Drugs used in headache and migraine

- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

EDITING FILE

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.

Introduction

Headache

Pain anywhere in the region of the head or neck.

- It is caused by disturbance of the pain-sensitive structures around the brain:
  - **Within the cranium:** Blood vessels, Meninges, Cranial nerves.
  - **Outside the cranium:** Muscles, Nerves, Arteries, Veins, Subcutaneous tissues, Eyes, Ears & other tissues.

Migraine

Recurrent attacks of throbbing headache.

- Unilateral or on both sides.
- Lasting from > 2 up to 72 h.
- Pain is usually on one side of the head with facial & neck pain, nausea & vomiting.

± **Preceded** (or accompanied) by **AURA**.

**Pulsating /throbbing headache*: is a common feature of a migraine where the person wakes up in the morning feeling a sharp pain .

Types of Migraine

A. Common: without Aura (80%).
B. Classic: with Aura (20%).

AURA: "the patient feels that the migraine attack is coming"
Flashes of light, blind spots or tingling in your arm.
Perceptual disturbance of motor < sensory nature that develop over 5-20 min & last fewer than 60 min.

- **Visual:** photophobia (↑ sensitivity to light)
- **Auditory:** phonophobia (↑ sensitivity to sound)
- **Olfactory:** unpleasant smell.
- **Sensory:** abnormal sensation at face, extremities.

Triggers of Migraine

01	Live style	06	Stress
02	Disease	07	Climate
03	Hormonal changes	eg: Menstrual migraine	
04	Therapy	Antibiotics, Antihypertensive, H_2 blockers, Vasodilators, Oral contraceptives.	
05	Diet	Aged cheese, Alcohol, Chocolate, Caffeine, Hot dogs, Avocado, Fermented or pickled foods, Yeast or protein extracts.	

Phases of Migraine

Aborative drugs used		*Symptomatic drugs used*	
Pro-dorm	***Aura***	***Headache***	***Post-dorm***
• A change in mood or behavior (irritability,neck stiffness) that starts hours or days before headache. • It is experienced by 60% of migraineurs.	• Sensory > motor symptoms. • Starts 5-20 min before the migraine attack. • It is experienced by 20% of migraineurs.	• 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.	• Still not normal • More likely fatigue → irritability /impaired concentration /scalp tenderness /mood changes and GIT symptoms.

Casual Theories of Migraine

"Focus on it to understand the MOA of drugs"

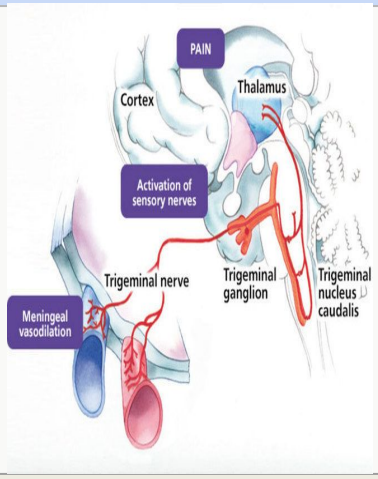
1- Vascular★

Triggers → intracranial **vasoconstriction** → **migraine aura** → focal ischemia → ↑ mediators → rebound **vasodilation** → ↑ permeability & leak → inflammatory reaction → activates perivascular **nociceptive** nerves → it throbs as blood flow at these sensitive area with each heartbeat "pressure on the nerves"→ **migraine headache**.

2- Neurovascular Theory★

1- Triggers → release K/glutamate → 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**.

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.



3- Cortical Spreading Depression	*4- Dopaminergic Hypersensitivity*	*5- Mediators "Serotonin"*

Treatment strategies

A) Prevent recurrence "*Prophylaxis*"

Overview

- ↑ **Responsiveness to abortive therapy.**
- ↓ Recurrence frequency, severity, duration and/or disability.
- **N.B.** Full effect of therapy **needs several weeks to manifest & should continue for 6 months & can be repeated.**

Drugs

Antiepileptics	Antidepressant	Antihypertensives
E.g. **Topiramate, Valproic** acid (Teratogenic)	TCAs; ★**Amitriptyline** & **Nortriptyline**	β-blockers; **Propranolol**
Block Na channel & augment GABA at $GABA_A$ receptors		Propranolol is commonly used in prophylaxis of migraine attack.

