Review

An Update on Pharmacotherapy of Glaucoma

Shalini Virani and Parveen Rewri *

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An Update on Pharmacotherapy of Glaucoma

Shalini Virani and Parveen Rewri *

* Correspondence: Agrasen Medical College

Abstract: Progressive loss of retinal ganglionic cells (RGC) causes blindness in glaucoma. Elevated intraocular pressure (IOP) is the most important, treatable risk factor. Currently, the management of glaucoma is centred at 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-hour IOP control and other IOP-independent risk factors affecting ocular blood flow and RGC toxicity is also recognised. The role of available drugs in controlling IOP over 24-hours is being evaluated. Improvement of ocular blood flow and neuroprotection are seen as potential drug targets in 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-hour IOP control; Neuroprotection; Ocular blood flow; Adjunctive therapy

Introduction

Glaucoma, characterised by 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], and compliance with treatment [5]. The only modifiable risk factors are IOP and its fluctuations, which 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-hour IOP control, ocular blood flow regulation, and neuroprotection are being explored.

Medical intervention in the form of topical eye drops is 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.

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 focal or diffuse loss of NRR and an alteration in cup-to-disc ratio (CDR), characteristic of glaucomatous damage (Figure 1b). RGC death is most often due to elevated IOP [8]. 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 apoptosis and RGC death.

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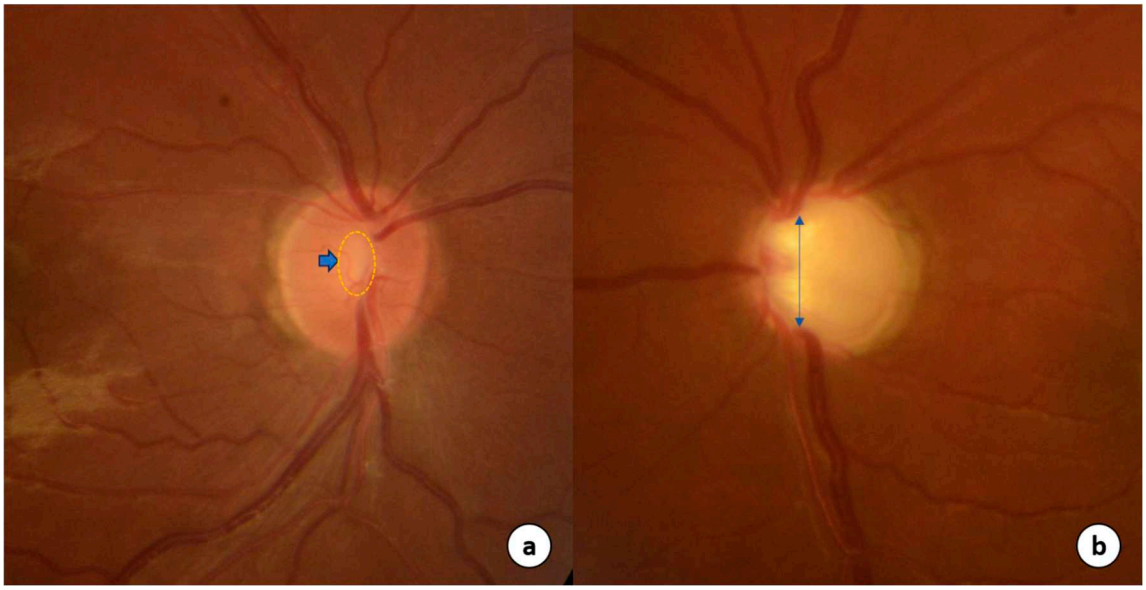

Figure 1. (a) The optic nerve head with healthy neuroretinal rim, area surrounding the inside dotted circle. There inside doted circle, marked with blue arrow is cup. (b) The optic nerve in glaucomatous eye. Note the loss of NRR and increase in cup size, marked with blue line.

