, et al. Investigative ophthalmology & visual science. [Internet]. Invest. Ophthalmol. Vis. Sci. [Association for Research in Vision and Ophthalmology, etc.]; 2006 [cited 2018 Nov 4]. Available from: https://iovs.arvojournals.org/article.aspx?articleid=2395251.

[71] Shibata M, Sugiyama T, Ishida O, et al. Clinical results of selective laser trabeculoplasty in open-angle glaucoma in Japanese eyes: comparison of 180 degree with 360 degree SLT. J. Glaucoma [Internet]. 2012 [cited 2018 Nov 4];21:17–21. Available from: https://insights.ovid.com/crossref?an=00061198-201201000-00004.

[72] Nagar M, Ogunyomade A, O'Brart DPS, et al. A randomised, prospective study comparing selective laser trabeculoplasty with latanoprost for the control of intraocular pressure in ocular hypertension and open angle glaucoma. Br. J. Ophthalmol. [Internet]. 2005 [cited 2018 Nov 4];89:1413–1417. Available from: http://bjo.bmj.com/cgi/doi/10.1136/bjo.2004.052795.

[73] Association for Research in Vision and Ophthalmology. AR, Hughes BA, Juzych MS, et al. Investigative ophthalmology & visual science. [Internet]. Invest. Ophthalmol. Vis. Sci. [Association for Research in Vision and Ophthalmology, etc.]; 2005 [cited 2018 Nov 4]. Available from: https://iovs.arvojournals.org/article.aspx?articleid=2399552.

[74] Prasad N, Murthy S, Dagianis JJ, et al. A comparison of the intervisit intraocular pressure fluctuation after 180 and 360 degrees of selective laser trabeculoplasty (SLT) as a primary therapy in primary open angle glaucoma and ocular hypertension. J. Glaucoma [Internet]. 2009 [cited 2018 Nov 4];18:157–160. Available from: https://insights.ovid.com/crossref?an=00061198-200902000-00013.

[75] Onakoya AO, Olowoyeye AO, Onyekwelu OMA, et al. Intraocular Pressure Changes Post Selective Laser Trabeculoplasty in the Contralateral Untreated Eyes of Nigerian Patients With Primary Open Angle Glaucoma. Nig. Q. J. Hosp. Med. [Internet]. [cited 2018 Nov 4];25:133–138. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27295834.

[76] Gulati V, Fan S, Gardner BJ, et al. Mechanism of Action of Selective Laser Trabeculoplasty and Predictors of Response. Invest. Ophthalmol. Vis. Sci. [Internet]. 2017 [cited 2018 Nov 4];58:1462–1468. Available from: http://iovs.arvojournals.org/article.aspx?doi=10.1167/iovs.16-20710.

[77] Latina MA, Gulati V. Selective laser trabeculoplasty: stimulating the meshwork to mend its ways. Int. Ophthalmol. Clin. [Internet]. 2004 [cited 2018 Nov 4];44:93–103. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14704524.

[78] Kara N, Altan C, Satana B, et al. Comparison of selective laser trabeculoplasty success in patients treated with either prostaglandin or timolol/dorzolamide fixed combination. J. Ocul. Pharmacol. Ther. [Internet]. 2011 [cited 2018 Nov 4];27:339–342. Available from: http://www.liebertpub.com/doi/10.1089/jop.2011.0015.

[79] Ayala M, Chen E. The influence of topical prostaglandin analogues in inflammation after selective laser trabeculoplasty treatment. J. Ocul. Pharmacol. Ther. [Internet]. 2012 [cited 2018 Nov 4];28:118–122. Available from: http://www.liebertpub.com/doi/10.1089/jop.2011.0084.

[80] Matos AG, Asrani SG, Paula JS. Feasibility of laser trabeculoplasty in angle closure glaucoma: a review of favourable histopathological findings in narrow angles. Clin. Experiment. Ophthalmol. [Internet]. 2017 [cited 2018 Nov 4];45:632–639. Available from: http://doi.wiley.com/10.1111/ceo.12938.

[81] Hamanaka T, Kasahara K, Takemura T. Histopathology of the trabecular meshwork and Schlemm's canal in primary angle-closure glaucoma. Invest. Ophthalmol. Vis. Sci. [Internet]. 2011 [cited 2018 Nov 4];52:8849–8861. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21960557.

[82] Garcés Fernández A, Piloto Díaz I, Miqueli Rodríguez M, et al. Revista Cubana de Oftalmologia. [Internet]. Rev. Cuba. Oftalmol. Centro Nacional de Informacion de Ciencias Medicas; 2010 [cited 2018 Nov 4]. Available from: http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S0864-21762010000100003.

[83] Narayanaswamy A, Leung CK, Istiantoro D V, et al. Efficacy of selective laser trabeculoplasty in primary angle-closure glaucoma: a randomized clinical trial. JAMA Ophthalmol. [Internet]. 2015 [cited 2018 Nov 4];133:206–212. Available from: http://archopht.jamanetwork.com/article.aspx?doi=10.1001/jamaophthalmol.2014.4893.

[84] Ho CL, Lai JSM, Aquino M V, et al. Selective laser trabeculoplasty for primary angle closure with persistently elevated intraocular pressure after iridotomy. J. Glaucoma [Internet]. 2009 [cited 2018 Nov 4];18:563–566. Available from: https://insights.ovid.com/crossref?an=00061198-200909000-00011.

[85] Tzimis V, Tze L, Ganesh J, et al. Laser trabeculoplasty: an investigation into factors that might influence outcomes. Can. J. Ophthalmol. [Internet]. 2011 [cited 2018 Nov 4];46:305–309. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0008418211000445.

[86] Ayala M, Chen E. Comparison of selective laser trabeculoplasty (SLT) in primary open angle glaucoma and pseudoexfoliation glaucoma. Clin. Ophthalmol. [Internet]. 2011 [cited 2018 Nov 4];5:1469–1473. Available from: http://www.dovepress.com/comparison-of-selective-laser-trabeculoplasty-slt-in-primary-open-angl-peer-reviewed-article-OPTH.

[87] Kent SS, Hutnik CML, Birt CM, et al. A randomized clinical trial of selective laser trabeculoplasty versus argon laser trabeculoplasty in patients with pseudoexfoliation. J. Glaucoma [Internet]. 2015 [cited 2018 Nov 4];24:344–347. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00061198-201506000-00002.

[88] Wang H, Cheng J-W, Wei R-L, et al. Meta-analysis of selective laser trabeculoplasty with argon laser trabeculoplasty in the treatment of open-angle glaucoma. Can. J. Ophthalmol. [Internet]. 2013 [cited 2018 Nov 4];48:186–192. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0008418213000021.

[89] Polat J, Grantham L, Mitchell K, et al. Repeatability of selective laser trabeculoplasty. Br. J. Ophthalmol. [Internet]. 2016 [cited 2018 Nov 4];100:1437–1441. Available from: http://bjo.bmj.com/lookup/doi/10.1136/bjophthalmol-2015-307486.

[90] Richter CU, Shingleton BJ, Bellows AR, et al. Retreatment with argon laser trabeculoplasty. Ophthalmology [Internet]. 1987 [cited 2018 Nov 4];94:1085–1089. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3684226.

[91] Wang W, He M, Zhou M, et al. Selective laser trabeculoplasty versus argon laser trabeculoplasty in patients with open-angle glaucoma: a systematic review and meta-analysis. Vavvas D, editor. PLoS One [Internet]. 2013 [cited 2018 Nov 4];8:e84270. Available from: https://dx.plos.org/10.1371/journal.pone.0084270.

[92] Damji KF, Bovell AM, Hodge WG, et al. Selective laser trabeculoplasty versus argon laser trabeculoplasty: results from a 1-year randomised clinical trial. Br. J. Ophthalmol. [Internet]. 2006 [cited 2018 Nov 4];90:1490–1494. Available from: http://bjo.bmj.com/cgi/doi/10.1136/bjo.2006.098855.

