Review

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Review

A Review of Ocular and Systemic Complications in Glaucoma Pharmacotherapy

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Abstract: Glaucoma, the second leading cause of irreversible blindness globally, encompasses a heterogeneous group of ocular disorders characterized by the progressive degeneration of retinal ganglion cells. Pharmacotherapy remains the cornerstone of treatment, primarily aimed at reducing intraocular pressure (IOP) by decreasing aqueous humor production or enhancing its outflow. The therapeutic classes employed include carbonic anhydrase inhibitors, β-blockers, α-adrenergic agonists, prostaglandin analogs, parasympathomimetics, Rho kinase inhibitors, and hyperosmotic agents. Despite their efficacy, these medications are associated with a range of ocular and systemic side effects, influenced by their mechanisms of action, formulation, and dosage. Ocular adverse effects, such as irritation, dry eye, allergic reactions, and infections, are common, while systemic absorption may lead to more severe outcomes, including organ dysfunction, exacerbation of comorbid conditions, or life-threatening cardiovascular events. Given these potential risks, it is critical for clinicians to understand and monitor these adverse effects, as they significantly affect patient adherence, quality of life, and treatment outcomes. Ongoing research is essential to develop novel therapeutic regimens, agents, or delivery methods that minimize side effects and improve compliance. Incorporating patient-reported outcomes in clinical practice may further enhance the assessment of treatment impact, facilitating more tailored and effective management of glaucoma.

Keywords: glaucoma; open-angle glaucoma; ocular hypertension; carbonic anhydrase inhibitors; β-blockers; α adrenergic agonists; prostaglandin analogue; parasympatomimetics; rho kinase inhibitor; hyperosmotic agents; adverse effects; vision loss; blindness

1. Introduction

Glaucoma encompasses a heterogenous group of ocular diseases characterized by progressive optic neuropathy, resulting from the degeneration of retinal ganglion cells (RGC) and nerve fibre layers in the retina [1,2]. Although elevated intraocular pressure (IOP) is neither required for diagnosis nor present in all patients with glaucoma, the first-line, evidence-based management for glaucoma typically involves IOP-lowering medications [3]. Glaucoma can be classified into two major types: primary or secondary, which can be further subdivided into open-angle or closed-angle glaucoma [4]. In 2013, an estimated 64.3 million people aged 40-80 years globally were affected with glaucoma, with a projection of 111.8 million by 2040 [5]. Primary open-angle glaucoma (POAG), the most common type of glaucoma, was estimated to affect 57.5 million people worldwide [6].

Globally, glaucoma is the second leading cause of vision loss and irreversible blindness [4]. Risk factors of glaucoma include demographic factors like age, gender, race, smoking, and genetics [4]. Since glaucoma is an insidious disease that can be challenging to diagnosis, many patients are untreated until irreversible vision loss occurs [4]. A meta-analysis found that undetected glaucoma was highly prevalent globally, with more than half of all cases went undetected on average prior to diagnosis in their respective study [7].

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Halting the progression of disease and maintaining vision as well as quality of life are key aspects for managing glaucoma. Multiple randomized control trials have demonstrated that lowering IOP slows down disease progression, and this practice has been a staple of clinical practice management for many years [8]. Various classes of medications are used; each with a different mechanism of action for lowering IOP.

The standard of care for the targeted IOP reduction should be achieved with the fewest medications and minimum adverse effects [3]. Yet, most IOP lowering medications often have undesirable adverse effects despite their effectiveness [9]. These could range from ocular complications like dry eye, irritation, or infection, to more serious systemic events like organ failure, allergic reactions, or exacerbation of co-morbidities [3,9,10]. Unbearable adverse effects, among other factors, is a significant threat to medical adherence, a long-standing challenge in glaucoma management. Uncontrolled glaucoma due to drop usage can subsequently lead to the development of new ocular issues, further complicating the management and deteriorating patients' quality of life. Therefore, the goal of this review is to highlight and summarize all ocular and systemic adverse effects of glaucoma pharmacotherapy, with an emphasis on why they occur and how to minimize them. This review can serve as a guide for clinicians to best tailor management based on individual patients and ensure greater adherence and overall better patient outcome.

2. Pharmacological Treatment of Glaucoma

IOP is primarily maintained by the balance between aqueous humor production and its outflow facility. Any disruption in this equilibrium can lead to an alteration in IOP [3]. Accordingly, glaucoma pharmacotherapy is broadly categorized based on their mechanisms of action: agents that reduce aqueous humor production and those that enhance its outflow.

2.1. Classes That Reduce Aqueous Inflow

2.1.1. Carbonic Anhydrase Inhibitors (CAIs)

Carbonic anhydrase (CA) is an enzyme that regulates the active secretion of bicarbonate ions into the anterior chamber of the eye. The osmotic gradient created by this active secretion leads to water movement into the anterior chamber via aquaporins, enhancing aqueous humour formation [11,12]. Consequently, this enzyme became an early target in investigational therapies for IOP control [13].

CAIs are available in both oral and topical formulations. Oral agents like acetazolamide, though capable of reducing IOP by up to 35%, are often reserved for refractory glaucoma due to their more serious adverse effect profile [9]. In contrast, newer topical formulations, such as dorzolamide and brinzolamide, selectively inhibit the carbonic anhydrase isoform in ciliary epithelium (type II) [14–16]. These topical agents, though less potent than their systemic counterparts, offer a preferable adverse event profile. Topical CAIs are typically administered two to three times daily, either as monotherapy or in combination with other agents [3]. The ocular and systemic adverse reactions to CAIs are summarized in Table 1.

2.1.2. Beta (β) Blockers

Initially developed as systemic agents, β-blockers were incidentally discovered to lower IOP in glaucoma patients, leading to the development of the first topical β-blocker, timolol maleate [3,17,18]. Despite its effectiveness, timolol's undesirable side-effect profile prompted the development of second-generation β-blockers, including betaxolol, carteolol, metipranolol, and others [19–23]. Beta-blockers reduce IOP by lowering aqueous humor production through the reduction of cAMP levels [18,24,25]. Although abundant β2-adrenergic receptors are present in the ciliary processes, the specific beta receptor involved in aqueous humor production remains unclear [3,10]. For instance, betaxolol, a β1-specific blocker, demonstrated similar efficacy of IOP reduction as the nonselective beta blockers [19].

