We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Pressure Lowering Medications

Liza-Sharmini Ahmad Tajudin and Yaakub Azhany

*Department of Ophthalmology,
School of Medical Sciences,
Universiti Sains Malaysia
Malaysia*

1. Introduction

Glaucoma is an irreversible chronic disease; thus, management is a great challenge. The main goal of treatment is to prevent further nerve fibre damage. The present modes of treatment include pressure-lowering medications, laser treatment, and surgical interventions, all of which aim to reduce IOP. Diversion of aqueous humour outflow through an iatrogenic fistula to the sub-conjunctival space is the principle underlying glaucoma surgery. Surgical intervention provides sustainable constant IOP reduction but not without intra- and postoperative complications (Migdal et al, 1994; Musch et al, 2009). In fact, glaucoma surgery hastens cataract formation, which may necessitate further surgical intervention (Musch et al, 2009; AGIS group, 2000). Surgical equipment, a proper operating theatre, and an experienced surgeon increase the cost of filtration surgery. The invasiveness of the procedure interrupts the natural defence mechanism of the eye, increasing the risk of infection. Laser treatment is less invasive and is associated with a lower risk of infection. Similar to the filtration surgery, it is a permanent procedure and does not require a high technology environment but requires an expensive high-maintenance laser machine. However, the pressure-lowering effect is insufficient and temporary (Glaucoma Laser Trial Research Group, 1995). Manipulation of aqueous humour production and outflow is the mainstay mechanism of topical pressure-lowering medications. Topical medications are widely available in industrialised nations, are non-invasive and easily transportable. In addition, they are relatively easy to instil without the need for special equipment or a high technology environment. Importantly, unlike surgical or laser treatment, it is non-permanent and easily discontinued if it is ineffective or produces unwanted side effects.

Topical pressure lowering medications was previously known as topical antiglaucoma drugs. However, many glaucomatologist deem the term inappropriate. The medications do not at all reverse the condition or totally halt the progression of glaucoma. In this chapter, the term pressure lowering medications or drugs will be used. The sprouting of new more effective pressure lowering medications has widened the choice of medications and at time cause difficulty in the selection of medication. Table 1.0 provide an overview on commonly available pressure lowering medication in the market currently. A guideline on selection of topical pressure lowering medications will be discussed in this chapter.

Group	Mode of action	Drugs (concentration)	Dose	IOP reduction
Parasympathomimetics	Increased aqueous outflow	Pilocarpine (0.25-4%)	TID or QID	20-25%
Sympathomimetics	<i>Non-selective</i> Decrease aqueous production and increase outflow	Epinephrine (0.25-2.0%)	TID	20-25%
		Dipiverfin (0.1%)	BD	
	<i>Selective</i> Decrease aqueous production	Apraclonidine (0.5-1.0%) Brimonidine (0.2%)	BD or TID BD	
Carbonic anhydrase inhibitor	Decrease aqueous production	Dorzolamide (2%) Brinzolamide (1%)	BD or TID	15-20%
Beta adrenoreceptor antagonist	<i>Non-selective</i> Decrease aqueous production	Timolol (0.1, 0.25, 0.5%) Levobunolol (0.25, 0.5%) Timolol GFS (0.25, 0.5%)	BD Once a day	20-25%
	<i>Selective</i> Decrease aqueous production	Betaxolol (0.25, 0.5%)	BD	15-20%
Prostaglandin analog		Latanoprost (0.005%) Travaprost (0.004%) Unoprostone (0.12, 0.15%)	Once a day	25-30%
		Bimatoprost (0.03%)	Once a day	25-30%

Table 1.0. Commercially available topical pressure lowering drugs

2. Beta antagonists

The potential benefit of systemic β -adrenoreceptor antagonists in lowering IOP was initially evaluated and intravenous propranolol was found to be the most effective (Philips et al,

1967). The profound corneal anaesthesia induced by propanolol, however, outweighs its potential utility. Intensive ophthalmic research eventually led to the introduction of topical timolol. In 1978, topical timolol revolutionized glaucoma management and is now the first-line treatment for glaucoma.

Topical β -blocker acts predominantly by decreasing aqueous humour production without any effect on outflow capacity, despite the presence of ADRB2 in the trabecular meshwork (Coakes and Brubaker, 1978; Yablonski and Zimmerman, 1978; Sonntag et al, 1978). β -Blocker action is predominantly mediated by the ADRB2 receptor, abundantly found in the ciliary epithelium and ciliary body. Aqueous humour is produced by ciliary bodies through ultra-filtration and active secretion by the ciliary epithelium. The reversible β -blocker binding prevents binding of catecholamine that in turn prevents activation of intracellular adenylate cyclase and reduces the intracellular concentration of cAMP at the ciliary body. Through an unknown mechanism, this process reduces aqueous humour production (Neufeld, 1979). The basal level of cAMP is maintained, as is the response to other transmitters. cAMP is an important second messenger in the intracellular cascade. Since the understanding of aqueous humour production is imprecise, the mechanism of action of topical β -blocker remains unknown.

β -blocker has a less potent effect on β 1-adrenoreceptor in decreasing cAMP synthesis (Juzych and Zimmerman, 1997). Serotonin receptor, particularly 5-HT_{1A}, is abundant in the iris and ciliary body and has a similar molecular structure as ADRB2 receptor, but has a negative impact on the adenylyl-cyclase cAMP cascade (Osborne and Chidlow, 1996). Timolol demonstrated high affinity towards 5-HT_{1A} in the ciliary process of rabbits, which further supports the effect of timolol as a suppressor of aqueous humour production (Osborne and Chidlow, 1996).

Although the classic association of reduced cAMP synthesis and aqueous humour production is widely accepted, other evidence disputes this postulation. Schmitt et al (1980) found no association between decreased cAMP and the pressure-lowering effect of β -blockers on rabbits. Drugs that increase intracellular cAMP such as forskolin and cholera toxin also reduce the IOP, which contradicts the previous popular hypothesis (Caprioli et al, 1984). Another hypothesis postulated that the reduction of aqueous humour formation is achieved by direct inhibition of adrenergic stimulation of the secretory ciliary epithelium by endogenous epinephrine (Topper and Brubaker, 1985). Decreased ocular blood flow induced by β -blockers provides another alternative hypothesis. The effect of β -blockers on the vascular smooth muscle of the ciliary body inhibits vasodilatation and induces vasoconstriction of ciliary arterioles, which reduces capillary perfusion and stromal ultra-filtration (Vareilles et al, 1977). Reduction of aqueous humour production is an indirect consequence of decreases ocular blood flow (Watanabe and Chiou, 1983). There is also direct evidence that dopamine plays a role in ocular blood circulation. Haloperidol, a dopamine-blocking agent, reduces IOP.

For more than 3 decades, the topical β -blockers, particularly timolol, have been proven effective ocular hypotensive drugs in many types of glaucoma. Currently, there are five topical beta blockers available worldwide; timolol maleate, betaxolol hydrochloride, levobunolol hydrochloride, carteolol hydrochloride and metipranolol (Table 1.1). Although the aqueous solution of timolol maleate is widely used but recently the gel forming solution has been introduced and well accepted. Gel forming solution is prepared from purified *P.elodea* cell wall that forms gel solution once in contact with monovalent and divalent cations in tear film. This novel ophthalmic vehicle provides similar pressure lowering effect

as the aqueous form with just once a day dosing (Shedden et al, 2001). It is believed to reduce the possible systemic adverse effects but with higher reported incidence of transient blurring of vision (Dickstein et al, 2001; Stewart et al, 1999). Topical beta blockers are inexpensive especially in the generic form that further increased their popularity especially in developing countries. It is still the treatment of choice in many parts of the world.

Property	Timolol	Betaxolol	Levobunolol	Carteolol	Metipranolol
Concentrations (%)	0.25, 0.5	0.25, 0.5	0.25, 0.5	1.0	0.3
Preservatives	BAC# 0.01%	BAC# 0.01%	BAC# 0.004%	BAC# 0.005%	BAC# 0.004%
Beta blocker potency*	4.7	1.0	14.6	10.0	1.8
Serum half life (hrs)	3-5	12-20	6	3-7	2
Cardioselective	-	++	-	-	-
Intrinsic sympathomimetic	-	-	-	++	-
Ocular discomfort	++	+++	++	±	+
Systemic side effect		±	++	+	++
Decrease heart rate	++	±	++	+	++
Respiratory impairment	++	?	?	-	?
Hyperlipidemia	+				
	±	±	?	±	?
Ocular perfusion					

* beta blockade potency as compared to propanolol (propanolol=1)
#BAC: benzylkonium chloride
? No data available or inconclusive data

Table 1.1. Properties of beta blockers

2.1 Topical timolol

Topical timolol is a lipophilic, non-cardio-selective β antagonist without intrinsic sympathomimetic activity. It also lacks the ability to act as partial agonist and lacks membrane-stabilizing ability. Its chemical name is (-)-1-(tert-butylamino)-3-[4-morpholino-1, 2, 5-thiadiazol-3-yl] oxy]-2 propanol maleate (1:1) (salt). The asymmetrical carbon atom in its structure forms a laevo-isomer (Figure 1.3). The optical rotation of timolol maleate is $[\alpha]_{405\text{nm}}^{25^\circ}$ in 1.0N HCl (C - 5%) = -12.2° (-11.7° to - 12.5°) with a molecular weight of 432.50. It is an enantiomer; D- and L-enantiomers are stereo-isomers that are non-super-imposable mirror images of each other.

Timolol maleate is a white crystalline powder soluble in water, methanol, and alcohol, with a pKa of approximately 9 in water at 25°C. It is available as a sterile, isotonic, buffered aqueous solution with pH approximately 7.0 and osmolarity of 274–328 mOsm. There are also inactive ingredients such as monobasic and dibasic sodium phosphate, sodium hydroxide for pH adjustment, and water for injection. Benzalkonium chloride 0.01% is added as a preservative. Timolol maleate as the pure chemical is extremely stable to light and temperature, but the formulated topical form is less stable with a shelf life of 2 years.

Fig. 1.0. Chemical structure and formula of timolol maleate

The ocular hypotensive effect of timolol is more profound when administered orally but significant effect is also achieved topically. Although the ocular hypotensive effect of topical timolol is achieved at a concentration as low as 0.008%, the optimal therapeutic dose is 0.25% and 0.5% twice daily in aqueous solution. The active ingredient in each millilitre of 0.25% of timolol maleate contains 2.5 mg of timolol (3.4 mg of timolol maleate) and each millilitre of 0.5% contains 5 mg of timolol (6.8 mg of timolol maleate). The concentration of timolol in the anterior chamber reaches 1–2 μ M (8–100 ng/mL) after an hour of topical instillation, which is much higher than the minimum amount required to bind ADRB2 in the ciliary body (Philips et al, 1985). Thus, the pressure-lowering effect is achieved just 20 to 30 minutes after instillation with the peak seen 2 hours post instillation (Zimmerman and Kaufman, 1977). This is followed by further pressure reduction that is sustained up to 24 hours. Surprisingly, the half-life of topical timolol is just 1.5 hours (Schmitt et al, 1980).

Reversible binding of timolol to ocular melanin provides a reservoir for slow release of the active drug and is responsible for prolonging the pressure-lowering effect of timolol despite its short half-life. Animal studies have shown that timolol has a high affinity for and binds easily to melanin. Dark-pigmented rabbits demonstrated higher concentration of timolol maleate in the iris ciliary body when compared to albino rabbits, reducing the amount of active ingredient available for pharmacological action (Menon et al, 1989). Melanin near to the site of pharmacological action did not inactivate the active drug. Paradoxically, melanin competitively inhibits timolol. The net effect is that highly pigmented eyes require a higher concentration than less pigmented eyes, which is reflected in clinical observations in Asians and Africans (Ong et al, 2005; Otaleju and Ajayi, 1999; Katz and Berger, 1979).

Zimmerman and Kaufman (1977) reported the first 24-hour dose response to topical timolol 0.25% and 0.5% was similar. Maximum pressure reduction was reported to be nearly 40% in glaucoma patients treated with 0.5% topical timolol in short- and long-term dose-response

studies (Zimmerman and Kaufmann, 1977; Boger et al, 1978; Lin et al, 1979). The pressure-lowering effect is best in daytime and poor at night, when aqueous humour production is reduced to less than half. In its early days, the effectiveness of timolol was compared only to topical pilocarpine and epinephrine, and was found to be significantly more effective with the added advantage of less frequent dosing (Boger et al, 1978; Zimmerman and Boger, 1979). The effectiveness of timolol has earned it status as the 'gold standard' used as the comparator for other new drugs that have flourished the glaucoma pharmaceutical market.

Topical timolol is effective in nearly all types of glaucoma including refractory glaucomas such as neovascular, aphakic, and uveitic glaucoma (Weber, 1981, Lin et al, 1979). Perhaps, due to its suppressive effect on aqueous humour production, it is also effective in angle-closure glaucoma (Lass and Pavan-Langston, 1979; Chew et al, 2004). Long-term treatment with timolol has been proven effective, but the effect is not sustained in more than half of patients after 5 years (Watson et al, 2001). Boger (1979) reported short-term escape and long-term drift phenomena in certain individuals. Upregulation of ADRB2 receptors in the iris and ciliary body is believed to be responsible for blunting the effect of timolol after short-term treatment (Boger, 1979). A meta-analysis comparing a wide range of topical anti-glaucoma drugs and prostaglandin analogue found that timolol is as effective as prostaglandin analogue in providing good IOP reduction at peak and trough (van de Valk et al, 2005). Prostaglandin analogue is slightly but not significantly better than timolol in pressure-lowering effectiveness.

