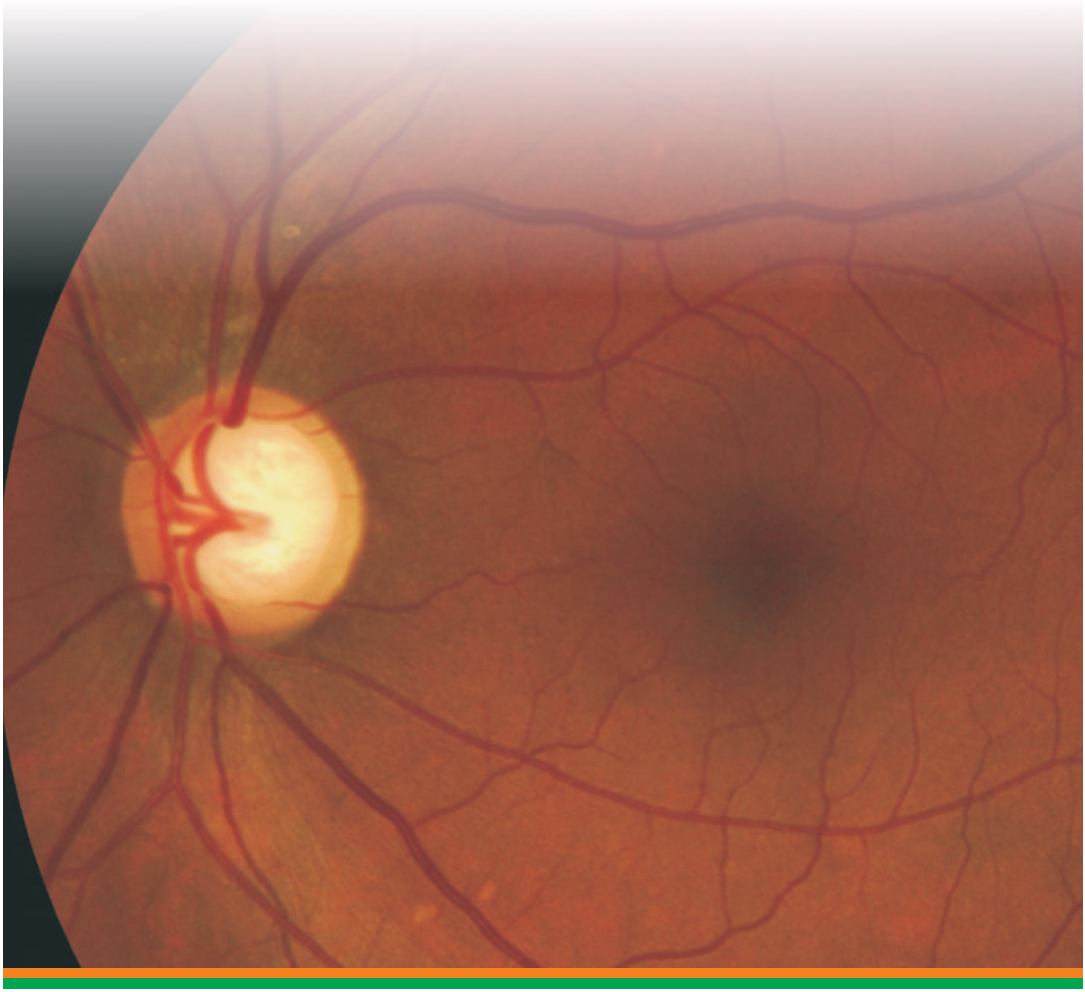
All India Ophthalmological Society

Guidelines for Medical Management Of Primary Open Angle Glaucoma



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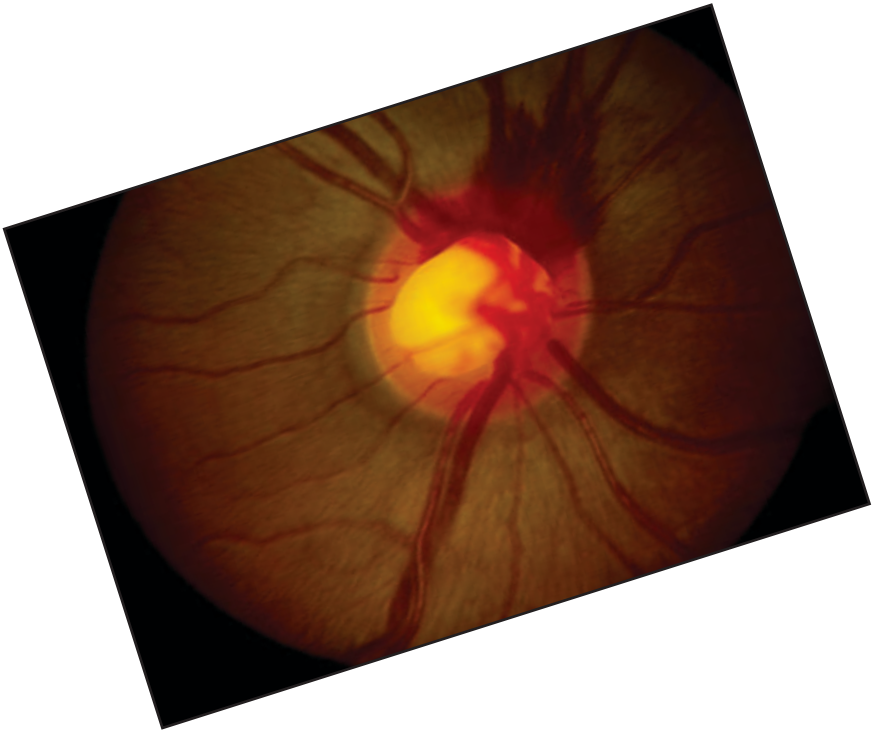

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Dedicated to the brave soldiers of the Indian Army Who have performed the supreme sacrifice for the nation

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Foreword

Medical management of Glaucoma has undergone a sea change , since the days of Pilocarpine. Newer drugs have evolved, fresh algorithms have been written. It is not uncommon to see Anti-Glaucoma drugs being started on a single reading of border-line high Intraocular pressure or drugs being added or substituted based on personal fancies, without deep understanding about the drug or the disease. Many Glaucoma specialists have hard time convincing their patients to stop the Anti-Glaucoma drops, which they have been putting for months and years.

This booklet by Dada, Ichhpujani, Vijaya, Krishnadas, Kaushik, Vyas and Sarma attempts to answer some of these questions : When to start ; How to monitor ; What are the goals of treatment; when to switch / resort to combination treatment in Open Angle Glaucoma. The highlight of this booklet is inclusion of the Summary of Key Randomised Trials on Glaucoma therapy.

Hope members enjoy reading & any queries can be addressed directly to the authors .

Thanks to M/S Cipla Ltd. for all the help.

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President (2010-2011)

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President (2011-2012)

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Introduction

Glaucoma is a group of eye diseases with multifactorial etiology, characterized by an acquired loss of retinal ganglion cells, progressive optic neuropathy with morphological abnormalities in the optic nerve head and, visual field defects, in which raised intraocular pressure (IOP) is a major risk factor. In short, it is a pressure sensitive optic neuropathy. Glaucoma is the leading cause for irreversible blindness. There are more than 65 million persons with glaucoma worldwide of which 12-15 million are in India. Hence, glaucoma is a significant public health problem in our country and requires a concerted effort on part of the health care community to alleviate the suffering caused by the disease. ***This write - up will focus on the preferred practice patterns for the medical management of Primary Open Angle Glaucoma (POAG).***

There are three major theories regarding the pathogenesis of glaucomatous optic nerve damage : -

- **Mechanical** (IOP related damage),
- **Vascular** (decrease in blood supply to optic nerve head) and
- **Biochemical** (decrease in neurotrophic factors / increased levels of neurotoxins)

Therefore the three possible therapeutic options would be to decrease IOP, increase perfusion to the optic nerve head and provide neuroprotection to retinal ganglion cells. *As of today the only viable option available to us is to decrease IOP* and treat systemic conditions which may compromise the vascular supply to the optic nerve head and decrease the perfusion pressure.

Making an Accurate Diagnosis

Since ***medical therapy*** once initiated will usually be ***lifelong***, the ophthalmologist must ensure that a correct diagnosis is made. In our experience many patients who actually have primary angle closure disease are started on medical therapy with an erroneous diagnosis of primary open angle glaucoma, as gonioscopy is often not performed.