[93] Hong BK, Winer JC, Martone JF, et al. Repeat selective laser trabeculoplasty. J. Glaucoma [Internet]. 2009 [cited 2018 Nov 4];18:180–183. Available from: https://insights.ovid.com/crossref?an=00061198-200903000-00002.

[94] Avery N, Ang GS, Nicholas S, et al. Repeatability of primary selective laser trabeculoplasty in patients with primary open-angle glaucoma. Int. Ophthalmol. [Internet]. 2013 [cited 2018 Nov 4];33:501–506. Available from: http://link.springer.com/10.1007/s10792-013-9729-3.

[95] Hutnik Cindy C, Crichton A, Ford B, et al. SLT Versus ALT in Glaucoma Patients Treated Previously with 360-degree SLT:A Randomized, Single-Blind, Equivalence Clinical Trial. Ophthalmology [Internet]. 2018 [cited 2018 Nov 4]; Available from:

https://linkinghub.elsevier.com/retrieve/pii/S016164201831563X.
[96] Francis BA, Loewen N, Hong B, et al. Repeatability of selective laser trabeculoplasty for open-angle glaucoma. BMC Ophthalmol. [Internet]. 2016 [cited 2018 Nov 4];16:128. Available from: http://bmcophthalmol.biomedcentral.com/articles/10.1186/s12886-016-0299-9.
[97] Lee R, Hutnik CML. Projected cost comparison of selective laser trabeculoplasty versus glaucoma medication in the Ontario Health Insurance Plan. Can. J. Ophthalmol. [Internet]. 2006 [cited 2018 Nov 4];41:449–456. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0008418206800062.
[98] Seider MI, Keenan JD, Han Y. Cost of selective laser trabeculoplasty vs topical medications for glaucoma. Arch. Ophthalmol. (Chicago, Ill. 1960) [Internet]. 2012 [cited 2018 Nov 4];130:529–530. Available from: http://archopht.jamanetwork.com/article.aspx?doi=10.1001/archophthalmol.2012.355.
[99] Lamoureux EL, Mcintosh R, Constantinou M, et al. Comparing the effectiveness of selective laser trabeculoplasty with topical medication as initial treatment (the Glaucoma Initial Treatment Study): study protocol for a randomised controlled trial. Trials [Internet]. 2015 [cited 2018 Nov 4];16:406. Available from: http://trialsjournal.biomedcentral.com/articles/10.1186/s13063-015-0924-6.
[100] Gazzard G, Konstantakopoulou E, Garway-Heath D, et al. Laser in Glaucoma and Ocular Hypertension (LiGHT) trial. A multicentre, randomised controlled trial: design and methodology. Br. J. Ophthalmol. [Internet]. 2018 [cited 2018 Nov 4];102:593–598. Available from: http://bjo.bmj.com/lookup/doi/10.1136/bjophthalmol-2017-310877.
[101] Association for Research in Vision and Ophthalmology. DD, Krishna R, Willoughby L. Investigative ophthalmology & visual science. [Internet]. Invest. Ophthalmol. Vis. Sci. [Association for Research in Vision and Ophthalmology, etc.]; 2005 [cited 2018 Nov 4]. Available from: https://iovs.arvojournals.org/article.aspx?articleid=2399559.
[102] Abramowitz B, Chadha N, Kouchouk A, et al. Selective laser trabeculoplasty vs micropulse laser trabeculoplasty in open-angle glaucoma. Clin. Ophthalmol. [Internet]. 2018 [cited 2018 Nov 4];Volume 12:1599–1604. Available from: https://www.dovepress.com/selective-laser-trabeculoplasty-vs-micropulse-laser-trabeculoplasty-in-peer-reviewed-article-OPTH.
[103] BERENS C. Glaucoma surgery; an evaluation of cycloelectrolysis and cyclodiathermy. AMA. Arch. Ophthalmol. [Internet]. 1955 [cited 2018 Nov 4];54:548–563. Available from: http://www.ncbi.nlm.nih.gov/pubmed/13257985.
[104] Hampton C, Shields MB, Miller KN, et al. Evaluation of a protocol for transscleral neodymium: YAG cyclophotocoagulation in one hundred patients. Ophthalmology [Internet]. 1990 [cited 2018 Nov 4];97:910–917. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2381706.
[105] SCHEIE HG, FRAYER WC, SPENCER RW. Cyclodiathermy; a clinical and tonographic evaluation. AMA. Arch. Ophthalmol. [Internet]. 1955 [cited 2018 Nov 4];53:839–846. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14375442.
[106] Peyman GA, Naguib KS, Gaasterland D. Trans-scleral application of a semiconductor diode laser. Lasers Surg. Med. [Internet]. 1990 [cited 2018 Nov 4];10:569–575. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2263156.
[107] Bloom PA, Tsai JC, Sharma K, et al. Cyclodiode. Trans-scleral diode laser cyclophotocoagulation in the treatment of advanced refractory glaucoma. Ophthalmology [Internet]. 1997 [cited 2018 Nov 4];104:1508-19; discussion 1519-20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9307649.
[108] Vernon SA, Koppens JM, Menon GJ, et al. Diode laser cycloablation in adult glaucoma: long-term results of a standard protocol and review of current literature. Clin. Experiment. Ophthalmol. [Internet]. 2006 [cited 2018 Nov

4];34:411–420. Available from: http://doi.wiley.com/10.1111/j.1442-9071.2006.01241.x.

[109] Zhekov I, Janjua R, Shahid H, et al. A retrospective analysis of long-term outcomes following a single episode of transscleral cyclodiode laser treatment in patients with glaucoma. BMJ Open [Internet]. 2013 [cited 2018 Nov 4];3:e002793. Available from: http://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2013-002793.

[110] Murphy CC, Burnett CAM, Spry PGD, et al. A two centre study of the dose-response relation for transscleral diode laser cyclophotocoagulation in refractory glaucoma. Br. J. Ophthalmol. [Internet]. 2003 [cited 2018 Nov 4];87:1252–1257. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14507761.

[111] Ramli N, Htoon HM, Ho CL, et al. Risk Factors for Hypotony After Transscleral Diode Cyclophotocoagulation. J. Glaucoma [Internet]. 2012 [cited 2018 Nov 4];21:169–173. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00061198-201203000-00007.

[112] Yap-Veloso MI, Simmons RB, Echelman DA, et al. Intraocular pressure control after contact transscleral diode cyclophotocoagulation in eyes with intractable glaucoma. J. Glaucoma [Internet]. 1998 [cited 2018 Nov 4];7:319–328. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9786561.

[113] Ansari E, Gandhewar J. Long-term efficacy and visual acuity following transscleral diode laser photocoagulation in cases of refractory and non-refractory glaucoma. Eye (Lond). [Internet]. 2007 [cited 2018 Nov 4];21:936–940. Available from: http://www.nature.com/articles/6702345.

[114] Walland MJ. Diode laser cyclophotocoagulation: longer term follow up of a standardized treatment protocol. Clin. Experiment. Ophthalmol. [Internet]. 2000 [cited 2018 Nov 4];28:263–267. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11021554.

[115] Ishida K. Update on results and complications of cyclophotocoagulation. Curr. Opin. Ophthalmol. [Internet]. 2013 [cited 2018 Nov 4];24:102–110. Available from: https://insights.ovid.com/crossref?an=00055735-201303000-00004.

[116] Uram M. Ophthalmic laser microendoscope ciliary process ablation in the management of neovascular glaucoma. Ophthalmology [Internet]. 1992 [cited 2018 Nov 4];99:1823–1828. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1480398.

[117] Falkenberry SM, Siegfried CJ. Endocyclophotocoagulation. Middle East Afr. J. Ophthalmol. [Internet]. 2009 [cited 2018 Nov 4];16:130–133. Available from: http://www.meajo.org/text.asp?2009/16/3/130/56225.

