DRUGS USED IN MYASTHENIA GRAVIS AND GLAUCOMA

Introduction:

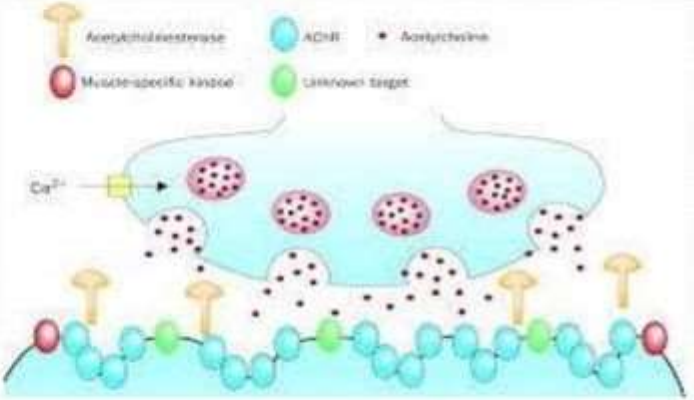
- Myasthenia gravis is an autoimmune disorder characterized by muscular weakness and chronic fatigue that is caused by a defect in the transmission of nerve impulses from nerve ending to muscles.

- In this case, the chemical transmitter, acetylcholine (ACh) is unable to bind to the receptors (AChR) on the postsynaptic membrane to transmit the nerve impulse to muscle fibers to produce a muscle contraction.

Anatomy of neuromuscular junction:

Components:

- Presynaptic membrane
- Synaptic cleft
- Postsynaptic membrane



- The neuromuscular junction is a Specialized synapse between a Neuron and the muscle.
- It allows signals from the nervous System to contact muscle fibers causing them to contract.
- Acetylcholine plays an important role in neurotransmission.

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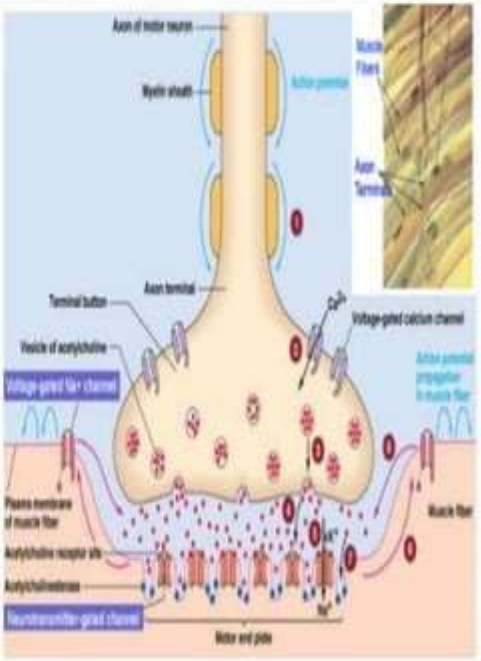
- Acetylcholine vesicles are present in presynaptic terminal.
- Once a motor nerve action potential reaches the presynaptic nerve terminal it causes an increase in intracellular calcium concentration.
- This increase in calcium concentration allows the Ach vesicle to fuse with the plasma membrane at the presynaptic membrane and thus releasing Ach into the synapse.



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- Once Ach is present in the synapse it is able to bind to nicotinic Ach receptor, increasing conductance of the certain cations, sodium and potassium in the postsynaptic membrane and producing an excitatory effect.

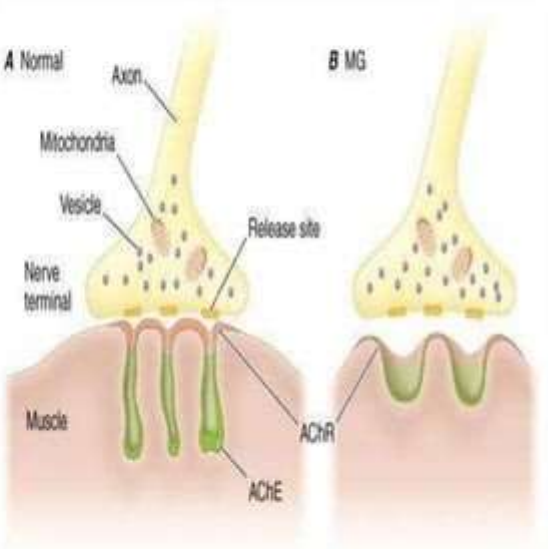
- Neuromuscular junction diseases are a result of a malfunction in one or more steps of the above pathway.