Before starting any therapy, the key issue is to distinguish between open angle glaucoma and angle closure glaucoma, which requires visualization of the angle with gonioscopy (Fig 1a,b)*

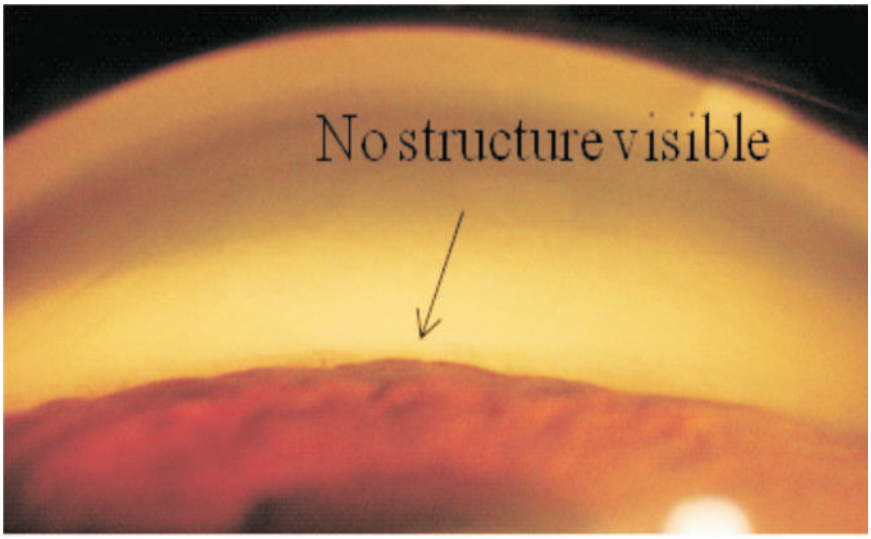

Figure 1a :
Closed Angle on Gonioscopy

On **gonioscopy**, **if the trabecular meshwork is not visualized** in more than half the circumference of the angle: **it denotes some form of angle closure disease** and if the IOP is raised, or there is evidence of Peripheral Anterior Synechiae (PAS) on gonioscopy or evidence of optic neuropathy, the first step is to do a laser peripheral iridotomy.

** Dr. Rajendra Prasad Centre for Ophthalmic Sciences has produced an educational DVD for training in gonioscopy under aegis of the All India Ophthalmological Society. This is available free to all AIOS members. (Contact : aiosoffice@yahoo.com)*

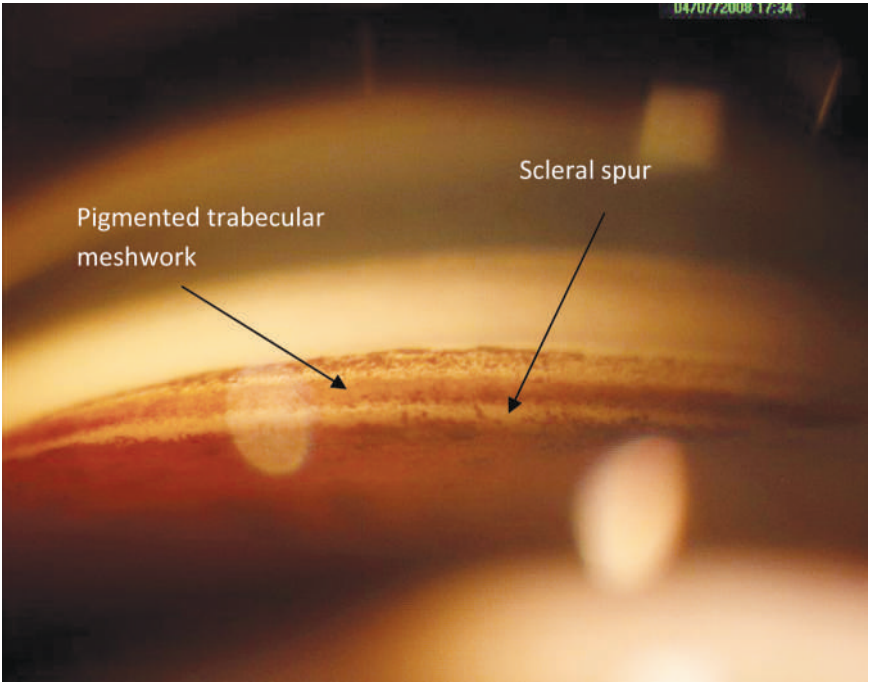

Figure 1b:
Open angle on Gonioscopy

After iridotomy, the residual glaucoma can be treated with medical therapy as for POAG.

The second critical issue is the **clinical evaluation of the optic nerve head** with a +78D or +90D lens on the slit lamp. Physiological cupping, especially in large discs must be distinguished from pathological disc changes. One must look for disc hemorrhages and retinal nerve fiber layer defects (Figure 2a, b) and other changes in the optic nerve head suggestive of glaucoma. These include a vertical cup-disc diameter ratio of 0.7 or more (Figure 3a), an asymmetry between the two eyes of 0.2 or more in the vertical cup:disc (C:D) ratio, diffuse/focal thinning or notching of the optic disc rim, especially at the inferior or superior poles (Figure 3b), sharp bending of vessels at the margin of the cup (bayonetting Figure 3c) and peripapillary atrophy (Figure 3d).

The neuroretinal rim in normal eyes shows a characteristic configuration. It is usually broadest in the inferior rim, followed by the superior and nasal rims, and thinnest in the temporal disc region. This pattern of rim width is known as the "**ISNT rule**" (inferior>superior>nasal>temporal).

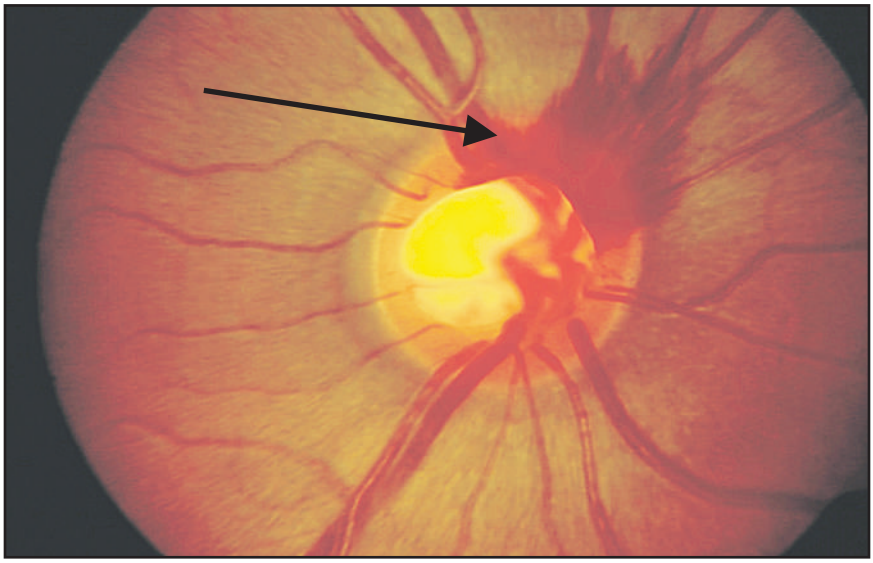

Figure 2a : Disc Hemorrhage

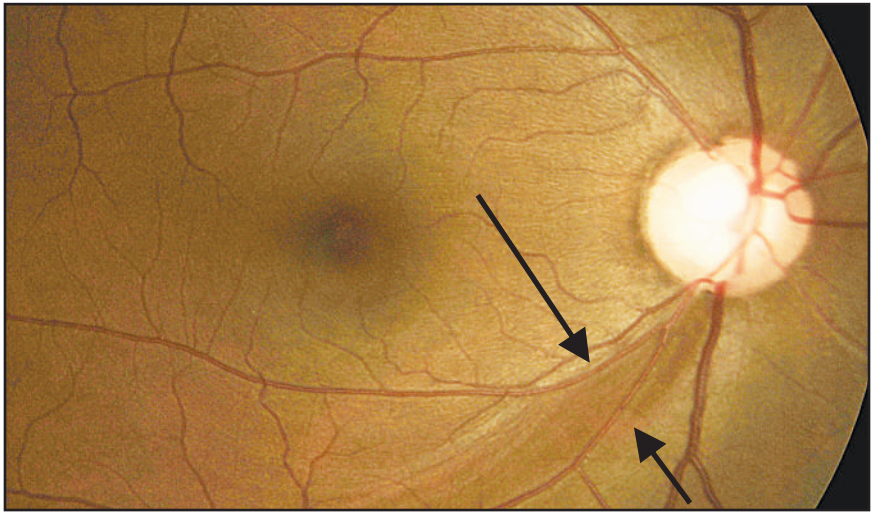

Figure 2b : Inferior retinal nerve fiber layer defect

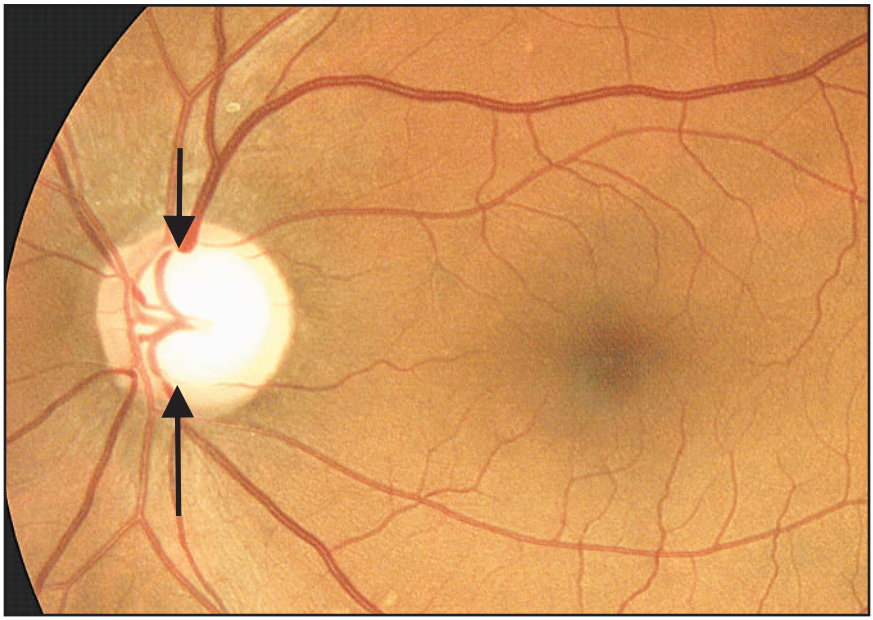

Figure 3a : Enlarged Vertical Cup Disc Diameter Ratio (0.8:1)

