Review

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Current and Emerging Therapies for Glaucoma: A Narrative Review

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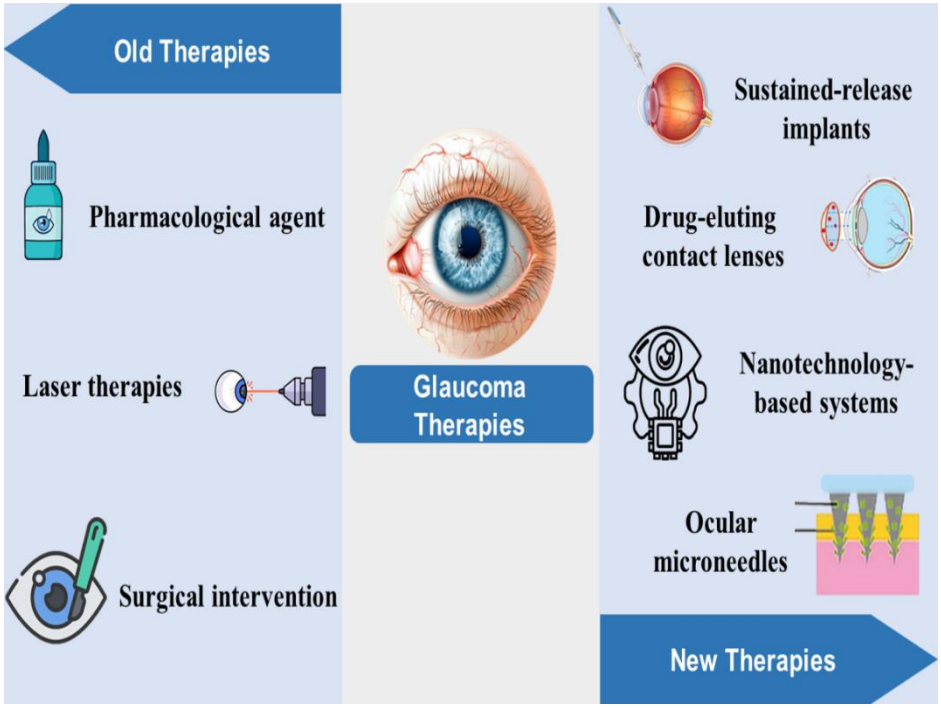

Abstract: The main goals of glaucoma management are to lower intraocular pressure (IOP) and enhance ocular perfusion. Though current therapeutic modalities—including pharmacological agents, laser procedures, and surgical interventions—have shown efficacy, certain limitations persist. Major issues include suboptimal adherence to topical drugs and the possibility of both transient and long-term consequences following laser or surgical treatment. These limitations call for the development of alternative and more effective therapeutic approaches. Novel approaches, such as sustained-release implants, drug-eluting contact lenses, nanotechnology-based delivery systems, ocular microneedles, and iontophoresis, promise more sustained, targeted IOP reduction. However, challenges like cost and accessibility could hinder their broad clinical acceptance. This review provides a comprehensive summary of both conventional and emerging methods of glaucoma treatment, comparing their mechanisms of action, clinical efficacy, and related constraints. It also combines pharmacological approaches, fundamental ophthalmological concepts, and recent technological advancements, which together drive the progression of present and future therapeutic modalities

Keywords: Glaucoma, Intraocular Pressure (IOP), Glaucoma Surgeries, Glaucoma Laser Therapy, New Antiglaucoma Medications, Durysta Implant, iDose Implant, Iontophoresis, Ocular Microneedles, Ocular Plugs and Inserts.

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Glaucoma Overview

Definition

Glaucoma is a spectrum of ocular diseases characterized by the gradual degeneration of the optic nerve, often connected to increased intraocular pressure (IOP). This chronic neurodegenerative condition progressively reduces the visual field and, if left uncontrolled, can lead to permanent vision loss. While many subtypes of glaucoma have a key modifiable risk factor—increasing IOP—some variants, such as normal-tension glaucoma, can develop even within the physiological range. Typically, glaucoma involves both continuous IOP elevation and a gradual decline in retinal ganglion cells (RGCs), which are essential for transmitting visual signals from the retina to the brain. Globally, glaucoma ranks among the leading causes of permanent blindness. Early stages of the disease often progress silently, making early diagnosis crucial [1–3].

Glaucoma Types

Primary open-angle glaucoma (POAG)

It is the most common form of glaucoma, caused by a slow rise in IOP due to reduced aqueous humor (AH) outflow through the trabecular meshwork. Early in its course, this chronic condition typically progresses silently, leading to gradual optic nerve damage without noticeable symptoms. While central vision usually remains intact until the later stages, peripheral vision often deteriorates as POAG advances. The condition is relatively rare before the age of 50, with a notably higher incidence among African American populations [1–3].

Angle-closure glaucoma (ACG)

ACG occurs when the drainage angle of the eye becomes blocked, preventing aqueous humor outflow and leading to a sudden or gradual elevation in intraocular pressure (IOP). The acute presentation is usually dramatic, consisting of extreme ocular pain, nausea, vomiting, headache, and blurred vision. Although symptoms in its chronic form may be more subdued, untreated cases can still result in significant vision loss. More often seen in those with hyperopia, ACG is especially common among some Asian populations [1–3].

Normal-tension glaucoma (NTG)

It is a subtype of glaucoma in which optic nerve damage occurs even when IOP remains within the typical physiological range (10–21 mmHg). While the exact pathophysiology of NTG remains unknown, poor ocular perfusion is believed to play a significant role. The clinical course of NTG typically mirrors that of POAG, with early peripheral vision loss and central vision usually preserved until the advanced stages. NTG is particularly more prevalent in certain populations, especially among Japanese individuals, likely due to a combination of environmental factors and genetic predisposition [1–3].

Secondary glaucoma

Secondary glaucoma can result from underlying diseases or external factors such as ocular trauma, intraocular inflammation, or prolonged corticosteroid use. The etiology determines whether IOP is elevated or remains within the normal range. Clinical symptoms typically resemble those seen in ACG or POAG, though they can vary. While secondary glaucoma is less common than primary forms, it can cause significant visual morbidity, especially in individuals with uveitis, a history of ocular damage, or prolonged corticosteroid use [1–3].

