1. **Recommended Books**
    a. **Katzung** B G. Basic and clinical pharmacology 12th Edition (New York) Mc Graw Hills
    b. **Lippincott's** Illustrated reviews Pharmacology 6th Ed
    c. Board review series by **Katzung**
    d. Board review series by **Lippincot's**
2. **For MCQs**
    a. Pre-test Pharmacology by Shlafer (one best type) 11th Edition
    b. Board review series by Katzung (at end of each chapter)
    c. Boar review series by **Lippincot's** (at end of each chapter)

SEROTONIN
5-HT
5-Hydroxytryptamine
5-HT

Initial observation
Vasoconstrictor substance released from the clot into the serum (**Serotonin)**
Smooth muscle contracting substance in intestinal mucosa **(Enteramine)**
In 1951 identified as metabolites of 5-hydroxytryptophan → **5-hydrxytrptamine**
Distribution of 5-HT
Intestine (entero-chromaffin cells)--- **90 %** of body's content
Platelets --- Accumulate it from plasma (as they pass through intestinal circulation) by an active transport mechanism & release it when they aggregate at the site of tissue damage
Brain --- Act as neurotransmitter
Highest concentration in the mid brain
5-HIAA (5-hydroxy indole acetic acid)
Excretion of 5-HIAA is a measure of serotonin synthesis
24 hour excretion of 5-HIAA – a diagnostic test for tumors that synthesize excessive quantities of serotonin like **cacinoid tumor**
Synthesis, storage, metabolism like catecholeamines
Like NA, 5-HT is actively taken up by **an amine pump into**
Serotonergic nerve endings --- Inhibited by **TCAs & SSRIs**
Platelets
Stored serotonin can be depleted by **reserpine**
5-HT is concentrated in vesicles by a vesicle associated transporter (VAT) that is blocked by reserpine

Sources of serotonin

Eggs. The protein in eggs can significantly boost your blood plasma levels of tryptophan, according to recent research …
Cheese. Cheese is another great source of tryptophan…
Pineapples…
Salmon…
Nuts and Seeds…
Turkey …

Receptors & subtypes of 5-HT
7 families and 14 receptors subtypes
5-HT$_1$ (5-HT 1A, B, D, E, F), 5-HT 1Da,b
5-HT$_2$ (3 sub types)
5-HT$_3$
5-HT$_{4\text{-}7}$ --- 5-HT$_5$ A, B, --- 5-HT $_{6,7}$

Actions of serotonin

CVS
Arteries are constricted (by action on smooth muscle) & dilated (through EDRF release) by direct action of 5-HT depending on vascular bed & basal tone.
It releases **Adrenaline** from adrenal medulla
In microcirculation, it dilates arterioles & constricts venules ,capillary pressure ↑ & fluid escapes
In intact animals, bradycardia seen due to activation of **coronary chemo-reflex** (Bezold Jarisch reflex) through action on vagal afferent nerve endings in coronary bed evoking bradycardia, hypotension & apnoea
CVS ------ serotonin

BP – **triphasic response** is classically seen on iv injection
Early **sharp fall** in BP-due to coronary chemo reflex
Brief **rise in BP-** due to vasoconstriction & ↑ CO
Prolonged fall in BP- due to arteriolar vasodilatation & extravasation of fluid.

GIT Smooth Muscle
↑ peristalsis & diarrhea (also due to ↑ secretion)

Glands – It inhibits gastric secretion (acid & pepsin) but ↑ mucus production -----ulcer protective property

Nerve endings & Adrenal medulla- Activation of afferent nerve endings- tingling & pricking sensation, pain

Respiration-
Brief stimulation of respiration & hyperventilation. Large doses can cause transient apnea (coronary chemoreflex).

Bronchi- It constricts bronchi but is less potent than histamine

Platelets- It causes changes in shape of platelets & is a weak aggregator (5-HT 2A receptor)
CNS -Direct injection in brain causes sleepiness, change in body temperature, hunger & behavioural effects.

