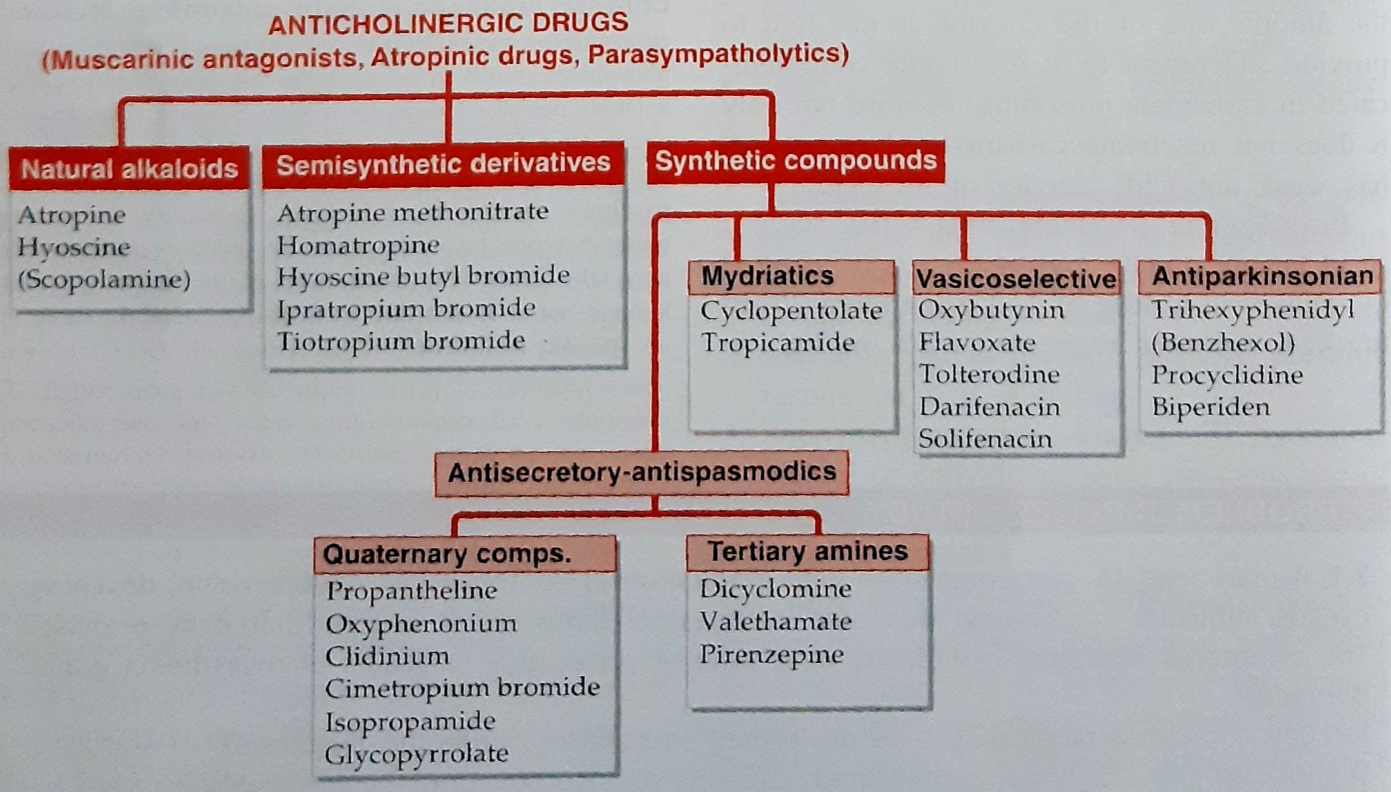
Chapter 8 Anticholinergic Drugs and Drugs Acting on Autonomic Ganglia

ANTICHOLINERGIC DRUGS (Muscarinic receptor antagonists, Atropinic, Parasympatholytic)

Conventionally, the term 'anticholinergic drugs' is restricted to those which block actions of ACh on autonomic effectors and in the CNS exerted through muscarinic receptors. Though nicotinic receptor antagonists also block certain actions of ACh, they are generally referred to as 'ganglion blockers' and 'neuromuscular blockers'.

Atropine, the prototype drug of this class, is highly selective for muscarinic receptors, but some of its synthetic substitutes do possess significant nicotinic blocking property in addition. The selective action of atropine can easily be demonstrated on a piece of guinea pig ileum where ACh induced contractions are blocked without affecting those evoked by histamine, 5-HT or other spasmogens. The selectivity is, however, lost at very high doses. All anticholinergics are competitive antagonists.



In addition, many other classes of drugs, i.e. TCAs, phenothiazines, antihistamines and disopyramide possess significant antimuscarinic actions.

The atropinic natural alkaloids are found in plants of the solanaceae family. The levo-isomers are much more active than the dextroisomers. Atropine is racemic while scopolamine is *l*-hyoscine.

PHARMACOLOGICAL ACTIONS
(Atropine as prototype)

The actions of atropine can be largely predicted from knowledge of parasympathetic responses. Prominent effects are seen in organs which normally receive strong parasympathetic tone. Atropine blocks all subtypes of muscarinic receptors.

1. CNS Atropine has an overall CNS stimulant action. However, these effects are not appreciable at low doses which produce only peripheral effects because of restricted entry into the brain. Hyoscine produces central effects (depressant) even at low doses.

- Atropine stimulates many medullary centres —vagal, respiratory, vasomotor.
- It depresses vestibular excitation and has antimotion sickness property. The site of this action is not clear—probably there is a cholinergic link in the vestibular pathway, or it may be exerted at the cortical level.
- By blocking the relative cholinergic overactivity in basal ganglia, it suppresses tremor and rigidity of parkinsonism.
- High doses cause cortical excitation, restlessness, disorientation, hallucinations and delirium followed by respiratory depression and coma.

