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Review Article

Improving Compliance with Glaucoma Therapies through the Examination of Environmental Factors and the Localized Side Effects of Glaucoma Drugs

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Abstract

Glaucoma is a prominent cause of permanent blindness, with an estimated 111.8 million people expected to be diagnosed with the disease by 2040. While prevalent across all demographics, this condition particularly impacts the most marginalized individuals in our communities. Treatment options range from various pharmacologic therapies to laser and surgery. Medical therapy presents risks to patients in a number of different forms but one of the most prevalent is corneal toxicity. Negative side effects can contribute to patient noncompliance with ocular medications. This paper examines corneal toxicity, the adverse effects of some of the most commonly prescribed glaucoma medications, and the causes of noncompliance in patients. Analyzing the causes of noncompliance can help physicians to create more personalized treatment plans and achieve better patient outcomes.

Keywords: Glaucoma; Corneal toxicity; Non-adherence; Noncompliance; Glaucoma treatments; Glaucoma medication toxicity

Introduction

Glaucoma is a degenerative neuropathy of the optic nerve that is multifactorial in nature, resulting in the loss of retinal ganglion cells. It is influenced by a combination of vascular, genetic, anatomical, and immune factors. At present, there is no cure available for this condition. Nonetheless, early detection and treatment continue to be the cornerstone of management. Current known treatments focus on reducing the intraocular pressure, which is the sole modifiable risk factor identified so far [1]. This condition presents a considerable public health issue [2]. It is the second leading cause of blindness worldwide and the number one cause of irreversible blindness [2]. A major problem facing the treatment of glaucoma today is noncompliance.3 Many of the topical medications used to treat glaucoma come with a range of side effects including local as well as systemic side effects.

The objective of our study is to examine the local adverse reactions that can result in corneal toxicity, which may hinder medication adherence. We analyze the typical sources of corneal toxicity, various forms of glaucoma, topical medication therapies, and their impact on medication compliance. Failure of glaucoma patients to comply with prescribed medication can result in the progression of glaucoma, leading to damage to the optic nerve and subsequent loss of visual field and vision. A thorough review of

the literature available on PubMed was conducted to examine the various environmental, occupational, and pharmacologic causes of corneal toxicity, with particular attention given to topical glaucoma medications. Our analysis is also centered on the different classes of glaucoma medications and their potential adverse effects, both topical and systemic, as a contributing factor to patient noncompliance.

Corneal Toxicity and Ocular Surface Disease

There are various manifestations and indications of corneal toxicity, which can arise from different sources such as environmental factors, occupational hazards, and the use of topical ocular medications. The symptoms and signs associated with corneal toxicity encompass sensations of foreign bodies, irritation, burning, redness, excessive tearing, impaired focus, blurred vision, eye fatigue, and stinging. Toxicities can result in ocular surface disorders ranging from mild to severe allergy to dry eye and meibomian gland dysfunction [4]. It is important to understand the effects of topical medications on the ocular surface in order to provide patients with the best possible care. Failure to adhere to prescribed medications, especially for patients who suffer from chronic diseases such as glaucoma, can be detrimental to their visual outcomes. Although it is well known that glaucoma medications have the potential for adverse reactions as described previously, there are many other types of medications and environmental factors that can affect the ocular surface [5,6].

Environmental and Occupational Causes of Corneal Toxicity

There are a number of different ways that the environment can affect human health. In particular, ocular surface health is affected by factors like pollution, pesticides, chemicals, and climate change [5]. Pollution is known to have detrimental effects on the human body. Substances like ozone, particulate matter, carbon dioxide, carbon monoxide, and nitrogen oxides have all been linked to increased morbidity and reduced life expectancy [5]. The cornea is highly susceptible to airborne pollutants due to the thin nature of the tear film. Ozone is known to cause corneal toxicity in the forms of chemosis, inflammation, injection, and swelling of conjunctival vessels. Particulate matter in the air from fuel exhaust or dust can also irritate the ocular surface. Studies in mice have demonstrated that fine particulates in the air caused dry eye, as evidenced by inflammation, tear film damage, and decreases in tear volume [5,7]. A study in Korea found that the incidence rate of conjunctivitis and keratitis was elevated for those residing in regions in the 80th percentile for PM10 (particulate matter 10 micrometers) concentrations compared to those in the 20th percentile [5,8]. Pollutants like PM10, carbon monoxide, and nitrogen oxides have been correlated with increased dry eye and irritation. A study of ophthalmic outpatients in urban areas of China demonstrated an increased risk of ocular surface disease related to these pollutants [9,5].

Pesticides and other chemicals that are often found in workplaces can have detrimental effects on the cornea as well and can cause ocular surface disease. The effects of pesticides in particular are a global health concern as there are approximately 866 million agricultural workers worldwide [5]. Pesticides like insecticides, herbicides, and fungicides can commonly enter the eye through splashing or rubbing with contaminated hands or clothing. Paraquat is an herbicide that generates free radicals in the body. Free radicals have been linked to corneal toxicity through conjunctivalization with vascular pannus [5]. Other common herbicides containing chemicals like glyphosate or other organophosphates have also been linked to conjunctival irritation and superficial corneal injuries [5]. Further, the insecticide flubendiamide was studied in drosophila melanogaster and was shown to alter compound eye architecture and bristle pattern orientation in multiple generations [10,11,5]. It is clear that both herbicides and insecticides can be dangerous chemicals in humans and lead to various ocular surface diseases. Fungicides can also cause significant harm in the human eye. Mancozeb was associated with toxic epidermal necrolysis and ocular lesions with human exposure [12,5].