Congenital glaucoma

Congenital glaucoma, typically found in infancy or early childhood, results from developmental abnormalities within the ocular drainage system. Excessive tearing, photophobia, and corneal enlargement—clinical features that sometimes suggest increased intraocular pressure—are hallmark signs. Early intervention can reduce optic nerve damage and help preserve visual function, making prompt diagnosis absolutely essential. Considering the possible involvement of hereditary factors in its pathogenesis, the diagnostic process heavily relies on knowing a thorough family history [4,5].

Glaucoma Pathology

Glaucoma's pathogenesis consists of a complex interaction of elements, including elevated IOP, compromised optic nerve perfusion, genetics, and various systemic influences

Elevated IOP

Primarily caused by reduced AH drainage, elevated IOP is essential to the pathogenesis of glaucoma. AH, produced by the ciliary body, empties via Schlemm's canal and the trabecular meshwork. In POAG, structural changes in the trabecular meshwork impede aqueous humor outflow. These changes are commonly linked to extracellular matrix (ECM) remodeling, which results in the accumulation of ECM proteins such as collagen and fibronectin. This dysfunction causes the trabecular meshwork to stiffen, reducing its drainage efficiency. In ACG, either acute or chronic closure of the iridocorneal angle physically blocks the aqueous humor drainage pathway, raising IOP [6–8].

Optic nerve damage

The main cause of optic nerve damage in glaucoma is raised IOP, which mechanically stresses the optic nerve head (ONH), leading to characteristic glaucomatous changes. According to the "mechanical theory," elevated IOP presses on the lamina cribrosa—a porous structure at the ONH—causing deformation and subsequent axon damage in RGCs. This mechanical stress triggers a series of cellular events, including structural remodeling of the ONH, RGC death, and disruption of axonal transport. At the same time, the "vascular theory" suggests that reduced blood flow to the ONH, possibly resulting from impaired autoregulation and lower perfusion pressure, worsens tissue damage and contributes to glaucomatous degeneration. Both mechanical and vascular factors interact to ultimately cause neuroretinal rim thinning and an increased cup-to-disc ratio [6–8].

Genetic factors

Recent developments in genetic research have highlighted several genes linked to glaucoma pathogenesis. Primary congenital glaucoma has been associated with mutations in the MYOC gene, while alterations in the CYP1B1 gene are linked to several forms of hereditary glaucoma. These genetic factors may trigger abnormal cellular activities, including altered cellular metabolism and increased oxidative stress. Additionally, recent studies emphasize the critical role of the transforming growth factor-beta (TGF-β) signaling pathway in facilitating ECM remodeling and fibrosis within the trabecular meshwork, influencing IOP and disease progression [6,7].

Systemic and environmental factors

By influencing ocular perfusion pressure and increasing oxidative stress, systemic disorders such as hypertension, diabetes, and sleep apnea have been shown to contribute to the pathogenesis of glaucoma. Additionally, environmental factors, including smoking, high-fat diets, and prolonged UV light exposure, influence the risk of glaucoma by affecting vascular health and exacerbating oxidative stress [6–8].

Inflammatory conditions

Glaucoma is known to develop in part due to inflammatory diseases, including uveitis and ocular trauma. Chronic inflammation can alter the trabecular meshwork, increasing resistance to AH outflow. Trauma can similarly lead to secondary glaucomatous changes through scarring, hemorrhage, or structural damage within the drainage system [6, 8, 9].

Given the multifactorial nature of glaucoma and the limitations of existing therapies, a more comprehensive understanding of the disease is crucial. This review explores both established and emerging treatment modalities, with an emphasis on their mechanisms of action and clinical efficacy. It also incorporates interdisciplinary insights from ophthalmology, pharmacology, and recent technological advancements to present an integrated perspective on current practices and future directions in glaucoma management.

Relevant data were obtained through a systematic search of databases such as PubMed, Scopus, Web of Science, and Google Scholar, focusing on key studies and publications pertaining to glaucoma therapy. Both historical and recent advancements have been considered to ensure a well-rounded overview of available and developing treatment strategies.

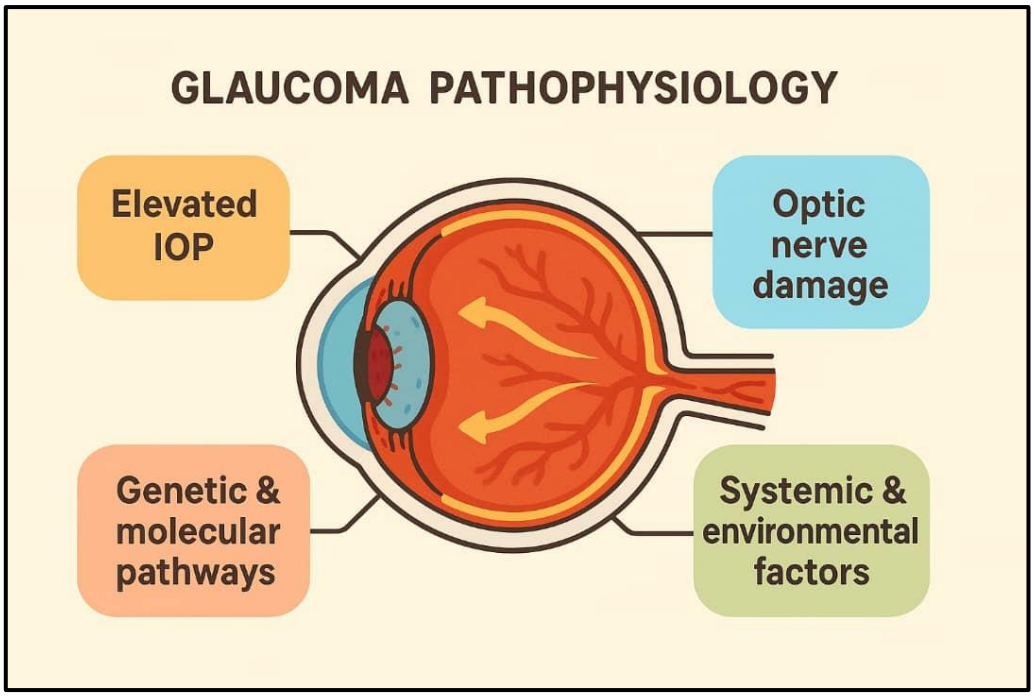

Fig. 1. Pathophysiology of Glaucoma. This diagram illustrates the multifactorial mechanisms involved in the development of glaucoma. Elevated IOP is a major risk factor contributing to optic nerve damage, the hallmark of the disease. Genetic and molecular pathways also play a critical role in susceptibility, alongside systemic and environmental factors.