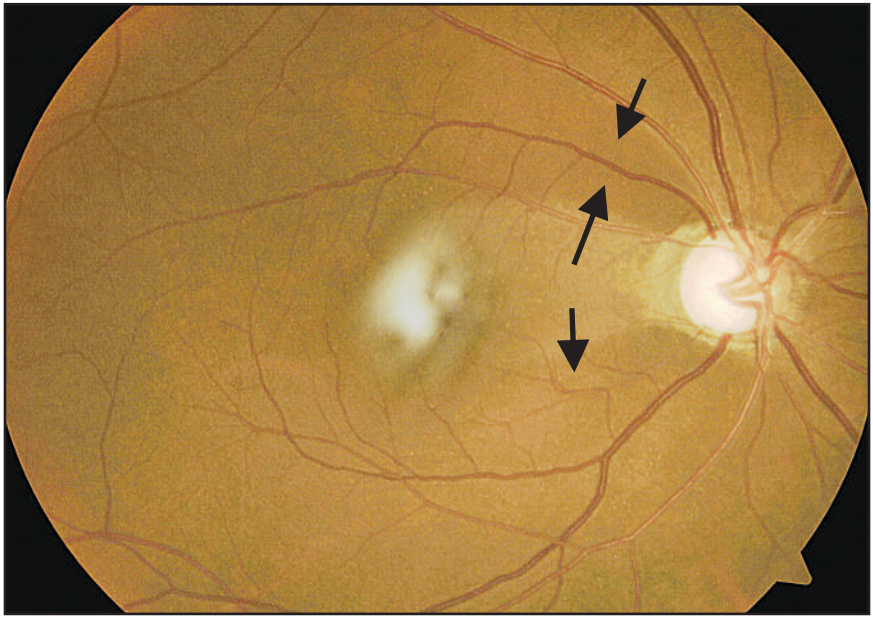

Figure 3b : Loss of superior and Inferior retinal nerve fibers

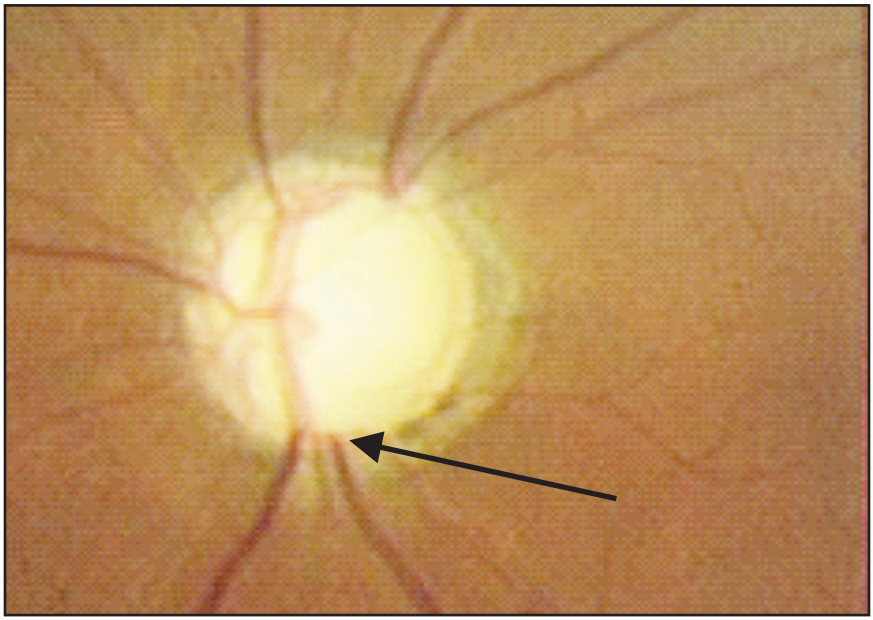

Figure 3c : Bayonetting of vessels in advanced glaucomatous cupping

After the examination of the optic nerve head and the anterior chamber angle, visual field assessment is performed as it is a test of the function of the retinal nerve fiber layer/optic nerve. **Atleast 3 visual fields should be performed to establish a baseline and taking into account the learning effect.**

Once glaucoma is diagnosed, treatment has to be initiated to lower the IOP.

Never start therapy based on a single IOP reading.It is important to establish the baseline IOP. To get baseline IOP, the IOP should be checked at multiple time points to assess the diurnal variation and fluctuation of IOP and timing of the peak IOP. If the IOP is more than 30 mmHg, it should be checked once again to confirm the high IOP and therapy started without the need for performing a diurnal phasing.

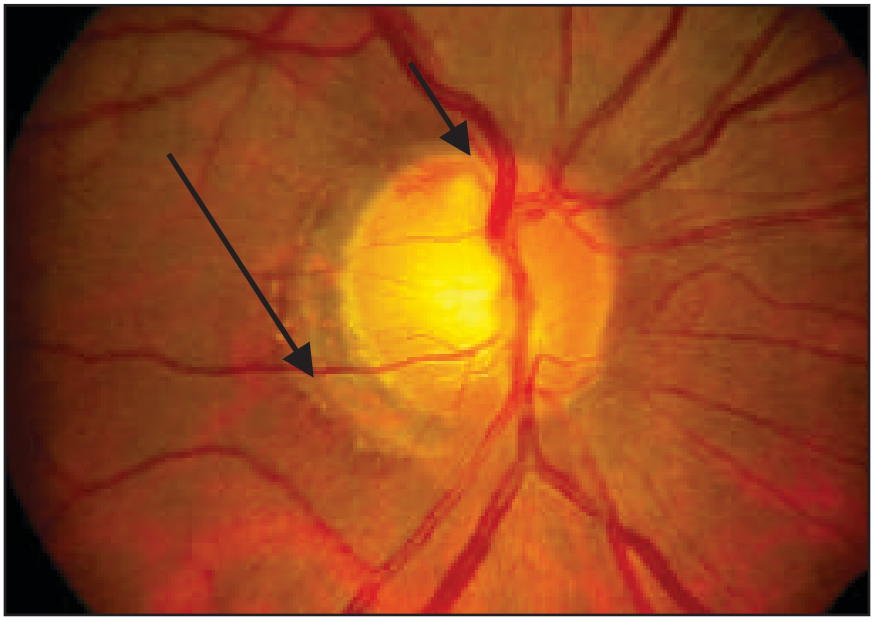

Figure 3d : Peripapillary atrophy with polar notching (Superior)

Although elevated IOP is the most important risk factor in glaucoma, one does not require an elevated IOP to diagnose glaucoma. A diagnosis of established glaucoma depends on the characteristic optic nerve changes and visual field defects. Baseline IOP and diurnal phasing are required to determine the target IOP and to assess the effects of anti-glaucoma drugs.

Important points to note in the history before initiating medical therapy

It is essential to rule out associated ocular and systemic conditions which can impact diagnosis and therapy. Specific questions regarding the socioeconomic status, insurance coverage, availability of eye drops must be asked before prescribing any medication as there can be serious problems of compliance due to socio-economic-geographical factors.

Specific points that must be noted include:

- Any systemic medications prescribed which can influence IOP or visual field or have a drug interaction :-
  - Anti-hypertensive medications (esp. **systemic beta blockers** and **calcium channel blockers**) can reduce ocular perfusion pressure and topical beta blockers should not be prescribed in patients receiving systemic beta blockers like atenolol.
  - **Anticholinergics** (eg. atropine, ipratropium, dicyclomine, etc.) / **Tricyclic antidepressants** (eg. imipramine, amitriptyline, doxepin, clomipramine, nortriptyline, etc.) can precipitate angle closure in eyes with occludable or narrow angles.
  - **Topiramate** used for seizures can lead to ciliochoroidal effusion and secondary angle closure.
  - Anticonvuslsants like **Vigabatrin** may lead to visual field defects.
  - Alpha agonists like **Brimonidine** are not to be given in patients on Monoamine Oxidase (MAO) inhibitors (eg. nialamide, tranylcypromine, moclobemide, selegiline, etc.)

- Use of **corticosteroids** as inhalers, nasal sprays or skin creams (esp. on the face) in addition to routine use as drops, tablets or injections.