Both agricultural and industrial occupations are at high risk of experiencing exposure to chemicals or other substances that can result in corneal toxicity and ocular surface disease. Workplace ocular injuries can be categorized into 3 main types: striking or scraping, penetrating, and chemical or thermal burns [5]. Striking or scraping constitutes small objects entering the ocular surface and causing damage like dust, wood chips, or cement. Penetrating damage is typically the result of nails, staples, wood, or metal that penetrates the surface of the eye and can cause permanent damage. Chemical and thermal burns can be caused by cleaning materials, industrial chemicals, and welding [5]. Occupational ocular injuries that cause corneal toxicity can typically be preventable with the appropriate use of eye and face protection. It is important to implement these types of protection and adhere to safety guidelines in order to avoid corneal toxicity from these types of hazards.

Office positions may also pose a potential threat of corneal toxicity due to prolonged exposure to screens and LED lighting. Many workers utilize computers or computer-generated devices during their working hours, resulting in prolonged periods of staring at a screen. This extended screen time can lead to a decrease in their natural blinking reflexes and other ocular surface issues, like digital eye strain and dry eye [13-15]. Additionally, these workers are often exposed to artificial LED lighting, which can potentially impact corneal and ocular surface health [16-18].

Climate change is also an environmental factor that can impact ocular health. The effects of climate change that are currently being observed include rising global temperatures, increased atmospheric carbon dioxide levels, increased sea levels, glacial melting, and ozone depletion [19,5]. Some aspects of climate change that have been associated with ocular surface damage and corneal toxicity include increasing temperatures, poorer air quality, and increased ultraviolet radiation. Increased global temperatures have been linked to ocular diseases like corneal toxicity, cataracts, glaucoma, and retinal damage [5]. In addition, rising temperatures

have also been associated with increased instances of infections like bacterial, fungal, and amoebic keratitis [5]. Further damage associated with rising temperatures includes inflammatory responses to thermal energy surrounding ocular tissues with increased levels of cytokines like IL-1 β and IL-6 in cornea cells [20,5]. The thermal energy increase affecting the cornea could be caused by increased temperature of the cornea resulting from increased air temperature or from higher body temperatures due to living in a warmer climate [21,5].

Decreased air quality from climate change can cause corneal toxicity and ocular disease in the form of dry eye, ocular irritation, and inflammation. Some of the effects of climate change on air quality include higher levels of smoke, allergens, carbon monoxide, nitrous oxide, and ground level ozone [5,22]. Multiple studies have indicated a positive correlation between these pollutants and ocular surface disease. Two studies conducted in Delhi found that there was a greater occurrence of ocular surface disorders among individuals who frequently traveled through heavily polluted areas of the city [23,5,24]. Additionally, another intriguing study compared individuals residing in highly polluted areas with those in less polluted areas, as determined by the Air Quality Index (AQI) [25]. Goblet cells are highly specialized cells that function to secrete mucins to lubricate the ocular surface [26]. Jing et al. reported that conjunctival injection and goblet cell density were correlated with AQI, levels of PM2.5, PM10 and levels of Nitrogen dioxide [5,25]. The concentration of cytokine IL-6 was also higher in those living in more polluted areas. Pollutants associated with climate change may have a significant impact on ocular surface disease and corneal toxicity.

Climate change increases ultraviolet (UV) radiation [27]. UV radiation is well known for the damaging effects it can have on the human body and the ocular surface is no different. The various structures that exist within the eye have different reactions to UV radiation. For example, chronic exposure to ultraviolet light is known to cause a clouding of the lens within the eye, also known as a cataract [28]. Common problems associated with the ocular surface and chronic ultraviolet light exposure include pterygia and squamous cell carcinoma of the cornea and conjunctiva [5]. A patient's environment can drastically affect the amount and form of ocular surface disease and corneal toxicity that they experience. Although not typically associated with nonadherence, it is important not to overlook non-pharmacologic factors in patient noncompliance.

The health outcome of an individlual is influenced by various factors known as social determinants of health. These factors encompass healthcare access and quality, educational access and quality, social and community context, economic stability, and neighborhood and environment [29]. It is imperative to take this into consideration when analyzing a patient's probability of medical noncompliance. The number of individuals diagnosed with glaucoma is projected to rise to 111.8 million by 2040 [30]. This disease disproportionately affects Black and Hispanic populations in the US and worldwide. It is the most common cause of blindness in Black persons with a prevalence of 6.1% [1]. The prevalence in Latino communities is second highest at 4.1%, followed by Asian Americans at 3.5% and non-Hispanic White persons at 2.8% [1]. The groups at the greatest risk of glaucoma often reside in densely populated urban areas. They are also exposed to high levels of environmental and occupational factors. Even prior to beginning pharmacologic treatment for glaucoma, those most affected by this disease face significant challenges. The inclusion of pharmaceutical components may result in an additional increase level of ocular side effect and non-compliance and lack of adherence [31].

Pharmacologic causes of Corneal Toxicity and Ocular Surface Disease

There are several medications that have been connected to ocular surface disorders. It is important for healthcare providers to exercise caution when prescribing medications such as topical aminoglycosides, chemotherapeutics, NSAIDs, and certain cardiac medications like Amiodarone. These commonly prescribed treatments have been linked to a range of adverse effects and ocular surface disorders. Informing patients about these potential side effects can enhance their understanding and reduce anxiety.