B) Acute attack "*Controls Attack*"

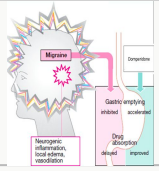
1- Rescue therapy *treats the symptoms*

Overview

- For ★**mild-moderate** pain
- **Non-specifically** target **individual symptoms** i.e. alleviating pain, emesis (vomiting) and associated symptoms.

drugs

Analgesic	**Acetaminophen**	
Analgesic	**NSAIDs**	• Aspirin (weaker than Acetaminophen) • **Ibuprofen, Naproxen** → for **mild to moderate** attack with **no nausea & vomiting.**
Analgesic	**Non-opioid/ opioid-like**	• Weak μ agonist → **Tramadol** (in moderate-severe pain) **(also inhibits 5HT reuptake)**
Antiemetic	**Dopamine Antagonists**	• **Domperidone** → **Gastric-Prokinetic**: ↑ Absorption & bioavailability of abortive therapy. ↑Gastric motility → ↓Gastric content → ↓ **vomiting** + ↑ drug absorption • **Phenothiazines** (**Promethazine**): Has a **sedative** effect.
Antiemetic	**5-HT_3 Antagonists**	For **severe** nausea & vomiting. most powerful, best choice antiemetic • **Ondansetron, Granisetron** "For chemotherapy patients"
Antiemetic	**H_1 Antagonist**	Has Antihistamine, Sedative & Anticholinergic effects (vestibular suppressant → ↓ CTZ stimulation → ↓ N&V related to balance) • **Meclizine, diphenhydram**

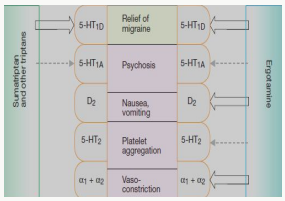


2- Abortive therapy *treats the migraine*

overview

- For ★**severe/disabling** pain. "highly effective in aura stage, not after attack has begun"
- They **specifically** target pathways of migraine by: **reducing meningeal dilatation** & reducing neural activation via **5-HT_1** agonism → i.e stopping headache as it's evolving.
- Effective if **taken early, just before the pain starts**, losing effectiveness once the attack has begun So they must be **rapidly acting.**

Abortive therapy: *Ergots in Refractory cases*

Drugs	**Ergotamine Tartrate** **Restricted**: rare clinical use due to severe adverse effects	**DiHydroErgotamine (DHE)** **Preferred** in clinical setting
Source	**Ergot:** product of *Claviceps purpurea;* a fungus growing on rye/grains. 	
Important **MOA**	1) **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 2) **Partial agonist effect on α-adrenoceptors** → vasoconstriction (peripherally so more CVS ADRs, not desirable) 	
P.K	• **Given:** orally, sublingual, rectal suppository, inhaler. • Oral absorption is incomplete (erratic) & slow → low bioavailability. • Can be taken orally (**Cafergot** is a formula which contains **caffeine** & **ergotamine**) • Despite t½ nearly 2 h, ergotamine produces vasoconstriction → 24 h or longer due to high & **long tissue binding ability**. • Has significant side effects, and may worsen the nausea & vomiting associated with migraine.	• **Given**: parenterally, nasal spray, inhaler and **injectable** forms **(good to use if patient is vomiting)** • Eliminated more rapidly than ergotamin 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 & numbness of limbs, tingling (due to peripheral vasoconstriction) • Anginal pain due to **coronary spasm**, and disturbed cardiac rhythm (tachycardia or bradycardia). If used with B-blockers, it can cause reflex tachycardia or arrhythmia. "May activate peripheral 5HT → ↑ platelet aggregation and vasoconstriction" • **Prolong use →★ rebound headache** due to vasodilation followed by vasoconstriction. "compensatory mechanism" • **Prolong use & high dose** → paraesthesia (tingling or burning sensation).	
Important **#**	• **★Pregnancy**; fetal distress & miscarriage (ergot is uterine stimulant & vasoconstrictor) Uterine contraction is due to **α1 stimulation.** • Peripheral & coronary vascular diseases • Hypertension "vasoconstriction" • **★Liver & kidney diseases** (impaired metabolism by liver & clearance by kidney → toxicity) • Prophylaxis of migraine (Rebound headaches) • **In concurrent use with triptans** (given at least **6** h from last dose of triptans **<u>or</u> 24** h from stopping ergotamine & B-blockers) Not prefered because they have the same M.O.A.	