Mechanisam of action of MG:

- In MG, antibodies are directed toward the acetylcholine receptor at the neuromuscular junction of skeletal muscles.

Result in:

1) Destruction of about one third of receptors at all neuromuscular junctions of skeletal muscles,
2) Flattening of the postsynaptic folds,
3) Widening of the synaptic cleft.



- Acetylcholine (ACh) is an important neurotransmitter that stimulates muscle tissue to contract.

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- Under normal circumstances, a nerve cell, stimulated by a nerve impulse, release the neurotransmitter acetylcholine, which cross the neuromuscular junction and binds to receptors on the muscle cell, thus triggering the muscle contraction.
- MG is an autoimmune disease in which antibodies are formed against ACh and a reduction in Ach receptor sites at the neuromuscular junction and thus preventing the muscle from responding to the nerve signal.
- Acetylcholinesterase (AChE) molecule can rapidly hydrolyze the ACh.
- In people with MG, it's believed that the thymus is incorrectly instructing some of the immune system's cells to create abnormal antibodies.
- These antibodies mistakenly attack some of muscle cell receptors.

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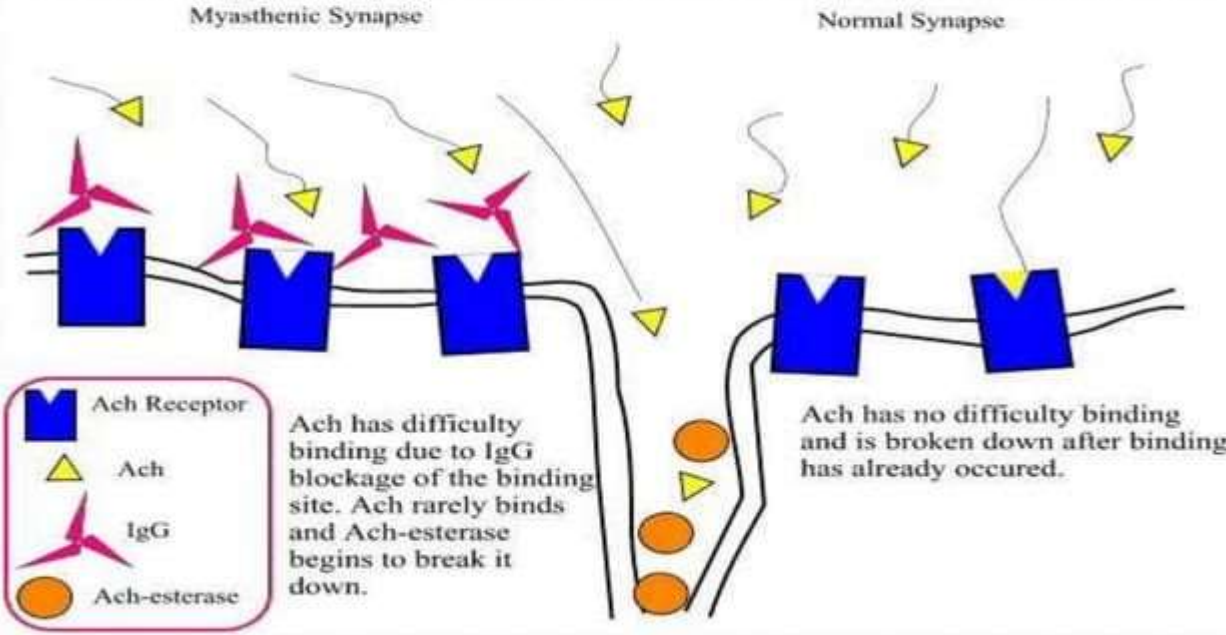
Antibody Mediated Mechanism: Blockade of Ach



Drugs used in MG

1) AChE inhibitors:

- Anticholinesterase inhibit Acetylcholinesterase (AchE), allowing the same Ach molecules to repeatedly interact with the available nicotinic receptors (NRs); frequency of Ach-NR interaction is increased.
- **Drugs:**
  1) Pyridostigmine bromide
  2) Prostigmine

2) Immunosuppressant medicines:

- They inhibit the immunity system, and limiting antibody production.
- **Drug:** Azothiaprine in addition to steroid medication (Prednisolone)

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3) Thymectomy

- Removal of thymus gland, which is part of the immune system, may reduces the MG symptoms.

