#14
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.

Color index:

- Drugs names
- Doctors notes
- Important
- Extra

تمّ، بحمد الله.

Pharmacology 435

كل الشكر والتقدير لأعضاء فريق علم الأدوية الكرام على عملهم الجادّ،
نفع الله بعلمهم، وجعل مشاركتهم للعلم شفيعًا لهم.

أسرار باطرفي
العنود العمير
آية غانم
حصه المزيني
دلال الحزيمي
رغدة قاسم
ريم العقيل
سارا الحسين
ساره الخليفة
لمى الزامل
لولوه الصغيّر
لينا إسماعيل
ملاك اليحيا
نورة البصيص

إبراهيم العسعوس
احمد الخياري
زياد السالم
عبدالعزيز الحماد
فوزان العتيبي
فارس المطيري
قصي عجلان
ماجد العسبلي
محمد ابونيان
محمد السحيباني
يوسف الصامل

قادة فريق علم الأدوية:
أثير النشوان & خالد أبوراس

To Understand Better

Headache:	Migraine:
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.)	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.** 1:37 minutes

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%.)

داء الشقيقة متلازمة لها أعراض كثيرة لكن الصداع هو أشهرها ولا نقارنها بالصداع العادي لشدته **المحاضرة تركيزها الأساسي على علاج الصداع الناتج من الشقيقة**
So headache ≠ migraine, headache is a symptom of migraine

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 + 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.

3:56 minutes

Migraine Causal Theories

Explained in the next page

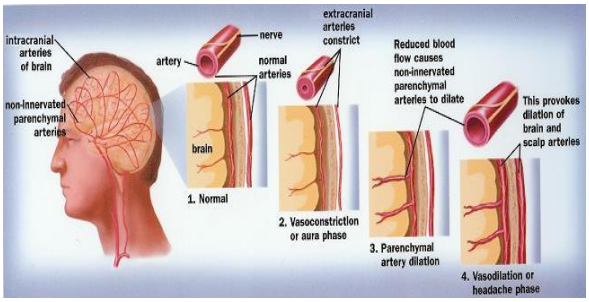
Vascular, Cortical Spreading Depression, Neurovascular theory, Mediators [Serotonin], Dopaminergic Hypersensitivity.

Vascular theory:

Triggers → Intracranial vasoconstriction → migraine aura → focal ischemia → ↑ mediators (damaging inflammatory 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.



The vascular theory: MG is a direct result of general vasoconstriction/vasodilatation of the small-innervated arteries that supply brain

1. The extracranial arteries, which supply scalp and periosteum of the skull and intracranial arteries located inside the skull and supply brain tissue, are linked via reflex pathways.
2. Tension in the posterior cervical muscles developed as a result of trauma and physical or emotional stress triggers vasoconstriction of extracranial arteries that supply the scalp. The vasoconstriction of extracranial arteries via reflex pathways triggers vasoconstriction of intracranial arteries that supply the brain. This vasoconstriction corresponds with the aura stage of MG.
3. As soon as the blood supply to the brain is even slightly compromised, the body will do whatever it takes to maintain normal blood perfusion through the brain. Thus, as a reflex reaction to vasoconstriction in the intracranial brain arteries, the parenchymal arteries (i.e., arteries that enter the brain tissue) dilate.
4. This dilation causes an exit of liquid into the surrounding brain tissue and even mild local swelling, which triggers an increase of the intracranial pressure. At this point, the MG attack begins.

الفكرة كلها ان الجسم اذا ضاقت الأوعية الداخلية للمخ ينخرش ويحاول يوسعها بسرعة فلما تتوسع تخرج السوائل وترفع الضغط الداخلي
فتقسيم الأدوية يعتمد هل هي راح تعالج السبب (التوسع) ولا الأعراض (الصداع والغثيان)

Treatment Strategy

Prevent reccurence

↓ Recurrence frequency, severity, duration & / or disability.
↑Responsiveness to abortive therapy

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

Acute attack (Controls attack)

ABORTIVE therapy (severe-disabling) Treat the **cause**

They **specifically** target pathways of migraine by ↓ meningeal dilatation & ↓ neural activation via **5HT1 agonism** (serotonin constrict blood vessels) i.e. Stopping headache as it is evolving. Abortive medications effective if taken early, just before the pain starts (before vasodilatation), losing effectiveness once the attack has begun (may prevent further attacks only) So **they must be rapidly acting**.

RESCUE therapy (mild to moderate) Treat **Symptoms**

Non-specifically target individual symptoms. i.e. Alleviating Pain, emesis and associated symptoms

Step 1 USMLE Tutorial - All About Headaches

This video summarizes the whole lecture in a simple way

muscle relaxants;
Botulinum toxins, **Tizanidine**

Anti-spastic

PREVENT RECURRENCE

Anti-epileptics

Block Na^+ channel & augment GABA at GABA-A receptors
Topiramate, **Valproic**

Anti-depressants

TCA; **amitryptylin** and **nortryptyline.**
Why TCA? Bc they have 5-HT & H1 actions, which are good for migraine

Anti-hypertensives

B-blockers; **propranolol**
Ca^{2+} Channel Blockers
Propranolol is commonly used in **prophylaxis** of migraine attack.