- Any ocular treatment such as laser or surgery, e.g. laser iridotomy, pan retinal photocoagulation, focal/grid laser for diabetic macular oedema.
- Family history of glaucoma.
- Past history of ocular trauma (do gonioscopy to look for angle recession).
- Any other chronic diseases - cardiovascular or respiratory disease, diabetes, hypertension, hyperlipidemia, renal problems, prostatic hypertrophy, thyroid disorders, **depression**, sleep apnea syndrome and musculoskeletal disorders affecting self administration of eye drops. Beta blockers like timolol are contraindicated in bronchial asthma, COPD, cardiac conduction defects and patients with depression. Use of beta blockers in diabetic patients may mask the warning signs of hypoglycemia. Carbonic anhydrase inhibitors like acetazolamide are contraindicated in patients with known allergy to sulphonamides, severe renal impairment and nephrolithiasis.
- Cerebrovascular accidents (may cause visual field defects).
- Migraine, peripheral vasospasm and hypotension (associated with low tension glaucoma).
- Yogic exercises with head down posture (**Shirshasana**), excessive water drinking, valsalva maneuver (playing wind instruments), smoking, intake of caffeine, and use of a tight neck tie are some of the factors which may lead to rise in IOP and should be inquired into.
- In eyes with suspected normal pressure glaucoma (low tension glaucoma) the central corneal thickness should be checked and additional investigations may be done on a case to case basis in consultation with a physician/cardiologist :
    - Lipid profile, complete blood count, coagulation profile.
    - Carotid doppler testing: To rule out carotid insufficiency.

- 24 hr blood pressure monitoring, ECG
- MRI/CT scan may be performed in consultation with a neurologist (esp. in eyes where disc pallor exceeds cupping, unilateral cupping)

When to Start Therapy

Determining when to start treatment is a complex decision-making process, which must be individualized for each patient. Any decision to initiate therapy must weigh the patient's risk factors for the development or progression of glaucoma against the risk of side effects and inconveniences of treatment. The main goals of glaucoma therapy are to **preserve functional vision and quality of life**.

Treatment should be started for the following individuals:

1. Patients with optic nerve head changes suggestive of glaucoma and reproducible glaucomatous visual field loss.

2. Patients with progressive changes in Retinal Nerve Fiber Layer (RNFL) and /or optic nerve head (ONH) in the absence of visual field changes – as these are predictive of future functional loss. Treatment is indicated for patients whose rates of progression are likely to result in loss in vision-related quality of life over the projected remaining years of life.

3. Glaucoma Suspects (including ocular hypertensives) who are at a ***"high risk"*** of developing functional impairment due to the presence of risk factors like age, family history, race, IOP, central corneal thickness (thin cornea), increased vertical CD ratio, disk hemorrhages, pseudoexfoliation, central retinal vein occlusion, one eyed patients and those with systemic microvascular/ cardiovascular diseases associated with a reduced perfusion pressure.

Goals for Glaucoma Therapy

The purpose of glaucoma therapy is **to preserve the vision related quality of life of the patient** such that the patient does not develop any functional impairment in the entire life span (during his/her lifetime). The specific goals of therapy include :

1. To **achieve target IOP** and reduce IOP fluctuations with minimal possible medications.
2. To administer glaucoma medication which have the least side effects on the quality of life of the patient.
3. To achieve treatment at an affordable and sustainable cost for the patient.
4. Monitor the structure and function of the optic nerve for further damage and adjust the target IOP to a lower level if deterioration occurs.
5. To treat systemic factors (systemic hypertension, low diastolic perfusion pressures [diastolic blood pressure minus IOP], diabetes, hyperlipidemia, vasospasm) which may contribute to the development and worsening of glaucomatous optic neuropathy.
6. To educate and involve the patient and his family in the management of the disease process.

Setting the Target IOP

Target IOP is defined as *"A range of acceptable IOP levels within which the progression of glaucomatous neuropathy will be halted/ retarded"*.

The target IOP is dependent on:

a) IOP level before treatment (lower the untreated IOP levels, lower the target IOP).

b) Stage of glaucoma (greater the pre-existing damage, lower the target IOP).

c) Rate of progression during follow up.

d) Age and life expectancy (younger age requires lower target IOP).

e) Presence of other risk factors, e.g., exfoliation syndrome, disc hemorrhages, thinner CCT.

f) Family history.

g) Systemic microvascular diseases (Diabetes, Hypertension, Stroke, coronary artery disease).

When initiating therapy, it is assumed that the measured pretreatment pressure range resulted in optic nerve damage, so, the initial target pressure selected is at least 20% lower than the pretreatment IOP.

As a general guideline the IOP in any established case of glaucoma should always be kept below 18 mmHg and the fluctuation between peak and trough IOP $\leq$ 3 mmHg. The specific target IOP can be set by classifying the disease based on severity of glaucomatous damage as follows:

Mild Disease

Glaucomatous optic nerve / RNFL abnormalities (progressive structural damage) with normal visual fields and patients with ocular hypertension who are at "high risk" for conversion to POAG.

Target IOP: 20 % IOP reduction from baseline values; keep IOP < 18 mmHg.

Moderate Disease

Visual field abnormalities in one hemifield but not within 5 degrees of fixation (figure 4)

Target IOP: 30% IOP reduction; set IOP below 15 mmHg

Severe Disease

Visual field abnormalities in both hemifields or field loss within 5 degrees of fixation (figure 5)

Target IOP: 50% IOP reduction; set IOP below 13 mmHg

At each patient visit the target IOP should be reassessed and may need to be modified depending upon the stability & worsening of the glaucomatous damage. It is important to remember that the actual "target" of glaucoma therapy is the "patient" not the "IOP". In some elderly patients with a stable disease over several years of follow up, the target IOP may actually be reset at a higher level (esp. if glaucoma medications are causing side effects and worsening the quality of life of the patient). In other words, setting target IOP is not an one time exercise.

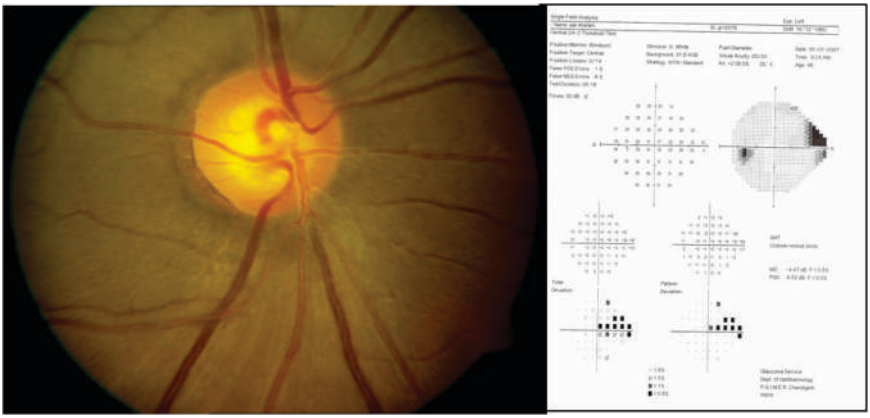

Figure 4: Moderate disease with primary involvement of one hemifield

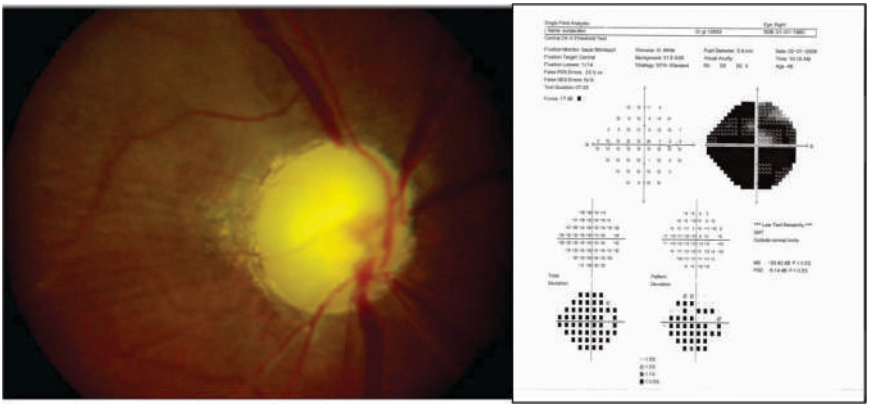

Figure 5: Severe disease with both hemifields and central 5 degrees involved

How to start therapy?

Once the diagnosis of glaucoma has been confirmed, ocular hypotensive medications can be given, **starting with one drug at a time.** Therapy is usually started in worse eye (usually with higher IOP/more structural and functional damage) first. This is known as the "***one eye therapeutic trial***". The reduction in IOP in the treated eye minus the reduction in IOP in the fellow eye gives an estimate of the IOP lowering capability of the drug. However there may be a cross over effect due to systemic absorption of beta blockers and IOP reduction in the untreated eye. If the office setting permits, multiple IOP readings may be taken before (diurnal variation) and after starting therapy (diurnal control) to get an accurate idea of the peak IOP, IOP fluctuation, timing of IOP spike and the drop in IOP induced by the drug.

