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E S G

The Egyptian Society for the Glaucomas

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By

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Medical treatment of Glaucoma and recent advances

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*Definition of Glaucoma

Glaucoma is a progressive optic neuropathy with a characteristic morphological changes of the ONH and NFLs that subsequently followed by characteristic VF changes.

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Anatomical Physiologcal facts

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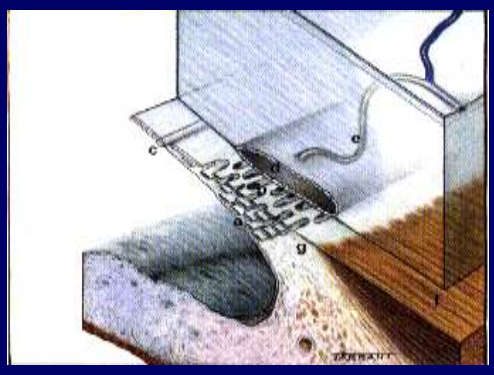
Anatomy of the angle:

- Schwalb's line (SL)
- Trabecular meshwork (TM)
- Scleral spur (SS)
- Ciliary body (CB)
- Root of the iris
- Canal of Schlemm (CS)
- Aqueous veins (AV)



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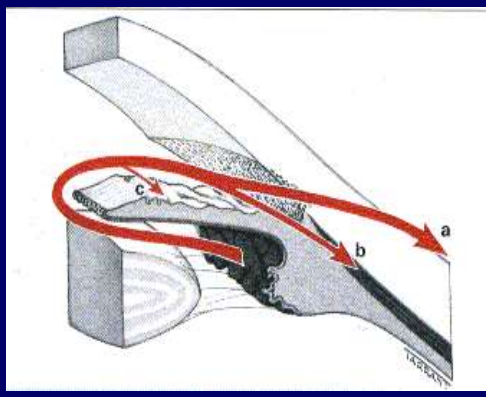
The aqueous outflow from the ciliary processes via the posterior chamber through the pupil to the anterior chamber where it exits the eye by 2 roots:

a. Trabecular meshwork (90%): TM → SC → AV

b. Uveoscleral (10%): across the CB to the suprachoroidal space to be drained by the choroid



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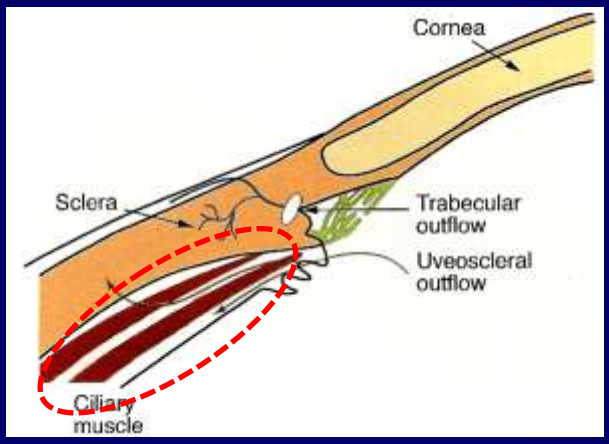

Relaxation of Ciliary muscle increase uveoscleral outflow.

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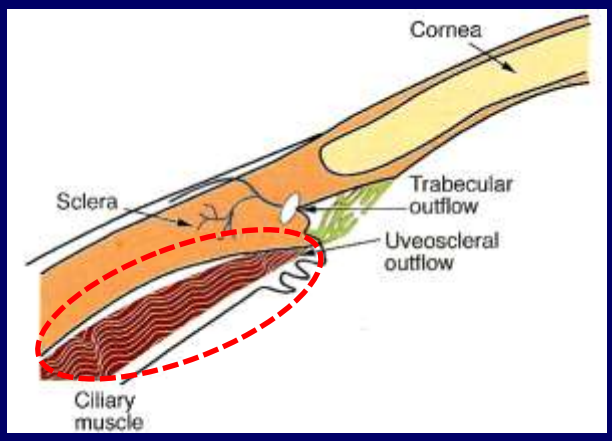

Contraction of Ciliary muscle decrease uveoscleral outflow.

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Glaucoma Treatment Plan (Principles and options)

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The goal of glaucoma treatment is to reduce the IOP to a level that maintain

The patient's visual function

The related quality of life (QoL) at a sustainable coast.

The efficacy and minimal side effect is another main factor.

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The used drugs act either by decreasing the rate of aqueous formation or by increasing the rate of aqueous outflow, or both

Recently two other concepts were introduced to enhance the blood flow of the ONH and protect the RGCs from early death (Neuroprotection)

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Glaucoma management is a complex puzzle with many factors

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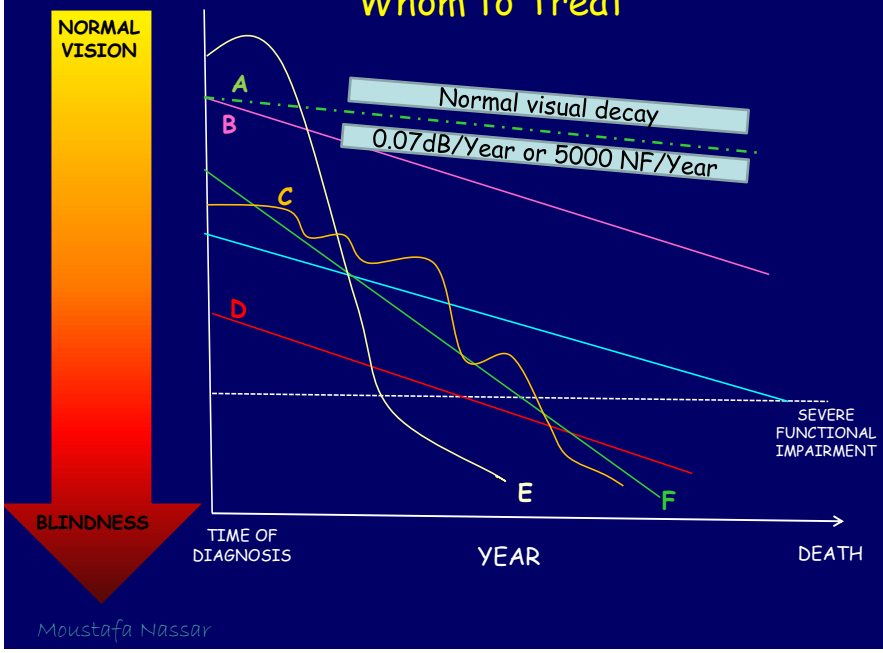
Whom to Treat



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Normal visual decay

0.07 dB / Year

- 5000 NF / Year
- 416 NF / Month
- 13 NF / Day
- 0.6 NF / Hour

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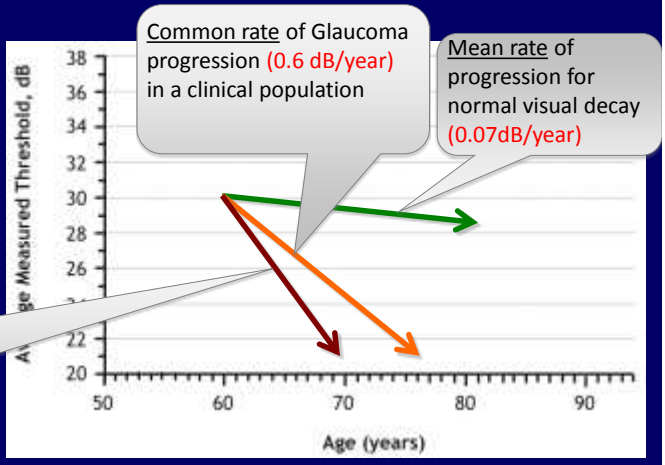
*Rate of progression in glaucoma

Glaucoma progression is **almost 10 times faster** than the normal rate of visual decay with age



Heijl et al. Arch Ophthalmol 1987;105:1544–9. Haas et al. Am J Ophthalmol 1986;101:199–203. Heijl et al. Ophthalmology 2009;116:2271–6.