4) Plasmapheresis:

- Plasmapheresis is also known as a plasma exchange.
- This process removes harmful antibodies from the blood, which may result in an improvement in muscle strength.

5) Combinations of medicine:

- Steroids in addition with Immunosuppressant tends to work better than alone.

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6) Others:

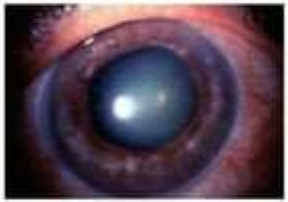
- These drugs interfere with neuromusclar transsmission and exacerbate the symptoms of MG
  - Aminoglycoside anibiotics
  - Beta adrenoreceptor antagonists
  - Phenytoin
  - Chloroquine
  - Penicillamine

What is Glaucoma

Introduction:

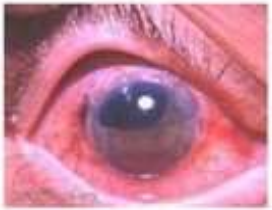
- glaucoma is a disease that damages the eye's optic nerve.
- It usually happens when fluid builds up in the front part of the eye.
- That extra fluid increases the pressure in the eye, damaging the optic nerve.

What is glaucoma ?

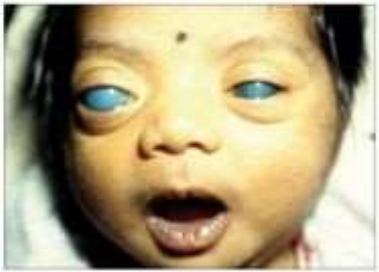


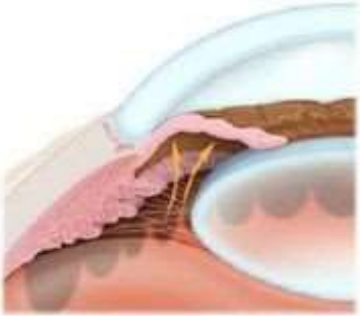
- Glaucoma – ancient meaning (Greek) clouded or blue-green hue
- Glaucoma – blindness coming from advancing years (!)
- Second leading cause of blindness
- Glaucoma is a group of disorders characterized by a progressive optic neuropathy resulting in a characteristic appearance of optic disc & specific pattern of irreversible visual field defects that are associated frequently but not invariably with ↑IOP (>21 mm Hg)
- All types of glaucoma – progressive optic neuropathy due to the death of retinal ganglion cells (RGCs)

Types of glaucoma



- Congenital glaucoma
- Primary glaucoma
  - Open angle
  - Closed angle
- Secondary glaucoma – lens induced, traumatic or steroid induced
- Absolute glaucoma





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❑ **Types of glaucoma:**

A) Primary open angle glaucoma:

- Most common
- It happens gradually, where eye does not drain fluid
- Which can results in eye pressure builds and starts to damage optic nerve
- This glaucoma is painless and causes no vision

B) Angle closure glaucoma:

- This happens when someone's iris is very close to drainage angle in their eye

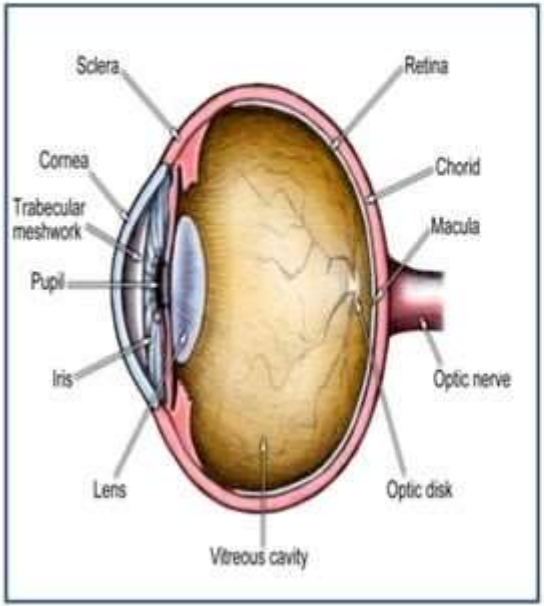
Therapeutic goal

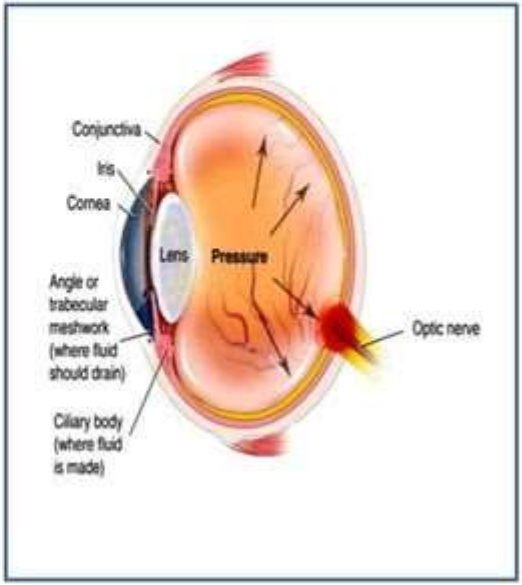
- Lower IOT by
  - Reduction of aqueous humor secretion
  - Promoting aqueous drainage
- Lowering of IOT retards the progression of optic nerve damage even in normal/low i.o.t

Open angle/wide angle/chronic simple glaucoma

- Genetically predisposed degenerative disease affecting patency of trabecular meshwork
- Meshwork becomes less efficient at draining
- IOP builds up progressively
- Damage of the optic nerve
- Has no symptoms in its early stages after middle age
- Ocular hypotensive drugs - reduce formation of AH, increase drainage or protect optic nerve

Open-angle Glaucoma (OAG)

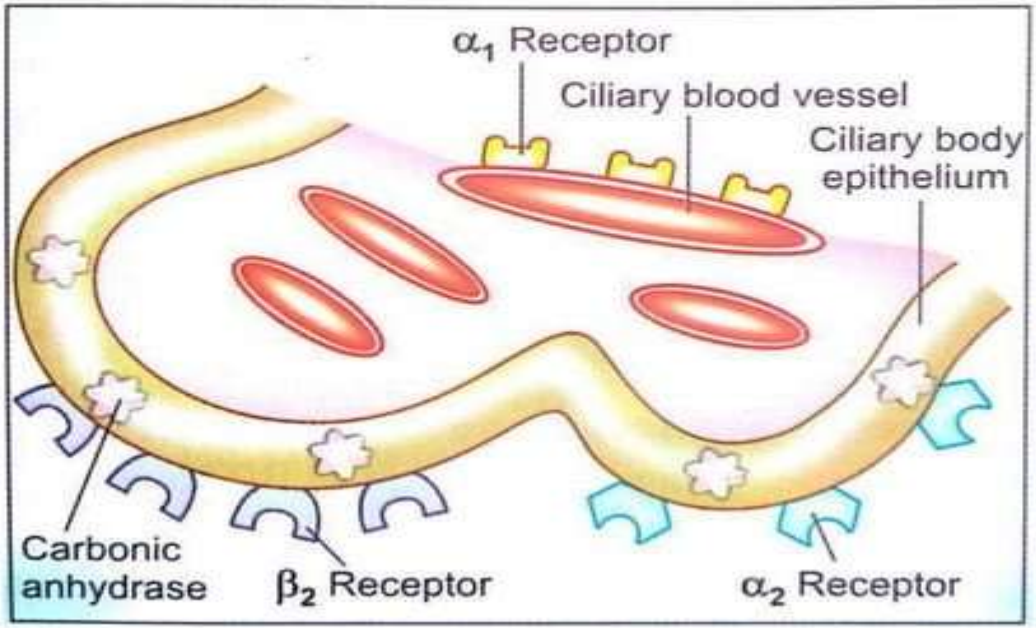




Available drugs

- **β- adrenergic** blockers: Timolol, Betaxolol and Levobunolol
- **α- adrenergic** agonists: Dipivefrine, Apraclonidine and Brimonidine
- **PG analogues:** Latanoprost, Travoprost and Bimatoprost
- **Carbonic anhydrase** inhibitors: Acetazolamide and dorzolamide
- **Miotics:** Pilocarpine and Physostigmine