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. The aqueous drains through two independent pathways-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 [12]. The aqueous drainage decreases with age through trabecular meshwork pathway [13] as well as the uveoscleral pathway [14]. 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 [15], whereas in angle-closure conditions, access to the trabecular meshwork is blocked by iris tissue [16].

Targets for pharmacotherapy

Currently, the management of glaucoma is limited to lowering the IOP. The two ways in which 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 [17]. The latest addition to the armamentarium of IOP-lowering drugs is Omidenepag Isopropyl (OMPI), which was approved by the FDA in 2022 to treat open-angle glaucoma and ocular hypertension [18] (Figure 2). Topical IOP-lowering drugs are available either as 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 IOP by suppressing the aqueous humour secretion, and two, which reduce IOP by improving the aqueous humour outflow. The latter is further sub-grouped based on whether these drugs reduce 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 are grouped based on their chief mechanism of IOP reduction.

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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%

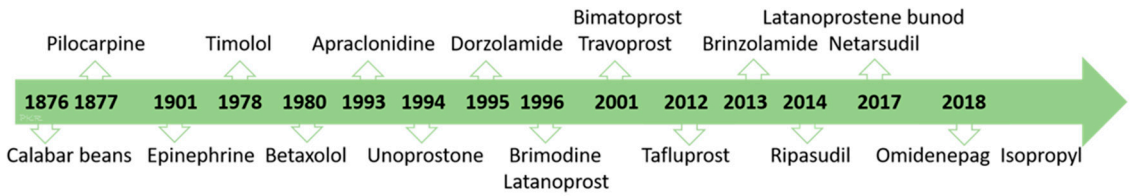

Figure 2. The graphical representation of time-line of introduction of IOP-lowering drugs.

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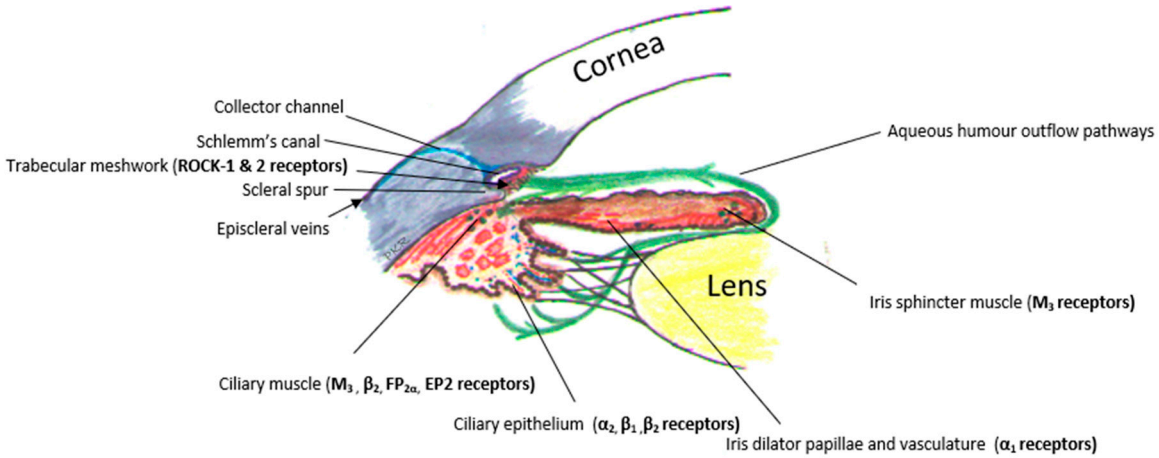

Figure 3. Schematic diagram of structures of the anterior chamber of the eye to illustrate site of action and receptors of the IOP-lowering drugs.

