GLAUCOMA TREATMENT

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This chapter includes a review of:

- Patient compliance
- Glaucoma management
- Target IOP
- Ocular hypertension
- Choice of treatment
- Anti-glaucoma drugs
- Glaucoma challenge

TREATMENT OF GLAUCOMA

The aim of glaucoma treatment is to reduce the intraocular pressure. This prevents both, damage to nerve fibres and the subsequent development of visual defects. The drugs used to treat glaucoma either reduce the formation of aqueous humour or increase its outflow.

- The European Glaucoma Society (EGS) has published the third edition of its treatment guidelines for glaucoma (2008).
    - Guideline can be downloaded from EGS website.
- These incorporate the latest clinical research and thinking on glaucoma together with an update on the evidence for the latest therapies and surgical techniques.
- National Institute for Health and Clinical Excellence (NICE) guidelines aim to standardise care and prevent visual loss (www.nice.org.uk)

Prior to Treatment

Before treatment is started:

- Full eye exam and fundus check is required
- Measures of IOP and of diurnal changes are required, as well as knowledge of the moment and when peak occurs
- Also, automated perimetry must confirm visual field changes. Three independent visits and consistent measures are indicated

- A glaucoma suspect may make several visits to ophthalmologist before drugs are prescribed

PATIENT COMPLIANCE

- As a progressive disease requiring topical medication and follow-up appointments, glaucoma requires continuous compliance from patients for its successful management. Glaucoma is the third leading preventable cause of blindness, affecting approximately 105 million people worldwide. Non-compliance plays a large role in progression to blindness.

ELDERLY PATIENTS AND GLAUCOMA

- Patients are frequently elderly and may have diminished cognitive abilities, poor hearing and other ailments, which may impede or reduce their ability to administer medication correctly
- Patients may not fully understand the chronic progressive nature of the disease and importance of medication compliance
- It is important to fully inform the patient of how medication is to be administered, how often, etc
    - Always make them fully aware of any changes

POTENTIAL TREATMENT OPTIONS

- Reduction of IOP
- Improvement of ocular blood flow
- Direct neuro-protection

Presently the only approach proven to be efficient in preserving visual function is reduction in IOP.

> Vascular disorders affecting peripheral circulation (e.g. Raynaud's disease) have been associated with glaucoma. Raynaud's disease is a rare disorder causing vasoconstriction of fingers and toes.

Goal of Treatment: Quality of Life

- All glaucoma treatment is aimed at lowering IOP
- The ultimate goal in treatment is to maintain a patients quality of life (QOL).
- QOL is closely linked to visual function.
- The only approach proven to be efficient in preserving visual function is to lower the intra-ocular pressure (IOP)
- QOL takes into consideration how condition affects the person on a daily basis, i.e. anxiety due to diagnosis, functional loss due to the disease, inconvenience of treatment and side effects

Consideration regarding choice of drug for treatment

- Reduction of IOP
    - Actual figure for control varies between studies and patients, . i.e. a px with normal tension glaucoma might need a lower IOP for control
- Duration of effect
    - Prevent fluctuation. Consider patient compliance, i.e. 4 x per day, etc
- Preservation of visual field
- No loss of effect with time

    - Monitor treatment to ensure it is still effective after a few years
- Compatibility with other treatment
- Lack of topical and systemic effects
    - For example stinging, LA effect, affect tears
- ANS effects
    - Many of these drugs will have effects on the autonomic nervous system and may interact with other drugs the patient is taking
- Patient compliance
    - The drug should be easy to use

TARGET IOP

- An estimate of the mean IOP obtained with treatment that is expected to prevent further glaucomatous damage
    - Different individuals have different levels of IOP and different targets
- No single IOP level is safe for every patient
- The aim to achieve at least 20% IOP reduction from initial pressure.
- In advanced glaucoma, the aim to lower IOP to less than 18mmHg at all visits.
- Very important that IOP is stable and doesn't fluctuate during day. Visual field is better preserved with more stable levels of IOP

Factors causing variation of target IOP

- Pre-treatment IOP
- Overall risk of IOP related optic nerve damage
- Stage of glaucoma
- Rate of progression of glaucomatous disease
- Age of patient
- Life expectancy of patient
- Presence of other risk factors

> The more advanced the stage of glaucoma, the lower the target IOP. Target IOP may need to be adjusted during the course of the disease. It is difficult to assess patient compliance. Poor patient compliance has a very important negative impact.