Aminoglycoside antibiotics like Tobramycin and Gentamicin are commonly used to treat corneal infections and bacterial conjunctivitis. They are however associated with superficial punctate lesions on the cornea, keratitis, and delays in corneal reepithelialization [6]. Topical chemotherapeutic medications like 5-Fluorouracil (5-FU) and Mitomycin C (MMC) are often utilized with cornea and glaucoma surgical procedures and post-operative adjunctive care. Although useful in surgical care, these medications are toxic to the ocular surface and are linked to corneal thinning, ulceration, and delayed wound healing [6]. 5-FU has been shown to be particularly problematic in post-operative glaucoma surgery patients with preexisting corneal abnormalities. One study followed four patients who all developed epithelial defects after being treated with 5-FU post-operatively [32]. Additionally, topical NSAID medications like diclofenac and ketorolac are associated with ocular irritation and toxicity [6]. NSAIDs are typically prescribed post-operatively and have a wide range of uses to ophthalmologists. Systemic medications must also be considered when analyzing the relationship between ocular surface disease and patient noncompliance. Cardiac agents like amiodarone have been linked to numerous adverse ocular effects. Alshehri et al. found that among 25 case reports of patients on amiodarone, 60% reported halos around lights or decrease in vision after use. Ophthalmic examination findings discovered that 76% of subjects experienced corneal verticillata and vortex keratopathy [33]. Although an efficacious antiarrhythmic medication, physicians must be able to recognize the potential adverse ocular effects of amiodarone.

Corneal toxicity can greatly affect an individual's wellbeing, whether it stems from glaucoma medications, environmental factors, or other pharmacologic agents. The persistent pain, irritation, itchiness, redness, and allergic reactions can impact various aspects of one's life, including self-esteem, mental state, employment, and

overall quality of life. When the negative effects of medications become too much for a patient to handle, they are likely to become noncompliant and stop their treatment recommendations. This is especially problematic when treating glaucoma patients due to the high prevalence of ocular adverse reactions from topical medications. When these patients discontinue the use of their medications, they often unknowingly put themselves at increased risk for elevated intraocular pressure, damage to their optic nerves, and resultant visual field loss. Therefore, it is critical to monitor the extent of adverse effects when treating patients with the various classes of pharmacologic glaucoma options, using Preservative free medications or recommend other options i.e. laser or incisional surgery. Explaining the potential side effects and clinically evaluating the risk of each form of medication may help reduce the negative outcomes associated with noncompliance. Limiting the extent of corneal toxicity in a patient is likely to increase patient compliance and improve patient outcomes.

Glaucoma and its Therapeutics as Forms of Corneal Toxicity

The term "glaucoma" encompasses a group of diseases each presenting with different characteristics and standards of treatment. There are 2 major types of glaucoma, primary and secondary. The 2 major subtypes that exist are open angle and closed angle glaucoma.1 Although primary open angle glaucoma (POAG) is the most commonly seen form of disease, it is important to understand the other frequently observed manifestations in order to properly distinguish and treat them. An understanding of the different forms of glaucoma allows us to compare their characteristics and various treatments.

Primary Open Angle Glaucoma

Primary open angle glaucoma (POAG) is the most common form of glaucoma. POAG affects more than 2 million Americans, and many people who do not even know that they have it [34]. It is largely asymptomatic and gradually reduces the visual field of the affected patient. In most cases, POAG vison loss starts in the periphery and moves toward the central vision. If left untreated, it can result in permanent blindness. There are a multitude of risk factors that can cause primary open angle glaucoma, with genetics likely playing a role. The pathophysiology of POAG centers on the effects of elevated intraocular pressure (IOP) in the eye. However, ophthalmic evaluation and diagnostic testing both factor into a clinical diagnosis. There are numerous options for pharmacologic treatment of POAG. As there is no cure for the disease, the most common clinical strategy is to manage intraocular pressure with a goal of decreasing progression and reducing the risk of visual field loss. In severe cases, surgical treatment is also performed.

Normal Tension Glaucoma

Normal tension glaucoma (NTG) is a progressive optic neuropathy that is very similar to primary open angle glaucoma. However, it is characterized by an intraocular pressure that falls within the normal range. This includes a value between 10-21 mm Hg [35]. The existence of normal tension glaucoma emphasizes the importance of diagnosis based on the condition of the optic nerve and not simply a single risk factor such as elevated intraocular pressure.

Primary Angle Closure Glaucoma

Primary angle closure glaucoma (PACG) is another significant form of glaucoma. It induces disease differently than primary open angle glaucoma due to differences in the anatomical structure of the eye. It is characterized by an elevation in intraocular pressure as a result of mechanical obstruction of the trabecular meshwork of the eye. This can be due to anatomical apposition of the iris at the trabecular meshwork or a synechial closed angle [36]. A fundamental difference between POAG and PACG is that angle closure is the significant problem in PACG while elevated IOP is secondary. Open angle remains more prevalent than angle closure as it is estimated that 5.9 million people experience bilateral blindness worldwide from POAG compared to 5.3 million people with PACG [36].

Primary Congenital Glaucoma

The last major variation of glaucoma is primary congenital glaucoma (PCG). As the name implies, this form of disease is inherited. It is a significant cause of global pediatric visual impairment and can often lead to permanent blindness [37]. What most differentiates primary congenital glaucoma from other forms of glaucoma is its heritability and development in patients below the age of 3. The underlying mechanism in PCG is the development of an obstruction that prevents adequate drainage of aqueous humor caused by abnormalities in the trabecular meshwork and anterior chamber angle [38].