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	No effect	No effect		Decrease [22]
Apraclonidine	Decrease	Decrease [27]		Decrease [28]		
Brimodine	Decrease	No effect	Increase [14]	Decrease [26]	+ [29, 123, 124]	No effect [30,31]
Brinzolamide	Decrease	No effect	No effect	No effect		? / No effect [31,121]
Dorzolamide	Decrease	No effect				Increase [9, 110]/No effect [30]
Bimatoprost	Increase	Increase#	Increase	Increase/ Decrease [109]		
Latanoprost	Increase	Increase#	Increase	Increase		Increase [11,13]
Tafluprost		Increase#	Increase			Increase [117]
Travoprost	Increase	Increase#	Increase			Increase [13]
Unoprostone		Increase#	Increase	No effect		

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Omidenepag isopropyl	No effect		Increase			
Pilocarpine	No effect [46]	Increase	Decreases [206]	No effect		Increase [9,10]
Latanoprostene bunod		Increase	Increase	Ongoing Trial		Increase [122]
Netarsudil	Decrease	Increase	No effect	Decrease [106, 107]	+ [129, 130]	
Ripasudil		Increase		Decrease [108]	+ [129, 130]	

Aqueous suppressants drugs

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 [19], extraocular muscles, conjunctiva, epithelium and endothelium of the cornea, trabecular meshwork, and ciliary muscle [20]. The precise mechanism of β-adrenergic receptor antagonism-mediated decrease in aqueous humour secretion is not completely understood. In non-primate animal studies, beta-blockers decrease aqueous humour secretion by inhibiting catecholamine-stimulated synthesis of cyclic-adenosine monophosphate [21] 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 animal experimental studies beta-blockers reduced ocular blood flow [22].

Adrenergic agonists

Alpha-adrenergic drugs lower 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 [23]. 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 intracellular cyclic adenosine monophosphate (cAMP) level [24]. These drugs may have some effect on the outflow pathway owing to the presence of α-2A receptors [25]. 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 uveoscleral outflow, and this effect is supposed to be the main mechanism for IOP reduction in long-term treatment [14]. In experimental studies on mice, brimonidine reduced episcleral venous pressure [26]. Apraclonidine does not appear to improve uveoscleral outflow but perhaps reduces aqueous secretion and episcleral venous pressure [27,28]. The presence of alpha-adrenergic receptors in the retina is seen as a potential target for the neuroprotective effects of these drugs [29]. Brimodine did not show cause any clinically beneficial improvement in ocular blood flow in humans. [30, 31].

Carbonic anhydrase inhibitors

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Carbonic anhydrase inhibitors (CAIs) belong to sulphonamide compounds and are the only class of IOP-lowering drugs that is 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 [32]. 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 [33]. 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 [34]. Their role in improving the ocular blood flow has been studied in humans [30, 31]. In topical form, two drugs are available: dorzolamide 2% and brinzolamide 1%.

Uveoscleral outflow drugs

Prostaglandin analogues

The PGF2α subtype of FP receptors and the EP2 subtype of EP receptors [35] regulate IOP. The circular muscles and collagenous connective tissue of ciliary tissue have both PGF2α and EP1 receptors. Through activation of these receptors, PGA increases the expression of metalloproteinases 1, 2, 3 and 9 in human ciliary muscle cells [36, 37]. The increased level of metalloproteinases results in remodeling of the extracellular matrix of the ciliary muscle bundles of the uveoscleral pathway, which augments the aqueous outflow [38]. The PGF2α analogues except for bimatoprost, which is an amide prodrug; rest are ester prodrugs of the corresponding acids, including PGEP2 receptor analogue OMPI. These drugs are hydrolysed by corneal esterase into biologically active agents [39, 40, 41]. The OMPI is supposed to increase aqueous outflow through both the trabecular meshwork and uveoscleral pathway [42].