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Long-term β-blocker therapy may lead to diminished efficacy over time, a phenomenon known as "long-term drift" [26]. This gradual upward shift in IOP is hypothesized to result from increased expression and density of beta receptors on cell membranes in response to constant long-term blockade [27].

Various topical medications of β-blockers have been developed over the years. Generally, ocular adverse effects are relatively infrequent in β-blockers and are often shared by different agents, with ranging frequencies and degree of severity [10].

2.1.3. Alpha (α) Adrenergic Agonists

These agents can be categorized into selective (α2) and non-selective (α1 and α2) receptor agonist [9]. Selective α agonists like brimonidine and apraclonidine act selectively on α2 receptors, thereby decreasing intracellular cAMP [28]. This mechanism decreases aqueous inflow and enhances uveoscleral outflow (the drainage of aqueous humor from the ciliary body and partially through supraciliary space and across the sclera), partly through prostaglandin activation [29,30]. To date, apraclonidine is particularly effective for controlling IOP spikes post-laser procedures but is less suitable for chronic glaucoma due to rapid tachyphylaxis [31–33]. Alternatively, brimonidine tartrate 0.2% twice daily has demonstrated comparable efficacy as timolol 0.5% twice daily [34]. IOP reduction at peak and trough IOP can reach 6 mmHg after 2-3 hours and 4 mmHg after 10-14 hours, respectively [35–37]. Its efficacy has made it a widely used agent for chronic glaucoma.

On the other hand, epinephrine and dipivefrine, stimulate both α1 and α2 adrenergic receptors, resulting in vasoconstriction and reduced blood flow to the ciliary muscles [38]. Since the ciliary body plays a foundational role in aqueous humor production, α agonists reduce aqueous production, thereby decreasing IOP [39].

2.2. Classes That Increase Outflow

2.2.1. Prostaglandin Analogues (PGAs)

PGA primarily enhance uveoscleral outflow, along with a modest increase in trabecular facility and aqueous production [40]. Proposed mechanisms of PGAs involve inducing ciliary muscle relaxation and remodeling of the extracellular matrix of the trabecular meshwork [40]. Collectively, these mechanisms result in ~30% reduction in IOP [41]. Latanoprost, a PGA dosed once daily, has shown efficacy superior to β-blockers with fewer side effects [41]. Subsequent developments in this class include bimatoprost, travoprost, and tafluprost [9,41,42].

2.2.2. Parasympatomimetics

Being one of the first agents developed for glaucoma, parasympathomimetics held a colorful history. Physostigmine, derived from the Calabar bean, was the first agent discovered in this class and found to induce pupil constriction [43]. Pilocarpine, a less toxic derivative, was later used for glaucoma with the goal of widening the spaces between corneoscleral trabeculae and distending the endothelial meshwork [44]. However, this effect seems to be modulated by age, ciliary body contraction, and initial configuration of the angle [45]. To date, pilocarpine remains a viable option in the acute management of angle-closure glaucoma, though it is ineffective in ischemic or atonic pupils [46].

These agents can be categorized into two major subtypes, direct-acting and indirect acting parasympathomimetics [9]. The former includes drugs like pilocarpine and carbachol, which directly stimulate cholinergic receptors. The latter include agents like physostigmine and echothiophate, which inhibit acetylcholinesterase enzyme at the synapse, thereby increasing acetylcholine concentrations available to act on receptors. Through actions on the parasympathetic system, these agents stimulate ciliary muscle contraction and open the trabecular meshwork, thereby increasing aqueous flow [9].

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2.2.3. Rho Kinase Inhibitors

Rho kinase inhibitors, a recent addition to glaucoma therapy, work by modifying cell morphology, disrupting actin microfilaments bundles, and impairing focal adhesion formation networks in the trabecular meshwork covering the inner wall of Schlemm's canal. This, along with induced relaxation of ciliary muscle, is thought to increase trabecular outflow facility and lower IOP [47,48]. Recently approved medications include Netarsudil in the United States and Europe, as well as Ripasudil in Japan [3]. Clinical trials have illustrated that while rho-kinase inhibitors provide modest IOP reduction as a monotherapy, their efficacy is improved when combined with other agents like latanoprost (Netarsudil/Latanoprost fixed-dose combination), a combination recently approved by the FDA [3,49,50].

2.1.4. Hyperosmotic Agents

Hyperosmotic agents, such as mannitol and glycerol, increase serum osmolarity when absorbed or administered into the blood. This change increases the osmolarity gradient between the vitreous and blood, causing an efflux of fluid and reduction of vitreous volume [3]. Since IOP is positively linked with the vitreous volume, reduced volume results in a subsequent IOP reduction.

However, the vitreous becomes more hypertonic over time (as water leaves) while the hyperosmotic agent is cleared from the blood [51]. This change may reverse the osmotic gradient between vitreous and blood, resulting in water backflow into the vitreous and an IOP pressure rebound. Mannitol and oral glycerol are commonly used agents in this class. Mannitol, typically administered intravenously as a 20% solution, does not cross the blood brain barrier or enter the eye [3]. It can thus be used for acute angle-closure crises unresponsive to other topical therapies or oral CAIs, such as acetazolamide.

Table 1. Reported ocular and systemic adverse effects of classes of glaucoma pharmacotherapy.