Pseudoexfoliation and Pigmentary Glaucoma

Secondary glaucomas comes in a variety of different forms and are distinguished by a clinically identifiable cause for increase in intraocular pressure. They can be traumatic or medical. The most common of which is pseudoexfoliation glaucoma [39]. This type of glaucoma is characterized by the buildup of abnormal extracellular matrix material in the outflow pathway that leads to an increase in IOP [39]. Pigmentary glaucoma is often grouped with pseudoexfoliation glaucoma as both forms are resultant upon material from inside the eye blocking the outflow of aqueous humor. The difference in in pigmentary glaucoma is that the debris is made up of pigment from the iris. It occurs at an earlier age and is affects males greater than females [40].

Neovascular and Uveitic Glaucoma

Neovascular and uveitic glaucoma are other major forms of secondary disease. Neovascular glaucoma is usually a result of complications from other diseases such as diabetic retinopathy, retinal vascular occlusions, or carotid artery obstructive disease. These can lead to retinal ischemia and the release of proangiogenic factors that cause neovascularization and disrupt aqueous humor outflow [39]. Like other forms of glaucoma, this disruption of aqueous humor outflow is likely to increase intraocular pressure.

Steroid Response and Medication Induced Glaucoma

Lastly, steroid response and medication induced glaucoma share a similar etiology. It is important to note that chronic corticosteroid use can in some cases cause an increase in intraocular pressure. This is most common with topical ophthalmic or systemic steroid use, but can also be observed as a result of dermal, inhaled, nasal, and intra-articular application [39]. Some medications can induce angle closure glaucoma by mechanisms such as pupillary block and idiosyncratic reactions [39] (Tables 1 & 2).

Table 1: Types of Glaucoma.

Primary Glaucoma	Primary Open Angle Glaucoma (POAG)	Primary Angle Closure Glaucoma (PACG)	Normal Tension Glaucoma (NTG)	Primary Congenital Glaucoma (PCG)
Secondary Glaucoma	Pseudoexfoliation/ Pigmentary Glaucoma	Neovascular Glaucoma	Uveitic Glaucoma	Steroid Response and Medication Induced Glaucoma

Table 2: Classes of Medications and Adverse Effects.

Class of Medication	Example	Dosage	Mechanism of Action	Adverse Effects
Cholinergic agents	Pilocarpine, Carbachol	4x a day but may vary	Increase aqueous humor outflow	Ciliary cramps, retinal detachment, blurred vision
Alpha adrenergic agonists	Brimonidne, Apraclonidine	2-3x a day	Initially decrease aqueous humor production, subsequently increase aqueous humor outflow	Hypotension, fatigue, allergic conjunctivitis, hyperemia
Beta adrenergic antagonists (blockers)	Timolol, Betaxolol	1x a day AM	Reduce aqueous humor production	Irritation, pulmonary effects, cardiovascular effects
Carbonic anhydrase inhibitors	Dorzolamide, Brinzolamide, Acetazolamide (oral)	2-3x a day	Reduce aqueous humor production	Allergic conjunctivitis, bitter taste, punctate keratitis, headache
Nitric Oxides	Latanoprostene Bunod	1x a day PM	Increase trabecular and uveoscleral aqueous humor outflow	Hyperemia, eyelash growth, increased iris pigmentation, increased skin pigmentation around eyes
Prostaglandin analogs	Latanoprost, Travoprost, Bimatoprost	1x a day PM	Increase uveoscleral outflow of aqueous humor	Hyperemia, eyelash growth, increased iris pigmentation, increased skin pigmentation around eyes
Rho-kinase inhibitors	Netarsudil	1x a day PM	Increase trabecular aqueous humor outflow, decrease production of aqueous humor, decrease episcleral venous pressure	Hyperemia, corneal verticillata, conjunctival hemorrhage

Drug Classes

There are 7 major types of commonly used topical medications used to reduce intraocular pressure (IOP) in glaucoma patients. Each has their own mechanisms of action, dosages, and side effects. These classes are cholinergic agents, alpha adrenergic agonists, beta adrenergic antagonists (beta blockers), carbonic anhydrase inhibitors, nitric oxides, prostaglandin analogs, and rho-kinase inhibitors. Of course, these drug classes can be combined to form commonly prescribed topical medications like Dorzolamide-Timolol (Cosopt), Brinzolamide-Brimonidine (Simbrinza), Brimonidine-Timolol (Combigan) and Netarsudil-Latanoprost (Rocklatan) combinations [41]. The advantage of combination medications is that they allow for greater efficacies through multiple mechanisms of action, while requiring lower frequencies of instillation. This is easier on the patient and may contribute to greater compliance.

There are also various additives to glaucoma therapeutics that can contribute to adverse reactions. These additives could be stabilizing agents, preservative agents, buffering agents, isotonizing agents, thickening agents, and solubilizing agents [42]. Preservatives often play a role in corneal toxicity in patients being treated with glaucoma medications. Many of the ways in which preservatives act on bacteria can also work to damage the corneal and conjunctival cells and cause ocular surface issues [42]. Some examples of ocular surface reactions from preservatives include superficial punctate keratitis, corneal erosion, conjunctival allergy, conjunctival injection, and anterior chamber inflammation [42]. Some of the more common preservative agents used in glaucoma therapeutics include parabens, chlorobutanol, sodium chlorite, and a boric acid, D-sorbitol, and zinc chloride combination [42]. However the most frequently associated with ocular surface toxicity is benzalkonium chloride. It is found in a wide range of common glaucoma therapeutics including Latanoprost, Brimonidine, Timolol, and Dorzolamide [42]. In the clinical setting, providers are able to lessen the ocular toxicity brought on by preservatives in glaucoma treatment by prescribing preservative free options, managing the therapeutics they use by taking into account which preservatives are present, and by treating the effects

of preservatives with artificial tears or other similar medications. Some commonly prescribed preservative free medications include Zioptan (tafluporst), Cosopt PF (Dorzolamide-Timolol) and Timoptic PF (Timolol).