Majority of the central actions are due to blockade of muscarinic receptors in the brain, but some actions may have a different basis.

2. CVS

Heart The most prominent effect of atropine is tachycardia. It is due to blockade of M_2 receptors on the SA node through which vagal tone decreases HR. Higher the existing vagal tone— more marked is the tachycardia (maximum in young adults, less in children and elderly). On i.m./s.c. injection transient initial bradycardia often occurs. Earlier believed to be due to stimulation of vagal centre, it is now thought to be caused by blockade of muscarinic autoreceptors (M_1) on vagal nerve endings, thereby augmenting ACh release. This is suggested by the finding that selective M_1 antagonist pirenzepine is equipotent to atropine in causing bradycardia. Moreover, atropine substitutes which do not cross blood-brain barrier also produce initial bradycardia. Atropine abbreviates refractory period of A-V node and facilitates A-V conduction, especially if it has been depressed by high vagal tone. P-R interval is shortened.

BP Since cholinergic impulses are not involved in the maintenance of vascular tone, atropine does not have any consistent or marked effect on BP. Tachycardia and vasomotor centre stimulation tend to raise BP, while histamine release and direct vasodilator action (at high doses) tend to lower BP.

Atropine blocks vasodepressor action of cholinergic agonists.

3. Eye The autonomic control of iris muscles and the action of mydriatics as well as miotics is illustrated in Fig. 8.1. Topical instillation of atropine causes mydriasis, abolition of light reflex and cycloplegia lasting 7–10 days. This results in photophobia and blurring of near vision. The ciliary muscles recover somewhat earlier than sphincter pupillae. The intraocular tension tends to rise, especially in narrow angle glaucoma. However, conventional systemic doses of atropine produce minor ocular effects.

4. Smooth muscles All visceral smooth muscles that receive parasympathetic motor innervation are relaxed by atropine (M_3 blockade). Tone and amplitude of contractions of stomach and intestine are reduced; the passage of chyme is slowed—constipation may occur, spasm may be relieved. However, peristalsis is only incompletely suppressed because it is

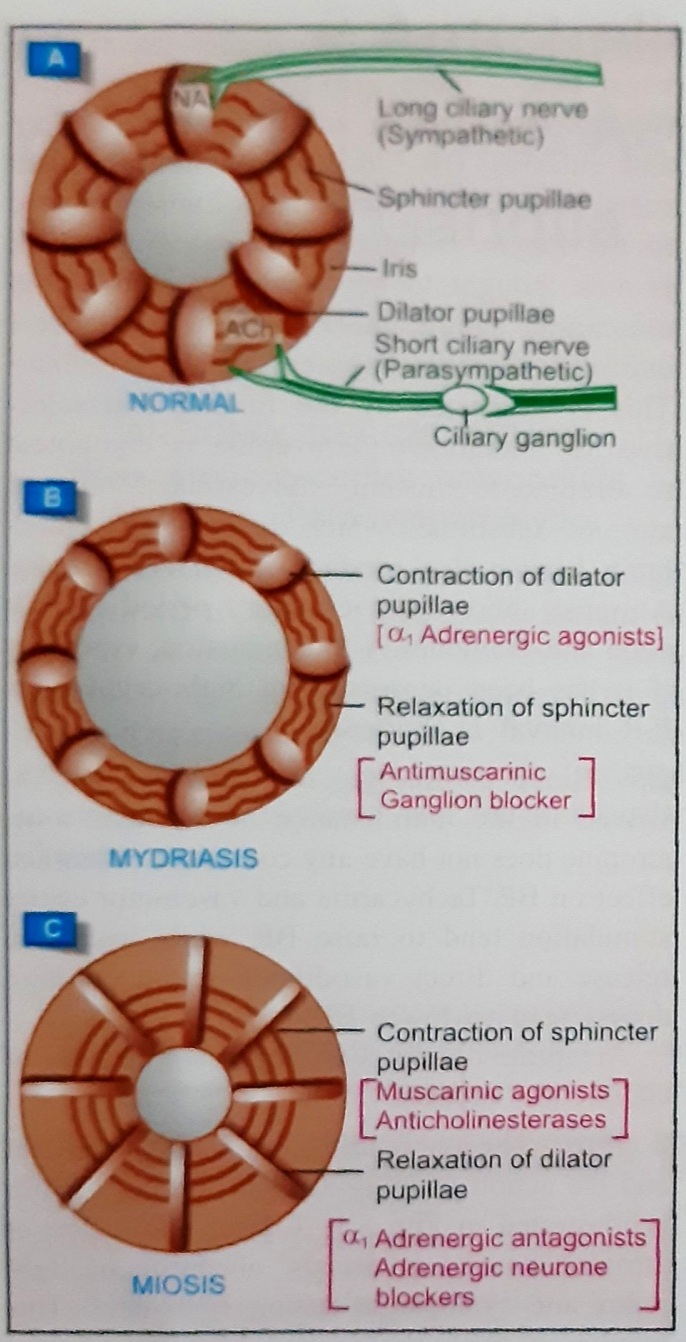


Fig. 8.1: Autonomic control of pupil (A); and site of action of mydriatics (B) and miotics (C)

primarily regulated by local reflexes in the enteric plexus, and other neurotransmitters (5-HT, enkephalin, etc.) are involved. Enhanced motility due to injected cholinergic drugs is more completely antagonised than that due to vagal stimulation, because intramural neurones which are activated by vagus utilize a number of noncholinergic transmitters as well.

Atropine causes bronchodilatation and reduces airway resistance, especially in COPD and asthma patients. Inflammatory mediators like histamine, PGs, leucotrienes and kinins which participate in asthma increase vagal activity in addition to their direct stimulant action on bronchial muscle and glands. Atropine attenuates their action by antagonizing the reflex vagal component.