Trabecular outflow drugs

Cholinergic

Cholinergic or parasympathomimetic drugs mediate their pharmacological effects through direct stimulation of muscarinic receptors located on 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 [43, 44]. Direct stimulation of these receptors contracts ciliary muscle, which pulls the scleral spur, resulting in the widening of trabecular meshwork lamellae and an increase in 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 also results in reduced uveoscleral outflow [45, 46]. Contrarily, direct stimulation of M_3 receptors on TM results in decreased aqueous outflow, but the net effect is improved aqueous outflow through TM and reduction in IOP [47]. Lower concentrations of pilocarpine increased the outflow facility in human cadaveric eyes with a disinserted ciliary body [48]. In the case of angle-closure diseases, these drugs mediate their effect through action on M_3 receptors located on the sphincter pupillae muscle of the iris. The muscle contraction results in meiosis (hence, also called miotics), which widens the angle in eyes with narrow angles, resulting in improved aqueous outflow through the TM and a lowering of IOP. Pilocarpine is the most widely available topical cholinergic drug.

Nitic Oxide donors

Nitric oxide (NO) is synthesised endogenously in the human body, including the trabecular meshwork, Schlemm's canal, and ciliary body, from L-arginine NO synthase enzyme [49, 50].

The NO donor drugs have targets in the conventional pathway [40]. 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 [40]. Latanoprost increases aqueous outflow through the uveoscleral pathway, whereas the butanediol mononitrate metabolites 1,4-butanediol and NO are supposed to enhance aqueous outflow through the trabecular meshwork [50]. The NO

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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 aqueous humour outflow [51].

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 [52]. (ROCK has two isoforms ROCK 1 and ROCK 2, both of which are expressed in trabecular meshwork [53]. ROCK inhibits two enzymes, LIM kinase and myosin light chain phosphatase (MLCP), which respectively facilitate actin fibre relaxation and polymerisation, resulting in increased resistance to aqueous outflow in trabecular meshwork [54]. Rho-Kinase inhibition results in actin fibre contraction and depolymerisation and facilitates aqueous outflow through the trabecular meshwork [53]. The reduction of aqueous secretion through norepinephrine transporter inhibition has been seen in non-human primates and non-primate animals [55]. In animal studies, these drugs lowered IOP by increasing aqueous outflow, reducing aqueous secretion, and decreasing episcleral venous pressure [56]. Two ROCK inhibitor drugs are available in topical forms to treat glaucoma: Netarsudil 0.02% and Ripasudil 0.4%.

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 [51-53, 56,65,83,110,203].

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

IOP-related

IOP-lowering effect

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The IOP-lowering effect of prostaglandins is superior to other classes of topical IOP-lowering drugs [57, 58], followed by nonselective β-blockers, α-adrenergic agonists, selective β-blockers, and topical CAIs [59]. The newer class of ROCK inhibitors, netarsudil is less efficacious in reducing IOP compared to latanoprost or timolol [60], 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 [61], although bimatoprost 0.03% and travoprost 0.004% reduced the IOP slightly more than latanoprost 0.005% [62, 63]. IOP reduction with tafluprost was comparable to latanoprost [61]. Unlike other PGAs, unoprostone 0.15% has the disadvantage of twice-daily dosing and the least IOP-lowering efficacy [63]. 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 20-35% [64], and when compared to latanoprost 0.005%, the IOP reduction with OMPI was slightly less and the difference was significant statistically but not clinically [65].

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 [66].

Timolol reduces IOP by 10-25% from baseline [57]. The maximum effect may last up to 12 hours of application, and nearly 25% IOP reduction is maintained at 24 hours [67]. IOP reduction with betaxolol 0.5% is comparable to that seen with timolol 0.5% [68]. Non-selective beta-blockers are most efficacious in reducing IOP, second only to PGA [59].

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% [57]. Apraclonidine reduces IOP comparable to brimonidine, but its effects last for a shorter duration [69]. The absolute reduction of 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 [70].

The CAIs reduce the IOP typically by 15-20% [57, 71]. The IOP-lowering effect of brinzolamide is slightly lower than that of dorzolamide, though the difference may not be of clinical significance [58]. 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 [34]. Oral acetazolamide reduces IOP by 30-40%, and the effect lasts for 6-8 hours.