Monitoring of treatment over time

- Patient must always be monitored carefully
- If the visual fields start to worsen at a rate that is clinically significant, it may be necessary to aim for a lower target IOP
- Glacuoma treatment is a dynamic process. Medication, dose, duration, etc can be changed to manage patient appropriately

OCULAR HYPERTENSION

- In individuals with an IOP between 24mmHg and 32mmHg in one eye and between 21mmHg and 32mmHg in the fellow eye, a reduction of IOP by 20% or below 24mmHg is effective in delaying onset of primary open angle glaucoma (POAG).

  These results were gathered from a large group of research in this area, which included multicentre large randomised controlled trials of people with primary open angle glaucoma. These studies demonstrated that by reducing IOP by 20%, this was effective in delaying the onset of POAG

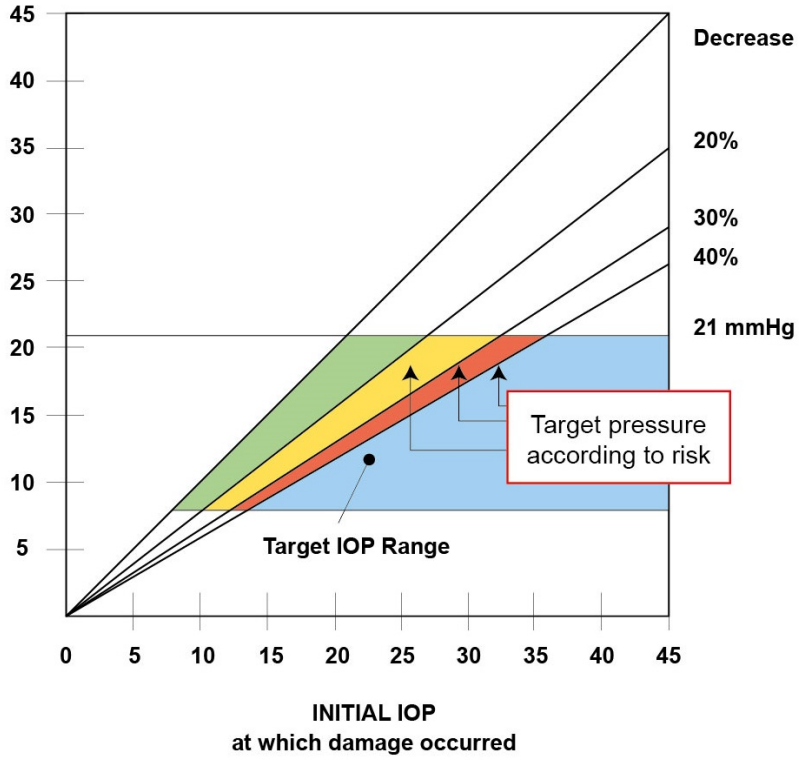


Figure 8.1 *Target pressures according to the risk . The top line is initial IOP. If the patient is in the high risk of visual field loss category with fast progression aim for lower IOP. Percentage of reduction depends on risk of visual field damage and rate of progression.*

CHOICE OF TREATMENT

Over past few years there has been gradual shift in the choice of medical therapy. Prostaglandin derivatives have superseded beta blockers as first choice of treatment.

EGS Guidelines 2008

- Updated version - reflect recent results from large, randomised controlled trials.
- In many cases, prostaglandin derivatives have superseded beta-blockers as first line therapy as reflected in recommendations.
- If first choice therapy not measurably effective on IOP, change initial therapy rather than adding in second drug. A lower IOP means better protection against vision loss.
- Provide treatment recommendations for the various types of glaucoma:
- Juvenile, primary open angle, normal tension, acute closed angle glaucoma and ocular hypertension.

