future pharmacology

MDPI

Review

A Narrative Review of Pharmacotherapy of Glaucoma

Shalini Virani [1,*] and Parveen Rewri [2,*]

[1] Department of Pharmacology, Maharaja Agrasen Medical College, Agroha 125047, India
[2] Department of Ophthalmology, Maharaja Agrasen Medical College, Agroha 125047, India
* Correspondence: drshalinivrewri@mamc.edu.in (S.V.); drparveenrewri@mamc.edu.in (P.R.)

Abstract: Progressive loss of retinal ganglionic cells (RGC) causes degeneration of optic nerve axons, which leads to blindness in glaucoma. Elevated intraocular pressure (IOP) is the most important, treatable risk factor. Currently, the management of glaucoma is centred on reducing the IOP, and drugs in the form of topical drops are the first line of management. Drugs reduce IOP either by suppressing aqueous humour secretion or improving the aqueous humour outflow. Newer drugs added during the past three decades to the armamentarium of glaucoma treatment have targeted the aqueous outflow. With an evolving understanding of the pathogenesis of glaucoma, the role of 24-h IOP control and other IOP-independent risk factors affecting ocular blood flow and RGC toxicity is also being actively studied in clinical and pre-clinical models of glaucoma. The role of available drugs in controlling IOP over 24 h is being evaluated. Improvement of ocular blood flow and neuroprotection are seen as potential drug targets for preventing the loss of RGC. In this article, we review the pharmacotherapy of glaucoma based on current therapeutic principles.

Keywords: Glaucoma; Pharmacotherapy; Intraocular pressure; 24-h IOP control; Neuroprotection; Ocular blood flow; Adjunctive therapy

Citation: Virani, S.; Rewri, P. A Narrative Review of Pharmacotherapy of Glaucoma. *Future Pharmacol.* **2024**, *4*, 395–419. https://doi.org/10.3390/futurepharmacol4020022

Academic Editors: Francisco Javier Otero-Espinar and Fabrizio Schifano

Received: 19 March 2024
Revised: 1 May 2024
Accepted: 17 May 2024
Published: 27 May 2024

1. Introduction

Glaucoma, characterised by a progressive loss of retinal ganglionic cells (RGC) [1], is the cause of 11% of global blindness in individuals aged 50 years and older [2]. The risk of blindness is related to the level of untreated intraocular pressure (IOP), wider IOP fluctuations [3], the extent of RGC loss at the time of diagnosis [4], compliance with treatment [5], and other IOP-independent factors. The increase in IOP in glaucoma results from resistance to the drainage of aqueous humour through outflow pathways. Lowering the elevated IOP and controlling IOP fluctuations is the current accepted therapeutic approach in the management of glaucoma and can be achieved with drugs, LASER, and surgical intervention. The effective IOP-lowering, called target IOP, slows down the progression of glaucoma and delays blindness [6]. However, in a subset of patients, RGC continue to die even after effective IOP-lowering. In these patients, the role of IOP fluctuations and other IOP-independent factors like ocular blood flow and neurotoxicity is anticipated. The current interventions mainly lower the IOP, and their other benefits like 24 h IOP control, ocular blood flow regulation, and neuroprotection are being explored.

Medical interventions in the form of topical eye drops are often offered as the first-line therapy. Several drugs of different classes are available that effectively lower the IOP [7]. In this article, we review the pharmacotherapy of glaucoma based on the current understanding of therapeutic principles.

2. Pathophysiology of Glaucoma

Axons of approximately 1.2 million RGC converge at the scleral lamina cribrosa to exit from the eye and form the optic nerve head (ONH), the intra-ocular portion of the optic nerve. The ONH is visible on fundus examination as a pinkish disc with a peripheral rim of axons, called the neuroretinal rim (NRR), and a central space filled with glial cells, known

as the optic disc cup (Figure 1a). The death of RGC manifests as the focal or diffuse loss of NRR and an alteration in the cup-to-disc ratio (CDR), characteristic of glaucomatous damage (Figure 1b). RGC death is most often due to elevated IOP [8], though it occurs over a range of IOPs. The pressure-induced changes at the level of lamina cribrosa [9] affect the retrograde transport of essential factors [10] to the cellular body of the RGC, which culminates in RGC death mainly via apoptosis.

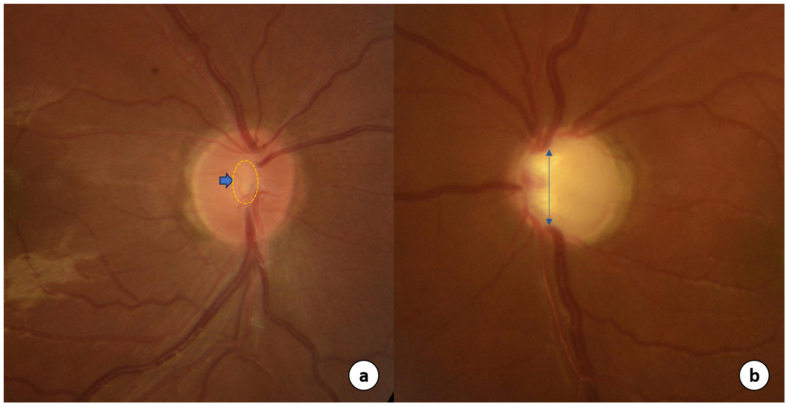

Figure 1. (**a**) The optic nerve head with healthy neuroretinal rim, area surrounding the inside dotted circle. There inside dotted circle, marked with blue arrow is cup. (**b**) The optic nerve in glaucomatous eye. Note the loss of NRR and increase in cup size, marked with blue line.

The net IOP is an outcome of the relationship between the rate of aqueous secretion, the rate of aqueous drainage, and episcleral venous pressure [11]. It is the drainage of aqueous humour that is almost always impaired in all types of glaucoma, apart from normal-tension glaucoma [12]. The aqueous drains through two independent pathways—the trabecular meshwork (or conventional or major pathway) and the uveoscleral pathway (or non-conventional or minor pathway). Conventional outflow accounts for nearly 85% of aqueous drainage, and 5–25% of drainage is through uveoscleral outflow in adult human eyes [13]. Some studies estimated uveoscleral flow to account for 12–54% of the total aqueous outflow [14]. The aqueous outflow facility decreases with age through the trabecular meshwork pathway [15,16] as well as the uveoscleral pathway [14,16,17]. The IOP increases following impaired aqueous drainage through the trabecular meshwork. The mechanisms responsible for impaired aqueous drainage through the trabecular meshwork are documented primarily based on the gonioscopic state of the angles of the anterior chamber. In open-angle conditions, the resistance to aqueous outflow is at the level of the trabecular meshwork [18], whereas in angle-closure conditions, access to the trabecular meshwork is blocked by iris tissue [19].

3. Targets for Pharmacotherapy

Currently, the management of glaucoma is limited to lowering the IOP. The two ways in which the IOP can be lowered are by reducing aqueous humour secretion and improving aqueous humour drainage. The global availability of topical IOP-lowering drugs varies based on approval by the official local controlling body. Pilocarpine, a cholinergic agent, was the first topical drug used to treat glaucoma [20]. The latest addition to the armamentarium of IOP-lowering drugs is Omidenepag Isopropyl (OMPI), a prostaglandin E_2 receptor analogue, which was approved in the USA by the FDA in 2022 to treat open-angle glaucoma and ocular hypertension [21] (Figure 2). Topical IOP-lowering drugs are available either as a monotherapy or as fixed-drug combinations (FDC). These drugs fall broadly into two groups (Table 1) based on their main mechanism of IOP reduction: one, which reduces the IOP by suppressing the aqueous humour secretion, and two, which reduces the IOP by improving the aqueous humour outflow. The latter is further sub-grouped based on whether these drugs reduce the IOP by improving aqueous outflow through the

conventional or unconventional pathway (Figure 3). IOP-lowering drugs developed in the early years targeted aqueous secretion reduction until the role of prostaglandin analogues in facilitating the aqueous outflow was recognized. The recent addition of drugs acting on the trabecular meshwork represents the most physiological way of reducing IOP. Few drugs lower IOP by more than one mechanism (Table 2), but they are grouped based on their chief mechanism of IOP reduction. Based on their target mechanism of action, currently available IOP-lowering drugs are classified into seven classes.

Table 1. Classification of topical IOP-lowering drugs.

Aqueous Suppressants Drugs
Alpha-adrenergic agonist
Apraclonidine 0.5%
Brimodine 0.1%, 0.15%, 0.2%
Beta-adrenergic antagonist
Betaxolol 0.5%
Timolol 0.5%
Carbonic anhydrase inhibitors (CAIs)
Brinzolamide 1%
Dorzolamide hydrochloride 2%
Aqueous Outflow Drugs
Trabecular meshwork outflow pathway
Cholinergic
Carbachol 0.75%, 1.5%, 3%
Demecarium 0.125%, 0.25%
Echothiophate 0.125%
Pilocarpine 1%, 2%, 4%
Rho-Kinase inhibitors
Netarsudil 0.02%
Ripasudil 0.4%
Nitric acid donors
Latanoprostene bunod
Unconventional outflow pathway
Prostaglandin analogues
Bimatoprost 0.01%, 0.03%
Latanoprost 0.005%
Tafluprost 0.0015%
Travoprost 0.04%
Unoprostone Isopropyl 0.15%
Omidenepag Isopropyl 0.002%

Table 2. The IOP-lowering mechanisms of topical drugs.

Drugs	**IOP-Related Effects**				**IOP Independent Effects**	
	Aqueous Secretion	**Trabecular Meshwork Outflow**	**Uveoscleral Pathway Outflow**	**Episcleral Venous Pressure**	**Neuroprotection**	**Ocular Blood Flow**
Betaxolol	Decrease	No effect	No effect			
Timolol	Decrease	No effect/Uncertain Decrease [22]	No effect	No effect		Decrease [23]
Apraclonidine	Decrease	Decrease [24]		Decrease [25]		
Brimonidine	Decrease	No effect	Increase [17]	Decrease [26]	Yes [27–29]	No effect [30,31]
Brinzolamide	Decrease	No effect	No effect	No effect		No effect [31,32]
Dorzolamide	Decrease	No effect				Increase [9,33]/No effect [30]
Bimatoprost	Increase/No effect	Increase	Increase	Increase/Decrease [34]		
Latanoprost	Increase/No effect	Increase	Increase	Increase		Increase [11,15]
Tafluprost		Increase	Increase			Increase [35]
Travoprost	Increase/No effect	Increase	Increase			Increase [15]
Unoprostone		Increase	Increase	No effect		
Omidenepag isopropyl	No effect		Increase			
Pilocarpine	No effect [36]	Increase	Decrease [37]	No effect		Increase [9,10]
Latanoprostene bunod		Increase	Increase	Ongoing Trial		Increase [38]
Netarsudil	Decrease	Increase	No effect	Decrease [39,40]	Yes [41,42]	
Ripasudil		Increase		Decrease [43]	Yes [41,42]	

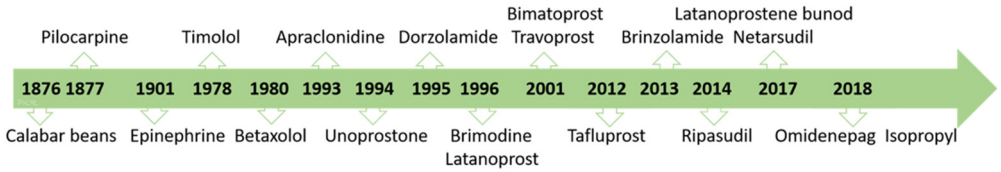

Figure 2. The graphical representation of timeline of introduction of IOP-lowering drugs.

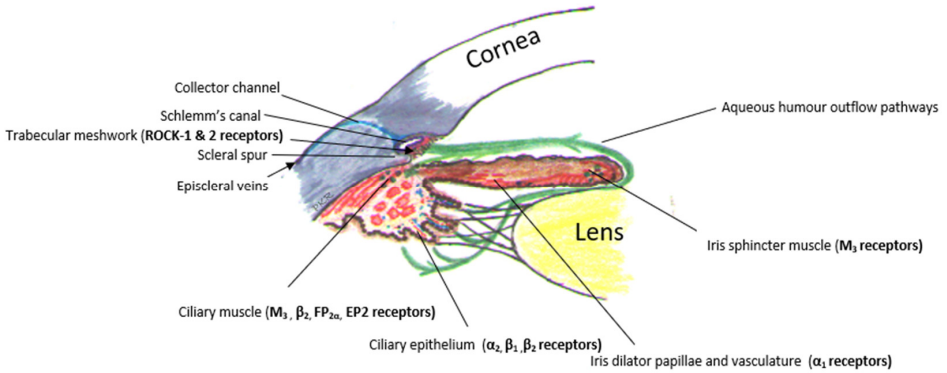

Figure 3. Schematic diagram of structures of the anterior chamber of the eye to illustrate site of action and receptors of the IOP-lowering drugs.

4. Aqueous Suppressants Drugs

4.1. Beta-Adrenergic Antagonists

Three types of beta-adrenergic receptors are known: β1, β2, and β3. In the human eye, beta-adrenoceptors have been localised in the ciliary process [44], extraocular muscles, conjunctiva, epithelium and endothelium of the cornea, trabecular meshwork, and ciliary muscle [45]. The precise mechanism of a β-adrenergic receptor antagonism-mediated decrease in aqueous humour secretion is not completely understood. In rabbits, beta-blockers decrease aqueous humour secretion by inhibiting the catecholamine-stimulated synthesis of cyclic-adenosine monophosphate (cAMP) [46]. The inhibition of cyclic adenosine monophosphate (cAMP) synthesis is believed to reduce aqueous humour production, but the relationship between cAMP reduction and IOP-lowering is yet to be established [22]. Ocular beta-blockers are competitive inhibitors of β1 and β2 receptors, having a very low affinity for β3 receptors. Non-selective ocular beta-blocker drugs like timolol inhibit both β1 and β2 receptors, whereas selective inhibitors such as betaxolol block only the β1 receptors. In healthy human eyes, timolol reduces the outflow facility, and the effect is more marked in eyes with a higher baseline IOP. The precise mechanism of this is not understood, but it appears to be related to decreased aqueous production [47]. In animal experimental studies, beta-blockers reduced the ocular blood flow [23].

4.2. Adrenergic Agonists

Alpha-adrenergic drugs lower the IOP through their agonist action on α-2 adrenergic receptors. The α-2 adrenergic receptors have been localised in the ciliary body, retinal pigmented epithelium–choriocapillaris, iris, and neurosensory retina in the human eye, and the predominant subtype in the ciliary body is α-2A [48]. The activation of α-2 receptors in the ciliary body reduces aqueous secretion. The precise mechanism leading to a decrease in aqueous humour secretion is not known but appears to mediate through a decrease in the intracellular cyclic adenosine monophosphate (cAMP) level [49]. These drugs may have some effect on the outflow pathway owing to the presence of α-2A receptors in the ciliary body [50]. Three drugs available in the topical form are apraclonidine, brimonidine, and clonidine. All three drugs are α-2 agonists but have some α-1 properties, which result in conjunctival vasoconstriction, lid retraction, and slight mydriasis. Brimonidine increases the uveoscleral outflow, and this effect is supposed to be the main mechanism for

IOP reduction in long-term treatment [17]. In experimental studies on mice, brimonidine reduced the episcleral venous pressure [26]. Apraclonidine does not appear to improve uveoscleral outflow but perhaps reduces the aqueous secretion and episcleral venous pressure [32,33]. The presence of alpha-adrenergic receptors in the retina is seen as a potential target for the neuroprotective effects of these drugs [34]. Brimonidine did not show any clinically beneficial improvement in ocular blood flow in humans [30,31].

4.3. Carbonic Anhydrase Inhibitors

Carbonic anhydrase inhibitors (CAIs) belong to sulphonamide compounds and are the only class of IOP-lowering drugs that are available in both topical and systemic formulations for glaucoma treatment. Topical as well as systemic CAIs lower the IOP by reducing aqueous humour formation by inhibiting the enzyme carbonic anhydrase II (CA II) isoform in the epithelial cells of ciliary processes [51]. The inhibition of CA II reduces the formation and accumulation of bicarbonate ions, with a resultant decrease in sodium and fluid accumulation in the posterior chamber [52]. Systemic CAIs are non-selective and inhibit CA II and CA IV isoenzymes. The non-selective inhibition of CA isoenzymes by oral acetazolamide accounts for a greater IOP reduction compared to topical CAIs [53]. Their role in improving ocular blood flow has been studied in humans [30,31]. In a topical form, two drugs are available: dorzolamide 2% and brinzolamide 1%.

