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Review Article

Glaucoma: A review of current management, patients' adherence, direct and indirect cost, and barriers to drug delivery

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Abstract

Glaucoma is the world's leading cause of permanent blindness, influenced by numerous variables, including socio-demographic factors. This review considered existing management practices and innovative methods of drug delivery, as well as how they relate to patient adherence and therapy costs. Literatures were compiled using search engines including ScienceDirect, PubMed, Google Scholar and WHO database. The eye is a complex organ with various anatomical barriers presenting significant challenges in treating glaucoma due to poor patient compliance with topical ocular medications. Advanced drug delivery systems like implants, nano or microparticles, punctal plugs, contact lenses, topical ring-type systems, gels, and other depot systems such as intracameral, supraciliary, and intravitreal applied in the extraocular, periocular, or intraocular sites, significantly enhance medication absorption, reduce adverse effects, and improve patient compliance. Poor treatment adherence, stemming from various reasons, lead to inadequate glaucoma management, increasing direct (34 to 45 %) and indirect costs (55 to 66 %) of therapy. As a result, a variety of treatments including enhanced drug delivery systems have been tested to address these concerns, and some modern pharmaceuticals and drug delivery technologies are being developed.

Keywords: *Drug delivery, Glaucoma, Healthcare costs, Ocular barriers, Patient compliance*

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INTRODUCTION

Glaucoma is a disease that causes cupping of the optic disc leading to impairment in vision and is considered a leading cause of blindness worldwide [1]. Various risk factors such as advanced age, hyperopia (far-sightedness), high intraocular pressure (IOP), myopia, African and East Asian ethnic origins, and family history contribute to the progression of glaucoma as well as Primary Open-Angle Glaucoma (POAG) [1,2]. Notably, a reduction in IOP significantly reduces the chances of glaucoma development [1].

Glaucoma accounts for 7.7 million of one billion cases of vision impairment (moderate to severe) or blindness that could have been averted globally [3]. According to a meta-analysis of prevalence studies published from 2000 to 2020, global prevalence of POAG was 2.4 %, with

Africa having the highest rate at 4 %. Furthermore, older men are particularly more prone to develop POAG [4].

The eye is a complex organ in the human body with regard to structure and function, and it comprises three layers. The sclera and conjunctiva form the outer layer, the middle layer is formed from the ciliary body, iris, and choroid, and the inner layer is the retina. The structure of the eye and the ocular barriers are illustrated in Figure 1. Tears form a thin film which acts as the primary physiological barrier against entry of drug molecules. Principal route for medication delivery to the anterior chamber is via the cornea (I). The complex nature of the retina poses a major challenge in systemic ocular delivery systems (II). However, intravitreal injections offer a direct drug delivery to the vitreous (III). Drugs disperse through the surface of the iris (1), and exit from the anterior chamber through aqueous outflow or venous blood flow (2). Drugs exit the vitreous either by dispersion into the anterior chamber (3) or crossing the blood-retina barrier (4).

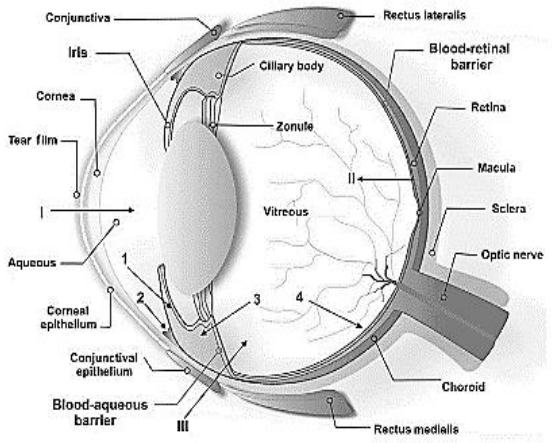

Figure 1: Structure and barriers of the eye [5]

Bioavailability of ocular drugs in different compartments of the eye is influenced by their lipophilic or hydrophilic nature and this plays a significant role in the management of eye diseases like glaucoma. The bioavailability of most hydrophilic medication is higher in the iris-ciliary body than in the aqueous humor, suggesting that they are absorbed primarily through a non-corneal route (conjunctival-scleral), while lipophilic drugs are predominantly absorbed via the cornea [6]. A pharmacokinetic study of Brinzolamide given by various routes (e.g., intracameral, topical, and intravenous) revealed that topical application of drugs had absolute bioavailability in aqueous humor, reducing systemic toxicity [7].

