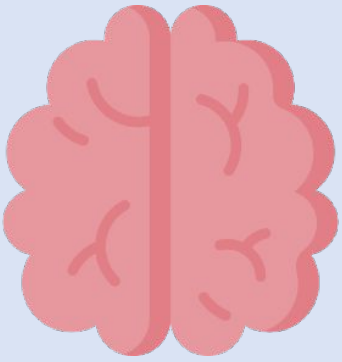

Revised & Approved

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Pharmacology 439

MED439

Neuropsychiatry Block

Pharmacology Team 439

Helpful video

Color index:

Main Text

Important

Dr's Notes

Female Slides

Male Slides

Extra

Drugs used in Headache & Migraine

Objectives:

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

Editing file

Headache

1

Pain anywhere in the region of the head or neck

▪ It is caused by disturbance of the Pain-Sensitive Structures around the brain:

A. Within the cranium:
Blood vessels, Meninges, Cranial nerves.

B. Outside the cranium:
Muscles, Nerves, Arteries, Veins, Subcutaneous tissues, Eyes, Ears & other tissues.

Migraine

2

Recurrent attacks of throbbing* headache.
▪ Unilateral or on both sides of the head.
▪ Lasting from > 2 up to 72 hrs.
▪ Pain is usually on one side of head with facial & neck pain, nausea & vomiting.
± **Preceded** (or accompanied) by **AURA**.

*Pulsatile (ينبض): intensity varies due to increase & decrease in blood flow.
Pulsating or throbbing headache is a Characteristic feature of a migraine where the person wakes up in the morning feeling a sharp & throbbing headache

Type of Migraine:
A. Common: without Aura (80%). **B. Classic:** with Aura (20%).

AURA: (Changes in sensitivity)
flashes of light, blind spots or tingling in your arm.
Perceptual disturbance of motor < sensory nature.
- **Visual:** Photophobia (↑ sensitivity to light)
- **Auditory:** Phonophobia (↑ sensitivity to sound)
- **Olfactory:** Unpleasant smell.
- **Sensory:** Abnormal sensation at face, extremities.

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

Phases of Migraine

Not Imp

Pro-drom Phase 01

▪ A change in mood or behavior (irritability,neck stiffness) that starts hours or days before headache.
▪ It is experienced by 60% of migraineurs.

Aura Phase 02

▪ Sensory > motor symptoms.
▪ Starts 5-20 min before the migraine attack.
▪ It is experienced by 20% of migraineurs.

Abortive drugs are used

Symptomatic drugs are used

Headache Phase 03

▪ Moderate to severe pain, increases with activity + anorexia, vomiting,
▪ Intolerance to light, sounds, odors
▪ Blurry vision /Blocked nose /Pale face / Sensations of heat or coldness /Sweating and Tenderness of the scalp.

Post-drom Phase 04

▪ Still not normal
▪ More likely fatigue → irritability /impaired concentration /scalp tenderness /mood changes and GIT symptoms.

Migraine Triggers

Skipped by male dr

1 2 3 4 5 6 7

Life style

Stresses

Diet
Aged cheese, Alcohol, Chocolate, Caffeine, Hot dogs, Avocado, Fermented or pickled foods, Yeast or protein extracts.

Climate

Hormonal changes
Menstrual migraine (Most Common)

Diseases

Therapy (drugs)
Antibiotics, Antihypertensive, H_2 blockers, Vasodilators, Oral contraceptives.

Migraine Causal Theories

Keep in mind:

- Intracranial vasoconstriction → Migraine Aura
- Intracranial vasodilation → Migraine headache

1 Vascular (most drugs work based on it)

Triggers → **Intracranial vasoconstriction** → **migraine aura** → focal ischemia → ↑ inflammatory mediators → rebound vasodilation → ↑ permeability & leak → inflammatory reaction → activates perivascular **nociceptive** (pain) nerves → It throbs as blood flow at these sensitive area with each heartbeat → migraine headache.

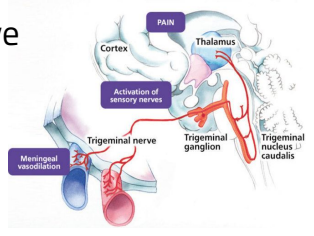
2 Neurovascular Theory

Trigeminal nerve:

(1) Triggers[1] → Release K/glutamate[2] → 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[3] complex** → vasodilation → Migraine headache.

(2) Stimulation of the **trigeminal nerve** causes the release of vasoactive peptides **(Calcitonin Gene-Related Peptide (CGRP), Substance P, Neurokinin A)***, this is responsible for the head pain, as well as the facial and neck pain experienced during migraine.

