

# ACETYLCHOLINE (Direct-Acting)

- Quaternary ammo. compound, can't permeate memb. and rapidly hydrolysed, so no therap use
- Multiplicity of Action
- Rapid inactiv. by AChE
- Both Musc. & Nicotinic Action. (Pre-gangl., and post-gangl. of parasymp)

## ACTIONS

- Heart** — [recholinergic effect]
- mimic vagal (parasymp.) stim.
  - ↓ HR
  - ↓ SV (stroke vol.)
  - ↓ B.P. by indirect mech.
- (ACh activate M<sub>3</sub> on endothelial smooth muscle → diffuse to smooth muscle cells → NO produce from arginine → protein Kinase G → Hyperpolarization → Hypertension)
- Other Actions:
- salivary secretion
  - Intestinal secre.
  - Bronchiolar secre.
  - Uination → Detrusor contract → Trigone & sphincter → Relax
  - Stimulate ciliary muscle/circular contract. for near vision
  - Miosis (ACh 1%).
  - lacrimation
  - motility ↑ use tone
- via Phosphodiesterase-3 inhibitory (Vasodilation)
- [PDE-5-Inhib = pulmonary HT treatment: Sildenafil].

atropine

## PHYSOSTIGMINE (Indirect - Anti-AChE) (Reversib)

- Nitrogenous carbanic acid ester
- Tertiary amine (lipid solub) substrate for AChE
- form stable carbamoylated inteme enzyme (reversible)
- ACTION**
- Stimulate muscar., Nicotin sites of ANS as well as nicotin recep of NMJ
- Duration = 30min - 2hr (Interm. acting)
- enter & stimulate CNS
- Therapeutic uses**
- ↑ use intestinal & bladder motility
- So use in atony of any of these organs
- Antidote of atropine (CNS effect of atropine)
- ADR: cardiac effect of TCAs
- convulsions (high doses)
- Bradycardia
- Inhibit AChE at NMJ → ACh accumulate → paralysis of Skelet. muscle
- Pralidoxime can't reverse its effect

NM-block

## NEOSTIGMINE (Indirect - Anti-AChE) (Reversib)

- carbanic acid ester
- Inhibit AChE similar to physo.
- ACTION**
- has quaternary N<sup>+</sup> → Q.A = H<sub>2</sub>O solub
- Polar more - poorly absorbed
- NOT enter CNS
- effect at skeletal muscle greater than physostigmine (contract. → paralytic)
- Duration 30min - 2hr.
- Apppl
- stimulate bladder & GI
- Antidote for competitive NM-block agent
- manage symp of myasthenia gravis (chronic autoimmune NM disease = muscle weakness → breathing muscle, masticatory muscle, leg & arm)
- ADR:
- gener. cholin. stim.
- salivation
- flushing
- ↓ B.P.
- N/D
- Abd. pain
- No CNS effect
- GI → intest or urinary obstruction

parathion & malathion (irrev. anti-AChE) used as insecticides.

pralidoxime → reactivate AChE Aging = loss of alkyl gp.

(2-PAM) → unable to penetrate CNS

↳ given before aging of alkyl. enzyme → reverse musc. & nicotinic peripheral effect of organophosphorus BUT NOT CNS effect

↳ also useful as weak AChE inhibitor (esp at high doses)

## Bethanechol (Direct-Act)

- unsubs. carbamoyl ester
- NOT hydrolysed by AChE
- **Lack NICOTINIC, STRONG MUSCARI. ACTION**
- Major action smooth mus. of bladder
- DOA = 1 hour.

**ACTION:** • ↑ intestin. motility & TONE

**Urination** → stimulate detrusor

**Applic.**

• Stimulate atonic bladder • **Neurogenic atony**

• Non-obs. urinary retention • **megacolon**

• **ADRS:** sweating, saliva, flushing, ↓ BP  
N/D bronchosp.

## PILOCARPINE: (Direct acting)

• Less potent • uncharged • penetrate CNS

• exhibit muscarinic activ. • primarily in opth.