Similar reduction of pressure by timolol was also reported in the contralateral, untreated eye (Dunham et al, 1994; Piltz et al, 2000). Absorption of timolol by the nasopharyngeal mucosa has raised concerns of potentially life-threatening side effects following topical administration (Passo et al, 1984; Diggory and Franks, 1997). The elderly and those with cardio-respiratory impairment are at risk, and prescribing timolol in these patients must be done with caution (Diggory et al, 1998; Diggory et al, 1994; Leier et al, 1986). In spite of great concern regarding the systemic side effect of timolol but there is no evidence suggesting increase in mortality in patients on topical timolol therapy (Müsken et al, 2008). Although timolol has some effects on hypoglycaemia and hyperlipidaemia, the effect is minimal with low clinical importance (Coleman et al, 1990; Shorr et al, 1997). Decreased libido, depression, and hallucination are among the reported side effects of timolol (Lama, 2002). Due to the potential cardiorespiratory side effect, timolol is contraindicated in asthmatic or those with history of asthma, severe chronic obstructive pulmonary diseases, severe heart block, overt cardiac failure, bradycardic patients and those with history of allergic to timolol or its preservatives.

The introduction of gel-forming timolol solution has lessened its systemic effect (Shedden et al, 2001). Timolol gel-forming solution (GFS) increases the viscosity of the drug, promotes ocular bioavailability, and facilitates ocular drug penetration. The prolongation of ocular contact depends on the gel formulation, which acts as a physical barrier to drainage or as a viscosity promoter. The gel in Timolol XE 0.5% promotes viscosity and bleb formation, which creates a temporary plug in the inner canthus and impedes timolol drainage through the punctum. Once-daily dosing of timolol GFS provides a similar pressure-lowering effect as timolol maleate in aqueous form with twice-daily instillation in glaucoma and ocular hypertensive patients (Roselund, 1996; Shedden et al, 2001). Plasma concentrations of timolol GFS are significantly lower than timolol ophthalmic solution, which perhaps explains the reduced systemic side effects associated with the gel solution (Shedden et al, 2001; Dickstein et al, 2001; Uusitalo et al, 2006). Blurred vision upon instillation of timolol in gel solution and ocular discomfort were reported in many patients (Shedden et al, 2001).

Ocular allergic reaction is one of the commonest ocular side effects following topical timolol instillation, which can manifest as blepharoconjunctivitis, erythema and edema of the eyelids (Akingbehin and Sunder Raj, 1990). Allergic reaction can occur at any duration of treatment and as early as the first month. Timolol has similar ability as topical propanolol to induce corneal anaesthesia but at lesser extent (van Buskirk, 1980). Superficial punctate keratitis has been reported and may lead to epitheliopathy and corneal epithelial erosions. Dry eye and reduce break up time has also been documented in patients treated with topical timolol (Kuppens EV et al, 1992; Kuppens EV et al 1995; Fasina O et al, 2008).

2.2 Betaxolol

Betaxolol is a cardioselective beta antagonist with relative specificity for β_1 -adrenoceptor and without intrinsic sympathomimetic activity. Based on available evidences, β_1 -adrenoceptors are thought to be involved in regulating heart rate, rhythm and force (Murphree and Saffitz, 1988). However, the distribution of subtype of β -adrenoceptors is more complex than it is believed to be (Carstairs et al, 1985; Satoh et al, 1990). It is believed that the selectivity of certain drug during pre-clinical experiments may not truly reflective in the actual clinical setting.

Betaxolol is a safer alternative for glaucoma patients with mild respiratory impairment due to asthma or other chronic obstructive pulmonary diseases. However, there are reported cases of pulmonary side effect in patients on betaxolol especially in high risk population (Diggory et al, 1994). Even in healthy volunteers, systemic side effects are still present but with lesser degree as compared to metapronalol and timolol (Bauer et al, 1991). There was still unchanged in respiratory symptoms after changing from timolol to betaxolol (Diggory et al, 1994). Perhaps, this is due to the presence of β_1 adrenoreceptor in human lung tissue with the ratio of 1:3 (β_1 : β_2) (Carstairs et al, 1985). Betaxolol does not confer total protective effect in patients with respiratory impairment and need to prescribe with caution. Perhaps, prostaglandin analogues provide better protective effect for those with respiratory impairment.

Similar to timolol, betaxolol acts as aqueous suppression through unknown mechanism. However, betaxolol is less potent than timolol as pressure lowering medication. Timolol and levobunolol provides approximately 2 mmHg more IOP reduction compared to betaxolol (Allen et al, 1986; Gaul et al, 1989). Smaller amount of β_1 adrenoreceptors in the ocular tissue especially ciliary body as compared to β_2 adrenoceptors is postulated to be the causative factor for lack of effectiveness of betaxolol. Topical instillation of betaxolol 0.5% results in plasma level of approximately 0.5ng/ml or half that of timolol 0.25% (Vuori et al, 1993). Betaxolol is the drug of choice in Early Manifest Glaucoma Trial (EMGT). EMGT reported IOP reduction of 25% from baseline with combination of laser trabeculoplasty and topical betaxolol treatment (Heijl et al, 2002). Treatment has significantly reduced the progression of visual field in patients with early stage of glaucoma.

However, the striking benefit of betaxolol than other topical beta blocker is its potential neuroprotective effect. Neuroprotective effect of betaxolol is believed to be due to its ability to block calcium channels on the vessels and retinal ganglion cells (Yu et al, 1999, Wood et al, 2003). It is postulated that the effect of betaxolol on calcium channels is independent of the β -adrenoceptor (Setoguchi et al, 1995). In addition, betaxolol also inhibits glutamate (Hong et al, 2003; Chen et al, 2007). The effect of betaxolol in optic nerve head vasculature is also believed to improve the perfusion and reperfusion of the optic nerve head (Hester et al, 1994, Cheon et al, 2003). However, the clinical effectiveness of betaxolol as neuroprotective

is rather inconclusive. Although there is evidence suggesting the effectiveness of betaxolol in halting the progression of glaucoma but the association is not strong enough (Messmer et al, 1991; Araie et al, 2003).

2.3 Other beta antagonists

Levobunolol, metipranolol and carteolol are non-selective topical β blockers without significant intrinsic sympathomimetic activity, which require metabolization to their active metabolites to achieve their function. Levobunolol is metabolized to dihydrobunolol that has similar potency as timolol at β_2 adrenoreceptor found in the iris and ciliary body (Wax and Molinoff, 1987). It is available in 0.25% and 0.5%, effective both as once daily dosing as well as twice daily (Wandell et al, 1988). Metipranolol is metabolized to des-acetyl-metipranolol. It is an effective as pressure lowering effect with concentration ranging from 0.1% to 0.6% (Mirza et al, 2000). There is also evidence of increase in retinal perfusion pressure and blood flow in patients treated with metipranolol (Wolfs et al, 1998). Peculiarly, drug induced anterior uveitis has been associated with metipranolol treatment (Watanabe and Hodes, 1997). Similar to levobunolol and metipranolol, carteolol is metabolized to active metabolite, 8-hydroxycarteolol. Unlike other topical β blockers, carteolol possesses intrinsic sympathomimetic activity. Although carteolol is less irritating than 0.5% timolol but moderate corneal anaesthesia has been reported (Bartlett et al, 1999). Carteolol appears to have negligible effect on serum lipid profile (Stewart et al, 1999).

3. Prostaglandin analogues

For 25 years, topical timolol maleate has been widely accepted as the treatment of choice for glaucoma. It is undoubtedly efficacious in almost all types of glaucoma. A lack of intolerable side effects in comparison to topical non-selective sympathomimetics and mitotics further contributed to the popularity of topical timolol. The quest for more potent agents began in the early 1980s. During the frenzy of interest in prostaglandin's possible ocular anti-inflammatory effects and potential therapeutic role, prostaglandin was infused into cannulated experimental animal eyes and was found to cause ocular hypertension with breakdown of the blood-aqueous barrier (Bito et al, 1989a). Accidentally, the ocular hypotensive effect was achieved with a low concentration of topical prostaglandin with breakdown of the blood-aqueous barrier even without cannulation. Naturally occurring prostaglandins are relatively polar, hydrophilic molecules that poorly cross biological membranes due to their carboxylic acid moiety and several hydroxyl groups. Prostaglandin effects differ between species (Bito et al, 1989b). Different prostanoids have different side effects on the human eye, consistent with the reported multiplicity and low selectivity of naturally occurring prostaglandin for different subtypes of prostanoids (Woodward et al, 1997).

There was a major setback in the first experiment with topical prostaglandin in human volunteers using a high concentration (200 μ g) tromethamine salt form of $\text{PGF}_{2\alpha}$, which resulted in severe ocular hyperaemia, ocular pain, and headache (Giuffre, 1985). Lower concentrations (up to 100-fold) were found to potentiate better ocular hypotensive effects with esterification of the prostaglandin carboxylic acid group, which is the basis of the pro-drug principle (Kerstetter et al, 1988). Esterification of the carboxylic acid reduces polarity and facilitates penetration of the prodrug through biological lipid membranes. The prodrug is then converted to free acids to activate the specific FP receptors once it crosses the corneal

epithelium in the specific direction known as orthorectified transport or the slow release system, which is ideal for chronic therapy in glaucoma and minimizes unwanted ocular and systemic side effects (Figure 1.2).

Fig. 1.2. Chemical structure of major topical prostaglandin analogue pro-drugs and their hydrolyzed free acids.

After more than 2 decades in search of a topical prostaglandin with an acceptable therapeutic index, Unoprostone (13, 14-dihydro-15-keto metabolite of PGF_{2α}) with the trade name of Rescula (Ciba Vision, Duluth GA) was made commercially available in Japan. The drug failed to gain popularity worldwide due to lack of efficacy and the requirement for twice-daily administration. In 1996, latanoprost (13, 14-dihydro-17-phenyl-18, 19, 20-trinor-PGF_{2α}-isopropyl ester) was marketed as Xalatan (Pfizer Inc, New York) and gained approval worldwide. Later, travoprost (Travatan; Alcon) and bimatoprost (Lumigan; Allergan) were introduced. Unlike latanoprost and travoprost, bimatoprost has been controversially known as prostamide owing to the presence of a C1 ethyl amide group that activates different receptors. However, topical prostaglandin analogues are believed to achieve pressure-lowering effects by increasing uveoscleral outflow without any effect on aqueous humour production (Toris et al, 1993). However, their effect on the trabecular meshwork remains unclear (Oh et al, 2006; Johnson et al, 2010). There was no statistically significant difference in efficacy between the 3 commercially available topical prostaglandin analogues but there was a reported borderline increased incidence of ocular hyperaemia with bimatoprost (van

de Valk et al, 2005; Zimmerman et al, 2009). Bimatoprost has the edge in effectiveness but with slightly more pronounced side effects (Cracknell and Grierson, 2009).

Topical prostaglandin analogues have changed the paradigm of glaucoma management, most notably with the declining rate of glaucoma surgeries in the late 1990s (Bateman et al, 2002). Currently, due to their efficacy and better tolerability, topical prostaglandin analogues are replacing topical timolol as the first-line drug of choice in glaucoma management (Holmstrom et al, 2006). It is amazing that low lipid solubility drugs in low concentrations can achieve such an impact in glaucoma management.

3.1 Topical latanoprost 0.005%

Topical prostaglandin analogue PhXA34 (13, 14-dihydro-17-phenyl-18, 19, 20-trinor-PGF_{2α}-isopropyl ester) known as latanoprost, differs from the naturally occurring PGF_{2α}, where C18 to C20 have been substituted by a benzene ring, the double bond between C13 and C14 has been saturated, and the carboxylic acid moiety on C1 has been esterified with isopropanol (Figure 1.7). The molecular weight of latanoprost is 432.6 and the hydrolysed compound (free acid) is 390.5 (Stjernschantz and Alm, 1996). The octanol-water partition coefficient is 4.3 at pH 7.4, with poor solubility in water. It is available as a colourless to slightly yellow oil solution in 0.005% concentration (50 µg/ mL) preserved with 0.02% benzalkonium chloride. It is commercially available in 5 mL plastic bottles (2.5 mL latanoprost solution), which requires refrigeration to maintain a temperature of 2 to 8°C for unopened bottles. The recommendation for refrigeration was made based on experimental finding in the laboratory. There was 10% degradation after extreme exposure to 50°C for 198 hours (Morgan et al, 2001). In clinical practice, it is safe to transport and store at room temperature without reducing the effectiveness of the drug (Novak and Evans, 2001; Varma et al, 2006). Latanoprost can be prescribed as either evening or morning once-daily dosing but evening dosing is more efficacious (Alm and Stjernschantz, 1995).

Latanoprost is a selective FP receptor agonist with marginal spillover effect on other prostanoid receptors, resulting in fewer unwanted side effects. Naturally occurring PGF_{2α} has greater affinity than latanoprost for the FP receptor but also interacts with other prostaglandin receptors, which is partly responsible for side effects such as iritis and conjunctival hyperaemia (Alm and Stjernschantz, 1997). As a prodrug, it is relatively inactive until the hydrolyzation of the isopropyl ester to free acid in the cornea and plasma. Latanoprost in free acid form is measurable in the aqueous humour within 4 hours of instillation. Approximately 1% of topically applied latanoprost is absorbed into the eye, the majority being absorbed into the systemic circulation through either conjunctiva vessels and nasal mucosa or gastrointestinal tract absorption. The peak concentration is reached about 2 hours after topical instillation with the distribution volume of 0.16 ± 0.02 L/kg in humans (Sjöquist and Stjernschantz, 2002). The half-life of free acid in human plasma is about 17 minutes. Plasma levels of latanoprost acid were below the detection limit in patients treated with latanoprost for a year. Latanoprost is metabolized by β -oxidation in the liver; it is not metabolized in the cornea and is mainly excreted in the urine (88–98%).