Traditional therapies overview

1.1. Medications

Prostaglandin analogs: Prostaglandin analogs including latanoprost, bimatoprost, tafluprost, and travoprost are acting act by increasing the expression of matrix metalloproteinases (MMPs) in ciliary muscle cells, inducing remodeling of extracellular matrix in ciliary muscle bundles of the uveoscleral pathway, subsequently enhancing aqueous humor (AH) outflow. They are the most effective antiglaucoma medications and are usually administered on a once-daily schedule. Although they are well tolerated, prostaglandin analogs may be associated with certain side effects, including conjunctival hyperemia, eyelash growth, and changes in iris pigmentation [10-14].

Beta-blockers: Ocular blockers (e.g betaxolol, timolol) are essential antiglaucoma medications that have long been used in glaucoma treatment. By blocking β_2-adrenergic receptors in the ciliary body, these drugs reduce AH production and thereby decrease IOP, with possible systemic adverse effects, particularly in patients with pre-existing pulmonary or cardiovascular conditions [10,11,15].

Alpha agonists: α_2-Adrenergic agonists, such as brimonidine and apraclonidine, lower IOP by stimulating α_2-receptors in the ciliary body, resulting in reduced AH production. In

addition to their primary effects, these agents exhibit α_1-adrenergic activity, inducing conjunctival vasoconstriction, lid retraction, and mild mydriasis. Brimonidine has also been reported to enhance uveoscleral outflow, contributing to further IOP reduction [10,11,15].

Carbonic anhydrase inhibitors: These antiglaucoma agents lower AH production by inhibiting carbonic anhydrase II (CA II) in the ciliary epithelium, thereby reducing sodium transport and fluid accumulation in the posterior chamber. Used topically (e.g., dorzolamide, brinzolamide) and systemically (e.g., acetazolamide), CAIs are effective in lowering IOP. However, systemic use of CAIs is associated with side effects such as fatigue, paresthesia, nausea, dizziness, hypokalemia, and nephrolithiasis, which limits their long-term use [10,11,15,16].

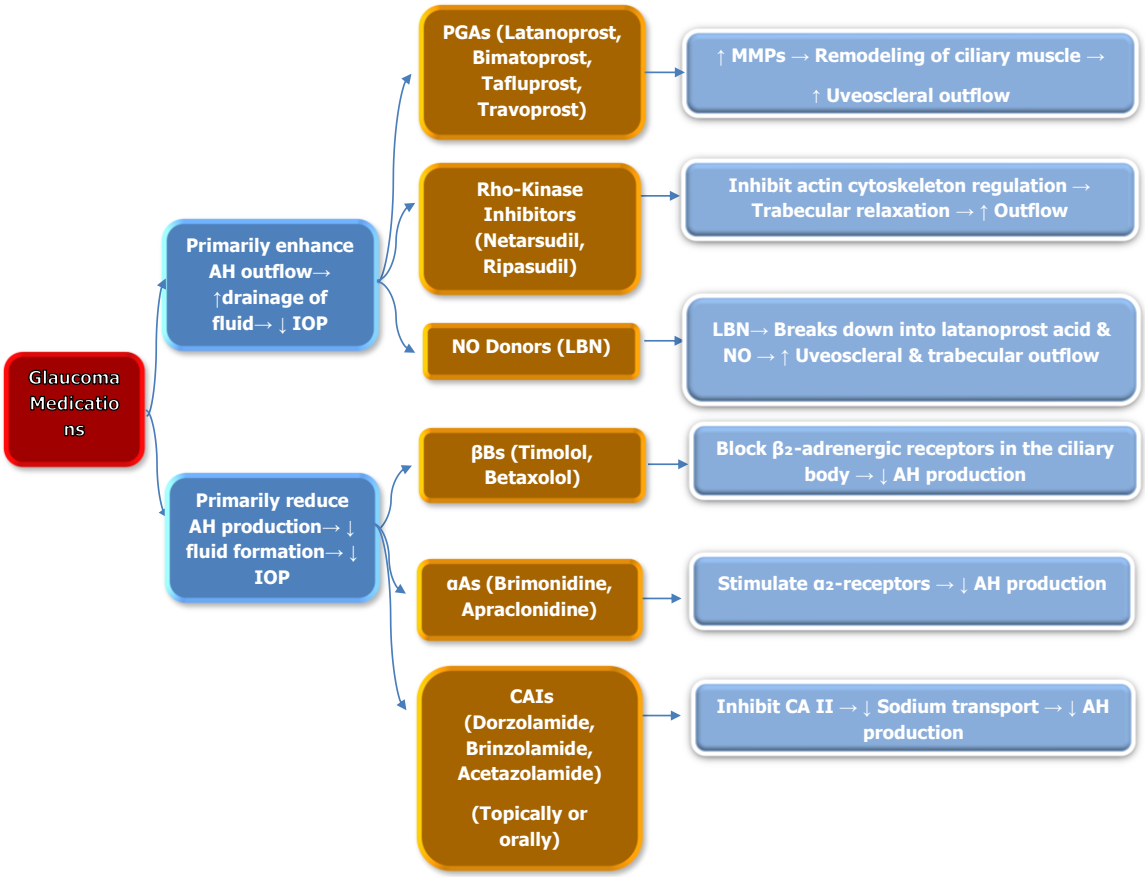

Fig. 2. Schematic diagram of Glaucoma medications.

Rho-kinase inhibitors: Rho-kinase inhibitors, including ripasudil and netarsudil, reduce IOP by enhancing aqueous humor outflow. They inhibit the phosphorylation of proteins that regulate the actin cytoskeleton in the trabecular meshwork, hence reducing outflow resistance. Additionally, they may decrease aqueous secretion by inhibition of the norepinephrine transporter. Approved in Japan (ripasudil) and the US (netarsudil), these inhibitors are often used alongside other glaucoma treatments to effectively manage IOP.