[118] Yang Y, Zhong J, Dun Z, et al. Comparison of Efficacy Between Endoscopic Cyclophotocoagulation and Alternative Surgeries in Refractory Glaucoma: A Meta-analysis. Medicine (Baltimore). [Internet]. 2015 [cited 2018 Nov 4];94:e1651. Available from: https://insights.ovid.com/crossref?an=00005792-201509050-00059.

[119] Lima FE, Magacho L, Carvalho DM, et al. A prospective, comparative study between endoscopic cyclophotocoagulation and the Ahmed drainage implant in refractory glaucoma. J. Glaucoma [Internet]. 2004 [cited 2018 Nov 4];13:233–237. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15118469.

[120] Rathi S, Radcliffe NM. Combined endocyclophotocoagulation and phacoemulsification in the management of moderate glaucoma. Surv. Ophthalmol. [Internet]. 2017 [cited 2018 Nov 4];62:712–715. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0039625715300400.

[121] Lima FEL, Carvalho DM de, Avila MP de. [Phacoemulsification and endoscopic cyclophotocoagulation as primary surgical procedure in coexisting cataract and glaucoma]. Arq. Bras. Oftalmol. [Internet]. [cited 2018 Nov 4];73:419–422.

Available from: http://www.ncbi.nlm.nih.gov/pubmed/21225125.
[122] Berke SJ. Endolaser Cyclophotocoagulation in Glaucoma Management. Tech. Ophthalmol. [Internet]. 2006 [cited 2018 Nov 4];4:74–81. Available from: https://insights.ovid.com/crossref?an=00145756-200606000-00008.
[123] Lin SC, Chen MJ, Lin MS, et al. Vascular effects on ciliary tissue from endoscopic versus trans-scleral cyclophotocoagulation. Br. J. Ophthalmol. [Internet]. 2006 [cited 2018 Nov 4];90:496–500. Available from: http://bjo.bmj.com/cgi/doi/10.1136/bjo.2005.072777.
[124] Clement CI, Kampougeris G, Ahmed F, et al. Combining phacoemulsification with endoscopic cyclophotocoagulation to manage cataract and glaucoma. Clin. Experiment. Ophthalmol. [Internet]. 2013 [cited 2019 Jan 9];41:546–551. Available from: http://doi.wiley.com/10.1111/ceo.12051.
[125] Chen J, Cohn RA, Lin SC, et al. Endoscopic photocoagulation of the ciliary body for treatment of refractory glaucomas. Am. J. Ophthalmol. [Internet]. 1997 [cited 2018 Nov 4];124:787–796. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9402825.
[126] Tan AM, Chockalingam M, Aquino MC, et al. Micropulse transscleral diode laser cyclophotocoagulation in the treatment of refractory glaucoma. Clin. Experiment. Ophthalmol. [Internet]. 2010 [cited 2018 Nov 4];38:266–272. Available from: http://doi.wiley.com/10.1111/j.1442-9071.2010.02238.x.
[127] Aquino MCD, Barton K, Tan AMWT, et al. Micropulse versus continuous wave transscleral diode cyclophotocoagulation in refractory glaucoma: a randomized exploratory study. Clin. Experiment. Ophthalmol. [Internet]. 2015 [cited 2018 Nov 4];43:40–46. Available from: http://doi.wiley.com/10.1111/ceo.12360.
[128] Emanuel ME, Grover DS, Fellman RL, et al. Micropulse Cyclophotocoagulation: Initial Results in Refractory Glaucoma. J. Glaucoma [Internet]. 2017 [cited 2018 Nov 4];26:726–729. Available from: http://insights.ovid.com/crossref?an=00061198-201708000-00009.
[129] Kuchar S, Moster MR, Reamer CB, et al. Treatment outcomes of micropulse transscleral cyclophotocoagulation in advanced glaucoma. Lasers Med. Sci. [Internet]. 2016 [cited 2018 Nov 4];31:393–396. Available from: http://link.springer.com/10.1007/s10103-015-1856-9.
[130] Yelenskiy A, Gillette TB, Arosemena A, et al. Patient Outcomes Following Micropulse Transscleral Cyclophotocoagulation: Intermediate-term Results. J. Glaucoma [Internet]. 2018 [cited 2018 Nov 4];27:920–925. Available from: http://insights.ovid.com/crossref?an=00061198-900000000-98391.
[131] Bar-David L, Blumenthal EZ. Evolution of Glaucoma Surgery in the Last 25 Years. Rambam Maimonides Med. J. 2018;9:e0024.
[132] Coleman AL. Advances in glaucoma treatment and management: surgery. Invest. Ophthalmol. Vis. Sci. 2012;53:2491–2494.
[133] Masoumpour MB, Nowroozzadeh MH, Razeghinejad MR. Current and Future Techniques in Wound Healing Modulation after Glaucoma Filtering Surgeries. Open Ophthalmol. J. 2016;10:68–85.
[134] Borisuth NS, Phillips B, Krupin T. The risk profile of glaucoma filtration surgery. Curr. Opin. Ophthalmol. 1999;10:112–116.
[135] Broadway D, Grierson I, Hitchings R. Racial differences in the results of glaucoma filtration surgery: are racial differences in the conjunctival cell profile important? Br. J. Ophthalmol. 1994;78:466–475.
[136] Issa de Fendi L, Cena de Oliveira T, Bigheti Pereira C, et al. Additive Effect of Risk Factors for Trabeculectomy Failure in Glaucoma Patients. J. Glaucoma. 2016;25:e879–e883.
[137] Landers J, Martin K, Sarkies N, et al. A twenty-year follow-up study of trabeculectomy: risk factors and outcomes. Ophthalmology. 2012;119:694–702.
[138] Lavin MJ, Wormald RP, Migdal CS, et al. The influence of prior therapy on the

success of trabeculectomy. Arch. Ophthalmol. 1990;108:1543–1548.
[139] Khaw PT, Chiang M, Shah P, et al. Enhanced Trabeculectomy–the Moorfields safer surgery system. Glaucoma Surg. Karger Publishers; 2012. p. 1–28.
[140] Husain R, Liang S, Foster PJ, et al. Cataract Surgery After Trabeculectomy. Arch. Ophthalmol. 2012;130:165.
[141] Musch DC, Lichter PR, Guire KE, et al. The Collaborative Initial Glaucoma Treatment Study: study design, methods, and baseline characteristics of enrolled patients. Ophthalmology [Internet]. 1999 [cited 2019 Jan 9];106:653–662. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10201583.
[142] AGIS (Advanced Glaucoma Intervention Study) Investigators. The Advanced Glaucoma Intervention Study: 8. Risk of cataract formation after trabeculectomy. Arch. Ophthalmol. (Chicago, Ill. 1960) [Internet]. 2001 [cited 2019 Jan 9];119:1771–1779. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11735786.
[143] Adelman RA, Brauner SC, Afshari NA, et al. Cataract formation after initial trabeculectomy in young patients. Ophthalmology [Internet]. 2003 [cited 2019 Jan 9];110:625–629. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0161642002017694.
[144] Musch DC, Gillespie BW, Niziol LM, et al. Cataract Extraction in the Collaborative Initial Glaucoma Treatment Study. Arch. Ophthalmol. [Internet]. 2006 [cited 2019 Jan 9];124:1694. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17159028.
[145] Aykan U, Bilge AH, Akin T, et al. Laser Suture Lysis or Releasable Sutures After Trabeculectomy. J. Glaucoma. 2007;16:240–245.
[146] Wells AP, Bunce C, Khaw PT. Flap and suture manipulation after trabeculectomy with adjustable sutures: titration of flow and intraocular pressure in guarded filtration surgery. J. Glaucoma. 2004;13:400–406.
[147] Jones E, Clarke J, Khaw PT. Recent advances in trabeculectomy technique. Curr. Opin. Ophthalmol. 2005;16:107–113.
[148] Dhingra S, Khaw PT. The moorfields safer surgery system. Middle East Afr. J. Ophthalmol. [Internet]. 2009 [cited 2019 Jan 9];16:112–115. Available from: http://www.meajo.org/text.asp?2009/16/3/112/56220.
[149] Wilkins M, Indar A, Wormald R. Intraoperative Mitomycin C for glaucoma surgery. Cochrane Database Syst. Rev. 2005;
[150] Wormald R, Wilkins MR, Bunce C. Post-operative 5-fluorouracil for glaucoma surgery. Cochrane Database Syst Rev. 2001;3.
[151] Cabourne E, Clarke JC, Schlottmann PG, et al. Mitomycin C versus 5-Fluorouracil for wound healing in glaucoma surgery. Cochrane Database Syst. Rev. 2015;
[152] Green E, Wilkins M, Bunce C, et al. 5-Fluorouracil for glaucoma surgery. Cochrane Database Syst. Rev. 2014;
[153] Seibold LK, Sherwood MB, Kahook MY. Wound Modulation After Filtration Surgery. Surv. Ophthalmol. 2012;57:530–550.
[154] Almatlouh A, Bach-Holm D, Kessel L. Steroids and nonsteroidal anti-inflammatory drugs in the postoperative regime after trabeculectomy - which provides the better outcome? A systematic review and meta-analysis. Acta Ophthalmol. 2018;
[155] Breusegem C, Spielberg L, Van Ginderdeuren R, et al. Preoperative Nonsteroidal Anti-inflammatory Drug or Steroid and Outcomes after Trabeculectomy. Ophthalmology. 2010;117:1324–1330.
[156] Starita RJ, Fellman RL, Spaeth GL, et al. Short- and long-term effects of postoperative corticosteroids on trabeculectomy. Ophthalmology. 1985;92:938–946.
[157] Azuara-Blanco A, Spaeth GL, Augsburger JJ. Oral prednisone in guarded filtration procedures supplemented with antimetabolites. Ophthalmic Surg. Lasers. 1999;30:126–132.