**ACTION:** - Non-spec. • Appl. **TOPICALLY**  
• Rapid miosis & contrac. of ciliary musc., the vision fixed at some partic. distance [Focus]

• potent stimulator of secreti

• treat xerostomia (Sjogren's syndrom. treated w/ oral pilocarp. tab. & cevimeline)

**Applic.** • **Glaucoma** (open & angle-closure)  
open Trabecular mesh → ↓ IOP "few minutes"  
duration 4-8 hrs] esp. in **EMERGENCY**

### SITUATION

**ADR:** - Blurred vision, Night blind.

• Brow ache

**Toxicity** → excess salivation & sweating similar to mushroom poisoning (genus *Inocybe*): antidote is parenteral atropine • Antidote for mushroom = Thioctic Acid

## EDROPHONIUM: (Indirect-acting Anti-cholinest.)

- Diagnosis of myasthenia gravis

• **Anti-dote** for competitive NM-blockers.

- short duration of action (10-20 min)

- **PROTOTYPE** sh AChE inhi (amongst NEO, PHYD)

- Rapid abs. - **Quatern Amine**

- Limited use. H<sub>2</sub>O-solub.

- Action limited to periphery.

- **Injection** = rapid rise in muscle strength

## Carbachol (carbamylcholine)<sup>OT</sup>

• **BOTH MUSCARIN & NICOTINIC**

• Like bethan., ester of carbamic acid

**ACTION:** ON CVS and GIT, first stimulate, then depress

• cause release of epi from adren. med. by nicotin. action (non-selective)

• Miosis topical.

**Applic (Rare)** uses except as **Miotic agent**, treat **glaucoma** ↓ IOP pupillary contracti

**ADRS:** At opth. dose → little/lack of S.E. due to lack of sys. penetration

(quatern. amine) c = carbachol c = common (N<sup>+</sup>)

## ECHOTHIOPHATE: - Indirect Acting (ANTI-CHOLINESTERASE, Irreversible) (ORGANOPHOSPHATE)

Echo + AChE → permanent inactivation  
Pau OH alkyl group (alkyl gp) release from AChE → aging → make it imp. for pralidoxime to break the bond.

### ACTION:

- generalized cholin. stimulus
- **paralysis** of motor function (breathing diff.)
- **convulsions**
- intense **MIOSIS**
- outflow of aque. humor → ↓ IOP

### Therap. Applic:

- open-angle glaucoma
- rarely use due to risk of **cataract**
- long. duration of act. (100 hours)

## RIVASTIGMINE, GALANTAMINE

• **DONEPEZIL** [Donepezil = mostly reversible inhibitors of AChE]

- **First-line** treat for **Alzheimer's** disas., though confer modest benefit

- ↓ Healthcare cost (Anti-Alzheimer's drug)

- can be used w/ memantine

(N-methyl-D-aspartate antagonist) w/ glutamate activator binds to it normally = excitatory model. to severe disease. • **Tacrine** = replaced (GIT distresses ADR) \*

# NON-Depolarizing NM-blockers Depolarizing NM-Blockers

- Block cholinergic transmission b/w motor nerve ending & nicotinic recep. on skeletal muscle

- They act as Antagonist

- First drug was curare

- They have 1st the safety of anesthesia

## Mechanism

At Low doses

competitively block Ach at nicotinic recep.

• Effect can be reverse by adm. cholinesterase inhibitors → ↑ Ach

**ACTION:** small contracting muscles of face & eyes > fingers > limbs > neck > trunk muscle > intercostal muscle > diaphragm

[order of contracting muscle blockade]  
[recovery in reverse manner]

**KINETICS:** minimal oral abs. Given IV or IM (rarely)

[2 or more quaternary amine in their bulky ring structure → ↓ absorption]

• Don't cross BBB

**Appl = Adjunct in anesthesia**

**D.I =** (1) cholinesterase inhib (2) Halogenated HC anesthetic (Desflurane → sensitize NMJ)

(3) Aminoglycoside Antibiotic = inhibit Ach release by competing  $\bar{e}$   $Ca^{2+}$  ion = ↑  $Ca^{2+}$  blockade.

**ADRS** ↓ B.P. ↑ H.R. (vagal HTIC) Post-op muscle pain  
• ↑ IOP & intraocular pres  
• ↑  $K^+$  • ↑ Histamine • Malignant hyperthermia

- Block cholin. trans. b/w motor nerve ending & Nicotinic recep on skeletal muscle

- Act as agonist on endplate NMJ

- work by depolarizing the memb. similar to ACh, & resistant to AChE

- Succinylcholine - only Dep. NMB.