Pilocarpine reduces IOP by 20-25%. A dose-response analysis of pilocarpine in reducing IOP showed the maximum effect with a 4% concentration [72]. 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 [73, 74].

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% [60]. Within the class of ROCK inhibitors, netarsudil once daily reduced IOP more effectively compared to ripasudil twice daily [60].

24- hour IOP control

The circadian rhythm of IOP is controlled in the suprachiasmatic nucleus [75]. In glaucomatous eyes, the diurnal phasic variation of IOP seems to be dysregulated [76, 77]. Short-term IOP fluctuation has been associated with glaucoma progression [78]. The IOP fluctuation tends to be wider in glaucomatous eyes. In most non-glaucomatous and glaucomatous subjects, IOP peaks during the early morning hours [76, 79]. IOP peak in nearly 50% of patients [80] and wider IOP fluctuation in 62% of glaucomatous patients [81] 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 become 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-hour.

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A more uniform circadian IOP reduction has been seen with PGF2α analogue drugs [82]. Three PGF2α analogues, namely bimatoprost, latanoprost, and travoprost, have been shown to be equally efficacious in reducing IOP and controlling 24-hour IOP [83, 84]. 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 [85]. Brimonidine 0.2%, like timolol, has reduced nocturnal IOP-lowering efficacy [86, 87]. Aqueous suppressant, due to its attenuated nocturnal IOP-lowering effect, exerts a non-uniform 24-hour IOP control.

Nocturnal effect

The aqueous suppressant drugs-beta-blockers, CAIs, and alpha-agonists have no or poor nocturnal IOP-lowering efficacy [87, 88]. The findings related to the nocturnal IOP-lowering efficacy of timolol and dorzolamide are not consistent. A meta-analysis concluded IOP-lowering efficacy of dorzolamide during the day and night is comparable [71]. Similarly, another meta-analysis concluded that the nocturnal IOP-lowering effect of timolol is attenuated but not absent [89]. In clinical studies, timolol did not lower the nocturnal IOP below 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 [90]. The drugs facilitating aqueous outflow effectively reduce the nocturnal IOP, but the reduction is less than that seen during the day [91, 92]. One reason for this could be that nocturnal IOP was measured in the supine position [93]. The nocturnal attenuation of the IOP lowering effect was not seen with OMPI [94]. 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 [95].

Long term efficacy

A kind of drug tolerance, often called long-term drift, is observed with 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 [96], and brimonidine [97], but not with dorzolamide [98] or PGA. In a few species of animals (rabbits), tachyphylaxis with PGA was demonstrated, but such a response is not expected in humans [99]. Travoprost was effective in lowering IOP at 5 years with consistent 24-hour control in humans [100].

Long-term drift is believed to occur due to compensatory upregulation of receptors to agonists or downregulation of receptors. The long-term drift to 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 [101].

Cross-over effect

Instillation of a topical IOP-lowering drug in one eye produces some reduction in 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 [102], alpha-agonists [103], and PGA [104]. The cross- over effect is due to the systemic absorption of the drug through the nasolacrimal pathway [105]. The amount of IOP reduction in 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 highest during the early hours of the day (~50-60%), and gradually decreased to 20% as the day progressed [104].

Episcleral venous pressure drugs

The effect of currently available IOP-lowering drugs on episcleral venous pressure is yet not clear. Netarsudil 0.02% reduced episcleral venous pressure in phase 2 trail and in a small clinical study [106, 107]. Ripasudil also increased episcleral venous flow [108]. The clinical benefits of these effects, especially in glaucoma associated with raised episcleral venous pressure, are still not known. Apraclonidine and brimonidine also reduce the episcleral venous pressure [26, 28]. Effect of PGA

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analogues varies with formulation. Topical preparations increased the episcleral venous pressure, but intra-cameral administration reduced it in non-primate animal study [109].