Atropine has relaxant action on ureter and urinary bladder; urinary retention can occur in older males with prostatic hypertrophy. However, this relaxant action can be beneficial for increasing bladder capacity and controlling detrusor hyperreflexia in neurogenic bladder/enuresis. Relaxation of biliary tract is less marked and effect on uterus is minimal.

5. Glands Atropine markedly decreases sweat, salivary, tracheobronchial and lacrimal secretion (M_3 blockade). Skin and eyes become dry, talking and swallowing may be difficult.

Atropine decreases secretion of acid, pepsin and mucus in the stomach, but the primary action is on volume of secretion so that pH of gastric contents may not be elevated unless diluted by food. Since bicarbonate secretion is also reduced, rise in pH of fasting gastric juice is only modest. Relatively higher doses are needed and atropine is less efficacious than H_2 blockers in reducing acid secretion. Intestinal and pancreatic secretions are not significantly reduced. Bile production is not under cholinergic control, so not affected.

6. Body temperature Rise in body temperature occurs at higher doses. It is due to both inhibition of sweating as well as stimulation of temperature regulating centre in the hypothalamus. Children are highly susceptible to atropine fever.

7. Local anaesthetic Atropine has a mild anaesthetic action on the cornea.

Atropine has been found to enhance ACh (also NA) release from certain postganglionic parasympathetic and sympathetic nerve endings, and thus produce paradoxical responses. This is due to blockade of release inhibitory muscarinic autoreceptors present on these nerve terminals.

The sensitivity of different organs and tissues to atropine varies and can be graded as—

Saliva, sweat, bronchial secretion > eye, bronchial muscle, heart > smooth muscle of intestine, bladder > gastric glands and smooth muscle.

The above differences probably reflect the relative dependence of the function on cholinergic tone *vis a vis* other influences, and variation in synaptic gaps in different organs. The pattern of relative activity is nearly the same for other atropine substitutes except *pirenzepine* which inhibits gastric secretion at doses that have little effect on other secretions, heart and eye. This is probably because atropine equally blocks M_1, M_2 and M_3 receptors whereas pirenzepine is a selective M_1 antagonist.

Atropine more effectively blocks responses to exogenously administered cholinergic drugs than those to parasympathetic nerve activity. This may be due to release of ACh very close to the receptors by nerves and involvement of cotransmitters (*see* p. 108).

Hyoscine This natural anticholinergic alkaloid differs from atropine in many respects; these differences are presented in Table 8.1.

PHARMACOKINETICS

Atropine and hyoscine are rapidly absorbed from g.i.t. Applied to eyes they freely penetrate cornea. Passage across blood-brain barrier is somewhat restricted. About 50% of atropine is metabolized in liver and rest is excreted unchanged in urine. It has a t½ of 3–4 hours. Hyoscine is more completely metabolized and has better blood-brain barrier penetration.

Atropine sulfate: 0.6–2 mg i.m., i.v. (children 10 µg/kg), 1–2% topically in eye.

ATROPINE SULPHATE: 0.6 mg/ml inj., 1% eye drop/ointment; ATROSULPH 1% eye drop, 5% eye oint.

Hyoscine hydrobromide: 0.3–0.5 mg oral, i.m.; also as transdermal patch.

Combinations of atropine with analgesics and antipyretics are banned in India.

ATROPINE SUBSTITUTES

Many semisynthetic derivatives of belladonna alkaloids and a large number of synthetic compounds have been introduced with the aim of producing more selective action on certain functions. Most of these differ only marginally from the natural alkaloids, but some appear promising.

Quaternary compounds

These drugs have certain common features—

- Incomplete oral absorption (10–30%).
- Poor penetration in brain and eye; central and ocular effects are not seen after parenteral/oral administration.
- Elimination is generally slower; majority are longer acting than atropine.
- Have higher nicotinic blocking property. Some degree of ganglionic blockade may occur at clinical doses producing postural hypotension and impotence as additional side effects.
- At high doses some degree of neuromuscular blockade may also occur.

Table 8.1: Comparative features of atropine and hyoscine

	Atropine	*Hyoscine*
1. Chief source	*Atropa belladonna, Datura stramonium*	*Hyoscyamys niger*
2. Alkaloidal ester of tropic acid with	Tropine (base)	Scopine (base)
3. CNS effect low dose high dose	Excitatory Excitation (mild) Excitation (strong), halucination	Depressant (amnesia, fatigue, drowsiness, N-REM sleep) Excitation, halucination
4. Anticholinergic property	More potent on heart, bronchial muscle and intestines	More potent on eye and secretory glands
5. Duration of action	Longer	Shorter
6. Anti-motion sickness	+ +	+ + +

Drugs in this category are—

1. *Hyoscine butyl bromide* 20–40 mg oral, i.m., s.c., i.v.; less potent and longer acting than atropine; used for esophageal and gastrointestinal spastic conditions.

BUSCOPAN 10 mg tab., 20 mg/ml amp.

2. *Atropine methonitrate* 2.5–10 mg oral, i.m.; for abdominal colics and hyperacidity.

MYDRINDON 1 mg (adult), 0.1 mg (child) tab; in SPASMOLYSIN 0.32 mg tab;

3. *Ipratropium bromide* 40–80 µg by inhalation; it acts selectively on bronchial muscle without altering volume or consistency of respiratory secretions. Another desirable feature is that in contrast to atropine, it does not depress mucociliary clearance by bronchial epithelium. It has a gradual onset and late peak (at 40–60 min) of bronchodilator effect in comparison to inhaled sympathomimetics. Thus, it is more suitable for regular prophylactic use rather than for rapid symptomatic relief during an attack. Action lasts 4–6 hours. It acts on receptors located mainly in the larger central airways (contrast sympathomimetics whose primary site of action is peripheral bronchioles, *see* Fig. 16.2). The parasympathetic tone is the major reversible factor in chronic obstructive pulmonary disease (COPD). Therefore, ipratropium is more effective in COPD than in bronchial asthma. Transient local side effects like dryness of mouth, scratching sensation in trachea, cough, bad taste and nervousness are reported in 20–30% patients, but systemic effects are rare because of poor absorption from the lungs and g.i.t. (major fraction of any inhaled drug is swallowed).