Netarsudil (Rhopressa®), while primarily categorized as a rho-kinase inhibitor, also has nitric oxide-donating properties [10,11,17,18,19].

Nitric oxide (NO)donors: NO donors are also a new class of antiglaucoma medications that act through dual mechanisms. A prime example is Latanoprostene bunod (LBN), which was approved by the FDA in 2017. LBN is hydrolyzed by ocular esterases into latanoprost acid (prostaglandin analog) and butanediol mononitrate (NO-donating). Latanoprost acid increases AH outflow through the unconventional pathway, while NO induces trabecular meshwork relaxation, thereby improving drainage through the conventional outflow pathway. Through this dual mechanism, nitric oxide donors may also have a neuroprotective effect [10,20,21,22,23].

1.2 Laser Therapies

Laser therapies aim to control IOP by either reducing AH production or enhancing its outflow.

1.2.1 Laser Trabeculoplasty

Selective Laser Trabeculoplasty (SLT) is a minimally invasive procedure used in the management of OAG to enhance AH outflow through the trabecular meshwork, thereby reducing IOP. SLT selectively targets pigmented trabecular meshwork cells using a frequency-doubled Nd:YAG laser (532 nm), inducing a biological response that increases AH drainage without causing thermal damage to adjacent tissues. Primarily recommended for patients with POAG, SLT is repeatable due to its minimal tissue disruption and lack of cumulative scarring, typically reducing IOP by approximately 20–30%. Complications are generally mild and transient, including inflammation and rare post-procedural IOP spikes, making SLT a favorable option with an established safety profile [24,25].

Argon Laser Trabeculoplasty (ALT) employs thermal energy from an argon laser (488/514 nm) to create controlled burns in the trabecular meshwork, thereby inducing localized scarring that promotes AH outflow. Although ALT also achieves an IOP reduction of 20–30%, its long-term efficacy tends to decline over time. Due to its permanent tissue effects and higher risk of collateral damage—particularly to the corneal endothelium—ALT is now less commonly used. Potential complications include transient IOP elevation, post-procedural inflammation, and injury to surrounding ocular structures [24, 25].

1.2.2 Laser Iridotomy

Nd:YAG laser iridotomy creates a small channel in the peripheral iris to facilitate AH flow and prevent or manage ACG. This procedure uses a 1064 nm Nd:YAG laser to precisely create an opening in the iris, allowing communication between the posterior and anterior chambers, thereby preventing IOP elevation. It is primarily indicated for patients with PACG or those at risk of acute angle-closure. Complications are usually mild and may include transient inflammation, IOP spikes, and, in rare cases, corneal damage or cataract formation. Due to its established efficacy and relatively safe profile, Nd:YAG iridotomy is commonly selected in clinical practice [24, 26].

For patients with heavily pigmented irises, argon laser iridotomy, which uses thermal energy to form a full-thickness iris opening, can be especially effective. It may be used alone or alongside Nd:YAG laser to ensure patency of the iridotomy. However, this technique carries a higher risk of complications such as iris bleeding, temporary IOP elevation, and thermal injury to adjacent tissues. Despite these risks, it remains a suitable option in selected cases of angle-closure glaucoma, making careful technique selection crucial based on individual patient features [24, 26].

1.2.3 Cyclophotocoagulation

Cyclophotocoagulation is a laser-based procedure designed to reduce AH production by targeting the ciliary body. In Transscleral Diode Laser Cyclophotocoagulation (TSCPC), a continuous-wave diode laser (810 nm) is used to coagulate the ciliary processes, thereby decreasing AH production. TSCPC is particularly effective in cases of refractory glaucoma—such as neovascular or end-stage glaucoma—when other treatment options have failed. While it can significantly lower IOP, potential complications include hypotony, inflammation, and, in rare instances, phthisis bulbi. Given its irreversible nature, the procedure should be reserved for advanced cases and used with caution [26, 27].

Micropulse Transscleral Cyclophotocoagulation (MPTSC) utilizes the same diode laser technology but delivers energy in short micropulses, allowing for intermittent cooling periods. This design reduces collateral tissue damage while still effectively targeting the ciliary body to suppress AH production. With a lower risk of complications such as hypotony and inflammation, MPTSC is considered safer than traditional TSCPC and is suitable for repeated treatments in patients with refractory glaucoma [27–29].

1.2.4 Laser peripheral iridoplasty (LPI)

LPI also known as gonioplasty—is a laser procedure that widens the drainage angle by inducing contraction of the peripheral iris. Using low-energy argon laser burns, the technique retracts the iris away from the trabecular meshwork, thereby improving AH outflow. LPI is particularly useful in situations such as plateau iris configuration or when laser iridotomy alone fails to adequately open the angle, and it is often employed alongside other glaucoma treatments like laser iridotomy. The procedure is generally safe, with complications usually limited to mild inflammation or transient IOP elevation. However, its effects may be temporary, and repeat treatments can sometimes be necessary to maintain long-term angle patency (24, 30, 31)

1.3 Surgical Interventions

Surgical interventions in glaucoma are typically performed when pharmacological and laser treatments fail to provide adequate IOP control. These procedures employ various techniques aimed at either improving AH drainage or reducing its production.

1.3.1 Trabeculectomy

Once regarded as the gold standard surgical intervention for glaucoma management, especially when pharmacological and laser treatments failed to effectively lower IOP, trabeculectomy involves creating a drainage flap in the sclera to allow AH to bypass the obstructed trabecular meshwork, thereby reducing IOP. Primarily used to treat both OAG and ACG, trabeculectomy is generally a successful procedure. However, it carries potential risks, including infection, bleb-related complications, hypotony, and scarring. Over time, newer, less invasive treatments with comparable efficacy but lower risks and shorter recovery times have increasingly replaced trabeculectomy [32, 33].

1.3.2 Glaucoma drainage devices (GDDs)

Designed to transfer AH from the anterior chamber to an external reservoir, GDDs, also known as tube shunts or implants (e.g., Ahmed valve, Baerveldt implant), lower IOP. They are particularly useful in cases of complicated or refractory glaucoma, including neovascular or uveitic glaucoma, where traditional surgical techniques may not be effective. GDDs primarily offer consistent IOP control, which is their main advantage. However, potential complications include diplopia, tube erosion, infection, and long-term risks such as tube obstruction or failure. While generally effective, GDDs are typically reserved for severe or challenging cases of glaucoma [34–36].