A drug with atleast 20% IOP lowering efficacy is chosen as the first line therapy (usually a ß blocker or prostaglandin analogue). After the peak IOP reduction ability of that drug is reached (usually 4-6 weeks), diurnal phasing of IOP (ideally IOP reading at every 3 h from early morning to late night e.g. 7 am, 10am, 1pm, 4pm, 7pm, 10 pm, 1am 4 am) is evaluated to look for reduction in IOP and fluctuation. In eyes with ocular hypertension - if a decision has been made to treat and in cases with early glaucoma, topical beta blocker therapy may be initiated as the first line therapy provided there are no systemic contra-indications. This is also a better option if a decision has been made to treat only one eye, due to the cosmetic side effect of prostaglandin analogues on unilateral use (lash growth, peri ocular pigmentation, iris color change, hyperemia).

Once there is moderate/severe visual field damage, a prostagladin analogue is preferred as it is more likely to achieve desired target IOP. ***A prostaglandin drop which is free from Benzalkonium chloride (BAK) is the preferred option*** for long term therapy as BAK is associated with dry eye and ocular surface disorders.

In eyes with NTG, prostaglandin analogues are the preferred choice to start therapy and beta blockers should be avoided as they are absorbed systemically and can lead to a decrease in optic nerve head perfusion pressure. Alpha agonists / carbonic anhydrase inhibitors can be added as second line therapy in such cases. Table 1 summarizes the salient feature of glaucoma medications.

The target IOP may be written in the outpatient card/file and at 6 weeks after starting therapy, it should be checked if the desired target IOP has been achieved or not.

When to switch or add another drug?

If the drug achieves the desired target IOP, it is continued and started in the second eye. **If the drug fails to reduce IOP by at least 20% IOP from baseline or produces severe side effects, we switch to another class of drugs.** However, if the first drug does reduce IOP more than 20% from baseline but target IOP level is not reached, a second drug is added. **A time interval of at least 5 minutes should be given before administering the second drop.** In case IOP does not reach target IOP with three topical anti glaucoma medications, laser trabeculoplasty / filtering surgery should be considered.

For example, let us consider treatment of a case of moderate glaucoma with a target IOP of below 15 mmHg. The baseline peak IOP is 25 mmHg. A prostaglandin is started and the IOP falls to 17.5 mmHg, i.e. a 30% drop in IOP. Hence, the first principle (>20% reduction from baseline) is satisfied but target IOP is not met. In this situation, a second drug is added to further lower IOP—like beta blocker, timolol.

Taking a similar situation, timolol is started as first line therapy and the IOP falls from 25 mmHg to 22.5 mmHg, i.e. a 10% reduction. Hence, the first rule (>20% IOP reduction) is not met and in this situation we should not add a second drug but substitute timolol with a different class of drug like prostaglandin or alpha agonist.

However, if a prostaglandin analogue is not found to be effective in adequately lowering IOP by >20% , in this situation we can perform an intraclass switch between prostaglandin analogue (e.g. switch travoprost/bimatoprost for latanoprost). ***Switching medications intraclass other than in prostaglandin analogues is not effective and should not be done.*** eg. timolol and betaxolol.

If the agent is ineffective or not tolerated, it is discontinued. It is important to be aware of the wash out effect of the drug which has

been stopped. ***Wash out period*** for beta blockers and prostaglandins is nearly 6 weeks, 3 weeks for adrenergic agonists, 1 week for topical carbonic anhydrase inhibitors, and 3 days for pilocarpine and oral acetazolamide.

Patients on long-term beta blocker therapy may suffer from tachyphylaxis (decreased effect of drug due to change in receptor sensitivity or number of receptors). In such cases a *"**reverse one-eye therapeutic trial**"* is performed in which the drug is discontinued in one eye, and the results are compared with those for the eye in which treatment is continued.

Combination Therapy

If IOP is not at target with a single drug, a second drug is added. These two drugs should have different mechanism of action and the best combination is a prostaglandin analogue (which increases outflow) with a beta blocker (which decreases inflow).

Using combination eye drops with two drugs in the same bottle is a good choice if more than one drug is required as it ***decreases number of eye drops to be instilled into the eye, decreases preservative induced conjunctival toxicity and increases compliance***. The most important benefits of fixed-combination therapies are that they provide equivalent IOP reductions with the potential benefits of improved compliance, patient convenience, and cost savings. Also, fewer drops per day mean decreased exposure of the ocular surface to long term side effects of preservatives.

A disadvantage that should be highlighted is that it is not possible to change the drug concentration or dosing schedule for one component of medication independently of the other when using a fixed combination. Additionally unless the IOP lowering capability of each component has been tested in the given patients, one is not sure about the individual effectivity of the drug in the combination. If more than two drops of glaucoma medication are required in a day, a combination therapy must be used as there is a drastic fall in compliance levels beyond this. The main purpose of combination therapy is simplify the dosing regimen for the patient to ensure a good compliance and adherence, as this is a very important issue for a therapy that may last for the entire life span of the patient.

Glaucoma Therapy in Pregnant and Lactating females

In managing the pregnant glaucoma patient with medical therapy, one must consider not only the systemic side effects on the mother but any potentially harmful effects on the developing fetus. Laser trabeculoplasty (esp. SLT - selective laser trabeculoplasty) can be considered as an alternative to medications.

Most topical glaucoma medications belong to the medication safety during pregnancy category C, deemed as having uncertain safety because of adverse fetal effects in animals. ***No glaucoma medications should be used at the time of conception or during the first trimester.*** If IOP is elevated in a patient with advanced glaucoma, surgery should be considered prior to conception.

Medication safety during pregnancy (US FDA)

- **Category A:** Safety established using human studies.
- **Category B:** Presumed safety based on animal studies.
- **Category C:** Uncertain safety; no human studies; animal studies show adverse effect.
- **Category D:** Unsafe; evidence of risk that in certain clinical circumstances may be justifiable.
- **Category E:** Studies, adequate, well-controlled or observational, in animals or pregnant women, have demonstrated positive evidence of fetal abnormalities.

Alpha agonists*:* Brimonidine has been ascribed **class B** status, which presumes safety based on animal studies only, however, it can cross the placenta and lead to apnea in neonates, so should not be given after the 8th month of pregnancy or before child birth. Apraclonidine is in category C and is generally not recommended.

Carbonic Anhydrase Inhibitors (CAIs) *:* Topical CAIs are in category C, while the fixed-combination timolol 0.5%/dorzolamide 2% has been designated category D. Systemic CAIs are generally contraindicated in pregnancy as they can lead to electrolyte imbalance and increase the risk of sacrococcygeal teratoma and transient renal tubular acidosis in neonates.

Prostaglandin agents*:* Prostaglandin-related drugs are in category C. Use of the prostaglandin analogues during pregnancy can stimulate uterine contractions and lead to premature labor.

Beta blockers*:* Beta blockers belong to category C but have a long track record and are even used by obstetricians for systemic hypertension during pregnancy. Cardioselective beta blockers are preferable, but beta blockers should be stopped after 8th month of pregnancy to avoid possible beta blockade in the neonate. It is preferable to use these drugs as a sustained release gel version which has low systemic absorption. Always perform tear duct occlusion for two minutes after instilling the eye drops.

Pilocarpine is a category C drug and may be used during pregnancy but is associated with headache/browache and generally not tolerated by young patients.

The recommendations during pregnancy are :

- Try to avoid ALL medications during pregnancy and breast-feeding if at all possible;
- All glaucoma medications are contraindicated in the first trimester
- Plan ahead - if pregnancy is desired, take time to control the glaucoma by laser or by surgery first and then conceive;
- If drugs HAVE to be used, use the least number, the lowest concentration, the least number of times each day, and employ special techniques (tear duct occlusion, sustained release

preparations) available to minimise drug concentrations in the blood.

- **Brimonidine, Betaxolol** and **Pilocarpine** are relatively safe drugs to use in the second and third trimester but should be discontinued in the 8th month, to avoid adverse effects on the fetus.

During lactation betaxolol can be used but tear duct occlusion must be done to decrease systemic absorption. Brimonidine should be avoided as it can lead to apnea, bradycardia and hypotension in the neonate.

Technique for eye drop instillation

Although this may sound very simple, in a recent study done by the author (Evaluating Eye Drop Instillation Technique in Glaucoma Patients. J Glaucoma. Feb 2011) ***it was found that 9 out of 10 glaucoma patients were unable to self administer eye drops correctly.*** Hence it is essential to teach our patients the correct technique and check this during follow up visits. The correct technique (Figure 6) is as follows:

- The patient should be instructed to wash both hands, sit down on a chair or lie in bed. If seated, the head is tilted slightly backwards while gazing upward.
- The lower lid is gently pulled down with the nondominant hand to form a small concavity in which the drops will be placed.
- With dominant hand, the dispenser is held above this concavity. The bottle should be near enough to make sure that the drop will enter the eye and far enough so as not to touch it (2-5 cm).
- Avoiding blinking and the body of the bottle is pressed so that a single drop falls into the eye. After application, lids should be kept closed (or digital compression is applied to the punctum for 2 minutes to minimize systemic absorption).
- The bottle cap should be replaced and any excess fluid wiped from the skin, especially when using prostaglandin medications that may darken the skin colour.
- The patient should be asked to schedule drops instillation with a daily activity (like brushing teeth, breakfast or dinner) and always keep one extra bottle at home/ during travel, so that the therapy is not stopped if a bottle finishes or the patient travels to another city.