Location of targets of drugs



β- adrenergic blocker in glaucoma - MOA

- Topical **β- adrenergic** blockers have been the first line of drugs - PG $F_{2\alpha}$ are preferred now
- Contrast to miotics – no effects on pupil size, tone of cilliary muscle and outflow facility
- Lower IOP by reducing aqueous formation
  - Down regulation of adenylylcyclase due to β_2 receptor blockade in cilliary epithelium
  - Reduction of blood flow
- Advantages over miotics – produce less ocular side effects, lipophillic and weak anaesthetic (corneal hyposthesia and damage)

β- adrenergic blockers – contd.

- Ocular side effects: mild and infrequent
  - Stinging, redness, dryness
  - Corneal hypoesthesia
  - Blurred vision
  - Blepharoconjunctivitis
- Systemic adverse effects: Major limitation of use
  - Nasolacrima duct
  - Life threatening bronchospasm – COPD and asthma
  - Bradycardia, heart block and CHF – ADRs
  - Inner canthus pressure – 5 min

Individual drugs – beta blockers

- **Timolol (0.25-0.5% eye drops):** Non-Selective- β1 + β2
  - No LA or sympathomimetic action
  - ↓ IOT by 20-35% - 1 hour to 12 hours
  - Smooth and well sustained action after chronic dosing→ high level of clinical safety – advantage
  - 30% patients response ?
- **Betaxolol (0.5 %)**
  - Selective β1 blocker - Less bronchopulmonary, probably less cardiac, central and metabolic effects
  - Exert protective effect on retinal neurones
  - Less efficacious in ↓ IOT than timolol (β2)
- **Levobunolol:** Once daily dosing alt. to timolol
  - Ocular and systemic side effects similar to timolol

α – adrenergic agonists

- **MOA**
  - α1 constrict ciliary BVs - reduced aqueous secretion
  - α2 in ciliary epithelium reduce aqueous secretion
  - Secondary role in enhancing drainage of aqueous mainly through uveoscleral outflow and also trabecular outflow
- **Dipivefrine (0.1 %)**
  - Adrenaline – ocular smarting, reactive hyperemia
  - Prodrug of adrenaline→ Adr. ↓ IOT by ↑ uveoscleral outflow, ↑ trabecular outflow (β2), ↓ aqueous production (α1 + α2)
    - Not used now due to systemic effects & ocular intolerance
    - Maybe used as an add-on therapy

α – adrenergic agonists – contd.

- **Apraclonidine (0.5- 1%): Clonidine congener**
  - No CNS penetration - acts on both α_1 & α_2 receptors of ciliary body→ ↓ aqueous production.
  - ↓ IOT by ~25%
  - ADRs: itching, lid dermatitis, follicular conjunctivitis, mydriasis, eyelid retraction, dryness of mouth and nose etc.
  - Use is restricted to short term control of IOT spikes (trabeculoplasty or iridotomy).
- **Brimonidine (0.2%):** Newer clonidine congener, more selective to α_2
  - More lipophilic than apraclonidine
  - ↓ IOT by 20-27% by ↓ aq. production and ↑ uveoscleral flow.
  - Uses both in short term (post surgery) and long term therapy in glaucoma. – add on therapy

Prostaglandin analogues

- Low concentration of PGF2α analogues ↓ IOT by:
  - Increase uveoscleral outflow (↑ciliary tissue permeability and vascular permeability)
  - Trabecular outflow less marked
  - Down regulation of ciliary body COX- 2 in wide angle glaucoma- role of PG in aq. humour dynamics.
- **Latanoprost (0.005% eye drop)**
  - Topically IOT ↓ 25-35%, well sustained
  - ↓ IOT in normal pressure glaucoma also
  - Ocular irritation and pain
  - Good efficacy, once daily application and absence of systemic complications – first choice in open angle glaucoma
  - **Other ADRs:** Blurring of vision, iris pigmentation, thickening and darkening of eye lashes etc.
- Travoprost and Bimatoprost: similar efficacy with Latanoprost