1.3.3 Minimally Invasive Glaucoma Surgery (MIGS)

MIGS are a spectrum of less invasive surgical procedures designed to lower IOP and minimize complications usually related to conventional glaucoma operations. The target anatomical sites for MIGS include the trabecular meshwork (e.g., iStent, Hydrus microstent), Schlemm's canal (e.g., ab-interno canaloplasty), the suprachoroidal space, the subconjunctival space (e.g., Xen Gel Stent), and aqueous production (e.g., endoscopic cyclophotocoagulation). Small devices implanted inside the drainage system of the eye improve aqueous outflow in procedures such as trabecular micro-bypass surgery, iStent, and Hydrus microstent. MIGS are typically recommended for patients with mild to moderate OAG especially when pharmacological treatments alone prove inadequate. MIGS primarily offers shorter recovery times, lower complication rates, and reduced reliance on drugs. However, restrictions include the potential for device failure or scarring over time, which might affect long-term efficacy [37, 38].

1.3.4 Non-Penetrating Glaucoma Surgeries (NPGS)

Designed to lower IOP, NPGS consists of three procedures: deep sclerectomy, viscocanalostomy, and canaloplasty, all of which avoid entering the anterior chamber.
Deep sclerectomy involves excising part of the sclera to allow AH drainage into a small reservoir beneath the ocular surface in the subconjunctival space. Compared to trabeculectomy, this procedure is generally recommended for patients with OAG and carries a lower risk of complications such as hypotony and infection. While effective for mild to moderate glaucoma, deep sclerectomy usually results in a more modest decrease in IOP. Although infrequent, complications at the drainage site may cause scarring that compromises long-term IOP control. In some instances, achieving optimal IOP management may necessitate additional surgical interventions [39, 40].

Viscocanalostomy increases AH drainage by dilating Schlemm's canal and placing viscoelastic materials. Associated with a reduced risk of complications, it is a less invasive alternative to conventional trabeculectomy. Typically, viscocanalostomy lowers IOP by 15–25%. However, especially in patients with advanced glaucoma, it may be less successful than trabeculectomy. Therefore, it is generally more suitable for those with mild to moderate glaucoma or those at higher risk of complications from more invasive surgical procedures [41–43].

Using a microcatheter and viscoelastic agents, canaloplasty aims to widen and open Schlemm's canal to improve AH outflow. This approach is especially recommended for

patients with OAG who require continuous IOP reduction without disrupting ocular structures. Canaloplasty carries a lower risk of complications compared to more traditional treatments like trabeculectomy, thereby lowering the chances of hypotony and infection. Studies show that, while maintaining a strong safety profile, canaloplasty provides significant long-term IOP reduction [44–46].

1.3.5 Angle Surgeries

Focusing on the trabecular meshwork and Schlemm's canal, these techniques—including goniotomy and trabeculotomy—help to increase aqueous outflow. Goniotomy, which is usually used to treat congenital or pediatric glaucoma, involves making an incision in the trabecular meshwork to enable aqueous humor discharge. It is particularly effective in young patients with developmental abnormalities in the ocular drainage system, such as those associated with congenital glaucoma. For young patients, goniotomy is a relatively simple procedure with fewer complications compared to more complex surgeries. However, anatomical and pathological differences typically reduce its efficacy in cases of secondary glaucoma in adults. Although complications are rare, they can include a sudden increase in IOP, hemorrhage, and inadequate IOP control, which may necessitate further surgical intervention [47].

Using an ab-externo approach, trabeculotomy opens the trabecular meshwork to enhance AH outflow. Both pediatric and adult glaucoma patients can benefit from this surgery, with younger patients typically experiencing significant IOP reduction. However, its success in adults is more variable and largely depends on the type of glaucoma and individual patient factors. Scarring of the trabecular meshwork is a potential complication, and further surgical procedures may be necessary to maintain long-term IOP control [48, 49].

1.3.6 Iridectomy

Laser treatments mostly eclipse surgical iridectomy; however, for some patients with ACG, it remains an option when laser iridotomy is not feasible. This surgery removes a portion of the iris to increase eye fluid dynamics, thus helping to lower IOP. It is still a necessary treatment choice for patients who cannot undergo laser therapy, despite possible complications such as inflammation, hemorrhage, and post-procedural IOP spikes being linked to it [50, 51].

While the previously mentioned surgical treatments are specifically for glaucoma, cataract surgery also helps control some types of glaucoma by lowering IOP. In patients with primary

POAG and ocular hypertension, cataract surgery alone is effective in reducing IOP; it can also aid in controlling IOP in some cases of PACG. However, in patients with moderate to advanced glaucoma, cataract surgery alone may not be enough to provide IOP control; therefore, other glaucoma surgeries are necessary to reach and sustain the intended IOP levels [52,53].

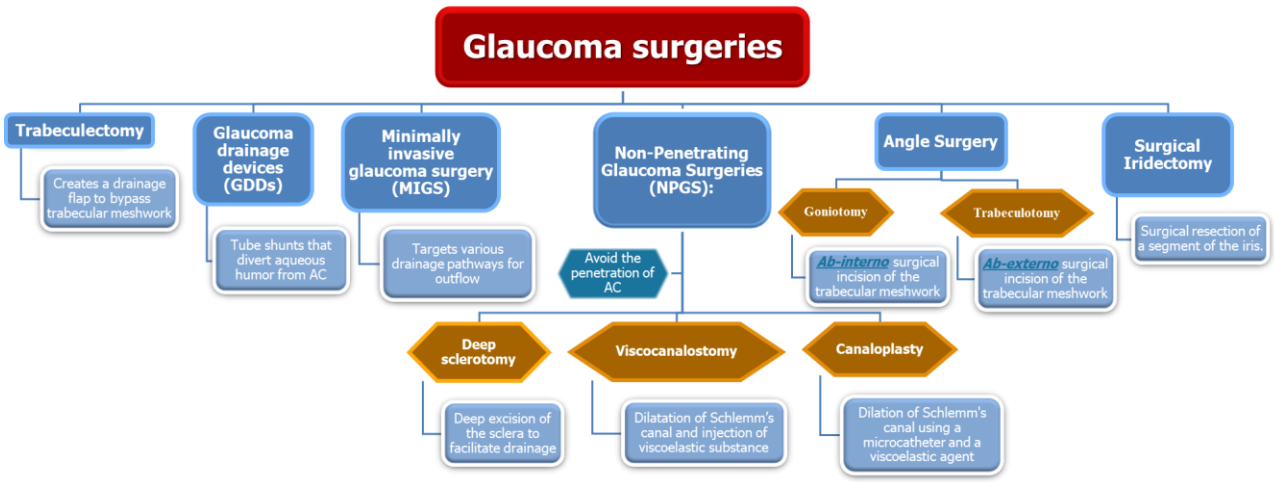

Fig. 3. Schematic diagram of Glaucoma surgeries.