Different classes of glaucoma medications have different systemic and local effects. It is important to understand how these adverse reactions impact patient satisfaction and lead to noncompliance and worsening of glaucomatous damage. Personalized patient care leads to the best patient outcomes. Strict management of pharmacotherapeutics, observation of adverse reactions, and patient input will lead to a higher likelihood of patient compliance.

Cholinergic Agents

Cholinergic agents like pilocarpine and carbachol are useful tools in treating glaucoma. Pilocarpine works by inducing smooth muscle contraction of the cells in the ciliary body. This leads to an increase in aqueous humor outflow through the trabecular meshwork pathway by widening the trabecular meshwork and Schlemm's canal [43]. Pilocarpine's usage has waned over time due to its problematic systemic adverse effects. The overstimulation of muscarinic acetylcholine receptors associated with use of pilocarpine induces bradycardia, negative cardiac inotropy, salivation, sweating, and gastrointestinal stimulation [44]. These systemic effects are enough to classify Pilocarpine as a last ditch effort in glaucoma treatment, especially for patients who are unable to tolerate the corneal toxicity of drugs that are more systemically favorable. Ocular adverse effects include miosis-caused aphose, visual field constriction, night vision loss, cataracts, ocular pemphigoid, and retinal detachment [42].

Alpha Adrenergic Agonists

Brimonidine and Apraclonidine are the most common alpha adrenergic receptor agonists used in glaucoma treatment. They operate by the stimulation of alpha receptors to release norepinephrine [43]. This causes vasoconstriction in the ciliary body, a decrease in aqueous humor production and a resultant lowering of intraocular pressure [43]. One advantage of brimonidine is its potential neuroprotective effects and prevention of retinal ganglion cell loss [43]. Although an effective IOP reducing agent with an average of 20-25% reduction, brimonidine is associated with several ocular and systemic effects [45]. Common ocular adverse effects include conjunctival hyperemia and anemia, pupil dilation, and allergic conjunctivitis [42]. Systemic effects that cause some concern in patients include hypotension, pulse reduction, fatigue, dizziness, and dry mouth [42].

Beta Adrenergic Antagonists

Beta adrenergic antagonists (beta blockers) like Timolol and Betaxolol are widely used to treat glaucoma. Their mechanism of action consists of reducing aqueous humor production in the ciliary body through decreasing cAMP production [43]. Like other effective IOP lowering medications, brimonidine averages a 20-25% reduction in intraocular pressure [45]. Timolol is a non-specific beta blocker and is associated with many problematic adverse reactions for patients. Ocular adverse reactions include conjunctival allergy, conjunctival injection, corneal epithelial disorders, and ocular pemphigoid [42]. The main reason why beta adrenergic antagonists like timolol have decreased in use is their potentially severe systemic side effects. Non-selective beta blockers cause both pulmonary and cardiac side effects such as bradycardia, hypotension, irregular pulse, and worsening of asthma or COPD [42]. These reactions make the prescription of beta adrenergic antagonists difficult for many patients.

Carbonic Anhydrase Inhibitors

Carbonic anhydrase plays a significant role in the creation of aqueous humor, and therefore its inhibition is an ideal target when treating glaucoma. Reducing the amount of aqueous humor in the eye can reduce the intraocular pressure. Carbonic anhydrase inhibitors can be used both topically and orally, the route of administration is important in determining the potential for adverse effects. Dorzolamide and Brinzolamide are the common topical medications while Acetazolamide remains a widely used oral option. Acetazolamide is a potent IOP reducing agent with a 25-30% reduction possible [46]. It has been used for over 50 years to treat glaucoma but its nature as an oral medication produces many side effects associated with its inhibition of carbonic anhydrase in tissues other than the eye. It is known to cause dyesthesia of the fingers and around the lips, frequent urination, lassitude, anorexia, weight loss, urolithiasis, metabolic acidosis, and hematopoietic cell restraint anemia [42]. These systemic issues prevent the more widespread use of acetazolamide and limit it to use in only particular circumstances. This might include when a patient has a severe ocular reaction to topical medications or an acute spike in IOP. Dorzolamide and brinzolamide are widely used topical IOP reducing pharmacologic options. Some ocular adverse effects associated with topical carbonic anhydrase inhibitors include conjunctival allergy, conjunctival hyperemia, corneal epithelial disorders, blepharitis, Stevens-Johnson syndrome, and toxic epidermal necrosis [42]. Topical carbonic anhydrase inhibitor medications however, are not associated with any systemic adverse effects, making them well tolerated in many glaucoma patients.

Nitric Oxides

Nitric oxides like Latanoprostene Bunod are modified prostaglandin analogs that act by dual mechanisms of action. The prostaglandin component works to increase aqueous humor outflow through the uveoscleral pathway in the eye while the nitric oxide component induces relaxation within the trabecular meshwork to increase outflow through the trabecular meshwork pathway and Schlemm's Canal [45]. Latanoprostene Bunod is generally well tolerated with a similar side effect profile to prostaglandin analogs. Ocular adverse effects include conjunctival hyperemia, eyelash growth, eye irritation, eye pain, and increased iris pigmentation [47]. There have been no significant systemic effects associated with latanoprostene bunod. This adds to its potential as a possible first line treatment for glaucoma.