IOP independent

Ocular blood flow

Low ocular perfusion is associated with RGC damage in primary open-angle glaucoma and progression [110-112]. Ocular perfusion pressure (OPP) is calculated as the difference between mean arterial pressure (MAP) and IOP [113]. The MAP is derived from systolic and diastolic blood pressures. Topical drops affect IOP and blood pressure and are therefore supposed to alter OPP. Bimatoprost increased OPP in open-angle glaucoma and ocular hypertension patients [91]. Latanoprost increased ocular perfusion pressure (OPP) in non-glaucomatous eyes [114]. In normal-tension glaucoma (NTG) patients with mean baseline IOP in the low teens, latanoprost did not affect OPP [115] but increased in NTG patients with IOP in the upper teens [116]. Tafluprost improved ocular blood flow in experimental studies [117]. The effect of timolol on OPP is not clear. Several studies have noted no change [116], an increase when calculated with diastolic blood pressure but reduced OPP when calculated with systolic blood pressure [114], or only a daytime increase in OPP without any change in nocturnal or 24-hour OPP [118]. Brimonidine 0.2% did not affect OPP in patients with normal tension glaucoma [119]. Pilocarpine increased systolic OPP in non-glaucomatous eyes [120]. Both dorzolamide and brinzolamide increase ocular blood flow [121]. Latanoprostene bunod 0.024% induced a significant increase in optic nerve head blood volume and oxygen saturation in healthy subjects aged between 21 and 62 years [122]. The FDC of brinzolamide/brimonidine did not change OPP in patients with open-angle glaucoma and ocular hypertension [118]. The clinical advantage of improved OPP in preserving the RGC is difficult to estimate in isolation from IOP-lowering.

Neuroprotection

In animal studies, the neuroprotective effects of IOP-lowering drugs, independent of IOP reduction, have been studied. Brimonidine 2% prevented loss of RGC in the chronic ocular hypertension rat model [123]. Indirect evidence of the presumed neuroprotective effect of brimonidine 2% comes from clinical studies. Brimonidine -2%- treated patients had an improvement in contrast sensitivity compared to patients treated with timolol, with comparable IOP reduction [124]. However, in a non-comparative study in open-angle glaucoma patients with travoprost, a reduction in IOP has been associated with improvement in central and peripheral contrast sensitivities [125]. Contrast sensitivity and retinal nerve fibre loss (RNFL) are not strongly correlated in clinical studies [126]. In ocular hypertension patients, RNFL loss was less with brimonidine 0.2% compared to timolol, irrespective of IOP reduction [127]. In clinical trials, IOP reduction has been shown to delay glaucoma progression [128], which may surrogate the neuroprotective effect. The neuroprotective effect of PGA, independent of IOP, was demonstrated against glutamate- or hypoxia-induced RGC death using rat primary RGC culture at clinically available intracameral concentrations [129]. 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 [130].

The development of drugs enhancing ocular blood flow or offering neuroprotective effects is still in the pre-clinical stage. The evidence for the available drugs is not strong enough to advocate their preferential use for these additional benefits.

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 IOP by 25-35% with once-daily dosing in patients with normal tension glaucoma [131, 132], pigment dispersion syndrome [133], primary

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angle-closure glaucoma [134, 135], and pseudo-exfoliation glaucoma. In pseudo-exfoliation glaucoma, lower IOP was achieved with bimatoprost 0.03% [136] and travoprost 0.04% [137] 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 IOP ≥20% from the wash-out period baseline in nearly 85% of poor or non-latanoprost responder patients with open-angle glaucoma [138]. Substitution with PGA or non-PGA drugs may be effective in lowering IOP in poor or non-responders [66, 139]. OMPI is effective in NTG [140] and secondary glaucoma [141].

The NO donor drug, latanoprostene bunod, is not inferior to latanoprost 0.005% in reducing IOP in open angle glaucoma and ocular hypertension [40].