[158] Constable PH, Crowston JG, Occleston NL, et al. Long term growth arrest of human Tenon's fibroblasts following single applications of beta radiation. Br. J. Ophthalmol. 1998;82:448–452.
[159] Li Z, Van Bergen T, Van de Veire S, et al. Inhibition of vascular endothelial growth factor reduces scar formation after glaucoma filtration surgery. Invest. Ophthalmol. Vis. Sci. 2009;50:5217–5225.
[160] Coote MA, Ruddle JB, Qin Q, et al. Vascular changes after intra-bleb injection of bevacizumab. J. Glaucoma. 2008;17:517–518.
[161] Kahook MY, Schuman JS, Noecker RJ. Needle bleb revision of encapsulated filtering bleb with bevacizumab. Ophthalmic Surgery, Lasers & Imaging. 37:148–150.
[162] Cornish KS, Ramamurthi S, Saidkasimova S, et al. Intravitreal bevacizumab and augmented trabeculectomy for neovascular glaucoma in young diabetic patients. Eye. 2009;23:979–981.
[163] Grewal DS, Jain R, Kumar H, et al. Evaluation of subconjunctival bevacizumab as an adjunct to trabeculectomy a pilot study. Ophthalmology. 2008;115:2141–2145.e2.
[164] Shaffer RN, Hetherington J, Hoskins HD. Guarded thermal sclerostomy. Am. J. Ophthalmol. 1971;72:769–772.
[165] Zhou M, Wang W, Huang W, et al. Trabeculectomy with versus without releasable sutures for glaucoma: a meta-analysis of randomized controlled trials. BMC Ophthalmol. 2014;14:41.
[166] Clement CI, Goldberg I. The management of complicated glaucoma. Indian J. Ophthalmol. 2011;59 Suppl:S141-7.
[167] Tseng VL, Coleman AL, Chang MY, et al. Aqueous shunts for glaucoma. Cochrane Database Syst. Rev. 2017;
[168] Christakis PG, Zhang D, Budenz DL, et al. Five-Year Pooled Data Analysis of the Ahmed Baerveldt Comparison Study and the Ahmed Versus Baerveldt Study. Am. J. Ophthalmol. 2017;176:118–126.
[169] Pimentel E, Schmidt J. Is Ahmed valve superior to Baerveldt implant as an aqueous shunt for the treatment of glaucoma? Medwave. 2018;18:e7239.
[170] HaiBo T, Xin K, ShiHeng L, et al. Comparison of Ahmed glaucoma valve implantation and trabeculectomy for glaucoma: a systematic review and meta-analysis. Acott TS, editor. PLoS One. 2015;10:e0118142.
[171] Islamaj E, Wubbels RJ, de Waard PWT. Primary Baerveldt versus trabeculectomy study after one-year follow-up. Acta Ophthalmol. 2018;96:e740–e746.
[172] Gedde SJ, Schiffman JC, Feuer WJ, et al. Treatment Outcomes in the Tube Versus Trabeculectomy (TVT) Study After Five Years of Follow-up. Am. J. Ophthalmol. 2012;153:789–803.e2.
[173] Gedde SJ, Schiffman JC, Feuer WJ, et al. The tube versus trabeculectomy study: design and baseline characteristics of study patients. Am. J. Ophthalmol. [Internet]. 2005 [cited 2019 Jan 9];140:275–287. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0002939405003272.
[174] Gedde SJ, Feuer WJ, Shi W, et al. Treatment Outcomes in the Primary Tube Versus Trabeculectomy Study after 1 Year of Follow-up. Ophthalmology [Internet]. 2018 [cited 2019 Jan 15];125:650–663. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29477688.
[175] Yalvac IS, Sahin M, Eksioglu U, et al. Primary viscocanalostomy versus trabeculectomy for primary open-angle glaucoma. J. Cataract Refract. Surg. [Internet]. 2004 [cited 2019 Jan 16];30:2050–2057. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15474813.
[176] O'Brart DPS, Shiew M, Edmunds B. A randomised, prospective study comparing trabeculectomy with viscocanalostomy with adjunctive antimetabolite usage for the management of open angle glaucoma uncontrolled by medical therapy. Br. J. Ophthalmol. [Internet]. 2004 [cited 2019 Jan 16];88:1012–1017. Available from: http://bjo.bmj.com/cgi/doi/10.1136/bjo.2003.037432.

[177] O'Brart DPS, Rowlands E, Islam N, et al. A randomised, prospective study comparing trabeculectomy augmented with antimetabolites with a viscocanalostomy technique for the management of open angle glaucoma uncontrolled by medical therapy. Br. J. Ophthalmol. [Internet]. 2002 [cited 2019 Jan 16];86:748–754. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12084743.

[178] Kobayashi H, Kobayashi K. Randomized Comparison of the Intraocular Pressure–Lowering Effect of Phacoviscocanalostomy and Phacotrabeculectomy. Ophthalmology [Internet]. 2007 [cited 2019 Jan 16];114:909–914. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17397924.

[179] Carassa RG, Bettin P, Fiori M, et al. Viscocanalostomy versus trabeculectomy in white adults affected by open-angle glaucoma: a 2-year randomized, controlled trial. Ophthalmology [Internet]. 2003 [cited 2019 Jan 16];110:882–887. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0161642003000812.

[180] El Sayyad F, Helal M, El-Kholify H, et al. Nonpenetrating deep sclerectomy versus trabeculectomy in bilateral primary open-angle glaucoma. Ophthalmology [Internet]. 2000 [cited 2019 Jan 16];107:1671–1674. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10964827.

[181] Dahan E, Drusedau MU. Nonpenetrating filtration surgery for glaucoma: control by surgery only. J. Cataract Refract. Surg. [Internet]. 2000 [cited 2019 Jan 16];26:695–701. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10831899.

[182] Sarodia U, Shaarawy T, Barton K. Nonpenetrating glaucoma surgery: a critical evaluation. Curr. Opin. Ophthalmol. [Internet]. 2007 [cited 2019 Jan 16];18:152–158. Available from: https://insights.ovid.com/crossref?an=00055735-200703000-00011.