Although the exact mechanism of action of latanoprost is still uncertain, FP receptor plays essential role and FP receptor-deficient mice do not exhibit any pressure-lowering effect (Ota et al, 2005; Crowston et al, 2004). Aqueous humour production is not significantly affected by latanoprost but the most consistent finding is a substantial increase in uveoscleral (pressure-insensitive) outflow; a less consistent finding is the role in trabecular (pressure-sensitive) outflow capacity (Toris et al, 2008; Lim et al, 2008; Johnson et al, 2010).

There are 3 potential mechanisms by which latanoprost could increase uveoscleral drainage. These include: (1) Remodelling of extracellular matrix of the ciliary muscle and sclera causing permeability changes, (2) widening of the connective tissue-filled spaces among the ciliary muscle bundles, which may be caused by relaxation of the ciliary muscle and (3) changes in the shape of ciliary muscle cells as a result of altered actin and vinculin localization (Toris et al, 2008; Lindsey et al, 1997). The remodelling of extracellular matrix is believed to be responsible for sustaining the long-term pressure-lowering effect (Johnson et al, 2010).

Ciliary muscle relaxation is believed to be responsible for the initial reduction of IOP but the effect is not prominent in latanoprost. Remodelling of the extracellular matrix within the ciliary muscle and sclera is the most thoroughly understood and most accepted mechanism. Latanoprost stimulates induction of Matrix Metallo-proteinases (MMP) 1, 2, and 3 that cause dissolution of collagen types I and III within the connective tissue-filled spaces between the outer longitudinal muscles (Lütjen-Drecoll and Tamm, 1988). Animal experimental studies showed evidence of changes in ciliary muscle; the tissue spaces of the ciliary muscle were enlarged and organized into tube-like spaces covered by endothelial-like cells with close basement membrane contact, and contained myelinated nerve fibre bundles that resembled a lymphatic system in the choroid (Krebs and Krebs, 1988; Richter et al, 2003).

Latanoprost induced MMP 3, 9, 17, and TIMP 3, and down-regulated MMP 1, 2, 12, 14, 15, 16, and TIMP 4. Latanoprost acid induced concentration-dependent increases in MMP 1, 3, and 9 gene transcriptions and a concentration- and time-dependent increase in TIMP 1 but not TIMP 2 mRNA and protein (Anthony et al, 2002). Cyclooxygenase (COX)-2 is also believed to play a role in the pressure-lowering effect of latanoprost (Sales et al, 2008). The mechanism of latanoprost-induced MMP secretion is through protein kinase C and extracellular signal-regulated protein kinase 1/2-dependent pathways (Chen et al, 2001). Mitogen-activated protein kinase and tumour necrosis factor α -dependent signalling pathways may also be involved (Sardar et al, 2000). The vasodilatation effect of latanoprost, although minimal, is also postulated to play a role in facilitating uveoscleral outflow. Although increases aqueous outflow through non-conventional pathways seems to be responsible for the pressure-lowering effect of latanoprost, there are ongoing studies providing evidence of the possible role of trabecular meshwork outflow (Oh et al, 2006).

In spite of uncertainty in the mechanism of latanoprost action, latanoprost is a clinically proven efficacious topical anti-glaucoma drug. Its effectiveness has been observed in many populations. Hedman and Larsson (2002), based on mean diurnal IOP reduction, found that latanoprost is more effective than timolol in 8 different populations with greater reduction among Mexican and Asian populations. A meta-analysis involving 1256 glaucoma patients found that latanoprost is superior to timolol in long-term IOP control (Zhang et al, 2001). Latanoprost has the advantage of achieving IOP reduction during both day and night while timolol has a minimal effect on nocturnal IOP (Larsson et al, 2002). In a long-term study, latanoprost sustained meaningful IOP reduction (Hedman et al, 2002). Latanoprost is not only effective in OAG but also in angle-closure glaucoma (Chew et al, 2004). In spite of its higher therapeutic index, there was a reported 18–25% non-responder rate (Scherer, 2002; Cheong et al, 2008; Camras and Hedmann, 2003). The definition of a responder varies according the predetermined cut-off point. Based on the US latanoprost study group, a greater proportion of patients classified as non-responders on any particular visit were responders on all other visits if treated with latanoprost rather than timolol (Camras and Hedmann, 2003). Among PG analogues, bimatoprost seems to be slightly superior in

reducing pressure but not without a price (van der Valk et al, 2005). Bimatoprost has a higher incidence of conjunctival hyperaemia.

Although $\text{PGF}_{2\alpha}$ is responsible for stimulating bronchial hyper-responsiveness, respiratory impairment induced by latanoprost has not been reported (Hedner et al, 1997). Short half-life and rapid clearance of the active latanoprost acid minimizes unwanted systemic side effects (Sjöquist and Stjernschantz, 2002). Furthermore, latanoprost free acids that enter the systemic circulation do not permeate tight-junction cell membrane barriers such as the blood-brain barrier, minimizing the potential for central nervous system side effects. However, some nonspecific systemic side effects such as headache, flulike syndromes, upper respiratory tract infections, and musculoskeletal pain have been reported (Alm et al, 1995).

Latanoprost-induced ocular side effects are a major concern. Conjunctival hyperaemia is a common side effect with the incidence range between 5 to 15% (Stewart et al, 2003; Walters et al, 2004). The incidence is much higher in travoprost and bimatoprost (Honrubia et al, 2009; Walters et al, 2004). Conjunctival hyperaemia is generally mild and transient, and commonly develops within 1 month of therapy initiation. Vasodilation induced by prostaglandin promotes the release of nitric oxide that may be responsible for conjunctival hyperaemia (Alm et al, 2008). The saturated double bond in C13 and C14 of latanoprost is partly responsible (Resul and Stjernschantz, 1993). Ocular irritation, burning sensation, and dry eye are also reported (Stewart et al, 2003). However, the most intriguing side effect is the ability of latanoprost to induce pigmentation in the iris, eyelid, and eyelashes. Latanoprost-induced iris darkening (LIID) was found in higher frequency in heterogeneous hazel irises and homogeneous gray and blue irises are less likely to develop LIID in Caucasians (Alm et al, 2008). Japanese and South East Asians, in spite of having homogeneous dark brown irises, were more likely to develop LIID (Chiba et al, 2004; Chou et al, 2005). During phase III of a latanoprost study, latanoprost was postulated to have the ability to promote iris melanocyte proliferation (Stjernschantz et al, 2002). However, there was no evidence of increases melanogenesis in tissue culture studies (Kashiwagi et al, 2002; Drago et al, 1999). Histopathological and morphometric studies found evidence of increased iris melanocytes in the stroma and redistribution of the melanocytes to the anterior iris stroma without a net increase in number (Cracknell and Gierson, 2009; Cracknell et al, 2003; Albert et al, 2008).

LIID is irreversible and causes cosmetic concerns, especially when it occurs in one eye, but has no incapacitating visual side effects. Hyperpigmentation, elongation, and thickening of the eyelashes (hypertrichosis) may cause the lashes to touch the spectacles or cause difficulty in topical drug instillation but is never a major concern (Johnstone, 1997; Shaikh and Bodla, 2006). Unlike LIID, hypertrichosis is reversible and disappears several weeks after discontinuation of treatment. Peri-ocular hyperpigmentation is also reported and is most likely due to accidental spillover during drug administration (Herndon et al, 2003). Similar to hypertrichosis, the reversal of ocular hyperpigmentation was also reported even without discontinuation of treatment (Sharpe et al, 2007). There were also reported cases of hypo-pigmentation (Herndon et al, 2003).

Disruption of the blood-aqueous barrier and posterior lens releases inflammatory mediators causes cystoids macular oedema (CME) following latanoprost treatment (Miyake et al, 1999). Latanoprost-induced CME may cause visual impairment but the incidence is uncommon in comparison to the frequency of pigmentation-induced side effects (Warwar et al, 1998). Prostaglandin at higher concentrations acts as an inflammatory mediator and anterior uveitis was reported following latanoprost treatment (Warwar et al, 1998).

Reactivation of herpes simplex keratitis has been reported in 3 patients with a history of herpes simplex infection (Wand et al, 1999). In patients with a high risk of CME, anterior uveitis, and past history of herpes simplex, latanoprost is not recommended for glaucoma treatment.

3.2 Topical Travaprost

Travoprost (AL-6221) is an isopropyl ester of the (+) enantiomer of fluprostenol and chemically known as isopropyl (z)-7-[1R, 2R, 3R, 5S]-3, 5-dihydroxy-2-[(1E, 3R)-3hydroxy-4-[(α , α , α -tri fluoro-m-tolyl) oxy]-1-butenyl) cyclopentyl]-5-heptenoate. Similar to latanoprost, travaprost is a prodrug that acts on FP receptor (Hellberg et al, 2001). It is believed through unknown mechanism, travaprost increase outflow through mainly unconventional pathway with some effect on conventional pathway (Torriss et al, 2008). Unlike latanoprost, travaprost provides prolong pressure lowering effect up to 40 hours post single instillation (Fellman et al, 2002).

Travoprost is reported to provide up to 28% pressure reduction from baseline, which is almost similar to latanoprost and significantly superior to timolol (Netland et al, 2001). However, travaprost provides lesser additional IOP reduction than bimatoprost in patients previously treated with latanoprost (Kammer et al, 2010). Similar to latanoprost, travaprost is efficacious in various type of glaucoma as monotherapy, adjunctive, replacement therapy and in fixed combination (Cheselita D, 2007; Orengo et al, 2001).

A retrospective metanalysis study found that travoprost is superior to both latanoprost and timolol in African derived patients (Netland et al, 2003). Halpern et al (2002) found that travoprost not only more efficacious to timolol and latanoprost but also less likely to cause visual field progression in African derived patients. A prospective randomized study was conducted to study the potential of racial influence on efficacy of prostaglandin analogs, found no significant different between races and different type prostaglandin analogs (Birt et al, 2010). However, this study was hampered by small sample size.

Conjunctival hyperaemia is the most common ocular side effect. The incidence and intensity was reported to be higher and more severe than in patients treated with latanoprost (Parmaksiz et al, 2006; Li N et al 2006). Prostaglandin induced iridial pigmentation (PIIP) is another common ocular side effect. Travaprost is a safe drug with no reported systemic side effect.

3.3 Topical Bimatoprost

Unlike latanoprost and travaprost, bimatoprost has ethyl amide group in the carbon-1 position (Cantor, 2001). Chemical structure of bimatoprost is pharmacologically similar to prostaglandin $F_{2\alpha}$ ethanolamide, better known as prostamides. Prostamides are biosynthesized from endocannabinoid anandamide by enzyme cyclo-oxygenase 2 (COX-2). Bimatoprost is a synthetic endogenous prostamides (Woodward et al, 2001). Bimatoprost acts on prostamide-sensitive receptor with minimal or no effect on prostaglandin F receptors. Bimatoprost as prostamide mimetic is fatty acid amide, which differs from fatty acid of prostaglandin (Woodward et al, 2003). Another striking difference from latanoprost and travaprost, it is not a prodrug (Woodward et al, 2001). There is no evidence of measurable free acid detected at the site of action in the eye. Therefore, hydrolysis is not required for bimatoprost to exert its pharmacological action. Latanoprost and travaprost require hydrolysis to free acid to act on FP receptor as agonist.

Bimatoprost produces more pronounced and prolonged pressure lowering effect. It is effective as monotherapy, adjunctive therapy, and replacement therapy and also as fixed combination with timolol. It was found to provide 35% pressure reduction in primary angle closure patients with 360° of posterior synechiae post ineffective laser peripheral iridotomy (Vyas et al, 2011). It is believed that bimatoprost acts on pressure sensitive and pressure insensitive outflow pathway (Brubaker et al, 2001). Latanoprost has minimal effect on pressure sensitive pathway; trabecular meshwork. Long term treatment of bimatoprost in animal experimental study has shown remodelling in uveoscleral as well as trabecular meshwork pathway. Similar to other prostaglandin analogs, bimatoprost produced significant better IOP reduction compared to timolol. In comparing between prostaglandin analogs, bimatoprost was found slightly superior to travaprost and latanoprost in pressure lowering medications. In addition, bimatoprost provides more constant IOP reduction and less fluctuation as compared to latanoprost and Timolol XE (Walters et al, 2004; Konstas et al, 2005). Fluctuation of IOP may cause further detrimental effect especially in already compromised optic nerve head.

Bimatoprost has the edge for pressure lowering effect but reported higher incidence of conjunctival hyperaemia. The incidence of conjunctival hyperaemia was reported in 15-45% in patients treated with bimatoprost as monotherapy (Feldman, 2003). The most recent meta-analysis of 13 randomized control trials in 2222 glaucoma patients found significant higher incidence of conjunctival hyperaemia with bimatoprost compared to latanoprost (Honrubia et al, 2009). However, there is evidence to suggest that conjunctival hyperaemia decreases with time (Arcieri et al, 2005). Other ocular side effects such as prostaglandin induced iridial pigmentation (PIIP), uveitis and cystoids macular edema are almost similar with other topical prostaglandin analogs.