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Module 6

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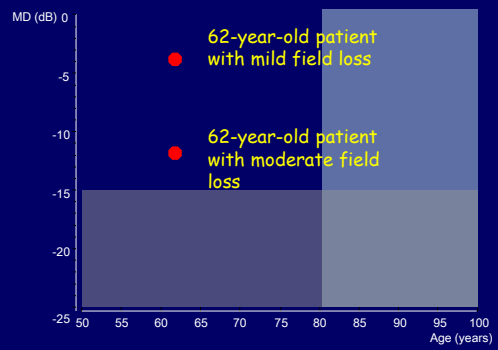
5 easy rules for management of the glaucoma patient

Newly diagnosed patients

1. See where the patient is on the age/function diagram



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5 easy rules for management of the glaucoma patient

Newly diagnosed patients

1. See where the patient is on the age/function diagram
2. Look at risk factors for progression and consider family history

Study	EMGT	CNTGS	AGIS	OHTS	EGPS
IOP	+	-	+	+	+
VF damage	+	-	+	N/A	N/A
Age	+	-	+	+	+
Exfoliation	+	x	x	x	+
Disc haemorrage	+	+	x	+	x
Gender	-	+	-	-	-

5 easy rules for management of the glaucoma patient

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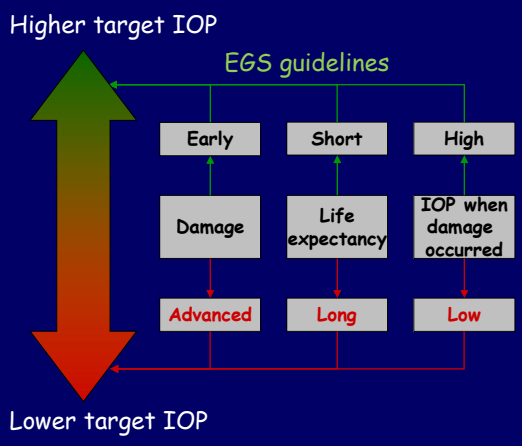
Newly diagnosed patients

1. See where the patient is on the age/function diagram
2. Look at risk factors for progression and consider family history
3. Determine target IOP, assess IOP on treatment and adjust if target is not met



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A target IOP should be adjusted to have an initial reduction of 20 – 30 % from the baseline IOP

However, it might not be enough to stop glaucoma progression.

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Target IOP

HIGHER TARGET IOP

LOWER TARGET IOP

EARLY | SHORT | HIGH | SLOW

GLAUCOMA DAMAGE | LIFE EXPECTANCY | UNTREATED IOP | RATE OF PROGRESSION

ADVANCED | LONG | LOW | FAST

Factors that should be considered as a whole in deciding the "individual target IOP"

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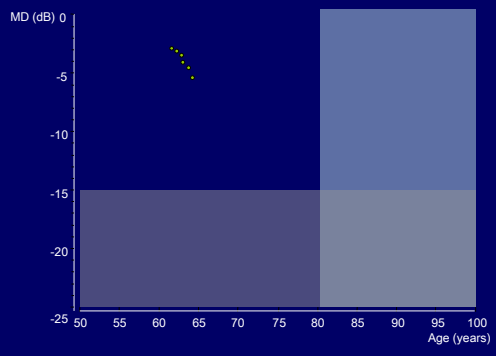
5 easy rules for management of the glaucoma patient

Newly diagnosed patients

1. See where the patient is on the age/function diagram
2. Look at risk factors for progression and consider family history
3. Determine target IOP, assess IOP on treatment and adjust if target is not met
4. Follow the patient by visual field testing every 4 months in the first 2 years (6 visual fields)



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5 easy rules for management of the glaucoma patient

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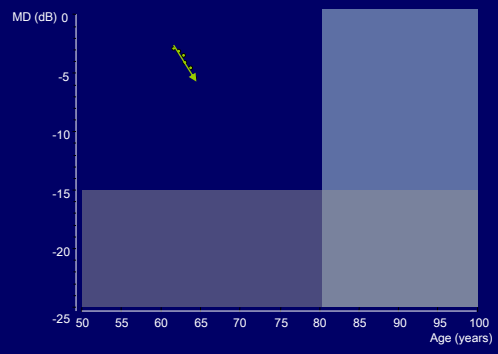
Newly diagnosed patients

1. See where the patient is on the age/function diagram
2. Look at risk factors for progression and consider family history
3. Determine target IOP, assess IOP on treatment and adjust if target is not met
4. Follow the patient and measure the VF defect on a regular basis
5. Estimate the rate of progression!



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5 easy rules for management of the glaucoma patient

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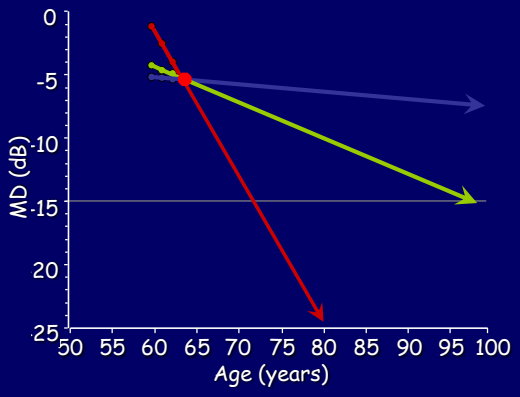
Treated patients

After 2-3 years

1. Where is the patient on the age/function diagram
2. How has the patient changed?
3. What is the rate of progression? Slow or fast?
4. Project forward!
5. OK? or time for more aggressive treatment?



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In glaucoma management it is important to consider:

-When to initiate treatment

-How to select and when to change medical treatment

-How to follow up the patient

-When to quit or when to shift to surgery

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When to start treatment

First exclude any pseudo-glaucomatous optic neuropathy

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REMEMBER

Normal Large Disc Has normal Large Cup

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Two ODs which of them is glaucomatous

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When the patient presents with established glaucomatous damage or dangerous high IOP, the descision to initiate treatment is usually clear

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How to select and When to change medical treatment