Prostaglandin Analogs

Prostaglandin analogs like latanoprost, travoprost and bimatoprost remain the gold standard for glaucoma pharmacotherapy and have been so since the 1990's. They are efficacious, well tolerated, have minimal adverse effects, and are easy to use with a dosage schedule of once a day before bed. Prostaglandin analogs decrease IOP by increasing aqueous humor outflow in the uveoscleral pathway. Prostaglandin receptors are activated in the ciliary muscle, iris root, and sclera and induce relaxation of ciliary muscle and alter cytoskeletal remodeling of the extracellular matrix of the uveoscleral pathway [48]. IOP reduction averages around 25-33% [46]. Although no systemic adverse reactions are noted with use of prostaglandins like latanoprost, mild ocular effects do occur. These can include conjunctival hyperemia, burning, stinging, eyelash growth and hyperpigmentation, increased periocular skin pigmentation, increased iris pigmentation and loss of periorbital fat. Additionally, some cases of cystoid macular edema as well as reactivation of herpes keratitis and anterior uveitis have been documented [43,45]. One study reported that out of 344 patients treated with prostaglandin monotherapy, 79.4% presented with at least one clinical indication or symptom of dry eye. 75% of patients had an unstable tear film [49]. The paper also indicates the growing popularity of preservative free prostaglandin analogs. Despite the ocular surface reactions, a lack of systemic effects and generally mild local toxicity keeps latanoprost and other prostaglandin analogs at the forefront of glaucoma pharmacotherapy.

Rho-Kinase Inhibitors

Rho-kinase inhibitors, also known as ROCK inhibitors are a fairly novel treatment for primary open angle glaucoma that is quickly becoming a very popular treatment option. Netarsudil was approved by the US Food and Drug Administration in 2017 and is notable for its efficacy in lowering intraocular pressure. Netarsudil operates through different mechanisms that relax the trabecular meshwork, Schlemm's canal, and the ciliary muscle to increase aqueous humor outflow through the trabecular pathway. It also decreases the production of aqueous humor and lowers episcleral venous pressure [50-52]. ROCK inhibitors have steadily increased in usage by physicians in glaucoma treatment, however ocular adverse reactions remain a prominent reason why patients discontinue their use. Side effects like conjunctival hyperemia, corneal verticillata, conjunctival hemorrhage, instillation site pain, blurred vision, increased lacrimation, eye pruritus, and erythema of the eyelid are all possible [46]. No systemic side effects were reported in the literature. Rho-kinase inhibitors are a promising addition to a wide array of glaucoma treatments available but ocular side effects remain an obstacle for many patients.

Difficulties with Treatment and Adherence

Low adherence to glaucoma medication is a common problem among glaucoma patients. Non-adherent patients are often at risk for faster disease progression and avoidable vision loss. A study done by Barr et al. calculated nonadherence rates for glaucoma medications with data from the Marshfield Clinic Healthcare System's pharmacy dispensing database using two standard measurements, the medication possession ratio (MPR) and the proportion of days covered (PDC) and found that over a 12 month period, 59% of patients were found to be non-adherent when using the MPR80 metric and 67% non-adherent when using the PDC80 metric [53]. In another study by Rajurkar et al., 49% of the patients were found to be non-adherent with their glaucoma medication with 16% of them being completely non-adherent [54].

There are many different factors that can lead to non-adherence. They can range from side effects such as irritation from the medication, cost of medications to genetic and environmental components. Boland et al. outlines other risk factors for medication non-adherence in their study, where the results showed that participants categorized to be in the non-adherent group were slightly younger, more likely to be of African descent, had a lower level of educational attainment, scored lower on mental health and depression, and took medications for a shorter period of time compared to participants who were categorized into the adherent group [55]. Additional barriers to medication adherence include lack of motivation, poor education, forgetfulness, proper eyedrop application, and other factors that vary between individuals [56].

Gene for Non-Adherence

Genetic predisposition is another factor that is currently being explored as a contributor to non-adherence. Barr et al. completed a genome-wide complex trait analysis (GCTA) with results showing that glaucoma medication non-adherence has a heritability of 57% (MPR80) and 48% (PDC80). They performed single SNP (single nucleotide polymorphism) analysis to identify SNPs and associated genes that may play a significant role in either increasing or reducing glaucoma medication adherence. One SNP that was identified to be significant was the coding SNP rs2272487 in CHCHD6, a mitochondrial gene that has been associated with Alzheimer's disease and other neurodegenerative diseases, suggesting the possibility that mitochondrial genes and pathways might play a role in non-adherence. rs6474264, located in intron 5 of ZMAT4, is another SNP of interest, and was found to be significantly associated with preventing glaucoma medication non-adherence [53,3].

They also identified possible biochemical pathways and mechanisms that may be attributed to non-adherence to glaucoma medications. One pathway that is of interest is the CREB signaling pathway in neurons, which increases neuron excitability leading to heightened occurrences of long term potentiation and long term synaptic plasticity resulting in changes in neuronal circuits and long term memory. Therefore, this pathway can be considered a protective pathway because it can potentially reduce non-adherence rates by enhancing long term memory circuits to combat any memory related causes for non-adherence. These results indicate that this pathway could be a potential target for addressing non-adherence [53].