4. Carbonic anhydrase inhibitors

Carbonic anhydrase inhibitor (CAI) was discovered by Becker in 1954 after several breakthrough findings. Bicarbonate was found to be an essential component of aqueous humour production and carbonic anhydrase enzyme was found in rabbit ciliary processes. Acetazolamide, a CAI, has gained popularity as an effective systemic anti-glaucoma medication when given orally or parenterally. Discontinuation of CAI is typically prompted by the occurrence of side effects such as general malaise, fatigue, depression, loss of appetite, weight loss, paraesthesia, and gastrointestinal disturbance. Intolerability to systemic CAI has been reported in 30% to 80% of patients, and is not ideal for long-term administration. In addition, devastating systemic side effects such as metabolic acidosis, hypokalaemia, and blood dyscrasia limit its usefulness. Haematological reactions such as agranulocytosis, aplastic anaemia, thrombocytopenia and neutropenia have also been reported (Fraunfelder et al, 1985). However, 40 years passed before the introduction of topical CAIs dorzolamide and brinzolamide, which have fewer unwanted extra-ocular side effects. The delay was due to failure to achieve 100% inhibition of carbonic anhydrase-II (CA-II), which is associated with poor ocular penetration. CA-II is an isoenzyme that plays an important role in the production of aqueous humour. The addition of an alkylamino side group improved the ocular penetration of topical CAI.

Topical dorzolamide 2% or brinzolamide 1% monotherapy administered 2 or 3 times daily provides pressure reduction ranging from 21.8% to 26.2% (Lippa et al, 1991; Lippa et al, 1992). Three applications per day provide better overall ocular hypotensive effect (Lippa et al, 1992). The combination of topical dorzolamide and oral acetazolamide failed to

demonstrate an additive effect (Rosenberg et al, 1998); therefore, combination therapy is not recommended as it may increase the risk of unwanted systemic side effects. Topical dorzolamide also provided further IOP reduction as adjunctive therapy with topical timolol, especially in gel solution (Adamsons et al, 1998a). The adjunctive effect of dorzolamide with topical timolol was similar to that of topical pilocarpine (4 times daily) but with better tolerability and compliance (Sthralman et al, 1996; Adamsons et al, 1998b). A fixed combination of 2% dorzolamide and 0.5% timolol, and 1% brinzolamide and 0.5% timolol was recently introduced; it is more efficacious than individual drug therapy and promotes better compliance (Boyle et al, 1998; Clineschmidt et al, 1998). Stinging, burning, or foreign body sensation and blurred vision are the most common ocular side effects. Others include superficial punctate keratitis, lid or conjunctival allergies, corneal oedema, and headache. Due to the effect of topical CAI on endothelium pump function, corneal edema has been reported especially in patient with underlying cornea problem such as guttata (Mathias et al, 2007). In fact, irreversible corneal decompensation following topical dorzolamide therapy has also been reported (Konowal et al, 1999). Systemic side effects similar to those associated with oral CAI have not been reported with dorzolamide, although bitter taste is reported.

5. Topical adrenergic agonists

Topical adrenergic agonists were introduced in the early 1920s when Hamburger (1923) applied topical epinephrine to patients with increased IOP. Epinephrine is a direct acting sympathomimetic amine with a combination of α - and β -adrenoreceptor-stimulating activities. The exact mechanism of the pressure-lowering effect of epinephrine is not fully understood. Based on evidence from fluorophotometry, tonography, and tonometry, epinephrine is believed to increase both conventional and unconventional outflow but certain observers found that uveoscleral outflow exceeded trabecular outflow (Weekers et al, 1955; Townsend and Brubaker, 1980; Schenker et al, 1981). Epinephrine may also stimulate aqueous humour production (Nagataki and Brubaker, 1981). β -receptor stimulation is believed to occur through a cyclic AMP (cAMP)-dependent mechanism, as demonstrated in animal studies and an *in vitro* human eye outflow pathway perfusion model (Neufeld et al, 1979, Boas et al, 1981). Unlike pilocarpine, epinephrine induced slight mydriasis, conjunctival decongestion, and pressure reduction in glaucoma and ocular hypertensive patients. The effect of vasoconstriction and mydriasis is temporary; lasting only 2 to 12 hours, but the IOP reduction lasts longer. The effect on IOP is biphasic with transient IOP elevation followed by a hypotensive period.

Epinephrine is no longer in use in many centres due to its low therapeutic index and its devastating ocular and systemic side effects. It was used as an additive or adjunctive drug at 0.25% to 2% concentrations. Deposition of the epinephrine in ocular tissue including choroids, retina, and optic nerve, especially in aphakic patients is common (Kramer, 1980). In fact, it may also deposit in the heart and spleen following topical instillation, especially without punctual occlusion, and is almost comparable to parenteral administration. Prolonged use may result in localised pigment deposition (believed to contain epinephrine oxidation products such as adrenochrome) particularly in the palpebral conjunctiva and occasionally in the lid margin and cornea (Fong et al, 1993). Epinephrine maculopathy characterised by macular oedema, vascular spasm, and small cysts or fine haemorrhages may occur in aphakic patients (Michels and Maumenee, 1975). Fortunately, it is reversible upon treatment withdrawal but may cause alarming visual symptoms in affected patients. It

is also not recommended for glaucoma patients wearing soft contact lenses due to deposition of adrenochrome during treatment initiation. Systemic sympathomimetic effects such as palpitation, tachycardia, premature ventricular contractions, severe headache, and even hypertensive crisis may also occur (Ballin et al, 1966). In order to promote tolerability and reduce side effects, an epinephrine analogue was introduced as dipivefrin. Dipivefrin was the first pro-drug commercially available in ophthalmic practice (Mandell and Podos, 1977). The lower concentration 0.1% of Dipivefrin is sufficient to achieve similar ocular hypotensive effects as 2% epinephrine with fewer ocular and systemic side effects.

Selective α_2 -adrenoreceptor agonists are replacing topical epinephrine; Apraclonidine and brimonidine have higher therapeutic indexes and fewer unwanted side effect. Apraclonidine, a relatively selective α_2 -adrenoreceptor agonist, is chemically related to clonidine. Therefore, it reduces IOP and has a systemic hypotensive effect. Apraclonidine reduces IOP by suppressing aqueous humour production and enhancing uveoscleral outflow (Gharagozloo et al, 1988). It has a minimal effect on ocular blood flow because of its limited activity at the α_1 receptor. It is commercially available in 0.5% and 1.0% concentrations. Although 1.0% apraclonidine produces slightly better IOP reduction (up to 31%) than the 0.5% solution (26%), the difference is statistically insignificant (Abrams et al, 1989). However, most patients responded with at least 20% IOP reduction from baseline, making it an excellent additive medication (Toris et al, 1995; Araujo et al, 1995; Gross et al, 1997). In fact, apraclonidine 0.5% 3 times a day for 90 days provides additional IOP reduction in glaucoma patients treated with concomitant timolol (Stewart et al, 1996). Through its ability to protect the blood-aqueous humour barrier, apraclonidine 1.0% is used to prevent a spike in IOP after cataract surgery or anterior segment laser surgery and as prophylaxis for post-cycloplegic IOP and for short-term IOP control prior to filtration surgery (Robin, 1989; Mori and Araie, 1992; Araie and Kiyoshi, 1993). Apraclonidine is not affected by the amount of ocular melanin. However, the effectiveness of apraclonidine is short-lived. The occurrence of tachyphylaxis and ocular allergy reduce its attractiveness for long-term treatment (Butler et al, 1995; Araoujo et al, 1995).

As a relatively selective α -adrenoreceptor agonist, apraclonidine also stimulates the α_1 receptor. Stimulation of the α_1 -adrenoreceptor is responsible for conjunctival hyperaemia, eyelid retraction, and a mild mydriatic effect (less than 1 mm). Ocular allergy is rare in short-term treatment but poses a major concern that warrants discontinuation in long-term therapy. Apraclonidine is also associated with dry mouth and dry nose, which limits its systemic absorption and reduces systemic side effect. The activity of brimonidine tartrate is similar to that of apraclonidine. Animal studies have shown that brimonidine may possess neuroprotective properties. However, unlike apraclonidine, brimonidine tartrate is a highly selective α_2 -adrenoreceptor agonist with 30 times more selectivity than apraclonidine and reduced risk of ocular allergy. In fact, there is no evidence of cross-reactivity in patients allergic to apraclonidine who were switched to brimonidine (William et al, 2000; Shin DH et al, 1999). Thus, prescribing brimonidine in patients allergic to apraclonidine is safe and effective (Shin DH et al, 1999). Brimonidine also binds to ocular melanin, which acts as drug reservoir, providing a slow-release effect. The pressure-lowering effect of brimonidine was almost equal to topical timolol in a short-term study.

6. Pilocarpine

Topical pilocarpine was the first topical pressure-lowering drug used in clinical practice. Pilocarpine, a direct-acting cholinergic agonist or parasympathomimetic, was introduced in

1876. An alkaloid derivative of natural plants, pilocarpine acts directly at neuro-effector junctions of the iris sphincter muscle and ciliary body causing pupillary constriction (miosis), spasm of accommodation, and reduction of IOP (Taylor, 1990). Although the precise mechanism of the pilocarpine effect has not been established, the most widely accepted explanation is that direct stimulation of the longitudinal muscle of the ciliary body causes widening of the trabecular spaces, facilitating aqueous humour outflow (Erikson and Schroeder, 2000). It is available in ophthalmic solution 0.5% to 10% and prescribed for application 4 times daily. There is an increasing hypotensive effect with increasing concentrations up to 4% in long-term therapy. Concentrations exceeding 4% provide minimal additional benefit. Due to its effect on ocular melanin, higher concentrations of pilocarpine are needed in darkly pigmented patients to achieve the same effect as in those with lighter-coloured irises (Harris and Galin, 1971). A sustained-release, membrane-bound drug delivery system (Ocusert) is available, which delivers pilocarpine at a controlled rate of 20–40 µg/hour. A 4% ophthalmic gel is also available.

IOP reduction up to 15% from baseline was observed in many types of glaucoma including POAG, PAC, PACG, and secondary glaucoma. The ability of pilocarpine to reduce or break the iridotrabecular contact in acute attacks of PAC is believed to be due to its miotic action. Its effectiveness in facilitating outflow has helped to sustain pilocarpine as a viable medication in glaucoma therapy. However, if the IOP exceeds 60 mmHg, pilocarpine has a limited effect on the iris sphincter, presumably because of ischaemia. It is widely used to stretch the iris in preparation for laser iridotomy and iridoplasty. Pilocarpine provides further IOP reduction in combination with topical beta blockers, CAI, adrenergic agonist and latanoprost (Airaksinen et al, 1987; Friston and Nielson, 1993).

The diminishing popularity of pilocarpine is partly due to the frequency of dosage required to achieve optimal results and to ocular side effects. The most troublesome ocular side effect is accommodative spasm, which may last for 2 to 3 hours and is frequently intolerable, especially in individuals less than 40 years old (Zimmerman, 1981). However, due to the aging process, a lesser effect on ciliary muscle contractility is seen in older patients. The miotic effect of pilocarpine can cause visual incapacitation and is unwelcome in patients with nuclear sclerotic and posterior sub-capsular cataract. Furthermore, long-term use of pilocarpine may hasten cataract development (Zimmerman and Wheeler, 1982). Paradoxically, although pilocarpine is used to break the iridotrabecular contact in PAC cases, there are reported cases of pupillary block induced by pilocarpine, which usually occurs in patients with narrow angles who have advancing cataract (Van Burskirk, 1982; Ritch, 1996). Other side effects include retinal detachment, allergic blepharoconjunctivitis, band keratopathy, iris cyst, and lid myokymia. Adverse systemic reactions to Ocusert are rare but may occur in patients with acute PAC or inadvertent drug leakage (Kushnick et al, 1996). Headache, nausea, vomiting, diaphoresis, and weakness are possible systemic side effects and can be easily confused with symptoms of acute PAC (Zimmerman and Wheeler, 1982). Other systemic side effects include increased salivation and lacrimation, diarrhoea, bronchiolar spasm, pulmonary oedema, systemic hypotension, and bradycardia (Zimmerman and Wheeler, 1982).

7. Fixed combination

Pressure lowering drugs therapy requires patient's compliance to ensure the maximum effectiveness of the drugs especially in long term administration and even more challenging

in asymptomatic disease at the early stage glaucoma. The term of compliance is deemed inappropriate. Instead, adherence and persistence provide better description of patient's behaviour toward medication instillation. Adherence is a measure of the degree of patient obeying pharmacotherapy instruction over a defined period of time (Schwartz and Quigley, 2008). For example, if topical timolol is prescribed twice a day for a month but the patient only instilled 40 times, his/her adherence is 66%. Persistence is a measure of time to discontinuation. Accurate assessment of adherence and persistence is quite a challenge especially when most patients routinely overestimate their adherence (Friedman et al, 2008; Friedman et al, 2007). Poor adherence and persistence is associated with cost of the drug, tolerability, difficulty in instillation, lack of education, forgetfulness, denial, schedule and travel issues (Tsai et al, 2003; Friedman et al, 2008). 'White coat adherence' is another issue, in which patients are at their best adherence during 5 days prior to the follow up appointment; follow by a declining pattern until near to the next follow up (Feinstein, 1990). Frequency of dosing and complexity of the regimen also play important role. Poorer adherence is observed in those receiving adjunctive treatment (Nordstrom et al, 2005).

Patients' understanding of the importance of taking medication, their satisfaction with the drug, tolerability and cost is reflected by persistency. Persistence is not doing any better, ranging from 20% to 67% (Dasgupta et al, 2002; Spooner, 2002) and differs according to the class of pressure lowering drugs. Latanoprost, a prostaglandin analog has demonstrated better persistency compared to other drugs (Reardon et al, 2004; Schwartz et al, 2004). Thus, recently there is a sprouting of fixed combination pressure lowering treatment such as prostaglandin-beta blocker, carbonic anhydrase inhibitor-beta blocker and pilocarpine-beta blocker, which aim to improve adherence and persistence.