IPRAVENT 20 µg and 40 µg/puff metered dose inhaler, 2 puffs 3-4 times daily; 250 µg/ml respirator soln., 0.4–2 ml nebulized in conjunction with a β_2 agonist 2–4 times daily. Also used to control rhinorrhoea in perennial rhinitis and common cold; IPRANASE-AQ 0.084% nasal spray (42 µg per actuation), 1–2 sprays in each nostril 3–4 times a day.

4. *Tiotropium bromide* A newer congener of ipratropium bromide which binds very tightly to bronchial M_1/M_3 muscarinic receptors producing long lasting bronchodilatation. Binding to M_2 receptors is less tight, confering relative M_1/M_3 selectivity (less likely to enhance ACh release from vagal nerve endings in lungs due to M_2 receptor blockade). Like ipratropium, it is not absorbed from respiratory and g.i. mucosa and has exhibited high bronchial selectivity of action.

TIOVA 18 µg rotacaps; 1 rotacap by inhalation OD.

5. *Propantheline* 15–30 mg oral; it was a popular anticholinergic drug used for peptic ulcer and gastritis. It has some ganglion blocking activity as well and is claimed to reduce gastric secretion at doses which produce only mild side effects. Gastric emptying is delayed and action lasts for 6–8 hours. Use has declined due to availability of H_2 blockers and proton pump inhibitors.

PROBANTHINE 15 mg tab.

6. *Oxyphenonium* 5–10 mg (children 3–5 mg) oral; similar to propantheline, recommended for peptic ulcer and gastrointestinal hypermotility.

ANTRENYL 5, 10 mg tab.

7. *Clidinium* 2.5–5 mg oral; This antisecretory-antispasmodic has been used in combination with benzodiazepines for nervous dyspepsia, gastritis, irritable bowel syndrome (IBS), colic, peptic ulcer, etc.

In SPASRIL, ARWIN 2.5 mg tab with chlordiazepoxide 5 mg. NORMAXIN, CIBIS 2.5 mg with dicyclomine 10 mg and chlordiazepoxide 5 mg.

8. *Cimetropium bromide* A quaternary ammonium anticholinergic-antispasmodic drug, especially promoted for IBS. About 50% patients of IBS get 30–70% relief in abdominal pain and loose motion. Dryness of mouth is the commonest side effect.

Dose: 50 mg 2–3 times a day. IBSCIM 50 mg tab.

9. *Isopropamide* 5 mg oral; indicated in hyperacidity, nervous dyspepsia, IBS and other gastrointestinal problems, specially when associated with emotional/mental disorders.

In STELABID, GASTABID 5 mg tab. with trifluoperazine 1 mg.

10. *Glycopyrrolate* 0.2–0.4 mg i.m. (4–5 µg/kg), potent and rapidly acting antimuscarinic lacking central effects. It is almost exclusively

used for preanaesthetic medication and during anaesthesia. GLYCO-P 0.2 mg/ml amp., 1 mg in 5 ml vial, PYROLATE 0.2 mg/ml, 1 ml amp, 10 ml vial.

An inhalational powder formulation has been approved for 50 µg once daily inhalation for symptomatic relief in chronic obstructive pulmonary disease (COPD).

Tertiary amines

1. *Dicyclomine* 20 mg oral/i.m., children 5–10 mg; has direct smooth muscle relaxant action in addition to weak and somewhat M_1 selective anticholinergic action. It exerts antispasmodic action at doses which produce few atropinic side effects. However, infants have exhibited atropinic toxicity symptoms and it is not recommended below 6 months of age. It also has antiemetic property: has been used in morning sickness and motion sickness. Dysmenorrhoea and irritable bowel are other indications.
CYCLOSPAS-D, 20 mg with dimethicone 40 mg tab; CYCLOPAM INJ. 10 mg/ml in 2 ml, 10 ml, 30 ml amp/vial, also 20 mg tab with paracetamol 500 mg; in COLIMEX, COLIRID 20 mg with paracetamol 500 mg tab, 10 mg/ml drops with dimethicone.

2. *Valethamate:* The primary indication of this anticholinergic-smooth muscle relaxant is to hasten dilatation of cervix when the same is delayed during labour, and as visceral antispasmodic, for urinary, biliary, intestinal colic.
Dose: 8 mg i.m., 10 mg oral repeated as required.
VALAMATE 8 mg in 1 ml inj, EPIDOSIN 8 mg inj., 10 mg tab.

3. *Pirenzepine* It selectively blocks M_1 muscarinic receptors (*see* p. 112) and inhibits gastric secretion without producing typical atropinic side effects (these are due to blockade of M_2 and M_3 receptors). The more likely site of action of pirenzepine in stomach is intramural plexuses and ganglionic cells rather than the parietal cells themselves. It was indicated in peptic ulcer, but has been overshadowed by H_2 blockers and proton pump inhibitors.