Drug class	Ocular side effects	Systemic side effects
Carbonic anhydrase inhibitor (CAIs)	Oral: color vision changes, bilateral transient myopia, angle-closure glaucoma, and choroidal detachment Topical: stinging sensation (12%), reddening or burning sensation of the eye (12%), blurred vision (9%), pruritus/itching (9%), and tearing (7%) [55]. Rarely: hyperemia, corneal decompensation, and contact dermatitis	Oral: Symptom complex (47.8%): general malaise, weight loss, fatigue, nausea, anorexia, depression and loss of libido [130]. Organs involved: gastrointestinal, neurological, and hematological Topical: transient bitter or metallic taste (25%) [16,54,55,139]; Rarely: nausea, fatigue, headache, skin rashes, paresthesia, and urolithiasis
Beta (β) blockers	- Burning or stinging sensation on instillation (~30-40% of patients), eye pain or discomfort, foreign body sensation, itchiness, and blurred vision (due to membrane stabilization property & formulation) [10,60–66]. - Allergic blepharoconjunctivitis, conjunctival hyperemia, punctate keratopathy (due to allergic reactions to benzalkonium chloride or beta-blocker) - Dry eye (11%) (due to reduced tear production) [74]	Systemic absorption leads to off-target multi-organ effects: - Cardiovascular: arrythmia (55%) was the most common side effect, followed by syncope (13%), heart failure (9%), palpitations (4%), and angina (3%) [147] - Respiratory: Bronchospasm-related reactions (58%) such as asthma exacerbation and chronic obstructive airways; dyspnea (29%), apnea (4%), respiratory distress (3%), and respiratory failure (2%) [147]

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		- Neurological: depression, decreased libido, anxiety, nausea, lethargy, emotional lability or irritability, and anorexia (due to lipophilicity and crossing blood brain barrier)
Alpha adrenergic agonist	Brimonidine: blurry vision (6.3-22.2%), burning or stinging sensation (14.6-28.1%), conjunctival hyperemia (5.9-30.3%), lid erythema (10.4%), photophobia (4.2-11.3%) and ocular pruritus (12.2-12.5%) [76–78]; allergic reactions are common (up to 26%) [79,80] Apraclonidine: follicular conjunctivitis and contact dermatitis (due to high oxidative potential) Non-selective agonists: irritation, pupillary dilation, hyperemia, follicular conjunctivitis, adrenochrome deposits	Brimonidine: fatigue/drowsiness (2.7-19.9%), sedation, and analgesic effects (alpha-2A and 2C receptors); reduced blood pressure, headache (4.3-19%) or dizziness (2.1%), and dry mouth (5.3-33%) (inhibition of norepinephrine release and sympathetic outflow) [76–78,164–166]. Apraclonidine: does not readily cross blood brain barrier. Epinephrine: cardiovascular (increased risk of benign ventricular extrasystoles, severe hypertensive reactions, and myocardial infarction)
Prostaglandin analogues (PGAs)	- Lash growth, periocular skin pigmentation (1.5-2.9%), iris pigmentation changes (7-30%), conjunctival hyperemia (5% to 68%), and peri-orbitopathy [83,89–98] - Extent of lash grow: 0-25% (latanoprost), 3-36% (bimatoprost), 0.7-52% (travoprost) [103–107]. - Rarely: anterior uveitis (4.9%-6.4%) and reactivation of herpetic simplex keratitis (0.44%) [118–121] - Caution in inflammatory glaucoma: risk of anterior uveitis and cystoid macular oedema	- Muscle/join aches and migraines (0.13%), rhinitis (0.26%), and non-ocular skin pigmentation (0.13%) [172–175]. - May elevate risk of asthma exacerbation
Parasympathomimetics	Direct acting: miosis (most common, pupillary sphincter constriction), ciliary muscle spasm (induced myopia/accommodative spasm), and brow ache	Direct acting: broad spectrum of cholinergic activation due to non-selectivity: - cardiovascular: bradycardia, arrhythmia, hypotension, flushing, and angina pectoris - central nervous system: headache, dizziness, somnolence - gastrointestinal: nausea, vomiting, salivation, diarrhea, urinary incontinence - respiratory: cough, dyspnea, asthma exacerbation, pulmonary edema

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		- Alzheimer's disease exacerbation Indirect acting: hypersalivation (9%), seizure (0.61%), vomiting (4.2%), abdominal cramps, bradycardia (0.35%), and arrhythmia (0.04%) [182]
Rho-kinase inhibitors	- conjunctival hyperemia (> 50% of patients for Netarsudil) [127,128] - corneal verticillate, instillation site pain, and conjunctival hemorrhages	
Hyperosmotic agents		Oral intake led to systemic absorption: - dry mouth, volume depletion, and cardiac effects (tachycardiac, hypotension, worsened heart failure) - gastrointestinal events (nausea, vomiting) - renal events (metabolic acidosis, urinary retention, acute kidney injury, peripheral edema) - subdural haematoma - anaphylactic reactions

3. Ocular Side Effects of Glaucoma Medications

A comprehensive summary of the ocular side effects of each medication class is presented in **Table 1.**

3.1. Classes That Reduce Aqueous Inflow

3.1.1. Carbonic Anhydrase Inhibitor (CAIs)

Oral CAIs, such as methazolamide, have been associated with cases of adverse events including color vision changes, bilateral transient myopia, angle-closure glaucoma, and choroidal detachment [52,53]. Colour vision changes may be interpreted as a specific effect of carbonic anhydrase inhibition in the retina [52]. The other complications are hypothesized to result from an idiosyncratic reaction to sulfur-containing methazolamide [53]. However, with the development of newer topical CAIs that have an improved safety profile, the use of oral acetazolamide and methazolamide is much rarer and has reduced by 95% [54].

Dorzolamide, the most studied topical CAI, is linked to a range of ocular symptoms, including stinging or burning sensation (12%), reddening or burning sensation of the eye (12%), blurred vision (9%), pruritus/itching (9%), and tearing (7%) in Phase III trials [16]. These effects are likely due to the drug's acidic pH (~5.5) [55]. Comparatively, brinzolamide, with a more neutral pH (~7.5), is less likely to cause burning or stinging (3%) but may more frequently induce blurred vision. Additionally, despite containing sulfa, topical CAIs have not been shown to induce more allergic reactions in patients with sulfa allergies compared to those with who do not have sulfa-related allergies [56]. Though rare, topical CAIs may also trigger local hyperemia (potentially due to local vasodilation), corneal decompensation, and contact dermatitis [57–59].