5. Uveoscleral Outflow Drugs

Prostaglandin Analogues

The PGF2α subtype of FP receptors and the EP2 subtype of EP receptors [54] regulate IOP. The circular muscles and collagenous connective tissue of ciliary tissue have both PGF2α and EP1 receptors. Through the activation of these receptors, PGA increases the expression of metalloproteinases 1, 2, 3, and 9 in human ciliary muscle cells [55,56]. The increased level of metalloproteinases results in the remodeling of the extracellular matrix of the ciliary muscle bundles of the uveoscleral pathway, which augments the aqueous outflow [57]. Of the PGF2α analogues, bimatoprost is an amide prodrug; the rest are ester prodrugs of the corresponding acids, including the PGEP2 receptor analogue OMPI. These drugs are hydrolysed by corneal esterase into biologically active agents [58–60]. The OMPI is supposed to increase aqueous outflow through both the trabecular meshwork and the uveoscleral pathway [61].

6. Trabecular Outflow Drugs

6.1. Cholinergic

Cholinergic or parasympathomimetic drugs mediate their pharmacological effects through the direct stimulation of muscarinic receptors located in the ciliary muscle and iris sphincter. Of the five subtypes of receptors, the iris–ciliary body–trabecular meshwork in human eyes predominantly has M_3 types of muscarinic receptors [62,63]. The direct stimulation of these receptors contracts ciliary muscle, which pulls the scleral spur, resulting in the widening of the trabecular meshwork lamellae and an increase in the aqueous humour outflow. This mechanism is responsible for the IOP-lowering effects of these drugs in ocular hypertension and open-angle glaucoma. The same action may result in a reduced uveoscleral outflow [36,64], but such an effect has not been observed when given at clinical doses [65]. Contrarily, the direct stimulation of M_3 receptors on TM results in a decreased aqueous outflow, but the net effect is an improved aqueous outflow through TM and a reduction in IOP [66]. Lower concentrations of pilocarpine increased the outflow facility in human cadaveric eyes with a disinserted ciliary body [67]. In the case of angle-closure diseases, these drugs mediate their effect through action on M_3 receptors located in the sphincter pupillae muscle of the iris. The muscle contraction results in meiosis (hence it is also called miotics), which widens the angle in eyes with narrow angles, resulting in an improved aqueous outflow through the TM and a lowering of the IOP. Pilocarpine is the most widely available topical cholinergic drug.

6.2. Nitic Oxide Donors

Nitric oxide (NO) is synthesised endogenously in the human body, including the trabecular meshwork, Schlemm's canal, and ciliary body, from the L-arginine NO synthase enzyme [68,69].

The NO donor drugs have targets in the conventional pathway [59]. Latanoprostene bunod (LBN), 0.024%, is a nitic oxide (NO)-donating $PGF_{2\alpha}$ analogue that is hydrolysed to latanoprost acid and butanediol mononitrate, a NO-donating moiety [59]. Latanoprost increases aqueous outflow through the uveoscleral pathway, whereas the butanediol mononitrate metabolites 1,4-butanediol and NO are supposed to enhance the aqueous outflow facility through the trabecular meshwork [69]. NO activates the soluble guanylyl cyclase/cyclic guanosine monophosphate signaling pathway, which inhibits the Rho pathway, promoting trabecular meshwork and Schlemm's canal cytoskeletal relaxation to improve the aqueous humour outflow facility [70].

6.3. Rho-Kinase Inhibitors

These drugs act by inhibiting the action of Rho-associated protein kinase (ROCK), a low-molecular-weight effector protein that is associated with the regulation of actin cytoskeleton organization and cellular processes [71]. ROCK has two isoforms, ROCK 1 and ROCK 2, both of which are expressed in the trabecular meshwork [59]. ROCK inhibits two enzymes, LIM kinase and myosin light-chain phosphatase (MLCP). These enzymes facilitate the relaxation and polymerisation of actin fibre and result in increased resistance to aqueous outflow in trabecular meshwork outflow facility regulation [72]. Rho-Kinase inhibition prevents the phosphorylation of LIM kinase and MLCP, and results in the contraction and depolymerisation of actin fibre, widening the passage in trabecular meshwork and improving the aqueous outflow facility [73]. The reduction of aqueous secretions through norepinephrine transporter inhibition has been seen in non-human primates and non-primate animals [74]. In animal studies, these drugs lowered the IOP by increasing the aqueous outflow facility, reducing aqueous secretions, and decreasing the episcleral venous pressure [75]. Two ROCK inhibitor drugs are available in topical forms to treat glaucoma: Netarsudil 0.02% and Ripasudil 0.4%.

7. Therapeutic Efficacy

The therapeutic efficacy of IOP-lowering drugs can be described in terms of their effect on IOP-related characteristics and IOP-independent benefits promoting the survival of RGC. The clinically relevant pharmacodynamic properties are summarised in Table 3.

Table 3. The IOP-related characteristics of topical drops [36,66,68,69,76–79].

Drug	Time			IOP Reduction (%)		Washout Period
	Onset	Peak Effect	Duration	Peak	Trough	
Betaxolol	30 min	2 h	12 h	−23	−20	1 week
Timolol	30 min	2 h	12–24 h	−27	−26	4 weeks
Brinzolamide	1 h	2–3 h	8–12 h	−17	−17	1 week
Dorzolamide	1 h	3 h	8 h	−22	−17	1 week
Apraclonidine	1 h	45–90 min	6–8 h	−27	−20	1–2 weeks
Brimonidine	1 h	2–3 h	8–10 h	−19	−14	1–2 weeks
Bimatoprost	4 h	8–12 h	24 h	−33	−28	4–6 weeks
Latanoprost	3–4 h	8–12 h	24 h	−31	−28	4–6 weeks
Tafluprost	2–4 h	12 h	24 h	−31	−27	4–6 weeks
Travoprost	2 h	12 h	>24 h	−31	−29	4–6 weeks
Unoprostone	30–90 min	2–3 h	2–5 h	−25	−10	2–4 weeks
Omidenepag isopropyl	2–4 h	12 h	>24 h	−25	−20	1 week
Pilocarpine	60 min	75 min	4–6 h	−25	−15	48 h
Netarsudil	1–2 h	-	>24 h	−25	−18	-
Ripasudil	1–2 h	-	12 h	-	-	-
Latanoprostene bunod	1–3 h	11–13 h	24 h	−32	−30	4–6 weeks
Acetazolamide	30 min	2 h	6–8 h	-	-	3 days

8. IOP-Related

8.1. IOP-Lowering Effect

The IOP-lowering effect of prostaglandins is superior to other classes of topical IOP-lowering drugs [80,81], followed by nonselective β-blockers, α-adrenergic agonists, selective β-blockers, and topical CAIs [76]. In the newer class of ROCK inhibitors, netarsudil is less efficacious in reducing IOP compared to latanoprost or timolol [82], hence it would find a place alongside or between adrenergic agonists and topical CAIs.

Within the class, the IOP-lowering effect of PGA is comparable [83], although bimatoprost 0.03% and travoprost 0.004% reduced the IOP slightly more than latanoprost 0.005% [84,85]. In another comparative study comprising of mixed population of patients of open-angle glaucoma and ocular hypertension, mainly Caucasians and African Americans, the mean (±SD) IOP reduction from the baseline at 12 weeks with bimatoprost 0.03% was 8.7 ± 3.8 mmHg, compared to 8.6 ± 3.7 mmHg with 0.005% latanoprost and 7.93.4 mmHg with 0.004% travoprost [86]. A similar study on Indian patients showed a mean (±SD) IOP reduction of 8.8 ± 1.1 mmHg from the baseline with bimatoprost 0.03%, 7.3 ± 1.1 mmHg with 0.005% latanoprost, and 7.6 ± 1.0 mmHg with 0.004% travoprost [87]. IOP reduction with tafluprost was comparable to latanoprost [83]. Unlike other PGAs, unoprostone 0.15% has the disadvantage of twice-daily dosing and the least IOP-lowering efficacy [85]. The affinity of unoprostone for the PGF2α receptor is 100 times less than that of latanoprost. The IOP reduction with OMPI 0.02% is between 20 and 35% [88], and when compared to latanoprost 0.005%, the IOP reduction with OMPI was slightly less and the difference was significant statistically, but not clinically [89].

A person is considered a non-or-poor responder if IOP reduction is <15% from baseline with a once-daily dose of PGA. The non-responsiveness is seen with all PGFα2 agonist drugs. The non-responsiveness is more frequent with latanoprost compared with other PGFα2 agonist drugs, but the difference is not significant [90]. The non-responsiveness is also seen with timolol, where 28% were non-responders at 12 weeks in one study [91]. In a study comparing the efficacy of brimonidine 0.2% and latanoprost 0.005% as a third-line adjunctive therapy, in nearly 15% of persons, the expected IOP reduction was not seen with brimonidine [92]. The IOP-lowering efficacy of non-PGA drugs is not well defined in the literature. The cut-off percentage IOP reduction for different drug classes is expected to vary based on their IOP-reducing efficacy.

Timolol reduces IOP by 10–25% from the baseline [80]. The maximum effect may last up to 12 h of application, and nearly 25% IOP reduction is maintained at 24 h [93]. IOP reduction with betaxolol 0.5% is comparable to that seen with timolol 0.5% [94]. Non-selective beta-blockers are most efficacious in reducing IOP, second only to PGA [76].

Clonidine is not popular due to its systemic side effects with long-term use. Brimonidine is 20-to-30 times more α-2-selective than apraclonidine. The IOP reduction seen with brimonidine 0.2% is between 14 and 19% [80]. Apraclonidine's reduction of IOP is comparable to brimonidine, but its effects last for a shorter duration [95]. The absolute reduction of the IOP was similar with the three formulations of brimonidine (0.1%, 0.15%, and 0.2%), but adverse events were more common at higher concentrations [96].

The CAIs reduce the IOP typically by 15–20% [80,97]. The IOP-lowering effect of brinzolamide is slightly lower than that of dorzolamide, though the difference may not be of clinical significance [81]. Systemic CAIs are non-selective and inhibit CA II and CA IV isoenzymes. The non-selective inhibition of CA isoenzymes by oral acetazolamide accounts for greater IOP reduction compared to topical CAIs [27]. Oral acetazolamide reduces IOP by 30–40%, and the effect lasts for 6–8 h.

Pilocarpine reduces IOP by 20–25%. A dose-response analysis of pilocarpine in reducing IOP showed the maximum effect with a 4% concentration [98]. However, a 2% concentration is most often used in clinical practice. Compared to other classes of IOP-lowering drugs, pilocarpine 2% had comparable efficacy in reducing the IOP in patients with open-angle glaucoma or ocular hypertension [77,99].

Netarsudil 0.02% is prescribed as a once-daily dose, whereas ripasudil is given in twice-daily doses. The IOP reduction with these drugs is between 15 and 25% [82]. Within the class of ROCK inhibitors, netarsudil once daily reduced IOP more effectively compared to ripasudil twice daily [82].

8.2. Twenty-Four-Hour IOP Control

The circadian rhythm of IOP is controlled in the suprachiasmatic nucleus [100]. In glaucomatous eyes, the diurnal phasic variation of IOP seems to be dysregulated [101,102]. Short-term IOP fluctuations have been associated with glaucoma progression [103]. The IOP fluctuation tends to be wider in glaucomatous eyes. In most non-glaucomatous and glaucomatous subjects, IOP peaks during the early morning hours [101,104]. IOP peaks in nearly 50% of patients [105] and wider IOP fluctuations in 62% of glaucomatous patients [106] occurred outside the office-hour time. Twenty-four-hour IOP monitoring is not practical for every patient until a suitable, affordable, and easy-to-use device becomes available. Therefore, when evidence about the deteriorating effects of IOP fluctuations, mostly occurring outside office hours, becomes available, the more practical way to address this problem is to have drugs that dampen the IOP acrophase and provide uniform IOP control over 24 h.

A more uniform circadian IOP reduction has been seen with PGF2α analogue drugs [107]. Three PGF2α analogues, namely bimatoprost, latanoprost, and travoprost, are are equally efficacious in reducing IOP and controlling 24 h IOP [108,109]. The three-time daily dosing regimen of brimonidine 0.2% provided better IOP control in the early night time and late afternoon over the daily two-time dosing [110]. Brimonidine 0.2%, like timolol, has a reduced nocturnal IOP-lowering efficacy [111,112]. Aqueous suppressants, due to their attenuated nocturnal IOP-lowering effect, exert non-uniform 24-h IOP control.

The availability of home-tonometry equipment may be useful in monitoring the 24-h therapeutic efficacy of IOP-lowering drugs [113].

8.3. Nocturnal Effect

The aqueous suppressant drugs-beta-blockers, CAIs, and alpha-agonists have no or poor nocturnal IOP-lowering efficacy [112,114]. The findings related to the nocturnal IOP-lowering efficacy of timolol and dorzolamide are not consistent. A meta-analysis concluded that the IOP-lowering efficacy of dorzolamide during the day and night is comparable [97]. Similarly, another meta-analysis concluded that the nocturnal IOP-lowering effect of timolol is attenuated but not absent [115]. In clinical studies, timolol did not lower the nocturnal IOP below the baseline. It was hypothesized that the lower baseline pressures at night compared to daytime probably result from diminished aqueous production, and limit the nocturnal IOP-lowering efficacy of timolol [116]. The drugs facilitating aqueous outflow effectively reduce the nocturnal IOP, but the reduction is less than that seen during the day [117,118]. One reason for this could be that the nocturnal IOP was measured in the supine position [119]. The nocturnal attenuation of the IOP-lowering effect was not seen with OMPI [120]. The potential studies on the nocturnal efficacy of ROCK inhibitors in humans are still not available, but in rabbits, drugs of this class effectively reduced nocturnal IOP [121].

8.4. Long-Term Efficacy

A kind of drug tolerance, often called long-term drift, is observed with the long-term use of some IOP-lowering drugs, which compromises their efficacy. This is most marked with beta-blockers, but has also been observed with pilocarpine, apraclonidine [122], and brimonidine [123], but not with dorzolamide [124] or PGA. In a few species of animals (rabbits), tachyphylaxis with PGA was demonstrated, but such a response is not expected in humans [78]. Travoprost was effective in lowering the IOP at 5 years with consistent 24-h control in humans [125].

Long-term drift is believed to occur due to the compensatory upregulation of receptors to agonists or the downregulation of receptors. The long-term drift of timolol occurs after a longer period of months or years of use. It is a reversible phenomenon, and IOP control returns to the pre-drift level after a few weeks (>2) of drug holiday [126].

8.5. Cross-Over Effect

The instillation of a topical IOP-lowering drug in one eye produces some reduction in the IOP in the contralateral eye. This phenomenon is known as the cross-over effect (or contralateral eye effect or consensual effect). It has been observed with beta-blockers [127], alpha-agonists [128], and PGA [129]. The cross-over effect is due to the systemic absorption of the drug through the nasolacrimal pathway [130]. The amount of IOP reduction in an untreated eye is between 25 and 50% of that in the treated eye. The highest reduction coincides with the peak effect of the drug in the treated eye, and the effect weans off with time. The mean cross-over effect with PGA was about 42% and was the highest during the early hours of the day (~50–60%), and gradually decreased to 20% as the day progressed [129].

8.6. Episcleral Venous Pressure Drugs

The effect of currently available IOP-lowering drugs on episcleral venous pressure is yet not clear. Netarsudil 0.02% reduced the episcleral venous pressure in phase 2 trials and in a small clinical study [39,40]. Ripasudil also increased the episcleral venous flow [43]. The clinical benefits of these effects, especially in glaucoma associated with raised episcleral venous pressure, are still not known. Apraclonidine and brimonidine also reduce episcleral venous pressure [25,26]. The effect of PGA analogues varies with the formulation. Topical preparations increased the episcleral venous pressure, but intra-cameral administration reduced it in a non-primate animal study [34].