Serotonin
has no clinical application as a drug
Diverse effects & heterogeneous nature of 5-HT receptors
Serotonin Agonists / Antagonists are used as drugs
Subtype-selective

Agonists/antagonists used as drugs
Agonists
Triptans
Trazodone
Buspiron
Dexfenfluramine
Cisapride
Tegaserod
Ergot derivatives
Antagonists
Ondansetron
Risperidone, Clozapine, Olanzapine
Antihistamines
Cyproheptadine,
Cinnarizine
Phenoxybenzamine
Ketanserin
Serotonin Agonists – clinical uses
Triptans (Sumatriptan, Zolmitriptan **)**
5-HT$_{1D\ /\ 1B}$ receptor agonist
Presynaptic trigeminal nerve endings --- to inhibit the release of vasodilating peptides (**CGRP**, substance p & neurokinin A)
Migraine
Serotonin Agonists – clinical uses
Buspiron (5-HT$_{1A}$) **Anxiolytic** (Nonbenzodiazepine)
Trazodone (5-HT$_{1B}$) – also block $\alpha_1$receptors
Antidepressant
Serotonin Agonists –
not used because of toxic effects
Dexfenfluramine -- 5HT$_{2C}$ agonist **Appetite suppressant**
not used – cardiac valve toxicity
Serotonin Agonists –
not used because of toxic effects
Cisapride (5-HT$_4$) **GERD & motility disorders**

↑ release of Ach from myenteric neurons --- ↑ gastric emptying and ↑ tone of LES
Tegaserod (5-HT_4 partial agonist) IBS with constipation

Some drugs are poorly selective
Ergot derivatives --
Agonist, partial agonist, and antagonist actions at α receptors **& serotonin receptors (especially $HT_{1A,}$ and HT_{1D} ; less for HT_2 and HT_3)**

5-HT_3 antagonist --- Antiemetic
Ondansetron, Granisetron, Dolasetron, Palonosetron , Ropisetron
Highly effective in treating **nausea & vomiting**
Cancer chemotherapy / radiotherapy induced
post operative nausea and vomiting
5-HT_3 antagonist --- Antiemetic
It does not block dopamine receptors and apomorphine or **motion sickness induced vomiting**
Ondansetron
(Prototype **selective 5-HT3 antagonists)**
Blocks emetogenic impulses
Peripheral – On vagal efferents in GIT and inhibitory myenteric interneurons – augment release of Ach in gut
Central --- blocks **5-HT_3** in the CTZ & nucleus tractus solitarious
Metabolized by CYP IA2 and 3 A but no significant drug interaction
I/V , oral Oral bioavailability 60-70 %
Granisetron
10 to 15 times more potent than ondansteron
Plasma t ½ is longer (6-8 hours)
Given twice daily on day of chemotherapy
Some drugs are poorly selective
Antihypertensive
ketaserine, phenoxybenzamine --- α blocking effects **& 5-HT_2** antagonists
Antihistamine
Cyproheptadine --- H_1 blocking effects **& 5-HT_2** antagonists & antimuscarinic effect & sedation
Some drugs are poorly selective Metoclopramide --- antemetic effects
??????????????????????????????
D_2 Receptor antagonist
Peripheral (+ 5-HT_4 Agonist) – prokinetic &↑ tone of LES
Central --- blocks D2 receptors in the CTZ
??????????????????????????????????????
Some drugs are poorly selective
Antipsychotics --- Risperidone, Clozapine, Olanzapine
5HT_2 Antagonists

Serotonin Antagonists – clinical uses
Carcinoid syndrome
The carcinoid tumor produce massive quantities of 5-HT (and peptides)
Diarrhoea, bronchoconstriction, and flushing
Pellagra -- may occur due to diversion of tryptophan for synthesizing 5-HT
The 24 hour excretion of **5-HIAA** is used as a diagnostic test for carcinoid tumor
Ketanserin, phenoxybenzamine, cyproheptadine (separately or in combination) --- treatment
SSRI
Selective serotonin reuptake inhibitors
Hyperpyrexic syndromes
Serotonin syndrome
Neuroleptic malignant syndrome
Malignant hyperthermia
Serotonin syndrome
Excessive serotonergic activity in the CNS
It is a **predictable and not idiosyncratic**
Overdose of a single drug or concurrent use of several drugs
Serotonin syndrome
Onset within hours
Hyperthermia
Hyperreflexia, clonus, tremor
Hyperactive bowel sounds, diarrhoea,
Mydriasis,
Agitation, coma;
Serotonin syndrome --- Treatment