Data source

Data for this study were collected using search engines namely ScienceDirect, PubMed, Google Scholar and the WHO database. A range of keywords such as drug delivery, glaucoma, current management, healthcare costs, direct cost, indirect cost, ocular barriers, ocular obstacles, patient compliance, and patient adherence were used to obtain relevant information.

Currently available drugs for the treatment of glaucoma

Glaucoma is an eye disease and a leading cause of blindness globally. Topical ocular medications such as eye drops are the preferred treatment for open-angle glaucoma. Various eye membranes regulate movement of drug molecules. The cornea which is the main pathway for drug delivery to the eye (especially the anterior chamber), is impeded by tight epithelial cell junctions and this limits penetration of macromolecules and hydrophilic drugs [8]. Inefficiencies in drug transport between eye chambers are exacerbated by aqueous turnover, often resulting in sub-therapeutic levels in the eye's posterior part. Barriers such as tear film, which quickly eliminates topically applied medications, and vital eye components like the conjunctiva, retina, cornea, and iris-ciliary body, present challenges in the effectiveness of ocular medications [9,10]. Other challenges with topical therapy include non-compliance, expenses, adverse effects, and variation in IOP are also considered [11].

The main option for treating posterior segment diseases is intravitreal treatments. Conversely, the effectiveness of oral medications and intravenous injections is constrained, owing to the eye's isolated position from the systemic bloodstream. The blood-retina barrier (BRB) is one of the ocular barriers that selectively limits the passage of medications into the retina after systemic and periocular injection (Figure 1). Even though there are some similarities between BRB and blood-brain barrier (BBB), the BRB differs from the blood-brain barrier due to a functional exterior impediment generated by the retinal pigment epithelium (RPE). On the contrary, the inner barrier of retinal vessels is formed by endothelial cells [9,10,12]. However, both barriers feature restricted tight connections that control the internal and outward flow of hydrophilic substances and macromolecules (vitreous to blood and blood to vitreous) [9]. Transcellular inactive infiltration is the primary

route for small particles to traverse the BRB, with RPE's paracellular permeability being minimal.

Despite the addition of new drug classes to glaucoma treatment, topical therapy faces challenges. These concerns are addressed with non-topical routes of drug administration, offering patients more treatment options. [11]. Laser trabeculoplasty and surgery are also utilized to decrease disease progression [13,14]. Most widely prescribed medication for the management of glaucoma is prostaglandin analogue (PGA) alone, followed by a combination of two drugs from two different classes (i.e., beta-blockers and carbonic anhydrase inhibitors-CAI), and similarly a three-drug combination from discrete groups (i.e., PGA, beta-blocker, and CAI) [15]. Prostaglandin analogues (PGA) are the most often used IOP-lowering topical glaucoma medications, which are considered the "gold standard" of treatment. Nitric oxide (NO) donating PGA, on the other hand, is a new prostaglandin counterpart with better IOP-lowering effectiveness. This is primarily due to the vasodilatory effect of NO, which encourages trabecular outflow [16,17]. Furthermore, intravitreal administration of neuroprotective glaucoma medicines such as cell, gene, and protein therapies, are rapidly advancing toward human trials [18].

Glaucoma treatment with a sustained-acting drug delivery system

Implants, nano or microparticles, punctal plugs, contact lenses, topical ring-type systems, gels, and other depot systems (e.g. intracameral, supraciliary, and intravitreal) applied in the extraocular, periocular, or intraocular sites are among drug delivery methods under research [18].

Many long-acting implants have been introduced in managing eye diseases, particularly involving the posterior segment of the eye. These implants are meant to transport the medication to the site of action that is difficult to reach through a topical route, and to release it over a long period. This reduces systemic drug exposure and the need for frequent topical drug applications, thereby enhancing patient compliance. However, there are drawbacks, such as cost and invasiveness of first surgery, as well as any additional surgery to remove the implant if an unfavorable reaction occurs [20]. These implants require a small incision in the sclera for the insertion of a small hollow gauge needle to introduce them into the eye [21].