Abortive therapy: *Triptans*

drug	★Sumatriptan	Zolmitriptan	Naratriptan
MOA	• **Selective agonism at 5-HT1** (5-$HT_{1D/1B}$) **receptors** • Similar to ergotamine except that triptans are **more selective** as serotonergic agonist. (they only differ in their P.K) • **No α_1, α_2, β-adrenergic, dopamine or muscarinic receptors.** • Inhibit the release of vasoactive peptides, promote vasoconstriction, and block pain pathways in the brainstem. • Inhibit transmission in the **trigeminal nucleus caudalis.**		
P.K "Numbers are not imp"	**Present as**: oral, nasal spray, & injectable forms **Bioavailability:** • Oral → low • **Subcutaneous** → 97% • Peaks after 2 min & t½ ~ 2 h. (**fast action with SC, good for patient with vomiting**) (Sumatriptan = Super fast acting)	**Present as:** nasal spray **Bioavailability:** • Oral → 40%, • Peaks after 2 h & t½ ~ 3 h.	**Present as**: injection, nasal spray and oral preparations **Bioavailability:** • Oral - 70% • Peaks after 2 h & t½ ~ 6 h (slower onset; less side effects) Remember that oral is a bad choice for cases with vomiting
Clinical use	• To abort attacks in patients with A) **frequent, moderate or** B) **infrequent but severe** attacks. • First-line therapy for acute migraine attacks in most patients • 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 & burning sensation at the site of injection. • Vasospasm, **ischemic heart, angina & arrhythmias.** • **Zolmitriptan**: chest & neck tightness, **coronary vasospasm** & somnolence) (Zolm/ظلم = it would be an injustice to give to CVS patients)		
#	• 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.		

Drug	T max (h)*	t½ (h)*
DHE	1	10
Sumatriptan SQ	0.25	2
Rizatriptan	1-1.5	2-3
Zolmitriptan	2.5	3

Drug	T max (h)*	t½ (h)*
Naratriptan	2-3	6
Eletriptan	2.8	4
Frovatriptan	2-3	26

* Drs: No need to know exact numbers

Important ★★★ Triptans or DHE?

- ★**With headache episodes lasting 2-3 days**:
DHE is often the optimal choice because it has longer t½.

- ★**With migraines a day or less & need rapid relief of pain**:
Triptans are often a better choice.

- ★**Pregnant woman**:Paracetamol or intranasal Sumatriptan &/or Diphenhydramine "H1 antagonist used in morning and motion sickness", Meclizine

- The form of drug preparation could influence the choice.

- Injectable Sumatriptan reaches T_{max} the fastest followed by DHE nasal spray & Rizatriptan.

Factors When Choosing a Triptan

- **Tmax:** differences in the time to peak blood concentration Tmax equates with faster relief of pain
  - For extremely fast relief within 15 min, **injectable Sumatriptan** is the only choice.

- **T½:** differences in t½ + a clinical effect in terms of recurrence of headache.
  - 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= 26 h) 2.5 mg twice per day beginning two days before the anticipated onset of menstrual migraine & continuing for 6 days. (Frovatriptan in Female)

Other TREATMENT:

1-Botulinum Toxin (Botox)	• Decreases pain signal from synaptic terminal that transmitted to trigeminal nerve thereby pain sensation.
2-Calcitonin Gene Related Peptide Inhibitor	• Erenumab • Block CGRP from binding to CGRP receptors, a key contributor to the trigeminal nerve pain and inflammation of migraine • Monoclonal antibody • Given subcutaneously

Summary

Abortive Therapy			
Drug	**MOA**	**Uses**	**ADRs**
ERGOTS: -Ergotamine Tartrate -Dihydroergotamine (DHE)	1) 5-HT1D/1B partial agonist in cerebral/meningeal vessels → ↓ vasodilators + ↓ firing of nerve endings. 2) α-adrenoreceptor partial agonist → vasoconstriction	Only used to abort attacks	Feeling cold, numbness & tingling of limbs • Prolonged use → rebound headache • Prolonged + in high doses → paraesthesia
TRIPTANS: -Sumatriptan -Zolmitriptan -Naratriptan	5-HT1 selective agonists → ↓ vasoactive peptides + vasoconstriction + block pain pathways & trigeminal nucleus.	-Abort attacks -Cluster headache For Sumatriptan: -Injectable for extremely fast relief -Pregnancy	Same as Ergots but better tolerated. • Vasospasm, ischemic heart, angina & arrhythmias Zolmitriptan: • Chest & neck tightness • Coronary vasospasm • Somnolence