3.1.2. Beta (β) Blockers

Subjective side effects may include burning or stinging sensation on instillation (in up to 30-40% of patients), eye pain or discomfort, foreign body sensation, itchiness, and blurred vision [10,60–66].

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These side effects are likely associated with the membrane-stabilizing (local anesthetic) property of β-blockers, as well as the different vehicles, pHs, and concentration of β-blockers [10,67].

Objective side effects may include allergic reactions on the eyelids, the conjunctiva, and rarely the cornea [68]. These include allergic blepharoconjunctivitis, conjunctival hyperemia, punctate keratopathy. In one study involving 467 patients, 15 patients (3.2%) were found to have periorbital dermatitis, 8 patients (1.7%) had eyelid and conjunctival infections of eyelids, and 4 patients (0.9%) had punctate keratitis [68]. Another national 3-month surveillance in the Netherlands found similar findings: of the 34 patients who experienced ocular side effects, 44% experienced periorbital dermatitis or blepharitis, 23% had blepharoconjunctivitis or periorbital dermatitis combined with conjunctivitis or conjunctival hyperemia, 21% had conjunctivitis or conjunctival hyperemia, and 12% had punctate keratitis [68]. These adverse reactions can be attributed to hypersensitivity reactions to either the preservative (e.g., benzalkonium chloride) or the β-blocker agent itself [69]. For instance, 6% of patients with conjunctivitis or contact dermatitis has been found to be sensitized with benzalkonium chloride [70,71]. Contact hypersensitivity has also been reported for all β-blockers except for carteolol [71,72].

Early animal studies have implicated the role of beta-adrenergic receptors in reduced tear production, specifically β-receptors [73]. This relationship prompted the investigation of dry eyes in patients using β-blockers. In an early human study of 63 patients, the symptom of dry eye was reported in 11% of patients [74]. A more recent case-control study found significantly increased odds ratio of dry eyes symptoms patients with glaucoma using β-blockers [75].

Given the membrane stabilizing properties of β-blockers, they may act as local anesthetics in the cornea at high concentrations [67].

3.1.3. Alpha (α) Adrenergic Agonists

Brimonidine is associated with several ocular side effects, including blurry vision (6.3-22.2%), burning or stinging sensation (14.6-28.1%), conjunctival hyperemia (5.9-30.3%), lid erythema (10.4%), photophobia (4.2-11.3%) and ocular pruritus (12.2-12.5%) [76–78]. Rebound hyperemia after treatment discontinuation can commonly occur [79].

The incidence of allergic reactions associated with brimonidine is relatively high, affecting up to 26% of patients [79,80]. This agent has been reported to cause an allergic conjunctivitis in at least 10% of patients within one year and occasionally cause a granulomatous anterior uveitis and granulomatous papillary conjunctivitis [81,82]. Such ocular allergy usually appears within two weeks of treatment [80]. Follicular conjunctivitis can occur in 10-12% of patients taking brimonidine within the first year, which were frequently associated with the loss of IOP control [83]. Patients are encouraged to report onset of redness to their ophthalmologists promptly so their treatment dosing could be adjusted. The newer formulation, brimonidine tartrate 0.15% is formulated with purite as the preservative and has demonstrated a lower risk of allergic reactions [3,84].

Apraclonidine is particularly known for causing follicular conjunctivitis and contact dermatitis due to its high oxidative potential [85]. Therefore, the high risk of allergic reactions made this agent unsuitable for long-term therapy [31,79].

Non-selective agonists may cause irritation, pupillary dilation, hyperemia, follicular conjunctivitis, adrenochrome deposits [86]. Pupillary dilation occurs due to contraction of the iris dilators, which are stimulated by α receptor activation [86]. Aphakic or pseudophakic eyes receiving non-selective agonists are also at increased risk of cystoid macular edema [87,88].

3.2. Classes That Increase Outflow

3.2.1. Prostaglandin Analogues (PGA)

There has been an array of ocular adverse events linked with the use of PGAs, including lash growth, periocular skin pigmentation (1.5-2.9%), iris pigmentation changes (7-30%), conjunctival hyperemia (5% to 68%), and peri-orbitopathy [83,89–98]. Hyperemia is associated with PGAs is caused by the vasodilation of the conjunctival vessels, stimulated by nitric oxide and neuropeptides

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[99]. Hyperemia typically occurs within the first week of therapy and gradually decrease over time [83]. The variation in incidence of hyperemia among different PGAs are reflective of their chemical structures. It can be found in as many as 50% of patients using travoprost and as few as 5% of patients using latanoprost [99]. Reversible eyelash changes, including increased length, thickness, and number may be associated with the agent's ability to enhance growth and hypertrophy in resting follicles through vasodilation in perifollicular vessels [100–102]. Degree of eyelash growth varies among PGAs, ranging from 0–25% for latanoprost, 3–36% for bimatoprost, and 0.7–52% for travoprost[103–107].

Furthermore, these drugs are capable of increasing melanin granule formation by increasing transcription and activity of tyrosinase, leading to permanent iris colour changes [95–97]. Similarly, darkening of periocular skin has also been described [91,103]. Furthermore, PGAs have been reported to induce periocular peri-orbitopathy, termed prostaglandin-associated peri-orbitopathy (PAP). This is a notable constellation of clinical and cosmetic changes, such as flattening of the lower eyelid bags (FLEB), superior sulcus deepening, orbital fat atrophy, ptosis, and dermatochalasis [108]{Aihara, 2011 #1076, [109,110]}. These changes can occur as early as within one month of starting PGA treatment [89]. The prevalence may be as high as over 40% of patients treated over 3 months and more than 60% of patients after 6 months of therapy [111,112]. Although not fully elucidated, the mechanism of PAP could be linked to PGF2α-induced suppression of adipogenesis and inhibition of preadipocyte proliferation and adipocyte differentiation [113–115]. Allergic reactions are relatively rare, reported in 1% of adult patients [116,117].