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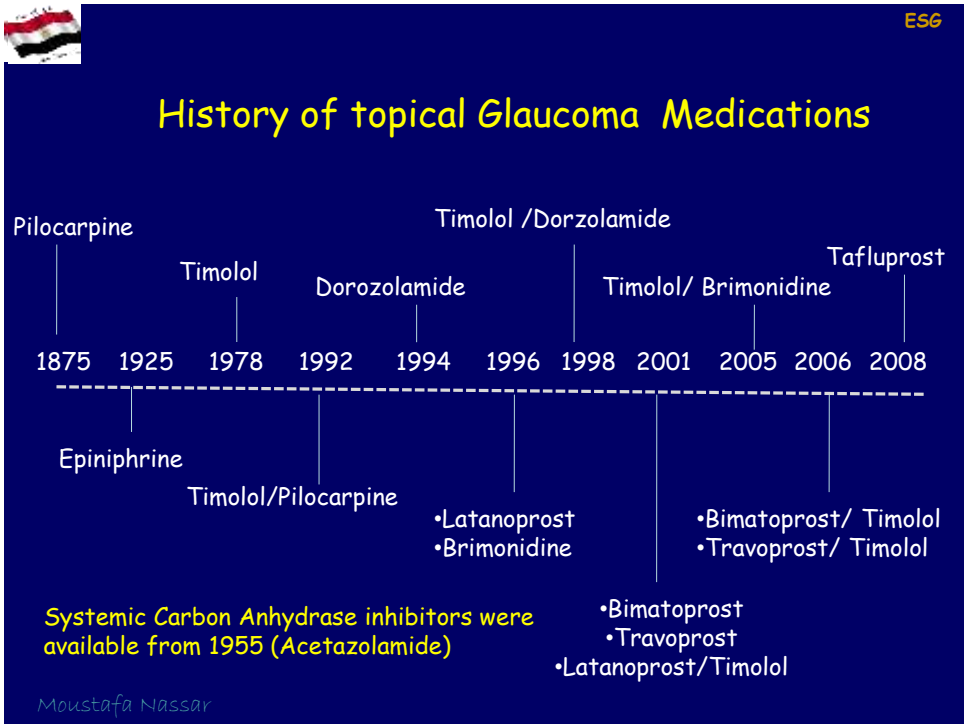
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History of topical Glaucoma Medications
Pilocarpine
Timolol
Dorozolamide
Timolol /Dorzolamide
Timolol/ Brimonidine
Tafluprost
1875
1925
1978
1992
1994
1996
1998
2001
2005
2006
2008
Epiniphrine
Timolol/Pilocarpine
•Latanoprost
•Brimonidine
•Bimatoprost/ Timolol
•Travoprost/ Timolol
Systemic Carbon Anhydrase inhibitors were available from 1955 (Acetazolamide)
•Bimatoprost
•Travoprost
•Latanoprost/Timolol
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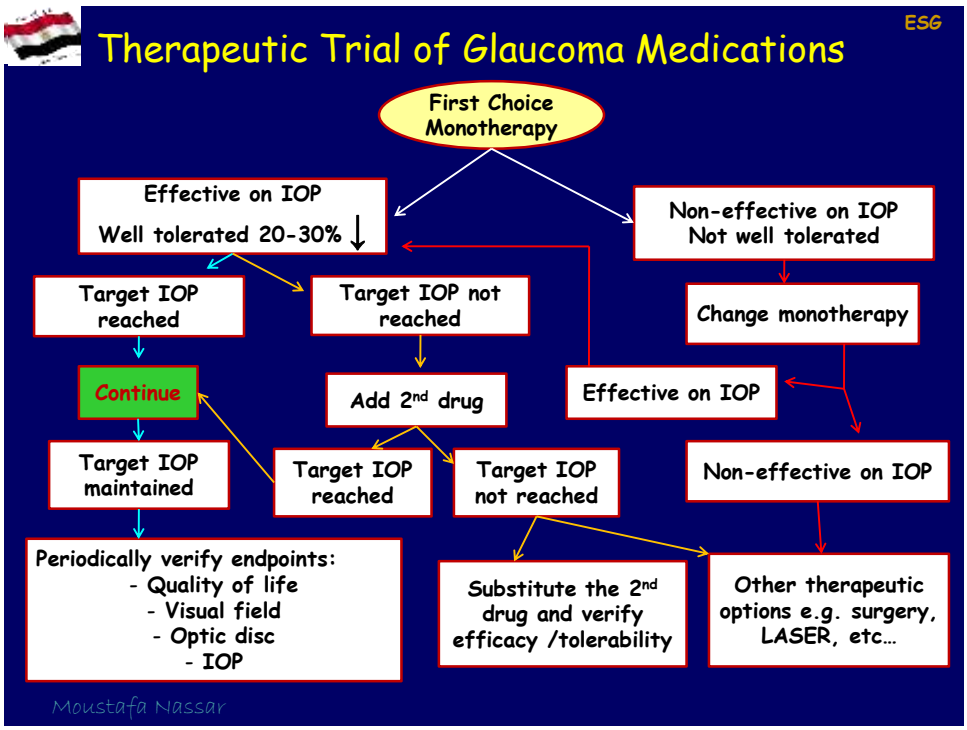
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Therapeutic Trial of Glaucoma Medications
First Choice Monotherapy
Effective on IOP
Well tolerated 20-30% ↓
Non-effective on IOP
Not well tolerated
Target IOP reached
Target IOP not reached
Change monotherapy
Continue
Add 2nd drug
Effective on IOP
Target IOP maintained
Target IOP reached
Target IOP not reached
Non-effective on IOP
Periodically verify endpoints:
- Quality of life
- Visual field
- Optic disc
- IOP
Substitute the 2nd drug and verify efficacy /tolerability
Other therapeutic options e.g. surgery, LASER, etc…
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Generic name	%IOP difference from baseline	
	Peek	Trough
Bimatoprost	-33	-28
Travoprost	-31	-29
Latanoprost	-31	-28
Timolol	-27	-26
Brimonidine	-25	-18
Betaxolol	-23	-20
Brinzolamide	-20	-17
Drozolamide	-20	-17

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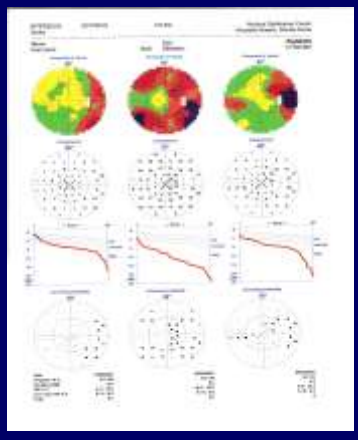
How to follow the patient in the 1st two year after diagnosis

1. Visual field testing <u>every 4 months in the first two years (6 VFs)</u> so as to be able to evaluate the rate of glaucoma progression