9. IOP-Independent

9.1. Ocular Blood Flow

Low ocular perfusion is associated with RGC damage in primary open-angle glaucoma and progression [33,131,132]. Ocular perfusion pressure (OPP) is calculated as the difference between the mean arterial pressure (MAP) and IOP [133]. The MAP is derived from systolic and diastolic blood pressures. Topical drops affect the IOP and blood pressure and are, therefore, supposed to alter the OPP. Bimatoprost increased the OPP in open-angle glaucoma and ocular hypertension patients [117]. Latanoprost increased the ocular perfusion pressure (OPP) in non-glaucomatous eyes [134]. In normal-tension glaucoma (NTG) patients with mean baseline IOP in the low teens, latanoprost did not affect the OPP [135] but increased in NTG patients with IOP in the upper teens [136]. Tafluprost improved the ocular blood flow in experimental studies [35]. The effect of timolol on OPP is not clear. Several studies have noted no change [136], an increase when calculated with the diastolic blood pressure, but a reduced OPP when calculated with the systolic blood pressure [134], or only a daytime increase in the OPP without any change in the nocturnal or 24-hour OPP [137]. Brimonidine 0.2% did not affect the OPP in patients with normal-tension glaucoma [138]. Pilocarpine increased the systolic OPP in non-glaucomatous eyes [139]. Both dorzolamide and brinzolamide increased the ocular blood flow [32]. Latanoprostene bunod 0.024% induced a significant increase in the optic nerve head-blood volume and oxygen saturation in healthy subjects aged between 21 and 62 years [38]. The FDC of brinzolamide/brimonidine did not change the OPP in patients with open-angle glaucoma and ocular hypertension [137]. The clinical advantage of improved OPP in preserving the RGC is difficult to estimate in isolation from IOP lowering.

9.2. Neuroprotection

Neuroprotection in general refers to the mechanisms and strategies employed to prevent neuronal cell death. In glaucoma, it implies non-IOP-related interventions that can

prevent RGC death, independent of IOP reduction. Several compounds have been shown to offer neuroprotection in glaucoma in pre-clinical studies, which include glutamate antagonists, ginkgo biloba extract, neurotrophic factors, antioxidants, calcium channel blockers, memantine, nicotinamide, and glaucoma drugs: brimonidine, nitric oxide synthase inhibitors, and Rho-kinase inhibitors [140]. In this review, we restrict the discussion to the neuroprotective effects of approved topical IOP-lowering drugs. In animal studies, the neuroprotective effects of IOP-lowering drugs, independent of IOP reduction, have been studied. Brimonidine 0.1% prevented the loss of RGC in a chronic ocular hypertension rat model [28]. Indirect evidence of the presumed neuroprotective effect of brimonidine 0.2% comes from clinical studies. Brimonidine 0.2%-treated patients had an improvement in contrast sensitivity compared to patients treated with timolol, with a comparable IOP reduction [29]. However, in a non-comparative study in open-angle glaucoma patients with travoprost, a reduction in the IOP has been associated with improvements in central and peripheral contrast sensitivities [141]. Contrast sensitivity and retinal nerve fibre loss (RNFL) are not strongly correlated in clinical studies [142]. In ocular hypertension patients, RNFL loss was less with brimonidine 0.2% compared to timolol, irrespective of IOP reduction [143]. In clinical trials, IOP reduction has been shown to delay glaucoma progression [144], which may surrogate the neuroprotective effect. The neuroprotective effect of PGA, independent of IOP, was demonstrated against glutamate- or hypoxia-induced RGC death using a rat primary RGC culture at clinically available intracameral concentrations [41]. Rho-kinase inhibitors are presumed to have neuroprotective effects based on their neuroprotective capabilities, such as cell survival and axon regeneration, in non-ocular tissue studies [42].

Drugs that improve the ocular blood flow or have neuroprotective properties are still in the pre-clinical stage of research. The present medications' evidence is insufficient to support their preferential use for these further benefits. It is difficult to study the direct neuroprotective benefits of these drugs in isolation from those gained from IOP lowering, and that presents the major challenge in demonstrating the IOP-independent benefits of IOP-lowering drugs.

10. Choice of Therapy

All IOP-lowering drugs currently available are approved for use in adults with primary open-angle glaucoma and ocular hypertension. These drugs have been studied for their efficacy and safety in other types of glaucoma as well. PGF2α agonists reduce the IOP by 25–35% with once-daily dosing in patients with normal-tension glaucoma [145,146], pigment dispersion syndrome [147], primary angle-closure glaucoma [148,149], and pseudo-exfoliation glaucoma. In pseudo-exfoliation glaucoma, a lower IOP was achieved with bimatoprost 0.03% [150] and travoprost 0.04% [151] when compared to latanoprost 0.005%. OMPI is effective in open-angle glaucoma and ocular hypertension and reduces IOP in patients with poor or no response to latanoprost. OMPI effectively reduced the IOP by $\geq$20% from the wash-out period baseline in nearly 85% of poor or non-latanoprost responder patients with open-angle glaucoma [152]. Substitution with PGA or non-PGA drugs may be effective in lowering the IOP in poor or non-responders [90,153]. OMPI is effective in NTG [154] and secondary glaucoma [155].

The NO donor drug, latanoprostene bunod, is not inferior to latanoprost 0.005% in reducing the IOP in open-angle glaucoma and ocular hypertension [59].

Beta-blockers are used in a twice-daily regimen spaced at 12 h intervals. A once-daily dose of timolol 0.1% gel was equally effective as a 0.5% solution twice daily in lowering IOP [156]. Beta-blockers are used for all types of glaucoma. Betaxolol reduced IOP nearly by 18% in normal-tension glaucoma with the baseline IOP in the mid-teens [157]. Beta-blockers are the drug of choice after PGA, provided their use is not limited by their systemic side effects.

Apraclonidine is approved for the short-term control of IOP due to the high rate of allergic reactions and tachyphylaxis and is mainly used to suppress post-laser IOP

spikes. Brimonidine is used for the long-term control of IOP in open-angle glaucoma and ocular hypertension. Brimonidine tartrate 0.2% has been shown to reduce IOP by 18% in normal-tension glaucoma [158], but in this study, the mean baseline IOP was in the upper teens (17.3 ± 0.7 mmHg). With a baseline mean IOP in the lower teens (13.9 ± 1.2 mmHg), brimonidine 0.1% preserved with sodium chloride reduced the IOP by 10% [159]. Alpha-agonist drugs, except for apraclonidine, which is hydrophilic, are lipophilic and easily penetrate through the cornea and blood–brain barrier. The CNS absorption of topical brimonidine resulted in hypotension and sedation in non-primate animal studies [160]. Due to CNS depressant effects in children [161], brimonidine is contraindicated for use in neonates and infants and is to be used with caution in patients on CNS depressants and children below 12 years.

Systemic CAIs are indicated for short-term use for the immediate management of very high IOP in conditions like acute angle-closure crisis or lens-related glaucoma. The long-term use of oral acetazolamide, especially in the elderly, may lead to life-threatening metabolic acidosis [162]. Dorzolamide and brinzolamide have been shown to produce comparable IOP reductions in open-angle and angle-closure glaucoma. The mean IOP reduction in eyes with angle-closure was slightly lower compared to eyes with open angle glaucoma, but the difference was not statistically significant [163]. In normal-tension glaucoma with a mean IOP of 16.8 ± 0.9 mmHg, dorzolamide reduced IOP by 18% at 4 weeks [156]. CAIs have been shown to reduce IOP in several types of glaucoma, including in young children [164].

The IOP-lowering effect of pilocarpine approximately begins 60 min after ocular instillation, peaks at 75 min, and lasts from four to eight hours [165]. Pilocarpine reduces IOP by 20–25%. In contemporary clinical practice, pilocarpine 2% is mainly used in the management of angle-closure diseases. It is used for its meiotic effect before and/or after laser iridotomy, iridoplasty procedures, and acute angle closure crisis to open an occluded angle once iris ischemia resolves. Pilocarpine and other cholinergic drugs are contraindicated in uveitis and inflammatory secondary glaucoma because their miotic effect may aggravate posterior synechiae formation [166].

Pilocarpine is finding newer applications beyond IOP control. Diluted concentrations (0.125% and 0.0625%) are used in the diagnosis of Adie's tonic pupil [167]. Newer indications for pilocarpine use are the management of xerostomia [168] and presbyopia [169].

Concerning ROCK inhibitors, netarsudil 0.02% is indicated in a once-daily dose, whereas ripasudil is given twice daily. The IOP reduction with these drugs is between 15 and 25% in open-angle glaucoma and ocular hypertension [82]. Ripasudil effectively reduced IOP in uveitic glaucoma, exfoliation glaucoma, and steroid-induced glaucoma [170].

11. Tolerability and Safety

11.1. Systemic Side Effects

Systemic side effects are a major limitation of beta blockers. The drugs in this class may worsen symptoms of coughing, dyspnoea, bronchial spasm, and wheezing in patients with reactive diseases. The bronchospasm seen with beta-blockers is due to the presence of β2-receptors on the smooth muscles of the airways [171]. The effect is more common and pronounced with non-selective agents in susceptible individuals [172]. The bronchoconstriction in otherwise healthy individuals without pre-existing reactive airways is not clinically significant [173]. Betaxolol has a 20-fold higher affinity for β1-receptors than for β2-receptors. The risk of airway obstruction among non-susceptible persons without a prior history of respiratory diseases was similar for selective and non-selective topical beta-blockers [174]. Eyelid closure, nasolacrimal occlusion for 5 min, or pressing the eye with tissue paper after applying the eyedrop reduced the systemic absorption of timolol by 60–67% [165,175]. However, how these manoeuvres affect respiratory functions is not known. The long-term use of beta-blocker eye drops has not been found to increase the risk of falls, dizziness, or orthostatic hypotension in older patients [176]. Therefore, the presence of cardio-pulmonary diseases like bronchial asthma, chronic obstructive pulmonary disease

(COPD), sinus bradycardia, and AV blocks is a relative or absolute contra-indication for the use of beta-blockers, especially non-selective ones.

Cholinergic drugs may cause sweating, gastro-intestinal (salivation, nausea, vomiting, and diarrhoea), respiratory (bronchospasm), and cardio-vascular (bradycardia and hypotension) symptoms due to their action through M1 and M2 receptors following systemic absorption [165,177].

Apraclonidine reduced the heart rate and systolic blood pressure [178] when used to suppress post-LASER IOP spikes. Brimonidine 0.2% reduced both systolic and diastolic blood pressure significantly [179], but not the pulse rate [180] when compared to baseline values. The systolic and diastolic blood pressures are the determinants of ocular perfusion pressure [181]. The precise role of OPP in the causation and progression of glaucoma is not yet clear.

The systemic side effects of topical CAIs are rare, except for the bitter taste. Metabolic acidosis in premature newborns [182] and adults with impaired renal function [183,184] has been reported.

PGA does not have any systemic side effects. The topical use of ROCK inhibitors caused little or no quantifiable systemic exposure [185]. However, systemic absorption produced hypotension and a reversible reduction in lymphocyte counts [186].

11.2. Local Side Effects

A stinging sensation immediately after applying drugs is seen with some of these drugs. This is related to the physiochemical properties of ophthalmic drug solutions. The topical dorzolamide is formulated in an acidic pH solution (~5.6), which is necessary for good ocular absorption, but causes a stinging sensation on application. Brinzolamide, being lipophilic, has good corneal penetration and is formulated in an ophthalmic solution close to physiological pH (7.4), which keeps it free from unpleasant stinging sensations. Several studies have shown that brinzolamide is better tolerated than dorzolamide [187,188]. Among PGA, stinging is more common with LBN than latanoprost [59].

Blurred vision, transient or prolonged, is a common adverse effect of most topical IOP-lowering drugs. Transient blurred vision results from changes in the refractive indices of the tear film due to changes in its tonicity. Pilocarpine causes ciliary spasms and induces accommodation, which results in brow aches and blurred vision. The blurred vision results from myopia caused by the forward displacement and thickening of the lens [189]. This is troublesome, especially for young patients. In presbyopic patients, this results in improved near vision. Alpha-adrenergic agonist drugs also cause headaches and fatigue in some patients [190].

Conjunctival hyperaemia is common with PGA, including OMPI, and ROCK inhibitors [191,192]. Among PGA drugs, it is most common with bimatoprost 0.003% and least common with latanoprost 0.005% [80,84]. Contrarily, the vasoconstrictive effects of α-adrenergic agonist drugs result in conjunctival blanching, a dry nose, and a dry mouth [190]. Most IOP-lowering drugs reduce the Schirmer score and ocular surface disease index, which is supposed to be because of preservatives [193].

The exact incidence of periorbital contact dermatitis with IOP-lowering drugs is not known. It has been reported with timolol, betaxolol [194], pilocarpine [195], brimonidine [196,197], dorzolamide [198], brinzolamide [199], bimatoprost [200], and latanoprost [201]. A cross-reactivity among beta-blockers has been observed [194], which is presumed to result from the common lateral aliphatic chain in their structure [202]. Brinzolamide and dorzolamide have been associated with toxic epidermal necrolysis in patients with impaired hepatic functions [203].

PGA drugs may cause cosmetically unacceptable, though reversible, changes in periorbital tissues, collectively described as prostaglandin-associated peri-orbitopathy [204]. This includes changes in the eyelid and orbit: the hyperpigmentation of eyelashes and periorbital skin; loss of peri-orbital fat; deepening of lid sulci; mild enophthalmos; and tight eyelids. These changes are seen with all types of PGF2α analogue drugs but are most marked

with bimatoprost 0.03% [79]. The higher absorption of drugs in peri-orbital skin [205] interferes with cellular adipose tissue metabolism [206] and causes peri-orbitopathy. The discontinuation of therapy or switching to an alternate, milder form may reverse changes in weeks or months [204].

Corneal edema has been reported with brinzolamide in eyes with a normal endothelial count [206], which is reversible [207]. Dorzolamide may cause irreversible corneal decompensation in the eye with a compromised cornea or complicated ocular history [208]. CAIs attenuate bicarbonate efflux by reversibly inhibiting CA II in corneal endothelial cells, which results in fluid retention [209]. Until a safe endothelial count for the use of CAI drugs is known, these drugs should be used with caution in patients with a compromised cornea. A decrease in the number and density of corneal sub-basal nerve fibre bundles without affecting the keratocyte density or corneal endothelial characteristics has been observed with the chronic use of topical IOP-lowering drugs in glaucomatous patients and healthy controls with normal endothelial cell count [210].

Granulomatous anterior uveitis may be seen with brimonidine 2% use [211,212]. The inflammation reverses with the discontinuation of brimonidine and a short shot of topical corticosteroid therapy, but IOP control may need surgical intervention in a proportion of patients with high-IOP glaucoma [212]. PGA is better avoided in eyes with iritis, herpes simplex keratitis, and eyes at risk of developing cystoid macular edema [89,213].

Pilocarpine increases cataract formation [214] and may cause retinal detachment in high myopia (≥ -6D), especially with higher concentrations [215].

12. Adjunctive Therapy

Adjunctive therapy is defined as one or more secondary interventions used concurrently with a primary intervention to enhance treatment effectiveness [216]. The effective reduction in IOP to preserve the RGC required more than one drug in 40–50% of the patients in major clinical trials [217,218]. Hence, in glaucoma management, adjunctive therapy can be defined as the concomitant use of a second or subsequent IOP-lowering drug(s) to achieve the target IOP while continuing the first-line therapy. The PGA is used as the first-line therapy in almost all cases of glaucoma due to its superior IOP-lowering effect, better 24-h IOP control, convenient once-daily dosing, and absence of systemic side effects. Almost any drug of any class, except cholinergic, can be used as adjunctive therapy to PGA. The concomitant use of pilocarpine and PGA drugs may be mutually antagonistic [37]. In a study on non-human primates, pilocarpine reduced the uveoscleral outflow [219]. However, an alteration in the order and timing of the administration of pilocarpine and latanoprost has been found effective in achieving additional IOP reduction [220].

Similarly, cholinergic and ROCK inhibitor drugs seem to have an antagonistic effect. Pilocarpine acts through the M_3 receptor by inducing the contraction of the ciliary muscle which pulls the scleral spur and resulting in the widening of the trabecular meshwork lamellae and an increase in aqueous humour outflow. Contrarily, ROCK inhibitors relax trabecular meshwork cells to open spaces. When used concomitantly, pilocarpine did not affect the relaxation effect of the ROCK inhibitor but had no additive effect, and pilocarpine interfered with the IOP reduction using ripasudil at the peak IOP reduction [221].

The IOP-lowering effect of topical CAIs as an adjunctive therapy to PGA is superior to timolol or brimonidine [222–225]. The PGA induces a CA enzyme in the epithelial cells of the ciliary process, which results in increased aqueous humour formation [226]. This slightly reduces the efficacy of PGA drugs. Since CAIs suppress this PGA-induced activity of the CA enzyme, they result in more efficacious IOP reduction as adjunctive therapy when compared with timolol or brimonidine. Compared to timolol 0.5% twice daily, brinzolamide 1% twice daily added to latanoprost 0.005% monotherapy resulted in superior IOP reduction and the flattening of diurnal variation [222]. The adjunctive IOP-lowering effect of timolol 0.5% (3.9 mmHg) with travoprost 0.004% was superior to brimonidine 2% (2.3 mmHg) [226]. The net IOP reduction in adjunctive therapy is also affected by the absolute IOP lowering effect of the adjunctive drug, which is higher for beta-

blockers than CAI. A meta-analysis comparing the effectiveness of brimonidine and CAIs as adjunctive therapies to PGAs and beta-blockers found that brimonidine was superior to CAIs in reducing acrophase and trough IOP as well as diurnal fluctuation [227]. Adjunctive therapy with the FDC of brinzolamide/timolol to travoprost was superior to the FDC of brimonidine/timolol in controlling the mean 24 h IOP owing to the greater efficacy in the late afternoon and during the night [228].