Rare cases of serious adverse effects have also been reported, including anterior uveitis (4.9%-6.4%) and reactivation of herpetic simplex keratitis (HSK) given their pro-inflammatory property [118,119]. For this reason, PGAs are relatively contraindicated in patients with inflammatory glaucoma as they may aggregate anterior uveitis and cystoid macular edema. Although early case reports and animal studies has reported re-activation of HSK after PGA use, a review of claims record of 93869 glaucoma patients revealed only 0.44% of patients with any HSK event [120,121]. This rate is comparable to the general population and did not correlate with PGA therapy. Furthermore, there have also been considerable efforts on exploring the relationship between PGAs use with pseudophakic cystoid macular edema (CME) [3]. While co-existing potential risk factors make it difficult to ascertain a causative relationship, it is recommended to exercise caution when considering PGAs prescription for patients with risk factors for CME [122]. Finally, benzalkonium chloride, a preservative used in some PGAs, may cause side effects such as conjunctival hyperemia and superficial punctate keratitis [123].

3.2.2. Parasympatomimetics

Activation of cholinergic M3 receptors by pilocarpine constricts pupillary sphincter and ciliary muscles, leading to miosis (most common side effect), ciliary muscle spasm (induced myopia/accommodative spasm), and brow ache [124,125]. Possible retinal detachment and cataractogenesis have been reported with pilocarpine use previously, though it is difficult to conclude about the actual risk as the evidence is limited from early studies [3,125]}. Carbachol may also cause transient stinging and burning upon instillation [126].

3.2.3. Rho Kinase

The most prevalent adverse event associated with their vasodilatory property is conjunctival hyperemia, which was observed in more than 50% of patients in RCTs [127,128]. Approximately 20% of patients also experienced corneal verticillata, instillation site pain, and conjunctival hemorrhages (due to vasodilation). Additionally, conjunctival hemorrhage has been reported, but it was not dose-dependent [129].

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4. Systemic Side Effects of Glaucoma Medications

A comprehensive summary of the systemic side effects of each medication class is presented in **Table 1.**

4.1. Classes That Reduce Aqueous Inflow

4.1.1. Carbonic Anhydrase Inhibitor (CAIs)

Epstein et al. first presented a symptom complex commonly reported by patients taking acetazolamide or methazolamide. Of 92 patients, 44 (47.8%) experienced general malaise, weight loss, fatigue, nausea, anorexia, depression and loss of libido [130]. Given this, up to one-third of these glaucoma patients discontinued their CAI treatment despite its clinical efficacy [130]. Although the mechanism of these side effects has not been fully elucidated, it is mostly likely linked to the metabolic acidosis, as well as possible gastrointestinal and neuronal inhibition of carbonic anhydrase induced by CAIs [54].

Multi-organ adverse events of oral CAIs have been comprehensively explored previously [9]. In short, some of its prominent side effects include gastrointestinal (electrolyte imbalance, kidney stone formation, and urine alkalinization [131]), neurological (include paresthesia, dysgeusia, depression, loss of libido, tinnitus, and fatigue [130,132,133]), and hematologic (blood dyscrasias, aplastic anemia, thrombocytopenia, and agranulocytosis [134]) adverse reactions.

Interestingly, an analysis of human urine found that, in contrast to acetazolamide, which was excreted unchanged renally, only a quarter of methazolamide was excreted unchanged. Additionally, unlike acetazolamide, methazolamide was neither secreted nor concentrated by the kidney. Hence, at equal threshold doses, it produces less acidosis and renal effects like kidney stones than acetazolamide [135].

While oral CAIs are dosed in hundreds of mg daily (10–15 mg/kg), topical CAIs are administered in extremely small amount by weight (~0.05 mg/kg) such that their systemic absorption is minimal-to-none [54]. Several studies have observed no biochemical changes suggestive of systemic carbonic anhydrase inhibition from topical CAIs, ranging from four week to two-years [136–138]. Hence, the most common systemic side effect of topical CAIs was a transient bitter or metallic taste, reported in approximately 25% of patients [16,54,55,139]. This side effect is caused by the drug-laden lachrymal fluid draining into the oropharynx, resulting in inhibition of the carbonic anhydrase enzyme found in the saliva (CA VI) and the taste buds (CA II and CA VI) [16,140]. Infrequently recorded systemic side effects include nausea, fatigue, headache, skin rashes, paresthesia, and urolithiasis [16]. However, their association with topical CAIs use remains unclear given the minimal systemic concentration.

Risk of severe adverse reaction is relatively low and comparable for oral and topical CAIs. In a matched longitudinal cohort study of 128942 patients, the absolute risk of severe complication of either Stevens-Johnson syndrome, toxic epidermal necrolysis or aplastic anemia was 2.08 per 1000 patients for topical CAIs and 2.9 per 1000 patients for oral CAIs [141].

4.1.2. Beta (β) Blockers

Despite low dosage of topical β-blockers, it is possible that their systemic concentration is still significant enough to cause noticeable side-effects, especially since they bypass hepatic metabolism [10]. Systemic adverse effects are caused by unintentional actions on beta receptors in other organs, such as beta1 receptors in the heart and beta2 receptors in the lungs [10]. Additionally, lipophilic β-blockers like timolol may also cross the blood brain barrier, further exerting actions on beta receptors in the brain [142,143]. Consequently, long-term use of β-blockers can be associated with a wide range of multi-organ adverse events.

Cardiovascular side effects by blocking beta1 receptors in the heart may include bradycardia, arrhythmia, heart failure, syncope, angina, myocardial infarction, palpitation, and sudden death [60,61,144–147]. Between September 1978 and December 1985, the FDA documented 247 reports of severe cardiovascular events attributable to timolol, resulting in 13 deaths [147]. It also found that

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arrythmia (55%) was the most common side effect, followed by syncope (13%), heart failure (9%), palpitations (4%), and angina (3%) [147].