Therapeutic Trials

- Topical treatment should be started in one eye at a time.
- The differential IOP will give a better idea of the effect, with less influence from diurnal variations.
- For some drugs, a cross-over effect to the other eye must be taken into account.

General Principles

- The least amount of medication and side effects to achieve the therapeutic response should be a consistent goal
- Generally, topical treatment is preferred over systemic treatment

ANTI-GLAUCOMA DRUGS

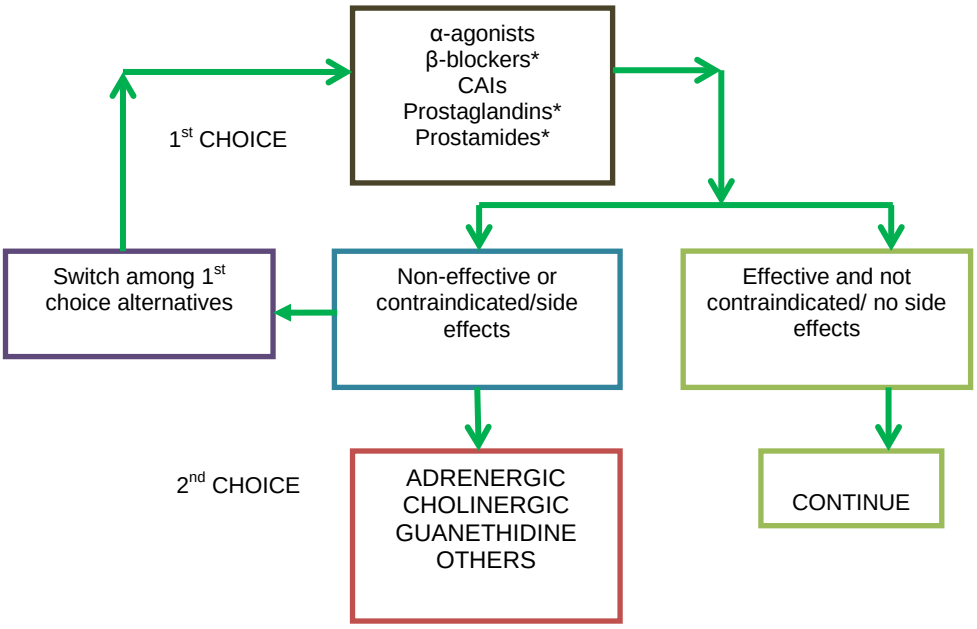
6 main strategies:

- Prostaglandin analogues
- Adrenergic antagonists (beta-blockers)
- Carbonic anhydrase inhibitors (CAI's)- systemic and topical.
- Adrenergic agonists (sympathomimetics)
- Parasympathomimetics (miotics)
- Combined drugs preparations

Instillation

To minimise drainage into nose or throat, and avoid systemic absorption, instruct patients to exert finger pressure on medial canthus to occlude puncta following instillation of drops. Wash any medication from hands after instillation.

CHOICE OF GLAUCOMA DRUGS



* β-blockers, latanoprost and travoprost are approved by regulatory bodies as first-line treatment options.

Figure 8.2 *Flow chart to demonstrate the use of glaucoma drugs. Source: European Glaucoma Society Guidelines.*