Carbonic anhydrase inhibitors

- Carbonic anhydrase present within ciliary epithelial cells generates $HC\bar{O}3$ ion secreted into aq. humour.
- Inhibition of carbonic anhydrase - Limits generation of bicarbonate ion → reduction of aqueous humour
- **Acetazolamide:**
  - Orally – 0.25 gm 6-12 hourly
  - Used to supplement ocular hypotensive drugs for short term indication like angle closure, before & after surgery/laser therapy
  - Long term use when IOP not controlled by topical drugs
- **Side effects:** Systemic s/e – paresthesia, anorexia, hypokalemia, acidosis, malaise, depression (on long term use)
- **Dorzolamide:** 2% eyedrop topical – 20% efficacy

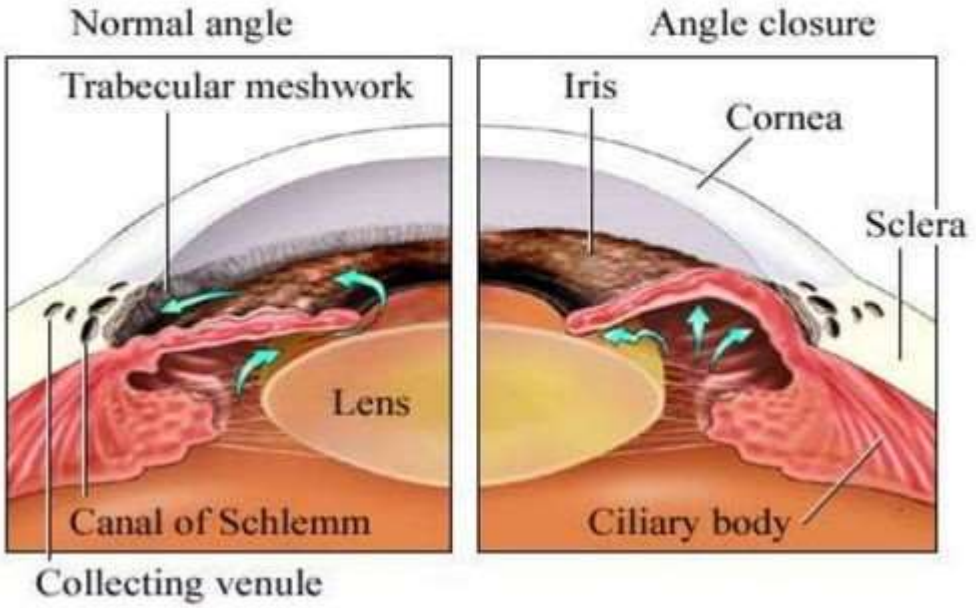
Miotics

- In 1970s – were standard antiglaucoma drugs
- Last option because of several drawbacks – myopia, diminution of vision, headache
- Pilocarpine:
  - Causes miosis by contraction of iris sphincter muscle → removes pupillary block and reverses obliteration of iridocorneal angle
  - Contraction of ciliary muscle → pulls on scleral spur and improves trabecular patency.
  - Max of 10-20% IOP reduction - 0.5% to 4% solution

Angle closure (narrow angle, acute congestive) Glaucoma

- Emergency situation occurring in person with narrow iridocorneal angle and shallow anterior chamber
- IOT raised after it is being precipitated by mydriasis
- IOT rises rapidly to very high levels (40 - 60 mmHg)
- Marked congestion of eyes and severe headache
- Failure to lower IOT → loss of sight
- Definite treatment – surgery (iridotomy/laser therapy)

Closed angle glaucoma



Therapy of closed angle glaucoma

1. Hypertonic mannitol (20%) 1.5-2 g/kg or Glycerol (10%):
   - IV infusion – decongest eye by osmotic action
   - Glycerine 50% - retention enema
2. Acetazolamide (0.5g) IV followed by oral BD started concurrently
3. **Miotic:** If above reduced the IOP -topical Pilocarpine 1-4 % every 10 mins initially & then at longer intervals.
4. Topical β blocker: Timolol 0.5% 12 hourly in addition.
5. Latanaprost (0.005%) / Apraclonidine (1%) may also be added.

Chronic narrow angle: miotic/other drugs for longer period