**Scopolamine:**
- Tertiary amine plant alkaloid.
- Produces peripheral effects similar to those of atropine.
- Unlike atropine, scopolamine has greater action on the CNS (observed at therapeutic doses).
- It has some special actions as follows:
  1. Most effective anti-motion sickness drugs.
  2. Blocks short-term memory (amnesia).
  3. In contrast to atropine, scopolamine produces sedation, but at higher doses it can produce CNS excitement.
  4. May produce euphoria and is susceptible to abuse.

**Therapeutic uses:**
- Prevention (not treatment) of motion sickness.
- An important adjunct drug in anesthetic procedures (as an amnesic agent).

**Pharmacokinetics and adverse effects:** These aspects are similar to those of atropine.

**Ipratropium and tiotropium:**
- Inhaled ipratropium & inhaled tiotropium, used as bronchodilators for treatment of chronic obstructive pulmonary disease (COPD).
- Used in asthmatic patients who are unable to take adrenergic agonist.
- They do not enter the systemic circulation or CNS.

**Tropicamide and cyclopentolate:**
- Their ophthalmic solutions are used as mydriatic and cycloplegic.
- Duration of action is shorter than that of atropine (Tropicamide produces mydriasis for 6 hours and cyclopentolate for 24 hours).

**Benztropine and trihexyphenidyl:**
- Centrally acting antimuscarinic agents used for treatment of Parkinson disease & extrapyramidal symptoms.

**Darifenacin & oxybutynin:**
- Synthetic atropine-like drugs, used to treat overactive urinary bladder.
- Oxybutynin is available as a transdermal patch, which is better tolerated because it causes less dry mouth than do oral formulations.
2. **Ganglionic blockers:**
   - Block both sympathetic & parasympathetic ganglia.
   - Not effective as neuromuscular antagonists.
   - Thus, these drugs block the entire output of the ANS at the nicotinic receptor. Therefore, ganglionic blockade is rarely used therapeutically,
   - Except nicotine, they all are nondepolarizing, competitive antagonists.

**Nicotine:**
- A component of cigarette smoke, nicotine is a poison with many undesirable actions. It is without therapeutic benefit and is deleterious to health.
- Depending on the dose, nicotine depolarizes autonomic ganglia, resulting first in stimulation and then in paralysis of all ganglia.
- The stimulatory effects are complex due to effects on both sympathetic and parasympathetic ganglia.
- These effects include increased BP and HR (due to release of transmitter from adrenergic terminals and from the adrenal medulla) and increased peristalsis and secretions.
- Higher doses, falls BP (because of ganglionic blockade), and cause atony of both GIT & bladder.

**Trimethaphan:**
- Short-acting competitive nicotinic ganglionic blocker that should be given by IV infusion.

**Mecamylamine:**
- Competitive nicotinic ganglionic blocker.
- Duration of action is about 10 hours after a single dose.
- Its oral absorption is good in comparison to trimethaphan.
- Like trimethaphan, it is primarily used for emergency lowering of BP.

**Neuromuscular - blocking drugs:**
- Structural analogs of ACh, they act either as antagonists (nondepolarizing type) or agonists (depolarizing type) at the nicotinic receptors on the endplate of the NMJ.
- Block cholinergic transmission on the neuromuscular (NM) endplate of skeletal muscle.
- Clinically useful during surgery for producing complete muscle relaxation, orthopedic surgery and in facilitating tracheal intubation.
Note: A 2nd group of muscle relaxants, the central muscle relaxants, are used to control spastic muscle tone. They include:

- **Diazepam** (binds at GABA receptors).
- **Dantrolene** (acts directly on muscles by interfering with the release of calcium from the sarcoplasmic reticulum).
- **Baclofen** (probably acts at GABA receptors in the CNS).

**A- Nondepolarizing (competitive) blockers:**

- The first drug was **curare** (hunters of the Amazon used it to paralyze prey)
- **Tubocurarine** then purified and introduced into clinical practice.
- Because of its adverse side effects, **tubocurarine** has been largely replaced by other agents.
- The NM -blocking agents have significantly increased the safety of anesthesia because less anesthetic is required to produce muscle relaxation.

[Note: Higher doses of anesthesia may produce respiratory paralysis and cardiac depression, increasing recovery time after surgery.]

**Mechanism of action:**

**a. At low doses:**

- They prevent depolarization of the muscle cell membrane and inhibit muscular contraction.
- They compete with ACh at the receptor without stimulating the receptor.
- Cholinesterase inhibitors as **neostigmine**, **pyridostigmine** and **edrophonium** are employed to shorten the duration of the NM blockade.

**b. At high doses:**

- Nondepolarizing blockers can block the ion channels of the endplate. This leads to further weakening of NM transmission, thereby reducing the ability of AChE inhibitors to reverse the actions of the non depolarizing muscle relaxants.

**Actions:**

- Not all muscles are equally sensitive to blockade by competitive blockers, the small, rapidly contracting muscles are most susceptible.
- The order of paralysis of the muscles occurs as follows, face > eye > fingers > limbs > neck > trunk > intercostal > diaphragm muscles.
- Muscles are recovered in the reverse manner.
- Agents that release histamine (eg. **tubocurarine**, **atracurium**) can produce a fall in BP, flushing & bronchoconstriction.
- Pancuronium increases HR (due to vagolytic effect).
Therapeutic uses:
- Adjuvant drugs in anesthesia during surgery, as well as during orthopaedic surgery also they facilitate intubation.

Notes:
1. **Rocuronium** has rapid onset of action that makes it useful for tracheal intubation in patient with gastric contents.
2. **Cisatracurium** is useful in mechanical ventilation.
3. **Mivacurium** has rapid recovery, thus it is useful for short surgical procedures.

Pharmacokinetics:
- Ineffective orally (administered as IV injection).
- Many of them are not metabolized, and their actions are terminated by redistribution.
- **Tubocurarine**, **pancuronium**, **mivacurium**, **metocurine & doxacurium** are excreted unchanged in urine.
  Note: **Atracurium** releases histamine and is metabolized to laudanosine, which can provoke seizures, thus it has been replaced by its isomer **cisatracurium**, which is less likely to have these effects.
- Clearance of **vecuronium & rocuronium** may be prolonged in patients with hepatic disease, they are also excreted unchanged in bile.
- **Cisatracurium** is the only nondepolarizing NM blocking drug that can be used in patient with renal failure without need for dose reduction.
- The choice of an agent depends on onset & duration of the muscle relaxation needed.

Adverse effects:
In general, agents are safe with minimal side effects.

Drug interactions:
1. **AchE inhibitors** can overcome the action of nondepolarizing NM blockers, but, with increased dosage, AchE inhibitors can cause a depolarizing block as a result of elevated Ach concentrations at the endplate membrane. If the NM blocker has entered the ion channel, AchE inhibitors are not as effective in overcoming blockade.
2. **Halogenated hydrocarbon anesthetics**, such as halothane act to enhance NM blockade by sensitizing the NMJ to the effects of NM blockers.

3. **Aminoglycoside antibiotics**, such as gentamicin and tobramycin inhibit Ach release from cholinergic nerves by competing with calcium ions, enhancing NM blockade.

4. **Calcium-channel blockers** may increase the NM block of both depolarizing & nondepolarizing NM blockers.

B. **Depolarizing agents:**
- Succinylcholine is the only depolarizing muscle relaxant in use today.

**Mechanism of action:**
- Succinylcholine acts like ACh to depolarize the junction.
- It is not destroyed by AChE in the synaptic cleft providing constant stimulation of the receptor).

[Note: Succinylcholine duration of action depends on its hydrolysis by plasma pseudocholinesterase]
- The depolarizing agent first opens the sodium channel, resulting in depolarization of the nicotinic receptor (Phase I). This leads to a transient twitching of the muscle (fasciculations).
- With time, continuous depolarization gives way to gradual repolarization as the sodium channel closes or is blocked. This causes a resistance to depolarization (Phase II) and flaccid paralysis.

**Actions:**
- Sequence of muscles paralysis may be slightly different but, as with the competitive blockers, the respiratory muscles are paralyzed last.
- Succinylcholine initially produces short-lasting muscle fasciculations, followed within a few minutes by paralysis.
- It does not produce a ganglionic block except at high doses.
- Has weak histamine-releasing action.
- Normally, Succinylcholine duration of action is extremely short (few minutes), because it is rapidly inactivated by pseudocholinesterase.

**Therapeutic uses:**
1. During the induction of anesthesia to provide rapid endotracheal intubation
Pharmacokinetics:
- **Succinylcholine** is injected IV.
- Has brief duration of action (several minutes) due to redistribution to the plasma. Therefore, it is sometimes given by continuous infusion to maintain a longer duration of effect.
- Its effects rapidly disappear upon discontinuation.

Adverse effects:

1. **Hyperthermia:**
The administration of **succinylcholine** in the presence of **halothane** (anesthetic), has occasionally caused malignant hyperthermia (muscular rigidity, metabolic acidosis, tachycardia & hyperpyrexia) in genetically susceptible people. This is treated by rapidly cooling the patient and by administration of **dantrolene**, which blocks release of Ca2+ from the sarcoplasmic reticulum of muscle cells.

2. **Apnea:**
In patient with genetic deficiency in plasma cholinesterase or who has an atypical form of the enzyme, **succinylcholine** can prolonged apnea due to paralysis of the diaphragm.

3. **Hyperkalemia:**
**Succinylcholine** increases potassium release from intracellular stores, which may be particularly dangerous in burn patients and patients with massive tissue damage.