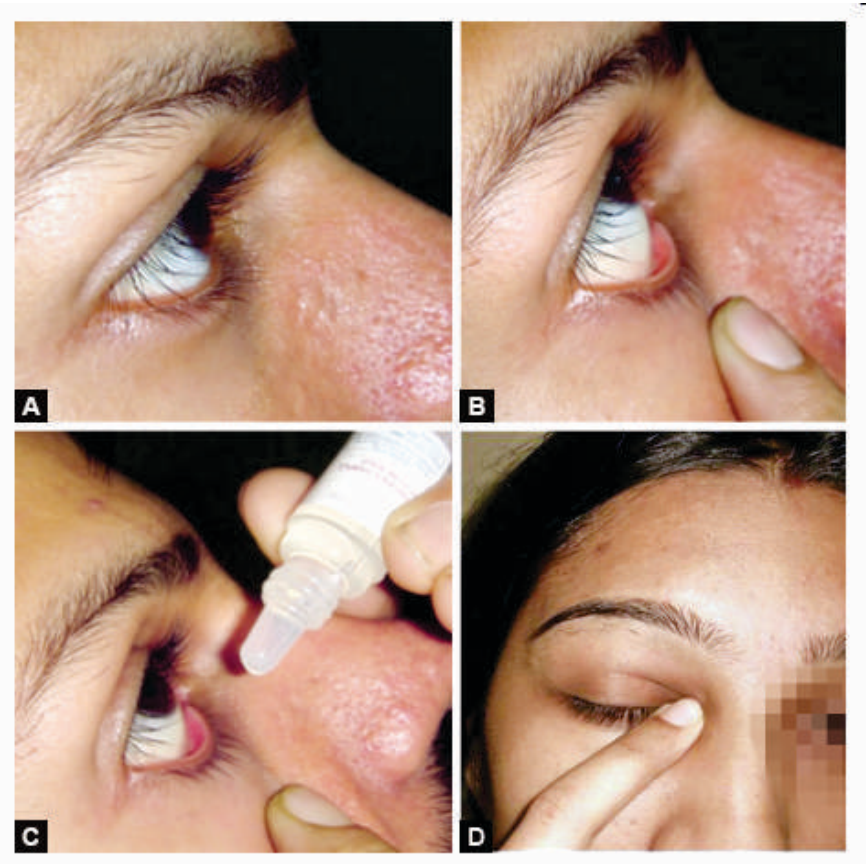

Figure 6: Technique for eye drop instillation
Double DOT technique
*(**'**Don't open the eyelid' and 'Digital occlusion of the tear duct')*

Follow Up

In general a patient with established glaucoma should be followed up every six months, however the frequency of follow up can be increased or decreased depending on the severity of disease and whether there is any progression or not over time. After the initial diagnosis has been made, 3-4 monthly follow up may be done for the first 1-2 years to establish the slope of progression (to see if the patient is progressing fast/slow or is stable). In suspects and stable patients with early disease, an yearly follow up may be adequate, while in advanced cases or documented progression, a 3-4 monthly follow up would be advised.

In addition to treating the ocular condition, the ophthalmologist should also focus on educating the patient to adopt a healthy life style and take care of any systemic disease factors. Such measures include asking the patient to stop smoking, wear a loose tie, regular exercise, decrease weight if obese, and meditation to decrease the stress associated with disease and improve the quality of life. ***For primary prevention and early detection, periodic checkup of other family members of the glaucoma patient is recommended.***

The patient and his family must be made partners in the decision making process and explained the **need for regular eye examinations and treatment throughout life.** It should be emphasized to the patient that vision lost in glaucoma cannot be restored and the purpose of therapy is to preserve existing vision.

Salient Features of Glaucoma Medications

Prostaglandin analogues (PGAs)

- Prostaglandin analogues (Latanoprost 0.005%, Bimatoprost 0.03% and 0.01%, Travoprost 0.004%, Tafluprost 0.0015%) act by increasing the uveoscleral outflow, this novel mechanism of action empowers them to potentially lower the IOP below the episcleral venous pressure, a potential advantage in Normal Tension Glaucoma.
- PGAs effectively lower the IOP during night as well as day – an advantage over the b blockers which are not effective at night.
- Their once a day dosing improves patient compliance.
- Preservative free versions are now available and should be preferred.
- Conjunctival hyperemia, lash growth, iris and periocular pigmentary changes are the common ocular side effects.
- Active uveitis, herpetic keratitis and active CME post cataract surgery are relative contra-indications.
- Due to their low therapeutic concentrations and rapid systemic inactivation, they do not have significant systemic side effects.

Beta Blockers

- Beta-blockers (Timolol and Betaxolol 0.25% and 0.5%) are no longer the most potent class of IOP-lowering medication available but they remain efficacious and well tolerated by most patients, making them a fair choice as first-line agent to this day.
- Beta-blockers induce ß receptor blockade which lowers aqueous humor formation and secretion, especially during day time.

- Beta-blockers are less effective at night because of physiologically less aqueous flow during sleep.
- Nonselective ß-blockers (timolol) lower IOP by 20 to 30 percent, while selective ß-blockers (Betaxolol) lower IOP by 16 to 20 percent.
- Topical ß-blocker therapy may produce a smaller than expected IOP reduction in patients under systemic b-blocker therapy and are preferably avoided in such patients.
- Contraindicated in COPD/asthma patients, sinus bradycardia, second degree heart block.
- Once-daily dosing with sustained release preparations, starting treatment with lower concentrations and use of nasolacrimal occlusion techniques may help decrease systemic exposure to the ß-blocker.

Alpha Agonists

- Brimonidine (0.1% to 0.2% , two times a day) reduces aqueous production and also increases uveoscleral outflow.
- Brimonidine is generally additive to other classes of glaucoma medications and recent studies show that 0.2% brimonidine may be efficacious to use in Low Tension glaucoma patients through a non-IOP dependant effect, although the high rate of ocular allergy (25-30%) is a serious drawback.
- The side effects of brimonidine include ocular allergy, follicular conjunctivitis, lid edema, dry mouth, sedation, headache, and fatigue.
- The use of brimonidine in children below 6 years should be avoided because it has been associated with a risk of central nervous system depression resulting in somnolence, hypotension, seizures, and apnea.

Carbonic anhydrase inhibitors (CAIs)

- CAIs (2%) Dorzolamide TDS and 1% Brinzolamide BD decrease aqueous humor formation by direct antagonistic activity on ciliary epithelium carbonic anhydrase.
- Long-term use of topical CAIs can have an adverse effect on the corneal endothelium—especially important in already compromised corneas.
- The CAIs belong to the sulfonamide class of drugs and therefore, can cause similar reactions and cross-reactivity in susceptible individuals.
- Oral CAIs (acetazolamide 5mg/kg/dose) remain a useful choice for acute IOP lowering in all types of glaucomas.
- Topical agents cause stinging, burning and a bitter taste in the mouth. Brinzolamide is preferable due to a more neutral pH and improved tolerance.

Table 1: Ocular hypotensive agents

Drug	Mechanism of action	Efficacy	Local side effects	Systemic side effects	Peak effect, washout period
Prostaglandin analogues: latanoprost, bimatoprost, travoprost, tafluprost	Increases uveo scleral outflow by remodeling the extracellular matrix between the ciliary musculature	Most efficacious of all topical anti glaucoma medications. Decrease IOP about 30-35% from baseline. Worldwide the first line drug	Conjunctival hyperemia, stinging, hypertrichosis, trichomegaly, periocular skin pigmentation, uveitis, cystoid macular edema in pseudophakes and aphakes	No known serious side effects. Some reports of transient flu like symptoms, joint pains	2 weeks, 6 weeks
Beta blockers: timolol, betaxolol (cardioselective), levobunalol,	Act on beta adrenergic receptor on the ciliary body and decrease aqueous production	Decrease IOP about 25-30% from base line. Efficacy decreases over a period of time called as long term tachyphylaxis	Ocular stinging, ocular hypesthesia, epitheliopathy.	Side effects common on long term instillation. Bradycardia, heart block, bronchospasm, hyperglycemia, depression, psychosis.	4-6 weeks, 4-6 weeks
Alpha adrenergic agonists: brimonidine, apraclonidine	Act on alpha adrenergic receptors on ciliary vasculature and decrease aqueous production and also increase uveo scleral outflow	20-25% decrease in IOP from base line. Very efficacious as a prophylaxis to decrease post laser IOP spike	Follicular conjunctivitis, associated periocular contact dermatitis, blepharo conjunctivitis, lid retraction.	Brimonidine crosses blood brain barrier to cause systemic hypotension and drowsiness. It is thus contraindicated in children (< 6yrs, < 20kg)	2 weeks, 2 weeks
Cholinergic agonists: Pilocarpine	Increases trabecular outflow	Decreases IOP by 20 - 25%	Headache, brow ache, induced myopia, miosis, conjunctival hyperemia, iris cyst, uveitis, cystoid macular edema, retinal detachment	Abdominal cramps, sweating, bronchospasm, diarrhoea	3 hours, 1 week
Carbonic anhydrase inhibitors: dorzolamide, brinzolamide	Decreases aqueous production by inhibiting carbonic anhydrase enzyme in the ciliary processes	Decreases IOP by 20-25% from baseline	Stinging and burning sensation, corneal decompensation in Fuch's cornea and post keratoplasty eyes	Bitter taste in the mouth, rarely drug hypersensitivity	72 hrs, 1 week

CAIs= carbonic anhydrase inhibitors. CME: Cystoid macular edema.