Topical β-blocker may also act on beta2 receptors in the respiratory system. Notable respiratory adverse reactions were increased bronchospasm-related events, among which the most severe reactions are asthma exacerbation and chronic obstructive airway disease [148–155]. Such events are especially high-risk for patients with pre-existing respiratory illnesses like asthma and can lead to fetal status asthmaticus [156,157]. Nelson et al. recorded 227 cases of respiratory adverse events attributable to timolol during an 8-year period between September 1978 and December 1985. Bronchospasm-related reactions (58%) was the most common, followed by dyspnea (29%), apnea (4%), respiratory distress (3%), and respiratory failure (2%) [147].

Newer, more cardioselective beta1-blockers, such as betaxolol, are designed to mitigate these respiratory complications relative to non-selective agents like timolol [10,62]. Nevertheless, clinicians should remain cautious prescribing these agents to patients with respiratory disease as these cardioselective agents do not entirely eliminate the risk of respiratory complications since they may still act on β2 receptors.

Due to the lipophilicity of most β-blockers, they readily cross the blood-brain barrier, capable of inducing neurological symptoms [158]. These neurological adverse events include depression, decreased libido, anxiety, nausea, lethargy, emotional lability or irritability, and anorexia [61,159–162]. Most of these events have been associated with timolol maleate, the earliest topical β-blocker approved for use. Given that these symptoms could be easily overlooked, physicians should remain vigilant when inquiring about adverse reactions.

Finally, the onset of adverse reactions may range from immediately upon instillation to many years after initial treatment [163]. Among 318 adverse events examined in one study, 23% occurred on the first day of therapy while 33% occurred after one week of treatment [147].

Therefore, given their potential serious systemic adverse effects, β-blockers should be prescribed with caution [3]. However, with over 20 years of use, they remain a valuable member of the management toolkit for glaucoma, either used as monotherapy or in combination with other agents. Several strategies should be employed to minimize systemic side effects of topical beta-blockers [10]. First, inquire about the patient's history of any possible cardiorespiratory disease and exclude patients at high-risk of adverse events. Second, administer the lowest possible dose to achieve therapeutic effectiveness, thereby minimizing systemic absorption and the risk adverse events. Third, engage in informative discussions with patients and their family regarding risks of systemic problems and the importance of active disclosure and stopping the medication when they occur [10].

4.1.3. Alpha (α) Adrenergic Agonists/Sympathomimetics

Brimonidine may bind to different subtypes of α-2 adrenoreceptors in non-ocular organ systems, producing unintentional effects. Given its lipophilicity, it crosses readily through the blood brain barrier, inducing fatigue/drowsiness (2.7-19.9%), sedation, and analgesic effects through central stimulation of the α-2A and 2C receptors [76–78,164]. Pre-synaptic α-2A activation may lower blood pressure through inhibition of norepinephrine release and sympathetic outflow, associated with headache (4.3-19%) or dizziness (2.1%) [76–78,165]. Decreased norepinephrine release may also contribute to dry mouth (5.3-33%) [76–78,166]. In addition to its impact on the central nervous system, Brimonidine is also associated with hypotension, bradycardia, and respiratory symptoms [31,77].

Apraclonidine, a non-selective agonist, has reduced risk of the above systemic adverse effects as it does not readily cross the blood-brain barrier [167].

Epinephrine, may bind to α receptors in the cardiovascular system, elevating the risk of benign ventricular extrasystoles, severe hypertensive reactions, and myocardial infarction [168,169]. Therefore, its use is contraindicated in patients with uncontrolled hyperthyroidism, as it elevates the risk of a hypertensive crisis [170]. Dipivefrine, a prodrug of epinephrine, has less adverse effects than epinephrine [171].

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4.2. Classes which Increase Outflow

4.2.1. Prostaglandin Analogues (PGAs)

Topical prostaglandins usually have desirable adverse effects profile and minimal systemic side effects due to their rapid half-life of elimination and low frequency of dosing (once-per-day) [9]. Minor side effects include muscle/joint aches and migraines (likely due to prostaglandins' role in mediating pain receptors) (0.13%), rhinitis (0.26%), and non-ocular skin pigmentation (0.13%) [172–175].

Generally, the impact of PGAs on cardiovascular and respiratory systems is relatively minimal; however, patients with pre-existing co-morbidity or risk factors may still be vulnerable. Prostaglandin F2α analogues like latanoprost activate the renin-angiotensin-aldosterone system and may thus elevate blood pressure [176]. Case reports of hypertensive events were reported in elderly patients [175,177]. Additionally, since these analogues are derivations of arachidonic acid via the cyclooxygenase pathway, they may induce bronchospasm and exacerbate asthma (predominantly latanoprost) like β-blockers [178,179]. In a Japanese database study of adverse drug event reports, Prostaglandin F2α analogues were positively associated with asthma (7 cases of 713 reports), and its combined therapy with β-blocker (5 cases of 90 reports) further elevated such association [179].

4.2.2. Parasympatomimetics

Direct-acting parasympathomimetics such as pilocarpine and carbachol are associated with a broad spectrum of adverse effects due to their non-selective interaction with cholinergic receptors across various systems including the central nervous, gastrointestinal, cardiovascular, respiratory systems, and the central nervous [9]. This risk is elevated due to the frequent dosing of pilocarpine (four times per day), which may induce cardiovascular (bradycardia, arrhythmia, hypotension, flushing, and angina pectoris), central nervous system (headache, dizziness, somnolence), gastrointestinal (nausea, vomiting, salivation, diarrhea, urinary incontinence), and respiratory (cough, dyspnea, asthma exacerbation, pulmonary edema) adverse events [9]. Pilocarpine use could also exacerbate symptoms of Alzheimer's disease and other neurodegenerative conditions given its cholinergic activity [180]. In addition to sharing all of these adverse reactions, carbachol can also activate nicotinic receptors, leading to central nervous system (lethargy, seizure, coma, central respiratory depression), sympathetic nervous system (tachycardia), and neuromuscular (muscle weakness, fasciculations, and paralysis) adverse events [181].