Table 1: Topical drugs for glaucoma [11,19]

Currently available Topical glaucoma medicines	Topical glaucoma medicines with fixed ratio combination	Topical glaucoma medicines under trial for future use
Beta-adrenergic antagonists (Betaxolol, Timolol, Carteolol, Levobunolol and Metipranolol)	Carbonic anhydrase inhibitors and beta- sympatholytic (e.g., Dorzolamide/Brinzolamide-timolol)	Prostanoid Receptor Agonists (e.g., DE-117(Omidenepag isopropyl) and ONO-9054)
Alpha-adrenergic agonists (Epinephrine, Brimonidine, Apraclonidine, and Dipivefrin)	Carbonic anhydrase inhibitors and alpha- sympathomimetic (e.g., Brinzolamide-brimonidine)	Oligonucleotide Based Compounds (e.g., SYL040012 (Bamosiran))
Prostaglandin analogues (Bimatoprost, Latanoprost, Travoprost, Tafluprost, and Unoprostenone)	Prostaglandin analogues and beta-adrenergic antagonists (e.g., Travoprost/Latanoprost/Bimatoprost/Tafluprost-timolol, Latanoprost-carteolol)	Adenosine Receptor Agonists (e.g., INO-8875 (Trabodenoson))
Nitric oxide donating prostaglandins (Latanoprostene, and Bunod)	Alpha-adrenergic agonists and beta-sympatholytic (e.g., Brimonidine-timolol)	
Cholinomimetics (Carbachol, and Pilocarpine)	Prostaglandin analogues and Rho kinase inhibitors (e.g., Latanoprost-netarsudil)	
Carbonic anhydrase inhibitors (Acetazolamide, Methazolamide, Brinzolamide and Dorzolamide),	Beta- sympatholytic and Cholinomimetics (e.g., Timolol-pilocarpine)	
Rho kinase inhibitors (Ripasudil and Netarsudil).		

Nanospheres bypass biological barriers due to their small size, allowing drugs to reach target cells directly [22]. Furthermore, the capacity of drug loading in smaller nanoparticles is higher compared to larger particles and this is attributed to the higher surface area of small nanoparticles [23]. However, they do not address issues relating to patient compliance and the effectiveness of topical eye drop administration [20]. Microparticles, ranging from 1 to 999 µm, are used for sustained drug release, offering improved therapeutic benefits [23].

Ring systems, or ring-like structures, serve as a sustained drug delivery system for administering topical ophthalmic medications to the eye's posterior segment. Their primary advantage lies in their ability to penetrate the external eye's hydrophilic barrier and safely access the lipophilic corneal surface, coupled with a prolonged residual period allowing for once-daily dosing. However, a significant drawback of these systems is the potential for inducing ocular irritation [21,23].

Punctal plugs put into the lacrimal puncta to prevent tear drainage, are reliable and efficient in maintaining natural tear film. Nonetheless, they are contraindicated in patients with allergies to the plug materials, ectropion, lacrimal duct obstruction, or existing eye infections (e.g., keratitis, conjunctivitis), and irritations may also occur [24]. Contact lenses, small lenses designed to fit over the cornea, have evolved beyond vision correction to become a method for ocular drug delivery. These drug-loaded contact lenses enhance drugs penetrability, resulting in increased therapeutic efficacy, reduced drug administration, and fewer adverse effects [25]. However, disadvantages of contact lenses include increased risk of ocular diseases, ocular infections, keratitis or keratoconjunctivitis and corneal neovascularization [26].

Gels are common viscous formulations that prolong medication presence on the eye surface by reducing drug elimination via the nasolacrimal drainage system. While it is effective in sustaining drug contact, their application is less precise and may result in complications manifested by lacrimation, crusting of eyelids, and blurred vision [27]. Alongside gels, bio-adhesive polymers are also employed to enhance the efficacy of topical glaucoma medications, like carbonic anhydrase inhibitors, by prolonging their action and helping to decrease intraocular pressure (IOP). These polymers are part of ongoing efforts to develop sustained drug delivery platforms, as presented in Table 2 [28].

Patient adherence

Intra-ocular pressure (IOP) lowering ocular drops are the cornerstone of managing glaucoma, however, a lack of compliance with topical application is a major problem [34].

Table 2: Long-acting ocular drug delivery systems are currently under development [29-33]

Device	Drug	Site of application	Developer/Development stage	Duration of action
Ocular Insert	Bimatoprost	Ring system (conjunctival cul-de-sac)	Allergan, Dublin, Ireland/Phase 2	Up to 6 months
Ocular Insert	Timolol+Latanoprost	Upper conjunctival fornix	Amorphex Therapeutics, Andover, MA, USA/Phase 1	Up to 6 months
Punctal Plug	Latanoprost/travoprost	Lacrimal punctum	Mati Therapeutics, Austin, TX, USA/Phase 2	≥1 month
Contact Lens	Timolol	Ocular surface	Preclinical	4 days
Contact Lens	Latanoprost	Ocular surface	Preclinical	>8 days
Subconjunctival injection	Beta adrenergic prodrug	Subconjunctival or intravitreal injection	Graybug Vision Inc., Redwood City, CA, USA/Phase 1-2a	Up to 6 months
Subconjunctival injection	Latanoprost	Subconjunctival insert	BioLight Life Sciences, Tel Aviv, Israel/Phase 1-2a	Up to 6 months
Biodegradable implant	Travoprost	Intracameral implant	Aerie Pharmaceuticals, Durham, NC, USA/Phase 3	≥ 4-6 months
Biodegradable implant	Bimatoprost	The inferior angle of the eye	Allergan, Dublin, Ireland/Phase 3	>10 days
Non-biodegradable implant	Travoprost	Intracameral implant	Glaukos, San Clemente, CA, USA/Phase 2	≥ 6 months
Biodegradable implant	Travoprost	intracameral implant	Ocular Therapeutix Inc., Bedford, MA, USA/Phase 1	4-6 months