A different research study examined the adherence to medication in patients with hypertension and diabetes by utilizing a genome-wide association study (GWAS). They found an SNP that was nominally significant located near the gene GCC1, surprisingly is

associated with decision making of people that deal with substance abuse disorder [57]. With an increasing list of genes and SNPs that could be implicated in medication non-adherence, research into this area could provide alternative solutions to increase medication adherence.

Improving Treatment and Adherence

Improving adherence to glaucoma medications, or medication in general is not a simple process, and often needs to be tailored to individual patients and their lifestyles. The causes of non-adherence can be different for each person [58]. Strategies to address this issue can be grouped into a few major categories: patient education and effective communication between patient and physician, reducing side effects, simplifying treatment regimens, tolerability, decreasing contributing factors (SDH), and reducing costs [58].

Inadequate early education has been recognized as a primary obstacle to compliance. Studies have shown that medication adherence can be reduced by incorrect beliefs about the efficacy of the medication and consequences of the disease if not treated. Boland et al. found that patients who were nonadherent were more likely to believe that eyedrops can cause problems and were less likely to follow physician instructions [55]. Therefore, physicians should make sure that patients understand the negative consequences of non-adherence and that if glaucoma is left untreated, permanent vision loss will occur at a faster pace. Furthermore, physicians should discuss and emphasize the efficacy of drops and the positive effects it can have in the long run [56]. Boland et al. also found in their study that non-adherent patients were less likely to be able to name their glaucoma medications [55]. Patients should also understand their treatment regimen completely, including the correct dosages, schedule to apply the medication, and the correct techniques to apply the medication. A study found that patient education on how to correctly administer glaucoma drops was positively associated with adherence [59]. It is important to take into account any situational, social, or environmental factors that may affect medication adherence [58].

Patient education must be accompanied by efficient communication between the patient and the physician. It is recommended to take a patient-centered approach in order to make sure any questions that patients may have are answered and that they are not left with any misconceptions about the treatment regimen. Studies have shown that better communication leads to increased self-efficacy in patients, which is correlated with increased glaucoma medication adherence [58-60]. In their study, Boland et al. found that participants who were non-adherent were less likely to agree that remembering to take their eyedrops is easy [55]. The belief that it is hard to remember their eyedrops can indicate low medication self-efficacy. Medication self-efficacy refers to the patient's confidence in how well they can perform behaviors related to their medication. A study done by Carpenter et al. examined whether 6 different behaviors during physician-patient communication impacted the medication self-efficacy of glaucoma patients. They measured 2 types of medication self-efficacy. of the 5 physician behaviors explored, only 2 were significantly associated with an increase in glaucoma patients' reported self-efficacy, while none of the behaviors were significantly associated with both types of self-efficacy. The two significant behaviors were educating the patient about glaucoma and asking the patient about their views on glaucoma and its treatment. This suggests that these methods may be effective for physicians when working with patients with low medication adherence [60].

The intricacy of the treatment plan also serves as a frequent obstacle to receiving proper care. Studies have shown that patients who have more complex treatment regimens find it more challenging to take the right doses or take them at the correct time. For example, it was found that treatments that required taking 3-4 doses a day resulted in higher levels of noncompliance when compared to treatments that required 2 doses a day. Also, patients who only had once-daily medications had high adherence. Ways around this challenge can include having patients who need more than one medication coordinate their doses with daily activities such as at meals, in the morning, or before bed [58]. Other methods to simplify treatment regimens that have been shown to increase adherence include using monotherapies [61]. Nordstrom et al. found that when patients used a treatment regimen containing a prostaglandin analog, they were more likely to be adherent and persist in using the medication when compared to all other classes of medications tested [62]. Using one medication is easier for patients. In terms of cost in simplifying the patient's treatment regimen, it is essential to establish policies that enable insurance companies to provide coverage for combination medications.

Sustained release medications are another option that can be used to simplify complex treatment regimens. Although not widely used, it is a method that has shown promising results [63]. Nanotechnology based systems have been developed and tested as novel ocular drug delivery systems. For example, there has been a growing interest in nanomicelles that can encapsulate drugs and can be delivered topically, but are able to reach the back of the eye. They are advantageous because they are small in size, easy to prepare, and have high bioavailability in ocular tissues. These aspects allow nanomicelle encapsulated drugs to stay in systemic circulation for a longer period of time. This may allow for reduced daily doses of glaucoma medications and simpler treatment regimens. Studies have been done to compare the irritation levels induced by nanomicellar formulations of voclosporin, a calcineurin inhibitor, compared to Restasis, and found that the nanomicellar formulations resulted in significantly less irritation and were better tolerated [64]. Other nanotechnology based systems include nanoparticles, which can come in the form of nanocapsules, and also Nano suspension, which are colloids of submicron drug particles suspended and stabilized by polymers or surfactants [65]. These options provide advantages such as reduced irritation, increased precorneal residence time, and increased ocular bioavailability. Ocular irritation is a factor of non-adherence, and reduced irritation would likely decrease non-adherence. Increased precorneal residence time and increased ocular bioavailability would likely

reduce the number of daily administrations and therefore simplify treatment regimens, leading to increased medication adherence. Furthermore, sustained release medications allow for a lower dosing frequency, which could reduce costs for patients.