Indirect-acting parasympatomimetics, such as physostigmine (a reversible acetylcholinesterase inhibitor) and echothiopate (an irreversible acetylcholinesterase inhibitor), are less commonly used topically because of their associated adverse effects [9]. Physostigmine can cause hypersalivation (9%), seizure (0.61%), vomiting (4.2%), abdominal cramps, bradycardia (0.35%), and arrhythmia (0.04%) due to accumulation of synaptic acetylcholine at nicotinic and muscarinic receptors [182]. Echothiopate is linked with a similar range of adverse reactions via the same mechanisms [183,184].

4.2.3. Rho Kinase

Currently, no clinically significant systemic adverse events have been reported for Rho kinase inhibitors since they were approved for clinical use in 2017 [185].

4.1.4. Hyperosmotic Agents

Systemic adverse events related to mannitol use include dry mouth, volume depletion, and cardiac effects (tachycardiac, hypotension, heart failure exacerbation), gastrointestinal events (nausea, vomiting), renal events (metabolic acidosis, urinary retention, acute kidney injury, peripheral edema), subdural hematoma, and anaphylactic reactions [186–191]. Therefore, extra vigilance is warranted for mannitol use in patients with pre-existing heart failure, known hypersensitivity to mannitol, active intracranial bleeding, pulmonary edema or vascular congestion, severe hypovolemia, electrolyte imbalance, and anuria [191].

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In addition to these events, glycerol may also cause nausea and vomiting due to its unpalatable sweet taste [191]. Patients with diabetes should receive the alternative, isosorbide, over glycerol to prevent ketoacidosis and hyperglycemic events [192].

4. Discussion

In this review, we conducted a comprehensive examination of the ocular and systemic side effects associated with all major classes of glaucoma pharmacotherapy. Notably, several undesirable ocular effects are shared across different drug classes. Discomfort upon instillation, including symptoms such as stinging, burning, itching, tearing, and blurred vision, are frequently reported with all classes of glaucoma medications [10,16,60–66,76–78,83,89–98]. Additionally, ocular allergic reactions, which may necessitate discontinuation in severe cases, commonly present as allergic conjunctivitis, granulomatous papillary conjunctivitis, or punctate keratopathy. These hypersensitivity reactions are particularly prevalent with brimonidine and β-blockers but are rarely associated with PGAs [56,68,79,80,123]. Similarly, hyperemia due to vasodilation is observed across several drug classes, including PGAs, brimonidine, and Rho kinase inhibitors, although it is less common with CAIs [57–59,79,80,83,127,128]. Another notable side effect, miosis, often occurs in medications that target the iris dilator or pupillary sphincter, such as non-selective α agonists and parasympathomimetics [86,124,125].

Beyond ocular effects, systemic side effects arise when glaucoma medications are absorbed into the systemic circulation, leading to off-target effects on other organ systems. Lipophilic drugs can cross the blood-brain barrier, resulting in neurological adverse effects such as depression, decreased libido, lethargy, and irritability. This is most frequently reported with β-blockers, α agonists, and direct-acting parasympathomimetics like pilocarpine and carbachol [9,61,76–78,159–162,164]. Furthermore, drugs that modulate the sympathetic or parasympathetic nervous systems, or affect blood osmolarity, may increase the risk of cardiovascular complications. These include β-blockers, non-selective adrenergic agents, parasympathomimetics, and hyperosmotic agents [60,61,144–147,168,169,186–191]. Consequently, such medications should be prescribed with caution in patients with underlying cardiovascular conditions. Respiratory complications may occur with β-blockers, parasympathomimetics, and, to a lesser extent, PGAs [9,148–155,179]. Gastrointestinal side effects, such as vomiting and diarrhea, are more common with parasympathomimetics, oral CAIs, and hyperosmotic [9,131,186–191].

The diverse side effect profiles of glaucoma medications are largely dictated by their specific mechanisms of action, formulations, preservatives, concentrations, and routes of administration. Among available options, topical PGAs, the first-line treatment, offer a favorable balance between efficacy, once-daily dosing, and safety [41]. While PGAs are associated with minimal systemic side effects, they are known to cause several ocular side effects, including irreversible iris hyperpigmentation, peri-orbitopathy, reversible eyelash growth, and transient conjunctival hyperemia [83,89–98]. PGAs are comparable to β-blockers for their efficacy in IOP reduction. However, beta-blockers are associated with a greater risk of systemic adverse reactions, which may also be life-threatening [147]. Thus, while PGAs can safely be prescribed across a wide range of patient populations, the use of beta-blockers should be prescribed with caution in individuals with cardiovascular or respiratory comorbidities [3]. For patients unable to tolerate long-term beta-blocker therapy, topical CAIs present a viable alternative [3]. CAIs are known to produce minimal systemic side effects aside from transient bitter taste [16,54,55,139]. Oral CAIs, however, are reserved for acute glaucomatous attacks due to their significant side-effect profile [9]. Alpha agonists hold a valuable place in both chronic (e.g., brimonidine) and acute (e.g., apraclonidine) glaucoma management; their side effects are mainly related to off-target stimulation of alpha agonist receptors and rebound hyperemia may occur after medication discontinuation [79]. Notably, they tend to have the highest risk of ocular allergic reactions [79,80]. Next, side effects of parasympatomimetics, either direct or indirect, can be attributed to their off-target stimulation of non-ocular cholinergic receptors [9]. Most prominent are neurological and cardiac symptoms described previously, but other parasympathetic responses like hypersalivation and neuromuscular effects like muscle weakness, fasciculations, and

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paralysis can also occur [181]. These agents are rarely used in practice now. Finally, as one of the newest agents, rho kinase inhibitors have shown promising results in clinical trials [3,49,50]. Most common ocular side effect patients should be aware of is conjunctival hyperemia [127,128]. So far, there are no known systemic side-effects related to topical rho kinase inhibitors. Finally, hyperosmotic agents should only be used in acute glaucoma attacks, and they present several systemic side effects related to volume depletion and electrolyte imbalance attributable to their hyperosmotic effects [3,51].