The addition of dorzolamide 2% to timolol 0.5% (6.8 ± 1.7 mmHg) was more effective in lowering IOP in comparison to its addition to brimonidine 0.2% (5.6 ± 1.9 mmHg) [229]. OMPI (0.0006%) has been shown to have an additive IOP-lowering effect with beta-blockers, CAIs, and alpha-2 adrenergic agonist drugs in normotensive conscious monkeys. The additive effect of OMPI was the maximum with brimonidine 2% [230].

An additive therapy of netarsudil with timolol or latanoprost reduced the mean pooled IOP by 2.66 mmHg [66]. Ripasudil caused an additional IOP reduction of 0.75 mmHg when added to timolol therapy. The additional IOP reduction with any drug is less when used as adjunctive therapy, compared to when used alone [231].

More than 50% of glaucoma prescriptions have more than one drug [216]. Hence, fixed-dose combinations (FDCs) offer a better option in terms of compliance and adherence [232]. A triple-fixed combination (TFC) containing bimatoprost 0.01%, brimonidine 0.15%, and timolol 0.5% used twice daily in patients with POAG and OHT has been shown to have a superior IOP-lowering effect over a dual-fixed combination of brimonidine 0.2% and timolol 0.5% at the end of 12 weeks [233]. The short-term safety and tolerability of FDCs compared to those of monotherapies are well established, but there is a lack of clinical trials evaluating their long-term efficacy, safety, and conclusive data on the reduction of adverse effects [234].

13. Future Perspectives

Newer targets for lowering the IOP are being explored. A phase II clinical trial is underway with QLS-111, which is an ATP-sensitive potassium (KATP) channel modulator, to reduce IOP by lowering the episcleral venous pressure (EVP) and improving the outflow distal to the trabecular meshwork [235,236]. Its role is also being investigated for normal-tension glaucoma [235].

IOP-independent mechanisms are being explored for glaucoma management. A deficiency of nicotinamide (NAM) has been documented in patients with POAG [237]. Dietary supplementation with niacin is believed to reduce the risk of glaucoma [238]. The Glaucoma Nicotinamide Trial (TGNT) is a prospective, randomized clinical trial studying the effect of the oral supplementation of nicotinamide on visual field progression in patients with POAG [239]. Nicotinamide and Pyruvate for Open-Angle Glaucoma is another prospective randomized clinical trial studying the effect of oral nicotinamide and pyruvate supplementation on changes in visual fields, retinal nerve fibres, and ganglion cell layer thickness [240]. The Nicotinamide and Glaucoma Clinical Trial is also a prospective randomized clinical trial studying the effect of oral nicotinamide supplementation on the perfusion density and flow index in the macula and optic nerve head [241]. Topical 2% citicoline and insulin are being explored for their neuroprotective and regenerative effects in the treatment of glaucoma [242,243].

Another molecule being studied for glaucoma is endothelin. An increased endothelin level has been associated with reduced ocular blood flow and glaucomatous progression. The selective inhibition of endothelin signaling increased the optic nerve head blood flow and neuroprotective effects on the RGC. An endothelin receptor antagonist, PER-001, is undergoing a phase II trial and is delivered as a 4mm bio-erodible intravitreal implant into the vitreous cavity of the eye [244,245].

Encapsulated cell therapy (ECT) with a high-dose ciliary neurotrophic factor-secreting NT-501 implant has completed phase I trials in patients with POAG, and randomized phase II clinical trials are underway [246].

14. Conclusions

Over a century since the first piece of evidence emerged, the medical management of glaucoma has evolved. In the past 30 years, many new drugs have made the journey from labs to clinics. The newer drugs target the pathophysiology of glaucoma and reduce IOP by improving the aqueous outflow. The focus is on compounds that act on the trabecular meshwork, have greater IOP-lowering efficacy, and have minimal local and systemic adverse effects. An understanding of drug efficacy helps select the most appropriate drug for the set target pressure. From the patient's perspective, the most efficacious drug with minimal adverse effects is desirable. In this article, we reviewed all the available classes of IOP-lowering drugs concerning current therapeutic principles like absolute IOP reduction, 24-h IOP control, the nocturnal effect, and IOP-independent benefits. We also investigated the efficacy of adjuvant therapy and its rationality when combining two or more drugs. The local adverse effects of IOP-lowering drugs are troublesome, especially those affecting the ocular surface. The availability of preservative-free formulations, new drug delivery systems, and newer molecules would strengthen the pharmacotherapy of glaucoma.

Author Contributions: S.V. and P.R. have equally contributed to the conceptualization, writing, and preparation of this manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: The research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Ventura, L.M.; Sorokac, N.; De Los Santos, R.; Feuer, W.J.; Porciatti, V. The relationship between retinal ganglion cell function and retinal nerve fiber thickness in early glaucoma. *Investig. Ophthalmol. Vis. Sci.* **2006**, *47*, 3904–3911. [CrossRef] [PubMed]
2. GBD 2019 Blindness and Vision Impairment Collaborators; Vision Loss Expert Group of the Global Burden of Disease Study; Steinmetz, J.D. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to vision 2020: The right to sight: An analysis for the global burden of disease study. *Lancet. Glob. Health* **2021**, *9*, e144–e160. [CrossRef] [PubMed]
3. Kooner, K.S.; Al Bdoor, M.; Cho, B.J.; Adams-Huet, B. Risk factors for progression to blindness in high tension primary open-angle glaucoma: Comparison of blind and non-blind subjects. *Clin. Ophthalmol.* **2008**, *2*, 757–762. [CrossRef] [PubMed]
4. Oliver, J.E.; Hattenhauer, M.G.; Herman, D.; Hodge, D.O.; Kennedy, R.; Fang-Yen, M.; Johnson, D.H. Blindness, and glaucoma: A comparison of patients progressing to blindness from glaucoma with patients maintaining vision. *Am. J. Ophthalmol.* **2002**, *133*, 764–772. [CrossRef] [PubMed]
5. Paula, J.S.; Furtado, J.M.; Santos, A.S.; Coelho Rde, M.; Rocha, E.M.; Rodrigues Mde, L. Risk factors for blindness in patients with open-angle glaucoma followed-up for at least 15 years. *Arq. Bras. Oftalmol.* **2012**, *75*, 243–246. [CrossRef] [PubMed]
6. Vaswani, R.; Singh, A. Importance of defining a target intra-ocular pressure: A Meta-Analysis. *Investig. Ophthalmol. Vis. Sci.* **2012**, *53*, 5052.
7. Boland, M.V.; Ervin, A.M.; Friedman, D.S.; Jampel, H.D.; Hawkins, B.S.; Vollenweider, D.; Chelladurai, Y.; Ward, D.; Suarez-Cuervo, C.; Robinson, K.A. Comparative effectiveness of treatments for open-angle glaucoma: A systematic review for the U.S. Preventive Services Task Force. *Ann. Intern. Med.* **2013**, *158*, 271–279. [CrossRef] [PubMed]
8. Qu, J.; Wang, D.; Grosskreutz, C.L. Mechanisms of retinal ganglion cell injury and defence in glaucoma. *Exp. Eye Res.* **2010**, *91*, 48–53. [CrossRef] [PubMed]
9. Burgoyne, C.F.; Downs, J.C.; Bellezza, A.J.; Suh, J.K.; Hart, R.T. The optic nerve head as a biomechanical structure: A new paradigm for understanding the role of IOP-related stress and strain in the pathophysiology of glaucomatous optic nerve head damage. *Prog. Retin. Eye Res.* **2005**, *24*, 39–73. [CrossRef] [PubMed]
10. Quigley, H.A.; McKinnon, S.J.; Zack, D.J.; Pease, M.E.; Kerrigan-Baumrind, L.A.; Kerrigan, D.F.; Mitchell, R.S. Retrograde axonal transport of BDNF in retinal ganglion cells is blocked by acute IOP elevation in rats. *Investig. Ophthalmol. Vis. Sci.* **2000**, *41*, 3460–3466.
11. Brubaker, R.F. Goldmann's equation and clinical measures of aqueous dynamics. *Exp. Eye Res.* **2004**, *78*, 633–637. [CrossRef] [PubMed]

12. Shields, M.B. Normal-tension glaucoma: Is it different from primary open-angle glaucoma? *Curr. Opin. Ophthalmol.* **2008**, *19*, 85–88. [CrossRef] [PubMed]
13. Bill, A. Uveoscleral drainage of aqueous humor: Physiology and pharmacology. *Prog. Clin. Biol. Res.* **1989**, *312*, 417–427. [PubMed]
14. Alm, A.; Nilsson, S.F. Uveoscleral outflow—A review. *Exp Eye Res.* **2009**, *88*, 760–768. [CrossRef] [PubMed]
15. Miyazaki, M.; Segawa, K.; Urakawa, Y. Age-related changes in the trabecular meshwork of the normal human eye. *Jpn. J. Ophthalmol.* **1987**, *31*, 558–569. [PubMed]
16. Toris, C.B.; Yablonski, M.E.; Wang, Y.L.; Camras, C.B. Aqueous humor dynamics in the aging human eye. *Am. J. Ophthalmol.* **1999**, *127*, 407–412. [CrossRef] [PubMed]
17. Toris, C.B.; Camras, C.B.; Yablonski, M.E. Acute versus chronic effects of brimonidine on aqueous humor dynamics in ocular hypertensive patients. *Am. J. Ophthalmol.* **1999**, *128*, 8–14. [CrossRef] [PubMed]
18. Acott, T.S.; Kelley, M.J.; Keller, K.E.; Vranka, J.A.; Abu-Hassan, D.W.; Li, X.; Aga, M.; Bradley, J.M. Intraocular pressure homeostasis: Maintaining balance in a high-pressure environment. *J. Ocul. Pharmacol. Ther.* **2014**, *30*, 94–101. [CrossRef] [PubMed]
19. Gedde, S.J.; Chen, P.P.; Muir, K.W.; Vinod, K.; Lind, J.T.; Wright, M.M.; Li, T.; Mansberger, S.L.; American Academy of Ophthalmology Preferred Practice Pattern Glaucoma Panel. Primary Angle-Closure Disease Preferred Practice Pattern®. *Ophthalmology* **2021**, *128*, P30–P70. [CrossRef] [PubMed]
20. Realini, T. A history of glaucoma pharmacology. *Optom. Vis. Sci.* **2011**, *88*, 36–38. [CrossRef] [PubMed]
21. US Food and Drug Administration. New Drug Approval 215092. 22 September 2022. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/215092Orig1s000ltr.pdf (accessed on 23 June 2023).
22. Shim, M.S.; Kim, K.Y.; Ju, W.K. Role of cyclic AMP in the eye with glaucoma. *BMB Rep.* **2017**, *50*, 60–70. [CrossRef] [PubMed]
23. Bylund, D.B.; Chacko, D.M. Characterization of α_2 adrenergic receptor subtypes in human ocular tissue homogenates. *Investig. Ophthalmol. Vis. Sci.* **1999**, *40*, 2299–2306.
24. Gharagozloo, N.Z.; Relf, S.J.; Brubaker, R.F. Aqueous flow is reduced by the alpha-adrenergic agonist, apraclonidine hydrochloride (ALO 2145). *Ophthalmology* **1988**, *95*, 1217–1220. [CrossRef] [PubMed]
25. Toris, C.B.; Tafoya, M.E.; Camras, C.B.; Yablonski, M.E. Effects of apraclonidine on aqueous humor dynamics in human eyes. *Ophthalmology* **1995**, *102*, 456–461. [CrossRef] [PubMed]
26. Yamagishi, R.; Honjo, M.; Aihara, M. Effect of IOP-lowering drugs on episcleral venous pressure in mouse eye. *Investig. Ophthalmol. Vis. Sci.* **2018**, *59*, 2712.
27. Galanopoulos, A.; Goldberg, I. Clinical efficacy and neuroprotective effects of brimonidine in the management of glaucoma and ocular hypertension. *Clin. Ophthalmol.* **2009**, *3*, 117–122. [PubMed]
28. Wolde Mussie, E.; Ruiz, G.; Wijono, M.; Wheeler, L.A. Neuroprotection of retinal ganglion cells by brimonidine in rats with laser-induced chronic ocular hypertension. *Investig. Ophthalmol. Vis. Sci.* **2001**, *42*, 2849–2855.
29. Evans, D.W.; Hosking, S.L.; Gherghel, D.; Barlett, J.D. Contrast sensitivity improves after brimonidine therapy in primary open-angle glaucoma: A case for neuroprotection. *Br. J. Ophthalmol.* **2003**, *87*, 1463–1465. [CrossRef] [PubMed]
30. Simsek, T.; Yanik, B.; Conkbayir, I.; Zilelioglu, O. Comparative analysis of the effects of brimonidine and dorzolamide on ocular blood flow velocity in patients with newly diagnosed primary open-angle glaucoma. *J. Ocul. Pharmacol. Ther.* **2006**, *22*, 79–85. [CrossRef] [PubMed]
31. Enz, T.J.; Bittner, M.; Tribble, J.R.; Williams, P.A.; Thiel, M.A.; Schmid, M.K.; Bachmann, L.M.; Bochmann, F. Comparative assessment of retinal blood flow velocity changes following brimonidine and brinzolamide administration using retinal function imaging. *Transl. Vis. Sci. Technol.* **2022**, *11*, 1. [CrossRef] [PubMed]
32. Siesky, B.; Harris, A.; Brizendine, E.; Marques, C.; Loh, J.; Mackey, J.; Overton, J.; Netland, P. Literature review and meta-analysis of topical carbonic anhydrase inhibitors and ocular blood flow. *Surv. Ophthalmol.* **2009**, *54*, 33–46. [CrossRef] [PubMed]
33. Leske, M.C.; Heijl, A.; Hyman, L.; Bengtsson, B.; Dong, L.; Yang, Z.; EMGT Group. Predictors of long-term progression in the early manifest glaucoma trial. *Ophthalmology* **2007**, *114*, 1965–1972. [CrossRef] [PubMed]
34. Lee, S.S.; Burke, J.; Shen, J.; Almazan, A.; Orilla, W.; Hughes, P.; Zhang, J.; Li, H.; Struble, C.; Miller, P.E.; et al. Bimatoprost sustained-release intracameral implant reduces episcleral venous pressure in dogs. *Vet. Ophthalmol.* **2018**, *21*, 376–381. [CrossRef]
35. Zhang, X.; Zhou, X.; Zhao, Y.; Yang, X.; Zhou, D.; Chen, B.; Duan, X. Effects of tafluprost on ocular blood flow. *Ophthalmol. Ther.* **2022**, *11*, 1991–2003. [CrossRef] [PubMed]
36. Kaufman, P.L.; Barany, E.H. Loss of acute pilocarpine effect on outflow facility following surgical disinsertion and retrodisplacement of the ciliary muscle from the scleral spur in the cynomolgus monkey. *Investig. Ophthalmol.* **1976**, *15*, 793–807.
37. Serle, J.B.; Wang, R.F.; Mittag, T.W.; Shen, F.; Podos, S.M. Effect of pilocarpine 4% in combination with latanoprost 0.005% or 8-iso prostaglandin E2 0.1% on intraocular pressure in laser-induced glaucomatous monkey eyes. *J. Glaucoma* **2001**, *10*, 215–219. [CrossRef] [PubMed]
38. Samaha, D.; Diaconu, V.; Bouchard, J.F.; Desalliers, C.; Dupont, A. Effect of latanoprostene bunod on optic nerve head blood flow. *Optom. Vis. Sci.* **2022**, *99*, 172–176. [CrossRef] [PubMed]
39. Sit, A.J.; Gupta, D.; Kazemi, A.; McKee, H.; Challa, P.; Liu, K.C.; Lopez, J.; Kopczynski, C.; Heah, T. Netarsudil improves trabecular outflow facility in patients with primary open angle glaucoma or ocular hypertension: A phase 2 study. *Am. J. Ophthalmol.* **2021**, *226*, 262–269. [CrossRef] [PubMed]