Glaucoma treatment trials

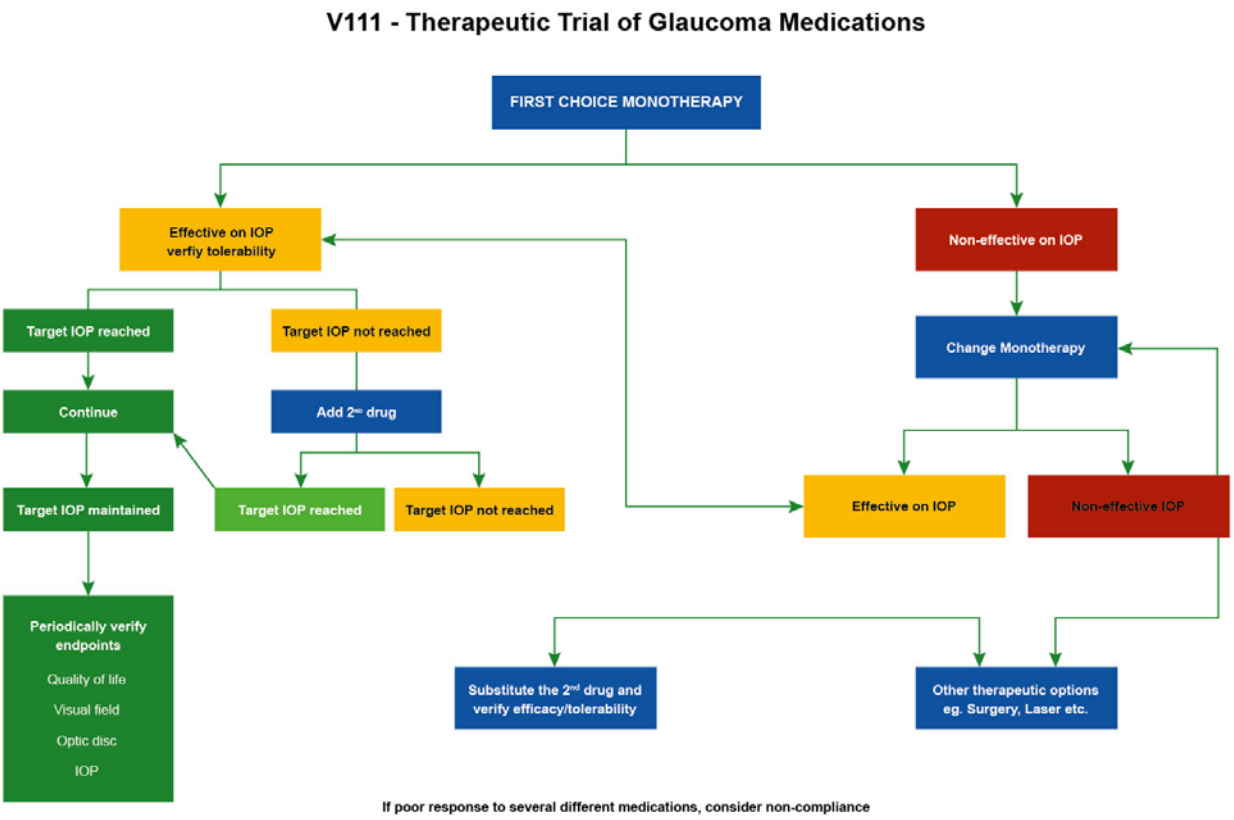


Figure 8.3 *Also found in European Glaucoma Society Guidelines*

PROSTAGLANDIN ANALOGUES

Topical:

- Latanoprost 0.005% (Trade name – Xalatan)
- Brimatoprost 0.03% (Trade name -Lumigan)
- Travoprost 0.004% (Trade name - Travatan)
- Unoprostone 0.12% (Trade name – Rescula)

These drugs are well tolerated by many patients and have equal potency compared to beta blockers. The treatment therapy is usually once a day.

> The majority of the aqueous humour leaves the eye via the conventional route of the trabecular meshwork, Schlemm's canal and episcleral veins. However, 10 to 20 per cent of outflow is via the non-conventional or uveoscleral route (up to 30% in non-Caucasians) where the aqueous humour passes between the ciliary muscle bundles and into the episcleral tissues where it is re-absorbed into orbital blood vessels and drained via the conjunctival vessels.

Mode of action:

Prostaglandin analogues increase aqueous humour outflow. Useful as they do not reduce the essential nutrients necessary for the cornea and lens via the aqueous humour.

They appear to be effective, well tolerated agents for the reduction of IOP in patients with Primary Open Angle Glaucoma and ocular hypertension. They are first line therapy in many cases.

The drug class offers potential as first choice drugs or an alternative for patients who do not achieve control IOP on another topical anti-glaucoma treatment.