2. OCT / 6th months



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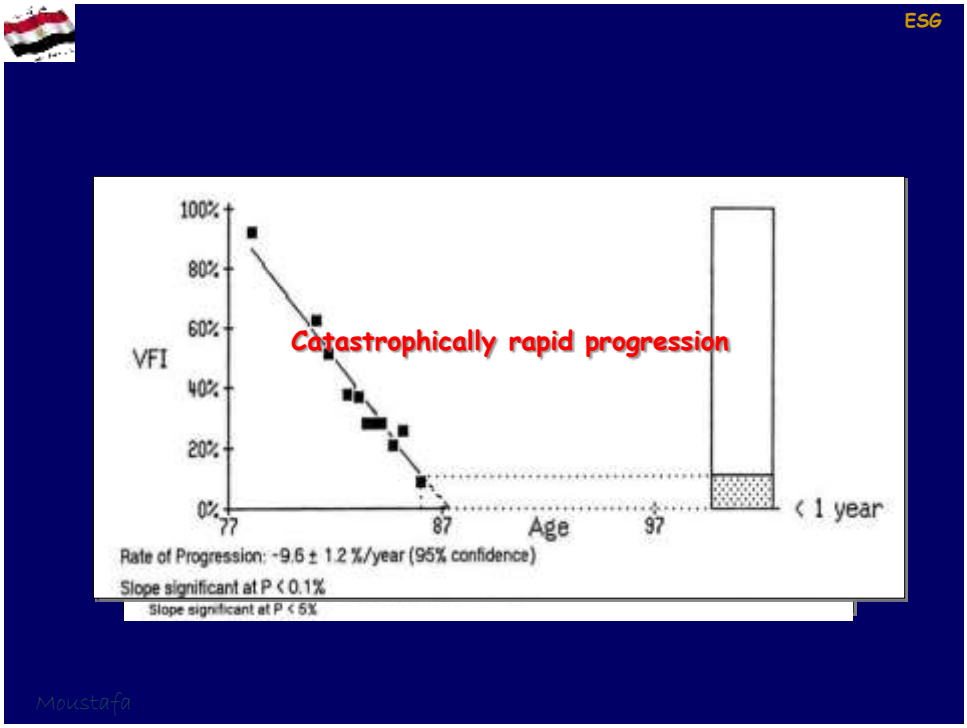
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100%
80%
60%
40%
20%
0%
VFI
Catastrophically rapid progression
77
87
Age
97
< 1 year
Rate of Progression: -9.6 ± 1.2 %/year (95% confidence)
Slope significant at P < 0.1%
Slope significant at P < 5%
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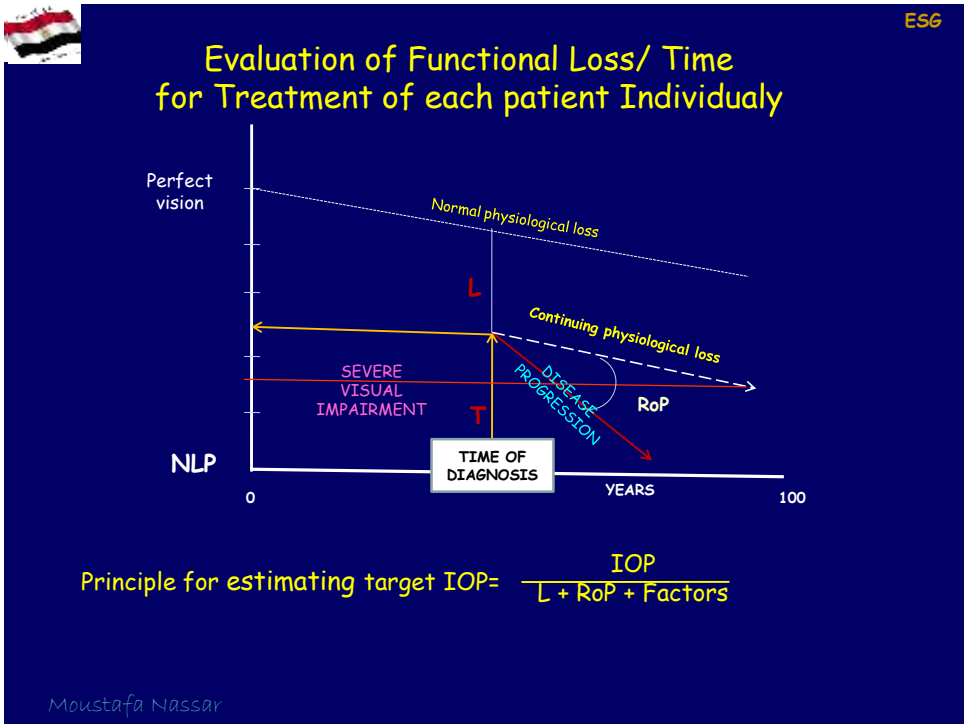
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Evaluation of Functional Loss/ Time
for Treatment of each patient Individualy
Perfect vision
Normal physiological loss
L
Continuing physiological loss
SEVERE VISUAL IMPAIRMENT
T
DISEASE PROGRESSION
RoP
NLP
TIME OF DIAGNOSIS
0
YEARS
100
Principle for estimating target IOP= IOP / L + RoP + Factors
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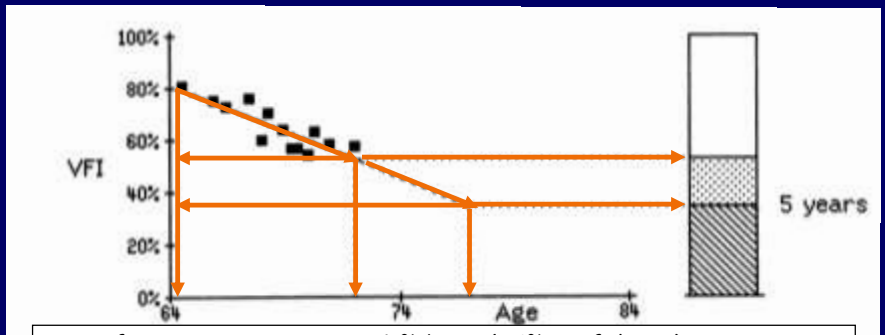
How to use the VF index to predict the future expected loss after 5 years

GPA II Rate of Progression analysis

We Provided:

- Estimation of velocity of progression
- Patient age at baseline and last visit
- Amount of current visual function
- Expected loss after 5 years



Rate of Progression: -3.6 ± 1.4 %/year (95% confidence)

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When to quit or when to move to surgery

- Unaffordable coast of medical treatment
- Low compliance
- Maximal medical treatment (2 bottles) with continuous progression of glaucoma

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Glaucoma medical treatment or "Ocular hypotensive agents"

1. Cholinergic agonist
2. Adrenergic agonist
3. Beta adrenergic antagonist
4. Carbonic Anhydrase Inhibitor
5. Prostaglandins

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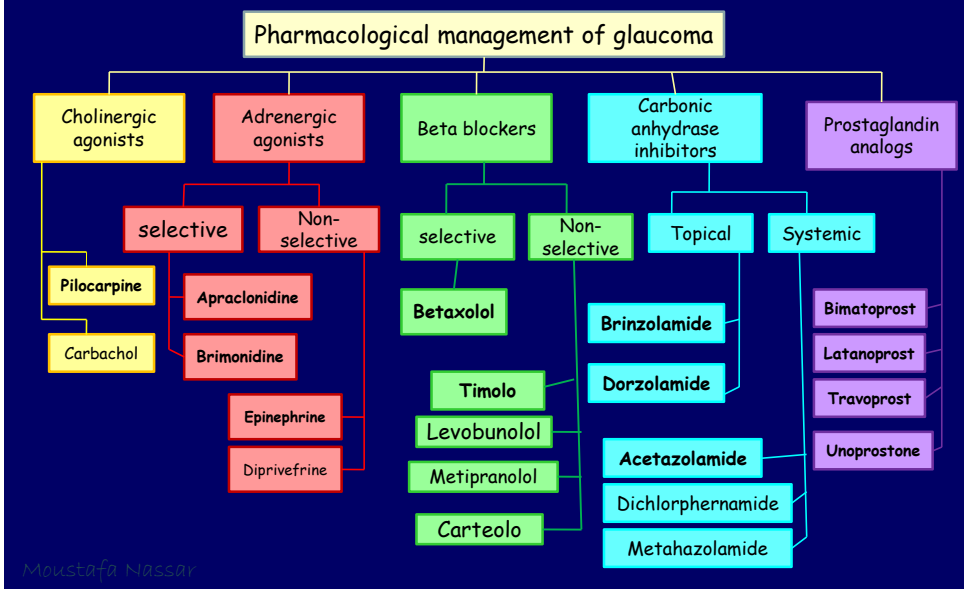

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1. Cholinergic agonists :

Nature: Para-sympatho-mimetic effect resembling the action of acetylcholine at the receptor sites.

1- Pilocarpine (1-4%):

- currently **less frequently used** in OAG
  - ↓ IOP by 15-25%
  - it pulls the scleral spur to tighten the TM to ↑ the aqueous outflow

Ocusert is an insert in the upper or lower fornix with a constant steady release for one week
Pilo20 system (1%) and Pilo40 system (2-4%)

2- Carbacol 1.5-3% three times/day

Complications: miosis → Decrease night vision
Decrease visual acuity
Myopia due to spasm of accommodation
Constriction of visual field
Might cause pupillary block

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2. Adrenergic agonists

Non-selective Selective

- Non-selective adrenergic agonist :
  Epinephrine and Dipiverfrin
  ↑ trabecular and uveoscleral outflow
  ↓ aqueous production
  Replaced with the more effective selective a_2 adrenergic agonist

- Selective a_2 adrenergic agonist:
  it ↑ ,↓ , protect, improve and regenerate
  Clonidine HCL
  Alpha Clonidine HC
  Briminodine (Alphagan P)