40. Kim, S.; Chen, V.; Cruz, M.; Pottenburgh, J.; Saeedi, O.J. Precise quantification of episcleral venous flow rates inhuman subjects before and after netarsudil 0.02%. *Investig. Ophthalmol. Vis. Sci.* **2022**, *63*, 3497.
41. Yamagishi, R.; Aihara, M.; Araie, M. Neuroprotective effects of prostaglandin analogues on retinal ganglion cell death independent of intraocular pressure reduction. *Exp. Eye Res.* **2011**, *93*, 265–270. [CrossRef]
42. Thomas, N.M.; Nagrale, P. Rho Kinase inhibitors as a neuroprotective pharmacological intervention for the treatment of Glaucoma. *Cureus* **2022**, *14*, e28445. [CrossRef] [PubMed]
43. Suzuki, M.; Suzuki, Y.; Komori, R.; Orii, Y.; Arimura, S.; Iwasaki, K.; Takamura, Y.; Inatani, M. Aqueous column changes in the episcleral veins after the instillation of ripasudil versus latanoprost: A randomized, double-blind, crossover clinical trial. *Sci. Rep.* **2022**, *12*, 15255. [CrossRef] [PubMed]
44. Trope, G.E.; Clark, B. Beta adrenergic receptors in pigmented ciliary processes. *Br. J. Ophthalmol.* **1982**, *66*, 788–792. [CrossRef] [PubMed]
45. Elena, P.P.; Denis, P.; Kosina-Boix, M.; Saraux, H.; Lapalus, P. Beta adrenergic binding sites in the human eye: An autoradiographic study. *J. Ocul. Pharmacol.* **1990**, *6*, 143–149. [CrossRef] [PubMed]
46. Bartels, S.P.; Roth, H.O.; Jumblatt, M.M.; Neufeld, A.H. Pharmacological effects of topical timolol in the rabbit eye. *Investig. Ophthalmol. Vis. Sci.* **1980**, *19*, 1189–1197.
47. Kazemi, A.; McLaren, J.W.; Trese, M.G.J.; Toris, C.B.; Gulati, V.; Fan, S.; Reed, D.M.; Kristoff, T.; Gilbert, J.; Moroi, S.E.; et al. Effect of timolol on aqueous humor outflow facility in healthy human eyes. *Am. J. Ophthalmol.* **2019**, *202*, 126–132. [CrossRef] [PubMed]
48. Chiou, G.C.; Chen, Y.J. Effects of antiglaucoma drugs on ocular blood flow in ocular hypertensive rabbits. *J. Ocul. Pharmacol.* **1993**, *9*, 13–24. [CrossRef] [PubMed]
49. Gilsbach, R.; Röser, C.; Beetz, N.; Brede, M.; Hadamek, K.; Haubold, M.; Leemhuis, J.; Philipp, M.; Schneider, J.; Urbanski, M.; et al. Genetic dissection of α_2-adrenoceptor functions in adrenergic versus nonadrenergic cells. *Mol. Pharmacol.* **2009**, *75*, 1160–1170. [CrossRef]
50. Stamer, W.D.; Huang, Y.; Seftor, R.E.; Svensson, S.S.; Snyder, R.W.; Regan, J.W. Cultured human trabecular meshwork cells express functional alpha 2A adrenergic receptors. *Investig. Ophthalmol. Vis. Sci.* **1996**, *37*, 2426–2433.
51. Krupin, T.; Sly, W.S.; Whyte, M.P.; Dodgson, S.J. Failure of acetazolamide to decrease intraocular pressure in patients with carbonic anhydrase II deficiency. *Am. J. Ophthalmol.* **1985**, *99*, 396–399. [CrossRef] [PubMed]
52. Maren, T.H. The rates of movement of Na^+, Cl^-, and HCO-3 from plasma to posterior chamber: Effect of acetazolamide and relation to the treatment of glaucoma. *Investig. Ophthalmol.* **1976**, *15*, 356–364.
53. Maus, T.L.; Larsson, L.I.; McLaren, J.W.; Brubaker, R.F. Comparison of dorzolamide and acetazolamide as suppressors of aqueous humor flow in humans. *Arch. Ophthalmol.* **1997**, *115*, 45–49. [CrossRef] [PubMed]
54. Camras, C.B.; Bito, L.Z.; Eakins, K.E. Reduction of intraocular pressure by prostaglandins applied topically to the eyes of conscious rabbits. *Investig. Ophthalmol. Vis. Sci.* **1977**, *16*, 1125–1134.
55. Lindsey, J.D.; Kashiwagi, K.; Boyle, D.; Kashiwagi, F.; Firestrin, G.S.; Weinreb, R.N. Prostaglandins increase proMMP-1 and proMMP-3 secretion by human ciliary smooth muscle cells. *Curr. Eye Res.* **1996**, *15*, 869–875. [CrossRef] [PubMed]
56. Weinreb, R.N.; Kashiwagi, K.; Kashiwagi, F.; Tsukahara, S.; Lindsey, J.D. Prostaglandins increase matrix metalloproteinase release from human ciliary smooth muscle cells. *Investig. Ophthalmol. Vis. Sci.* **1997**, *38*, 2772–2780.
57. Ocklind, A. Effect of latanoprost on the extracellular matrix of the ciliary muscle. A study on cultured cells and tissue sections. *Exp. Eye Res.* **1998**, *67*, 179–191. [CrossRef] [PubMed]
58. Davies, S.S.; Ju, W.-K.; Neufeld, A.H.; Abran, D.; Chemtob, S.; Roberts, L.J. Hydrolysis of bimatoprost (Lumigan) to its free acid by ocular tissue in vitro. *J. Ocul. Pharmacol. Ther.* **2003**, *19*, 45–54. [CrossRef] [PubMed]
59. Weinreb, R.N.; Ong, T.; Scassellati Sforzolini, B.; Vittitow, J.L.; Singh, K.; Kaufman, P.L.; VOYAGER Study Group. A randomised, controlled comparison of latanoprostene bunod and latanoprost 0.005% in the treatment of ocular hypertension and open-angle glaucoma: The VOYAGER study. *Br. J. Ophthalmol.* **2015**, *99*, 738–745. [CrossRef] [PubMed]
60. Kirihara, T.; Taniguchi, T.; Yamamura, K.; Iwamura, R.; Yoneda, K.; Odani-Kawabata, N.; Shimazaki, A.; Matsugi, T.; Shams, N.; Zhang, J.Z. Pharmacologic characterization of omidenepag isopropyl, a novel selective EP2 receptor agonist, as an ocular hypotensive agent. *Investig. Ophthalmol. Vis. Sci.* **2018**, *59*, 145–153. [CrossRef] [PubMed]
61. Fuwa, M.; Toris, C.B.; Fan, S.; Taniguchi, T.; Ichikawa, M.; Odani-Kawabata, N.; Iwamura, R.; Yoneda, K.; Matsugi, T.; Shams, N.K.; et al. Effects of a novel selective EP2 receptor agonist, omidenepag isopropyl, on aqueous humor dynamics in laser-induced ocular hypertensive monkeys. *J. Ocul. Pharmacol. Ther.* **2018**, *34*, 531–537. [CrossRef] [PubMed]
62. Gil, D.W.; Krauss, H.A.; Bogardus, A.M.; Wolde Mussie, E. Muscarinic receptor subtypes in human iris-ciliary body measured by immunoprecipitation. *Investig. Ophthalmol. Vis. Sci.* **1997**, *38*, 1434–1442.
63. Wiederholt, M.; Schäfer, R.; Wagner, U.; Lepple-Wienhues, A. Contractile response of the isolated trabecular meshwork and ciliary muscle to cholinergic and adrenergic agents. *Ger. J. Ophthalmol.* **1996**, *5*, 146–153. [PubMed]
64. Bleiman, B.S.; Schwartz, A.L. Paradoxical intraocular pressure response to pilocarpine. A proposed mechanism and treatment. *Arch. Ophthalmol.* **1979**, *97*, 1305–1306. [CrossRef] [PubMed]
65. Toris, C.B.; Zhan, G.L.; Zhao, J.; Camras, C.B.; Yablonski, M.E. Potential mechanism for the additivity of pilocarpine and latanoprost. *Am. J. Ophthalmol.* **2001**, *131*, 722–728. [CrossRef] [PubMed]
66. Wiederholt, M.; Thieme, H.; Stumpff, F. The regulation of trabecular meshwork and ciliary muscle contractility. *Prog. Retin. Eye Res.* **2000**, *19*, 271–295. [CrossRef] [PubMed]

67. Erickson, K.A.; Schroeder, A. Direct effects of muscarinic agents on the outflow pathways in human eyes. *Investig. Ophthalmol. Vis. Sci.* **2000**, *41*, 1743–1748.
68. Schneemann, A.; Dijkstra, B.G.; van den Berg, T.J.; Kamphuis, W.; Hoyng, P.F. Nitric oxide/guanylate cyclase pathways and flow in anterior segment perfusion. *Graefes. Arch. Clin. Exp. Ophthalmol.* **2002**, *240*, 936–941. [CrossRef]
69. Cavet, M.E.; Vittitow, J.L.; Impagnatiello, F.; Ongini, E.; Bastia, E. Nitric oxide (NO): An emerging target for the treatment of glaucoma. *Investig. Ophthalmol. Vis. Sci.* **2014**, *55*, 5005–5015. [CrossRef] [PubMed]
70. Kaufman, P.L. Latanoprostene bunod ophthalmic solution 0.024% for IOP lowering in glaucoma and ocular hypertension. *Expert. Opin. Pharmacother.* **2017**, *18*, 433–444. [CrossRef]
71. Ishizaki, T.; Maekawa, M.; Fujisawa, K.; Okawa, K.; Iwamatsu, A.; Fujita, A.; Watanabe, N.; Saito, Y.; Kakizuka, A.; Morii, N.; et al. The small GTP-binding protein Rho binds to and activates a 160 kDa Ser/Thr protein kinase homologous to myotonic dystrophy kinase. *EMBO J.* **1996**, *15*, 1885–1893. [CrossRef] [PubMed]
72. Rao, P.V.; Pattabiraman, P.P.; Kopczynski, C. Role of the Rho GTPase/Rho kinase signalling pathway in pathogenesis and treatment of glaucoma: Bench to bedside research. *Exp. Eye Res.* **2017**, *158*, 23–32. [CrossRef] [PubMed]
73. Buffault, J.; Brignole-Baudouin, F.; Reboussin, É.; Kessal, K.; Labbé, A.; Mélik Parsadaniantz, S.; Baudouin, C. The dual effect of Rho-Kinase inhibition on trabecular meshwork cells cytoskeleton and extracellular matrix in an in vitro model of glaucoma. *J. Clin. Med.* **2022**, *11*, 1001. [CrossRef] [PubMed]
74. Wang, R.F.; Williamson, J.E.; Kopczynski, C.; Serle, J.B. Effect of 0.04% AR-13324, a ROCK, and norepinephrine transporter inhibitor, on aqueous humor dynamics in normotensive monkey eyes. *J. Glaucoma* **2015**, *24*, 51–54. [CrossRef] [PubMed]
75. Toris, C.B.; McLaughlin, M.A.; Dworak, D.P.; Fan, S.; Havens, S.; Zhan, G.L.; Horan, N.; Prasanna, G. Effects of Rho Kinase inhibitors on intraocular pressure and aqueous humor dynamics in nonhuman primates and rabbits. *J. Ocul. Pharmacol. Ther.* **2016**, *32*, 355–364. [CrossRef] [PubMed]
76. van der Valk, R.; Webers, C.A.; Schouten, J.S.; Zeegers, M.P.; Hendrikse, F.; Prins, M.H. Intraocular pressure-lowering effects of all commonly used glaucoma drugs: A meta-analysis of randomized clinical trials. *Ophthalmology* **2005**, *112*, 1177–1185. [CrossRef] [PubMed]
77. Diestelhorst, M. The additive intraocular pressure-lowering effect of latanoprost 0.005% daily once and pilocarpine 2% t.i.d. in patients with open-angle glaucoma or ocular hypertension. a 6-month, randomized, multicenter study. German Latanoprost Study Group. *Graefes. Arch. Clin. Exp. Ophthalmol.* **2000**, *238*, 433–439. [CrossRef] [PubMed]
78. Bito, L.Z. A new approach to the medical management of glaucoma, from the bench to the clinic, and beyond: The Proctor Lecture. *Investig. Ophthalmol. Vis. Sci.* **2001**, *42*, 1126–1133.
79. Choi, H.Y.; Lee, J.E.; Lee, J.W.; Park, H.J.; Lee, J.E.; Jung, H.E. In vitro study of antiadipogenic profile of latanoprost, travoprost, bimatoprost, and tafluprost in human orbital preadipocytes. *J. Ocul. Pharmacol. Ther.* **2012**, *28*, 146–152. [CrossRef]
80. Stewart, W.C.; Konstas, A.G.; Nelson, L.A.; Kruft, B. Meta-analysis of 24-hour intraocular pressure studies evaluating the efficacy of glaucoma medicines. *Ophthalmology* **2008**, *115*, 1117–1122.e1. [CrossRef] [PubMed]
81. Li, T.; Lindsley, K.; Rouse, B.; Hong, H.; Shi, Q.; Friedman, D.S.; Wormald, R.; Dickersin, K. Comparative effectiveness of first-line medications for primary open-angle glaucoma: A systematic review and network meta-analysis. *Ophthalmology* **2016**, *123*, 129–140. [CrossRef] [PubMed]
82. Clement Freiberg, J.; von Spreckelsen, A.; Kolko, M.; Azuara-Blanco, A.; Virgili, G. Rho kinase inhibitor for primary open-angle glaucoma and ocular hypertension. *Cochrane Database Syst. Rev.* **2022**, *6*, CD013817. [PubMed]
83. El Hajj Moussa, W.G.; Farhat, R.G.; Nehme, J.C.; Sahyoun, M.A.; Schakal, A.R.; Jalkh, A.E.; Abi Karam, M.P.; Azar, G.G. Comparison of efficacy and ocular surface disease index score between bimatoprost, latanoprost, travoprost, and tafluprost in glaucoma patients. *J. Ophthalmol.* **2018**, *2018*, 1319628. [CrossRef] [PubMed]
84. Tang, W.; Zhang, F.; Liu, K.; Duan, X. Efficacy, and safety of prostaglandin analogues in primary open-angle glaucoma or ocular hypertension patients: A meta-analysis. *Medicine* **2019**, *98*, e16597. [CrossRef] [PubMed]
85. Lin, L.; Zhao, Y.J.; Chew, P.T.; Sng, C.C.; Wong, H.T.; Yip, L.W.; Wu, T.S.; Bautista, D.; Teng, M.; Khoo, A.L.; et al. Comparative efficacy and tolerability of topical prostaglandin analogues for primary open-angle glaucoma and ocular hypertension. *Ann. Pharmacother.* **2014**, *48*, 1585–1593. [CrossRef] [PubMed]
86. Parrish, R.K.; Palmberg, P.; Sheu, W.P.; XLT Study Group. A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure: A 12-week, randomized, masked-evaluator multicenter study. *Am. J. Ophthalmol.* **2003**, *135*, 688–703. [CrossRef] [PubMed]
87. Mishra, D.; Sinha, B.P.; Kumar, M.S. Comparing the efficacy of latanoprost (0.005%), bimatoprost (0.03%), travoprost (0.004%), and timolol (0.5%) in the treatment of primary open angle glaucoma. *Korean J. Ophthalmol.* **2014**, *28*, 399–407. [CrossRef] [PubMed]
88. Matsuo, M.; Matsuoka, Y.; Tanito, M. Efficacy and patient tolerability of omidenepag isopropyl in the treatment of glaucoma and ocular hypertension. *Clin. Ophthalmol.* **2022**, *16*, 1261–1279. [CrossRef] [PubMed]
89. Aihara, M.; Lu, F.; Kawata, H.; Iwata, A.; Odani-Kawabata, N.; Shams, N.K. Omidenepag isopropyl versus latanoprost in primary open-angle glaucoma and ocular hypertension: The Phase 3 AYAME Study. *Am. J. Ophthalmol.* **2020**, *220*, 53–63. [CrossRef] [PubMed]
90. Cai, Z.; Cao, M.; Liu, K.; Duan, X. Analysis of the responsiveness of latanoprost, travoprost, bimatoprost, and tafluprost in the Treatment of OAG/OHT patients. *J. Ophthalmol.* **2021**, *2021*, 5586719. [CrossRef] [PubMed]