Rescue Therapy		
ANALGESICS		
Acetaminophen		Acetaminophen is more effective than Aspirin
NSAIDs	Aspirin	
	Ibuprofen Naproxen	For mild to moderate attacks with no nausea & vomiting.
Opioids	Tramadol	If the attack is severe

Summary

Rescue Therapy		
ANTIEMETICS		
Dopamine Antagonists	Domperidone	Gastroprokinetic → ↑ absorption of abortive therapy
	Phenothiazines (Promethazine)	Has sedative effect
5-HT3 Antagonists	Ondansetron Granisetron	For severe nausea & vomiting
H1 Antagonists	Meclizine Diphenhydramine	Antihistamine, anticholinergic & sedative effects

Preventative Therapy		
Group	**Drugs**	**Mechanism**
Antiepileptics	Topiramate Valproate	Block Na channel & augment GABA at GABA A receptor
Antidepressants	Amitriptyline Nortriptyline	Unknown mechanism related to headache & migraine
Antihypertensives	Propranolol	β-Blocker (common in migraine prophylaxis)

MCQ

1. **patients came to the er with headache episodes lasting 2 or 3 days at a time which of the following is the drug of choice?**			
A.**Sumatriptan**	B.**Meclizine**	C.**Ondansetron**	D.**Dihydroergotamine**
2.**26 years old patient come to your clinic For migraines that last for a day or less and he need rapid relief of his pain, which of the following is the drug of choice?**			
A.**Sumatriptan**	B.**Propranolol**	C.**Dihydroergotamine**	D.**Diphenhydramine**
3.**a pregnant women came to the er with migraines which of the following is the drug of choice?**			
A.**Propranolol**	B.**Sumatriptan**	C.**Dihydroergotamine**	D.**Valproate**
4.**in Menstrual migraine which of the following is the drug of choice?**			
A.**Propranolol**	B.**Sumatriptan**	C.**Valproate**	D.**Frovatriptan**
5.“Sensory > motor symptoms” presented by which phase of migraine?			
A.Pro-drum phase	B.Aura phase	C.Headache phase	D.Post-drum phase
6.Which of the following is NOT considered as a strategy for treating migraine by preventing recurrence?			
A.Propranolol	B.Topiramate	C.Amitriptyline	D.Tramadol

1:D ,2:A ,3:B ,4:D ,5:B ,6:D

SAQ

01

Mention one of the Migraine Causal Theories and explain its

Vascular:

Triggers → Intracranial vasoconstriction → migraine aura → focal ischemia → ↑ inflammatory mediators → rebound vasodilation → ↑ permeability & leak → inflammatory reaction → migraine headache.

02

patients came to the er with headache episodes lasting 2 or 3 days at a time which of the following is the drug of choice and its MOA?

Ergot,↓ Release of vasodilating peptides↓ Excessive firing of nerve endings → reducing pain sensation ↓ vasodilation & stretching of the pain endings

03

Mention 2 ADRs and 2 Contraindications

-**rebound headache,**Anginal pain due to **coronary spasm.**

-Pregnancy,Liver & kidney diseases.

04

List 5 of migraine triggers.

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

Team Leaders

Muhannad Al-otabi

Reema Almotairi

Sarah Alajaji

Maryam Alghannam

Team members

Abdulaziz Alamri

Sami Mandoorah

Salma Alkhlassi

Faisal Alateeq

Omar Alamri

Huda bin jadaan

Nazmi M Alqutub

Mohammed Alqutub

Manar Aljanubi

Sultan Almishrafi

Reena Alsadoni

Wasan Alanazi

Mohammed Maashi

Almas Almutairi

Jana Almutlaqah

Mohammed Alasmary

Fatimah Alghamdi

Farah Abukhalaf

Nazmi A Alqutub

Lama Alotaibi

Norah Almalik

Ziad Alhabardi

Salma Alsaadoun

Rawan Alqahtani

Mohammed Alrobeia

Jouri Almaymoni

Aroub Almahmoud

Mohammed Alhudaithi

Faisal alzuhairy

Remaz Almahmoud

Special thanks to norah almania for the amazing logo