Vasicoselective anticholinergics

1. *Oxybutynin* This antimuscarinic has high affinity for receptors in urinary bladder and salivary glands alongwith additional smooth muscle relaxant and local anaesthetic properties. It is relatively selective for M_3 and M_1 subtypes with less action on the M_2 subtype. Because of vasicoselective action, it is used for detrusor instability resulting in urinary frequency and urge incontinence. Beneficial effects have been demonstrated in post-prostatectomy vasical spasm, neurogenic bladder, spina bifida and nocturnal enuresis. Anticholinergic side effects are common after oral dosing, but intravesical instillation increases bladder capacity with few side effects. Oxybutynin is metabolized by CYP3A4; its dose should be reduced in patients being treated with inhibitors of this isoenzyme.
Dose: 5 mg BD/TDS oral; children above 5 yr 2.5 mg BD.
OXYBUTIN, CYSTRAN, OXYSPAS 2.5 mg and 5 mg tabs.

2. *Tolterodine:* This relatively M_3 selective muscarinic antagonist has preferential action on urinary bladder; less likely to cause dryness of mouth and other anticholinergic side effects. It is indicated in overactive bladder with urinary frequency and urgency. Since it is metabolized by CYP3A4, dose should be halved in patients receiving CYP3A4 inhibitors (erythromycin, ketoconazole, etc.)
Dose: 1–2 mg BD or 2–4 mg OD of sustained/extended release tab. oral. ROLITEN, TOLTER 1, 2 mg tabs, TORQ 2, 4 mg SR tab.

3. *Flavoxate* It has properties similar to oxybutynin and is indicated in urinary frequency, urgency and dysuria associated with lower urinary tract infection.
URISPAS, FLAVATE, FLAVOSPAS 200 mg tab, 1 tab TDS.

4. *Darifenacin* Another relatively M_3 selective antimuscarinic with preferential action on bladder muscles; indicated in urinary incontinence, urgency and frequency. The biological $t_{1/2}$ is 13–19 hours and the extended release tablet works for 24 hours.
Dose: 7.5–15 mg OD
DARILONG, ESIGARD 7.5 mg, 15 mg ER tabs.

5. *Solifenacin* It is similar to darifenacin; no clinically significant difference between the two has been observed in clinical trials on patients with overactive bladder.
Dose: 5–10 mg OD
BISPEC, SOLICEPT 5, 10 mg tabs.

Drotaverine It is a non-anticholinergic smooth muscle antispasmodic which acts by inhibiting

phosphodiesterase-4 (PDE-4) selective for smooth muscle. Elevation of intracellular cAMP/cGMP attends smooth muscle relaxation. Changes in membrane ionic fluxes and membrane potential have also been shown. It has been used orally as well as parenterally in intestinal, biliary and renal colics, IBS, uterine spasms, etc. without anticholinergic side effects. Adverse effects reported are headache, dizziness, constipation and flushing. Fall in BP can occur on i.v. injection.

Dose: 40–80 mg TDS; DROTIN, DOTARIN, DOVERIN 40, 80 mg tabs, 40 mg/2 ml inj.

Mydriatics

Atropine is a potent mydriatic but its slow and long-lasting action is undesirable for refraction testing. Though the pupil dilates in 30–40 min, cycloplegia takes 1–3 hours, and the subject is visually handicapped for about a week. Atropine substitutes attempt to overcome these difficulties. However, atropine itself is used in iridocyclitis, keratitis, etc.

1. *Homatropine* It is 10 times less potent than atropine. Instilled in the eye, it acts in 45–60 min, mydriasis lasts 1–3 days while accommodation recovers in 1–2 days. It often produces unsatisfactory cycloplegia in children who have high ciliary muscle tone.

HOMATROPINE EYE, HOMIDE 1%, 2% eye drops.

2. *Cyclopentolate* It is potent and rapidly acting; mydriasis and cycloplegia occur in 30–60 min and last about a day. It is preferred for cycloplegic refraction, but children may show transient behavioural abnormalities due to absorption of the drug after passage into the nasolacrimal duct. It is also used in iritis and uveitis.

CYCLOMID EYE 0.5%, 1%; CYCLOGYL, CYCLOPENT 1% eye drops.

3. *Tropicamide* It has the quickest (20–40 min) and briefest (3–6 hours) action, but is a relatively unreliable cycloplegic. However, it is satisfactory for refraction testing in adults and as a short acting mydriatic for fundoscopy. The mydriatic action can be augmented by combining with phenylephrine.

OPTIMIDE, TROPICAMET, TROMIDE 0.5%, 1.0% eye drops. TROPAC-P, TROPICAMET PLUS 0.8% with phenylephrine 5% eye drops.

Antiparkinsonian drugs (*see* Ch. 31)

USES

1. As antisecretory

• *Preanaesthetic medication* When irritant general anaesthetics (ether) were used, prior administration of anticholinergics (atropine, hyoscine, glycopyrrolate) was imperative to check increased salivary and tracheobronchial secretions. However, with current use of nonirritating anaesthetics (halothane, etc.) the requirement has decreased, though atropine may still be employed because halothane sensitizes the heart to NA mediated ventricular arrhythmias which are specially prone to occur during vagal slowing. Atropinic drugs also prevent laryngospasm, not by an action on laryngeal muscles, which are skeletal muscles, but by reducing respiratory secretions that reflexly predispose to laryngospasm. Vasovagal attack during anaesthesia can also be prevented.

• *Pulmonary embolism* Atropine befefits by reducing pulmonary secretions evoked reflexly by embolism.

• To check excessive sweating or salivation, e.g. in parkinsonism. Use of anticholinergics in peptic ulcer is obsolete.

2. As antispasmodic

1. Intestinal and renal colic, abdominal cramps: symptomatic relief is afforded if there is no mechanical obstruction. However, in renal colic parenteral opioids and NSAIDs provide greater pain relief than atropine. Atropine is less effective in biliary colic and is not able to completely counteract biliary spasm due to opiates (nitrates are more effective).
2. Nervous, functional and drug induced diarrhoea may be controlled to some extent, but anticholinergics are not useful in infective diarrhoea.