91. Camras, C.B.; Hedman, K.; US Latanoprost Study Group. Rate of response to latanoprost or timolol in patients with ocular hypertension or glaucoma. *J. Glaucoma* **2003**, *12*, 466–469. [CrossRef] [PubMed]
92. Simmons, S.T.; Samuelson, T.W. Comparison of brimonidine with latanoprost in the adjunctive treatment of Glaucoma ALPHA-GAN/XALATAN Study Group. *Clin. Ther.* **2000**, *22*, 388–399. [CrossRef] [PubMed]
93. Zimmerman, T.J.; Kaufman, H.E. Timolol, dose response and duration of action. *Arch. Ophthalmol.* **1977**, *95*, 605–607. [CrossRef] [PubMed]
94. Berry, D.P., Jr.; Van Buskirk, E.M.; Shields, M.B. Betaxolol and timolol: A comparison of efficacy and side effects. *Arch. Ophthalmol.* **1984**, *102*, 42–45. [CrossRef] [PubMed]
95. Schadlu, R.; Maus, T.L.; Nau, C.B.; Brubaker, R.F. Comparison of the efficacy of apraclonidine and brimonidine as aqueous suppressants in humans. *Arch. Ophthalmol.* **1998**, *116*, 1441–1444. [CrossRef] [PubMed]
96. Bhatti, A.; Singh, G. Efficacy of three different formulations of brimonidine for control of intraocular pressure in primary open-angle glaucoma: A 6-week randomized trial. *Oman. J. Ophthalmol.* **2018**, *11*, 140–143. [CrossRef] [PubMed]
97. Stewart, W.C.; Konstas, A.G.; Kruft, B.; Mathis, H.M.; Stewart, J.A. Meta-analysis of 24-h intraocular pressure fluctuation studies and the efficacy of glaucoma medicines. *J. Ocul. Pharmacol. Ther.* **2010**, *26*, 175–180. [CrossRef] [PubMed]
98. Harris, L.S.; Galin, M.A. Dose response analysis of pilocarpine-induced ocular hypotension. *Arch. Ophthalmol.* **1970**, *84*, 605–608. [CrossRef] [PubMed]
99. Hartenbaum, D.; Maloney, S.; Vaccarelli, L.; Liss, C.; Wilson, H.; Gormley, G.J. Comparison of dorzolamide and pilocarpine as adjunctive therapy in patients with open-angle glaucoma and ocular hypertension. *Clin. Ther.* **1999**, *21*, 1533–1538. [CrossRef] [PubMed]
100. Ikegami, K.; Shigeyoshi, Y.; Masubuchi, S. Circadian regulation of IOP rhythm by dual pathways of glucocorticoids and the sympathetic nervous system. *Investig. Ophthalmol. Vis. Sci.* **2020**, *61*, 26. [CrossRef] [PubMed]
101. Liu, J.H.; Weinreb, R.N. Asymmetry of habitual 24-hour intraocular pressure rhythm in glaucoma patients. *Investig. Ophthalmol. Vis. Sci.* **2014**, *55*, 7398–7402. [CrossRef] [PubMed]
102. Neroev, V.; Malishevskaya, T.; Weinert, D.; Astakhov, S.; Kolomeichuk, S.; Cornelissen, G.; Kabitskaya, Y.; Boiko, E.; Nemtsova, I.; Gubin, D. Disruption of 24-hour rhythm in intraocular pressure correlates with retinal ganglion cell loss in Glaucoma. *Int. J. Mol. Sci.* **2020**, *22*, 359. [CrossRef] [PubMed]
103. Matlach, J.; Bender, S.; König, J.; Binder, H.; Pfeiffer, N.; Hoffmann, E.M. Investigation of intraocular pressure fluctuation as a risk factor of glaucoma progression. *Clin. Ophthalmol.* **2018**, *13*, 9–16. [CrossRef] [PubMed]
104. Drance, S.M. The significance of the diurnal tension variations in normal and glaucomatous eyes. *Arch. Ophthalmol.* **1960**, *64*, 494–501. [CrossRef] [PubMed]
105. Tsironi, S.; Almaliotis, D.; Ntonti, P.; Sidiropoulos, G.; Theodoridou, E.; Theofrastou, E.; Karachrisafi, S.; Psimenidou, E.; Sarafi, A.; Kapourani, V.; et al. Clinical outcomes of the implementation of IOP monitoring, in and out of office time, to 1500 patients—A cohort study. *Vision* **2022**, *6*, 69. [CrossRef] [PubMed]
106. Barkana, Y.; Anis, S.; Liebmann, J.; Tello, C.; Ritch, R. Clinical utility of intraocular pressure monitoring outside of normal office hours in patients with Glaucoma. *Arch. Ophthalmol.* **2006**, *124*, 793–797. [CrossRef] [PubMed]
107. Orzalesi, N.; Rossetti, L.; Invernizzi, T.; Bottoli, A.; Autelitano, A. Effect of timolol, latanoprost, and dorzolamide on circadian IOP in glaucoma or ocular hypertension. *Investig. Ophthalmol. Vis. Sci.* **2000**, *41*, 2566–2573.
108. Yildirim, N.; Sahin, A.; Gultekin, S. The effect of latanoprost, bimatoprost, and travoprost on circadian variation of intraocular pressure in patients with open-angle Glaucoma. *J. Glaucoma* **2008**, *17*, 36–39. [CrossRef] [PubMed]
109. Orzalesi, N.; Rossetti, L.; Bottoli, A.; Fogagnolo, P. Comparison of the effects of latanoprost, travoprost, and bimatoprost on circadian intraocular pressure in patients with glaucoma or ocular hypertension. *Ophthalmology* **2006**, *113*, 239–246. [CrossRef] [PubMed]
110. Konstas, A.G.; Stewart, W.C.; Topouzis, F.; Tersis, I.; Holmes, K.T.; Stangos, N.T. Brimonidine 0.2% given two or three times daily versus timolol maleate 0.5% in primary open-angle Glaucoma. *Am. J. Ophthalmol.* **2001**, *131*, 729–733. [CrossRef] [PubMed]
111. Orzalesi, N.; Rossetti, L.; Bottoli, A.; Fumagalli, E.; Fogagnolo, P. The effect of latanoprost, brimonidine, and a fixed combination of timolol and dorzolamide on circadian intraocular pressure in patients with glaucoma or ocular hypertension. *Arch. Ophthalmol.* **2003**, *121*, 453–457. [CrossRef] [PubMed]
112. Liu, J.H.; Medeiros, F.A.; Slight, J.R.; Weinreb, R.N. Diurnal and nocturnal effects of brimonidine monotherapy on intraocular pressure. *Ophthalmology* **2010**, *117*, 2075–2079. [CrossRef] [PubMed]
113. Scott, A.T.; Kanaster, K.; Kaizer, A.M.; Young, C.C.; Pantcheva, M.B.; Ertel, M.K.; Kahook, M.Y.; Seibold, L.K. The utility of iCare home tonometry for detection of therapy-related intraocular pressure changes in glaucoma and ocular hypertension. *Ophthalmol. Glaucoma* **2022**, *5*, 85–93. [CrossRef] [PubMed]
114. Gulati, V.; Fan, S.; Zhao, M.; Maslonka, M.A.; Gangahar, C.; Toris, C.B. Diurnal and nocturnal variations in aqueous humor dynamics of patients with ocular hypertension undergoing medical therapy. *Arch. Ophthalmol.* **2012**, *130*, 677–684. [CrossRef] [PubMed]
115. Lee, P.W.; Doyle, A.; Stewart, J.A.; Kristoffersen, C.J.; Stewart, W.C. Meta-analysis of timolol on diurnal and nighttime intraocular pressure and blood pressure. *Eur. J. Ophthalmol.* **2010**, *20*, 1035–1041. [CrossRef] [PubMed]
116. Topper, J.E.; Brubaker, R.F. Effects of timolol, epinephrine, and acetazolamide on aqueous flow during sleep. *Investig. Ophthalmol. Vis. Sci.* **1985**, *26*, 1315–1319.

117. Oddone, F.; Rossetti, L.; Tanga, L.; Berardo, F.; Ferrazza, M.; Michelessi, M.; Roberti, G.; Manni, G.; Centofanti, M. Effects of topical bimatoprost 0.01% and timolol 0.5% on circadian IOP, blood pressure and perfusion pressure in patients with glaucoma or ocular hypertension: A randomized, double masked, placebo-controlled clinical trial. *PLoS ONE* **2015**, *10*, e0140601. [CrossRef] [PubMed]
118. Liu, J.H.K.; Slight, J.R.; Vittitow, J.L.; Scassellati Sforzolini, B.; Weinreb, R.N. Efficacy of latanoprostene bunod 0.024% compared with timolol 0.5% in lowering intraocular pressure over 24 Hours. *Am. J. Ophthalmol.* **2016**, *169*, 249–257. [CrossRef] [PubMed]
119. Walters, T.R.; Du Biner, H.B.; Carpenter, S.P.; Khan, B.; Van Denburgh, A.M.; Bimatoprost Circadian IOP Study Group. 24-Hour IOP control with once-daily bimatoprost, timolol gel-forming solution, or latanoprost: A 1-month, randomized, comparative clinical trial. *Surv. Ophthalmol.* **2004**, *49* (Suppl. 1), S26–S35. [CrossRef] [PubMed]
120. Shiratori, N.; Nishio, Y.; Takeda, A.; Sugimoto, S.; Takazawa, K.; Otsuka, N.; Ishida, N.; Shii, D.; Hori, K.; Nakamoto, K. Twenty-four-hour intraocular pressure control with omidenepag isopropyl 0.002% in patients with glaucoma and ocular hypertension. *Clin. Ophthalmol.* **2021**, *15*, 3997–4003. [CrossRef] [PubMed]
121. Van de Velde, S.; Van Bergen, T.; Sijnave, D.; Hollanders, K.; Castermans, K.; Defert, O.; Leysen, D.; Vandewalle, E.; Moons, L.; Stalmans, I. AMA0076, a novel, locally acting Rho kinase inhibitor, potently lowers intraocular pressure in New Zealand white rabbits with minimal hyperemia. *Investig. Ophthalmol. Vis. Sci.* **2014**, *55*, 1006–1016. [CrossRef] [PubMed]
122. Araujo, S.V.; Bond, J.B.; Wilson, R.P.; Moster, M.R.; Schmidt, C.M., Jr.; Spaeth, G.L. Long term effect of apraclonidine. *Br. J. Ophthalmol.* **1995**, *79*, 1098–1101. [CrossRef] [PubMed]
123. Derick, R.J.; Robin, A.L.; Walters, T.R.; Barnebey, H.S.; Choplin, N.; Schuman, J.; Kelley, E.P.; Chen, K.; Stoecker, J.F. Brimonidine tartrate: A one-month dose response study. *Ophthalmology* **1997**, *104*, 131–136. [CrossRef] [PubMed]
124. Strahlman, E.; Tipping, R.; Vogel, R. A double-masked, randomized 1-year study comparing dorzolamide (Trusopt), timolol, and betaxolol. International Dorzolamide Study Group. *Arch. Ophthalmol.* **1995**, *113*, 1009–1016. [CrossRef] [PubMed]
125. Riva, I.; Katsanos, A.; Floriani, I.; Biagioli, E.; Konstas, A.G.; Centofanti, M.; Quaranta, L. Long-term 24-hour intraocular pressure control with travoprost monotherapy in patients with primary open-angle Glaucoma. *J. Glaucoma* **2014**, *23*, 535–540. [CrossRef] [PubMed]
126. Steinert, R.F.; Thomas, J.V.; Boger, W.P., 3rd. Long-term drift and continued efficacy after multiyear timolol therapy. *Arch. Ophthalmol.* **1981**, *99*, 100–103. [CrossRef] [PubMed]
127. Piltz, J.; Gross, R.; Shin, D.H.; Beiser, J.A.; Dorr, D.A.; Kass, M.A.; Gordon, M.O. Contralateral effect of topical beta-adrenergic antagonists in initial one-eyed trials in the ocular hypertension treatment study. *Am. J. Ophthalmol.* **2000**, *130*, 441–453. [CrossRef] [PubMed]
128. Yuksel, N.; Karabas, L.; Altintas, O.; Yildirim, Y.; Caglar, Y. A comparison of the short-term hypotensive effects and side effects of unilateral brimonidine and apraclonidine in patients with elevated intraocular pressure. *Ophthalmologica* **2002**, *216*, 45–49. [CrossRef] [PubMed]
129. Rao, H.L.; Senthil, S.; Garudadri, C.S. Contralateral intraocular pressure lowering effect of prostaglandin analogues. *Indian. J. Ophthalmol.* **2014**, *62*, 575–579. [CrossRef] [PubMed]
130. Dunham, C.N.; Spaide, R.F.; Dunham, G. The contralateral reduction of intraocular pressure by timolol. *Br. J. Ophthalmol.* **1994**, *78*, 38–40. [CrossRef] [PubMed]
131. Leske, M.C.; Wu, S.Y.; Hennis, A.; Honkanen, R.; Nemesure, B. Risk factors for incident open-angle glaucoma: The Barbados Eye Studies. *Ophthalmology* **2008**, *115*, 85–93. [CrossRef] [PubMed]
132. Cherecheanu, A.P.; Garhofer, G.; Schmidl, D.; Werkmeister, R.; Schmetterer, L. Ocular perfusion pressure and ocular blood flow in Glaucoma. *Curr. Opin. Pharmacol.* **2013**, *13*, 36–42. [CrossRef] [PubMed]
133. Hayreh, S.S. Blood flow in the optic nerve head and factors that may influence it. *Prog. Retin. Eye Res.* **2001**, *20*, 595–624. [CrossRef] [PubMed]
134. Kolli, A.; Toris, C.B.; Reed, D.M.; Gilbert, J.; Sit, A.J.; Gulati, V.; Kazemi, A.; Fan, S.; Musch, D.C.; Moroi, S.E. The effects of topical timolol and latanoprost on calculated ocular perfusion pressure in non-glaucomatous volunteers. *J. Ocul. Pharmacol. Ther.* **2021**, *37*, 565–574. [CrossRef] [PubMed]
135. Ishibashi, S.; Hirose, N.; Tawara, A.; Kubota, T. Effect of latanoprost on the diurnal variations in the intraocular and ocular perfusion pressure in normal tension Glaucoma. *J. Glaucoma* **2006**, *15*, 354–357. [CrossRef] [PubMed]
136. Costagliola, C.; Parmeggiani, F.; Virgili, G.; Lamberti, G.; Incorvaia, C.; Perri, P.; Campa, C.; Sebastiani, A. Circadian changes of intraocular pressure and ocular perfusion pressure after timolol or latanoprost in Caucasians with normal-tension Glaucoma. *Graefes. Arch. Clin. Exp. Ophthalmol.* **2008**, *246*, 389–396. [CrossRef]
137. Seibold, L.K.; DeWitt, P.E.; Kroehl, M.E.; Kahook, M.Y. The 24-hour effects of brinzolamide/brimonidine fixed combination and timolol on intraocular pressure and ocular perfusion pressure. *J. Ocul. Pharmacol. Ther.* **2017**, *33*, 161–169. [CrossRef] [PubMed]
138. Liu, C.J.; Ko, Y.C.; Cheng, C.Y.; Chiu, A.W.; Chou, J.C.; Hsu, W.M.; Liu, J.H. Changes in intraocular pressure and ocular perfusion pressure after latanoprost 0.005% or brimonidine tartrate 0.2% in normal-tension glaucoma patients. *Ophthalmology* **2002**, *109*, 2241–2247. [CrossRef] [PubMed]
139. Pillunat, L.; Stodtmeister, R. Effect of different antiglaucomatous drugs on ocular perfusion pressures. *J. Ocul. Pharmacol.* **1988**, *4*, 231–242. [CrossRef] [PubMed]
140. Doozandeh, A.; Yazdani, S. Neuroprotection in Glaucoma. *J. Ophthalmic. Vis. Res.* **2016**, *11*, 209–220. [CrossRef] [PubMed]