Side effects: dry mouth, drowsiness and lethargy
Contraindicated in infants

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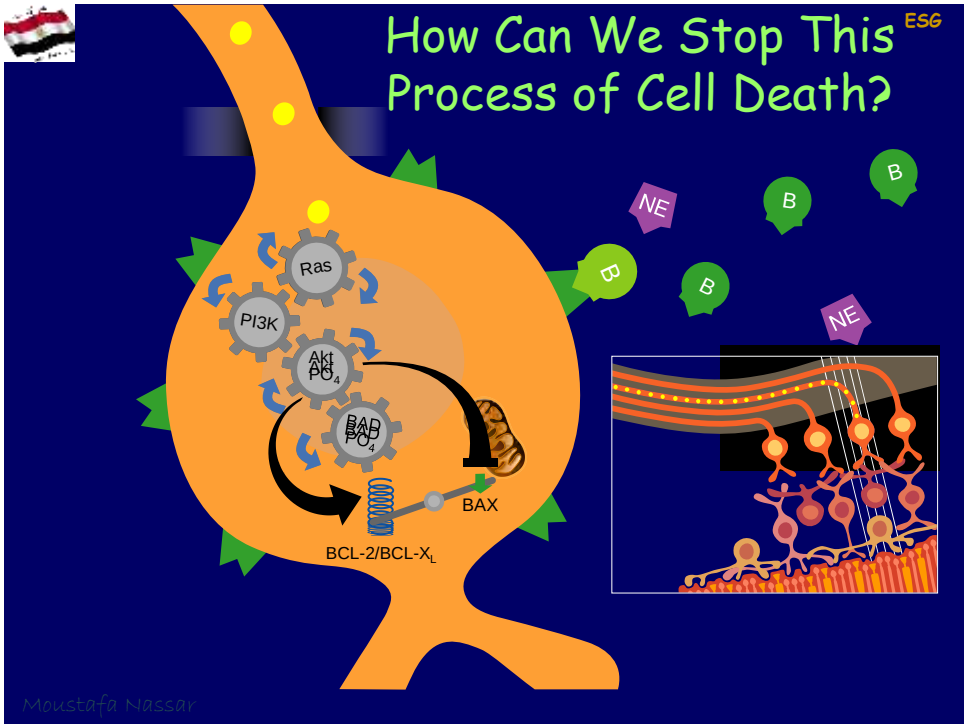
How Can We Stop This Process of Cell Death?
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Ras
PI3K
Akt
PO4
BAD
PO4
BAX
BCL-2/BCL-XL
NE
B
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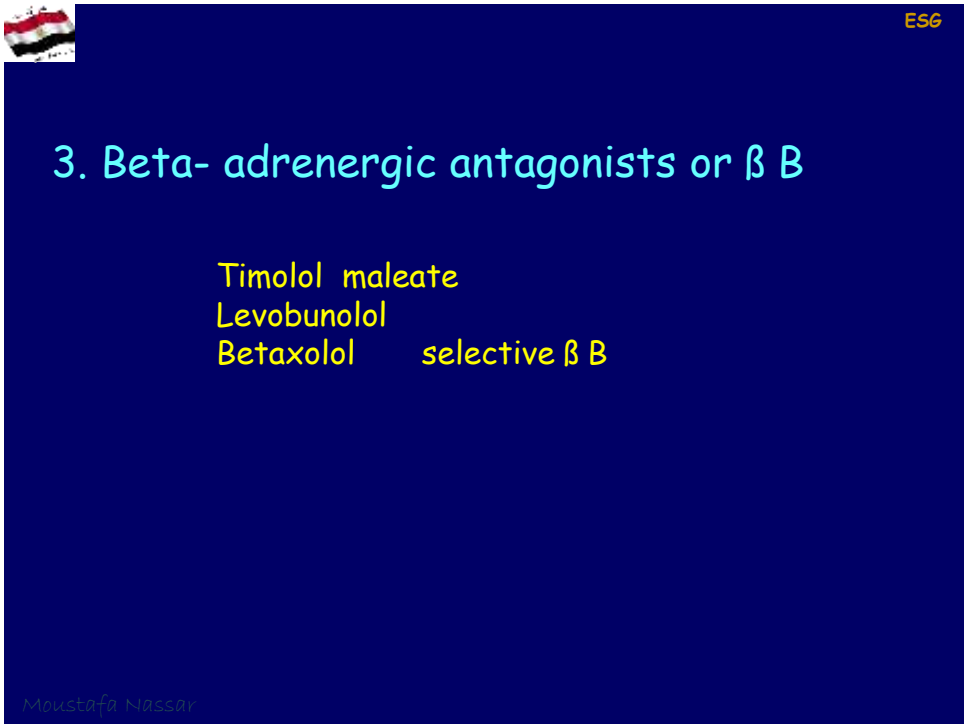
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3. Beta- adrenergic antagonists or ß B
Timolol maleate
Levobunolol
Betaxolol selective ß B
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Since 1978 of the FDA approval to the use of topical BB, it had become the most widely prescribed anti glaucoma drug.

These drugs lower IOP by reducing aqueous production after pharmacological effect on more than 90% of the ciliary epithelium.

They are non selective (i.e blocking **B1** & **B2** receptors) or selective (i.e. primarily blocking **B1** receptor)

Concentration range from 0.25-0.5 to 1.0% and used twice or once/D.

Contraindicated to be used with bronchia asthma or bundle branch block of the heart.

The selective B-blocker betaxolol has fewer complication but it is less effective, also it has neuroprotective effect by ↓ ca+ influx into RGCs.

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4. Carbonic Anhydrase Inhibitors (CAI)

-↓ aqueous formation by direct inhibition of carbonic anhydrase enzyme of the ciliary epithelium.
- CAI s may be administered systemically or topically

A. Systemic CAIs:
- Acetazolamide 250mg 4times/D
  it ↓ IOP by 15 -20 %
- Dichorphenamide (Daranide) 50 mg twice/D
  long duration of action
- Methazolamide (Naptazane) 25mg twice/D
  does not cause systemic acidosis

B. Topical CAIs:
- Dorzolamide HCL (2%) 2-3 times/D
- Brinzolamide (1%) 2-3 times/D

Topical CAIs are Sulfonamides and have an additive effect with Timolol

CAIs are derived from sulfa drugs and may cause allergic reactions
CAI s should not be administered systimically for a long duration as they cause acidosis, paresthesia, anorexia, nausea, vomiting, nephropathy, lenticular myopia and retinal oedema

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5. Prostaglandins or Hypotensive lipids druges

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Prostaglandins (PGs) and prostamide have been approved as 1st line of treatment because of controlling IOP by ↑ uveoscleral outflow. This is theoretically an advantage over BB that ↓ aqueous production as PGs simulate the natural pathway.

This is because the lens and cornea receive nourishment from aqueous humour production. Reducing this circulation decreases the nutrient supply to them and cosequently increases the concentration of waste products in the AC.

These waste products might also ↑ the resistance of TM and probably be the cause of what is called BB tolerance.

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PGs are naturally occurring local hormones in the eye, mainly during IO inflammation.

It was noticed that during acute iritis with excess PGs there is a ↓ in the IOP.