Action

- Increase in uveo-scleral outflow, reducing IOP by 20% to 35%.
- Unoprostone appears to have a different mode of action (does not act at FP receptors)- mechanism of action and safety profile may be different to Latanoprost- not yet available in Europe
    - Controversy over site of action
- Reduction of IOP 2-4 hours after first instillation
- Peak effect after 8 hours
- Prostaglandins originally discovered to mediate inflammatory response
- Reduce collagen levels in the ciliary muscle and adjacent sclera and reduced resistance to outflow, i.e. Increased outflow

Contraindications

- Known sensitivity to Latanoprost/ Unoprostone or any other product ingredient (benzalkonium chloride)
- Drops not to be instilled with contact lenses in situ - remove for 15mins

Side Effects

- Local- conjunctival hyperaemia, burning/ stinging, foreign body sensation, itching, cystoid macular oedema in aphakes/ pseudophakes (few reports), anterior uveitis, hypertrichosis of eye lashes

- Increased iris pigmentation by 6-18% after 1 year especially with green-brown, blue/grey-brown or yellow-brown irides
- Systemic- no reports this far
- Darker longer lashes, 2nd row lashes
    - Eyelash changes reversible after ceasing medication
- Systemic: may exacerbate asthma
- Tendency to induce red eye
- Darkening of iris in 5-20%
- Change in eye colour permanent
- Stimulation of cell growth: extra eye lashes

Cautions

- Pregnancy/ nursing mothers
- Potential drug interaction with thiomersal- containing eye drops (precipitation)
- Cystic macular oedema in aphakes/ pseudophakes has been reported with latanoprost
- Unilateral treatment with latanoprost may cause difference in iris colours between the two eyes
- Useful drug for patients with respiratory disorders unlike beta blockers or miotics
- In aphakic eyes the concentration of drug reaching the choroid and retina was higher than in phakic eyes

Adrenergic Antagonists: Beta Blockers

- Common first choice drug for existing glaucoma patients.
- Relatively inexpensive
- Good efficacy and few side effects.
- Reduce IOP by 20-30%.

- May act on alpha or beta receptors
- Originally for cardiac disorders
- Mode of action: blocking beta receptors (stimulation of which caused secretion/production of aqueous).
- Patient selection important
- Non-selective: block both Beta-1 and Beta-2 receptors
- B-1 selective (Cardio-selective): block Beta-1 receptors only
- No effect on outflow
- Important that General Practitioner (GP) aware of treatment
- Beta-1 selective: Betaxolol 0.5% (Trade name - Betoptic)
- Non-selective: Befunolol 0.5% (Trade name Betaclar)
- Levobunolol 0.25% (Trade name - Betagan), 0.5%, Metipranolol 0.1%, 0.3%, Timolol 0.25% (Trade name Timoptol) 0.5%.
- With ISA: Carteolol 1% (Trade name - Teoptic), 2%, Pindolol 2% (Trade name – Pindoptic)

Mode of action

- Decrease IOP by reduction in aqueous humour production- peak effect at 2 hours
- Lowest concentration giving expected clinical effect is used - to limit side-effects.
- Dosing more than twice a day will not enhance IOP lowering effect.
- Beta-1 selective agents despite reducing IOPs less than non-selective, protect visual fields equally well.

Contra-indications

- Non-selective- asthma, history of obstructive pulmonary disease, sinus bradycardia (less that 60 beats per min), heart block or cardiac failure.
    - Sinus bradycardia – reduced heart rate in an otherwise healthy person
    - Heart block is a type of bradycardia (too-slow heartbeat) that also is called atrioventricular (AV) block. In this condition, the electrical signals that stimulate heart muscle contractions are partially or totally blocked between the upper chambers (atria) and the lower chambers (ventricles).
- B1 selective- relative contra-indication/I in asthma, history of obstructive pulmonary disease, sinus bradycardia, heart block, cardiac failure.

Major side-effects

- Non-selective - Systemic:- bradycardia, arrhythmia, heart failure, syncope, bronchospasm, airways obstruction. Distal oedema, hypotension, depression - hypoglycaemia masked in IDDM (insulin dependent diabetes mellitus).
- Ocular (uncommon)- Epithelial keratopathy, slight reduction in corneal sensitivity.
- Beta-1 selective- better tolerated where sensitivity to non-selective exists.
- Avoid if history of bronchospasm, or any chronic airways disease. Avoid if patient uses beta blockers.