Irritation and non-adherence among glaucoma patients are exacerbated by changes in drug or polypharmacy, adverse effects, socioeconomic status, education, social support, cognitive capacity, and adjunctive therapy, which are difficult to monitor in clinical practice [30]. Similarly, poor medication adherence has been observed in male glaucoma patients and those with disabilities [15]. Poor patient compliance is of particular concern among older glaucoma patients and those with lower educational level. These patients require more comprehensive planning, including suitable educational interventions and follow-ups [32]. Glaucoma patients who fail to adhere to their treatment plan at least 80 % of the time are significantly more likely to develop visual field abnormalities [30]. Therefore, it is inevitable to improve medication adherence in glaucoma patients which is accomplished by the use of smart drop bottles, instillation aids, reminders, and by increasing patients' awareness of the disease. Adopting simpler therapy regimens, such as drops containing medications in a fixed proportion, strategies with prolonged medicine release profile, or innovative surgical technique for glaucoma with a lower risk profile, are also beneficial [38].

Cost (direct, indirect, cost-effectiveness)

The overall cost of a disease encompasses both direct and indirect costs associated with the disease. While many studies have focused on the direct costs of diagnostic tests and treatment methods, fewer have examined the indirect costs, such as the cost of having someone accompany the patient during outpatient visits or the costs of lost work ability due to the disease or appointments [31].

Following a three-year follow-up after therapy, the average expenditure for caring for a patient suffering from POAG was approximately $ 2746 ± 1560, with the first year of treatment being substantially more expensive than subsequent years. Additionally, costs increased with disease severity [39]. As disease severity worsened, consumption of resources directly concerned with ophthalmology increased, which include ophthalmologist appointments, glaucoma operations, and use of medication [40]. The median cost for glaucoma outpatient department services was higher in patients with severe open-angle glaucoma (OAG) compared to those with moderate and mild OAG, corresponding to $ 639, $ 546, and $ 476 respectively. Patients with severe OAG also had greater glaucoma-related pharmacy expenses than patients with moderate and mild OAG, at $ 493, $ 244, and $ 139, respectively [41]. The average annual direct treatment cost for a glaucoma patient varies, ranging from $ 623 for early-stage disease to $ 2511 for end-stage disease. Across all stages of illness, medication expenses constitute the largest portion of total direct costs ranging from 24 to 61 % [40]. Cost of medication plays a critical role in treatment adherence. If patients are unable to afford prescribed glaucoma medication, adherence reduces resulting in a significant correlation between costs and adherence. This is because, poor adherence leads to disease progression, which in turn results in a rise in costs [42].

A large fraction (54 to 66 %) of the total cost of glaucoma therapy is represented by non-medical and indirect costs [43,44]. Average cost of transportation (a direct non-medical cost) to a clinic is around $ 16.7 per visit, with three to eight hours of work missed per follow-up appointment, resulting in an approximate loss of $ 30 for each hospital visit. The cost escalates if the patient's companion takes time off work [45]. Poor patient adherence to glaucoma medication worsens the disease which leads to increased indirect and direct therapy costs [44].

CONCLUDING REMARKS

Glaucoma is a significant cause of permanent vision loss worldwide, influenced by various socio-demographic factors. Risk factors such as ethnicity, a positive family history, and advanced age play a role in its development. Primary barrier to the effectiveness of medications to treat glaucoma is the intricacy of the eye's anatomy, which includes various anatomical barriers. Furthermore, poor drug adherence due to a variety of factors contribute to poor glaucoma management resulting in sub-optimal management of glaucoma, thereby increasing direct (34 to 45 %) and indirect (55 to 66 %) costs of therapy. In response, a variety of medications and improved drug delivery strategies have been investigated, with new pharmaceuticals and technologies continually under consideration.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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