Fixed combination therapy is based on the concept that different group of drugs act on different site of receptors or enzymes. It is postulated to provide additional pressure reduction of at least 15% from non-fixed combination. However, the pressure reduction with fixed combination is usually less than the sum of both drugs (Philip and Luc, 2000). The earliest fixed combination introduced in glaucoma management was beta-blockers and pilocarpine; 0.5% timolol and 2% pilocarpine, 0.5% timolol and 4% pilocarpine, and 0.1% metipranolol and 2% pilocarpine (Table 1.3). Pressure lowering effect of these fixed combination were found to be similar to the non-fixed combination or concomitant therapy (Maclure et al, 1989). The most important success in fixed combination of beta blockers and pilocarpine is convenience and reduction of instillation frequency of pilocarpine (Puustjärvi and Repo, 1992).

Topical beta-blockers have been the most reliable pressure lowering drug for many decades. Currently, beta blockers not only used as the gold standard for comparative studies with other medications but also the most popular for fixed combination therapy. The success of fixed combination of beta blockers and pilocarpine has later inspired the drug manufacturers to produce other fixed combination (table 1.3). Fixed combination therapy provides additional option for ophthalmologists but the actual impact in clinical practice is not well established.

Comparison of the fixed combination therapy with monotherapy of individual drug has shown promising result. Fixed combination of 0.5% timolol and 2% dorzolamide provides an additional 13 to 20% pressure reduction at peak and 5 to 14% at trough compared to timolol monotherapy (Strohmaier et al, 1998; Boyle et al, 1998). Fixed combination of 0.5% timolol and 0.2% brimonidine has also shown significantly better pressure lowering effect of

4.4 to 7.6 mmHg as compared to brimonidine and timolol individually. Most important advantage of fixed combination timolol-brimonidine is lesser side effect compared to brimonidine monotherapy but increase compared to timolol monotherapy (Mark et al, 2006).

Brand name	Constitutents	Preservatives
Timpilo-2®	0.5% Timolol maleate + 2%Pilocarpine hydrochloride	BAK
Timpilo-4®	0.5% Timolol maleate + 4%Pilocarpine hydrochloride	BAK
Normoglaucan®	0.1% Metipronalol + 2% Pilocarpine hydrochloride	BAK
Cosopt®	0.5% Timolol maleate + 2% Dorzolamide hydrochloride	BAK
Azarga®	0.5% Timolol maleate + 1% Brinzolamide	BAK
Combigan®	0.5% Timolol maleate + 0.2% Brimonidine tartrate	BAK
Duo Trav®	0.5% Timolol maleate + 0.004% Travaprost	BAK
Ganfort®	0.5% Timolol maleate + 0.03% Bimatoprost	BAK
Xalacom®	0.5% Timolol maleate + 0.005% Latanoprost	BAK

BAK: benzalkonium chloride

Table 1.3: Fixed combination of pressure lowering drugs

It is seem unfair to compare the fixed combination therapy with monotherapy treatment. Fixed combination is basically mixing the two drugs together, how the individual constituent of the drugs is adjusted or mixed is not known. The possibility of drug-drug interaction and drug-preservative interaction is not well established. Majority of clinical data available are on the comparison between fixed combination and concomitant therapy (Khoury et al, 2007). The efficacy of fixed combination and concomitant therapy is controversial. There are evidences that suggest the superiority of fixed combination (Diestelhorst and Larsson, 2004; Schuman et al, 2005). On the other hand, there are adequate evidences to suggest otherwise (Strohmaier et al, 1998; Diestelhorst and Larsson, 2006; Hughes et al, 2005). However, there are many factors such time of IOP measurement, time of instillation, diurnal variation and the possibility of wash out period that are not taken into consideration and lead to over or underestimation (Khoury et al, 2007).

A systematic review involving seven randomized controlled trials on various fixed combination with 0.5% timolol; travaprost, latanoprost, dorzolamide and brimonidine found that the concomitant treatment with individual drug has the edge in efficacy. However, the difference failed to exert pre-determined non-inferiority measure of $\leq 1.5\text{mmHg}$ upper confidence limit (Cox et al, 2008). Similar outcome is also noted in another systematic review and metanalysis of 29 studies involving fixed combination of prostaglandin analogs and timolol (Webers et al, 2010). Fixed combination therapy has advantages over multiple drop and multiple bottle therapy, improving patient convenience and adherence and perhaps more economical in a long run. However, the efficacy is still doubtful especially in advance cases when 1mmHg pressure reduction is meaningful. Prescription of fixed combination therapy needs to be tailored and customized according to patients.

8. The impact of topical pressure lowering drugs on glaucoma surgery

Apart from adherence and persistence problem, topical pressure lowering drug may potentially induced subclinical conjunctival inflammation. Subclinical conjunctival

inflammation is believed to be associated to the success of trabeculectomy. Long term and multiple treatments of topical pressure lowering drugs are believed to induce subclinical inflammation of the conjunctival that may induce excessive scarring of the bleb and eventually responsible for trabeculectomy failure (Sherwood et al, 1989; Broadway et al, 1994a; Broadway et al, 1994b). The histological evidence is inconsistent. Although there is evidence that suggest pressure lowering drugs induced mark increased in inflammatory markers and macrophages, there is also evidence against it (Sherwood et al, 1989; Broadway et al, 1994a; Baun et al, 1995; Liza-Sharmini et al, 2007). In addition, it is still not clear whether the active ingredient or the preservative exerts more detrimental effect. Benzalkonium chloride, the most common preservative used in topical antiglaucoma medication has been implicated to cause elevation of inflammatory markers in tissue culture and animal models (De Saint Jean et al, 1999; Debbasch et al, 2001; Becquet et al, 1998). Preservative free timolol was found to express less interleukins and inflammatory markers (Baudouin et al, 2004). On the other hand, sympathomimetics has been postulated to induce significant conjunctival cell profile changes and associated with poorer trabeculectomy outcome (Broadway et al, 1994a). In fact, discontinuation of sympathomimetics and steroid treatment has been proven to reverse this silent effect of pressure lowering medication (Broadway et al, 1996). Medical treatment versus surgical intervention as the first line management of glaucoma is still debatable.

9. References

- Abrams DA, R. A. C. A. e. a. 1989, "Dose response evaluation of apraclonidine in subjects with normal and elevated intraocular pressures", *Am J Ophthalmol*, vol. 108, pp. 230-237.
- Abramsons I, C. C. P. A. e. a. 1998, "The efficacy and safety of dorzolamide as adjunctive therapy to timolol gellan solution in patients with elevated intraocular pressure", *J Glaucoma*, vol. 7, pp. 253-260.
- Adamson IA, P. A. O. C. e. a. 1998, "Two-year safety study of dorzolamide as monotherapy and with timolol and pilocarpine", *J Glaucoma*, vol. 7, pp. 395-401.
- Airaksinen PJ, V. R. S. T. e. a. 1987, "A double-masked study on timolol and pilocarpine combined", *Am J Ophthalmol*, vol. 104, pp. 587-590.
- Akingbehin T and Sunder Raj P 1990, "Ophthalmic topical beta blockers: a review of ocular and systemic adverse effects", *J Toxicol -Cut Ocul Toxicol*, vol. 9, pp. 131-147.
- Albert DM, G. R. G. H. e. a. 2008, "A study of histopathological features of latanoprost-treated irides with or without darkening compared with non-latanoprost-treated irides", *Arch Ophthalmol*, vol. 126, pp. 626-631.
- Albert, D. M., Gangnon, R. E., Grossniklaus, H. E., Green, W. R., Darjatmoko, S., & Kulkarni, A. D. 2008, "A Study of Histopathological Features of Latanoprost-Treated Irides With or Without Darkening Compared With Non-Latanoprost-Treated Irides", *Archives of Ophthalmology*, vol. 126, no. 5, pp. 626-631.
- Allen RC, H. E. W. A. E. D. 1986, "A double-masked comparison of betaxolol vs. timolol in the treatment of open-angle glaucoma", *Am J Ophthalmol*, vol. 101, pp. 535-541.
- Alm A and Stjernschantz J, t. S. L. S. G. 1995, "Effects on intraocular pressure and side effects of 0.005% latanoprost applied once daily, evening or morning. A comparison to timolol", *Ophthalmology*, vol. 102, pp. 1743-1752.

- Alm, A. 1998, "Prostaglandin derivatives as ocular hypotensive agents", *Progress in Retinal and Eye Research*, vol. 17, no. 3, pp. 291-312.
- Alm, A., Grierson, I., & Shields, M. B. 2008, "Side Effects Associated with Prostaglandin Analog Therapy", *Survey of Ophthalmology*, vol. 53, no. 6, Supplement 1, p. S93-S105.
- Anthony TL, LJD, W.RN. 2002, "Latanoprost's effects on TIMP-1 and TIMP-2 expression in human ciliary muscle cells.", *Invest Ophthalmol Vis Sci.*, vol 43(12), pp3705-11.
- Araie M and Kiyoshi I 1993, "Effects of apraclonidine on intraocular pressure and blood-aqueous barrier permeability after phacoemulsification and intraocular lens implantation", *Am J Ophthalmol*, vol. 116, pp. 67-71.
- Araie M, A. I. K. Y. 2003, "Influence of topical betaxolol and timolol on visual field in Japanese open-angle glaucoma patients", *Jpn J Ophthalmol*, vol. 47, pp. 199-207.
- Araujo SV, Bond JB, Wilson RP, Moster MR, Schmidt CM Jr, Spaeth GL. 1995, "Long term effect of apraclonidine", *Br J Ophthalmol*, vol 79, pp. 1098-101.
- Arcieri ES, S. A. R. F. e. a. 2005, "Blood-aqueous barrier changes after the use of prostaglandin analogues in patients with pseudophakia and aphakia", *Arch Ophthalmol*, vol. 123, pp. 186-192.
- Bartlett JD, O. M. R. T. e. a. 1999, "Central nervous system and plasma lipid profiles associated with carteolol and timolol in postmenopausal black women", *J Glaucoma*, vol. 8, pp. 388-395.
- Baudouin C, H.P, L.H, e. a. 2004, "Conjunctival epithelial cell expression of interleukins and inflammatory markers in glaucoma patients treated over the long term." *Ophthalmology*, vol 111(12), pp 2186-92.
- Bauer K, B.-F. F. D. L. e. a. 1991, "Assessment of systemic side effects of different ophthalmic β -blockers in healthy volunteers", *Clin Pharmacol Ther*, vol. 49, pp. 658-664.
- Becker B 1954, "Decrease in intraocular pressure in man by a carbonic anhydrase inhibitor, Diamox: a preliminary report", *Am J Ophthalmol*, vol. 37, pp. 13-15.
- Becquet F, G.M, M.MS, e. a. 1998, "Histopathological effects of topical ophthalmic preservatives on rat corneconjunctival surface." *Curr Eye Res*, vol 17(4), pp 419-25.
- Birt CM, B. Y. A. I. e. a. 2010, "Prostaglandin efficacy and safety study undertaken by race", *J Glaucoma*, vol. 19, pp. 460-467.
- Bitto LZ, S. J. e. The Ocular Effects of prostaglandins and Other Eicosanoids. Bitto LZ, Camras CB, Gum CG, Resul B. The ocular hypotensive effects and side effects of prostaglandins on the eyes of experimental animals. 349-368. 1989. New York, Alan R Liss. Ref Type: Serial (Book, Monograph)
- Boas RS, M. M. M. T. P. S. 1981, "The effects of topically applied epinephrine and timolol on intraocular pressure and aqueous humor cyclic-AMP in the rabbit", *Exp Eye Res*, vol. 32, pp. 681-690.
- Boger WP 1983, "Short-term 'escape' and longterm 'drift'. The dissipation effects of the beta adrenergic blocking agents", *Surv Ophthalmol*, vol. 28, pp. 235-242.
- Boger WP III, S. R. P. C. e. a. 1978, "A double-masked clinical trial comparing timolol ophthalmic solution and pilocarpine in the therapy of open-angle glaucoma", *Am J Ophthalmol*, vol. 86, pp. 8-18.
- Boger WP, P. C. S. R. e. a. 1978, "Long-term experience with timolol ophthalmic solution in patients with open-angle glaucoma", *Ophthalmology*, vol. 85, pp. 259-267.