Malignant hyperthermia
Onset within minutes
Volatile anesthetics, Succinylcholine
Hyperthermia
Muscle rigidity
Hypertension
Tachycardia
Treatment ----- **Dantrolene, cooling**

Neuroleptic malignant syndrome
Onset over 1 to 3 days
Hyperthermia, acute severe parkinsonism, hypertension
Normal or reduced bowel sounds
Treatment – **diphenhydramine (parentral)**
Cooling if temperature is very high, sedation with benzodiazepines

Cyproheptadine
Antihistamine of the phenothiazine class
Anticholinergic & sedative properties
5-HT_1 and 5-HT_2 antagonist
It increases appetite --- weight gain
Causes relaxation of smooth muscles. It is used to control excessive smooth muscle contractions
in the **Carcinoid** syndrome
Post gastrectomy dumping syndrome
Antagonizes priapism / orgasmic delay caused by 5- HT up take inhibitors like fluoxetine and trazodone
Ketanserin and Ritanserin
Ketaserin is Prototype under investigation drug
selective 5-HT_2 receptor blocking activity
5-HT 2A > 5-HT2C
Antagonizes 5-HT induced **vasoconstriction, platelets aggregation and contraction of airway smooth muscles**
Weak alpha 1 blocking activity
Effective **antihypertensive**
Dizziness, tiredness, nausea and dry mouth
Symptomatic improvement only in **Raynaud's disease**
Weak alpha $_1$, H_1 and dopaminergic blocking activity
Ritanserin
A relatively more 5-HT 2A selective antagonist than ketanserin
Clozapine and risperidone
Are **atypical antipsychotic**
Resistant cases of schizophrenia
Improves negative symptoms of schizophrenia
Extrapyramidal side effects only at higher doses
Clozapine
5-HT2A/2C blocker
Dopamine antagonist (weaker than typical neuroleptics)

Risperidone
5-HT 2A + dopamine D2 antagonist

Subtype-selective Agonists used as drugs
Ergot derivatives
Ergotamine, ergonovine, and methysergide
Partial agonists at **5-HT_2** vascular +
α adrenergic receptors +
some have **agonists at the dopamine r**eceptors

Migraine is the episodic Headache
A severe, unilateral, pulsating (throbbing) lasting from a few hours to 1-2 days accompanied by N, V & photophobia
Migraine without aura (**common migraine**) – 85%
Migraine with aura (**classical migraine**)
Headache preceded by (20-40 minutes) neurological symptoms called aura which can be visual, sensory, and/or cause speech or motor disturbances
Pathogenesis of migraine
Release of vasodilating peptides neurotransmitter **(CGRP)** by **trigeminal nerve endings** to intra cranial (& extra cranial) arteries
Substance P & **neurokinin A** may also be involved
Cerebral **vasodilation** ----- Extravasation of plasma ---- Perivascular edema—mechanical stretching – activation of pain nerve endings in dura --- pain

Migraine treatment in old times
Trepanation, the deliberate drilling of holes into a skull, was practiced as early as 7,000 BCE.
While sometimes people survived, many would have died from the procedure due to infection
It was believed to work via "letting evil spirits escape"
Treatment of migraine
Treatment of migraine
Non-specific (**symptomatic**)
Migraine specific leads either to
to **vasoconstriction** or
to **inhibition of the release of pro-inflammatory neuropeptides**
Migraine prophylaxis
Regular medications to reduce the frequency & or severity of attack

Non-specific (symptomatic)
Treatment of migraine
NSAIDs like paracetamol or aspirin /+
antiemetic
like metoclopramide , domperidone, prochlorperazine
Opioids -- in severe migraine

Specific Treatment of migraine
Drug treatment according to severity of disease
Triptans
Sumatriptan, Zolmitriptan, Rizatriptan, Eletriptan, Almotriptan, Fravotriptan, Naratriptan

Triptans
First line treatment for acute severe attack
Not useful for prophylaxis

Triptans are Selective agonists for **presynaptic (inhibitory)**

5-HT$_{1D}$ & 5-HT$_{1B}$

Activates **5-HT$_{1D/1B}$** receptors on presynaptic trigeminal nerve endings to inhibit the release of vasodilating peptides

