Lecture 12

Drugs used in headache and migraine.

Objectives:

- Differentiate between types of headache regarding their symptoms, signs and pathophysiology.
- Recognize drugs used to prevent migraine
- Identify drugs used to rescue and abort migraine
- Elaborate on the pharmacokinetics, dynamic and toxic profile of some of these drugs.

- Additional Notes
- Important
- Explanation –Extra-

For any correction, suggestion or any useful information do not hesitate to contact us:
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Headache:

Pain anywhere in the region of the head or neck.
It is caused by disturbance of the Pain – Sensitive Structures around the brain:

1. **Within the cranium:** (blood vessels, meninges, cranial nerves.)
2. **Outside the cranium:** (muscles, nerves, arteries, veins, subcutaneous tissues, eyes, ears and other tissues.)

Migraine: pain is usually on one side of head with facial and neck pain and nausea and vomiting.

- It's called *Curtain like effect* over one eye.

Recurrent attacks of throbbing headache. Unilateral or on both sides. Lasting from > 2 up to 72 hrs.
+ Preceded (or accompanied) by **AURA.**

Aura: seeing flashes of light, blind spots or feeling tingling in arm.
Perceptual disturbance of motor < sensory nature.

- **Visual**: Photophobia (↑ sensitivity to light)
- **Auditory**: Phonophobia (↑ sensitivity to sound)
- **Olfactory** unpleasant smell ….
- **Sensory;** abnormal sensation of at face, extremities.

Develops over 5-20 min. & last fewer than 60 min.

Types of migraine:

1- **Common** (*without* aura 80%.)
2- **Classis** (with aura 20%.)


Migraine Headache

Phases of Migraine:

1. Pro-drom Phase	• a change in mood or behavior (irritability, neck stiffness) that starts hours or days before headache. It is experienced by **60%** of migraineurs.
2. Aura Phase	• Sensory > motor symptoms starts 5-20 min before the migraine attack. It is experienced by 20% of migraineurs.
3.Headache Phase	• Moderate to severe pain, ↑ with activity + anorexia, vomiting, • Intolerance to light, sounds, odors • Blurry vision, Blocked nose, Pale face Sensations of heat or coldness, Sweating, Tenderness of the scalp
4. Post-drom Phase	• Still not normal, either; More likely fatigued → irritability, impaired concentration, scalp tenderness, mood changes, GIT symptoms,

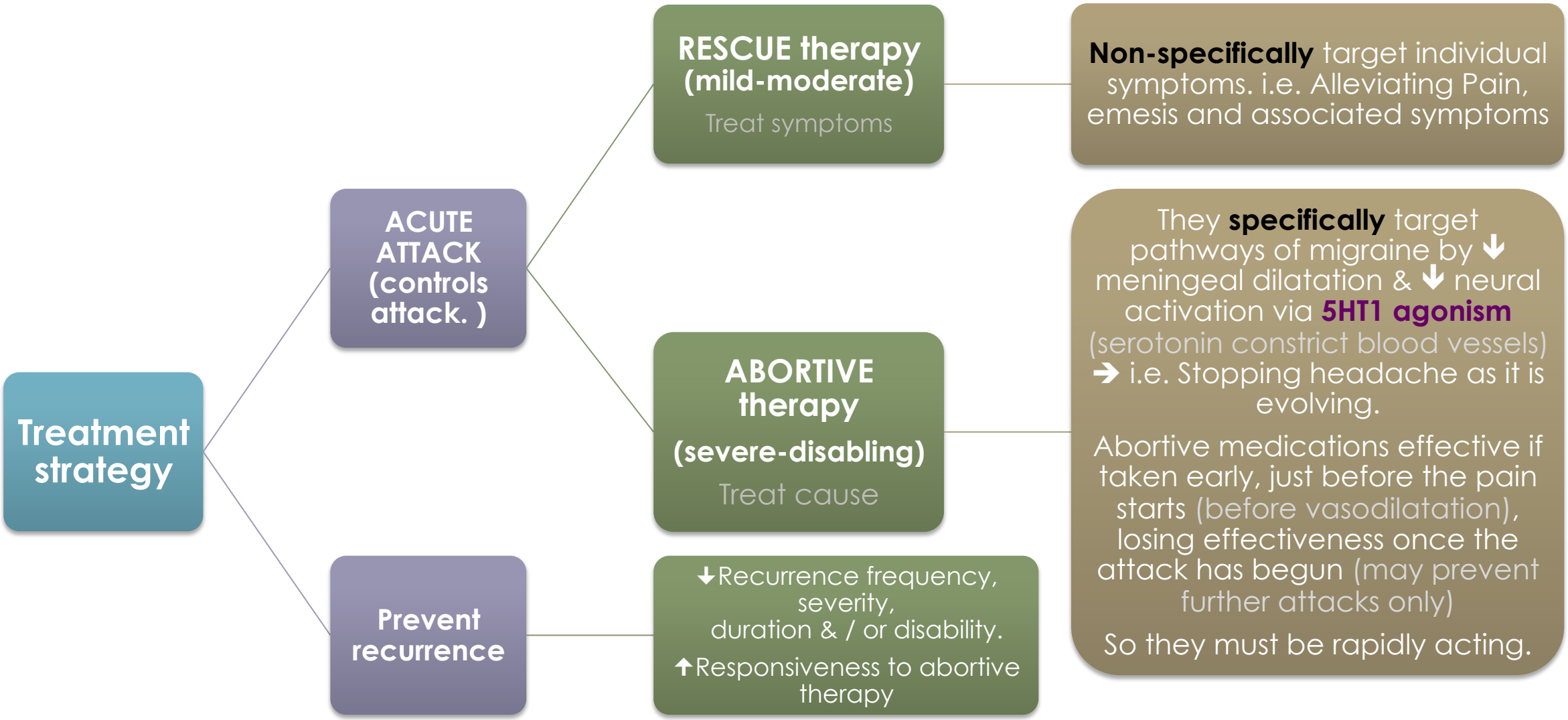
Migraine Triggers:

- **Diet:** Aged cheese (contains tyramine → constrict blood vessels → hypertension), Alcohol, Chocolate, Caffeine, Hot dogs, Avocado, Fermented or pickled foods, Yeast or protein extracts, Aspartame.
- **Therapy:** Antibiotics, Antihypertensive, H_2 blockers, Vasodilators, Oral contraceptives (negative feedback when body feel that estrogen levels are elevated).
- **Diseases** (e.g. hypertension).
- **Hormonal changes:** Menstrual migraine (Most common) Because estrogen is neuroprotective & its declining during menstrual cycle.
- **Stresses, Climate & Life Style.**

Migraine Causal Theories:

Vascular, Cortical Spreading Depression, Neurovascular theory, Mediators [Serotonin], Dopaminergic Hypersensitivity.

- Triggers → Intracranial vasoconstriction → migraine aura → focal ischemia → ↑ mediators → rebound vasodilatation (cause of throbbing pain) → ↑ permeability & leak → inflammatory reaction → activates perivascular nociceptive nerves → migraine headache → It throbs as blood flow at these sensitive area with each heart beat.
- Triggers → Release K / glutamates (too much excitation) → Creates a slowly well-defined depolarizing wave → depolarize adjacent tissues → propagating at a rate of 2-6 mm/min → vasoconstriction → migraine aura → activate trigemino-vascular complex → vasodilation → migraine headache.
    - ✓ Stimulation of the trigeminal nerve causes the release of vasoactive peptides; this is responsible for the head pain, as well as the facial and neck pain, experienced during migraine.



N.B. Full effect of therapy needs several weeks to manifest & should continue for 6 m. & can be repeated

RESCUE THERAPY

Analgesics		➢ **NSAIDs:** • **Aspirin** (weak) • **Acetaminophen** (Drug of choice) for mild to moderate attack with no nausea & vomiting. ➢ **Mild-opioid (μ agonis): tramadol** (narcotic analgesic - causes tolerance)
Anti-emetics (prevent nausea and vomiting)	**Dopamine Antagonists**	**Domperidone** • Drug of choice to avoid sedation and sleeping (not *sedative).* • Gastro-prokinetic effect (gastric empting) (increase gastric motility → increase absorption of drug & reduce vomiting) → ↑ *Absorption & bioavailability of abortive therapy.*
		Phenothiazines (Promethazine): Has a sedative effect
	$5HT_3$ antagonists	**Ondanseteron, Granisetron:** For severe nausea and vomiting
	H_1 antagonist	**Meclizine, diphenhydramine:** Has a sedative effect
Others	***Steroids***	

- Paracetamol works better than ibuprofen in treating fever because it works on COX-3 enzyme in the brain. Ibuprofen is good as analgesic.
- Pregnant women use Paracetamol rather than ibuprofen because it's saver.
- Panadol extra: Combined with antihistamine (sedating).

ABORTIVE THERAPY

$5HT_1$ PARTIAL AGONISTS (ERGOTS) Non-Selective (↑ *side effects*)

- Product of fungs.
- ↓ release of vasodilating peptides → sever vasoconstriction + ↓ excessive firing of nerve endings
- Partial agonist effect on **α-adrenoceptors** → vasoconstriction (contraindicated in cardiovascular patients → hypertension)
- Antagonist to some dopaminergic & serotonergic receptors

Ergotamine tartarate	Dihydroergotamine
Low oral bioavailability, sublingual, rectal suppository ,inhaler	Nasal spray, inhaler & injectable forms (good to use if patient is vomiting)
Rare clinical use due to sever adverse effect used when 1st line doesn't't work	Preferred in clinical setting
$t_{1/2}$ of 2 hours > vasoconstriction for 24 hours (due to high and long tissue binding ability)	Given parenterally, and eliminated more rapidly (due to rapid hepatic clearance)
Has significant side effects: may worsen the nausea and vomiting associated with migraine.	Less adverse effects.