[183] Mendrinos E, Mermoud A, Shaarawy T. Nonpenetrating glaucoma surgery. Surv. Ophthalmol. [Internet]. 2008 [cited 2019 Jan 16];53:592–630. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0039625708001483.

[184] Lachkar Y, Neverauskiene J, Jeanteur-Lunel MN, et al. Nonpenetrating deep sclerectomy: a 6-year retrospective study. Eur. J. Ophthalmol. [Internet]. [cited 2019 Jan 16];14:26–36. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15005582.

[185] Demailly P, Lavat P, Kretz G, et al. Non-penetrating deep sclerectomy (NPDS) with or without collagen device (CD) in primary open-angle glaucoma: middle-term retrospective study. Int. Ophthalmol. [Internet]. [cited 2019 Jan 16];20:131–140. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9112177.

[186] Hamard P, Lachkar Y. [Non penetrating filtering surgery, evolution and results]. J. Fr. Ophtalmol. [Internet]. 2002 [cited 2019 Jan 16];25:527–536. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12048520.

[187] Stegmann R, Pienaar A, Miller D. Viscocanalostomy for open-angle glaucoma in black African patients. J. Cataract Refract. Surg. [Internet]. 1999 [cited 2019 Jan 16];25:316–322. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10079435.

[188] Lüke C, Dietlein TS, Jacobi PC, et al. A prospective randomised trial of viscocanalostomy with and without implantation of a reticulated hyaluronic acid implant (SKGEL) in open angle glaucoma. Br. J. Ophthalmol. [Internet]. 2003 [cited 2019 Jan 16];87:599–603. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12714403.

[189] Yarangümeli A, Köz OG, Alp MN, et al. Viscocanalostomy with mitomycin-C: a preliminary study. Eur. J. Ophthalmol. [Internet]. [cited 2019 Jan 16];15:202–208. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15812760.

[190] Netland PA, Sarkisian SR, Moster MR, et al. Randomized, Prospective, Comparative Trial of EX-PRESS Glaucoma Filtration Device versus Trabeculectomy (XVT Study). Am. J. Ophthalmol. 2014;157:433–440.e3.

[191] Dahan E, Ben Simon GJ, Lafuma A. Comparison of trabeculectomy and Ex-PRESS implantation in fellow eyes of the same patient: a prospective, randomised study. Eye. 2012;26:703–710.
[192] Wagschal LD, Trope GE, Jinapriya D, et al. Prospective Randomized Study Comparing Ex-PRESS to Trabeculectomy. J. Glaucoma. 2015;24:624–629.
[193] Beltran-Agullo L, Trope GE, Jin Y, et al. Comparison of Visual Recovery Following Ex-PRESS Versus Trabeculectomy. J. Glaucoma. 2015;24:181–186.
[194] de Jong LAMS. The Ex-PRESS glaucoma shunt versus trabeculectomy in open-angle glaucoma: a prospective randomized study. Adv. Ther. 2009;26:336–345.
[195] Berdeaux G, de Jong, Lafuma A, et al. Five-year extension of a clinical trial comparing the EX-PRESS glaucoma filtration device and trabeculectomy in primary open-angle glaucoma. Clin. Ophthalmol. 2011;527.
[196] Francis BA, Singh K, Lin SC, et al. Novel glaucoma procedures: a report by the American Academy of Ophthalmology. Ophthalmology [Internet]. 2011 [cited 2018 Nov 4];118:1466–1480. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21724045.
[197] Caprioli J, Kim JH, Friedman DS, et al. Special Commentary: Supporting Innovation for Safe and Effective Minimally Invasive Glaucoma Surgery. Ophthalmology [Internet]. 2015 [cited 2018 Nov 4];122:1795–1801. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0161642015001712.
[198] Coleman AL, Richter G. Minimally invasive glaucoma surgery: current status and future prospects. Clin. Ophthalmol. [Internet]. 2016 [cited 2018 Nov 4];10:189. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26869753.
[199] Craven ER, Katz LJ, Wells JM, et al. 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. [Internet]. 2012 [cited 2018 Nov 5];38:1339–1345. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22814041.
[200] Neuhann TH. Trabecular micro-bypass stent implantation during small-incision cataract surgery for open-angle glaucoma or ocular hypertension: Long-term results. J. Cataract Refract. Surg. [Internet]. 2015 [cited 2018 Nov 4];41:2664–2671. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26796447.
[201] Giamporcaro JE, Katz LJ, Erb C, et al. Prospective, randomized study of one, two, or three trabecular bypass stents in open-angle glaucoma subjects on topical hypotensive medication. Clin. Ophthalmol. [Internet]. 2015 [cited 2018 Nov 4];9:2313. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26715834.
[202] Voskanyan L, García-Feijoó J, Belda JI, et al. Prospective, Unmasked Evaluation of the iStent® Inject System for Open-Angle Glaucoma: Synergy Trial. Adv. Ther. [Internet]. 2014 [cited 2018 Nov 4];31:189–201. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24452726.
[203] Pfeiffer N, Garcia-Feijoo J, Martinez-de-la-Casa JM, et al. A Randomized Trial of a Schlemm's Canal Microstent with Phacoemulsification for Reducing Intraocular Pressure in Open-Angle Glaucoma. Ophthalmology [Internet]. 2015 [cited 2018 Nov 4];122:1283–1293. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25972254.
[204] Vold S, Ahmed IIK, Craven ER, et al. Two-Year COMPASS Trial Results: Supraciliary Microstenting with Phacoemulsification in Patients with Open-Angle Glaucoma and Cataracts. Ophthalmology [Internet]. 2016 [cited 2018 Nov 4];123:2103–2112. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27506486.
[205] Preliminary ASCRS CyPass Withdrawal Consensus Statement | ASCRS [Internet]. [cited 2018 Nov 4]. Available from: http://ascrs.org/CyPass_Statement.
[206] Hoeh H, Ahmed IIK, Grisanti S, et al. Early postoperative safety and surgical outcomes after implantation of a suprachoroidal micro-stent for the treatment of open-angle glaucoma concomitant with cataract surgery. J. Cataract Refract. Surg.