To avoid side effects of PGs , it is used in a very low concentration

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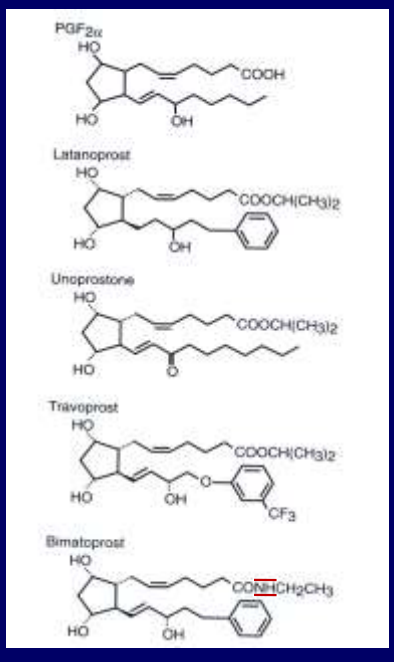
*Pharmacology of PGs:

Based on similarity of PGs chemical structures, Latanoprost, Unoprost, Travoprost and Bimatoprost ,act selectively on the FP receptors

Bimatoprost is similar to analog, but has an amide group in place of the isopropyl ester group.
The presence of this group is responsible for its designation as "prostamide" rather than a "prostaglandin analog"



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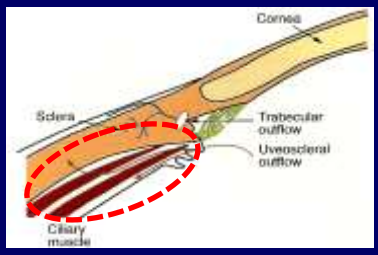
*Site of action:

-The precise mechanism by which PGs ↑ uveoscleral outflow is unclear

-The exact site of action for lowering IOP is in the ciliary muscles through FP receptors

- It is possibly related to structural modification of the extracellular matrix in the ciliary muscle and subsequently widening of the connective tissue that ↑ uveoscleral outflow



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Long term use of hypotensive lipids cause :

- iris pigmentation
- conjunctival hyperemia
- trichiasis
- pigmentation of the eye lids
- long lashes
- CME
- uveitis

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Hypotensive lipids includes

Prostaglandin analogs (Latanoprost and Travoprost)
Prostamide (Bimatoprost)
Unoprostone

Latanoprost (Xalatan) 0.005% once/D
- it is a prodrug activated by corneal estrase
- ↓ IOP by 25-32% by ↑ uveoscleral outflow
- It has additive effect when combined with Timolol (stability **?**)

Travoprost (Travatan) 0.004% once/D
- it is hydrolyzed by corneal estrase
- ↓ IOP by 25-31% by ↑ uveoscleral outflow
- It has additive effect when combined with Timolol

Bimatoprost (Lumigan) 0.03-0.01% once/D
- it is a prostamide
- it ↓ IOP by 27- 33% by ↑ uveoscleral outflow and trabecular outflow
- It has additive effect when combined with Timolol

Unoprostone (Rescula) 0.15% twice/D
- it is a docosanoid derivative
- it ↓ IOP by 13 – 18 % by ↑ uveoscleral outflow
- least side effect

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Generic name	%IOP difference from baseline	
	Peek	Trough
Bimatoprost	-33	-28
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Betaxolol	-23	-20
Brinzolamide	-20	-17
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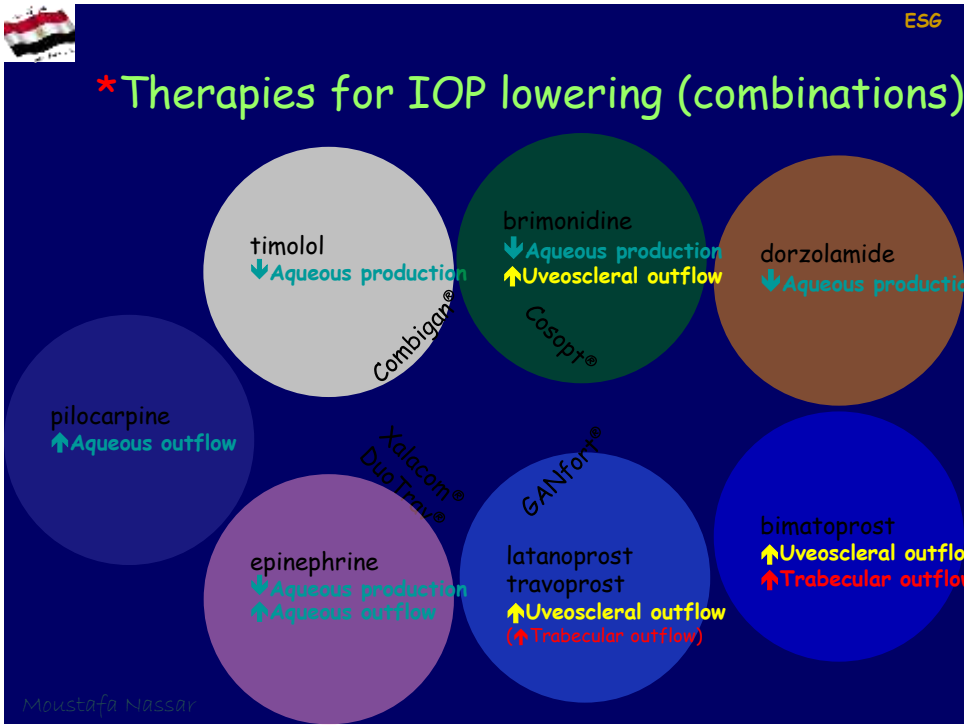
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*Therapies for IOP lowering (combinations)
timolol
Aqueous production
Combigan®
brimonidine
Aqueous production
Uveoscleral outflow
Cosopt®
dorzolamide
Aqueous productio
pilocarpine
Aqueous outflow
Xalacom®
DuoTrav®
epinephrine
Aqueous production
Aqueous outflow
GANfort®
latanoprost
travoprost
Uveoscleral outflow
(Trabecular outflow)
bimatoprost
Uveoscleral outflo
Trabecular outflo
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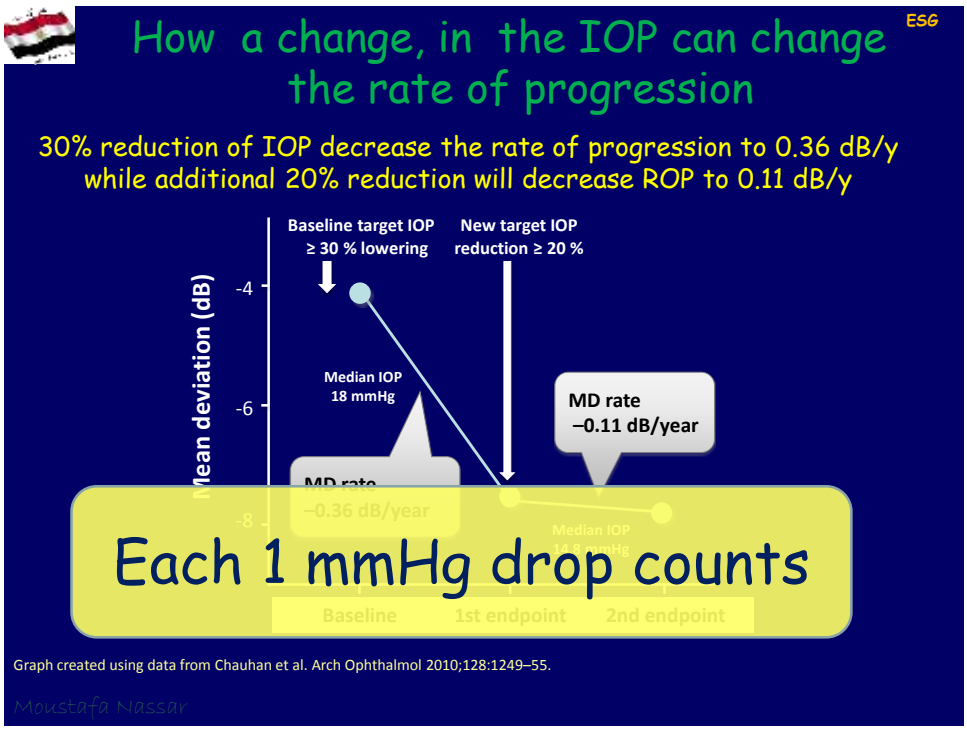
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How a change, in the IOP can change the rate of progression
30% reduction of IOP decrease the rate of progression to 0.36 dB/y while additional 20% reduction will decrease ROP to 0.11 dB/y
Baseline target IOP ≥ 30 % lowering
New target IOP reduction ≥ 20 %
Mean deviation (dB)
-4
-6
-8
Median IOP 18 mmHg
MD rate –0.11 dB/year
MD rate –0.36 dB/year
Median IOP
Baseline
1st endpoint
2nd endpoint
Each 1 mmHg drop counts
Graph created using data from Chauhan et al. Arch Ophthalmol 2010;128:1249–55.
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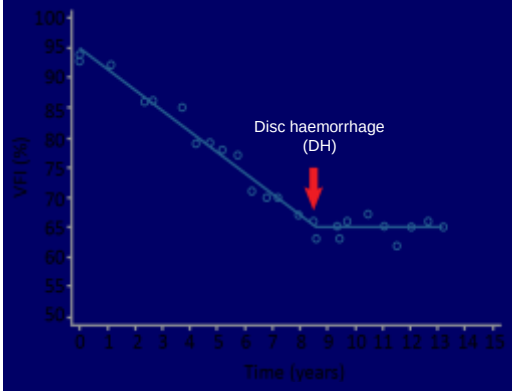
Change in the IOP is associated with a change in the rate of progression