2. Newer therapies: Focus on novel drug delivery systems

New drug delivery systems, which seek to increase patient adherence, boost the efficacy of medications, and offer better overall therapeutic outcomes, have resulted from recent developments in glaucoma therapy. These approaches help address some of the difficulties of conventional treatments, including the requirement for regular dosing and the possibility of side effects [54].

2.1 Sustained-release Delivery Implant

Sustained-release intraocular implants have become a major development in glaucoma treatment, offering controlled, prolonged drug delivery that helps maintain stable IOP and reduces adherence issues usually linked with daily topical therapies. Classified as either biodegradable or non-biodegradable, these implants have different pharmacokinetic effects and procedural considerations. A well-known biodegradable implant is Durysta® (bimatoprost), which received FDA approval in March 2020 [55] and is indicated for the treatment of ocular hypertension or open-angle glaucoma (OAG). The implant, which targets the iris-ciliary body, is intended for intracameral injection into the anterior chamber using a single-use, preloaded applicator, thus delivering the drug directly to the iris-ciliary body. Pupil dilation must be avoided before insertion, and the insertion process requires strict aseptic technique, magnification-assisted vision, and head stabilization. After implantation,

the poly(lactic-co-glycolic acid) matrix breaks down via hydrolysis, releasing bimatoprost over 4 to 6 months. For patients unable or reluctant to follow topical treatment, this continuous release guarantees consistent pharmacological action and reduces IOP variability, thus providing a reasonable alternative. With a favorable safety profile, clinical data supports the efficacy of the implant in lowering long-term IOP [55, 56]. On the other hand, the FDA approved the non-degradable, sustained-release intraocular implant known as iDose® TR in December 2023 for the treatment of ocular hypertension or open-angle glaucoma (OAG). This implant is designed to progressively release the prostaglandin analogue travoprost over a 6 to 12-month period, thus lowering the daily need for eye drop treatment. While reducing the common side effects of topical treatments, such as ocular irritation and conjunctival hyperemia, the iDose® TR improves patient compliance and has the potential to enhance therapeutic outcomes by simplifying treatment regimens [55,57].

Three main components make up the iDose® TR implant: a titanium body acting as the drug reservoir; a scleral anchor, which secures the implant to the inner scleral wall via the trabecular meshwork; and a membrane that allows for the slow release of travoprost. This arrangement enables continuous drug delivery for 6 months to 1 year. Under the direction of an operating microscope, both insertion and removal are performed for precise placement. The implant has demonstrated a good safety profile; no notable adverse events related to corneal or conjunctival health have been recorded [57].

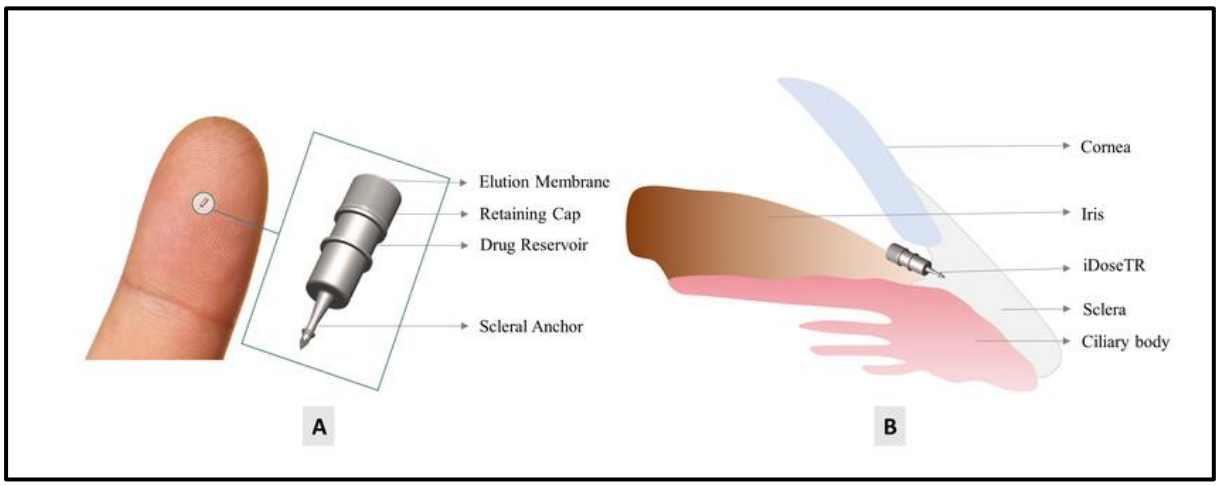

Fig. 4. (A) iDose® TR implant; (B) placement of the iDose® in the anterior chamber. Reproduced from Ichhpujani et al. (2023), under the Creative Commons Attribution 4.0 International License (CCBY 4.0). [58]

2.2 Contact Lenses

Beyond their conventional use in vision correction, contact lenses are now emerging as innovative tools for glaucoma management. These specialized lenses are designed to

embed therapeutic agents—typically prostaglandin analogues—that are gradually released to effectively lower IOP. By conforming to the corneal surface, they enhance patient adherence by delivering medication directly to the target site, thereby reducing the need for frequent eye drops. Drug-eluting contact lenses offer targeted medication release, improved patient convenience, and potentially fewer side effects compared to traditional eye drop therapies [60, 61].