[Internet]. 2013 [cited 2018 Nov 4];39:431–437. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23506920.
[207] Höh H, Grisanti S, Grisanti S, et al. Two-year Clinical Experience with the CyPass Micro-Stent: Safety and Surgical Outcomes of a Novel Supraciliary Micro-Stent. Klin. Monbl. Augenheilkd. [Internet]. 2014 [cited 2018 Nov 4];231:377–381. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24771171.
[208] García-Feijoo J, Rau M, Grisanti S, et al. Supraciliary Micro-stent Implantation for Open-Angle Glaucoma Failing Topical Therapy: 1-Year Results of a Multicenter Study. Am. J. Ophthalmol. [Internet]. 2015 [cited 2018 Nov 4];159:1075–1081.e1. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25747677.
[209] Lewis RA. Ab interno approach to the subconjunctival space using a collagen glaucoma stent. J. Cataract Refract. Surg. [Internet]. 2014 [cited 2018 Nov 4];40:1301–1306. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24943904.
[210] Sheybani A, Lenzhofer M, Hohensinn M, et al. Phacoemulsification combined with a new ab interno gel stent to treat open-angle glaucoma: Pilot study. J. Cataract Refract. Surg. [Internet]. 2015 [cited 2019 Mar 12];41:1905–1909. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0886335015010391.
[211] Sheybani A, Dick HB, Ahmed IIK. Early Clinical Results of a Novel Ab Interno Gel Stent for the Surgical Treatment of Open-angle Glaucoma. J. Glaucoma [Internet]. 2016 [cited 2019 Mar 13];25:e691–e696. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26561420.
[212] Smith M, Charles R, Abdel-Hay A, et al. 1-year outcomes of the Xen45 glaucoma implant. Eye [Internet]. 2018 [cited 2019 Jan 15]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/30552422.
[213] Batlle JF, Fantes F, Riss I, et al. Three-Year Follow-up of a Novel Aqueous Humor MicroShunt. J. Glaucoma [Internet]. 2016 [cited 2018 Nov 4];25:e58–e65. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26766400.
[214] Brubaker RF, Schoff EO, Nau CB, et al. Effects of AGN 192024, a new ocular hypotensive agent, on aqueous dynamics. Am. J. Ophthalmol. 2001;131:19–24.
[215] Nilsson SFE, Drecoll E, Lütjen-Drecoll E, et al. The prostanoid EP2receptor agonist butaprost increases uveoscleral outflow in the cynomolgus monkey. Investig. Ophthalmol. Vis. Sci. 2006;47:4042–4049.
[216] Christiansen GA, Nau CB, McLaren JW, et al. Mechanism of ocular hypotensive action of bimatoprost (Lumigan) in patients with ocular hypertension or glaucoma. Ophthalmology. 2004;111:1658–1662.
[217] Dinslage S, Hueber A, Diestelhorst M, et al. The influence of Latanoprost 0.005% on aqueous humor flow and outflow facility in glaucoma patients: A double-masked placebo-controlled clinical study. Graefe's Arch. Clin. Exp. Ophthalmol. 2004;242:654–660.
[218] Wan Z, Woodward DF, Cornell CL, et al. Bimatoprost, prostamide activity, and conventional drainage. Investig. Ophthalmol. Vis. Sci. 2007;48:4107–4115.
[219] Bahler CK, Howell KG, Hann CR, et al. Prostaglandins Increase Trabecular Meshwork Outflow Facility in Cultured Human Anterior Segments. Am. J. Ophthalmol. 2008;145:114–119.
[220] Lim KS, Nau CB, Byrne MMO, et al. NIH Public Access. Evaluation. 2009;115:790–795.
[221] Takagi Y, Nakajima T, Shimazaki A, et al. Pharmacological characteristics of AFP-168 (tafluprost), a new prostanoid FP receptor agonist, as an ocular hypotensive drug. Exp. Eye Res. 2004;78:767–776.
[222] Toris CB, Zhan GL, Zhao J, et al. Potential mechanism for the additivity of pilocarpine and latanoprost. Am. J. Ophthalmol. 2001;131:722–728.
[223] Schumer RA, Camras CB, Mandahl AK. Putative side effects of prostaglandin analogs. Surv. Ophthalmol. 2002;47.

[224] Agange N, Mosaed S. Prostaglandin-induced cystoid macular edema following routine cataract extraction. J. Ophthalmol. 2010;2010:690707.
[225] Warwar RE, Bullock JD, Ballal D. Cystoid macular edema and anterior uveitis associated with latanoprost use. Ophthalmology. 1998;105:263–268.
[226] Lai I-C, T Kuo M, Teng M-C. Iris pigment epithelial cyst induced by topical administration of latanoprost. Br. J. Ophthalmol. 2003.
[227] Kroll DM, Schuman JS. Reactivation of herpes simplex virus keratitis after initiating bimatoprost treatment for glaucoma. Am. J. Ophthalmol. 2002;133:401–403.
[228] RL C, RF B. The mechanism of timolol in lowering intraocular pressure: In the normal eye. Arch. Ophthalmol. 1978;96:2045–2048.
[229] Zimmerman TJ, Boger WP. The beta-adrenergic blocking agents and the treatment of glaucoma. Surv. Ophthalmol. 1979;23:347–362.
[230] Uusitalo H, Niño J, Tahvanainen K, et al. Efficacy and systemic side-effects of topical 0.5% timolol aqueous solution and 0.1% timolol hydrogel. Acta Ophthalmol. Scand. 2005;83:723–728.
[231] Stewart WC, Castelli WP. Systemic side effects of topical beta-adrenergic blockers. Clin. Cardiol. 1996;19:691–697.
[232] Nelson WL, Fraunfelder FT, Sills JM, et al. Adverse Respiratory and Cardiovascular Events Attributed to Timolol Ophthalmic Solution, 1978–1985. Am. J. Ophthalmol. 1986;102:606–611.
[233] Holló G. Carbonic Anhydrase Inhibitors. Glaucoma Second Ed. 2014;1:559–565.
[234] BNF. BNF. ACETAZOLAMIDE (Systemic): Side effects and Contraindications.
[235] BNF. BNF. Dorzolamide: Side effects and contraindications.
[236] Lee S-J, Kim M. Allergic contact dermatitis caused by dorzolamide eyedrops. Clin. Opthalmology. 2015;9:575–577.
[237] Delaney YM, Salmon JF, Mossa F, et al. Periorbital dermatitis as a side effect of topical dorzolamide. Br. J. Ophthalmol. 2002;86:378–380.
[238] CC S, Tran V, Mermoud A, et al. Sterile mucopurulent conjunctivitis associated with the use of dorzolamide eyedrops. Arch. Ophthalmol. 1999;117:1429–1431.
[239] CB T, ML G, CB C, et al. Effects of brimonidine on aqueous humor dynamics in human eyes. Arch. Ophthalmol. 1995;113:1514–1517.
[240] Toris CB, Tafoya ME, Camras CB, et al. Effects of Apraclonidine on Aqueous Humor Dynamics in Human Eyes. Ophthalmology. 1995;102:456–461.
[241] Wheeler LA, Tatton NA, Elstner M. Alpha-2 adrnergic receptor activation by brimonidine reduces neuronal apoptosis through Akt (Protein Kinase B) dependent new synthesis of BCL-2. Investig. Opthalmology Vis. Sci. 2001;42:411.
[242] Woldemussie E, Ruiz L, Wijono M, et al. Neuroprotection of Retinal Ganglion Cells by Brimonidine in Rats with Laser-Induced Chronic Ocular Hypertension. Invest. Ophthalmol. Vis. Sci. 2001.
[243] Reitsamer HA, Posey M, Kiel JW. Effects of a topical α2 adrenergic agonist on ciliary blood flow and aqueous production in rabbits. Exp. Eye Res. 2006;82:405–415.
[244] Honjo M, Tanihara H, Inatani M, et al. Effects of Rho-Associated Protein Kinase Inhibitor Y-27632 on Intraocular Pressure and Outflow Facility AND. 2018;137–144.
[245] Tanihara H, Inatani M, Honjo M, et al. Intraocular pressure–lowering effects and safety of topical administration of a selective rock inhibitor, snj-1656, in healthy volunteers. Arch. Ophthalmol. 2008;126:309–315.
[246] Arnold JJ, Hansen MS, Gorman GS, et al. The Effect of Rho-Associated Kinase Inhibition on the Ocular Penetration of Timolol Maleate. Invest. Ophthalmol. Vis. Sci. 2013;54:1118–1126.
[247] Johnson DH. Histologic findings after argon laser trabeculoplasty in glaucomatous eyes. Exp. Eye Res. [Internet]. 2007 [cited 2018 Nov 4];85:557–562. Available