It is evident that side effects—whether mild or severe—can significantly impact medication adherence, patient quality of life, and overall treatment outcomes. Long-term compliance with glaucoma medications remains a challenge, with fewer than half of patients adhering to their prescribed therapy beyond one year [193]. There are multiple factors that can influence patient compliance, with medication side-effects being one of the most predominant [194–198]. Interestingly, some studies have shown that sensations such as stinging or burning may paradoxically improve adherence, as patients perceive them as indicators of drug activity. Hyperemia, however, was the most commonly reported side effect and it was consistently associated with reduced adherence and higher rates of discontinuation [199].

Beyond compliance, side effects often contribute to a diminished quality of life, particularly in patients experiencing long-term use. For instance, in a survey by Nordmann et al., nearly two-thirds of patients reported at least one local side effect, with significant associations between medication side-effects and reduced vision-related quality of life, as well as treatment dissatisfaction [200]. Similarly, Quaranta et al. also studied how adverse effects like hyperemia, blurred vision, and stinging/burning sensation can negatively interfere with patients' environmental and social aspects of life, leading to greater patient dissatisfaction with therapy [201]. When asked what aspects of their glaucoma management patients would be willing to pay extra for, patients wished for reduced side effects, such as eye drops that did not cause blurred vision, drowsiness, or stinging/tearing [202]. Collectively, these factors could significantly impact the overall treatment outcome, leading to subsequent vision loss and permanent optic neuropathy [194]. However, the subjective nature of non-compliance and diminished quality of life can make these issues difficult to assess in routine practice. Integrating patient-reported outcomes into clinical practice may offer a valuable approach to monitoring medication adherence, assessing quality of life, and identifying individualized barriers to effective treatment [198].

Recognizing the importance of minimizing side effects in glaucoma management, ongoing research has focused on exploring novel drug classes and innovative treatment strategies that could enhance future therapeutic approaches. Notably, combination therapies involving PGAs have shown considerable promise. Recent trials have demonstrated that a combination of Netarsudil 0.02% and Latanoprost 0.005% provides greater and more sustained IOP reduction than either agent used alone [203]. Similarly, Latanoprostene bunod, a fixed combination of latanoprost and a nitric oxide-donating moiety, has demonstrated superior IOP reduction compared to timolol 0.5%, alongside a favorable safety profile [204,205]. This combination exerts its therapeutic effects via dual mechanisms, acting on both prostaglandin receptors and nitric oxide synthase to enhance aqueous humor outflow and lower IOP [206]. Through activation of guanylyl cyclase and cyclic guanosine monophosphate signaling pathway, nitric oxide causes relaxation of the cytoskeleton of the trabecular meshwork, increasing outflow and decreasing IOP. Through phase 1-3 trials, the most common side effects were associated with PGAs, such as conjunctival hyperemia (5.9-17.7%), eye lash growth (16.2%), and iris hyperpigmentation, with no known systemic adverse effects reported [207,208]. In addition to combination therapies, novel agents such as prostanoid receptor agonists (DE-117 and ONO-9054) targeting new pathways in prostaglandin signaling are being investigated [209–212]. If approved, these agents may become viable options for patients with uncontrolled IOP on prostaglandins. Based on existing clinical trial results, both agents have shown greater IOP reduction than latanoprost.

Finally, considerable interest has been dedicated to preservative-free formulations of glaucoma medications. Benzalkonium chloride (BAK), a preservative widely used in glaucoma medications, has been linked to significant ocular surface toxicity, including conjunctival hyperemia and

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superficial punctate keratitis [123]. Preservative-free formulations, such as those of tafluprost and latanoprost, hold promise for reducing ocular surface irritation, particularly in patients with pre-existing ocular surface disease [213]. However, further research is necessary to evaluate the long-term efficacy and safety of these preservative-free alternatives, especially in formulations containing multiple active ingredients [214–216].

5. Conclusions

This comprehensive review has outlined the major ocular and systemic side effects associated with all major pharmacotherapies used in glaucoma. Notable ocular side effects such as instillation discomfort, hyperemia, allergic conjunctivitis, and miosis are frequently encountered across multiple drug classes. Systemic side effects, though less common, warrant additional vigilance when using β-blockers and parasympathomimetics, as these may potentially lead to severe cardiovascular, respiratory, and neurological complications in high-risk individuals. The burden of side-effects can significantly affect patient adherence to therapy, often resulting in suboptimal treatment outcomes, decreased quality of life, and ultimately contributing to the progression of glaucoma and permanent vision loss. PGAs, with their favorable balance of efficacy, convenience, and safety, remain the gold standard for first-line therapy, although they too come with their own set of unique ocular side-effects including permanent iris hyperpigmentation, eyelash growth, and peri-orbitopathy. Ultimately, the choice of glaucoma medication(s) should be tailored to each unique patient's IOP requirements, past medical history, and preference to maximize efficacy and adherence while minimizing the risk of complications.

Future research efforts should prioritize the development of preservative-free agents, combination regimens, and novel agents or delivery systems. Advancements in drug design that limit systemic absorption, target specific ocular pathways, and mitigate local side effects have the potential to improve both adherence and patient outcomes. Combination therapies, such as those incorporating PGAs with novel agents like nitric oxide-donating compounds, offer promise for enhanced IOP control while reducing polypharmacy. Additionally, preservative-free formulations are crucial for minimizing ocular surface toxicity, especially in patients with pre-existing ocular surface disease. Patient management should also evolve to integrate routine assessments of adherence and quality of life through patient-reported outcomes. Such strategies will enable clinicians to tailor treatment to individual needs, enhancing long-term efficacy and satisfaction. With ongoing innovation and a deeper understanding of patient-specific factors, future glaucoma therapies hold the potential to be safer, more effective, and more widely tolerated, significantly alleviating the global burden of this vision-threatening disease.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Figure S1: title; Table S1: title; Video S1: title.

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