Indications	They are only used to abort the attacks (*Exception Dihydroergotamine can be given for severe, recurrent attacks not responding to other drugs.)*. frequent, moderate or infrequent but severe attacks.
ADRs (linked to vasoconstriction)	**GIT upset** (worsen nausea & vomiting), Feeling of cold and numbness of limbs, tingling. Prolong use and high dose → paraesthesia (tingling or burning sensation). anginal pain due to coronary spasm, and disturbed cardiac rhythm (tachycardia or bradycardia). Prolong use → rebound headache due to vasodilatation followed by vasoconstriction.
Contraindications	Pregnancy; fetal distress and miscarriage (ergot is uterine stimulant and vasoconstrictor). Peripheral and coronary vascular diseases. Hypertension. Liver and kidney diseases. prophylaxis of migraine. In concurrent use with triptans (at least 6 hrs from last dose of tryptans or 24 hrs from stopping ergotamine β-blockers

ABORTIVE THERAPY

$5HT_1$ AGONISTS (TRIPTANES) Selective

- Same as ergotamine but more selective as serotonergic agonist: ↓ vasoactive peptides → vasoconstriction and block pain pathways in the brainstem (inhibit transmission in the trigeminal nucleus caudalis).
- No α_1, α_2, β –adrenergic , dopamine or muscarinic receptors. (lesser side effects than Ergots)

	SUMATRIPTAN	ZOLMITRIPTAN	NARATRIPTAN
Oral bioavailability	*low*	40%, > peaks after 2 hrs & $t_{1/2}$ nearly 3 hours (slower)	70% >peaks after 2 hrs & $t_{1/2}$ nearly 6 hours (slower onset)
injectable forms	bioavailability is 97%, peaks after 2 min & $t_{1/2}$ nearly 2 hours (fast action with Sc, good for patient with vomiting)		
nasal spray			
Side effects	-	• Chest & neck tightness • Somnolence	less side effects

Indications: frequent, moderate or infrequent but severe attacks. In cluster headache. Used a lot in clinic - safe for pregnancy.

ADRs: Same as with ergot but triptans are *better tolerated*. Mild pain and burning sensation at the site of injection. Vasospasm, Ischemic heart; Angina and Arrhythmias.

Contraindications:
Peripheral vasospastic diseases. Uncontrolled hypertension. History of ischemia. Cerebrovascular disorders. In concurrent use with ergots or others inducing vasospasm. In concurrent use with MAOIs, lithium, SSRIs (selective serotonin uptake inhibitor), ….→(5HT increased to toxic level) → Serotonin syndrome. Renal or hepatic impairment

DECIDING WHETHER BETTER WITH A TRIYPTAN OR WITH DHE.

- For patients with headache episodes lasting 2 or 3 days at a time, DHE is often the optimal choice because it has longer $t_{1/2.}$
- For patients with migraines a day or less and need rapid relief of pain, triptans are often a better choice.
- For pregnant women: paracetamol or intranasal sumitriptan and or diphenhydramin, meclizine are safe to be used..
- The form of drug preparation could influence the choice → Injectable sumatriptan reaches T_{max} the fastest followed by DHE nasal spray and rizatriptan.

CHOOSING A TRIPTANS.

- Differences in the time to peak blood concentration T_{max}, equates with faster relief of pain.
- Differences in $t_{1/2}$ → a clinical effect in terms of recurrence of headache

For extremely fast relief within 15 min. injectable sumatriptan is the only choice.
If expected re-dosing is needed & / or recurrence of headache Naratriptan , frovatriptan, have slower onset, fewer side effects, and a lower recurrence rate
Menstraul migraine: Frovatriptan 2.5 mg twice per day beginning two days before the anticipated onset of menstrual migraine and continuing for six days

	PREVENT RECURRENCE			
	Anti-spastic	**Anti-epileptics**	**Antidepressants**	**Anti-hypertensives**
MOA	muscle relaxants	*Block Na channel & augment GABA at GABA-A receptors*		
	Botulinum toxins Tizanidine	Topiramate; Valproic;	TCA (Tricyclic antidepressant) amitryptylin & Nortryptyline	β blockers; propranolol *pophylaxis of migraine attack*
			SSRIs (Selective serotonin reuptake inhibitor) better than TCA	Ca Channel Blockers

Good luck!

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