## Mechanism

### PHASE - I

open Na<sup>+</sup> channel assoc.  $\bar{e}$  Nicotinic recep → depolarization → Transient Twitching

**PHASE - II** (Fasciculation) muscle soreness  
continued binding → render receptor incapable of transmitting impulses

with time, continuous depolarization → gradual repolarization → Na<sup>+</sup> channel close

Resistance to depo. & Flaccid PARALYSIS

## ACTION:

• duration = short due to rapid hydrolysis by PSEUDO-cholinesterase

• At NMJ - NOT metabolized by AChE

• Fasciculation that causes muscle soreness is prevented by adm of small dose of Non-depo. prior to SC

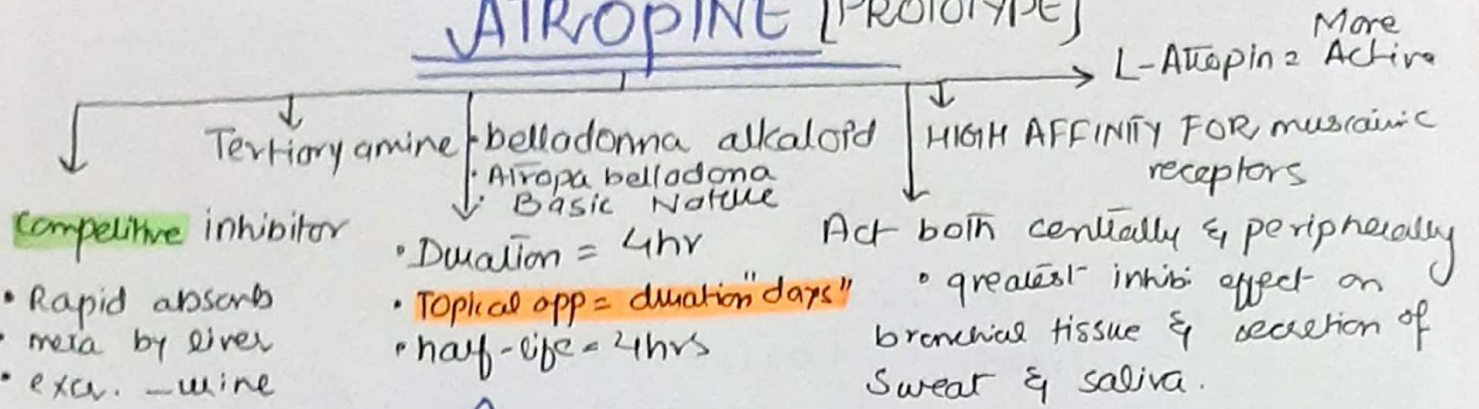
**APPLICATION** - ET - EC  
• useful when endotracheal intubation is req. during induction anesthesia  
• Electroconvulsive shock treatment