Summary of Key Randomized Controlled Trials on Glaucoma Therapy

In the last two decades several landmark collaborative multicentric Randomized Controlled Trials (RCTs) have been conducted regarding medical therapy in various stages in glaucoma. We can derive certain important guidelines from these studies which may benefit us while treating individual patients.However one has to understand that these trials have been done in largely caucasian populations with rigid inclusion and exclusion criteria in a well controlled environment and may not be directly applicable to our patients in the clinic. Key messages from these trials are summarized below:

Ocular Hypertension Treatment Study (OHTS)

Primary Goals

1. To evaluate the safety and efficacy of topical ocular hypotensive medication in delaying or preventing the development of POAG in individuals with elevated IOP
2. To identify baseline demographic and clinical factors that predict which participants will develop POAG

OHTS Entry Criteria

1. Age 40 -80
2. Normal visual fields –Humphrey 30-2
3. Normal optic discs
4. Untreated IOP:
   - 24 to 32 mmHg in qualifying eye
   - 21 to 32 mmHg in fellow eye

Treatment Goals

Reduce pressure to less than or equal to 24 mm Hg with a minimum pressure reduction of 20% from the baseline.

Outcome Measures

1. Development of a reproducible visual field abnormality and/ or
2. Development of glaucomatous optic disc defects.

5 year OHTS Results:

Incidence of POAG was found to be 4.4% in the treatment group and 9.5% in the control group; nearly 60% risk reduction in the medication group at 60 months. (Hazard ratio for medication group 0.40 (0.27-0.59); $P \leqslant 0.001$).

More than 90% of the untreated group did not progress. End points for POAG conversion were reached by both disc and visual field findings in 10% of the patients, by optic disc findings alone in approximately 50% and visual field defects alone in around 40% of the patients. Cataract formation was more common in treatment group (6.4% vs 4.3%).

OHTS High Risk parameters for onset of POAG:

1. Decreased Central corneal thickness (strongest risk factor)
2. Higher vertical and horizontal cup disc ratio
3. Greater Pattern Standard Deviation (PSD)
4. Higher IOP

Limitations

OHTS Phase 1 provided proof of concept that medication reduces the incidence of conversion to POAG. But the conversion rate of ocular hypertension to POAG remains low at 9.5%. Also, it does not indicate

when in the course of disease, medications should begin. Moreover, it does not indicate if all OHT patients should receive early medication and if there exists a penalty for delaying medication in OHT. To provide answers to these questions, OHTS phase II study was formulated.

OHTS Phase 2: Methods

After 7.5 years of observation of phase 1, participants originally randomized to observation group were also started on medication. This created:

1. A delayed treatment group which was initially the observation group for 7.5 years and then treated for 5.5 years
2. An early treatment group in which medications were administered for median of 13 years from the beginning.

Purpose of the study was to compare incidence of POAG at 13.0 years between the two groups.

Results of OHTS Phase 2

Incidence of POAG was not different between observation (11%) and medication groups (12%) for the last five years (Hazard Ratio for medication group 1.06 (0.74-1.50, P= .77)

However, the high-risk (based on OHTS risk calculator : 5 yr risk > 13%), late-treatment group's cumulative incidence of development of POAG at the end of 13 years was 40% vs. 28% for the high-risk, early-treatment group.

Delaying Treatment of OHT may cause:

1. Increased cumulative incidence of POAG at 13 years (22% vs.16%)
2. More eyes with structural and functional damage (8% vs. 5%)
3. More participants with bilateral disease (6% vs. 4%)

4. Shorter time to develop POAG (6.0 vs. 8.7 years)

Starting treatment of POAG only at the time of confirmed diagnosis had no major negative effect on prognosis over 5 years. However, most OHT patients are at low risk; and can be followed without medication for long periods.

- Waiting does not have a large effect on MD and PSD (0.5db for PSD) within 5 years of developing POAG.
- Delaying treatment for 7.5 years resulted in only a small absolute increase in POAG in low risk participants

High risk OHT patients may benefit from more frequent examinations and early treatment taking into consideration patient's age, health status, life expectancy, and personal preference.

Summary: OHTS

1. Treatment produced about a 20% reduction in IOP.
2. Treatment reduced incidence of POAG in OHT participants by 60% at 5 years from 9.5% in the Observation Group to 4.4 % in the Medication Group.
3. African Americans have a higher prevalence and incidence of POAG; this racial effect may be due to thinner CCT and larger cup/disc ratios.
4. Early medical treatment reduces the cumulative incidence of POAG.
5. The absolute effect is greatest in high risk individuals.
6. There is little absolute benefit of early treatment in low risk individuals.
7. There are safe and effective treatment options for most ocular hypertensive patients.

8. The risk of developing POAG continues over at least a 15 year follow-up.

9. For earliest detection of glaucomatous damage, both Visual Fields and Optic Disc D must be monitored, because either alone may show signs of damage.

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Collaborative Initial Glaucoma Treatment Study (CIGTS)

Objective:

CIGTS is a randomized, controlled clinical trial designed to determine whether patients with newly diagnosed POAG are better treated by initial treatment with medications or immediate filtration surgery. This study was unique in that the target pressures were individualized for each patient.

Inclusion criteria: 607 patients with newly diagnosed open angle glaucoma were recruited.

1. POAG, pseudoexfoliative, or pigmentary glaucoma in one or both eyes.
2. 1/3 combinations of qualifying IOP, visual field changes, and optic disc findings as follows:
   a. IOP of > 20 mm Hg, Humphrey 24-2 with 3 contiguous points on the total deviation plot at the < 2% level & GHT "outside normal limits" and OD compatible with glaucoma.
   b. IOP > 20-26 mm Hg, Humphrey 24-2 with 2 contiguous points on the total deviation plot at <2% level & glaucomatous optic disc damage.
   c. IOP >26 mm Hg and glaucomatous optic disc damage
3. VA > 20/40 on ETDRS chart.
4. Age between 25 and 75 years; FU 5 years

Treatment Flow Sheet

CIGTS defined Target IOP based on the patient's reference IOP (i.e., the mean of six separate IOP measurements taken in the course of the 2 baseline visits) and reference visual field score (i.e., the mean of at least 2 visual fields taken during 2 baseline visits)

Target IOP = (1-[reference IOP + visual field score] x ref.IOP)/ 100

IOP related intervention failure: If on 2 follow-up visits, the IOP was >1 mm Hg above the target IOP, it was considered failure and treatment was stepped up.

Visual field related intervention: If visual field score was found to be > 3 units above reference V.F.S. on 3 consecutive tests performed at separate clinic visits, it was considered criteria for failure of existing treatment. (Visual field score: Ranges from 0 (no defect) to 20 (all points showing a defect at $p<0.005$ level))

These criteria were to be met each time before a further treatment step was initiated.

Outcome Assessment Methods:

1. Primary outcome measures : Visual field loss, quality of life
2. Secondary outcome measures : IOP, cataract formation, visual acuity

Results at the end of four years:

1. VF comparison: Clinically substantial VF loss occurred in 10.7% of the medically treated group in comparison to 13.5% of the surgically treated cases.
2. Initial surgery resulted in 0.36 unit worst VF score than initial medical treatment.
3. Significant decline in visual field score was related to age, race, history of diabetes and time in study.
4. IOP reduction 48% in the surgical group (17 mmHg) compared to 35% in the medical group (14 mmHg).
5. Surgery group's average IOP over time was 3.0 mmHg lower than

the medicine group. (P< 0.0001)

6. Initial surgical treatment resulted in the development of more cataracts than initial medical treatment (17% vs 6%)

7. Quality of life was initially better with drugs.

Risk factors found by logistic regression analysis to be associated with higher VF loss:

1. Older age: 40% risk every 10 yr (OR: 1.40)

2. Nonwhites: 50% risk relative to whites (OR: 1.50)

3. Diabetic patients: 59% relative to non-diabetics (OR: 1.59)

4. Patients with cataract (OR: 4.71)

5. Initial surgery: marginally positive association (OR: 1.36)

Surgical Complications:

525 trabeculectomies were performed in 300 patients randomized to the surgical arm. Incidence of complications occuring during the first post-operative month was:

1. Intraoperative bleeding: 13.5%

2. Shallow or flat anterior chamber: 14.2%

3. Encapsulated bleb: 11.9%

4. Ptosis: 11.9%

5. Serous choroidal detachment:11.3%

6. Anterior chamber bleeding: 10.5%

5 year follow-up results of CIGTS:

87.1% eyes underwent no change in optic discs whereas 6.3% experienced enlargement of the cup (progression) of whom 10%

belonged to the medicine group vs 3% in the surgical group; (p=0.007). 6.6% of eyes featured a reduction in the cup size (reversal of cupping) with 13% in the surgical group vs 1% in the medicine group (P<0.001). However this reversal of cupping was associated with lower postoperative IOP only and not with improvement of visual acuity/ central visual fields.