141. Ichhpujani, P.; Rodrigues, A.M.; Kumar, S.; Singh, R.B. Analysing the change in contrast sensitivity post-travoprost treatment in primary open-angle glaucoma patients using Spaeth Richman contrast sensitivity test. *Int. Ophthalmol.* **2023**, *43*, 2037–2047. [CrossRef] [PubMed]
142. Amanullah, S.; Okudolo, J.; Rahmatnejad, K.; Lin, S.C.; Wizov, S.S.; Manzi Muhire, R.S.; Hark, L.A.; Zheng, C.X.; Zhan, T.; Spaeth, G.L. The relationship between contrast sensitivity and retinal nerve fiber layer thickness in patients with Glaucoma. *Graefes. Arch. Clin. Exp. Ophthalmol.* **2017**, *255*, 2415–2422. [CrossRef] [PubMed]
143. Tsai, J.C.; Chang, H.W. Comparison of the effects of brimonidine 0.2% and timolol 0.5% on retinal nerve fiber layer thickness in ocular hypertensive patients: A prospective, unmasked study. *J. Ocul. Pharmacol. Ther.* **2005**, *21*, 475–482. [CrossRef] [PubMed]
144. Heijl, A.; Leske, M.C.; Bengtsson, B.; Hyman, L.; Bengtsson, B.; Hussein, M. Reduction of intraocular pressure and glaucoma progression: Results from the Early Manifest Glaucoma Trial. *Arch. Ophthalmol.* **2002**, *120*, 1268–1279. [CrossRef] [PubMed]
145. Tomita, G.; Araie, M.; Kitazawa, Y.; Tsukahara, S. A three-year prospective, randomized and open comparison between latanoprost and timolol in Japanese normal-tension glaucoma patients. *Eye* **2014**, *18*, 984–989. [CrossRef] [PubMed]
146. Inoue, K.; Shiokawa, M.; Fujimoto, T.; Tomita, G. Effects of treatment with bimatoprost 0.03% for 3 years in patients with normal-tension Glaucoma. *Clin. Ophthalmol.* **2014**, *8*, 1179–1183. [CrossRef] [PubMed]
147. Mastropasqua, L.; Carpineto, P.; Ciancaglini, M.; Gallenga, P.E. A 12-month, randomized, double-masked study comparing latanoprost with timolol in pigmentary Glaucoma. *Ophthalmology* **1999**, *106*, 550–555. [CrossRef] [PubMed]
148. Sihota, R.; Saxena, R.; Agarwal, H.C.; Gulati, V. Crossover comparison of timolol and latanoprost in chronic primary angle-closure Glaucoma. *Arch. Ophthalmol.* **2004**, *122*, 185–189.
149. Chen, M.J.; Chen, Y.C.; Chou, C.K.; Hsu, W.M. Comparison of the effects of latanoprost and travoprost on intraocular pressure in chronic angle-closure Glaucoma. *J. Ocul. Pharmacol. Ther.* **2006**, *22*, 449–454. [CrossRef] [PubMed]
150. Konstas, A.G.; Holló, G.; Irkec, M.; Tsironi, S.; Durukan, I.; Goldenfeld, M.; Melamed, S. Diurnal IOP control with bimatoprost versus latanoprost in exfoliative glaucoma: A crossover, observer-masked, three-centre study. *Br. J. Ophthalmol.* **2007**, *91*, 757–760. [CrossRef] [PubMed]
151. Konstas, A.G.; Kozobolis, V.P.; Katsimpris, I.E.; Boboridis, K.; Koukoula, S.; Jenkins, J.N.; Stewart, W.C. Efficacy, and safety of latanoprost versus travoprost in exfoliative glaucoma patients. *Ophthalmology* **2007**, *114*, 653–657. [CrossRef] [PubMed]
152. Aihara, M.; Ropo, A.; Lu, F.; Kawata, H.; Iwata, A.; Odani-Kawabata, N.; Shams, N. Intraocular pressure-lowering effect of omidenepag isopropyl in latanoprost non-/low-responder patients with primary open-angle glaucoma or ocular hypertension: The FUJI study. *Jpn. J. Ophthalmol.* **2020**, *64*, 398–406. [CrossRef] [PubMed]
153. Rossetti, L.; Gandolfi, S.; Traverso, C.; Montanari, P.; Uva, M.; Manni, G.; Carassa, R.; Mastropasqua, L.; Quaranta, L.; Marchini, G.; et al. An evaluation of the rate of nonresponders to latanoprost therapy. *J. Glaucoma* **2006**, *15*, 238–243. [CrossRef] [PubMed]
154. Inoue, K.; Inoue, J.; Kunimatsu-Sanuki, S.; Nozaki, N.; Shimizu, K.; Ishida, K.; Tomita, G. Short-term efficacy and safety of omidenepag isopropyl in patients with normal-tension Glaucoma. *Clin. Ophthalmol.* **2020**, *14*, 2943–2949. [CrossRef] [PubMed]
155. Miki, A.; Miyamoto, E.; Ishida, N.; Shii, D.; Hori, K.; LESPOIR Research Group. Efficacy and safety of omidenepag isopropyl 0.002% ophthalmic solution: A retrospective analysis of real-world data in Japan. *Adv. Ther.* **2022**, *39*, 2085–2095. [CrossRef] [PubMed]
156. Rouland, J.F.; Morel-Mandrino, P.; Elena, P.P.; Polzer, H.; Sunder Raj, P. Timolol 0.1% gel (Nyogel 0.1%) once daily versus conventional timolol 0.5% solution twice daily: A comparison of efficacy and safety. *Ophthalmologica* **2002**, *216*, 449–454. [CrossRef] [PubMed]
157. Harris, A.; Arend, O.; Chung, H.S.; Kagemann, L.; Cantor, L.; Martin, B. A comparative study of betaxolol and dorzolamide effect on ocular circulation in normal-tension glaucoma patients. *Ophthalmology* **2000**, *107*, 430–434. [CrossRef]
158. Gandolfi, S.A.; Cimino, L.; Mora, P. Effect of brimonidine on intraocular pressure in normal tension glaucoma: A short-term clinical trial. *Eur. J. Ophthalmol.* **2003**, *13*, 611–615. [CrossRef]
159. Tsumura, T.; Yoshikawa, K.; Kimura, T.; Suzumura, H.; Kawashima, M.; Nanno, M.; Ishijima, K.; Takeda, R. The efficacy and safety of add-on 0.1% brimonidine tartrate preserved with sodium chlorite in on-treatment Japanese normal-tension glaucoma patients. *Clin. Ophthalmol.* **2014**, *8*, 1681–1687. [CrossRef] [PubMed]
160. Ogata, N.; Kanda, T.; Kawahata, M.; Ichikawa, T.; Matsumoto, Y.; Morimitsu, W.; Nishino, Y.; Itoi, T.; Furumoto, K. Sedative and physiological effects of brimonidine tartrate ophthalmic solution in healthy cats. *Vet. Anaesth. Analg.* **2017**, *44*, 1091–1100. [CrossRef]
161. Enyedi, L.B.; Freedman, S.F. Safety, and efficacy of brimonidine in children with Glaucoma. *J. AAPOS* **2001**, *5*, 281–284. [CrossRef]
162. Greiner, R.C.; Beasley, H.M.; Bodhireddy, H.; Bouterse, C.R.; Eggleston, M.T.; Pfeiffer, D.C. Revisiting acidosis in acetazolamide treatment of severe glaucoma: A case report. *Am. J. Ophthalmol. Case Rep.* **2022**, *27*, 101658. [CrossRef] [PubMed]
163. Nakamura, Y.; Ishikawa, S.; Nakamura, Y.; Sakai, H.; Henzan, I.; Sawaguchi, S. 24-hour intraocular pressure in glaucoma patients randomized to receive dorzolamide or brinzolamide in combination with latanoprost. *Clin. Ophthalmol.* **2009**, *3*, 395–400. [PubMed]
164. Ott, E.Z.; Mills, M.D.; Arango, S.; Getson, A.J.; Assaid, C.A.; Adamsons, I.A. A randomized trial assessing dorzolamide in patients with glaucoma who are younger than 6 years. *Arch. Ophthalmol.* **2005**, *123*, 1177–1186. [CrossRef] [PubMed]
165. Zimmerman, T.J.; Kooner, K.S.; Kandarakis, A.S.; Ziegler, L.P. Improving the therapeutic index of topically applied ocular drugs. *Arch. Ophthalmol.* **1984**, *102*, 551–553. [CrossRef] [PubMed]

166. Phillips, C.I.; Clark, C.V.; Levy, A.M. Posterior synechiae after glaucoma operations: Aggravation by shallow anterior chamber and pilocarpine. *Br. J. Ophthalmol.* **1987**, *71*, 428–432. [CrossRef] [PubMed]
167. Yoo, Y.J.; Hwang, J.M.; Yang, H.K. Dilute pilocarpine test for diagnosis of Adie's tonic pupil. *Sci. Rep.* **2021**, *11*, 10089. [CrossRef] [PubMed]
168. Tanasiewicz, M.; Hildebrandt, T.; Obersztyn, I. Xerostomia of various etiologies: A review of the literature. *Adv. Clin. Exp. Med.* **2016**, *25*, 199–206. [CrossRef] [PubMed]
169. Tucker, T.; Early, J. Pilocarpine 1.25% ophthalmic solution (Vuity) for the treatment of presbyopia. *Am. Fam. Physician* **2023**, *107*, 659–660. [PubMed]
170. Futakuchi, A.; Morimoto, T.; Ikeda, Y.; Tanihara, H.; Inoue, T.; ROCK-S Study Group Collaborators. Intraocular pressure-lowering effects of ripasudil in uveitic glaucoma, exfoliation glaucoma, and steroid-induced glaucoma patients: ROCK-S, a multicentre historical cohort study. *Sci. Rep.* **2020**, *10*, 10308. [CrossRef] [PubMed]
171. Carstairs, J.R.; Nimmo, A.J.; Barnes, P.J. Autoradiographic visualization of beta-adrenoceptor subtypes in human lung. *Am. Rev. Respir. Dis.* **1985**, *132*, 541–547. [PubMed]
172. Avorn, J.; Glynn, R.J.; Gurwitz, J.H.; Bohn, R.L.; Monane, M.; Everitt, D.E.; Gilden, D.; Choodnovskiy, I. Adverse pulmonary effects of topical β-blockers used in the treatment of Glaucoma. *J. Glaucoma* **1995**, *2*, 158–165. [CrossRef]
173. Sadiq, S.A.; Fielding, K.; Vernon, S.A. The effect of timolol drops on respiratory function. *Eye* **1998**, *12 Pt 3a*, 386–389. [CrossRef] [PubMed]
174. Kirwan, J.F.; Nightingale, J.A.; Bunce, C.; Wormald, R. Do selective topical beta antagonists for glaucoma have respiratory side effects? *Br. J. Ophthalmol.* **2004**, *88*, 196–198. [CrossRef] [PubMed]
175. Müller, L.; Jensen, B.P.; Bachmann, L.M.; Wong, D.; Wells, A.P. New technique to reduce systemic side effects of timolol eye drops: The tissue press-method: Cross-over clinical trial. *Clin. Exp. Ophthalmol.* **2020**, *48*, 24–30. [CrossRef] [PubMed]
176. Ramdas, W.D.; van der Velde, N.; van der Cammen, T.J.; Wolfs, R.C. Evaluation of risk of falls and orthostatic hypotension in older, long-term topical beta-blocker users. *Graefes. Arch. Clin. Exp. Ophthalmol.* **2009**, *247*, 1235–1241. [CrossRef] [PubMed]
177. Farkouh, A.; Frigo, P.; Czejka, M. Systemic side effects of eye drops: A pharmacokinetic perspective. *Clin. Ophthalmol.* **2016**, *10*, 2433–2441. [CrossRef] [PubMed]
178. Sridharrao, B.; Badrinath, S.S. Efficacy and safety of apraclonidine in patients undergoing anterior segment laser surgery. *Br. J. Ophthalmol.* **1989**, *73*, 884–887. [CrossRef]
179. Quaranta, L.; Gandolfo, F.; Turano, R.; Rovida, F.; Pizzolante, T.; Musig, A.; Gandolfo, E. Effects of topical hypotensive drugs on circadian IOP, blood pressure, and calculated diastolic ocular perfusion pressure in patients with Glaucoma. *Investig. Ophthalmol. Vis. Sci.* **2006**, *47*, 2917–2923. [CrossRef] [PubMed]
180. Mizoue, S.; Nitta, K.; Shirakashi, M.; Nitta, A.; Yamabayashi, S.; Kimura, T.; Ueda, T.; Takeda, R.; Matsumoto, S.; Yoshikawa, K. Multicenter, randomized, investigator-masked study comparing brimonidine tartrate 0.1% and timolol maleate 0.5% as adjunctive therapies to prostaglandin analogues in normal-tension Glaucoma. *Adv. Ther.* **2017**, *34*, 1438–1448. [CrossRef] [PubMed]
181. Zheng, Y.; Wong, T.Y.; Mitchell, P.; Friedman, D.S.; He, M.; Aung, T. Distribution of ocular perfusion pressure and its relationship with open-angle glaucoma: The Singapore Malay Eye Study. *Investig. Ophthalmol. Vis. Sci.* **2010**, *51*, 3399–3404. [CrossRef] [PubMed]
182. Morris, S.; Geh, V.; Nischal, K.K.; Sahi, S.; Ahmed, M.A. Topical dorzolamide and metabolic acidosis in a neonate. *Br. J. Ophthalmol.* **2003**, *87*, 1052–1053. [CrossRef] [PubMed]
183. Hoffmanová, I.; Sánchez, D. Metabolic acidosis and anaemia associated with dorzolamide in a patient with impaired renal function. *Br. J. Clin. Pharmacol.* **2018**, *84*, 796–799. [CrossRef] [PubMed]
184. Wang, Y.C.; Ling, X.C.; Tsai, W.H.; Liu, J.S.; Kuo, K.L. Risks of topical carbonic anhydrase inhibitors in glaucoma patients with chronic kidney disease: A nationwide population-based study. *Am. J. Ophthalmol.* **2023**, *253*, 49–55. [CrossRef] [PubMed]
185. Levy, B.; Ramirez, N.; Novack, G.D.; Kopczynski, C. Ocular hypotensive safety and systemic absorption of AR-13324 ophthalmic solution in normal volunteers. *Am. J. Ophthalmol.* **2015**, *159*, 980–985.e1. [CrossRef] [PubMed]
186. Defert, O.; Boland, S. Rho kinase inhibitors: A patent review (2014–2016). *Expert. Opin. Ther. Pat.* **2017**, *27*, 507–515. [CrossRef] [PubMed]
187. Rouland, J.F.; Le Pen, C.; Gouveia Pinto, C.; Berto, P.; Berdeaux, G. Cost-minimisation study of dorzolamide versus brinzolamide in the treatment of ocular hypertension and primary open-angle glaucoma: In four European countries. *Pharmacoeconomics* **2003**, *21*, 201–213. [CrossRef] [PubMed]
188. Michaud, J.E.; Friren, B.; International Brinzolamide Adjunctive Study Group. Comparison of topical brinzolamide 1% and dorzolamide 2% eye drops given twice daily in addition to timolol 0.5% in patients with primary open-angle glaucoma or ocular hypertension. *Am. J. Ophthalmol.* **2001**, *132*, 235–243. [CrossRef] [PubMed]
189. Abramson, D.H.; Coleman, D.J.; Forbes, M.; Franzen, L.A. Pilocarpine. Effect on the anterior chamber and lens thickness. *Arch. Ophthalmol.* **1972**, *87*, 615–620. [CrossRef] [PubMed]
190. Schuman, J.S.; Horwitz, B.; Choplin, N.T.; David, R.; Albracht, D.; Chen, K. A 1-year study of brimonidine twice daily in glaucoma and ocular hypertension. A controlled, randomized, multicenter clinical trial. Chronic Brimonidine Study Group. *Arch. Ophthalmol.* **1997**, *115*, 847–852. [CrossRef] [PubMed]