Although most first-generation lenses remain in the experimental and research phases, numerous studies have evaluated their safety and efficacy. No contact lenses specifically designed for glaucoma drug delivery have yet received full FDA approval. However, some have been approved for other therapeutic uses, such as the treatment of dry eye [59, 62].

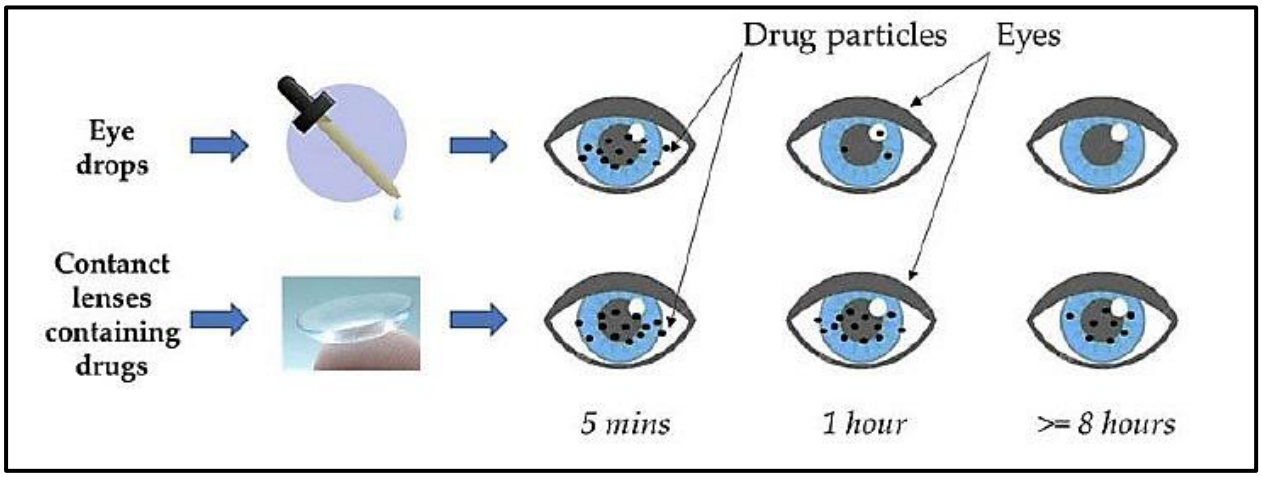

Fig. 5. Schematic of drug release time for contact lenses and a conventional topical formulation. Reproduced from Aljabri et al. (2023), under the Creative Commons Attribution 4.0 International License (CCBY 4.0) [63].

2.3 Nanotechnology-Based Delivery

Nanotechnology is an emerging approach in advanced drug delivery systems for glaucoma treatment. Designed to specifically target ocular structures, microspheres and nanospheres are part of the broader field of nanotechnology-based drug delivery systems aimed at improving therapeutic outcomes by increasing medication efficacy and improving IOP control. Ranging from 1 to 1000 micrometers in size, microspheres serve as carriers for slow drug release, thereby guaranteeing continuous IOP control over long periods [64]. Although microspheres have been extensively used in other medical disciplines, their use in glaucoma therapy remains experimental; there is currently no FDA-approved system available for this specific indication [60]. By contrast, a more recent development involves

nanospheres—particles ranging from 1 to 1000 nanometers in size. Their smaller dimensions enable more precise drug delivery to target areas by allowing deeper penetration into ocular tissues, thereby minimizing systemic side effects. While preclinical and clinical studies have shown encouraging outcomes, these technologies are still under investigation; at this point, no FDA-approved glaucoma treatment based on these systems exists [59].

2.4 Microneedles

Microneedles, ranging from 25 to 1000 μm, show great potential in the treatment of various ocular diseases even though they are still in the experimental stage. Applied directly to the eye, microneedles allow localized drug delivery of antibiotics, anti-inflammatory agents, anti-vascular endothelial growth factor (anti-VEGF) treatments, and antiglaucoma drugs. Several forms of microneedles are currently under research for their ability to efficiently deliver solutions or nano/microparticles to targeted ocular tissues, including solid (coated), dissolving, hollow, and bio-inspired designs. These technologies hold particular promise to control diseases including diabetic retinopathy (DR) and glaucoma [65, 66].

2.5 Hydrogen release systems

Using the antioxidant and anti-inflammatory qualities of molecular hydrogen, hydrogen-based drug delivery systems improve therapeutic efficacy in ocular diseases [67]. Designed to provide controlled and continuous hydrogen release, these technologies incorporate hydrogen into several platforms: hydrogen-rich solutions, hydrogels, and nanoparticles. Within ocular tissues, this focused approach might reduce oxidative stress and provide cellular protection [68]. Based on preliminary studies, hydrogen seems able to protect retinal cells and lower inflammation, so helping to regulate IOP and minimize side effects related to conventional treatments [68]. Notwithstanding these encouraging results, hydrogen-based systems are still at the experimental stage, and FDA approval for the treatment of glaucoma has not yet been granted [69].

2.6 Plugs and ocular inserts

Complementing existing systems such as the Durysta® implant, recent innovations—including punctal plugs and ocular inserts—have shown promise as adjuncts in the pharmacological management of glaucoma. Punctal plugs are small, biocompatible devices inserted into the tear ducts to reduce tear drainage, thereby prolonging the retention of topical drugs on the ocular surface. Although they do not directly release medication, their ability to enhance drug bioavailability and reduce dosing frequency significantly contributes

to improved treatment adherence [60, 70]. Placed in the conjunctival sac, ocular inserts—specifically designed for sustained drug delivery in glaucoma—are biodegradable devices that release medications steadily over extended periods. These inserts address adherence challenges associated with frequent eye drop use by maintaining consistent intraocular drug concentrations. Unlike conventional topical therapies, ocular inserts can provide therapeutic effects for several weeks or even months, potentially improving both treatment efficacy and patient compliance. Although approved for other ophthalmic indications, neither punctal plugs nor ocular inserts have yet received FDA approval for glaucoma treatment, despite their promising potential [61, 70].

2.7 Iontophoresis

Iontophoresis, currently under study for the treatment of glaucoma, is a non-invasive, electrically-assisted drug delivery system. Using a low-intensity electrical current, this method drives charged drug molecules across ocular barriers—particularly the cornea—enhancing penetration into anterior segment tissues. By enabling localized drug distribution, iontophoresis reduces systemic exposure and associated side effects while offering the potential for improved IOP control. Furthermore, it may reduce the need for frequent dosing by allowing controlled and sustained drug release, thereby supporting better patient adherence [62,65].