Beta-blockers are used in a twice-daily regimen spaced at 12-hours intervals. A once daily dose of timolol 0.1% gel was equally effective as a 0.5% solution twice-daily in lowering IOP [142]. Beta-blockers are used for all types of glaucoma. Betaxolol reduced IOP nearly by 18% in normal tension glaucoma with baseline IOP in the mid-teens [143]. Beta-blockers are the drug of choice after PGA, provided their use is not limited by their systemic side effects.

Apraclonidine is approved for 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 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 [144], 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±1.2mmHg) brimonidine 0.1% preserved with sodium chloride reduced IOP by 10% [145]. 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 [146]. Because of CNS depressant effects in children [147], 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. Long-term use of oral acetazolamide, especially in the elderly, may lead to life-threatening metabolic acidosis [148]. 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 [149]. In normal-tension glaucoma with a mean IOP of 16.8±0.9 mmHg, dorzolamide reduced IOP by 18% at 4 weeks [142]. CAIs have been shown to reduce IOP in several types of glaucoma, including in young children [150].

The IOP-lowering effect of pilocarpine approximately begins 60 minutes after ocular instillation, and peaks at 75 minutes, and lasts from four to eight hours [151]. 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 [152].

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 [153]. Newer indications for pilocarpine use are the management of xerostomia [154] and presbyopia [155].

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 [60]. Ripasudil effectively reduced IOP in uveitic glaucoma, exfoliation glaucoma, and steroid-induced glaucoma [156].

Tolerability and safety

Systemic side effects

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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 [157]. The effect is more common and pronounced with non-selective agents in susceptible individuals [158]. The bronchoconstriction in otherwise healthy individuals without pre-existing reactive airways is not clinically significant [159]. Betaxolol has a 20-fold higher affinity for β1-receptors than for β2-receptors. The risk of airway obstruction among non-susceptible persons without prior history of respiratory diseases was similar for selective and non-selective topical beta-blockers [160]. Eyelid closure, nasolacrimal occlusion for 5 minutes, or pressing the eye with tissue paper after applying the eyedrop reduced the systemic absorption of timolol by 60-67% [151, 161]. 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 [162]. 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 contraindication for the use of beta-blockers, especially non-selective ones.

Cholinergic drugs may cause sweating, gastro-intestinal (salivation, nausea, vomiting, diarrhoea), respiratory (bronchospasm), and cardio-vascular (bradycardia, hypotension) symptoms due to their action through M1 and M2 receptors following systemic absorption [151, 163].

Apraclonidine reduced heart rate and systolic blood pressure [164] when used to suppress post-LASER IOP spikes. Brimonidine 0.2% reduced both systolic and diastolic blood pressure significantly [165] but not the pulse rate [166] when compared to baseline values. The systolic and diastolic blood pressures are the determinants of ocular perfusion pressure [167]. 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 [168], and adults with impaired renal function [169, 170] has been reported.

PGA does not have any systemic side effects. Topical use of ROCK inhibitors caused little or no quantifiable systemic exposure [171]. However, systemic absorption produced hypotension and a reversible reduction in lymphocyte counts [172].

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 [173, 174]. Among PGA, stinging is more common with LBN than latanoprost [40].

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 forward displacement and thickening of the lens [175]. 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 [176].

Conjunctival hyperaemia is common with PGA, including OMPI, and ROCK inhibitors [177, 178]. Among PGA drugs, it is most common with bimatoprost 0.003% and least common with latanoprost 0.005% [57, 62]. Contrarily, the vasoconstrictive effects of α-adrenergic agonist drugs result in conjunctival blanching, a dry nose, and a dry mouth [176]. Most IOP-lowering drugs reduce Schirmer score, and ocular surface disease index, which is supposed to be because of preservatives [179].