**KINETICS** IV - IV infusion to maintain longer duration - due to pseudocholine.

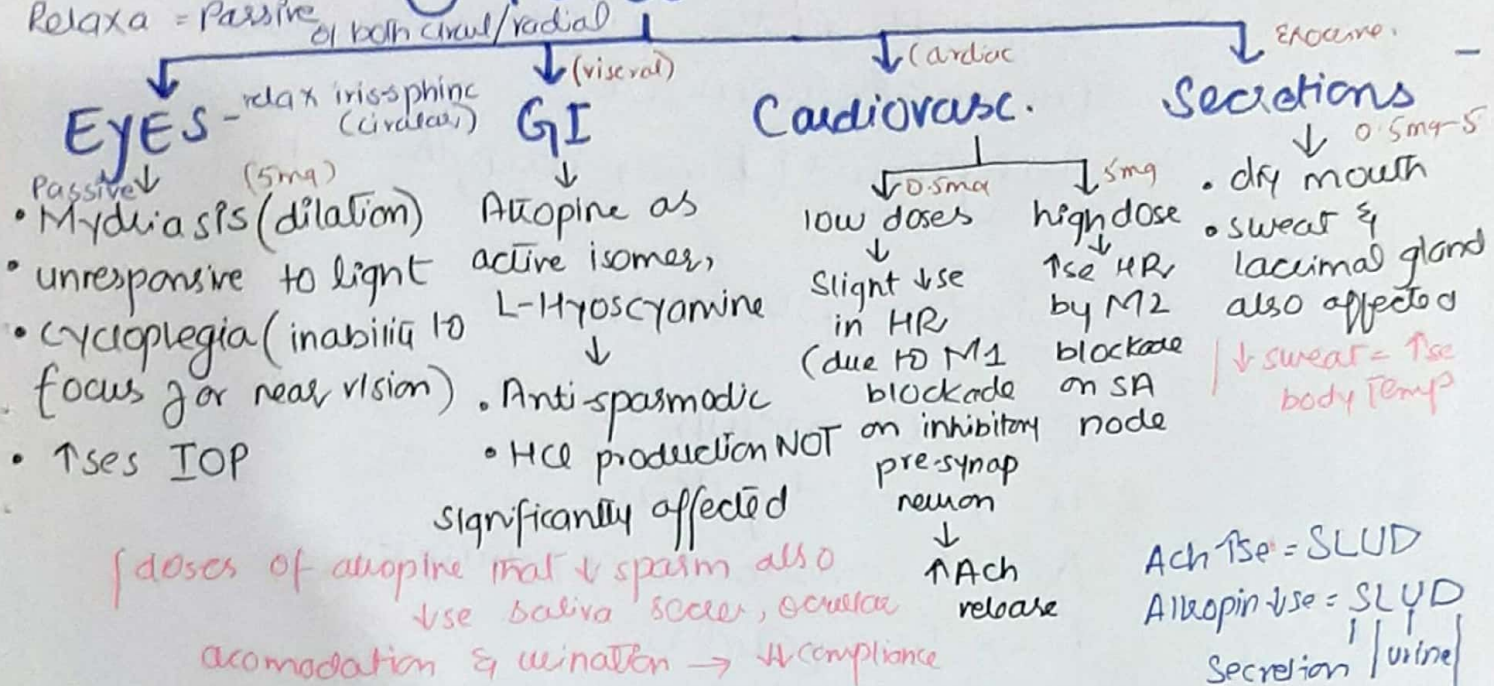
## ADRS:

• Hyperthermia • Hyperkalemia (apnea = breathing stops & restricts many times when u sleep)  
• Apnea [in pts & ↓ cholinesterase rapid release of  $K^+$ ]  
• Caution / Avoid co-adm  $\bar{e}$  Digoxin / Diuretic / HF patient

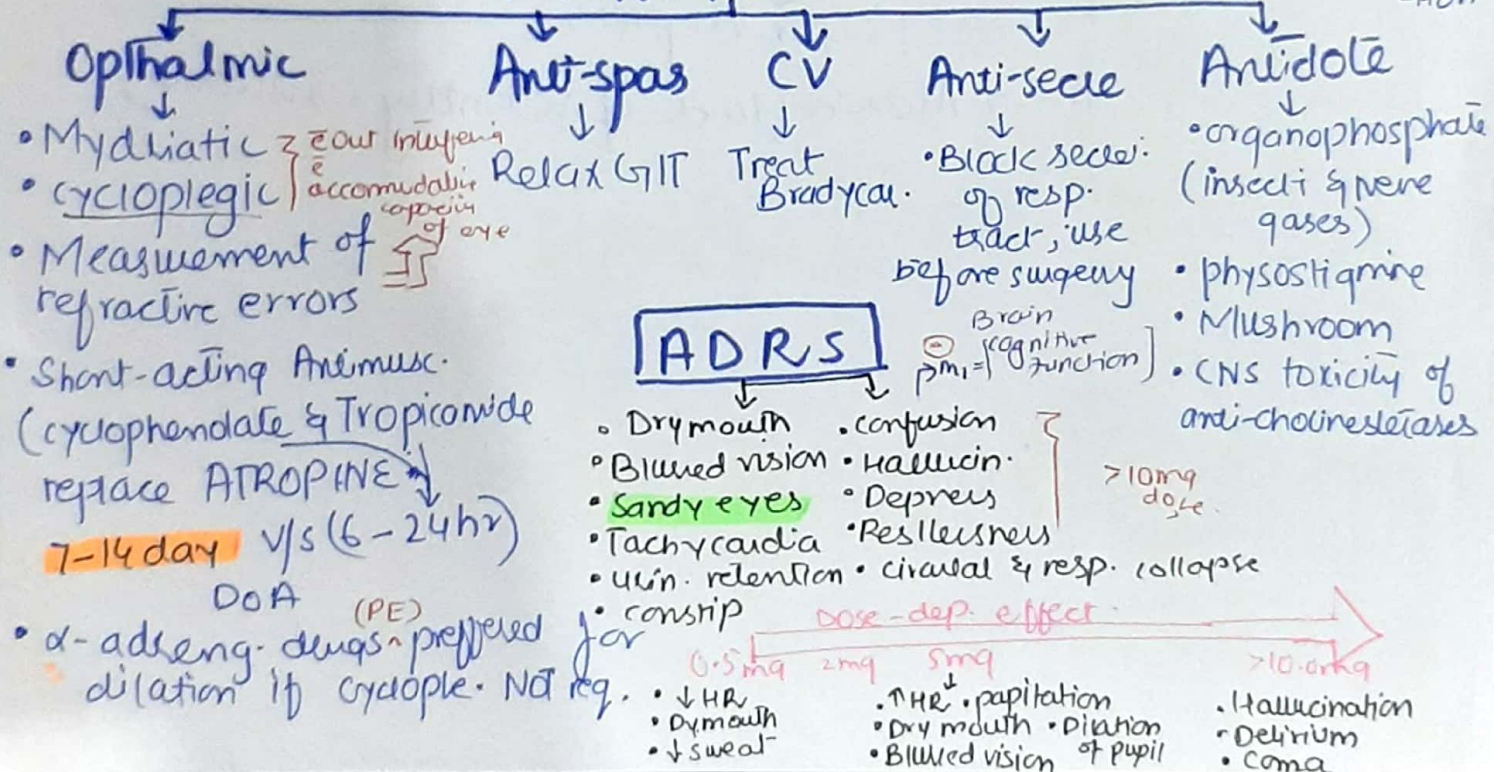
## ATROPINE [PROTOTYPE]