- Example of an eye that had a steep rate of progression before DH (–3.41%/year) and with a mean IOP of 18.6 mmHg
- When mean IOP was lowered 37% post DH (to 11.7 mmHg), rate of progression decreased to –0.07%/year
- Each 1 mmHg IOP reduction was associated with a difference in rate of progression of 0.31%/year

Each 1 mmHg reduction of IOP is associated with a decrease in rate of progression by 0.31%/year

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*Relationship between IOP and progressive loss of the RNFL in glaucoma

- 344 eyes recruited from the DIGS
- At baseline, 98 confirmed POAG, 246 glaucoma suspect
- GDx ECC, stereophotos, SAP
- Average change 0.25 µm/year at an average IOP of 17 mmHg

For progressors, each 1 mmHg higher of the IOP is associated with an additional loss of 0.13 µm/y of RNFL

Medeiros et al. Ophthalmology 2009;116:1125–33.

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Rate of progression: is important for correction of glaucoma management decision

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*Individualised treatment according to rate of progression

Patients progress at different rates, and treatment must be individualised to patient needs and rate of progression

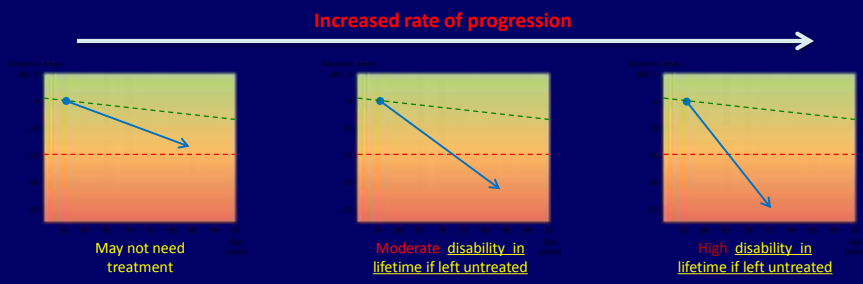

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Figure adapted from EGS guidelines, 3rd edn, 2008.

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In Glaucoma management

- First, establish risk profile and set a target IOP
- Follow up the patient throughout to establish an adequate baseline
- Repeat visual field testing during the first 2 years to establish progression rate (2–3 times/year)[1]
- Change treatment accordingly and revise visual field measurement frequency depending on rate of progression[2]

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1. European Glaucoma Society, 2003. Terminology and guidelines for glaucoma.
2. Heijl A. Oral presentation. AIGS, Singapore, 2007.

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Future glaucoma therapy

Gene therapy
Brimonidine insert
Bimatoprost insert
Steam cell implantation

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GENE THERAPY IN GLAUCOMA

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*Genetic therapy of glaucoma

Ideally, gene therapy would simulate transplantation surgery, i.e. removal of mutant gene and replace it with a normal one.

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Different approaches for genetic glaucoma therapy includes.

1. Viral vector therapy (using the virus as a carrier)
   - Retrovirus
   - Adenovirus
   - Herpes virus
2. Non-Viral vector therapy by
   - Liposomes
   - Oligonuclutoide antisense
   - Recombinant proteins
   - Human artificial chromosomes
   - ribozymes

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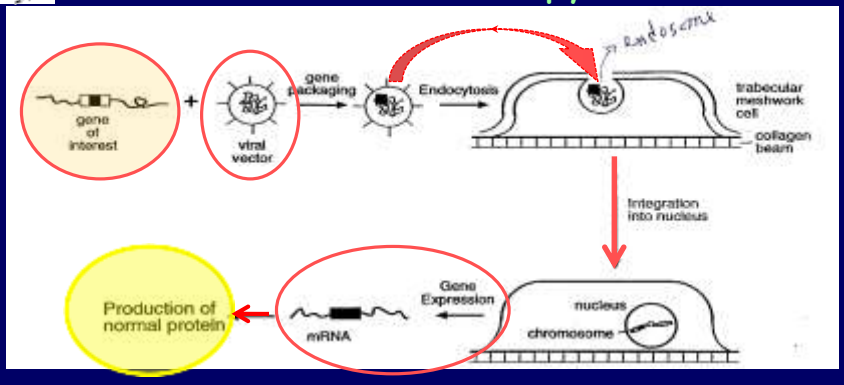
1. Viral vector therapy



The gene* of interest-is carried out* by a viral vector to be-introduced *into the nucleus of the TM cell by a process called* endocytosis.
This restores *the mutant gene to a normal one.
Thus-normal gene expression* with a normal mRNA and- protein production would be expected.

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2. Non-viral vector therapy:

Have more immediate potential and greater versatility and may be more accepted.

They can either replace defective genes, inhibit transcription, correct mutant m-RNA, or directly replace needed protein.

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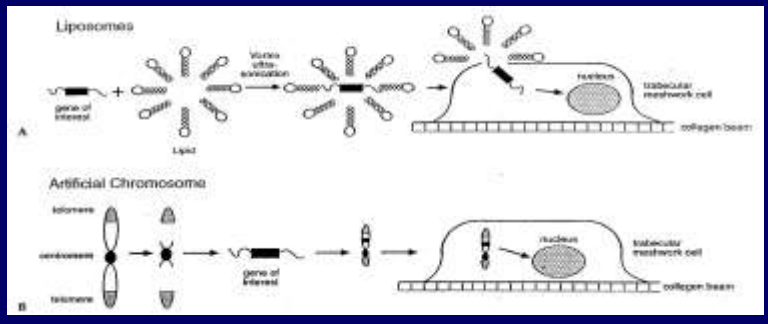

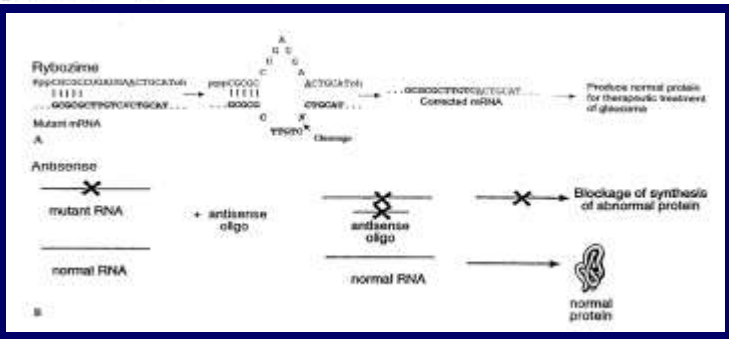

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*Future therapy

For Glaucoma stem cell therapy

Stem cells offer the potential to develop new treatment to incurable neurodegenerative diseases such as glaucoma. This is by replacing the dead cells to achieve functional recovery.