- Boyle JE, G. K. G. D. e. a. 1998, "A randomized trial comparing the dorzolamide-timolol combination given twice daily to monotherapy with timolol and dorzolamide", *Ophthalmology*, vol. 105, pp. 1945-1951.
- Broadway DC, G. I. O. C. H. R. 1994, "Adverse effects of topical antiglaucoma medication. I. The conjunctival cell profile", *Arch Ophthalmol*, vol. 112, pp. 1437-1445.
- Broadway DC, G. I. O. C. H. R. 1994, "Adverse effects of topical antiglaucoma. II. The outcome of filtration surgery", *Arch Ophthalmol*, vol. 112, pp. 1446-1454.
- Broadway DC, G. I. S. J. H. R. 1996, "Reversal of topical antiglaucoma medication effects on the conjunctiva", *Arch Ophthalmol*, vol. 114, pp. 262-267.
- Brubaker RF, S. E. N. C. e. a. 2001, "Effects of AGN192024, a new ocular hypotensive agent, on aqueous dynamics", *Am J Ophthalmol*, vol. 131, pp. 19-24.
- Butler P, Mannschreck M, Lin S, Hwang I, Alvarado J. 1995, "Clinical experience with the long-term use of 1% apraclonidine. Incidence of allergic reactions", *Arch Ophthalmol*, vol. 113, pp. 293-6.
- Camras CB, H.K. 2003, "Rate of response to latanoprost or timolol in patients with ocular hypertension or glaucoma." *J Glaucoma*, vol. 12(6), pp. 466-9.
- Cantor LB 2001, "Bimatoprost: a member of a new class of agents, the prostamides, for glaucoma management", *Expert Opin Investig Drugs*, vol. 10, pp. 721-731.
- Caprioli JC, S. M. B. L. e. a. 1984, "Forskolin lowers intraocular pressure by reducing aqueous outflow", *Invest Ophthalmol Vis Sci*, vol. 25, pp. 268-277.
- Carstairs JR, N. A. B. P. 1985, "Autoradiographic visualization of beta-adrenoceptor subtypes in human lung", *Am Rev Respir Dis*, vol. 132, pp. 541-547.
- Chen YN, Yamada H, Mao W, Matsuyama S, Aihara M, Araie M 2007, "Hypoxia-induced retinal ganglion cell death and the neuroprotective effects of beta-adrenergic antagonists", *Brain Res*, vol. 7, pp. 28-37.
- Cheon EW, P. C. K. S. e. a. 2003, "Betaxolol attenuates retinal ischemia/reperfusion damage in the rat", *Neuroreport*, vol. 14, pp. 1913-1917.
- Cheslita D 2007, "Evaluation of the role of travoprost 0.004% ophthalmic solution in the management of open angle glaucoma and ocular hypertensive patients", *Ophthalmologica*, vol. 51, pp. 81-86.
- Chew PT, A.T, A.MV, R.P. 2004, "Intraocular pressure-reducing effects and safety of latanoprost versus timolol in patients with chronic angle-closure glaucoma.", *Ophthalmology*, vol. 111(3), pp. 427-34.
- Chiba T, K. K. I. K. e. a. 2004, "A prospective study of iridial pigmentation and eyelash changes due to ophthalmic treatment with latanoprost", *Jpn J Ophthalmol*, vol. 48, pp. 141-147.
- Chou SY, C.CK, K.TM, e.a. 2005, "Incidence and severity of iris pigmentation on latanoprost-treated glaucoma eyes." *Eye (Lond)*, vol. 19(7), pp. 784-7.
- Clineschmidt CM, W. R. S. E. e. a. 1998, "A randomized trial in patients inadequately controlled with timolol alone comparing the dorzolamide-timolol combination to monotherapy with timolol or dorzolamide", *Ophthalmology*, vol. 105, pp. 1952-1959.
- Coakes RL and Brubaker RF 1978, "The mechanism of timolol in lowering intraocular pressure", *Arch Ophthalmol*, vol. 96, pp. 2045-2048.
- Coleman AL, D. D. J. H. e. a. 1990, "Topical timolol decreases plasma-high-density lipoprotein cholesterol level", *Arch Ophthalmol*, vol. 108, pp. 1260-1263.

- Cox JA, M. S. B. J. R. R. 2008, "Efficacy of antiglaucoma fixed combination therapy versus unfixed components in reducing intraocular pressure: a systematic review", *Br J Ophthalmol*, vol. 92, pp. 729-734.
- Cracknell K and Grierson I 2009, "Prostaglandin analogues in the anterior eye: Their pressure lowering action and side effects", *Exp Eye Res*, vol. 88, pp. 786-791.
- Cracknell KPB, G. I. H. P. e. a. 2003, "Latanoprost-induced iris darkening: a morphometric study of human peripheral iridectomies", *Exp Eye Res*, vol. 77, pp. 721-730.
- Crowston JG, L. J. A. M. W. R. 2004, "Effect of latanoprost on intraocular pressure in mice lacking the prostaglandin FP receptor", *Invest Ophthalmol Vis Sci*, vol. 45, pp. 3555-3559.
- Damji KF, B. R. W. L. 2003, "Target IOP workshop participants. Canadian perspectives in glaucoma management: setting target intraocular pressure range", *Can J Ophthalmol*, vol. 38, pp. 189-197.
- Dasgupta S, O. V. B. B. e. a. 2002, "Population-based persistency rates for topical glaucoma medications measured with pharmacy claims data", *Am J Manag Care*, vol. 8, no. Suppl, p. S255-S256.
- De Saint Jean M, B. F. B. A. e. a. 1999, "Effects of benzalkonium chloride on growth and survival of Chang conjunctival cells", *Invest Ophthalmol Vis Sci*, vol. 40, pp. 619-630.
- Debbasch C, P. PJ, D. SJ, e. a. 2001, "Mitochondrial activity and glutathione injury in apoptosis induced by unpreserved and preserved beta-blockers on Chang conjunctival cells." *Invest Ophthalmol Vis Sci*, vol 42(11), pp 2525-33.
- Dickstein K, H. R. A. T. 2001, "Comparison of aqueous and gellan ophthalmic timolol with placebo on the 24-hour heart rate response in patients on treatment for glaucoma", *Am J Ophthalmol*, vol. 132, pp. 626-631.
- Dielstelhorst M and Larsson L-I 2004, "A 12 week study comparing the fixed combination of latanoprost and timolol with the concomitant use of the individual components in patients with open angle glaucoma and ocular hypertension", *Br J Ophthalmol*, vol. 88, pp. 199-203.
- Dielstelhorst M and Larsson L-I 2006, "A 12-week, randomized, double masked, multicenter study of the fixed combination of Latanoprost and Timolol in the evening versus individual components", *Ophthalmology*, vol. 113, pp. 70-76.
- Diggory P, C.-B. A. V. A. H. J. 1998, "Randomised, controlled trial of spirometric changes in elderly people receiving timolol or betaxolol as initial treatment for glaucoma", *Br J Ophthalmol*, vol. 82, pp. 146-149.
- Diggory P, H. P. C. G. M. S. S. A. 1994, "Unsuspected bronchospasm in association with topical timolol- a common problem in elderly people: can we easily identify those affected and do cardioselective agents lead to improvement", *Age and Ageing*, vol. 23, pp. 17-21.
- Drago TP, O.-D. M. P. J. A. D. 1978, "Alpha-methyl-p-tyrosine inhibits latanoprost-induced melanogenesis in vitro", *Invest Ophthalmol Vis Sci*, vol. 17, pp. 511-514.
- Dunham CN, S. R. D. G. 1994, "The contralateral reduction of intraocular pressure by timolol", *Br J Ophthalmol*, vol. 78, pp. 38-40.
- Emiru VP 1971, "Response to mydriatics in the African", *Br J Ophthalmol*, vol. 55, pp. 538-543.
- Fasina O, Ashaye AO, Ajayi BG. 2008, "The effect of timolol maleate on tear film break-up time in Nigerians", *Afr J Med Med Sci*. Mar, vol 37, pp 43-7.

- Feldman RM 2003, "Conjunctival hyperemia and the use of topical prostaglandins in glaucoma and ocular hypertension", *J Ocul Pharmacol Ther*, vol. 19, pp. 23-36.
- Fellman RL, S. E. R. M. e. a. f. T. S. G. 2002, "Comparison of travoprost 0.0015% and 0.004% with timolol 0.5% in patients with elevated intraocular pressure: a 6 month, masked, multicentre trial", *Ophthalmology*, vol. 109, pp. 998-1008.
- Fong DS, F. A. R. C. J. F. 1993, "Adrenochrome deposit", *Arch Ophthalmol*, vol. 111, pp. 1142-1143.
- Fraunfelder FT, M. S. B. J. e. a. 1985, "Hematological reactions to carbonic anhydrase inhibitor", *Am J Ophthalmol*, vol. 91, pp. 79-81.
- Friedman DS, H. S. G. L. e. a. 2008, "Doctor-patient communication and health-related beliefs: Results from the Glaucoma Adherence and Persistency Study (GAPS)", *Ophthalmology*, vol. 115, pp. 1320-1327.
- Friedman DS, Q. H. G. L. e. a. 2007, "Using pharmacy claims data to study adherence to glaucoma medications methodology of the Glaucoma Adherence and Persistency Study (GAPS)", *Invest Ophthalmol Vis Sci*, vol. 48, pp. 5052-5057.
- Friston B and Nielson SE 1993, "Interaction of PhXA41, a new prostaglandin analogue, with pilocarpine: a study on patients with elevated intraocular pressure", *Arch Ophthalmol*, vol. 111, pp. 662-665.
- Gandolfi S, S. S. S. R. e. a. 2001, "Three-month comparison of bimatoprost and latanoprost in patients with glaucoma and ocular hypertension", *Adv Ther*, vol. 18, pp. 110-121.
- Gaul GR, W. N. B. R. 1989, "Comparison of a non-cardioselective beta adrenoceptor blocker and a cardioselective blocker in reducing aqueous flow in humans", *Arch Ophthalmol*, vol. 107, pp. 1308-1311.
- Gross RL, P. A. O.-N. S. 1997, "Clinical experience with apraclonidine 0.5%", *J Glaucoma*, vol. 6, pp. 298-302.
- Halpern MT, C. D. R. A. 2002, "Projected impact of travoprost versus both timolol and latanoprost on visual field deficit progression and costs among black glaucoma subjects", *Trans Am Ophthalmol Soc*, vol. 100, pp. 109-117.
- Hedman K and Larsson LI 2002, "The effect of latanoprost compared with timolol in African-American, Asian, Caucasian and Mexican open-angle glaucoma or ocular hypertensive patients", *Surv Ophthalmol*, vol. 47 (Suppl 1), p. S77-S89.
- Hedman K, W. P. A. A. 2002, "The effect of latanoprost on intraocular pressure during 2 years of treatment", *Surv Ophthalmol*, vol. 47 (Suppl 1), p. S65-S76.
- Hedner J, S. N. L. H. M. A. 1997, "The lack of respiratory effects of the ocular hypertensive drug latanoprost in patients with moderate asthma", *Surv Ophthalmol*, vol. 41, no. Suppl 2, p. S111-S115.
- Hellberg MR, M. M. S. N. e. a. 2000, "Preclinical efficacy of travoprost, a potent selective FP prostaglandin receptor agonist", *J Ocul Pharmacol Ther*, vol. 17, pp. 421-432.
- Herndon LW, R.DW, W.M, e. a. 2003, "Increased periocular pigmentation with ocular hypotensive lipid use in African Americans." *Am J Ophthalmol*, vol 135(5), pp 713-5.
- Hester RK, C. Z. B. E. e. a. 1994, "The direct vascular relaxing action of betaxolol, carteolol and timolol in porcine long posterior ciliary artery", *Surv Ophthalmol*, vol. 38, no. Suppl, pp. 125-134.
- Hitchings R, T. J. 2001, "Target pressure", *J Glaucoma*, vol. 10 (Suppl 1), p. S68-S70.

- Holmstrom S, B. P. W. J. e. a. 2006, "The cost-effectiveness of bimatoprost, latanoprost and timolol in treatment of primary open angle glaucoma in five European countries", *Curr Med Res Opin*, vol. 22, pp. 897-905.
- Hong SJ, Wu KY, Wang HZ, Fong JC. 2003, "Effects of commercial antiglaucoma drugs to glutamate-induced $[Ca^{2+}]_i$ increase in cultured neuroblastoma cells", *J Ocul Pharmacol Ther*, vol.19, pp.205-15.
- Honrubia F, G.-S. J. P. V. e. a. 2009, "Conjunctival hyperemia with the use of latnoprost versus other prostaglandin analogues in patients with ocular hypertension or glaucoma: a meta-analysis of randomised", *Br J Ophthalmol*, vol. 93, pp. 316-321.
- Hughes BA, B. J. C. R. e. a. 2005, "A three-month, multicentre, double masked study of the safety and efficacy of Travaprost 0.004%/Timolol 0.5% ophthalmic solution compared to Travaprost 0.004% ophthalmic solution and Timolol 0.5% dosed concomitantly in subjects with open angle or ocular hypertension", *J Glaucoma*, vol. 14, pp. 392-399.
- Hylton C and Robin AL 2003, "Update on prostaglandin analogs", *Curr Opin Ophthalmol*, vol. 14, pp. 65-69.
- Jampel HD 1996, "Target pressure in glaucoma therapy", *J Glaucoma*, vol. 6, pp. 133-138.
- Johnson TV, F.S, Z.G, e.a. 2010, "Efficacy and mechanisms of intraocular pressure reduction with latanoprost and timolol in participants with ocular hypertension: a comparison of 1 and 6 weeks of treatment." *J Glaucoma*, vol 19(6), pp 356-64.
- Johnstone MA 1997, "Hypertrichosis and increased pigmentation of eyelashes and adjacent hair in the region of the ipsilateral eyelids of patients treated with unilateral topical latanoprost", *Am J Ophthalmol*, vol. 124, pp. 544-547.
- Juzych MS and Zimmerman TJ 1997, "Beta-blockers," in *Textbook of Ocular Pharmacology*, Zimmerman TJ, ed., Lippincott-Raven, Philadelphia, pp. 261-275.
- Kammer JA, K. B. A. S. e. a. 2010, "Efficacy and tolerability of bimatoprost versus travoprost in patients previously on latanoprost: a 3 month, randomised, masked evaluator, multicentre study", *Br J Ophthalmol*, vol. 94, pp. 74-79.
- Kashiwagi K, T.K, S.M, e. a. 2002, "Effects of isopropyl unoprostone and latanoprost on melanogenesis in mouse epidermal melanocytes.", *J Glaucoma*, vol 11(1), pp 57-64.
- Katz IM and Berger ET 1979, "Effects of iris pigmentation on response of ocular pressure to timolol", *Surv Ophthalmol*, vol. 23, pp. 395-398.
- Khoury AS, R. T. F. R. 2007, "Use of fixed-dose combination drugs for the treatment of glaucoma", *Drugs Aging*, vol. 24, pp. 1007-1016.
- Konowal A, M. J. B. S. e. a. 1999, "Irreversible corneal decompensation in patients treated with topical dorzolamide", *Am J Ophthalmol*, vol. 127, pp. 403-406.
- Konstas AG, K. J. L. N. e. a. 2005, "Latanoprost 0.005% versus bimatoprost 0.03% in primary open-angle glaucoma patients", *Ophthalmology*, vol. 112, pp. 262-266.
- Kramer SG 1980, "Epinephrine distribution after topical administration to phakic and aphakic eyes", *Trans Am Ophthalmol Soc*, vol. 78, pp. 947-981.
- Kuppens EV, Stolwijk TR, de Keizer RJ, van Best JA, 1992, "Basal tear turnover and topical timolol in glaucoma patients and healthy controls by fluorophotometry", *Invest Ophthalmol Vis Sci*, vol 33, pp. 3442-8
- Kuppens EV, de Jong C A, Stolwijk T R, de Keizer R J, van Best J A, 1995, "Effect of timolol with and without preservative on the basal tear turnover in glaucoma", *Br J Ophthalmol*, vol 79, pp. 339-342