The exact incidence of periorbital contact dermatitis with IOP -lowering drugs is not known. It has been reported with timolol, betaxolol [180], pilocarpine [181], brimonidine [182, 183],

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dorzolamide [184], brinzolamide [185], bimatoprost [186], and latanoprost [187]. A cross-reactivity among beta-blockers has been observed [180], which is presumed to result from the common lateral aliphatic chain in their structure [188]. Brinzolamide and dorzolamide have been associated with toxic epidermal necrolysis in patients with impaired hepatic functions [189].

PGA drugs may cause cosmetically unacceptable, though reversible, changes in periorbital tissues, collectively described as prostaglandin-associated peri-orbitopathy [190]. This includes changes in the eyelid and orbit: 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% [191]. The higher absorption of drugs in peri-orbital skin [192], which interferes with cellular adipose tissue metabolism [191], and causes peri-orbitopathy. Discontinuation of therapy or switching to an alternate, milder form may reverse changes in weeks or months [190].

Corneal edema has been reported with brinzolamide in eyes with normal endothelial count [193], which is reversible [194]. Dorzolamide may cause irreversible corneal decompensation in eye with compromised cornea or complicated ocular history [195]. CAIs attenuate bicarbonate efflux by reversibly inhibiting CA II in corneal endothelial cells, which results in fluid retention [196]. Until a safe endothelial count for the use of CAI drugs is known, these drugs should be used with caution in patients with compensated cornea. A decrease in the number and density of corneal sub-basal nerve fibre bundles without affecting keratocyte density or corneal endothelial characteristics has been observed with chronic use of topical IOP-lowering drugs in glaucomatous patients and healthy controls with normal endothelial cell count [197].

Granulomatous anterior uveitis may be seen with brimonidine 2% use [198, 199]. The inflammation reverses with 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 [199]. PGA is better avoided in eyes with iritis, herpes simplex keratitis, and eyes at risk of developing cystoid macular edema [65, 200].

Pilocarpine increased cataract formation [201] and may cause retinal detachment in high myopia (≥ -6D), especially with higher concentrations [202].

Adjunctive therapy

Adjunctive therapy is defined as one or more secondary interventions used concurrently with a primary intervention to enhance treatment effectiveness [203]. The effective reduction in IOP to preserve the RGC required more than one drug in 40-50% of the patients in major clinical trials [204, 205]. 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 first-line therapy in almost all cases of glaucoma due to its superior IOP-lowering effect, better 24-hour 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 [206]. In study on non-human primates, pilocarpine reduced the uveoscleral outflow. [207] However, alteration in the order and timing of administration of pilocarpine and latanoprost has been found effective in achieving additional IOP reduction [208].

Similarly, cholinergic and ROCK inhibitors 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 by ripasudil at the peak IOP reduction [209].

The IOP-lowering effect of topical CAIs as adjunctive therapy to PGA is superior to timolol or brimonidine [210-213]. The PGA induces a CA enzyme in epithelial cells of the ciliary process, which results in increased aqueous humour formation [214]. 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 an 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 flattening of diurnal variation [210]. The adjunctive IOP-lowering effect of timolol 0.5% (3.9 mmHg) with travoprost 0.004% was superior to brimonidine 2% (2.3 mmHg) [214]. A meta-analysis comparing the effectiveness of brimonidine and CAIs as adjunctive therapies to PGAs and beta-blocker found that brimonidine was superior to CAIs in reducing acrophase and trough IOP as well as diurnal fluctuation [215]. Adjunctive therapy with FDC of brinzolamide/timolol to travoprost was superior to FDC of brimonidine/timolol in controlling mean 24-hour IOP owing to the greater efficacy in the late afternoon and during the night [216].

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±1.9mmHg) [217]. 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 maximum with brimonidine 2% [218].

Additive therapy of netarsudil with timolol or latanoprost reduced the mean pooled IOP by 2.66 mmHg [60]. 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 [219].

Conclusions

Over a century since the first 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-hour IOP control, 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 and new drug delivery systems would help overcome some of these adversities soon.

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