from: http://linkinghub.elsevier.com/retrieve/pii/S0014483507001984.
[248] Rodrigues MM, Spaeth GL, Donohoo P. Electron microscopy of argon laser therapy in phakic open-angle glaucoma. Ophthalmology [Internet]. 1982 [cited 2018 Nov 4];89:198–210. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7088502.
[249] Bradley JM, Anderssohn AM, Colvis CM, et al. Mediation of laser trabeculoplasty-induced matrix metalloproteinase expression by IL-1beta and TNFalpha. Invest. Ophthalmol. Vis. Sci. [Internet]. 2000 [cited 2018 Nov 4];41:422–430. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10670472.
[250] Alvarado JA, Katz LJ, Trivedi S, et al. Monocyte modulation of aqueous outflow and recruitment to the trabecular meshwork following selective laser trabeculoplasty. Arch. Ophthalmol. (Chicago, Ill. 1960) [Internet]. 2010 [cited 2018 Nov 4];128:731–737. Available from: http://archopht.jamanetwork.com/article.aspx?doi=10.1001/archophthalmol.2010.85.
[251] Kagan DB, Gorfinkel NS, Hutnik CML. Mechanisms of selective laser trabeculoplasty: a review. Clin. Experiment. Ophthalmol. [Internet]. 2014 [cited 2018 Nov 4];42:675–681. Available from: http://doi.wiley.com/10.1111/ceo.12281.
[252] Izzotti A, Longobardi M, Cartiglia C, et al. Trabecular meshwork gene expression after selective laser trabeculoplasty. Schönbach C, editor. PLoS One [Internet]. 2011 [cited 2018 Nov 4];6:e20110. Available from: http://dx.plos.org/10.1371/journal.pone.0020110.
[253] Kramer TR, Noecker RJ. Comparison of the morphologic changes after selective laser trabeculoplasty and argon laser trabeculoplasty in human eye bank eyes. Ophthalmology [Internet]. 2001 [cited 2018 Nov 4];108:773–779. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11297496.
[254] SooHoo JR, Seibold LK, Ammar DA, et al. Ultrastructural Changes in Human Trabecular Meshwork Tissue after Laser Trabeculoplasty. J. Ophthalmol. [Internet]. 2015 [cited 2018 Nov 4];2015:476138. Available from: http://www.hindawi.com/journals/joph/2015/476138/.
[255] Lee JWY, Yau GSK, Yick DWF, et al. MicroPulse Laser Trabeculoplasty for the Treatment of Open-Angle Glaucoma. Medicine (Baltimore). [Internet]. 2015 [cited 2018 Nov 4];94:e2075. Available from: https://insights.ovid.com/crossref?an=00005792-201512080-00011.
[256] Luttrull JK, Sramek C, Palanker D, et al. Long-term safety, high-resolution imaging, and tissue temperature modeling of subvisible diode micropulse photocoagulation for retinovascular macular edema. Retina [Internet]. 2012 [cited 2018 Nov 4];32:375–386. Available from: https://insights.ovid.com/crossref?an=00006982-201202000-00022.
[257] Detry-Morel M, Muschart F, Pourjavan S. Micropulse diode laser (810 nm) versus argon laser trabeculoplasty in the treatment of open-angle glaucoma: comparative short-term safety and efficacy profile. Bull. Soc. Belge Ophtalmol. [Internet]. 2008 [cited 2018 Nov 4];21–28. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18700451.
[258] Assia EI, Hennis HL, Stewart WC, et al. A comparison of neodymium: yttrium aluminum garnet and diode laser transscleral cyclophotocoagulation and cyclocryotherapy. Invest. Ophthalmol. Vis. Sci. [Internet]. 1991 [cited 2018 Nov 4];32:2774–2778. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1894475.
[259] Benson MT, Nelson ME. Cyclocryotherapy: a review of cases over a 10-year period. Br. J. Ophthalmol. [Internet]. 1990 [cited 2018 Nov 4];74:103–105. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2310722.
[260] Murdoch I. How I approach trabeculectomy surgery. Community Eye Heal. 2006;19:42–43.

[261] Brandão LM, Grieshaber MC. Update on Minimally Invasive Glaucoma Surgery (MIGS) and New Implants. J. Ophthalmol. [Internet]. 2013 [cited 2018 Nov 4];2013:1–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24369494.
[262] Manasses DT, Au L. The New Era of Glaucoma Micro-stent Surgery. Ophthalmol. Ther. [Internet]. 2016 [cited 2018 Nov 4];5:135–146. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27314234.
[263] Saheb H, Ianchulev T, Ahmed I 'Ike' K. Optical coherence tomography of the suprachoroid after CyPass Micro-Stent implantation for the treatment of open-angle glaucoma. Br. J. Ophthalmol. [Internet]. 2014 [cited 2018 Nov 4];98:19–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23743436.

Table 1: Intraocular pressure lowering drops

Agent	Mode of action	Side effects
Prostaglandin analogues Bimatoprost Lumigan® 0.01% and 0.03% Latanoprost Xalatan® 0.005% Tafluprost Saflutan® 0.0015% Travoprost Travatan® 0.004% Unoprostone Rescula® 0.12% and 0.15%	• Increase the outflow of aqueous humor[214] via the unconventional uveoscleral pathway[215–219] • Might also affect the conventional trabecular pathway[220–222].	**Common ocular side effects:** • Conjunctival hyperemia • Eyelash changes • Darkening of the iris and periocular skin pigmentation[223]. **Less common, but more serious, side effects:** • Cystoid macular oedema[224,225] • Iris cysts[226] • Anterior uveitis[225] • Reactivation of previous herpes simplex keratitis[227].
Beta-blockers **Beta 1 selective** Betaxolol 0.25%, 0.5% Betoptic® Betoptic S® Betoptima® **Non selective** Befunolol 0.5% Betaclar® Levobunolol 0.25%, 0.5% Betagan® Vistagan® Metipranolol 0.1%, 0.3% Betaman® Beta-ophtiole®, Optipranolol®, Turoptin® Timolol 0.1%, 0.25%, 0.5% Aquanil® Arutimol® Cusimolol® Nyogel® Opimol® Oftamolol® Timoptic® Timoptic-XE® Timoptol® Timabak® Timogel® Timolabak® Timosine XE® Timosan® **With intrinsic sympathomimetic activity** Carteolol 0.5%, 1%, 2% Carteol® Carteabak® Teoptic® Arteoptic® Ocupress® Pindolol 2% Pindoptic®	• Decrease the production of aqueous humor[228,229], with no effect on outflow	**Topical side effects:** uncommon **Systemic side effects:** • Hypotension • Bradycardia[230] • Fatigue, shortness of breath (in patients with asthma or other respiratory diagnoses)[231,232]. • Reduced libido an depression have been reported[231] (rare)
Carbonic anhydrase inhibitors **Topical** Brinzolamide 1% Azopt®	• Decrease the production of aqueous humor[23,233].	**Systemic side effects:** **Common side effects** • Ataxia • Depression

Dorzolamide 2% Trusopt® **Systemic** Acetazolamide Diamox® Diamox SR® Diamox Retard® Odemin® Dichlorphenamide Antidrasi® Daranide® Glaumid® Oralcon® Methazolamide Neptazane®		• Diarrhea • Fatigue • Headache • Paraesthesia **Less common side effects:** • Anaemia • Confusion • Dermatological adverse drug reactions • Renal calculi • Increased renal loss of sodium, potassium and water which can cause metabolic acidosis[234] **Ocular side effects of the topical CAIs include** • Ocular stinging, burning or discomfort [235] (more common in Dorzolamide) • Visual blurring immediately after administration of brinzolamide, due to the viscous suspension in which it is formulated[233] • Periorbital contact dermatitis[236,237] • Allergic conjunctivitis[238].
Parasympathomimetics (cholinergics) **Direct acting** Pilocarpine 0.5% 1% 2% 4% E-Pilo® Isopto Carpine® Pilagan® Pilocar® Pilogel® Pilomann® Pilopine® Pilopine HS gel® Pilostat® Spersacarpine® Aceclidine 2% Glaucostat®Glaunorm® Carbachol 0.75%–3% Isopto Carbachol® Acetylcholine 1% Miochol® **Indirect acting** Demecarium bromide 0.125%	• Directly stimulate the muscarinic receptors of the ciliary muscle resulting in widening of the anterior chamber angle • Increase outflow through the trabecular meshwork	**Systemic side effects:** • Gastro intestinal upset **Local side effects:** • Miosis • Accommodative spasm • Pseudomyopia • Brow ache • Retinal detachment • Ciliary spasm and increased • Pupil block