As mentioned earlier, the occurrence of adverse reactions associated with glaucoma medications is another factor that contributes to non-compliance. Common side effects that are reported by patients include redness, blurry vision, burning, tearing, and itching. In a study done by Wolfram et al., among the participants who reported side effects from their glaucoma medication, 37.6% of them were nonadherent with their glaucoma treatment. For the patients that didn't experience any side effects, the non-adherence rate was 18.4%. These results show that eliminating even small unfavorable effects can have significant impacts on medication adherence [61]. One cause of these side effects is the presence of preservatives in glaucoma medications, many of which have cytotoxic effects and lead to the onset of ocular surface diseases [66]. In this study, it was found that among participants taking medications that contained preservatives, 32.0% of them were non-adherent, and patients who took a combination of preservative-containing and preservative-free medications, 25% of them were non-adherent. Whereas for the patients taking preservative-free medication, only 12.5% of them were non-adherent. Preservative-free medication can lower toxicity, reduce corneal epithelial cell loss, and decrease the risk of ocular surface disease [61]. Therefore, physicians should consider preservative-free glaucoma medications for individuals who are more prone to experience side effects.

Medication cost imposes another potential barrier to adherence, but is not mentioned enough during office visits. Overall, patients diagnosed with glaucoma face more cost-related barriers than do patients who have never been diagnosed with glaucoma [58]. Without prior knowledge about medication cost, patients might face financial barriers when purchasing medication and may be less adherent as a result.

Non-adherence due to cost-related barriers is faced more often by racial and ethnic minorities when compared to non-Hispanic white individuals. A study done by Delavar et al. examined the rates of cost-related barriers to medication non-adherence among racial and ethnic minorities when compared to non-Hispanic white individuals. The results indicated that the odds of patients reporting difficulty affording medication was significantly higher among non-Hispanic African American and Hispanic individuals when compared to non-Hispanic white individuals. Both groups were associated with a higher likelihood to delay filling medications and using other treatments that are lower in cost, when compared non-Hispanic white individuals. Also, non-Hispanic African Americans were more likely to take less medication or skip medication in order to save money. Further, they found that these cost disparities were still present after controlling the data for socioeconomic factors among individuals, indicating there could potentially be methods that physicians can use to lessen these disparities [67].

Increased prescription of generic drugs, which typically have lower prices, is another potential solution. Currently, they are underused due to factors such as patient preference, unfamiliarity with these options, and sometimes, limited number or lack of generic alternatives for certain medications [68]. Therefore, generic drugs and other options that cost less should be made known to all patients, especially as some are more hesitant to discuss cost with their physician or might not know these lower-cost medication options are available. Delavar et al. also found from their study that even though only 6.8% of non-Hispanic White individuals indicated they were not able to afford medications, 19.3% asked for lower-cost medications. Among non-Hispanic African American individuals, 18.9% reported not being able to afford medications, and 16.4% asked for lower-cost medications [67].

Even as the reasons for cost-related barriers are multifaceted, practices aimed to improve health equity and medication adherence can include routine discussions about costs during visits to help mitigate any cost-related nonadherence barriers. Physicians can also provide free samples of medications to see if they are well tolerated, or if there are any adverse effects before prescribing. Furthermore, costs can be complicated by variable coverage from different insurance plans. Delavar, et al. suggests that information about medication cost could be integrated into electronic health records so that both the patient and the physician are aware of what the patient will pay. Moreover, insurance companies should provide better coverage of essential medications [67]. It is essential to have preservative free medications, combination medications and Intracameral implants such as Durysta and IDose TR available as alternative treatments.

Early diagnosis plays a crucial role in reducing the burden of diseases. Various approaches such as screening, monitoring, education, and expanding healthcare options can be explored to facilitate early detection. AI is a powerful screening tool that can be used to read and analyze OCT scans and determine if there are changes that may indicate the development of early glaucoma, especially for those more at risk. Repeating these scans at intervals recommended by the physician is an effective method to monitor any development or progression of early glaucoma. Additionally, to enhance healthcare options, patients could potentially self-monitor their IOP at home. This approach would reduce the reliance on IOP measurements solely obtained during clinic visits, as these readings may not accurately reflect their daily IOP levels. A study done by Astakhov et al. showed that patients used Icare® HOME tonometers to monitor their IOP at home showed a higher level of adherence to medications. They attribute this correlation to the idea that independent participation in the diagnostic process leads a better understanding of the disease and an increased awareness of the need to adhere to the treatment regimen [69]. The measurements obtained by these tonometers were shown to be reliable and accurate by Chen et al. with the mean difference between measurements obtained by Goldmann applanation tonometry and Icare® HOME tonometers varying from 0 to 1 mmHg [70]. To cover the costs of these new programs, it would be advantageous

to have insurance coverage for glaucoma screening and home monitoring equipment. Incorporating any of these approaches into the treatment of glaucoma has the potential to decrease the impact of the disease and enhance patient engagement in their care, consequently leading to better adherence to treatment.

Conclusion

Non-adherence and noncompliance to medication is different in every patient and there is not one universal solution for this problem. Therefore, ophthalmologist should focus on personalized care, curating treatment plans based on each patient's individual situation, including genetic, environmental, and lifestyle variability. These treatment plans can include previously suggested methods to address non-adherence such as patient education and better communication coupled with novel technology like sustained release medications, preservative-free medication and tonometers for self-measuring. Sustained release medications such as those nanotechnology based are advantageous in that they cause low irritation, have high ocular residence time, and have high bioavailability, thereby reducing treatment complexity. Tonometers designed for self-measurement encourage compliance by involving individuals in the diagnostic process. Due to the complex issues of corneal toxicity and compliance, and until all social determinants of health issues are fully addressed, this problem will persist. Laser treatment and surgical intervention are crucial components of glaucoma management, but medication drops continue to be the preferred method of treatment for many. Improving adherence in various ways can enhance patient compliance and reduce the risk of blindness associated with this condition.

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