- Kushnick H, L. J. R. R. 1996, "Systemic pilocarpine toxicity from Ocusert leakage", *Arch Ophthalmol*, vol. 114, p. 1432.
- Lama PJ 2002, "Systemic adverse effects of beta-adrenergic blockers: An evidence-based assessment", *Am J Ophthalmol*, vol. 134, pp. 749-760.
- Larson RS and Brubaker RF 1988, "Isoproterenol stimulates aqueous flow in humans with Horner's syndrome", *Invest Ophthalmol Vis Sci*, vol. 29, p. 621.
- Larsson LI, M. H. T. M. e. a. 2002, "The effect of latanoprost on circadian intraocular pressure", *Surv Ophthalmol*, vol. 47(Suppl 1), p. S90-S96.
- Lass JH and Pavan-Langston D 1979, "Timolol therapy in secondary angle-closure glaucoma post penetrating keratoplasty", *Ophthalmology*, vol. 86, pp. 51-59.
- Leier CV, B. N. W. P. 1986, "Cardiovascular effects of ophthalmic timolol", *Annals of Internal Medicine*, vol. 104, pp. 197-199.
- Li N, C. X. Z. Y. e. a. 2006, "Travoprost compared with other prostaglandin analogues or timolol in patients with open-angle glaucoma or ocular hypertension: meta-analysis of randomized controlled trials", *Clin Experiment Ophthalmol*, vol. 34, pp. 755-764.
- Lim KS, N.CB, O.MM,e.a. 2008, " Mechanism of action of bimatoprost, latanoprost, and travoprost in healthy subjects. A crossover study.", *Ophthalmology*, vol 115(5), pp 790-795.
- Lin LL, G. M. O. S. K. I. 1979, "Longterm timolol therapy", *Surv Ophthalmol*, vol. 23, pp. 377-380.
- Lindsey JD, K. K. K. F. W. R. 1997, "Prostaglandins alter extracellular matrix adjacent to human ciliary muscle cells in vitro", *Invest Ophthalmol Vis Sci*, vol. 38, pp. 2214-2223.
- Lippa EA, C. L. E. B. e. a. 1992, "Dose response and duration of action of dorzolamide, a topical carbonic anhydrase inhibitor", *Arch Ophthalmol*, vol. 110, pp. 495-499.
- Liza-Sharmini AT, Mutalib O Abdul, Manoharan M. 2007, "The effects of topical antiglaucoma drugs on the conjunctival cell profile of Asian patients." *Asian J Ophthalmol*, vol 9, pp 17-20
- Lu, V. H., Goldberg, I., & Lu, C. Y. 2010, "Use of Glaucoma Medications: State of the Science and Directions for Observational Research", *American Journal of Ophthalmology*, vol. 150, no. 4, pp. 569-574.
- Lütjen-Drecoll E, T.E. 1988, " Morphological study of the anterior segment of cynomolgus monkey eyes following treatment with prostaglandin F2 alpha." *Exp Eye Res*, vol 47(5), pp 761-9.
- Maclure GM, V. R. S. T. e. a. 1989, "Effect on the 24 hour diurnal curve of intraocular pressure of a fixed ratio combination of timolol 0.5% and pilocarpine 2% in patients not controlled on timolol 0.5%", *Br J Ophthalmol*, vol. 73, pp. 827-831.
- Mandell AI and Podos SM 1977, "Dipivalyl epinephrine (DPE): A new prodrug in the treatment of glaucoma," in *Symposium on ocular therapy*, Leopold IH and Burn RP, ed., John Wiley & Sons, New York, pp. 109-117.
- Mark BS, R. C. C. C. e. a. 2006, "Twice daily 0.2% brimonidine- 0.5% timolol fixed combination therapy vs monotherapy with timolol or brimonidine in patients with glaucoma or ocular hypertension", *Arch Ophthalmol*, vol. 124, pp. 1230-1238.
- Mathias GW, O. F. H. H. e. a. 2007, "Effect of dorzolamide hydrochloride on central corneal thickness in human with corneal guttata", *Arch Ophthalmol*, vol. 125, pp. 1345-1350.

- Menon IA, T. G. B. P. W. D. P. S. 1989, "Binding of timolol to iris-ciliary body and melanin: an in vitro model for assessing the kinetics and efficacy of long acting antiglaucoma drugs", *J Ocul Pharmacol*, vol. 5(4), pp. 313-324.
- Messmer C, F. J. S. D. 1991, "Influence of betaxolol and timolol on visual field of patients with glaucoma", *Am J Ophthalmol*, vol. 112, pp. 678-681.
- Michels RG and Maumenee AE 1975, "Cystoid macular edema associated with topically applied epinephrine in aphakic eyes", *Am J Ophthalmol*, vol. 80, pp. 379-388.
- Migdal C, G. W. H. R. 1994, "Long-term functional outcome after early surgery compared with laser and medicine in open-angle glaucoma", *Ophthalmology*, vol. 101, pp. 1651-1656.
- Mirza GE, K. S. T. E. 2000, "Comparison of the effects of 0.5% timolol malaete, 2% carteolol hydrochloride, and 0.3% metipranolol on intraocular pressure and perimetry findings and evaluation of their ocular and systemic effects", *J Glaucoma*, vol. 9, pp. 45-50.
- Miyake K, O. I. M. K. e. a. 1999, "Latanoprost accelerates disruption of the blood-aqueous barrier and the incidence of angiographic cystoid macular edema in early postoperative pseudophakias", *Arch Ophthalmol*, vol. 117, pp. 34-40.
- Mori M and Araie M 1992, "Effect of apraclonidine on blood aqueous barrier permeability to plasma protein in man", *Exp Eye Res*, vol. 54, pp. 555-559.
- Morgan PV, P. S. B. J e. A. 2001, "Effect of temperature and light on the stability of latanoprost and its clinical relevance", *J Glaucoma*, vol 10, pp 401-405.
- Murphree SS and Saffitz JE 1988, "Delineation of the distribution of β -adrenergic receptor subtypes in canine myocardium", *Circulation Research*, vol. 63, pp. 117-125.
- Musch DC, G. B. L. P. e. a. 2009, "Visual field progression in the Collaborative Initial Glaucoma Treatment Study. The impact of treatment and other baseline factors", *Ophthalmology*, vol. 116, pp. 200-207.
- Müsken RPHM, W. R. W. J. e. a. 2008, "Topical β -blockers and mortality", *Ophthalmology*, vol. 115, pp. 2037-2043.
- Nagataki S and Brubaker RF 1981, "Early effect of epinephrine on aqueous formation in normal eyes", *Ophthalmology*, vol. 88, pp. 278-282.
- Nelson WL, F. F. S. J. e. a. 1986, "Adverse respiratory and cardiovascular events attributed to timolol ophthalmic solution, 1978-1985", *Am J Ophthalmol*, vol. 102, pp. 606-611.
- Netland PA, R. S. S. E. e. a. 2003, "Travoprost Study Group: Response to travoprost in black and non black patients with open angle glaucoma or ocular hypertension", *Adv Ther*, vol. 20, pp. 149-163.
- Neufeld AH 1979, "Experimental studies on the mechanism of action of timolol", *Surv Ophthalmol*, vol. 23, pp. 363-370.
- Nordstrom BL, F.DS, M.E, e. a. 2005, "Persistence and adherence with topical glaucoma therapy." *Am J Ophthalmol*, vol 140(4), pp 598-606.
- Novack GD and Evan R. 2001, "Commercially available ocular hypotensive products: preservative concentration, stability, storage and in-life utilization", *J Glaucoma*, vol 10, pp. 483-486
- Oh DJ, M. J. W. A. e. a. 2006, "Effect of latanoprost on the expression of matrix metalloproteinases and their tissue inhibitors in human trabecular meshwork cells", *Invest Ophthalmol Vis Sci*, vol. 47, pp. 3887-3895.

- Ong LB, L.-S. A. C. L. e. a. 2005, "The efficacy of timolol in gel-forming solution after morning or evening dosing in Asian glaucomatous patients", *J Ocul Pharmacol Ther*, vol. 21, pp. 388-394.
- Orengo-Nania S, L. T. V. T. M. e. a. f. T. S. G. 2001, "Evaluation of travoprost as adjunctive therapy in patients with uncontrolled intraocular pressure while using timolol 0.5%.", *Am J Ophthalmol*, vol. 132, pp. 860-866.
- Osborne NN and Chidlow G 1996, "Do beta-adrenoceptors and serotonin 5-HT_{1A} receptors have similar functions in the control of intraocular pressure in the rabbit?", *Ophthalmologica*, vol. 210, pp. 308-314.
- Osborne NN, W. J. C. G. e. a. 2004, "Effectiveness of levobetaxolol and timolol at blunting retinal ischemia is related to their calcium and sodium blocking activities: relevance to glaucoma", *Brain Res Bull*, vol. 62, pp. 525-528.
- Ota T, A. M. N. S. A. M. 2005, "The effects of prostaglandin analogues on IOP in prostanoid FP-receptor-deficient mice", *Invest Ophthalmol Vis Sci*, vol. 46, pp. 4159-4163.
- Otaleju SO and Ajayi AA 1999, "The lack of efficacy of topical beta-blockers, timolol and betaxolol on intraocular pressure in Nigerian healthy volunteers", *Eye*, vol. 13, pp. 758-763.
- Parmaksiz S, Y. N. K. V. e. a. 2006, "A comparison of travoprost, latanoprost, and the fixed combination of dorzolamide and timolol in patients with pseudoexfoliation glaucoma.", *Eur J Ophthalmol*, vol. 2006, pp. 73-80.
- Passo MS, P. E. V. B. E. 1984, "Plasma timolol in glaucoma patients", *Ophthalmology*, vol. 91, pp. 1361-1363.
- Philip FJH and Luc MB 2000, "Pharmacological therapy for glaucoma. A review", *Drugs*, vol. 59, pp. 411-434.
- Piltz J, G.R, S.DH, e.a. 2000, "Contralateral effect of topical beta-adrenergic antagonists in initial one-eyed trials in the ocular hypertension treatment study.", *Am J Ophthalmol*, vol. 130(4), pp 441-53.
- Puustjärvi TJ and Repo LP 1992, "Timolol-pilocarpine fixed-ratio combinations in the treatment of chronic open angle glaucoma. A controlled multicenter study of 48 weeks. Scandinavian Timpilo Study Group", *Arch Ophthalmol*, vol. 110, pp. 1725-1729.
- Reardon G, S.GF, M.E. 2004, "Patient persistency with topical ocular hypotensive therapy in a managed care population." *Am J Ophthalmol*, vol 137(1 Suppl), pp 3-12.
- Richter M, K. A. W. D. e. a. 2003, "Morphological changes in the anterior eye segment after long-term treatment with different receptor selective prostaglandin agonists and a prostamide", *Invest Ophthalmol Vis Sci*, vol. 44, pp. 4419-4426.
- Ritch R 1996, "The pilocarpine paradox", *J Glaucoma*, vol. 5, pp. 225-227.
- Robin AL 1987, "The role of apraclonidine hydrochloride in laser therapy for glaucoma", *Trans Am Ophthalmol Soc*, vol. 87, pp. 729-761.
- Roselund EF 1996, "The intraocular pressure lowering effect of timolol in gel-forming solution", *Acta Ophthalmol Scand*, vol. 74, pp. 160-162.
- Rosenberg LF, K. T. T. L. e. a. 1998, "Combination of systemic acetazolamide and topical dorzolamide in reducing intraocular pressure and aqueous humor formation", *Ophthalmology*, vol. 105, pp. 88-93.
- Salminen L, I. G. H. R. 1985, "The effect of ocular pigmentation on intraocular pressure response to timolol", *Acta Ophthalmol*, vol. 173 (Suppl), pp. 15-18.