Cautions

- Pregnancy/ breastfeeding- only where potential benefits outweigh risks to foetus.
- Drug interactions: Per Os (PO)/Intra-Venous (IV) Ca2+ antagonists - risk of atrioventricular conduction disturbances, left ventricular failure and hypotension.
- Digoxin- prolongation of conduction time
- Catecholamine depleting drugs- additive effects/ hypotension/ bradycardia
- Avoid if patient already uses systemic beta blockers (for high blood pressure, arrhythmias or migraines)

CARBONIC ANHYDRASE INHIBITOR (CAI)

- Topical:
    - Dorzolamide 2% (Trade name Trusopt)
    - Brinzolamide 1% (Trade name Azopt)
- Systemic:
    - Acetazolamide (Trade name - Diamox)
    - Dichlorphenamide (Trade name – Glaumid)
    - Methazolamide (Trade name - Neptazane)

- Used if patient is unresponsive to beta blockers or if betablockers are contraindicated
- Can be used as monotherapy or in combination

In 1949 Friednewald discovered that bicarbonate (carbonic anyhydrase is an enzyme that is involved with production) was an essential component of aqueous humour. It was demonstrated that by blocking production of this agent, IOP could be reduced. This is done by preventing action of the enzyme carbonic anhydrase.

Mode of action

- Reduces aqueous formation resulting in lowered IOP.
- Reduces IOP by 18-20%.
- Less effective than beta blockers or prostaglandins
- Useful second or third line therapy
- Safe in selected patients and when blood electrolytes are carefully monitored
- Enter eye via ciliary circulation and inhibit aqueous humour secretion
- Diamox interferes with electrolyte concentrations in body

Contra-indications

- **Topical:** Hypersensitivity to any component of the product.
- **Systemic:**Hyponatraemia/ hypokalaemia (steroid use), liver/kidney disease or dysfunction, suprarenal gland failure, hyperchloraemic acidosis.

- Hyponatraemia - Low Na concentration in blood
- Hypokalaemia – low K in blood
- Hyperchloraemic acidosis – increased Na concentration
- Contra-indicated in severe kidney disease
- Electrolyte balance

Side-effects

- **Topical:** Ocular burning, stinging, bitter taste, SPK, blurred vision, tearing, headache, urticaria (hives – allergic reaction), angioedema (rapid swelling of the skin), pruritus (itchy skin), asthenia, dizziness, paresthesia (pins and needles), transient myopia.
- **Systemic:** Paraesthesia, hearing dysfunction, tinnitus, loss of appetite, taste alteration, GI disturbances, depression, reduced libido, kidney stones, blood dyscrasias- metabolic acidosis and electrolyte imbalance may occur.

- Also tiredness, malaise
- Avoid in patients with kidney disease, with electrolyte imbalances
- Avoid in patients with adrenal insufficiency or hepatic dysfunction

Cautions

- Topical - Use systemic CAI when ACAG (acute closed angle glaucoma) with corneal oedema/ inflamed conjunctiva
- Allergy to sulphonamides- risk of Stevens-Johnson syndrome
- Do not use where CrCl (creatinine clearance) is less than 30ml/min i.e severe renal impairment.
- Systemic - sulphonamide- allergy- Stevens-Johnson syndrome, anaphylaxis/ erythema multiforme, bone marrow depression, thrombocytopenia purpura, haemolytic anaemia, leukopenia, pancytopenia pancytopenia pancytopenia / agranulocytosis
    - **Stevens-Johnson syndrome** (SJS) is a severe and life-threatening condition. It is thought to be a hypersensitivity complex affecting the skin and the mucous membranes. Blisters on skin. Can follow infection, allergy or malignancy.