3. Spastic constipation, IBS: modest symptomatic relief in abdominal discomfort and irregular bowel evacuation may be obtained. Amitriptyline and other TCAs may befefit non-responders.
4. Pylorospasm, gastric hypermotility, gastritis, nervous dyspepsia may be partially suppressed.
5. To relieve urinary frequency and urgency, enuresis in children. Vasicoselective M_3 antimuscarinics like oxybutynin, tolterodine, flavoxate and darifenacin have demonstrated good efficacy. They may also increase bladder capacity, but dry mouth and other anticholinergic effects are dose limiting.
6. Dysmenorrhoea: Anticholinergics are not very effective; NSAIDs are superior.

3. Bronchial asthma, asthmatic bronchitis, COPD

Reflex vagal activity is an important factor in causing bronchoconstriction and increased secretion in chronic bronchitis and COPD, but to a lesser extent in bronchial asthma. Orally administered atropinic drugs are bronchodilators, but less effective than adrenergic drugs; not clinically used. They dry up secretion in the respiratory tract, may lead to its inspissation and plugging of bronchioles resulting in alveolar collapse and predisposition to infection. The mucociliary clearance is also impaired. Inhaled ipratropium bromide has been found specially effective in asthmatic bronchitis and COPD, though less so in bronchial asthma. Given by aerosol, it neither decreases respiratory secretions nor impairs mucociliary clearance, and there are few systemic side effects. Thus, it has a place in the management of COPD. Its time course of action makes it more suitable for regular prophylactic use rather than for control of acute attacks. The additive bronchodilator action with adrenergic drugs is utilised to afford relief in acute exacerbation of asthma/COPD by administering a combination of nebulised ipratropium and β_2 agonist through a mask.

Tiotropium bromide is an equally effective and longer acting alternative to ipratropium bromide, good for once daily maintenance therapy. After regular use, it has been found to reduce episodes of COPD exacerbations.

4. As mydriatic and cycloplegic

(i) *Diagnostic* For testing error of refraction, both mydriasis and cycloplegia are needed. Tropicamide having briefer action has now largely replaced homatropine for this purpose. Phenylephrine is often combined with tropicamide for faster and stronger mydriatic action. These drugs do not cause sufficient cycloplegia in children: more potent agents like atropine or hyoscine have to be used. Atropine ointment (1%) applied 24 hours and 2 hours before is often preferred for children below 5 years. Cyclopentolate drops are a more rapidly acting alternative to atropine.

To facilitate fundoscopy only mydriasis is needed; a short acting antimuscarinic may be used, but phenylephrine is preferred, especially in the elderly, for fear of precipitating or aggravating glaucoma.

(ii) *Therapeutic* Because of its long lasting mydriatic-cycloplegic and local anodyne (pain relieving) action on cornea, atropine is very valuable in the treatment of iritis, iridocyclitis, choroiditis, keratitis and corneal ulcer. It gives rest to the intraocular muscles and cuts down their painful spasm. Atropinic drugs alternated with a miotic prevent adhesions between iris and lens or iris and cornea and may even break them if already formed.

5. As cardiac vagolytic

Atropine is useful in counteracting sinus bradycardia and partial heart block in selected patients where increased vagal tone is responsible, e.g. in some cases of myocardial infarction and in digitalis toxicity. However, cardiac arrhythmias or ischaemia may be precipitated in some cases.

6. For central action

• *Parkinsonism* (*see* Ch. 31) Central anticholinergics are less effective than levodopa. They

are used in mild cases, in drug-induced extrapyramidal syndromes and as adjuvant to levodopa.

• *Motion sickness* Hyoscine is the most effective drug for motion sickness. It is particularly valuable in highly susceptible individuals and for vigorous motions. The drug should be given prophylactically (0.2 mg oral), because administration after symptoms have setin is less effective; action lasts 4–6 hours. A transdermal preparation applied behind the pinna 4 hours before journey has been shown to protect for 3 days. Side effects with low oral doses and transdermal medication are few, but dry mouth and sedation can occur: driving is risky. Dicyclomine is another anticholinergic used for motion sickness. These drugs are not effective in other types of vomiting.

• Scopolamine had earned a reputation as a 'lie detector' during world war II: its amnesic and depressant action was believed to put the subject 'off guard' in the face of sustained interrogation and sleep deprivation, so that he came out with the truth.

7. To antagonise muscarinic effects of drugs and poisons

Atropine is the specific antidote for anti ChE and early mushroom poisoning (*see* Ch. 7). Atropine or glycopyrrolate is also given to block muscarinic actions of neostigmine used for myasthenia gravis, decurarization or cobra envenomation.

SIDE EFFECTS AND TOXICITY

Side effects are quite common with the use of atropine and its congeners. These are due to facets of its action other than for which it is being used. They cause inconvenience but are rarely serious.

Belladonna poisoning may occur due to drug overdose or consumption of seeds and berries of belladonna/datura plant. Children are highly susceptible. Manifestations are due to exaggerated pharmacological actions.

Dry mouth, difficulty in swallowing and talking.

Dry, flushed and hot skin (especially over face and neck), fever, difficulty in micturition, decreased bowel sounds. A scarlet rash may appear.

Dilated pupil, photophobia, blurring of near vision, palpitation.

Excitement, psychotic behaviour, ataxia, delirium, dreadful visual hallucinations.

Hypotension, weak and rapid pulse, cardiovascular collapse with respiratory depression. Convulsions and coma occur only in severe poisoning.

Diagnosis Methacholine 5 mg or neostigmine 1 mg s.c. fails to induce typical muscarinic effects.