5-HT$_{1D}$ receptor agonist activity results in **vasoconstriction** of dilated cerebral vessels

Rapidly & effectively abort or markedly ↓ the severity of migraine in about **75 %** of patients

Sumatriptan --- oral, nasal, S/C, or rectal

Zolmitrytan --- oral, nasal

All other agents are taken **orally**

Onset --- Parenteral – 20 minutes

Orally 1 to 2 hours

Sumatriptan and other tryptans

Nausea much less than ergot derivatives

Adverse effects include altered sensation (tingling, warmth), dizziness, muscle weakness, neck pain, injection site reaction

A slight increase in BP, coronary vasospasm (1-5% of patients) and risk of MI

Contraindications of tryptans

Coronary artery disease and angina ----------5-HT$_{1B}$ activity in the coronaries --- cause coronary vasospasm

Naratriptan & eletriptan --- severe hepatic, renal impairment & peripheral vascular syndrome

Frovatriptan --- **peripheral vascular disease**

Zolmitriptan --- **Wolff-Parkinson-White (WPW) syndrome**

Disadvantages of tryptans --- duration of action

Duration of action shorter than the duration of the headache---- elimination t ½ is 2 hrs

Several doses required during prolonged migraine

Adverse effects limit the maximum safe daily dose

Extremely expensive drugs

Ergotamine for acute attack of migraine

Ergotamine tartrate, Dihydro-ergometrine

Highly specific for migraine pain; not analgesic for any other condition

Effective during prodrome & during the attack ----- progressively less effective if delayed

As compared to sumatriptan

Efficacy similar

Nausea is more common

Oral, S/L, I/M, rectal suppository, intranasal & inhaler (I/V for intractable migraine)

Ergotamine is given in combination with caffeine, why?

Combines with caffeine (100 mg caffeine for each 1 mg ergotamine tartrate) to facilitate absorption of ergot alkaloid

Not > 6 mg to be taken for each attack and no more than 10 mg per week

Cumulation and prolong vasoconstriction

Contraindications of ergotamine

Pregnancy

1st and 2nd stages of labour

Peripheral vascular diseases

Coronary Artery disease
Indications of Prophylaxis of migraine
Attack ≥ 2 / month
If the headache is **severe** or accompanied by serious **neurological signs**
Patient grossly **incapacitated** during the attack
Analgesics/NSAIDs usually do not afford adequate relief
Specific drugs like ergot alkaloids/ triptans + ant emetics have to be prescribed
Prophylactic regimens lasting **6 months or more** are recommended
Drugs used for prophylaxis of migraine
(no value in treatment of acute attack)
β-blockers
Anticonvulsant - Valproic acid, Topiramate ---- **suppress excessive firing of the nerve endings**
CCB --- Flunarizine (a relatively weak CCB that also inhibit Na^+ channel). It is claimed to be **cerebro selective CCB**
Verapamil
Antidepressants --- TCA, SSRI
Obsolete drugs --- ergonovine & methysergide
β- adrenergic blockers
Propranolol is the drug of choice
Reduce frequency as well as severity of attack in up to 70 % of patients
Effect seen in 4 weeks and is sustained
40 mg BD --- 160 mg BD
Nadolol is also effective
β blockers with ISM activity are ineffective e.g., pindolol
Methysergide have been used for prophylaxis. Why it is obsolete now?
Methysergide is **relatively ineffective in treatment of impending or active episodes** of migraine
Although relatively free of the rapidly cumulative vasospastic toxicity of the ergotamine, chronic use of methysergide may induce **retroperitoneal fibroplasia and sub-endocardial fibrosis**
Name the drugs that are Selective agonists for **presynaptic (inhibitory) 5-HT_{1D} & 5-HT_{1B}**
Triptans & ergotamine
What is the effect of activation of **HT_{1D}** receptors **?**
Activation of HT_{1D} receptors leads either to vasoconstriction or to inhibition of the release of proinflammatory neuropeptides
Triptans & dihydroergotamine have similar efficacy.
Why tryptan is preferred over ergotamine?
Nausea is a common adverse effect with dihyrdoergotamine.