By definition, a stem cell is multipotent, with the capacity of self-renew and to produce daughter cells capable of differentiating into multiple mature cell types.

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Stem cell therapy could be achieved via the transplantation of cultured stem cells or by manipulating endogenous repair mechanism.

The problem is that stem cells would not only integrate RGC layer, and differentiate into mature RGCs , but also establishing a connections with appropriate afferent neurons, extend and make functional connections within the brain to preserve the retrograde axoplasmic flow.

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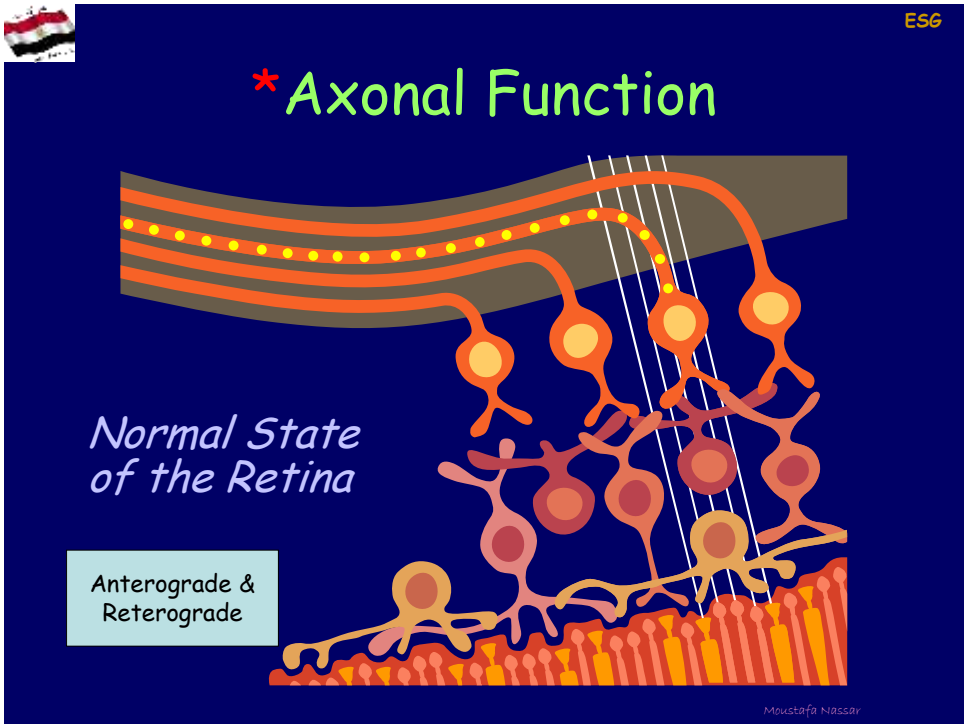
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*Axonal Function
Normal State of the Retina
Anterograde & Reterograde
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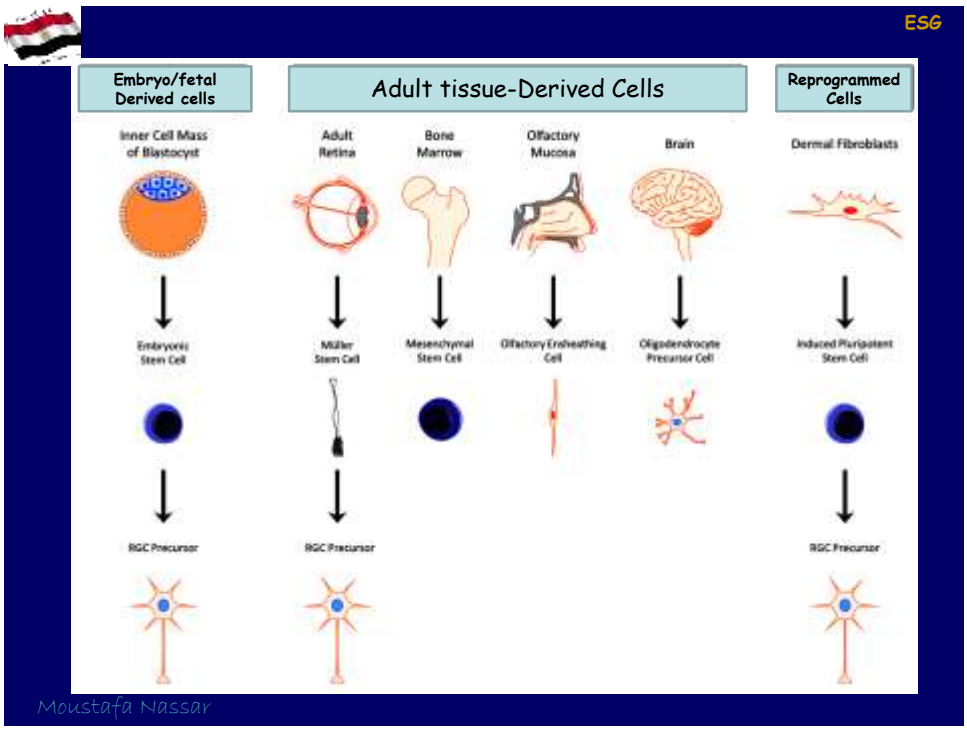
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Embryo/fetal Derived cells
Adult tissue-Derived Cells
Reprogrammed Cells
Inner Cell Mass of Blastocyst
Adult Retina
Bone Marrow
Olfactory Mucosa
Brain
Dermal Fibroblasts
Embryonic Stem Cell
Müller Stem Cell
Mesenchymal Stem Cell
Olfactory Ensheathing Cell
Oligodendrocyte Precursor Cell
Induced Pluripotent Stem Cell
RGC Precursor
RGC Precursor
RGC Precursor
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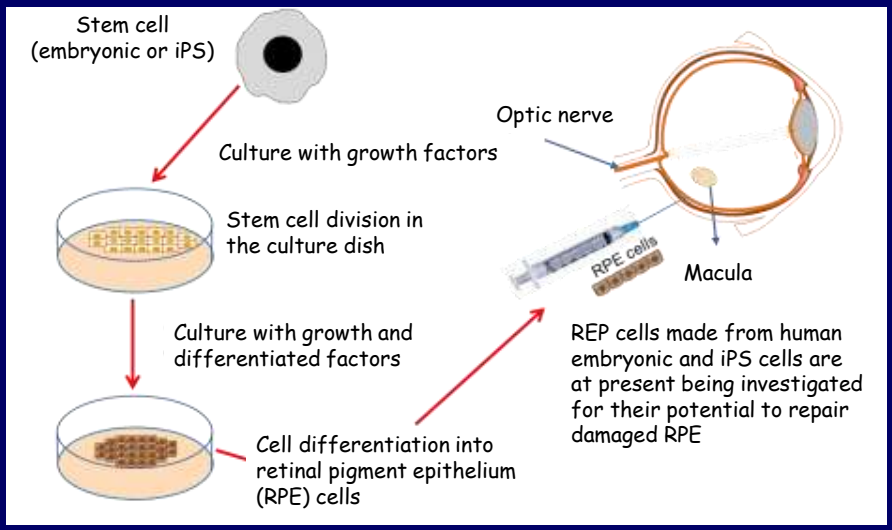

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In general ,the rule of thumb to follow on prescribing medication is

"to use the least amount of medication with maximum desired therapeutic effect and fewest adverse reactions"

Once daily dose has the benefits of increased compliance and decreased side effects.
However, if once daily medication is not achieving the target IOP, moving to twice daily medications may be the next step but not more than 2 botles.
The problem with glaucoma is the resistance to aqueous out flow and it is not because of excess aqueous secretion

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1866

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1937

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تحيا مصر
تحيا مصر
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على إسم مصر التاريخ يقدر يقول ماشـا..
انا مصر عندي أحب وأجمل الأشيـا..
Thank you
Moustafa Nassar