- Pregnancy/ breastfeeding- as before
- Used to assess kidney function
- Estimates filtration rate of kidneys
- Erythema multiforme is a skin disorder resulting from an allergic reaction to illness, infection or medications. thrombocytopenia purpura – a disorder of blood affecting clotting
- Leukopenia – reduction in number of white blood cells
- Pancytopenia – reduction in red and white blood cells

ADRENERGIC AGONISTS

- An agonist is a chemical that binds to a receptor and stimulates a response (as opposed to an antagonist)
- May act on both alpha or beta adrenergic receptors (non-selective) or alpha-2 receptors (Alpha-2 selective)
- Although stimulation of beta adreno-receptors cause an increase in IOP by stimulation of production of aqueous from ciliary epithelium, stimulation of alpha receptors causes a reduction that cancels out increase.
- Also causes increase in outflow.
    - Net result – reduction in IOP

Mode of Action

- Non-selective – decreases aqueous humour production and increases outflow
- Alpha 2 Selective –
    - Apraclonidine - decreases AH production
    - Brimonidine - decreases AH production and increases uveoscleral outflow
    - Clonidine - decreases AH production
- Non-selective:
    - Dipivefrin 0.1% (Trade name - Propine)
    - Epinephrine 0.25%-2% (Trade name Epinephrine).
    - Specific to adrenergic receptors – more widespread effect (decreased secretion of salivary glands, relaxation of CB)
- Alpha 2 selective – only acting on alpha 2 receptors (vessels in anterior uvea and secretions from ciliary epithelium, i.e. will not affect pupil dilation)
    - Apraclonidine 0.5%- 1% (Trade name Iopidine)
    - Brimonidine 0.2% (Trade name- Alphagan)
    - Clonidine 0.125%- 0.5% (trade name Isoglaucon)
    - Causes increased outflow due to interfering with the osmotic potential of the aqueous and reducing aqueous production. (Sympathomimetic)

- Generally use for all: 1 drop in the eye 2-3 times daily.
- Apraclonidine- max effect is 4-5 hours- duration 12 hours- reduces IOP by 25-39%
- Brimonidine- duration 12 hours- reduces IOP by 27%- complete selectivity for alpha 2 receptors- no mydriasis/ vasoconstriction
- Clonidine- duration 6-12 hours- little effect on pupillary diameter or accommodation.

Contra-indications

- Non-selective- occludable angles (iridotomy needed), Aphakic patients (macular oedema).
- Alpha-2 selective- Oral monoamine oxidase (MAO) inhibitor users.

It has been recognized that topical epinephrine therapy may induce Cystoid Macular Oedema (CMO). In aphakic eyes the concentration of epinephrine reaching the choroid and retina was higher than in phakic eyes. A rebound hyperaemia phenomenon has been described and proposed as a possible mechanism for the development of CMO.

Side-effects

- Non-selective - follicular conjunctivitis, tachycardia, arrhythmias and arterial hypertension
- Alpha-2 selective - Dry mouth, lid elevation, pupil dilation (apraclonidine), allergy (brimonidine 10%/ apraclonidine up to 36%), decrease in systolic BP (clonidine) and fatigue/ sleepinesss

Cautions

- Pregnancy/ nursing mothers- only if potential benefits outweigh risks.
- Apraclonidine and brimonidine should not be used in patients receiving MAO inhibitors
- Possibility of additive or potentiating effect with CNS depressants- caution with Tricyclic antidepressants.
- Any medication with sympathomimetic effects
- Avoid in patients with severe cardiovascular disease and circulatory disorders

PARASYMPATHOMIMETICS (CHOLINERGIC DRUGS/MIOTICS)

- Increase in facility of outflow of aqueous humour
- Direct action on longitudinal ciliary muscle.
    - Stretching effect of trabecular meshwork- promotes access to canal schelmn
    - Some evidence that miotics also reduce production
    - Cholinergic vasodilation
    - Reduced IOP approx 15%
    - Darker eyes more resistance: may require a higher concentration than light eyes
- Cholinergic agonists/miotics therapy was the primary medical treatment for glaucoma for 50 years but rarely used now.
- Used for initial high IOPs >30. Darkly pigmented eyes.
- Can be used alongside beta blockers. Direct or indirect actiing
- Direct acting: pupil sphincter stimulated to contract by action of Ach on muscarinic receptors. Mimics action of Ach.
- Parasympathomimetics or direct acting muscarinic or cholinergics
    - Preventing breakdown of Ach (therefore more Ach) by cholinesterase at junctions: anticholinesterases
    - Anticholinesterases have a stronger and more prolonged effect. Physostigmine rarely used.