191. Aihara, M.; Lu, F.; Kawata, H.; Iwata, A.; Odani-Kawabata, N. Twelve-month efficacy and safety of omidenepag isopropyl, a selective EP2 agonist, in open-angle glaucoma and ocular hypertension: The RENGE study. *Jpn. J. Ophthalmol.* **2021**, *65*, 810–819. [CrossRef]
192. Tanihara, H.; Inoue, T.; Yamamoto, T.; Kuwayama, Y.; Abe, H.; Araie, M. Phase 2 randomized clinical study of a Rho kinase inhibitor, K-115, in primary open-angle glaucoma and ocular hypertension. *Am. J. Ophthalmol.* **2013**, *156*, 731–736. [CrossRef] [PubMed]
193. Lopes, N.L.V.; Gracitelli, C.P.B.; Chalita, M.R.; de Faria, N.V.L. Ocular surface evaluation after the substitution of benzalkonium chloride preserved prostaglandin eye drops by a preservative-free prostaglandin analogue. *Med. Hypothesis Discov. Innov. Ophthalmol.* **2019**, *8*, 52–56. [PubMed]
194. Nino, M.; Napolitano, M.; Scalvenzi, M. Allergic contact dermatitis due to the beta-blocker betaxolol in eyedrops, with cross-sensitivity to timolol. *Contact Dermat.* **2010**, *62*, 319–320. [CrossRef] [PubMed]
195. Cusano, F.; Luciano, S.; Capozzi, M.; Verrilli, D.A. Contact dermatitis from pilocarpine. *Contact Dermat.* **1993**, *29*, 99. [CrossRef] [PubMed]
196. Sodhi, P.K.; Verma, L.; Ratan, J. Dermatological side effects of brimonidine: A report of three cases. *J. Dermatol.* **2003**, *30*, 697–700. [CrossRef] [PubMed]
197. Napolitano, M.; Potestio, L.; Castagliola, C.; Fabbrocini, G.; Patruno, C. Allergic contact dermatitis probably due to brimonidine tartrate in eyedrops. *Contact Dermat.* **2021**, *85*, 382–384. [CrossRef] [PubMed]
198. Mitsuyama, S.; Abe, F.; Higuchi, T. Allergic contact dermatitis due to dorzolamide eyedrops. *Contact Dermat.* **2021**, *84*, 58–59. [CrossRef] [PubMed]
199. Navarro-Triviño, F.J.; Ruiz-Villaverde, R. Periocular allergic contact dermatitis caused by brinzolamide. *Contact Dermat.* **2021**, *84*, 274–276. [CrossRef] [PubMed]
200. Sodhi, P.K.; Verma, L.; Ratan, S.K. Contact dermatitis from topical bimatoprost. *Contact Dermat.* **2004**, *50*, 50. [CrossRef] [PubMed]
201. Lee, J.H.; Kim, T.H.; Kim, S.C. Allergic contact dermatitis caused by topical eye drops containing latanoprost. *Ann. Dermatol.* **2014**, *26*, 269–270. [CrossRef] [PubMed]
202. Corazza, M.; Virgili, A.; Mantovani, L.; Masieri, L.T. Allergic contact dermatitis from cross-reacting beta-blocking agents. *Contact Dermat.* **1993**, *28*, 188–189. [CrossRef] [PubMed]
203. Chun, J.S.; Yun, S.J.; Lee, J.B.; Kim, S.J.; Won, Y.H.; Lee, S.C. Toxic epidermal necrolysis induced by the topical carbonic anhydrase inhibitors brinzolamide and dorzolamide. *Ann. Dermatol.* **2008**, *20*, 260–262. [CrossRef] [PubMed]
204. Sakata, R.; Shirato, S.; Miyata, K.; Aihara, M. Recovery from deepening of the upper eyelid sulcus after switching from bimatoprost to latanoprost. *Jpn. J. Ophthalmol.* **2013**, *57*, 179–184. [CrossRef] [PubMed]
205. Woodward, D.F.; Krauss, A.H.; Chen, J.; Liang, Y.; Li, C.; Protzman, C.E.; Bogardus, A.; Chen, R.; Kedzie, K.M.; Krauss, H.A.; et al. Pharmacological characterization of a novel antiglaucoma agent, Bimatoprost (AGN 192024). *J. Pharmacol. Exp. Ther.* **2003**, *305*, 772–785. [CrossRef]
206. Tanimura, H.; Minamoto, A.; Narai, A.; Hirayama, T.; Suzuki, M.; Mishima, H.K. Corneal edema in glaucoma patients after the addition of brinzolamide 1% ophthalmic suspension. *Jpn. J. Ophthalmol.* **2005**, *49*, 332–333. [CrossRef] [PubMed]
207. Zhao, J.C.; Chen, T. Brinzolamide induced reversible corneal decompensation. *Br. J. Ophthalmol.* **2005**, *89*, 389–390. [CrossRef] [PubMed]
208. Adamsons, I. Irreversible corneal decompensation in patients treated with topical dorzolamide. *Am. J. Ophthalmol.* **1999**, *128*, 774–776. [CrossRef] [PubMed]
209. Sugrue, M.F.; Johns, B. Concentrations of dorzolamide in the pigmented rabbit eye after repeated dosing with TRUSOPT. *Investig. Ophthalmol. Vis. Sci.* **1999**, *40*, S171.
210. Baratz, K.H.; Nau, C.B.; Winter, E.J.; McLaren, J.W.; Hodge, D.O.; Herman, D.C.; Bourne, W.M. Effects of glaucoma medications on corneal endothelium, keratocytes, and subbasal nerves among participants in the ocular hypertension treatment study. *Cornea* **2006**, *25*, 1046–1052. [CrossRef] [PubMed]
211. Beltz, J.; Zamir, E. Brimonidine induced anterior uveitis. *Ocul. Immunol. Inflamm.* **2016**, *24*, 128–133. [CrossRef] [PubMed]
212. Hopf, S.; Mercieca, K.; Pfeiffer, N.; Prokosch-Willing, V. Brimonidine-associated uveitis—A descriptive case series. *BMC Ophthalmol.* **2020**, *20*, 489. [CrossRef] [PubMed]
213. Hu, J.; Vu, J.T.; Hong, B.; Gottlieb, C. Uveitis, and cystoid macular oedema secondary to topical prostaglandin analogue use in ocular hypertension and open-angle Glaucoma. *Br. J. Ophthalmol.* **2020**, *104*, 1040–1044. [CrossRef] [PubMed]
214. Abraham, S.V.; Teller, J.J. Influence of various miotics on cataract formation. *Br. J. Ophthalmol.* **1969**, *53*, 833–838. [CrossRef] [PubMed]
215. Beasley, H.; Fraunfelder, F.T. Retinal detachments and topical ocular miotics. *Ophthalmology* **1979**, *86*, 95–98. [CrossRef] [PubMed]
216. American Psychological Association. APA Dictionary of Psychology-Adjunctive Therapy. Available online: https://dictionary.apa.org/adjunctive-therapy (accessed on 6 July 2023).
217. Lichter, P.R.; Musch, D.C.; Gillespie, B.W.; Guire, K.E.; Janz, N.K.; Wren, P.A.; Mills, R.P.; CIGTS Study Group. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. *Ophthalmology* **2001**, *108*, 1943–1953. [CrossRef] [PubMed]

218. Kass, M.A.; Heuer, D.K.; Higginbotham, E.J.; Johnson, C.A.; Keltner, J.L.; Miller, J.P.; Parrish, R.K., 2nd; Wilson, M.R.; Gordon, M.O. The Ocular Hypertension Treatment Study: A randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle Glaucoma. *Arch. Ophthalmol.* **2002**, *120*, 701–713, discussion 829–830. [CrossRef] [PubMed]
219. Crawford, K.; Kaufman, P.L. Pilocarpine antagonizes prostaglandin F2 alpha-induced ocular hypotension in monkeys. Evidence for enhancement of uveoscleral outflow by prostaglandin F2 alpha. *Arch. Ophthalmol.* **1987**, *105*, 1112–1116. [CrossRef] [PubMed]
220. Kent, A.R.; Vroman, D.T.; Thomas, T.J.; Hebert, R.L.; Crosson, C.E. Interaction of pilocarpine with latanoprost in patients with glaucoma and ocular hypertension. *J. Glaucoma* **1999**, *8*, 257–262. [CrossRef] [PubMed]
221. Yamagishi-Kimura, R.; Honjo, M.; Komizo, T.; Ono, T.; Yagi, A.; Lee, J.; Miyata, K.; Fujimoto, T.; Inoue, T.; Tanihara, H.; et al. Interaction between pilocarpine and ripasudil on intraocular pressure, pupil diameter, and the aqueous-outflow pathway. *Investig. Ophthalmol. Vis. Sci.* **2018**, *59*, 1844–1854. [CrossRef]
222. Liu, J.H.; Medeiros, F.A.; Slight, J.R.; Weinreb, R.N. Comparing diurnal and nocturnal effects of brinzolamide and timolol on intraocular pressure in patients receiving latanoprost monotherapy. *Ophthalmology* **2009**, *116*, 449–454. [CrossRef] [PubMed]
223. O'Connor, D.J.; Martone, J.F.; Mead, A. Additive intraocular pressure lowering effect of various medications with latanoprost. *Am. J. Ophthalmol.* **2002**, *133*, 836–837. [CrossRef] [PubMed]
224. Feldman, R.M.; Tanna, A.P.; Gross, R.L.; Chuang, A.Z.; Baker, L.; Reynolds, A.; Prager, T.C.; Additivity Study Group. Comparison of the ocular hypotensive efficacy of adjunctive brimonidine 0.15% or brinzolamide 1% in combination with travoprost 0.004%. *Ophthalmology* **2007**, *114*, 1248–1254. [CrossRef] [PubMed]
225. Martinez-de-la-Casa, J.M.; Castillo, A.; Garcia-Feijoo, J.; Mendez-Hernandez, C.; Fernandez-Vidal, A.; Garcia-Sanchez, J. Concomitant administration of travoprost and brinzolamide versus fixed latanoprost/timolol combined therapy: Three-month comparison of efficacy and safety. *Curr. Med. Res. Opin.* **2004**, *20*, 1333–1339. [CrossRef] [PubMed]
226. Reis, R.; Queiroz, C.F.; Santos, L.C.; Avila, M.P.; Magacho, L. A randomized, investigator-masked, 4-week study comparing timolol maleate 0.5%, brinzolamide 1%, and brimonidine tartrate 0.2% as adjunctive therapies to travoprost 0.004% in adults with primary open-angle glaucoma or ocular hypertension. *Clin. Ther.* **2006**, *28*, 552–559. [CrossRef] [PubMed]
227. Cheng, J.W.; Cheng, S.W.; Yu, D.Y.; Wei, R.L.; Lu, G.C. Meta-analysis of α2-adrenergic agonists versus carbonic anhydrase inhibitors as adjunctive therapy. *Curr. Med. Res. Opin.* **2012**, *28*, 543–550. [CrossRef] [PubMed]
228. Konstas, A.G.; Holló, G.; Haidich, A.B.; Mikropoulos, D.G.; Giannopoulos, T.; Voudouragkaki, I.C.; Paschalinou, E.; Konidaris, V.; Samples, J.R. Comparison of 24-hour intraocular pressure reduction obtained with brinzolamide/timolol or brimonidine/timolol fixed-combination adjunctive to travoprost therapy. *J. Ocul. Pharmacol. Ther.* **2013**, *9*, 652–657. [CrossRef] [PubMed]
229. Oztürk, F.; Ermiş, S.S.; Inan, U.U.; Aşagidag, A.; Yaman, S. Comparison of the efficacy and safety of dorzolamide 2% when added to brimonidine 0.2% or timolol maleate 0.5% in patients with primary open-angle Glaucoma. *J. Ocul. Pharmacol. Ther.* **2005**, *21*, 68–74. [CrossRef] [PubMed]
230. Fuwa, M.; Shimazaki, A.; Odani-Kawabata, N.; Kirihara, T.; Taniguchi, T.; Iwamura, R.; Yoneda, K.; Kato, M.; Morishima, K.; Shams, N.K. Additive intraocular pressure-lowering effects of a novel selective EP2 receptor agonist, omidenepag isopropyl, combined with existing antiglaucoma agents in conscious ocular normotensive monkeys. *J. Ocul. Pharmacol. Ther.* **2021**, *37*, 223–229. [CrossRef] [PubMed]
231. Tanna, A.P.; Rademaker, A.W.; Stewart, W.C.; Feldman, R.M. Meta-analysis of the efficacy and safety of alpha2-adrenergic agonists, beta-adrenergic antagonists, and topical carbonic anhydrase inhibitors with prostaglandin analogs. *Arch. Ophthalmol.* **2010**, *128*, 825–833. [CrossRef] [PubMed]
232. Toumanidou, V.; Diafas, A.; Georgiadis, N.; Tsinopoulos, I. Fixed versus Unfixed Combination of Topical Latanoprost/Timolol for Glaucoma: An Observational Study Investigating the Level of Adherence and Ocular Surface Health. *J. Clin. Med.* **2023**, *12*, 3137. [CrossRef] [PubMed]
233. Menon, M.G.; Goodkin, M.L. Triple Fixed-Combination Bimatoprost/Brimonidine/Timolol in Glaucoma and Ocular Hypertension in India: A Multicenter, Open-Label, Phase 3 Study. *Clin. Ophthalmol.* **2022**, *16*, 3559–3569. [CrossRef] [PubMed]
234. Konstas, A.G.; Schmetterer, L.; Costa, V.P.; Holló, G.; Katsanos, A.; Denis, P.; Quaranta, L.; Irkec, M.; Castejón, M.A.; Teus, M.A.; et al. Current and emerging fixed combination therapies in glaucoma: A safety and tolerability review. *Expert Opin. Drug Saf.* **2020**, *19*, 1445–1460. [CrossRef] [PubMed]
235. Qlaris Bio's Novel IOP-Lowering Product, QLS-111, Is Dosed in Phase II Trials. Press Release; April 2, 2024. Available online: https://qlaris.bio/qlaris-bios-novel-intraocular-pressure-iop-lowering-product-qls-111-is-dosed-in-phase-ii-trials/ (accessed on 29 April 2024).
236. Qlaris Study of QLS-111 in Combination with a PGA for OAG and/or OHT Patients. ClinicalTrials.gov Identifier: NCT06249152. U.S. National Library of Medicine, 2024. Available online: https://classic.clinicaltrials.gov/ct2/show/NCT06249152 (accessed on 29 April 2024).
237. Kouassi Nzoughet, J.; Chao de la Barca, J.M.; Guehlouz, K.; Leruez, S.; Coulbault, L.; Allouche, S.; Bocca, C.; Muller, J.; Amati-Bonneau, P.; Gohier, P.; et al. Nicotinamide deficiency in primary open-angle Glaucoma. *Investig. Ophthalmol. Vis. Sci.* **2019**, *60*, 2509–2514. [CrossRef] [PubMed]
238. Taechameekietichai, T.; Chansangpetch, S.; Peerawaranun, P.; Lin, S.C. Association between daily niacin intake and glaucoma: National Health and Nutrition Examination Survey. *Nutrients* **2021**, *13*, 4263. [CrossRef] [PubMed]

239. The Glaucoma Nicotinamide Trial (TGNT). ClinicalTrials.gov Identifier: NCT05275738. U.S. National Library of Medicine, 2022. Available online: https://www.clinicaltrials.gov/study/NCT05275738?cond=Glaucoma&page=2&rank=13#study-plan (accessed on 27 April 2024).
240. Nicotinamide and Pyruvate for Open Angle Glaucoma: A Randomized Clinical Study. ClinicalTrials.gov Identifier: NCT05695027. U.S. National Library of Medicine, 2023. Available online: https://clinicaltrials.gov/study/NCT05695027 (accessed on 27 April 2024).
241. Nicotinamide and Glaucoma ClinicalTrials.gov Identifier: NCT05916066. U.S. National Library of Medicine, 2023. Available online: https://www.clinicaltrials.gov/study/NCT05916066?cond=Glaucoma&page=2&rank=14 (accessed on 27 April 2024).
242. Efficacy of Citicoline Eye Drops 2% on Visual Field Preservation in Patients with Open Angle Glaucoma ClinicalTrials.gov Identifier: NCT05710198. U.S. National Library of Medicine, 2024. Available online: https://clinicaltrials.gov/study/NCT05710198?cond=Glaucoma&aggFilters=phase:4%203%202,status:rec%20act,studyType:int%20obs&rank=9#study-overview (accessed on 29 April 2024).
243. Safety of Topical Insulin Drops for Open-angle Glaucoma ClinicalTrials.gov Identifier: NCT04118920. U.S. National Library of Medicine, 2023. Available online: https://clinicaltrials.gov/study/NCT04118920#study-overview (accessed on 28 April 2024).
244. Grant, C.; Crystal, J.; Juan, R.; Kristine, L.; Michaela, D.; Dawn, J.; Trinity, H.; Howard, L.; Stuart, K.G.; Lin, W.; et al. Pharmacodynamic response of optic nerve head (ONH) tissue blood flow measured by laser speckle flowgraphy (LSFG) after administration of PER-001, an endothelin receptor antagonist. *Investig. Ophthalmol. Vis. Sci.* **2022**, *63*, 4029-A0414.
245. A Study of PER-001 in Participants with Open-Angle Glaucoma ClinicalTrials.gov Identifier: NCT05822245. U.S. National Library of Medicine, 2023. Available online: https://www.clinicaltrials.gov/study/NCT05822245?term=A%20Study%20of%20PER-001%20in%20Participants%20With%20Open-Angle%20Glaucoma&rank=1#study-overview (accessed on 28 April 2024).
246. Goldberg, J.L.; Beykin, G.; Satterfield, K.R.; Nuñez, M.; Lam, B.L.; Albini, T.A. Phase I NT-501 Ciliary Neurotrophic Factor Implant Trial for Primary Open-Angle Glaucoma: Safety, Neuroprotection, and Neuroenhancement. *Ophthalmol. Sci.* **2023**, *3*, 100298. [CrossRef] [PubMed]