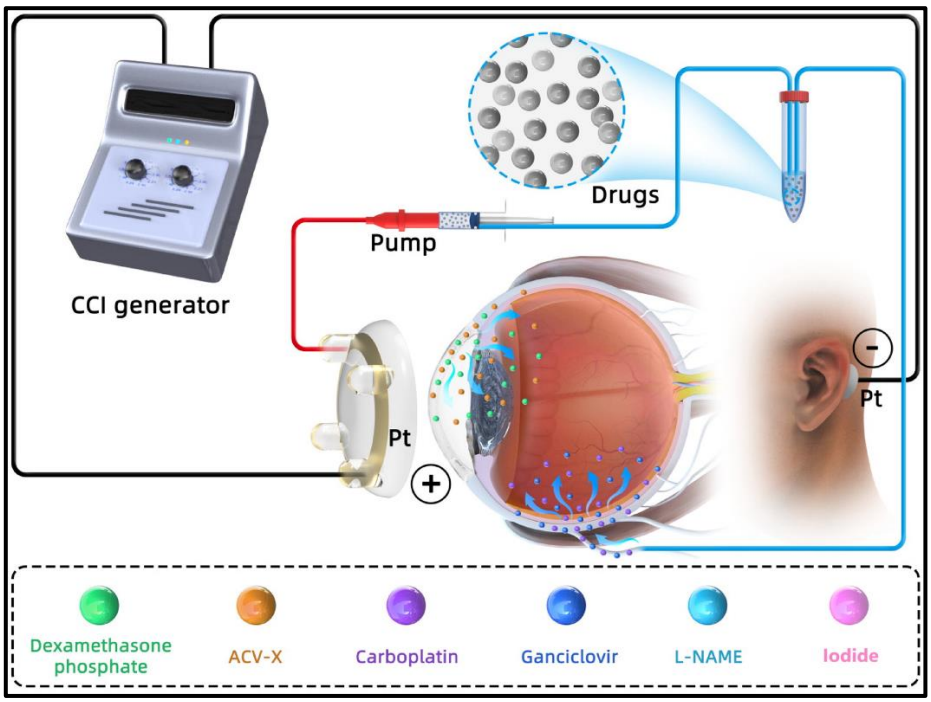

Fig. 6. CCI delivers different drugs to against multiple ophthalmological pathologies. Reproduced from Aljabri et al. (2023), under the Creative Commons Attribution 4.0 International License (CCBY 4.0).

[71] Abbreviations: CCI, Coulomb controlled iontophoresis; ACV-X, acyclovir (X = Arg, Gly and Trp); L-NAME, n'-nitro-L-arginine methyl ester.

2.8 Enhanced Topical Formulations

By utilizing innovative delivery systems like gels and emulsions to increase drug stability, corneal penetration, and overall therapeutic efficacy, enhanced topical formulations mark significant progress in glaucoma pharmacotherapy. These developments enable sustained IOP control and more effective ocular absorption, thus addressing the main limitations of conventional eye drops [61].

Formulations based on gels and emulsions help support controlled and prolonged drug release, thereby lowering the frequency of administration and increasing patient adherence. From an ophthalmological perspective, these systems have demonstrated better IOP control and greater patient comfort compared to conventional aqueous solutions. Gel-forming agents, for example, increase the ocular surface contact time of medications, thus improving clinical outcomes [70]. Current studies continue to refine these innovative formulations to further enhance their performance and expand their application in glaucoma management [72].

Monitoring the effectiveness of newer glaucoma therapies

Evaluating the clinical effectiveness of sustained-release implants, such as Durysta™ and iDose®, involves a multimodal approach centered around IOP control. Goldmann applanation tonometry remains the standard for IOP measurement and should be performed at baseline and during follow-up visits to assess therapeutic response. In parallel, optical coherence tomography (OCT) offers insight into structural changes in the optic nerve head and retinal nerve fiber layer, while standard automated perimetry (SAP) helps monitor functional visual field changes. For implant-specific assessment, slit-lamp examination is useful for confirming proper placement and identifying potential complications, including anterior chamber inflammation or conjunctival erosion. This combined strategy provides a comprehensive view of both the ocular response to treatment and the integrity of the implant over time [73-76].

Comparative analysis of newer therapies

Recent developments in glaucoma treatment provide better effectiveness than more traditional therapies. The dependability of IOP management has been greatly enhanced by creative drug delivery systems including advanced topical formulations and sustained-release implants. Systems like Durysta® for instance allow continuous drug release, thereby

lowering dosing frequency and improving treatment adherence. Likewise, better drug stability and ocular penetration provided by enhanced topical vehicles including gels and emulsions result in more consistent absorption and therapeutic results. By reducing systemic exposure and related side effects, these more recent modalities also show better safety profiles. While drug-eluting punctal plugs and ocular inserts provide continuous therapy directly at the site of action, targeted delivery technologies—including microneedles and iontophoresis—help to enable localized administration [57].

In addition, by lowering the need for regular dosing, reducing the total medication burden, and minimizing clinic visits, these new treatments offer possible long-term cost-effectiveness even if their initial costs are higher [59]. Moreover, the newer therapies are designed to increase quality of life and adherence by removing the need for daily eye drops, thereby improving patient satisfaction and adherence [57, 60].

Conclusions

The development of glaucoma treatment approaches is essential for overcoming the limitations of conventional therapies as glaucoma management increasingly emphasizes the attainment of optimal therapeutic outcomes. Although conventional interventions form the basis of glaucoma treatment, issues related to adherence, efficacy, and tolerability may impede them. By improving patient compliance and thereby enabling more consistent IOP, emerging drug delivery technologies—such as sustained-release implants, drug-eluting contact lenses, and minimally invasive techniques including microneedles and iontophoresis—offer promising options. Still, the effective incorporation of these developments into clinical practice depends on careful evaluation of elements including long-term safety, cost-effectiveness, and accessibility. Validation of the clinical advantages of these advanced treatments and their place alongside accepted treatment paradigms in thorough glaucoma management depends on ongoing research.

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