Read more in slide 8



3 Cortical Spreading Depression

4 Dopaminergic Hypersensitivity

5 Mediators [Serotonin][4]

1. Drugs, Environmental chemicals, Smells
2. Excitatory neurotransmitter
3. Trigeminal complex (Ganglia) innervates cerebral vasculature, when stimulated it releases Vasoactive peptides → vasodilation → Migraine
4. Affect mood, appetite, temperature, BP, perception of pain, vomiting and migraine

ACUTE ATTACK
Control attack

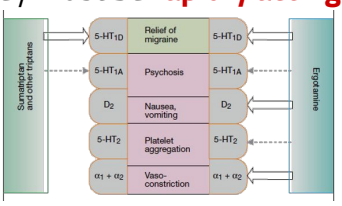
Treatment Strategy

PREVENT RECURRENCE
Prophylaxis

A) RESCUE therapy treat the symptoms
For **Mild-Moderate** pain
Non-specifically target **individual symptoms** i.e. alleviating pain, emesis (vomiting) and associated symptoms.

B) ABORTIVE therapy treat the migraine
For **Severe/ Disabling** pain
- They **specifically** target pathways of migraine by:
  - reducing meningeal dilatation &
  - reduces neural activation via 5-HT_1 agonism i.e stopping headache as it's evolving. Remember serotonergic drugs are Vasoconstrictors too

- **Abortive medication:** effective if taken early, just before the pain starts, losing effectiveness once the attack has begun So they must be **rapidly acting.**



- Reduce recurrence frequency, severity, duration and/or disability.

★ Increase responsiveness to abortive therapy.

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

A) Antiepileptics (in small doses)
- Block Na channel & augment GABA at $GABA_A$ receptors
- E.g. **Topiramate; Valproic**

B) Antidepressants
- TCAs; **Amitriptyline** and **Nortryptyline**

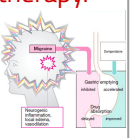
C) Antihypertensives Centrally modulating NE & 5-HT
- β-blockers; **Propranolol**

Propranolol is commonly used in prophylaxis of migraine attack.

Acute Attack

Rescue Therapy

Class	Analgesic	Antiemetic[1]
Drugs	**1- NSAIDs:** • Acetaminophen (Paracetamol) • Aspirin (weaker than Acetaminophen) • Ibuprofen, Naproxen ⟶ for **mild to moderate** attack with **no nausea & vomiting.**	**1- Dopamine Antagonists:** • **Domperidone ↑Gastric-Prokinetics:** 1) ↑ Absorption & bioavailability of abortive therapy.[2] 2) ↓Gastric content ⟶ ↓ vomiting 3) Great option for **mild** nausea & vomiting. • **Phenothiazines** (**Promethazine**): Has a **sedative** effect. Hence, not recommended
	2- Non-opioid[3]: Weak μ agonist: • Tramadol (in moderate-severe pain) **(Tramadol also inhibits serotonin reuptake & causes vasoconstriction)** ▪ Rarely, parenteral opioids may be needed in refractory cases.	**2- 5-HT_3 Antagonists** imp: most powerful ⟶ best choice antiemetic • **Ondansetron, Granisetron** for **severe** nausea & vomiting (for chemotherapy-induced N&V) **3- H_1 Antagonist** Has Antihistaminic, Sedative, Anticholinergic effects (Vestibular suppressant ⟶ ↓CRTZ stimulation ⟶ ↓N&V related to balance) • Meclizine, diphenhydramine



1) For more details, check Medications Affecting The Balance System Lecture
2) If Domperidone increases Gastric motility, How does it also increase absorption? Answer: Migraines decrease gastric motility which means that drugs will be stuck and degraded by gastric acids. So, Domperidone will increase the motility back to normal and move the drugs to the small intestines for them to be absorbed before they get degraded. **BUT** in normal people, Domperidone will DECREASE absorption since the gastric motility would be increased abnormally and the patient will have diarrhea.
3) Tramadol is not true opioid analgesic such as hydrocodone or codeine etc, due to its effect on serotonin and other neurotransmitters. In some literature it's not classified an opioid, but due to its effect opioid receptors it's also referred as opioid, though its analgesic effects are independent of the opioid receptors and it can be combined with opioids in management of neuropathic pain. Its true classification as an opioids is debatable. You could consider this as opioid analgesic with miscellaneous effects. For more details click here

Abortive Therapy : Ergots Refractory cases

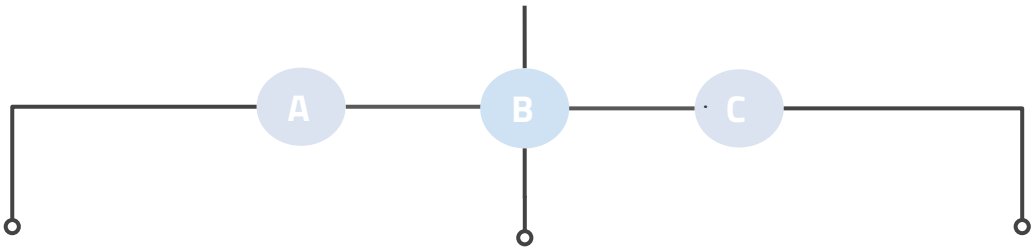
Drug	Ergotamine tartrate rare clinical use due to severe adverse effects	DiHydroErgotamine (DHE) preferred in clinical setting
M.O.A	▪ Product of Claviceps purpurea; a fungus growing on rye/grains  ★ **Non-Selective** ★ **Partial agonism at 5-HT$_1$ receptors** (5-HT$_{1D/1B}$ found in cerebral & meningeal vessels): • ↓ Release of vasodilating peptides • ↓ Excessive firing of nerve endings → reducing pain sensation • **At blood vessels** → ↓ vasodilation & stretching of the pain endings • **Partial agonist effect on α-adrenoceptors** → vasoconstriction (peripherally so more CVS ADRs, not desirable) • Hard to tolerate	
P.K	▪ **Given:** Orally, sublingual, rectal suppository, inhaler. ▪ Oral absorption incomplete (erratic) & slow → low bioavailability. ▪ Can be taken orally (**Cafergot** is a formula which contains caffeine and ergotamine) ▪ Despite T½ nearly 2 hours, **ergotamine** produces vasoconstriction → **24 hours or longer due to high and long tissue binding ability.** ▪ Has significant side effects, and may worsen the nausea & vomiting associated with migraine. Thus, rarely used clinically and only used if the patient isn't responding to other medications.	▪ **Given:** Parenterally. Nasal spray, inhaler and **injectable** forms (**good to use if patient is vomiting).** ▪ Eliminated more rapidly than ergotamine, presumably due to its rapid hepatic clearance & has less adverse effects.
Uses	▪ Only used to **abort** the attacks (**Except** DHE can be given for **severe, recurrent** attacks **not responding** to other drugs) (don't start with DHE only if not responsive) ▪ Their use is **restricted** to patients with frequent, moderate attack or infrequent but severe attacks.	
ADRs	▪ GIT upset ▪ Feeling of cold and numbness of limbs, tingling (due to peripheral vasoconstriction) ▪ Anginal pain due to **coronary spasm**, and disturbed cardiac rhythm (tachycardia or bradycardia) ▪ If used with β-blockers, it can cause reflex tachycardia or arrhythmia. ▪ **Prolong use** → rebound headache due to vasodilation followed by vasoconstriction. After some time the body compensates to long term vasoconstriction ▪ **Prolong use & high dose** → paraesthesia (tingling or burning sensation)	
C.I	▪ **Pregnancy;** fetal distress and miscarriage (ergot is uterine stimulant and vasoconstrictor) Used to induce abortion ▪ Peripheral and coronary vascular diseases ▪ Hypertension ▪ Liver & kidney diseases (impaired metabolism & clearance → Toxicity) ▪ Prophylaxis of migraine (Because of rebound headaches) ▪ **In concurrent use with triptans** (given at least 6 hrs from last dose of triptans **or** 24 hrs from stopping ergotamine & β-blockers) Not prefered because they have the same M.O.A	

Abortive Therapy : Triptanes

Drug	Sumatriptan	Zolmitriptan	Naratriptan
M.O.A	★ **Selective Agonism at 5-HT$_1$ (5-HT$_{1D/1B}$) receptors** ▪ Similar to ergotamine except that triptans are **more selective** as serotonergic Agonist. (they only differ in their P.K) ▪ First-line therapy for acute migraine attacks in most patients. ★ **No α1, α2, β –adrenergic, dopamine or muscarinic receptors.** ▪ Triptans inhibit the release of vasoactive peptides, promote vasoconstriction, and block pain pathways in the brainstem. ▪ Triptans inhibit transmission in the **trigeminal nucleus caudalis.**		
P.K	**Bioavailability:** ▪ Oral → low ▪ Subcutaneous → 97% ▪ Peaks after 2 min & T½ nearly 2 hours. (fast action with S.C, good for patient with vomiting, best option for acute cases) Male Dr mnemonic: S = Super fast acting ▪ You don't need to memorize the percentages ▪ **Given:** oral, nasal spray, & injectable forms	**Bioavailability:** ▪ Oral → 40%, ▪ Peaks after 2 hrs & T½ nearly 3 hours. ▪ **Given:** nasal spray, and injectable forms	**Bioavailability:** ▪ Oral → 70%, ▪ Peaks after 2 hrs & T½ nearly 6 hours (Slower onset less side effects) ▪ **Given:** Oral preparations Remember that oral is a bad choice for cases with vomiting
Uses	▪ To abort attacks in patients with frequent, moderate or infrequent but **severe** attacks. ▪ In cluster headache (extremely painful recurrent, unilateral migraine usually around the eyes)		
ADRs	▪ Most of ADRs are the 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 ▪ **Zolmitriptan:** Chest & neck tightness, **Coronary vasospasm** & Somnolence (drowsiness) Male Dr mnemonic: Zolm/ظلم = it would be an injustice to give to CVS patients		
C.I	▪ Peripheral vasospastic diseases ▪ Uncontrolled hypertension ▪ History of ischemia (may cause coronary spasm) ▪ Coronary artery disease ▪ Cerebrovascular disorders ▪ Renal or hepatic impairment (Liver & kidney diseases) they increase the drug toxicity ★ **In concurrent use with MAOIs, lithium, SSRIs,** → (5-HT increased to toxic level) ★ **In concurrent use with ergots** or others inducing vasospasm		

Deciding whether better with a triptans or with DHE

If the patient:



Has migraines a day or less and need rapid relief of pain:
Triptans are often a better choice

Pregnant woman:
paracetamol or intranasal[1] sumatriptan and/or diphenhydramine, meclizine

(H_1 Antagonists)

1) Doesn't expose the patients to high doses & also it will reach CNS without reaching the fetus, but other choices are preferable.

With headache episodes lasting 2-3 days:
DHE (Dihydroergotamine) is often the optimal choice because it has longer T½

- The form of drug preparation could influence the choice
- Injectable Sumatriptan reaches T_{max} the fastest followed by DHE nasal spray and Rizatriptan.

Factors When Choosing a Triptans

Male Dr mnemonic: S = Super fast

Male Dr mnemonic: F = Female

Differences in the time to peak blood concentration T_{max}, equates with faster relief of pain.	Differences in T½ → 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 **and/or** recurrence of headache → **Naratriptan**, **Frovatriptan**, have slower onset, fewer side effects, and a lower recurrence rate.	**Menstrual migraine: Frovatriptan** (longer T½= 26hrs) 2.5 mg twice per day beginning two days before the anticipated onset of menstrual migraine & continuing for 6 days.

Male Dr: exact numbers not imp

Drug	T_{max} (h)	T½ (h)	Drug	T_{max} (h)	T½ (h)
DHE	1	10	Naratriptan	2-3	6
Sumatriptan SQ	0.25	2	Eletriptan	2.8	4
Rizatriptan	1-1.5	2-3	Frovatriptan	2-3	26
Zolmitriptan	2.5	3			

Extra Notes

From the original PowerPoint

- ## Neurovascular Theory

  - The meninges are inflamed & dilated, this can increase pressure.
  - The trigeminovascular system (TVs) is thought to comprise neurons located in the trigeminal ganglion that innervate the cerebral vasculature.
  - Migraine involves the trigeminal nerve distribution to intracranial (& possibly extra-cranial) arteries. These nerves release peptide NTs, especially calcitonin gene-related peptide (CGRP), an extremely powerful vasodilator. Substance P & neurokinin A may also be involved.
  - Extravasation (leaking) of plasma & plasma proteins into the perivascular space appears to be found in biopsy specimens from migraine patients. This effect probably reflects the action of the neuropeptides , on the vessels.
    The mechanical stretching caused by this perivascular edema may be the immediate cause of activation of pain nerve endings in the dura.
  - Activation of trigeminal ganglion causes the release of several vasoactive neuropeptides that are associated with neurogenic inflammation such as substance P, CGRP, & neurokinin A.
  - Vasodilatation & extravasation of protein are the two main mechanisms of neurogenic inflammation, which prolongs & worsens the migraine headache.

- **Serotonin**
  - is an important neurotransmitter, a local hormone in the gut, a component of the platelet clotting process , and is thought to play a role in migraine headache.
  - Brain serotonergic neurons are involved in numerous diffuse functions such as mood, sleep, appetite, & temperature regulation, as well as the perception of pain, the regulation of BP, & vomiting.
  - Serotonin is clearly involved in psychiatric depression & also appears to be involved in conditions such as anxiety & migraine.

Extra Notes

From the original PowerPoint

Meclizine M.O.A

- The mechanism by which meclizine exerts its antiemetic, anti-motion sickness, and anti-vertigo effects is not precisely known but may be related to its central anticholinergic actions.
- It diminishes vestibular stimulation & depresses labyrinthine function.
- An action on the medullary CRTZ may also be involved in the antiemetic effect

Abortive Therapy:

- The triptans, the ergot alkaloids, & antidepressants may activate 5-$HT_{1D/1B}$ receptors on presynaptic trigeminal nerve endings to inhibit the release of vasodilating peptides, & antiseizure agents may suppress excessive firing of these nerve endings.
- Second, the vasoconstrictor actions of direct 5-HT agonists (the triptans and ergot) may prevent vasodilation & stretching of the pain endings. It is possible that both mechanisms contribute in the case of some drugs.
- The remarkably specific antimigraine action of the ergot derivatives was originally thought to be related to their actions on vascular serotonin receptors.
- Ergots are also available with Caffeine (like Panadol extra/plus) Caffeine is added in low dose like 1 mg can get relieve of headache.

- **Cluster Headaches:**
  - Generalized headache like with trauma or sinusitis, lithium carbonate oral and sumatriptan succinate both increase affecting serotonin levels in the blood.
  - Severe signs & symptoms include high BP & increased HR that lead to shock.
  - Too much serotonin is a potentially life-threatening situation.

MCQs

Q1: 23-years-old female patient suffering from Migraine Preceded by Phonophobia. What is she sensitive to?			
A- Unpleasant smell	B- Lights	C- Sounds	D- Caffeine
Q2: Which of the following is NOT considered as a strategy for treating migraine by preventing recurrence?			
A- Propranolol	B- Topiramate	C- Amitriptyline	D- Tramadol
Q3: which of the following is NOT used to treat acute attack of migraine?			
A- Antidepressant	B- 5-HT_3 Antagonists	C- H_1 Antagonist	D- NSAIDs
Q4: "Sensory > motor symptoms" presented by which phase of migraine?			
A- Pro-drum phase	B- Aura phase	C- Headache phase	D- Post-drum phase
Q5: A 25-year-old patient, who has a past history of cluster headaches, presents to the Acute Medical Unit with an acute attack of cluster headache.Which one of the following drugs is most likely to be an effective treatment?			
A- Aspirin	B- Atenolol	C- Paracetamol	D- Zolmitriptan
Q6: A 34-year-old woman has an acute attack of migraine, and is given a subcutaneous injection of sumatriptan that brings about prompt relief of her symptoms. Which of the following statements best explains the mechanism of action of sumatriptan?			
A- Acting on 5-HT receptors in the CNS	B- Blocking adrenergic receptors	C- Inhibiting cyclooxygenase	D- Blocking receptors to acetylcholine
Q7: Indicate the reversible non selective alpha-receptor antagonist?			
A- Ergotamine	B- Prazosin	C- Phenoxybenzamine	D- Carvedilol
Q8: Naratriptan differs from ergotamine in which the following ?			
A- It has antiemetic property	B- More selective as serotonergic agonist	C- It is a more potent a adrenergic blocker and less potent vasoconstrictor	D- It is a less potent a adrenergic blocker but more potent vasoconstrictor

1	2	3	4	5	6	7	8
C	D	A	B	D	A	A	B

SAQ

Q1) List the phases of migraine.

Q2) List 5 of migraine triggers.

Q3) List the treatment strategies of migraine.

Q4) 30-year-old man with headache episodes lasting 2 or 3 days, what is the best treatment?

Q5) For extremely fast relief within 15 min, injectable Sumatriptan is the only choice, why?

Q6) What are the special side effect of Zolmitriptan use?

Answers

A1) 1) Pro-drum phase 2) Aura phase 3) Headache phase 4) Post-drum phase

A2) Diet (alcohol) - climate - hormonal changes - stresses - therapy (oral contraceptives)

A3) 1) Acute attack (Rescue therapy/Abortive therapy)

2) Prevent Recurrence (Antiepileptic/Antidepressant/Antihypertensive)

A4) DHE is often the optimal choice because it has longer T½

A5) Injectable Sumatriptan reaches T_{max} the fastest followed by DHE nasal spray and Rizatriptan.

A6) Chest & neck tightness, Coronary vasospasm & Somnolence

Feedback Form

Neuropsychiatry Block

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