0.25% Humorsol® Tosmilen® Ecothiophate iodide 0.03% 0.25% Echodide®		
Alpha-adrenergic agonists **Non selective** Dipivefrin 0.1% Propine® Epinal® d-Epifrin® Glaucothil® Epinephrine 0.25% 0.5% 1.0% 2.0% **Alpha-2 selective** Apraclonidine 0.5% 1.0% Iopidine® Brimonidine 0.2% Alphagan® Clonidine 0.125% 0.25% 0.5% Isoglaucon® Catapres® Glaucopres® Aruclonin®	• Decrease the secretion of aqueous humor, and increasing uveoscleral outflow[239,240]. • May have a neuroprotective effect on retinal ganglion cells[241,242]	**Common side effects:** • Burning sensation immediately after application • Disturbances to the conjunctiva (blanching, follicle development, infections) • Corneal staining • Ocular hyperaemia • Photophobia and taste disturbances[31] **Less common side effects:** • Bradycardia[243] • Hypotension [31]
Combination Therapies Cosopt (timolol and dorzolamide) Combigan (brimonidine and timolol) Simbrinza suspension (brinzolamide and brimonidine) Fixed-combination PGA/timolol combinations including: (0.05% latanoprost/0.5% timolol, 0.0004% tavoprost/0.05% timolol, 0.0005% tafluprost/0.5% timolol).		
Novel Agents (Rho kinase inhibitors) Glanatec ophthalmic solution 0.4%	• Causes a dose-depended decrease in intraocular pressure, along with an increase in trabecular outflow facility[244].	• Conjunctival hyperaemia[11,245], due to vasodilator effect. • Reduction of the intraocular penetration of other intraocular pressure modulating drops [246]. (Of particular importance if using them in multi-drop regimen)

Table 2: Lasers in lowering the intraocular pressure

Type of Laser	Mechanism of action
Laser Trabeculoplasty • **Argon laser trabeculoplasty (ALT)**	**Increasing the outflow** • Causes TM contraction and increases or ensures continuity of flow in Schlemm's canal. • ALT is also associated with coagulative damage, fibrin deposition and damage to the trabecular beams, endothelium, and subsequent TM remodelling.[247,248]
• **Selective laser trabeculoplasty (SLT)**	• Uses a frequency-doubled, short pulse, Q-switched Nd:YAG laser applied at the slit-lamp • Act at a cellular level by inducing cytokine release,[249] matrix metalloproteinase (MMP) induction to remodel the ECM, and macrophage recruitment in order to clear debris.[250–252] • Causes little to no mechanical changes in the trabecular meshwork,[253,254] in contrast to ALT.
• **Micropulse laser trabeculoplasty (MLT)**	• MLT is thought to induce inflammatory cytokine release and lower intraocular pressure in a similar manner to SLT.[255] • The micropulse laser and longer wavelength (532/577nm) provides advantages over ALT by being less destructive in terms of collateral damage and scarring of the tissues,[256] however provides a smaller pressure-lowering effect.[257]
Cyclophotocoagulation • **Transscleral cyclophotocoagulation (TSCPC)**	**Reducing inflow** • The energy of TSCPC is selectively absorbed by the melanin-containing tissues, inducing necrosis of the ciliary epithelium and stroma.[258,259]
• **Endoscopic cyclophotocoagulation (ECP)**	• Using endoscopic probe held 3-4mm away from the ciliary

	processes, with the surgeon applying laser energy in a semi-continuous anterior to posterior fashion, circulating around 270-360 degrees ablating the visible ciliary epithelium, under direct endoscopic view
• **Micropulse transscleral cyclophotocoagulation (MP-TSCPC)**	• Micropulse laser technology is applied directly through the sclera and absorbed by pigmented tissues. • The on/off cycle of micropulses propagates a build-up of energy within the target tissues, whilst the surrounding tissues have a chance to dissipate their energy in the "off" periods, and avoid reaching the coagulative threshold[126], this leads to less hypotony and inflammation.[127]

Table 3: Different surgical approaches

Type of surgery	Description and mechanism
Trabeculectomy	• A fistula with a trap door is created between the anterior chamber and sub-tenon space at the level of the trabecular meshwork (TM) to allow the build up of aqueous humor to flow into a small reservoir (bleb) in the superior aspect of the globe[260] thus lowering IOP.[59]
Tube shunts: • **Valved**: Ahmed's valve ○ Adult model S2, ○ Pediatric model S3 ○ Newer model: M4 ○ Others: double plates, parsplana • **Non-valved:** ○ Molteno ○ Baerveldt ▪ 250mm^2 plate ▪ 350mm^2 plate ▪ Parsplana	• They are flexible silicone or polypropylene implanted tubes that drain aqueous humor from the anterior chamber to an external reservoir in the subconjunctival space
Non-penetrating glaucoma surgery (NPGS)	They improve aqueous drainage without penetrating into the anterior chamber at the time of the initial surgery
• **Deep sclerectomy**	• It involves making a 5 × 5 mm superficial scleral flap, then removing a second scleral flap 4 × 4 mm beneath the original to leave a residual scleral bed of 50–100 microns. • Schlemm's canal is de-roofed.
• **Viscocanalostomy**	• Injecting high viscosity sodium hyaluronate

	(Healon GV) into Schlemm's canal as a means of improving aqueous drainage.[187] • The superficial scleral flap is tightly sutured so aqueous reach the two surgically created ostia of Schlemm's canal, travel circumferentially within the canal and enter the collector channels and then the aqueous veins.
Express shunt (Alcon Laboratories, Inc., Fort Worth, TX)	• It is a stainless-steel non-valved shunt implanted under the scleral flap and to drain aqueous humor from the AC to an intrascleral space

Table 4: Minimally invasive glaucoma devices

Mechanism of action	**Devices that meet the definition of MIGS**	**Devices that doesn't meet the definition of MIGS**
The trabecular based devices work by improving trabecular outflow through Schlemm's canal	Canal based (trabecular microbpass stents) • Glaukos iStent (Glaukos Corp., Laguna Hills, CA, USA) • Hydrus (Ivantis Inc., Irvine, CA, USA)	Canal based includes: • Ab interno trabeculectomy: Trabectome (NeoMedix, Tustin, CA, USA) • Ab interno trabeculotomy: iScience catheter
The suprachoroidal-based devices improve the uveoscleral outflow by connecting the anterior chamber and the suprachoroidal space	Suprachoroidal based (Ab interno suprachoroidal stents) • Glaukos iStent supra (Glaukos Corp., Laguna Hills, CA, USA) • Transcend CyPass (Alcon, Fort Worth, TX, USA)	Suprachoroidal based (Ab externo suprachoroidal stents): • Solx Gold Shunt (SOLX, Waltham, MA, USA)
The subconjunctival devices create an alternative outflow pathway of the aqueous humor to the subconjunctival space.[261,262]	Subconjunctival based which includes: • Ab interno transscleral filtration devices (Aquesys Xen) (Allergan, Dublin, Ireland) • Ab externo transscleral filtration devices (InnFocus Microshunt) (Santen Pharmaceutical Company Ltd, Osaka, Japan)	Subconjunctival based (Ab externo transscleral filtration devices): • ExPress shunt (Alcon Laboratories, Inc., Fort Worth, TX)

Table 5: Description of the most commonly used Minimally invasive glaucoma devices.

Device	Description
iStent	• A heparin-coated, nonferromagnetic titanium device with a snorkel shape that is implanted into Schlemm's canal (SC)
Hydrus	• This is a crescent-shaped trabecular bypass device made of nitinol, a shape-memory alloy, which when deformed, returns to its original shape after being heated. • It measures 8 mm long, straddling 3 clock hours of SC. • It acts as a scaffold so that it does not block the collector channel ostia.
The CyPass	• It is a polyamide implant, 6.35 mm in length and 510 µm in external diameter t • Connects between the anterior chamber and the supraciliary space through the microholes placed along its length. • The collar of the device rests in the anterior chamber angle[263]
XEN Gel Stent	• It is an ab interno gelatin stent • It is 6 mm in length and composed of porcine gelatin crosslinked with glutaraldehyde. • Three models with inner diameters of 45, 63 and 140 µm,[209] with 45 µm being recommended by the manufacturer
InnFocus	• It is an ab externo drainage device • Formed of SIBS (polystyrene-blockisobutylene-block-styrene), which is a biocompatible and biostable thermoplastic elastomer