- Satoh N, S. J. B. H. e. a. 1990, "Effects of betaxolol on cardiohemodynamics and coronary circulation in anesthetized dogs: comparison with atenolol and propranolol", *Jpn J Pharmacol*, vol. 54, pp. 113-119.
- Schenker HI, Y. M. P. S. L. L. 1981, "Fluorophotometric study of epinephrine and timolol in human subjects", *Arch Ophthalmol*, vol. 99, pp. 1212-1216.
- Scherer WJ 2002, "A retrospective review of non-responders to latanoprost", *J Ocul Pharmacol Ther*, vol. 18, pp. 287-291.
- Schuman JS, K. G. L. R. e. a. 2005, "Efficacy and safety of a fixed combination of Travaprost 0.004%/Timolol 0.5% ophthalmic solution once daily for open angle glaucoma or ocular hypertension", *Am J Ophthalmol*, vol. 140, pp. 242-250.
- Schwartz GF and Quigley HA 2008, "Adherence and persistence with glaucoma therapy", *Surv Ophthalmol*, vol. 53, no. Suppl, pp. 57-68.
- Schwartz GF, P. R. R. G. e. a. 2004, "Persistency with latanoprost or timolol in primary open-angle glaucoma suspects", *Am J Ophthalmol*, vol. 137, no. Suppl, pp. S13-16.
- Setoguchi M, O. Y. A. I. e. a. 1995, "Inhibitory action of betaxolol, a beta1-selective adrenoceptor antagonist, on voltage-dependent calcium channels in guinea-pig artery and vein", *Br J Pharmacol*, vol. 115, pp. 198-202.
- Sharpe ED, R. A. C. S. G. L. e.a. 2007, "The clinical impact and incidence of periocular pigmentation associated with either latanoprost or bimatoprost therapy", *Curr Eye Res*, vol 32, pp. 1037-1043.
- Shedden A, L. J. T. R. f. t. T.-X. O. 5. S. G. 2001, "Efficacy and tolerability of timolol maleate ophthalmic gel-forming solution versus timolol ophthalmic solution in adults with open-angle glaucoma or ocular hypertension: a six-month, double-masked, multicenter study", *Clin Ther*, vol. 23, pp. 440-450.
- Shedden AH, L. J. B. A. O. T. 2001, "Plasma timolol concentrations of timolol maleate: timolol gel forming solution (TIMOPTIC-XE®) once daily versus timolol maleate ophthalmic solution twice daily", *Doc Ophthalmol*, vol. 103, pp. 73-79.
- Sherwood MB, G.I, M.L, e. a. 1989, "Long-term morphologic effects of antiglaucoma drugs on the conjunctiva and Tenon's capsule in glaucomatous patients." *Ophthalmology*, vol 96(3), pp 327-35.
- Shin DH, G.BK, C.SC, e. a. 1999, "Long-term brimonidine therapy in glaucoma patients with apraclonidine allergy." *Am J Ophthalmol*, vol 127(5), pp 511-5.
- Shorr RI, R.WA, D.JR. e.a. 1997, Antihypertensives and the risk of serious hypoglycemia in older persons using insulin or sulfonylureas.", *JAMA*, vol 2;278(1), pp40-3.
- Singh K, S. G. Z. T. e. a. 2000, "Target pressure-glaucomatologist's holey grail", *Ophthalmology*, vol. 107, pp. 629-630.
- Sjöquist B and Stjernschantz J 2002, "Ocular and systemic pharmacokinetics of latanoprost in humans", *Surv Ophthalmol*, vol. 47 (Suppl 1), p. S6-S12.
- Smith RJ 1972, "Medical versus surgical therapy in glaucoma simplex", *Br J Ophthalmol*, vol. 56, pp. 277-283.
- Sonntag JR, B. G. S. M. 1978, "Effect of timolol therapy on outflow facility", *Invest Ophthalmol Vis Sci*, vol. 17, pp. 293-296.
- South East Asia Glaucoma Interest Group 2008, *Asia Pacific Glaucoma Guidelines*, Second edn, Scientific Communications, Hong Kong.
- Spooner JJ, B.MF, I.LL, e. a. 2002, "Rates of discontinuation and change of glaucoma therapy in a managed care setting." *Am J Manag Care*, vol 8(10 Suppl), pp 262-70.

- Stewart WC, D. H. M. T. e. a. 1999, "Effects of carteolol and timolol on plasma lipid profiles in older women with ocular hypertension or primary open-angle glaucoma", *Am J Ophthalmol*, vol. 127, pp. 142-147.
- Stewart WC, K. A. S. J. L. J. J. A. 2003, "Conjunctival hyperemia in healthy subjects after short-term dosing with latanoprost, bimatoprost, and travaprost", *Am J Ophthalmol*, vol. 135, pp. 314-320.
- Stjernschantz J and Alm A 1996, "Latanoprost as a new horizon in the medical management of glaucoma", *Curr Opin Ophthalmol*, vol. 7, pp. 11-17.
- Stjernschantz JW, A. D. H. D. e. a. 2002, "Mechanism and clinical significance of prostaglandin-induced iris pigmentation", *Surv Ophthalmol*, vol. 47, no. Suppl 1, pp. 162-175.
- Stjernschantz, J., Seløen, G. r., Astin, M., & Resul, B. 2000, "Microvascular effects of selective prostaglandin analogues in the eye with special reference to latanoprost and glaucoma treatment", *Progress in Retinal and Eye Research*, vol. 19, no. 4, pp. 459-496.
- Strahlman ER, V. R. T. R. e. a. 1996, "The use of dorzolamide and pilocarpine as adjunctive therapy to timolol in patients with elevated intraocular pressure", *Ophthalmology*, vol. 103, pp. 1283-1293.
- Strohmaier K, S. E. D. H. e. a. 1998, "The efficacy and safety of the dorzolamide-timolol combination versus the concomitant administration of its components", *Ophthalmology*, vol. 105, pp. 1936-1944.
- Taylor P 1990, "Cholinergic agonists," in *Goodman and Gilman's The pharmacological basis of therapeutics*, R. T. N. A. e. a. Gilman AG, ed., Pergamon Press, New York, pp. 122-130.
- The AGIS investigators 2000, "The Advanced Glaucoma Intervention Study (AGIS):7. The relationship between control of intraocular pressure and visual field deterioration", *Am J Ophthalmol*, vol. 130, pp. 429-440.
- Topper JE and Brubaker RF 1985, "Effects of timolol, epinephrine, and acetazolamide on aqueous flow during sleep", *Invest Ophthalmol Vis Sci*, vol. 26, p. 1315.
- Toris CB, C.CB, Y.ME. 1993, "Effects of PhXA41, a new prostaglandin F2 alpha analog, on aqueous humor dynamics in human eyes." *Ophthalmology*, vol 100(9), pp 1297-304.
- Toris CB, G. A. K. P. 2008, "Update on the mechanism of action of topical prostaglandins for intraocular pressure reduction", *Surv Ophthalmol*, vol. 53 (Suppl 1), p. S107-S120.
- Toris CB, T. M. C. C. e. a. 1995, "Effect of apraclonidine on aqueous humour dynamics in human eyes", *Ophthalmology*, vol. 102, pp. 456-461.
- Townsend DJ and Brubaker RF 1980, "Immediate effect of epinephrine on aqueous formation in the normal eye as measured by fluorophotometry", *Invest Ophthalmol Vis Sci*, vol. 19, pp. 256-266.
- Uusitalo H, K. M. R. A. e. a. 2006, "Improved systemic safety and risk-benefit ratio of topical 0.1% timolol hydrogel compared with 0.5% timolol aqueous solution in the treatment of glaucoma", *Graefe's Arch Clin Exp Ophthalmol*, vol. 244, pp. 1491-1496.
- Van Buskirk EM 1980, "Adverse reactions from timolol administration", *Ophthalmology*, vol. 87, pp. 447-450.
- Van Buskirk EM 1982, "Hazards of medical glaucoma therapy in the cataract patient", *Ophthalmology*, vol. 89, pp. 238-241.

- van de Valk R, W. C. S. J. e. a. 2005, "Intraocular pressure lowering effects of all commonly used glaucoma drugs. A meta-analysis of randomized clinical trials", *Ophthalmology*, vol. 112, pp. 1177-1185.
- Vareilles P, S. D. P. B. e. a. 1977, "Comparison of the effects of timolol and other adrenergic agents on intraocular pressure in the rabbit", *Invest Ophthalmol Vis Sci*, vol. 16, pp. 987-996.
- Varma R, J.W. K.T e. a. 2006, "Concentration of latanoprost ophthalmic solution after 4 to 6 weeks' use in an eye clinic setting", *Invest Ophthalmol Vis Sci*, vol. 47, pp. 222-225.
- Vuori M, A.-M. T. K. T. e. a. 1993, "Plasma and aqueous humnour concentrations and systemic effects of topical betaxolol and timolol in man", *Acta Ophthalmol*, vol. 71, pp. 201-206.
- Vyas P, N. U. G. J. 2011, "Efficacy of bimatoprost 0.03% in reducing intraocular pressure in patients with 360° synechial angle closure glaucoma: A preliminary study", *Indian J Ophthalmol*, vol. 59, pp. 13-16.
- Walters TR, D. H. C. S. e. a. 2004, "24-hour IOP control with once-daily bimatoprost, timolo gel-performing solution, or latanoprost: a 1-month, randomized, comparative clinical trial", *Surv Ophthalmol*, vol. 491, no. Suppl, p. S26-S35.
- Wand M, G. C. L. T. 1999, "Latanoprost and herpes simplex keratitis", *Am J Ophthalmol*, vol. 127, pp. 602-604.
- Wandel TA, F. D. N. G. e. a. 1988, "Ocular hypotension efficacy of 0.25% levobunolol once-daily", *Ophthalmology*, vol. 95, pp. 252-254.
- Warwar RE, B.JD, B.D. 1998, "Cystoid macular edema and anterior uveitis associated with latanoprost use. Experience and incidence in a retrospective review of 94 patients." *Ophthalmology*, vol 105(2), pp263-8.
- Watanabe K and Chiou GC 1983, "Action mechanism of timolol to lower the intraocular pressure in rabbits", *Ophthalmic Res*, vol. 15, pp. 160-167.
- Watanabe TM and Hodes BL 1997, "Bilateral anterior uveitis associated with a brand metipranolol", *Arch Ophthalmol*, vol. 115, pp. 421-422.
- Watson PG, B. M. P. V. H. J. 2001, "A 7 year prospective comparative study of three topical β blockers in the management of primary open angle glaucoma", *Br J Ophthalmol*, vol. 85, pp. 962-968.
- Wax MB and Molinoff PB 1987, "Distribution and properties of β -adrenergic receptors in human iris/ciliary body", *Invest Ophthalmol Vis Sci*, vol. 28, pp. 420-430.
- Weber PA. 1981, "Neovascular glaucoma. Current management.", *Surv Ophthalmol*, vol. 26(3),pp. 149-53.
- Webers CA, B. H. Z. M. e. a. 2010, "The intraocular pressure-lowering effect of prostaglandin analogs combined with topical β -blocker therapy: a systematic review and meta-analysis", *Ophthalmology*, vol. 117, pp. 2067-2074.
- Weekers R, D. Y. G. J. 1955, "Treatment of ocular hypertension by adrenaline and diverse sympathomimetic amines", *Am J Ophthalmol*, vol. 40, pp. 666-672.
- Wolf S, W. E. S. K. e. a. 1998, "Acute effect of metipranolol on the retinal circulation", *Br J Ophthalmol*, vol. 82, pp. 892-896.
- Wood JP, S. K. M. J. e. a. 2003, "The beta-adrenoceptor antagonists metipranolol and timolol are retinal neuroprotectants: comparison with betaxolol", *Exp Eye Res*, vol. 76, no. 4, pp. 505-516.

- Woodward DF, K. A. C. J. e. a. 2001, "The pharmacology of bimatoprost (Lumigan)", *Surv Ophthalmol*, vol. 45, no. Suppl 4, p. S337-S345.
- Woodward DF, K. A. C. J. e. a. 2003, "Pharmacological characterization of a novel antiglaucoma agents, Bimatoprost (AGN 192024)", *J Pharmacol Exp Ther*, vol. 305, p. 772-785.
- Yablonski ME, Z. T. W. S. B. B. 1978, "A fluorophotometric study of the effect of topical timolol on aqueous humor dynamics", *Exp Eye Res*, vol. 27, pp. 135-142.
- Yu DY, S. E. C. S. e. a. 1999, "Systemic and ocular vascular roles of the antiglaucoma agents β -adrenergic antagonists and Ca^{2+} entry blockers", *Surv Ophthalmol*, vol. 43, no. Suppl 1, pp. 214-222.
- Zhang WY, P.AL, D.HS,e.a , 2001, "Meta-analysis of randomised controlled trials comparing latanoprost with timolol in the treatment of patients with open angle glaucoma or ocular hypertension." *Br J Ophthalmol.*, vol 85(8), pp 983-90.
- Zimmerman TJ 1981, "Pilocarpine", *Ophthalmology*, vol. 88, pp. 85-88.
- Zimmerman TJ and Boger WP III 1979, "The beta-adrenergic blocking agents and the treatment of glaucoma", *Surv Ophthalmol*, vol. 23, pp. 347-362.
- Zimmerman TJ and Kaufman HE 1977, "Timolol: dose response and duration of action", *Arch Ophthalmol*, vol. 95, pp. 605-607.
- Zimmerman TJ and Wheeler TM 1982, "Miotics.Side effects and ways to avoid them", *Ophthalmology*, vol. 89, pp. 76-80.
- Zimmerman TJ, H. S. G. L. T. H. K. E. 2009, "The impact of ocular adverse effects in patients treated with topical prostaglandin analogs: Changes in prescription patterns and patient persistence", *J Ocul Pharmacol Ther*, vol. 25, pp. 145-152.

IntechOpen

Glaucoma - Current Clinical and Research Aspects

Edited by Dr. Pinakin Gunvant

ISBN 978-953-307-263-0

Hard cover, 376 pages

Publisher InTech

Published online 09, November, 2011

Published in print edition November, 2011

This book summarizes current literature about research and clinical science in glaucoma and it is a synopsis and translation of the research conducted by individuals who are known in each of their respective areas. The book is divided into two broad sections: basic science and clinical science. The basic science section examines bench- and animal-modeling research in an attempt to understand the pathogenesis of glaucoma. The clinical science section addresses various diagnostic issues and the medical, laser and surgical techniques used in glaucoma management.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Liza-Sharmini Ahmad Tajudin and Yaakub Azhany (2011). Pressure Lowering Medications, Glaucoma - Current Clinical and Research Aspects, Dr. Pinakin Gunvant (Ed.), ISBN: 978-953-307-263-0, InTech, Available from: <http://www.intechopen.com/books/glaucoma-current-clinical-and-research-aspects/pressure-lowering-medications>

INTECH
open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](https://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen