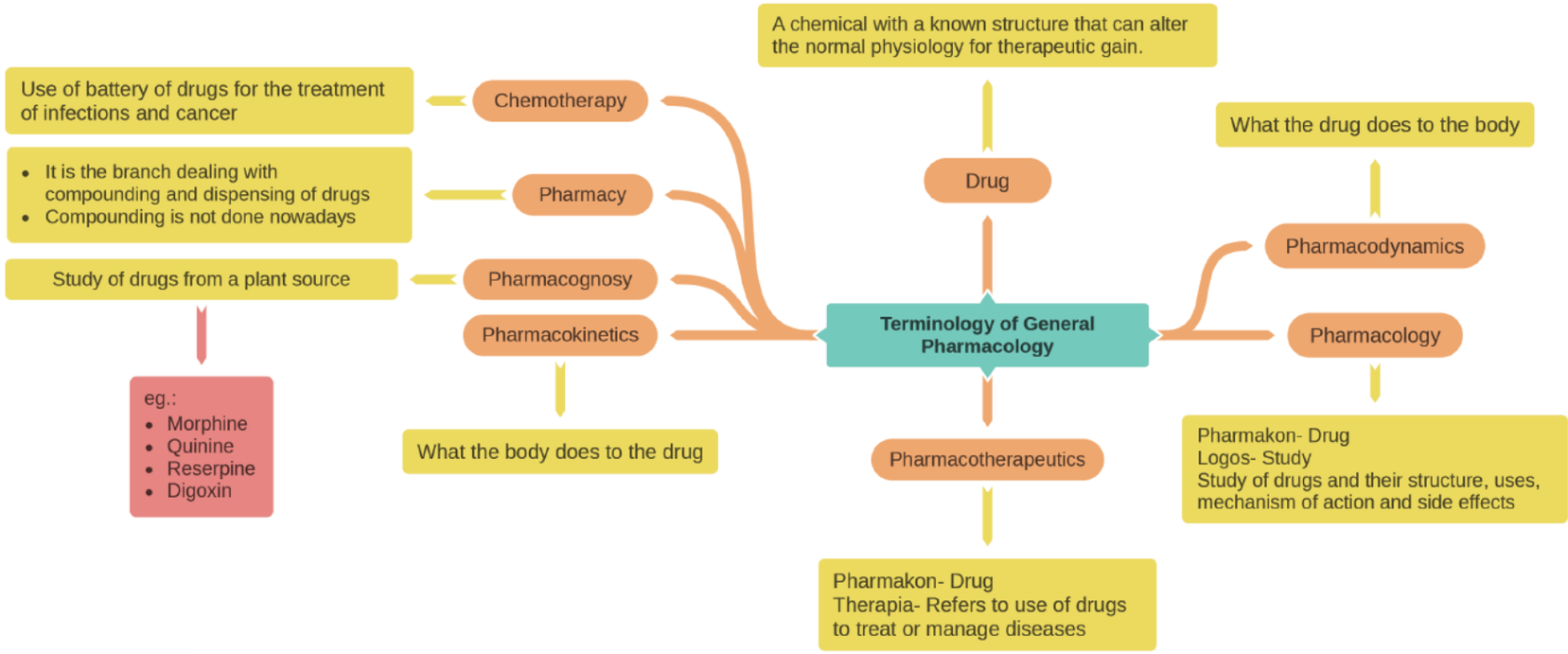
1.1 General Pharmacology: Overview and Receptors



KEY POINTS

Receptors

1. Ion channel receptors (fastest acting)

- GABA-A
- 5HT3
- Nicotinic
- Glutamate

2. Enzymatic receptors

Tyrosine Kinase

- Insulin
- EGFR
- VEGFR
- Her-2

Janus Kinase (JAK)

- Prolactin
- Growth hormone
- Cytokine

3. Nuclear receptors (slowest acting)

Located in Cytoplasm

- Androgen
- Glucocorticoid
- Mineralocorticoid
- Vitamin D

Located in Nucleus

- Estrogen
- Progesterone
- Vitamin A
- PPAR

4. GPCR (M.C. type)

Known as 7 transmembrane, heptahelical or serpentine receptors

Subtypes: Gq subtype

- Stimulates phospholipase-C → increases IP3, calcium → smooth muscle contraction
- α1, M1, M2, M3, H1, 5-HT2

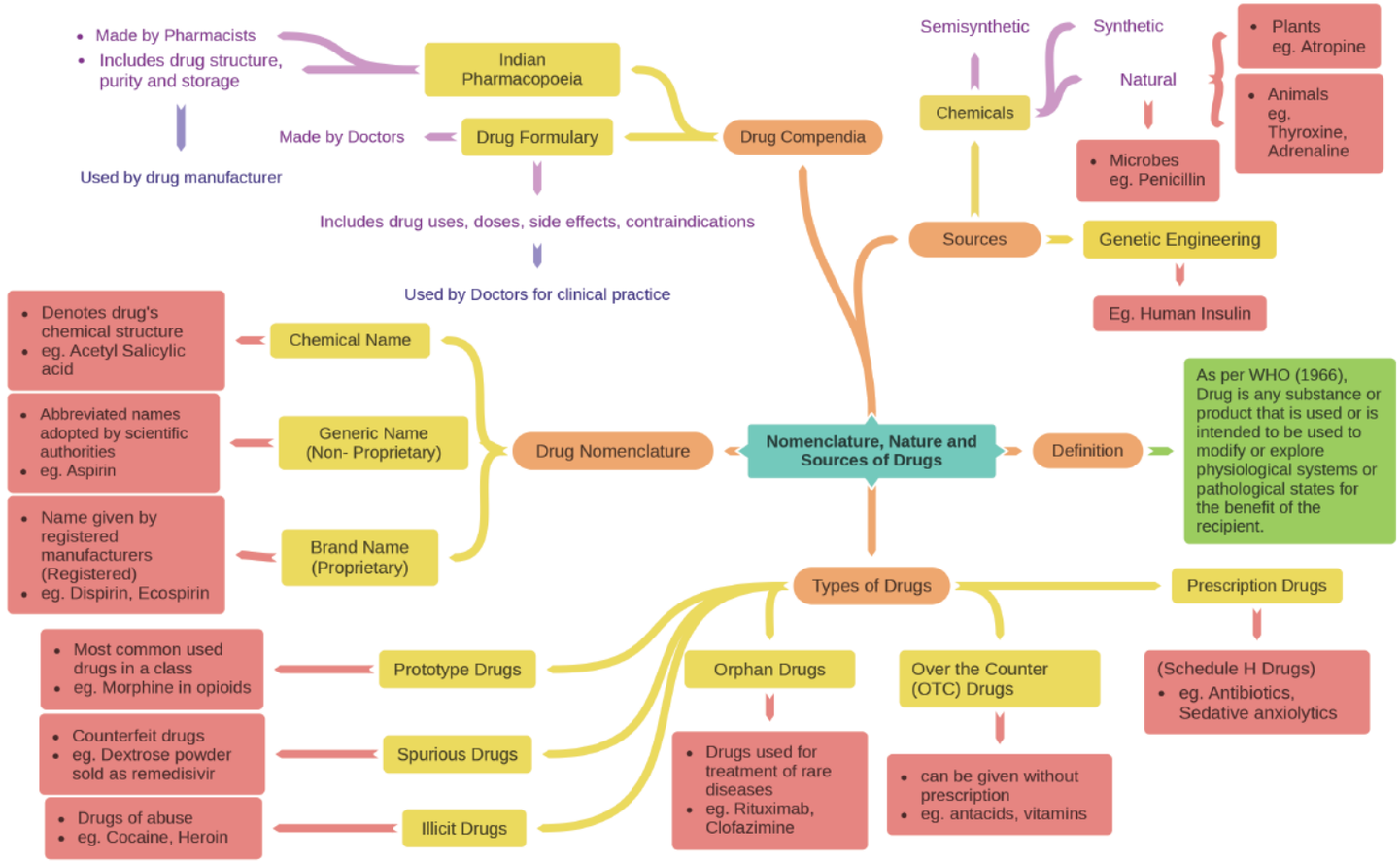
Gi/o Subtype

- Decreases cAMP, calcium, and opens potassium channels
- α2, M2, M4, H3, H4, 5-HT1, GABA-B, adenosine-1 (A1)

Gs Subtype

- Stimulates adenylate cyclase → increases cAMP → smooth muscle relaxation, cardiac/skeletal muscle contraction
- β1, β2, H2, 5-HT7

1.2 Drug: Nature, Sources and Nomenclature



KEY POINTS

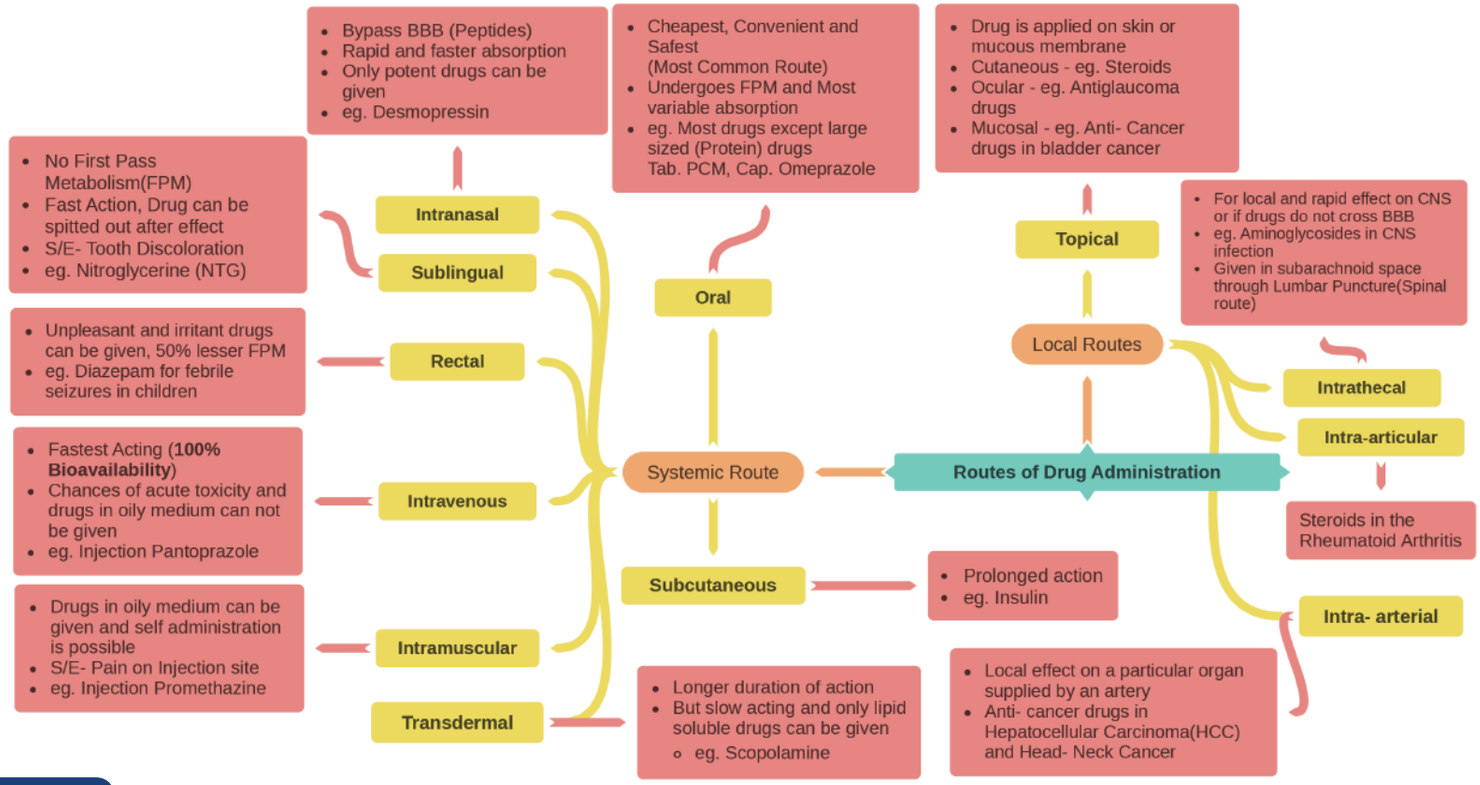
1. Schedule G/H/X drugs cannot be sold without prescription (label 'Rx' in black color)

- Schedule H1 was introduced later to stop unauthorized sale of antibiotics. (**'Rx'** in Red color)
- Other drugs are OTC (over-the-counter) drugs that can be sold without prescription

2. Essential drugs

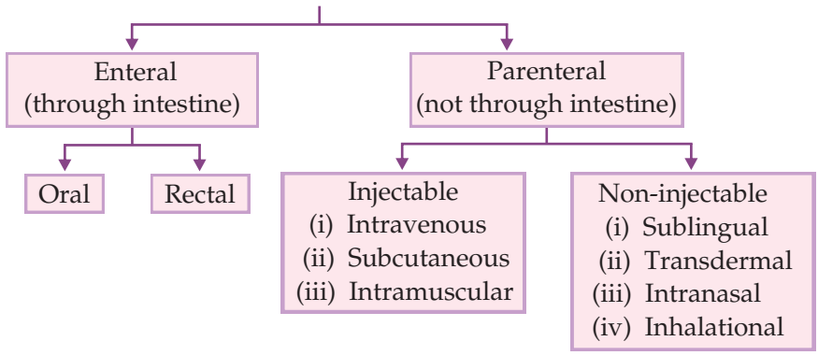
- These drugs cater the priority healthcare needs of the population
  - **These drugs should be →**
    - Always available
    - In adequate quantity
    - With assured quality
  - Mostly available as single compound drug
    - Example: Iron and folic acid preparations for anemia of pregnancy
    - Antitubercular drugs like Isoniazid, Rifampicin, Pyrazinamide, etc.

1.3 Routes of Drug Administration



KEY POINTS

1. Systemic route can be further classified as follows:

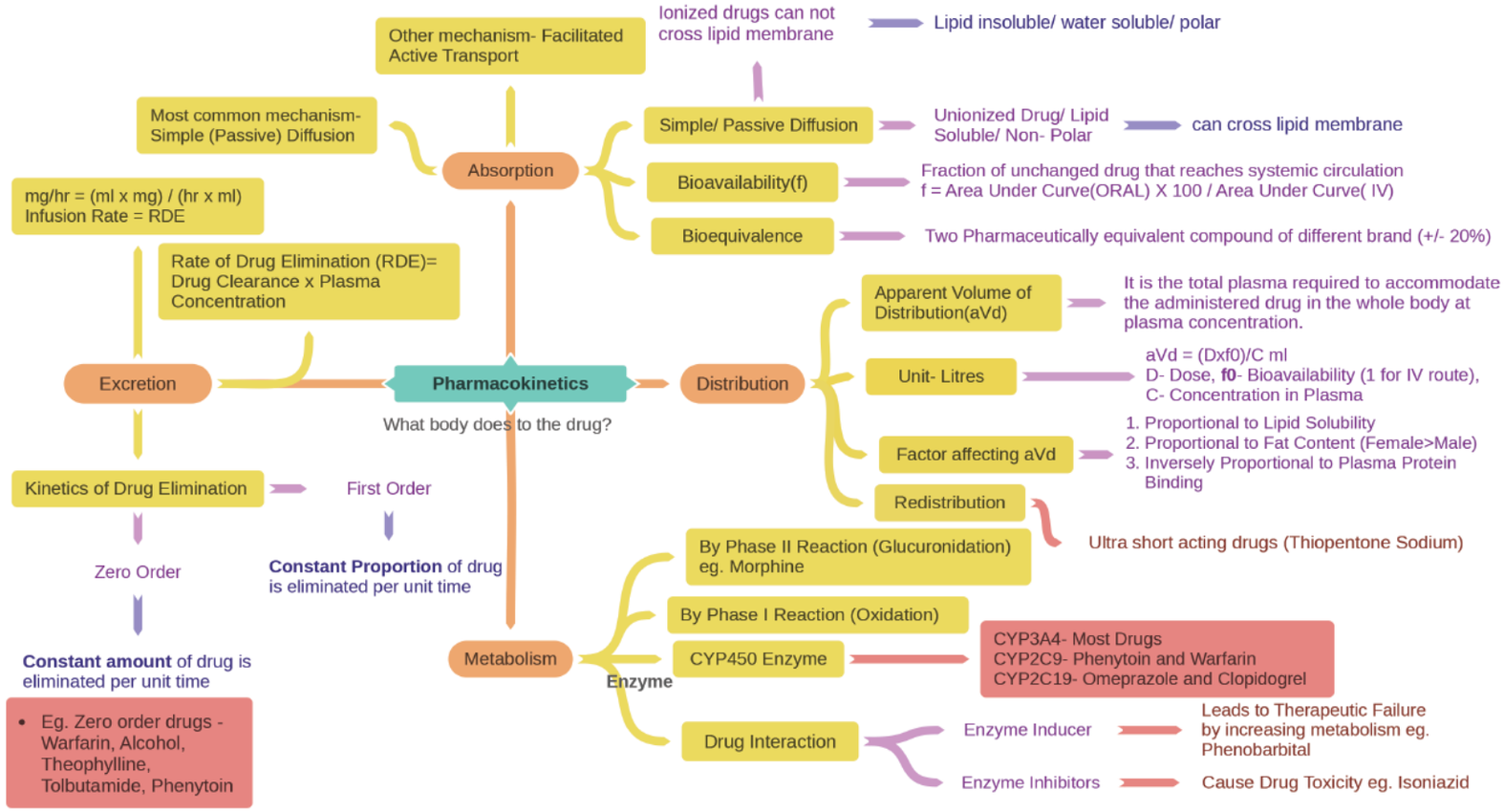


2. In intravenous route any volume of drug can be given but in intramuscular route, maximum 5–10 ml volume can be given

3.

Route	Angle of needle with horizontal
IV	25°
IM	90°
SC	45°
Intradermal	15°

1.4 Pharmacokinetics



KEY POINTS

1. Plasma protein binding

With albumin (acidic drugs)	With α1 acid glycopeptides (basic drugs)
Warfarin	Antiarrhythmic drugs, e.g.
Aspirin	Beta blockers
Sulfonamides	Amiodarone
CNS drugs (except opioids and tricyclic anti-depressant)	Lidocaine

2. t1/2: Time taken for drugs to reach 50% of plasma concentration

- Zero order—t1/2 increases with dose
- First order—t1/2 is constant

3. Enzyme inhibitors and inducers examples

Enzyme inducer	Enzyme inhibitor
Griseofulvin	Valproate
Phenytoin	Ketoconazole
Rifampicin	Cimetidine
Smoking	Ciprofloxacin
Carbamazepine	Erythromycin
Phenobarbitone	Isoniazid

1.5 Pharmacodynamics

Introduction

Response seen as binary → Either effect produced or not? → Done for Population

Quantal dose response curve

Pharmacodynamics: Introduction

What drug does to the body?

- Affinity
  - Tendency of the drug to bind to a target
  - Dose required to bind to receptor
- Efficacy
  - Effect produced
  - Maximum clinical effect produced under controlled condition
- Potency
  - Relative dose of a drug required to produce a particular effect
  - Potency proportional to 1/ dose
- Graded dose response curve
  - Graded response is seen → done for an individual

ED50 - Median Effective Dose → Dose that produced effect in 50 % population

TD50 - Median Toxic Dose → Dose that produce toxicity in 50 % Population

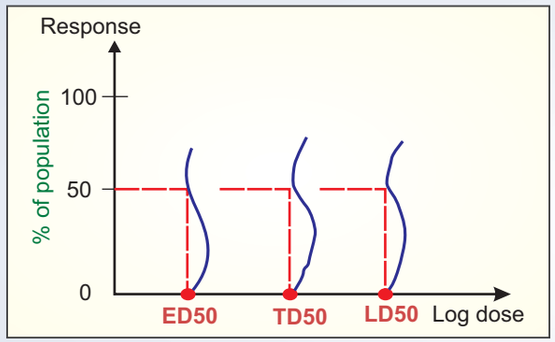
LD50 - Median Lethal Dose → Dose required to kill 50% of animals

Therapeutic Index (TI) = LD50/ED50
Describe Toxicity

- TI increased - Safer the Drug
- TI decreased - High risk of toxicity of the drug

KEY POINTS

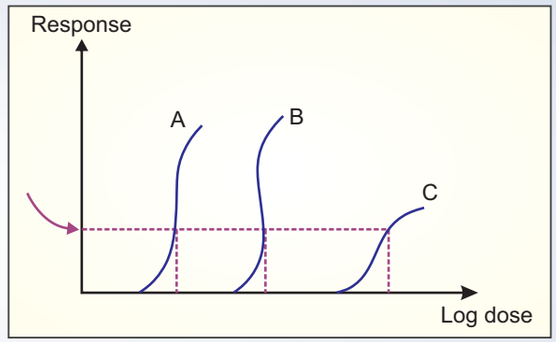
Quantal DRC (dose response curve)



- **ED:** Effective dose
- **TD**: Therapeutic dose
- **LD:** Lethal dose

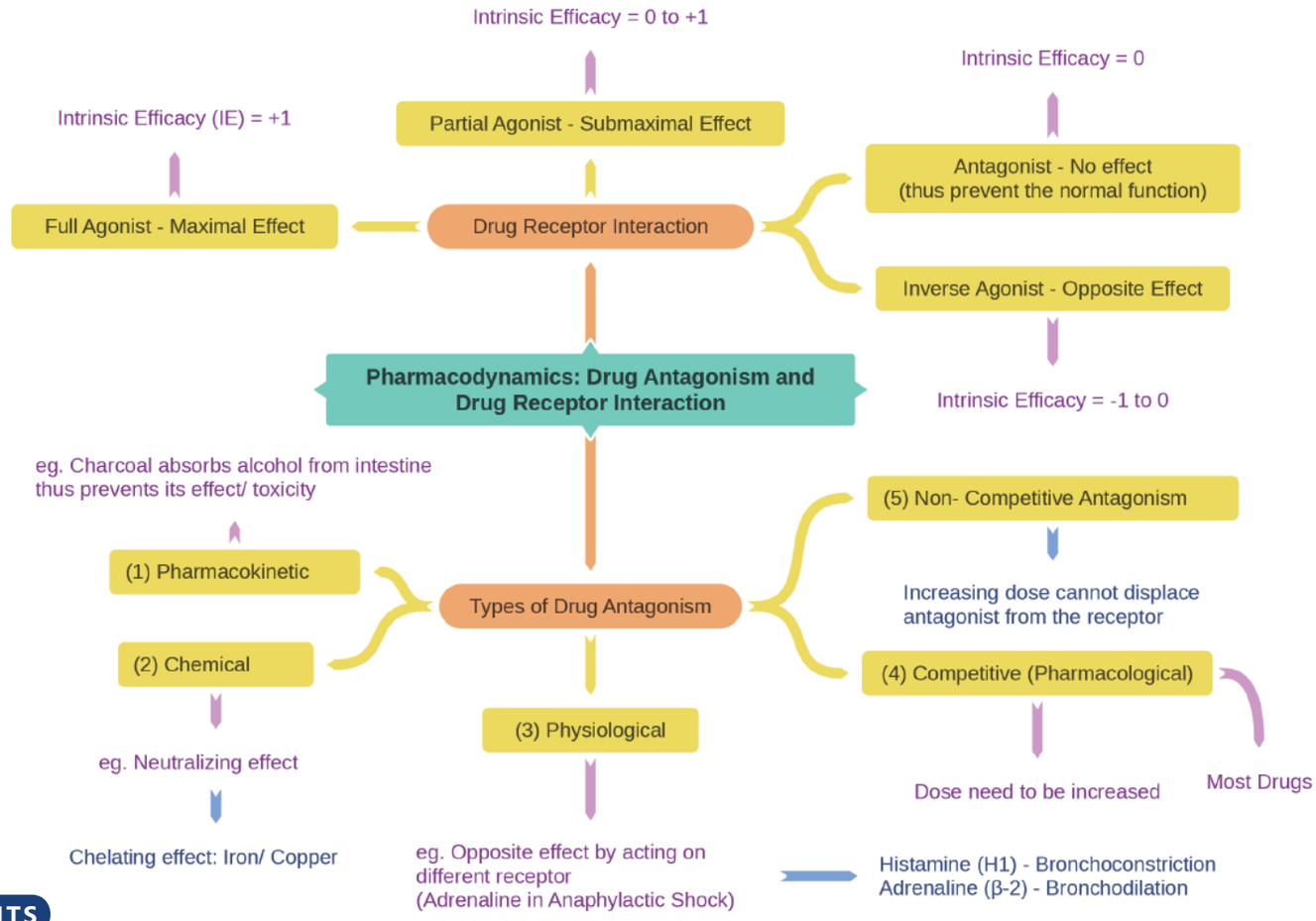
ED50: Dose required to produce effect in 50% population. Marker of potency
TD50: Dose required to produce toxicity in 50% population. Marker of toxicity
LD50: Only in animals. Dose required to kill 50% animals. Marker of toxicity

Graded DRC (dose response curve)



Efficacy: B > A > C. Higher peak response = Higher efficacy
Potency: A > B > C. More potent at lesser dose
Affinity: A > B. (Affinity can be compared only if the drugs act on the same target (only if DRCs are parallel)

Drug Antagonism and Drug Receptor Interaction



KEY POINTS

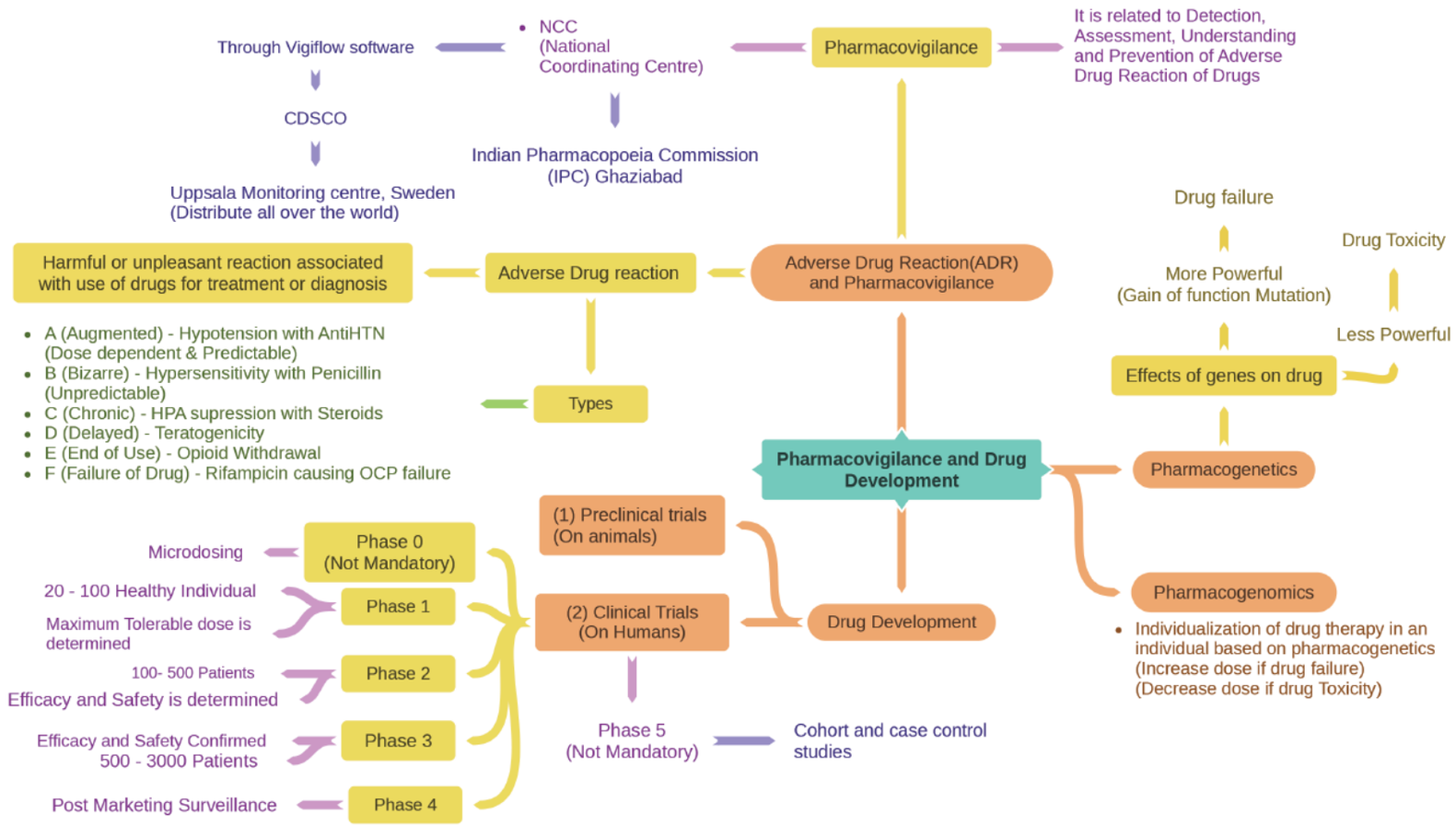
1. TDM (Therapeutic Drug Monitoring)

Indications

- If clinical effect of a drug cannot be measured easily
- To check the compliance in case of antipsychotic drugs
- Low therapeutic index drugs—e.g. Theophylline, Lithium, Digoxin
- Antiepileptics in pregnancy

1. **Inverse agonists have a unique clinical advantage:** They not only block receptor activity but actively reduce baseline activity, useful in diseases with constitutively active receptors.
2. **Drug antagonism has therapeutic implications:** Physiological antagonists are used in emergency settings (e.g., adrenaline for anaphylaxis), while competitive antagonists are dose-dependent.
3. **Non-competitive antagonists offer longer duration of action:** They bind irreversibly, useful for chronic conditions needing sustained receptor blockade such as hypertension and neurodegenerative disorders.

1.6 Pharmacovigilance and Drug Development



KEY POINTS

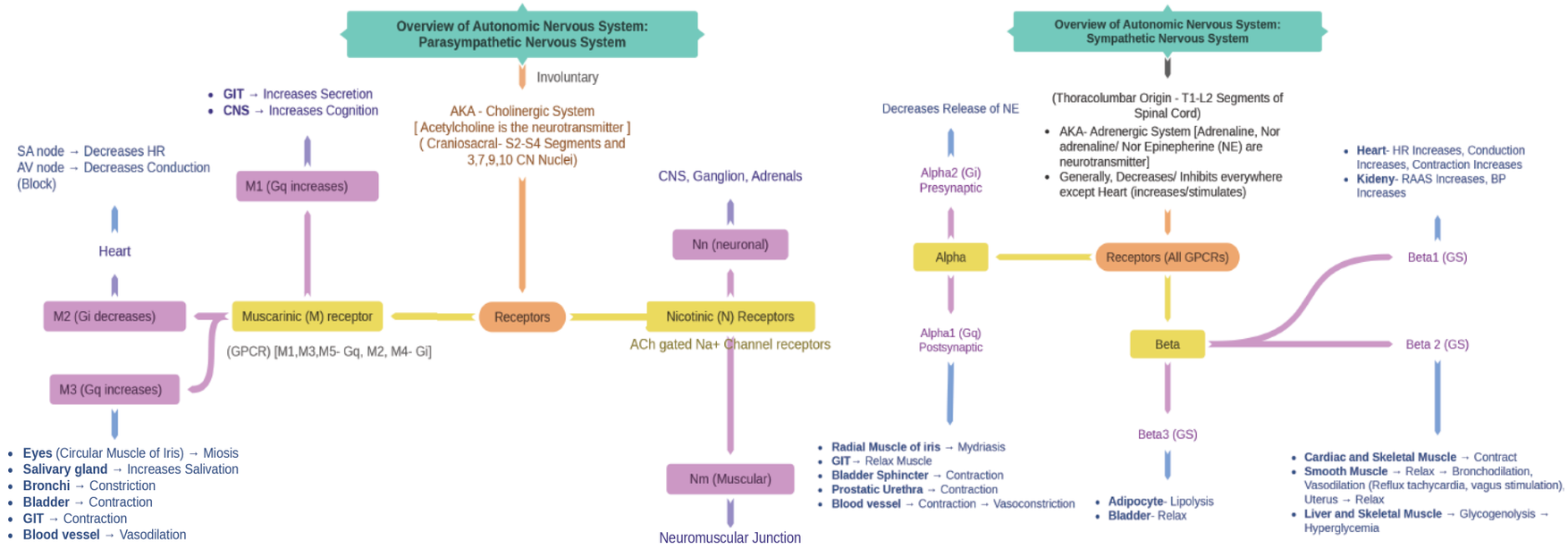
1. **Pharmacovigilance is an active and ongoing process:** It is not limited to post-marketing surveillance but should begin from clinical trials (phase 1 onward).
2. **Microdosing in Phase 0 helps minimize risks:** It allows early assessment of pharmacokinetics without exposing subjects to full therapeutic doses.
3. **Genetic testing can prevent drug failure or toxicity:** For example, testing for TPMT before giving azathioprine reduces the risk of severe myelosuppression.
4. **VigiFlow and global monitoring reduce delay in safety alerts:** Integration of national centers like IPC Ghaziabad into WHO's Uppsala Monitoring Center enhances real-time ADR detection.
5. **Drug development is cost-intensive and lengthy:** Most drugs fail in Phase 2 or 3 due to safety/efficacy issues, underlining the importance of robust preclinical research.

2

Autonomic Nervous System

- Overview of Autonomic Nervous System
- Cholinergic Drugs
- Anticholinergic Drugs
- Adrenergic Drugs
- Antiadrenergic Drugs

2.1 Overview of Autonomic Nervous System



1. The autonomic nervous system (ANS) regulates involuntary functions like heart rate, digestion, and respiration.
2. It is divided into sympathetic (fight or flight) and parasympathetic (rest and digest) systems.
3. Cholinergic neurons release acetylcholine and act on nicotinic and muscarinic receptors.
4. Adrenergic neurons release norepinephrine or epinephrine and act on alpha and beta receptors.
5. Most organs have dual innervation with opposing actions from sympathetic and parasympathetic nerves.

KEY POINTS

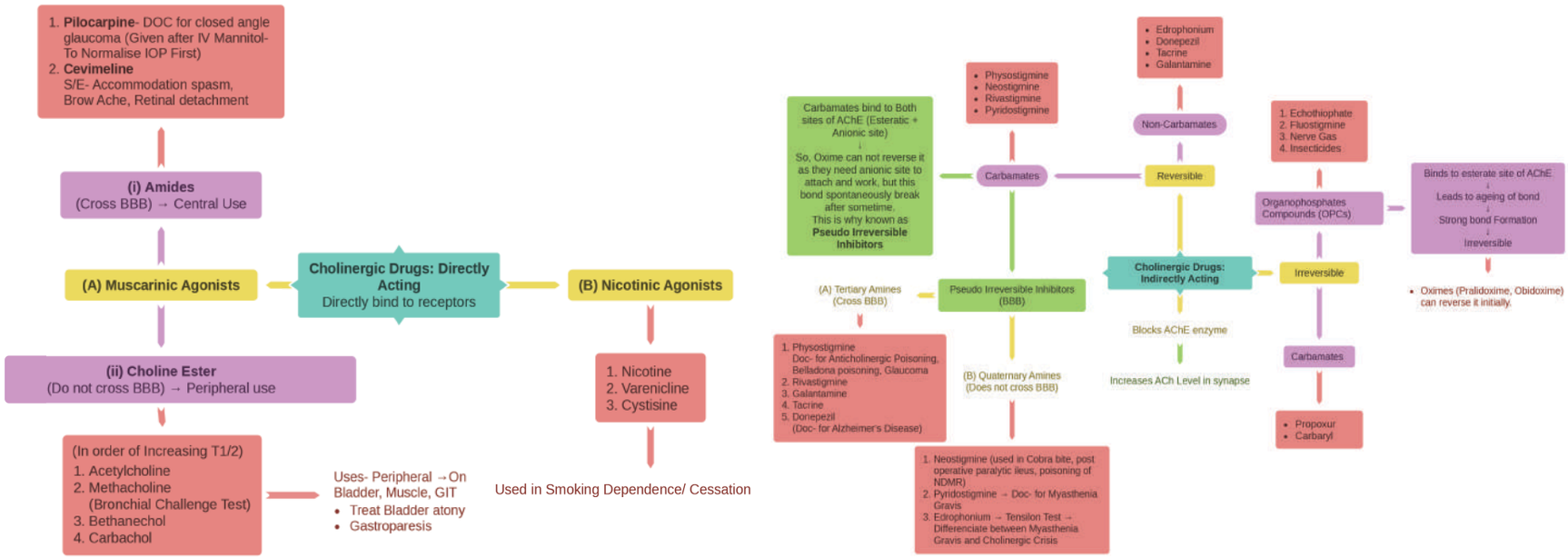
1. GPCR
(G protein coupled receptors)
(mnemonic—qis)

Gq	Gi	Gs
M1, M3, M5	M2, M4	–
α1	α2	β1, β2, β3

2. Effect of ANS

Organ/system	Sympathetic (↑ heart and rest↓)	Parasympathetic (↓ heart and rest↑)
• Heart	• HR↑, BP↑, Contraction↑	• HR↓, BP↓, Contraction↓
• CNS		• ↑ Cognition
• Eyes	• Radial muscle of iris→Mydriasis	• Circular muscles of iris→Miosis • Accommodation musles→Accommodation reflex
• Salivary glands	• ↓ Salivation	• ↑ Salivation
• Sweat glands	• ↑ Sweating	
• GIT	• ↓ Contraction and secretion	• ↑ Contraction and secretion
• Bronchi	• Bronchodilation	• Bronchoconstriction
• Bladder detrusor	• Relax (↓urination)	• Contract (↑urination)
• Bladder sphincter	• Contract (↓urination)	• Relax (↑urination)

2.2 Cholinergic Drugs



KEY POINTS

1. Cholinergic poisoning

Ex. OPC (organophosphate compounds) poisoning

- Bradycardia
- Agitation
- Salivation and Lacrimation↑
- Urination↑
- PINPOINT PUPIL (Miosis)
- Bronchospasm

DOC: • Atropine (monitor the effect by pupil size)
• Other drugs that can be given are oximes that are most specific drugs for this condition like Pralidoxime, Diacetyl monoxime, Obidoxime

Anticholinergic poisoning

Ex. Atropine, belladonna, Datura poisoning

- Tachycardia • Delirium • Dry mouth • Urination
- **DILATED PUPIL** (Mydriasis) • Constipation

DOC: Physostigmine

2. Myasthenia gravis

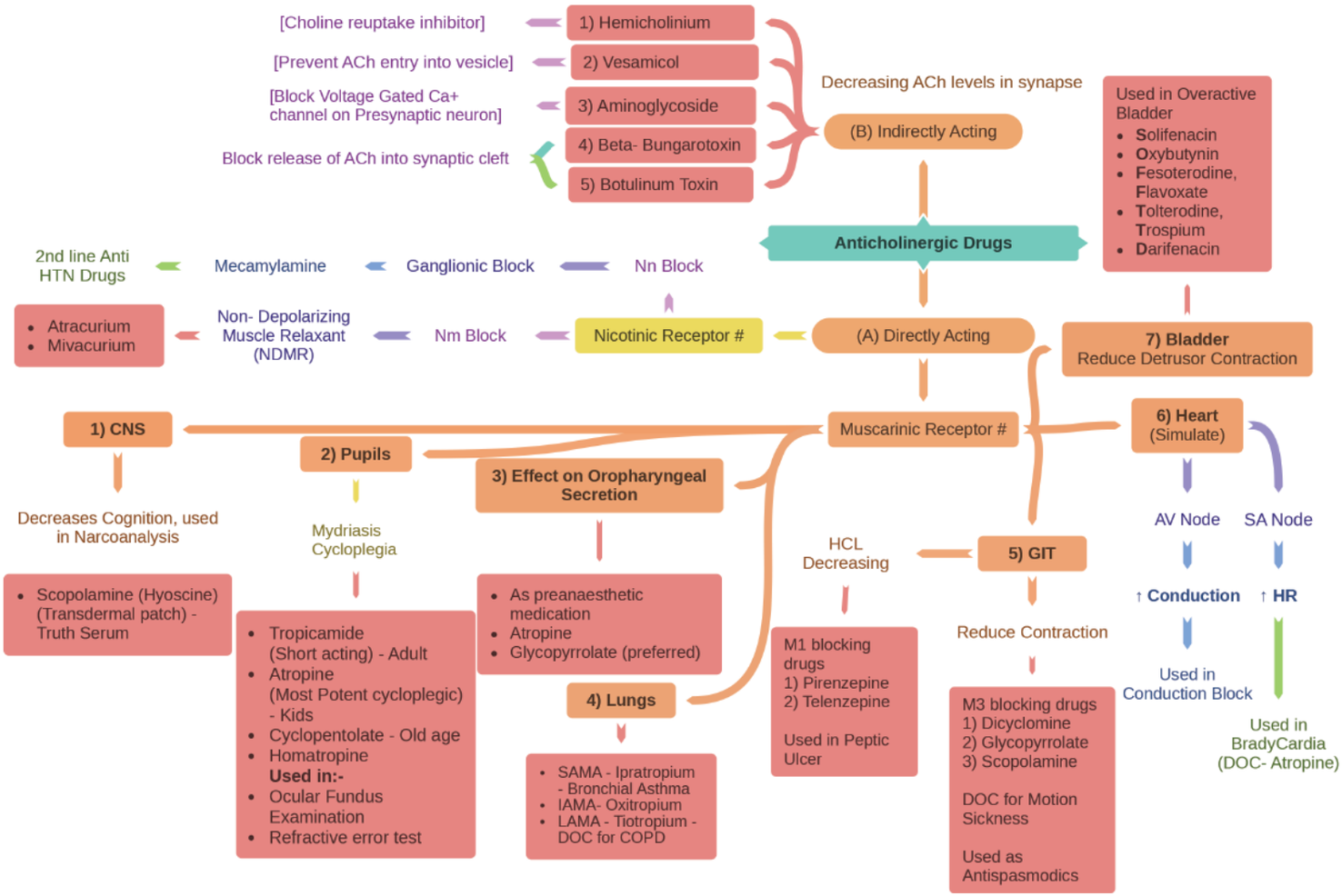
– Diagnosis→Atropine + Edrophonium (tensilon test)
– Treatment→

Generalized MG	Myasthenic crisis
DOC→Pyridostigmine ↓No response Steroids ↓No response Immunosuppressants (cyclosporine)	Intravenous immunoglobulin (IVIg)

Comparison of directly and indirectly acting cholinergic drugs

Feature	Directly acting cholinergic drugs	Indirectly acting cholinergic drugs
MOA	Act directly on cholinergic receptors (muscarinic/nicotinic)	Inhibit cholinesterase enzyme, increasing acetylcholine levels
Site of action, e.g.	Receptors on effector organs Pilocarpine, Bethanechol, Carbachol	Synaptic cleft (by preventing ACh breakdown) Neostigmine, Physostigmine, Organophosphates
Effect on acetylcholine (ACh)	Mimic ACh but do not alter its degradation	Enhance the action of ACh by delaying its breakdown
Clinical uses	Glaucoma, urinary retention, xerostomia	Myasthenia gravis, Alzheimer's disease, reversal of NM blockade

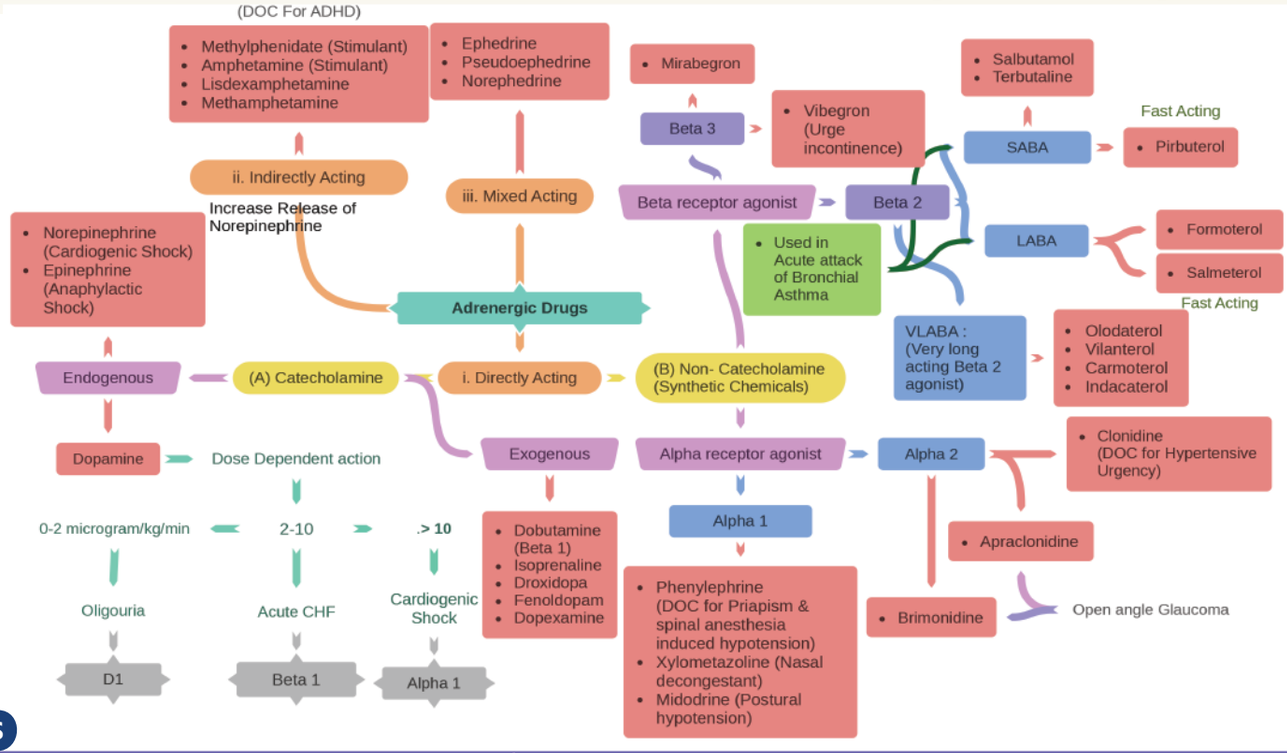
2.3 Anticholinergic Drugs



KEY POINTS

- Mnemonic—be SOFT—for Anticholinergics acting on bladder
  - Be (bladder)—Darifenacin
  - S—Solifenacin
  - O—Oxybutynin
  - F—Flavoxate, Fesoterodine
  - T—Tolterodine, Trospium
- Solifenacin and Darifenacin are selective M3 blockers

Adrenergic Drugs



KEY POINTS

1. Epinephrine/adrenaline

a. DOC: (i) Cardiac arrest, (ii) anaphylactic shock

- **Dosage:** 0.3–0.5 ml IM at 1:1000 dilution; If no response after multiple doses; Consider: 0.25 ml IV at 1:10,000 dilution

Note: As local vasoconstrictor: 1:100,000 dilution (with local anesthetic)

2. Dale phenomenon

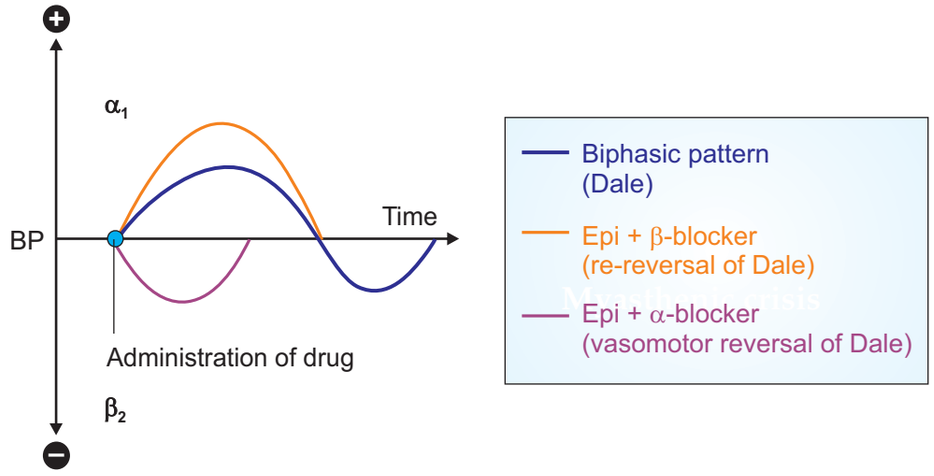
- Initially, epinephrine at high concentrations stimulates **α_1-receptors** that **increases BP**
- Later on at low concentrations, stimulates **β_2-receptors** that **decrease BP**

3. Vasomotor reversal of Dale

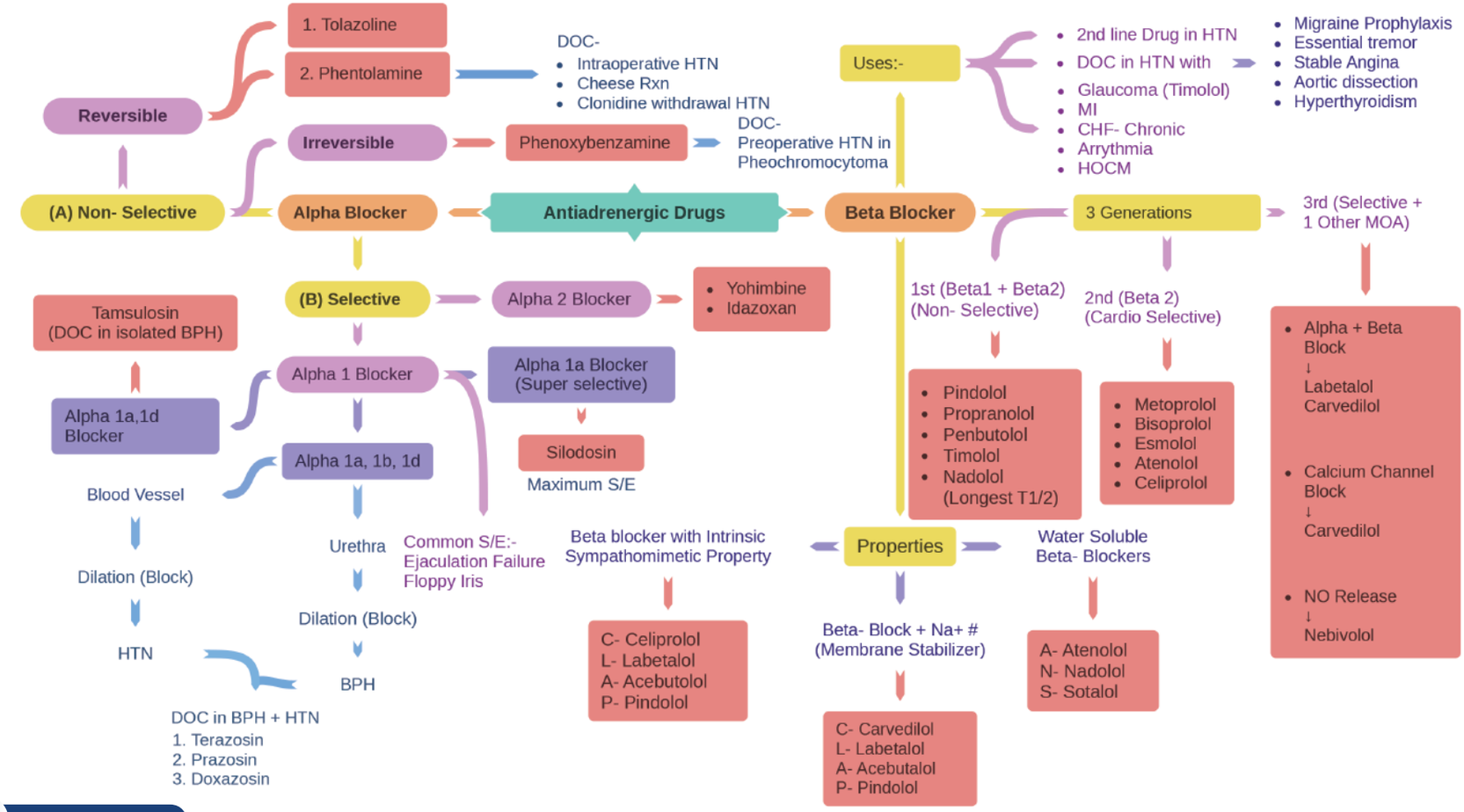
- Epinephrine + α-blocker: **Decreases blood pressure**

4. Vasomotor re-reversal of Dale

- Epinephrine + β-blocker: Significant **increase in blood pressure**



2.5 Antiadrenergic Drugs



KEY POINTS

1. Indirect acting sympatholytics

- Metyrosine {tyrosine hydroxylase (–) } →↓synthesis
- Reserpine, tetrabenazine, deutetrabenazine → VMAT2 (vesicular monoamine transporter) receptor (–)→↓synthesis

2. Treatment of BPH

Static component of obstruction (increased size of prostate)

Finasteride (5α-reductase type 2 inhibitor)

↓

Decrease dihydrotestosterone synthesis from testosterone

↓

Decrease size of prostate (takes time)

Dynamic component of obstruction (contraction of prostatic urethra)

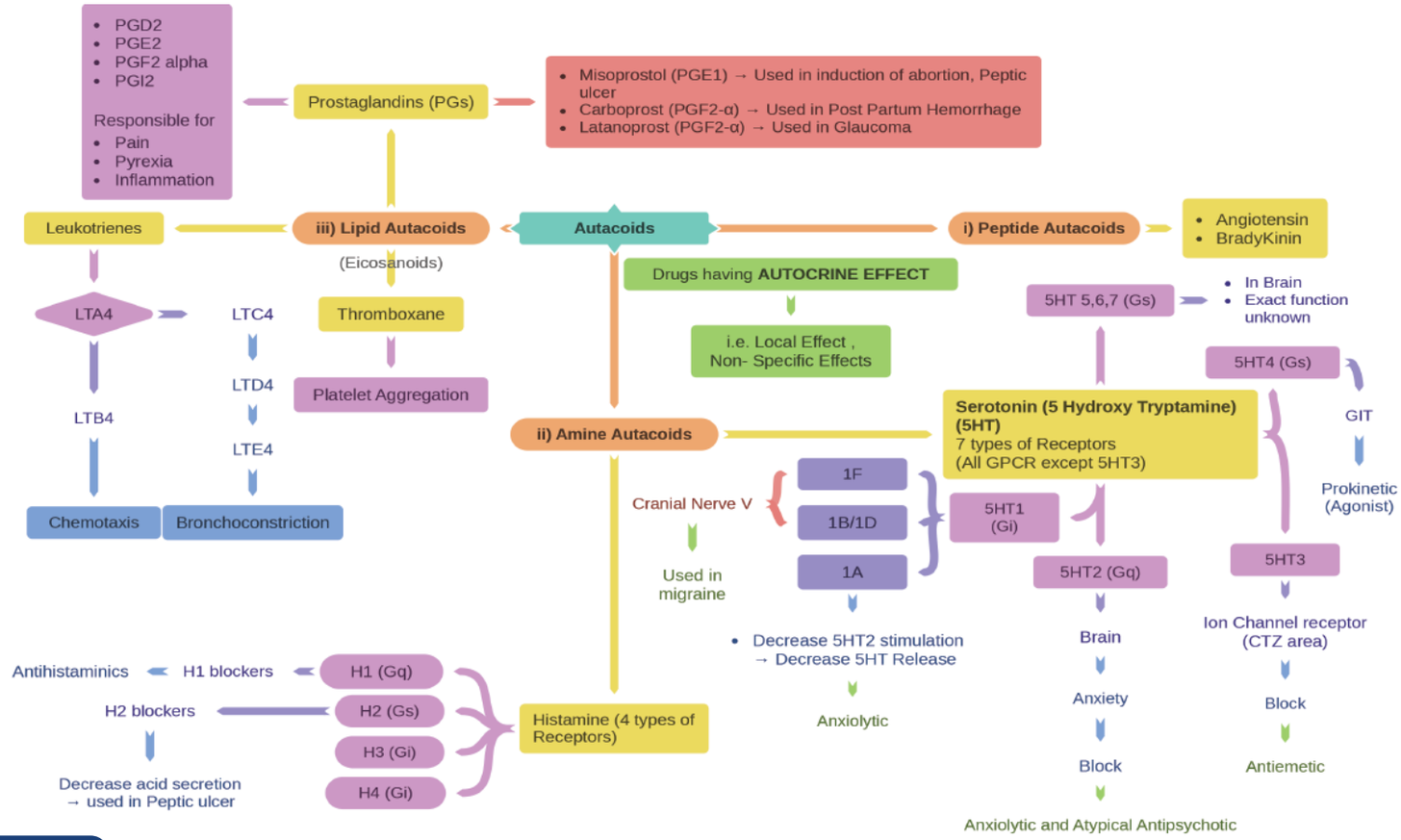
Tamsulosin (α-blocker) (immediate relief)

3

Autacoids

- Overview of Autacoids
- Antihistaminic Drugs
- Serotonin and Related Drugs
- Nonsteroidal Anti-inflammatory Drugs

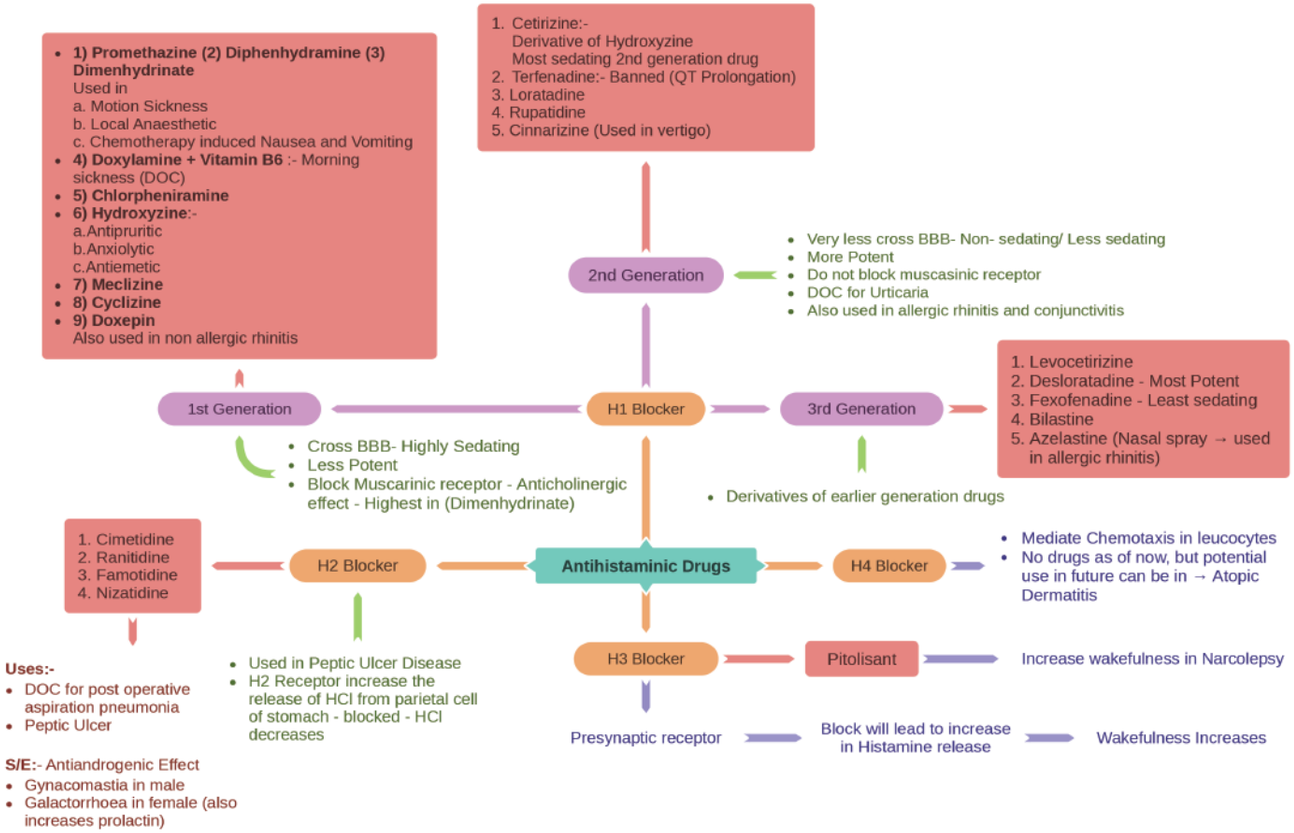
3.1 Overview of Autacoids



KEY POINTS

1. Histamine causes triple response (Lewis reaction):
   - Red spot (vasodilation), flare (axon reflex), and wheal (capillary permeability)
   - Antihistamines like cetirizine block H1 receptors
2. Serotonin (5-HT) regulates multiple systems:
   - Involved in mood (CNS), platelet aggregation, and GI motility
   - 5-HT3 antagonists (e.g. Ondansetron) are antiemetics used in chemotherapy
3. Bradykinin is a potent vasodilator and pain mediator:
   - Contributes to inflammation, ACE inhibitors increase bradykinin→ cough and angioedema
4. Prostaglandins have diverse roles:
   - PGE_2: Vasodilation, fever, pain
   - $PGE_{2\alpha}$: Uterine contraction (used in labor induction)
   - Thromboxane A_2 (TXA_2): Platelet aggregation
5. Leukotrienes cause bronchoconstriction and inflammation:
   - Key role in asthma; Montelukast, a leukotriene receptor antagonist, is used in prophylaxis
6. Autacoids act locally and have short duration:
   - Their effects are rapid and short-lived, making them ideal for moment-to-moment physiological adjustments

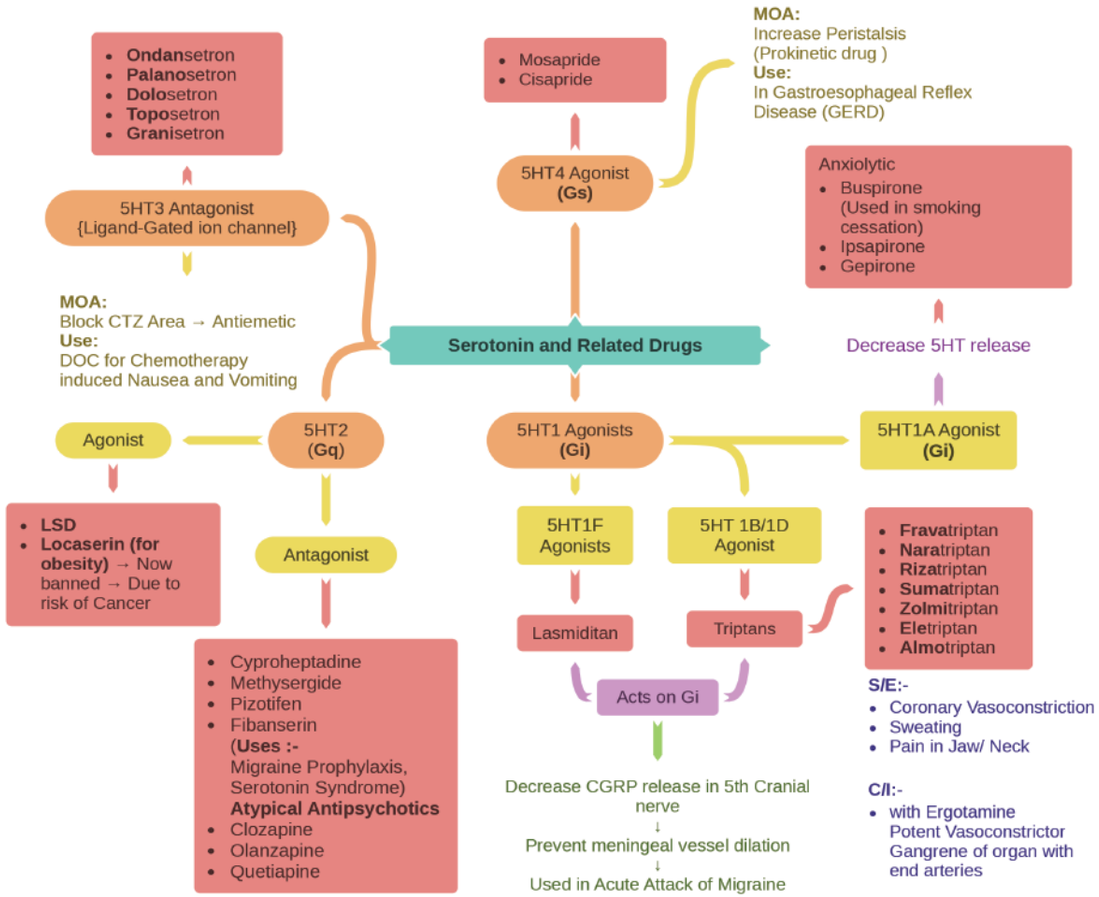
3.2 Antihistaminic Drugs



KEY POINTS

Receptor	GPCR	Effects	Block Effects
H1	Gq	Bronchoconstriction in bronchi Vasodilation in blood vessels (ENOS ⊕)→Anaphylactic shock ↑ Contraction in GIT ↑ Wakefulness in hypothalamus ↑ Itch in peripheral nervous system	Anti-allergic → antipruritic Anti-motion sickness Anxiolytic, e.g. Hydroxyzine, Cetirizine
H2	Gs	↑ Contraction, → heart rate in heart ↑ HCl release in GIT (parietal cells)	Anti acid secretory agent used in peptic ulcer disease, e.g. Ranitidine, Cimetidine
H3	Gi	Inhibits H1, H2 presynaptically ↓ Histamine release	↑ Wakefulness in narcolepsy, e.g. Pitolisant
H4	Gi	Mediates chemotaxis on leucocytes	

3.3 Serotonin and Related Drugs



KEY POINTS

Treatment and prophylaxis of migraine

Acute Attack of Migraine

1. Triptans (5-HT1B/1D agonists)
   - DOC for severe attack
2. Lasmiditan (5-HT1F agonist)
3. Rimegepant (CGRP ligand blockers)
4. Ergotamine (ergot alkaloids)
5. Paracetamol, ketorolac (NSAIDs)
   - DOC for mild to moderate attacks
   - Used in pregnancy with caution
6. Chlorpromazine
   - Metoclopramide (D2 blockers)
7. Opioids (oral Codeine)

Migraine Prophylaxis: (A) Antiepileptics:
- Topiramate
- Valproate

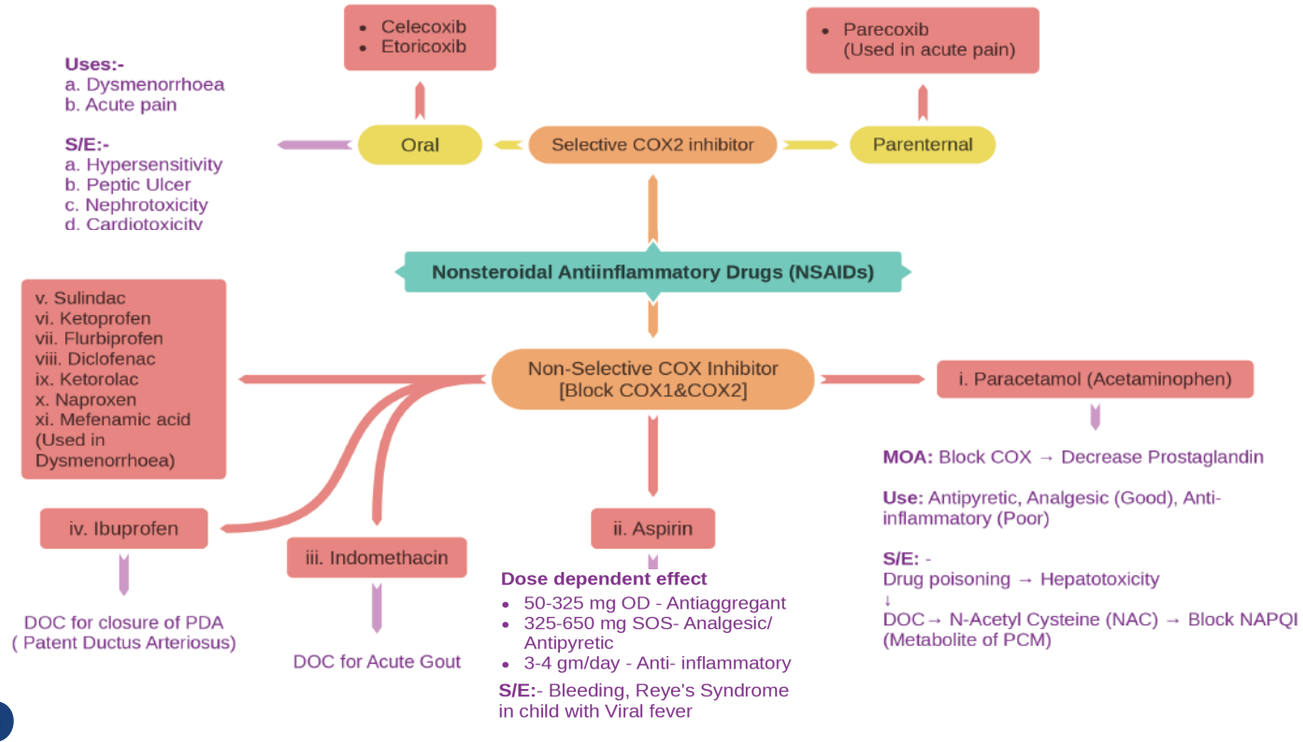
Antidepressant (Imipramine)

(B) Beta blockers:
- Propranolol—DOC (botulinum toxin)

(C)
- Calcium channel blockers: Flunarizine
- CGRP ligand blockers: Eptinezumab
- CGRP Receptor blockers: Erenumab

(D) Methysergide (ergot derivative) → Not preferred because it can cause pulmonary fibrosis

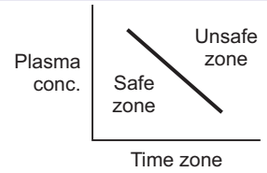
Nonsteroidal Anti-inflammatory Drugs



KEY POINTS

1. PARACETAMOL POISONING

Prediction of hepatotoxicity is done by "Rumack-Matthew nomogram"



2. EICOSANOIDS → prostaglandins + leukotrienes

Membrane phospholipid
↓ (phospholipase A2)
Arachidonic acid
/ \
COX pathway LOX pathway

Cyclooxygenase (COX) [blocked by NSAIDs]

☆ PGH2, PGG2 → ☆ TXA2 (Thromboxane)
- Platelet aggregation ☆ PGI2 (Prostacyclin) [endothelium]
- Analogues: **Iloprost, Beraprost, Treprostinil**
- Used in pulmonary hypertension ☆ PGE2
- PGE2 analogue: **Dinoprostone** • DOC for cervical ripenin
- PGE1 analogue: Act via same receptor to treat NSAIDs induced ulcers **(Misoprostol, Alprostadil)** ☆ PGF2α
- PGF2α analogue**: Latanoprost, Bimatoprost**
- DOC for open-angle glaucoma

Lipoxygenase (LOX) [blocked by Zileuton]

☆ 5HPETE → 5HETE
↓
☆ LTA4
↓
☆ LTC4, LTD4
- Causes attack of bronchial asthma
- Blocked by **Montelukast, Zafirlukast, Pranlukast**