Treatment If the poison has been ingested, gastric lavage should be done with tannic acid ($KMnO_4$ is ineffective in oxidizing atropine). The patient should be kept in a dark quiet room. Cold sponging or ice bags are applied to reduce body temperature. Physostigmine 1–3 mg s.c. or i.v. antagonises both central and peripheral effects, but has been found to produce hypotension and arrhythmias in some cases. As such, it is generally not recommended. Neostigmine does not antagonise the central effects. Therefore, most cases are just treated symptomatically.

Other general measures (maintenance of blood volume, assisted respiration, diazepam to control convulsions) should be taken as appropriate.

Contraindications Atropinic drugs are absolutely contraindicated in individuals with a narrow iridocorneal angle—may precipitate acute congestive glaucoma. However, marked rise in intraocular tension is rare in patients with wide angle glaucoma.

Caution is advocated in elderly males with prostatic hypertrophy—urinary retention can occur.

Interactions

1. Absorption of most drugs is slowed because atropine delays gastric emptying. This results in slower absorption and greater peripheral degradation of levodopa—less of it reaches the brain. This does not occur when a peripheral decarboxylase inhibitor is combined.

   On the other hand, extent of digoxin and tetracycline absorption may be increased due to longer transit time in the g.i.t.

2. Antacids interfere with absorption of anticholinergics.
3. Antihistaminics, tricyclic antidepressants, phenothiazines, disopyramide, pethidine have anticholinergic property—additive side effects occur with atropinic drugs.
4. MAO inhibitors interfere with metabolism of anticholinergic antiparkinsonian drugs—delirium may occur.

DRUGS ACTING ON AUTONOMIC GANGLIA

Acetylcholine is the primary excitatory neurotransmitter in both sympathetic and parasympathetic ganglia. Drugs which inhibit synthesis (hemicholinium) or release (botulinum toxin, procaine) of ACh can interfere with ganglionic transmission, but drugs which act on cholinergic receptors in the ganglia are more selective.

In addition to the dominant nicotinic N_N receptors, which mediate the primary rapid depolarization of ganglionic cells, there are modulatory muscarinic M_1, M_2, adrenergic, dopaminergic, amino acid and peptidergic receptors which bring about secondary, slowly developing but longer lasting changes in membrane potential, both positive and negative, that modulate the primary response. Separate catecholamine (NA, DA) and amino acid transmitter containing cells are present in ganglia, but peptide cotransmitters are released from the preganglionic cholinergic terminals themselves. Thus, autonomic ganglion is not merely a one transmitter—one cell junction, but a complex system capable of local adjustments in the level of excitability.

GANGLIONIC STIMULANTS

Selective nicotinic agonists	Nonselective/muscarinic agonists
Nicotine (small dose)	Acetylcholine
Lobeline	Carbachol
Dimethyl phenyl piperazinium (DMPP)	Pilocarpine
Tetramethyl ammonium	Anticholinesterases
Varenicline	MCN 343-A

Nicotine

It is the principal alkaloid in tobacco (*Nicotiana tabacum*). It acts as an agonist on both N_N and N_M subtypes of nicotinic cholinergic receptors (NRs). Sympathetic as well as parasympathetic ganglia are stimulated, but larger doses cause persistent depolarization and ganglionic blockade. Nicotine is important in the context of smoking and tobacco chewing. The only clinical indication of nicotine is short-term replacement therapy in tobacco abstinent subjects. There is no therapeutic application of ganglionic stimulants, because no useful purpose can be served by stimulating both sympathetic and parasympathetic ganglia concurrently.

Treatment of smoking cessation/ quitting tobacco chewing

Majority of smokers (and tobacco chewers) wish to quit smoking/chewing, but fail to do so because of nicotine dependence. The most important measure to help smokers quit is counselling and motivation. This may be supplemented by pharmacotherapy. The goals of such pharmacotherapy are:

- To reduce the craving for the satisfying (reward) effects of nicotine.
- To suppress the physical withdrawal symptoms of nicotine which manifest as restlessness, irritability, anxiety, aggression, inability to concentrate, depressed mood and unhappiness.

Heavy smokers may even develop tremors.

The drugs currently utilized for the above goals are:

- Nicotine replacement
- Partial agonists of α4β2 NRs (Varenicline)
- Antidepressants (Bupropion)

Nicotine transdermal This patch formulation of nicotine is applied once daily on the hip/abdomen/chest/upper arm as an aid to smoking cessation. It ameliorates the symptoms of nicotine withdrawal, but only partially suppresses the craving, because the intermittent peak nicotine blood levels that occur during smoking are not reproduced by the patch.

NICOTINELL-TTS 10, 20, 30 cm^2 patches releasing 7, 14, 21 mg nicotine per 24 hr respectively. in those smoking > 20 cigarettes every day-start with 30 cm^2 patch, shift to smaller patches every 5–8 days, treat for 3–4 weeks (max. 12 weeks).

Nicotine chewing gum Developed as an alternative to nicotine transdermal, this formulation is found more satisfying by some dependent subjects. The number of gum pieces chewed daily can be adjusted according to the need felt.

NULIFE 1, 2, 4 mg chewing gum; for those smoking >20 cigarettes/day—start with 4 mg gum chewed and retained in mouth for 30 min when urge to smoke is felt. After a few days change over to 2 mg gum and then to 1 mg gum. Not more than 15 pieces are to be allowed in a day. Treatment can be started at lower doses for less heavy smokers.

A nasal spray delivering 0.5 mg per activation, and an inhaler with nicotine cartridge are also available in some countries.

Side effects of nicotine replacement therapy are headache, dyspepsia, abdominal cramps, loose motions, insomnia, flu-like symptoms and local irritation. Vasospastic angina may be precipitated. Cardiac arrhythmias and ischaemic heart disease are the contraindications.

Varenicline This α4β2 subtype NR selective partial agonist has been marketed as oral tablets in many countries (UK, USA, Europe, etc), and recently in India, to help smoking cessation. Evidence has shown that the reward (reinforcing) action of nicotine is exerted through the α4β2 subtype of neuronal NRs which are mainly localized in nucleus accumbens and other mesolimbic areas. Activation of these NRs by nicotine induces DA release which produces feelings of satisfaction/reward and has reinforcing effect. Since varenicline is a partial agonist at these receptors, it provides some level of nicotine substitution, but blocks the reward effect of smoking. Clinically it has been found to reduce craving as well as nicotine withdrawal symptoms in those who stop smoking. Abstinence rates at one year of cessation are comparable to those of nicotine replacement and of bupropion. However, utility of varenicline is limited by its side effects which are mood changes, irrational behavior, appetite and taste disturbances, sleep disorders and agitation. Warning has been issued that it may promote suicidal thoughts.

Dose: Initially 0.25 mg BD; gradually increase upto 1 mg BD according to need, for not more than 12 weeks; then taper off.

CHAMPIX 0.5, 1.0 mg tabs.

Bupropion This atypical antidepressant inhibits reuptake of DA and NA, and has been marketed as a sustained release tablet specifically for smoking cessation. Clinical efficacy has been rated equivalent to nicotine replacement, and it has produced fewer side effects (*see* Ch. 33).

GANGLION BLOCKING AGENTS

The competitive ganglion blockers were used in the 1950s for hypertension and peptic ulcer, but have been totally replaced now because they produce a number of intolerable side

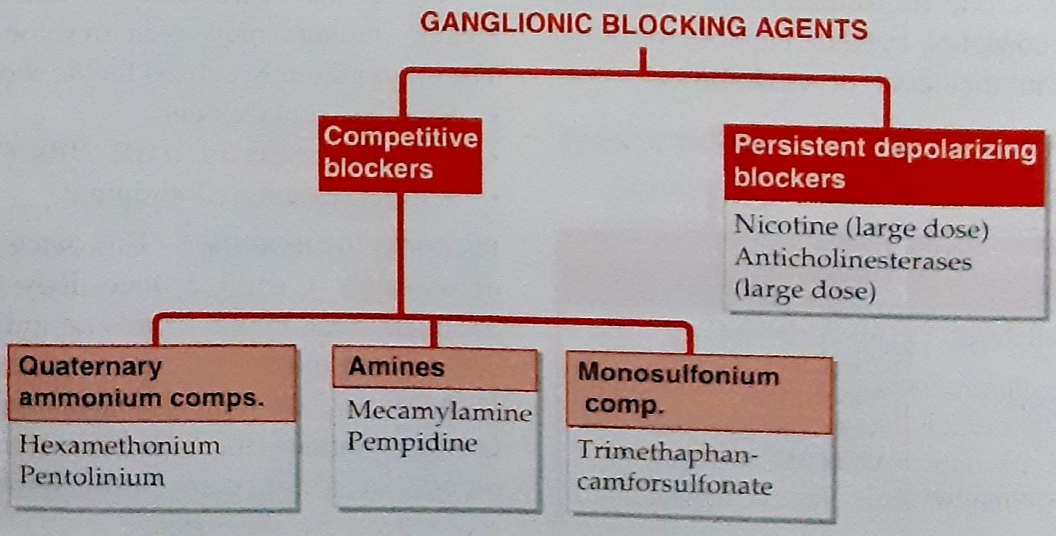


Table 8.2: Relative autonomic tone and effects of ganglionic blockade on organ function

Organ	*Dominant tone*	*Effect of ganglionic blockade (Side effect)*
1. Heart	Para-symp.	Tachycardia (palpitation)
2. Blood vessels	Symp.	Vasodilatation, abolition of reflexes (postural and exercise hypotension, syncope)
3. Iris	Para-symp.	Mydriasis (photophobia)
4. Ciliary muscle	Para-symp.	Cycloplegia (blurring of near vision)
5. Intestines	Para-symp.	Decreased motility (distension, constipation)
6. Bladder	Para-symp.	Decreased tone (difficulty in micturition)
7. Male sexual function	Para-symp. Symp.	Inhibition of erection Inhibition of ejaculation } (impotence)
8. Salivary glands	Para-symp.	Inhibition of salivation (dryness of mouth, difficulty in swallowing and talking)
9. Sweat glands	Symp. (cholinergic)	Inhibition of sweating (anhydrosis)

effects (*see* Table 8.2). In fact, these side effects help in understanding the relative roles of sympathetic and parasympathetic divisions in regulating the various organ functions. None of the ganglion blockers is commercially marketed now as a medicine, and these drugs have no clinical relevance.

Trimethaphan It is an ultrashort acting ganglion blocker, which was infused i.v. to produce controlled hypotension and to lower BP in hypertensive emergency due to aortic dissection.

Mecamylamine Either alone or in combination with nicotine patch, mecamylamine was tried for smoking cessation. It appears to block the reward effect of nicotine and improve abstinence rate compared to placebo.

PROBLEM DIRECTED STUDY

8.1 An elderly male aged 74 years was brought to the hospital since he had not passed urine for the past 24 hours and had severe pain in lower abdomen. On examination there was a bulge in the pubic region due to full urinary bladder. On catheterization, he passed 1.5L urine and the pain was relieved.

He gave the history of having difficulty in passing urine, poor stream, frequent urge to urinate and post-void dribbling for the last 3 years. Over the past few days he had been experiencing episodes of vertigo for which he was prescribed a medicine that he was taking for 2 days. Examination of the prescription revealed that he was taking tab. Dimenhydrinate 50 mg 3 times daily.

(a) Could there be any relationship between the anti-vertigo medication and the episode of acute urinary retention?

(see Appendix-1 for solution)