8 year follow-up visual field loss of CIGTS:

Substantial worsening (> or =3 dB) of MD from baseline found in 21.3% and 25.5% of the initial surgery and initial medicine groups, respectively.

Over the period to follow up to date, both initial medication and surgery were equally effective in minimizing visual field loss. This can be attributed to an aggressive IOP lowering treatment approach adopted by CIGTS. **However in the eyes with advanced POAG: Initial surgery caused less visual field progression in cases of advanced glaucoma in comparison to initial medicine group. The exception occurred in diabetics who developed greater VF loss if treated initially with surgery.**

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Early Manifest Glaucoma Treatment Study (EMGT)

Purpose:

To compare the effect of immediate therapy to lower the IOP versus late or no treatment on the progression of newly detected, previously untreated open angle glaucoma.

Methods:

1. Three hundred and sixteen eyes of 255 patients were recruited in a population based screening in the age range of 50- 80 years.
2. Visual field loss in three consecutive C30-2 Humphrey tests, optic disc changes, as determined from flicker chronoscopy and fundus photographs.
3. Follow up was done every 3 monthly with automated perimetry and 6 monthly with disc photographs.
4. The patients were divided into a treatment arm and a non treatment arm. Treatment administered included betaxolol and argon laser trabeculoplasty to lower the IOP by at least 25%.

Results:

1. EMGT treatment which reduced IOP by 25% halved the risk of progression of glaucoma (HR 0.50). **Risk decreased about 10% with each mmHg IOP reduction from baseline.**
2. Higher the IOP at follow-up, the higher the risk of progression.
3. No difference on quality of life between the two groups.
4. Increase in lens opacity was seen more in betaxolol + laser group than in no treatment group.
5. Thinner central corneal thickness was a risk factor in POAG patients and higher blood pressure was a risk factor in NTG patients.

Baseline factors increasing risk of glaucoma progression:

1. Higher IOP
2. Pseudo-exfoliation (independent risk factor)
3. Bilateral disease
4. Worse perimetric MD
5. Older age
6. Frequent disc hemorrhages

In addition to these, the study for the first time reported systemic factors associated with disease progression

7. Low ocular perfusion pressure
8. Low systolic blood pressure
9. History of cardiovascular disease

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Advanced Glaucoma Intervention Study (AGIS)

This was a prospective, multicentre, randomized study on advanced open angle glaucoma patients uncontrolled on maximal medical therapy.789 eyes of 591 patients were randomized into two groups: one was argon laser trabeculoplasty followed by trabeculectomy and then trabeculectomy (ATT) and the other was trabeculectomy followed by argon laser trabeculoplasty followed by trabeculectomy (TAT). Second and third interventions were done only after the failure of initial intervention. Patients recruited were either Caucasians or Afro-Americans.

Goals:

1. To evaluate effectivity of treatment starting with ALT and other with trabeculectomy in preserving visual function
2. Complication rate of each therapy.
3. Factors predicting outcomes of these treatment modalities.
4. To investigate the association between control of IOP after surgical intervention for glaucoma and VF deterioration over 6 years.

Outcome Measures:

1. Change from baseline in VF defect score (range 0 to 20 units)
2. Decrease of visual acuity
3. Failure of first surgery

Main outcomes:

1. Low IOP and low IOP fluctuation produce less VF progression in advanced glaucoma.
2. Eyes with IOP > 18 mmHg show greater VF deterioration; defect increases with time.

3. **Eyes with IOP< 18 mmHg at 100% visits did not show progression of initial VF defect.**

4. Eyes with IOP <18 mm Hg at < 50% of visits had an estimated worsening over follow up of 0.63 units of VF defect score (P= 0 .083).

5. Diabetes reduces the responsiveness to IOP–lowering treatments.

7 year follow up results:

1. Blacks and whites differed in their response to therapy; blacks responded better to initial ALT and whites to initial surgery.

2. Mean IOP decrease was greater for TAT; however cumulative failure rate was higher for ATT.

3. Trabeculectomy increased overall 5 year risk of cataract by 78% (RR 1.78). Marked postoperative inflammation (RR 3.29) and flat AC (RR 1.8) were particularly associated with higher incidence of cataract.

4. Trabeculectomy failure was associated with younger age, higher pre-intervention IOP, post operative inflammation and diabetes.

The main take home message from this study was that IOP in glaucoma patients must be always kept below 18 mmHg at all time points during the course of their follow up.

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Collaborative Normal Tension Glaucoma Study (CNTGS)

This study was performed to compare no treatment vs treatment in patients with normal tension/pressure glaucoma. Whether > 30% IOP reduction altered the course of NTG compared to untreated controls. Primary outcome was disease progression. Eligible patients had glaucomatous optic disc abnormality and visual field defects according to standardized criteria.

Treatment Goal: 30% reduction from baseline IOP, obtained either with medications, ALT or trabeculectomy. In case of surgery, a 20% reduction in IOP was permitted.

Methods:

140 patients with progressive NTG were randomised to:

1. Treatment arm - aiming for IOP reduction of 30% within 6 months and maintaining for 4 years.
2. Untreated arm

Inclusion Criteria:

Visual field defects: ⩾3 reliable VFs and BCVA ⩾20/30

Optic disc progression confirmed by stereo disk photographs

Results:

In about 50% cases, 30% drop in IOP was achieved either with medications, ALT or surgically. Progression occurred in 12% (7/61) of the treated eyes and 35% (28/ 79) of the untreated eyes.

Rate of glaucomatous visual field loss was significantly lower in those eyes which had achieved 30% reduction of IOP. In 50% of the cases, reduction in IOP was achieved without trabeculectomy. Cataract among treated eyes was 38% overall with 48% in surgically

treated group and 25% in medically treated group.

Risk Factors for development or progression of NTG in accordance with CNTGS:

1. Migraine: Risk ratio 2.58 (P .0058)
2. Disk hemorrhage: Risk ratio 2.72 (P.0036)
3. Female gender: Risk ratio 1.85 (P.0622).
4. Asians had a slower rate of progression (P.005)
5. No effect was found on progression of glaucoma of family history of glaucoma, age of the patient and untreated level of intraocular pressure

The main take home message from the study was that lowering IOP is effective in preventing progression of glaucomatous optic neuropathy even in eyes with normal pressure glaucoma.

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European Glaucoma Prevention Study (EGPS)

Objective: Efficacy of reduction of IOP by dorzolamide versus placebo in preventing or delaying POAG in patients affected by ocular hypertension

Participants: 1081 patients (age ⩾ 30 years)

Inclusion criteria: IOP 22 to 29 mmHg; 2 normal and reliable Visual fields (VFs), normal Optic Discs (OD) as determined by the OD Reading Center.

Outcome Measures: Efficacy end points were VF, OD changes or both. Safety end point was an IOP > 35 mmHg on 2 consecutive examinations.

Results:

Dorzolamide reduced IOP by 15% to 22% throughout the 5 years of the trial. However, the EGPS failed to detect a statistically significant difference between medical therapy and placebo in reducing the incidence of POAG among a large population of OHT patients at moderate risk for developing POAG, because placebo also significantly and consistently lowered IOP. At 60 months, the cumulative probability of converting to an efficacy end point was 13.4% in the dorzolamide group and 14.1% in the placebo group (hazard ratio, 0.86; 95% confidence interval [CI],0.58–1.26; *P* _ 0.45).

Risk factors for progression:

1. Older age
2. Thinner CCT
3. Higher Vertical Cip Disc (VCD) Ratio
4. Higher VCD ratio assymetry
5. Higher Humphrey Pattern Standard Deviation

The role of systemic blood pressure appears important with the observation in EGPS that diastolic pulse pressure < 50 mmHg and systolic pulse pressure < 125 mmHg were associated with glaucoma, and systemic diuretics were linked with a nearly 3-fold increased risk of glaucoma.

This study generated a lot of controversy as placebo was found to be as effective as dorzolamide in lowering IOP. The study results may partly be explained by a statistical effect known as "**regression to the mean**". The EGPS patients had to have at least two IOP measurements above 21 mmHg, but these could be two hours apart on the same day. That might have been the high point of the IOP fluctuation range, and because therapy was started apparently without other visits, the next IOP would be, on average, more likely lower than baseline. Hence an apparent lowering of IOP may be detected which is actually not due to the drug but a physiological dip/trough in the IOP. This is called regression to the mean, and can be minimized by having multiple IOP measurements at different times of the day (diurnal variation) or on a different day.

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Notes

Notes

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