## ACTIONS - Back



## THERAPEUTIC USES



# SCOPOLAMINE a.k.a Hyoscyamine

# IPRATROPIUM & Tiotropium

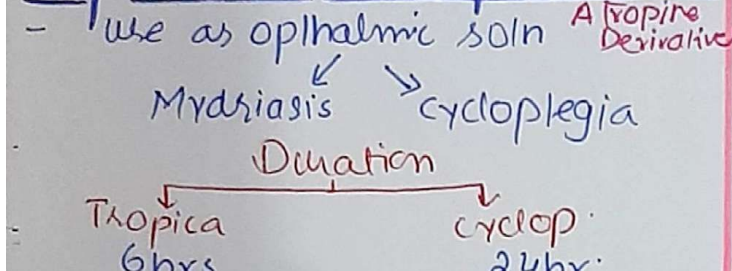
- Tertiary amine • CNS as well as periph
- long duration, comp. to atropine
- Actions
- unusual effect of **blocking memory**
- **sedation** at **high doses**
- excitement, **euphoria**, abusive potential

**Therapeutic uses:**

- motion sickness • post-oper. Nausea vomiting
- ↳ **Topical patch** (dur = 3 days)
- ↳ most imp prophylactically

• **Kinetics** similar to Atropine

## Tropicamide & Cyclophenolate



## Danifenacin, Fesoterodine, Oxybutynin, Solifenacin, Tolterodine & Tropicium Cl

- Treat **overactive bladder**
- Block musc. recep → ↓ intravesical pressure
- ↓ frequency ← ↑ bladder capacity
- S.E = Dry mouth, consti, blurred vision
- Oxybutynin = avail as **TDS**, less dry mouth, better tolerated

## Pharmaco-study YouTube

- \* Atropin. derivative - For peptic ulcer
- \* Atro. derivative = Glycopyrrate For perioperative Pre-anesthet
- \* Atro deriv = Anti-spasmo
- DOF ≈ UFF (due to pain)

- Both're **quaternary** amine, derivatives of atropine
- COPD → for bronchodilation.
- Both given via inhalation
- Ipratrop → Asthma (dilatation)
- Both're +ve charge & don't enter systemic or CNS circulation
- Tiotrop - given once (adv. over ipratro) daily

## Benzatropine & Trihexyphenidyl

- adjunct in Antiparkinson's
- and other similar symp, including anti-psychotic, EPS

## GANGLIONIC BLOCKERS

- Act NICOTINIC recep of both parasy and sym autonomic ganglia
- These agents have NO selectivity for para and symp

## NICOTINE

- component of cigarette smoke
- Dep. on **dose** → depolarize autonomic ganglia
- Result in first in **stimulation** → then **paralysis** of all ganglia
- stimulatory effects are complex result from ↑ release of neurotrans (NT)