Mode of action

- Direct acting:
    - Pilocarpine 1-4% (Trade name - Isopto)
    - Aceclidine 2% (Trade name Glauco stat)
    - Carbachol 0.75-3%, (Trade name Isopto Carbachol)
    - Acetylcholine 1% (Trade name Miochol)
- Indirect acting:
    - Demecarium bromide 0.125%, 0.25% (Trade name - Humorsol)
    - Ecothiophate 0.03, 0.25%, (Trade name – Phospholine Iodide)
    - Physostigmine (Trade name – Piloeserine)
- Combinations:

- Carbachol 0.75% + Pilocarpine 2% + HCL Procaine 2% (Mios)

Contra-indications

Direct-acting

Less than 40 years old, cataract, uveitis, neovascular glaucoma- assess worsening of pupillary block in each case of CAG.

Indirect acting

Active uveal inflammation

- CI – chronic inflammation
- Dilate blood vessels in inflamed eye (with already dilated vessels) and could lead to pupil block
- Light coloured eyes – pronounced miosis
- Should be used in extreme caution in patients with respiratory disorders
- Parasympathomimetics can cause constriction of airways

Side- effects

Direct acting

- **Systemic:** Intestinal cramps/ bronchospasm
- **Ocular:** Miosis, pseudomyopia (up to 8D), brow ache, retinal detachment, ciliary spasm, increased pupillary block

Indirect acting

- Cardiac irregularities
- Intestinal cramps
- Ocular: Stinging, burning, lacrimation, browache, pseudomyopia, retinal detachment, conjunctival thickening, increased pupillary block, iris cysts, cataract.

Cautions

- Pregnancy/ breastfeeding- only if potential benefits outweigh risks to foetus- indirect acting agents contra-indicated
- Drug interactions (Direct acting)- prostaglandins- competitive interaction on outflow (action on ciliary muscle)
- Indirect acting- Systemic anticholinesterases- possible additive effect. General anaesthesia with muscle relaxants.
- Miotic eye drops should not be used with patients with asthma
    - Cause bronchospasm

COMBINED DRUG PREPARATIONS

Table 8.1 Combination therapy

Starting	Additional	Remarks
α_2-agonists	β-blockers	
	Topical CAIs	Good additive IOP lowering effect
	Prostaglandin	
	Prostamides	
	Sympathomimetics	Additionl IOP lowering effect is relatively poor
β-blockers	α_2-agonists	Good additive IOP lowering effect
	Topical CAIs	Good additive IOP lowering effect Available in combined preparation
	Prostaglandin	Good additive IOP lowering effect Available in combined preparation
	Prostamides	Good additive IOP lowering effect
	Sympathomimetics	
Topical CAIs	α_2-agonists	
	β-blockers	Available in combined preparation
	Prostaglandin	
	Prostamides	
	Sympathomimetics	Additionl IOP lowering effect is relatively poor
Cholinergic	α_2-agonists	
	β-blockers	Available in combined preparation
	Topical CAIs	
Prostaglandin	α_2-agonists	
	β-blockers	Available in combined preparation
	Topical CAIs	
	Sympathomimetics	
Prostamides	α_2-agonists	
	β-blockers	
	Topical CAIs	
	Sympathomimetics	

Source: *European Glaucoma Society Guidelines. Outlines the additive effect of different groups of glaucoma drugs*

THE CHALLENGE IN GLAUCOMA TREATMENT

A large proportion of patients with progressive glaucoma still remain undiagnosed until too late. To discover and treat those at risk of losing functionally significant vision is a more preferable task than widespread treatment of IOP.

REFERENCES

- Heath G. Ocular therapeutic case studies. Medical management of glaucoma Optometry Today: 26th July 2002
- Doughty M. 2006. Drugs, Medications and the Eye. 14th Edition.
- Hopkins G, Pearson R. Ophthalmic Drugs - Fifth edition 2007. Butterworth Heinemann
- Bartlett J, Jaanus S. Clinical Ocular Pharmacology. Fourth Edition. Butterworth Heinemann 2001.