Acute attack (RESCUE THERAPY)

Drug	Analgesics	Anti-emetics (prevent nausea and vomiting)
Mech. of action	1- **NSAIDs:** • **Acetaminophen** • **Aspirin** (weaker) • **Ibuprofen**, **Naproxen** → (Drug of choice) for **mild to moderate** attack with **no** nausea & vomiting. 2- **Narcotic analgesic (μ agonis): tramadol** = (central analgesic) → causes tolerance.	**1- Dopamine Antagonists** A- **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. B- **Phenothiazines** (**Promethazine**): Has a **sedative** effect. **2- 5HT3 antagonists** **Ondanseteron**, **Granisetron**: For severe **nausea** and **vomiting**. **3- H1 antagonist** **Meclizine**, **diphenhydramine**: Has **anti-histaminic** + **sedative** + **Anti-cholinergic** effect. → Safe for pregnancy.

▶ 7:55 min

ACUTE ATTACK (ABORTIVE THERPY)

1- Ergots

Drug	Ergotamine tartarate (rare clinical use due to sever adverse effects) (resticted use)	Dihydroergotamine (DHE) (**preferred** in clinical setting)
Mech. of action	- Product of Claviceps purpurea; a fungs growing on rye/grains - **Non-Selective** - **Agonism at 5HT1** (5HT-1D/1B found in cerebereal And menigeal vessels) **receptors.** → - ↓ release of vasodilating peptides - ↓ excessive firing of nerve endings - At blood vessels → ↓ vasodilation & stretching of the pain endings - Partial agonist effect on **α**-adrenoceptors → vasoconstriction	
P.K	- Oral absorption (as **Cafergot from caffeine)** - Incomplete (erratic) + slow → low bioavailability. - **$T_{1/2}$** nearly **2 hours**, ergotamine produces vasoconstriction → **24 hours** or longer due to high and long **tissue binding ability.** - Can be taken sublingually, rectal suppository, inhaler. - **Ergotamine tartrate** -Reserve drug- has **significant side effects**, and may **worsen the nausea and vomiting associated with migraine.**	- Nasal spray, inhaler & **injectable forms** (good to use if patient is **vomiting**) - Given parenterally, and eliminated more rapidly than ergotamine, presumably due to its rapid hepatic clearance and has less adverse effects. * Better than Ergotamine tartarate bc of the P.K characteristics. * has an efficacy similar to that of sumatriptan, but nausea is a common adverse effect.
Indications	- They are only used to abort the attacks (Except **Dihydroergotamine** can be given for severe, recurrent attacks **not** responding to other drugs) - 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 • Anginal pain due to **coronary spasm**, and disturbed cardiac rhythm (tachycardia or bradycardia) • Prolong use → **rebound headache due to vasodilatation** followed by **vasoconstriction**. • Prolong use and high dose → paraesthesia (tingling or burning sensation)	
C.I	• **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 triptans or 24 hrs from stopping ergotamine and β-blockers)	

ACUTE ATTACK (ABORTIVE THERPY) Cont.

2- Triptanes

- **Selective** Agonist at 5-HT_1 (5-HT1D/1B) receptors. → better than ergots.
- Similar to **ergotamine** except that **triptans** are more **selective** as **serotonergic agonist**.
- **No a1, a2, β –adrenergic, dopamine or muscarinic receptors.**

All theses drugs are important to now it well, especially P.K

Drug	Sumatriptan Super fast.	Zolmitriptan	Naratriptan
	oral, nasal spray, and injectable	nasal spray, and injectable	Oral preparations
MOA	- **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 & $T_{1/2}$ nearly 2 hours (fast action with SC, subcutaneous, good for patient with **vomiting**)	**Oral** bioavailability **40%**, peaks after 2 hrs & $T_{1/2}$ nearly 3 hours.	**Oral** bioavailability **70%**, peaks after 2 hrs & $T_{1/2}$ nearly 6 hours (slower onset, **less side effects**)
Indications	• To abort attacks in patients with frequent, moderate or infrequent but **severe attacks**. • In **cluster headache** • Sumatriptan → first-line therapy for acute severe migraine attacks		
ADRs	• Most of adv 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**		
C.I	• Peripheral vasospastic diseases, Uncontrolled hypertension • **Coronary artery disease**. • History of ischemia • Cerebrovascular disorders • In concurrent use with **ergots** or others **inducing vasospasm.** • In concurrent use with **MAOIs**, **lithium**, **SSRIs**, → (5HT increased to toxic level) • Renal or hepatic impairment.		

Deciding whether better with a triptan or with dhe.

Patients

- migraines a day or less → **Triptans** (they give rapid relief)
- pregnant women → **paracetamol** or intranasal **sumitriptan** and or **diphenhydramin**, **meclizine** are **safe**.

Factors when Choosing a Triptans:

Medication	T_{max} (h)	$T_{1\backslash 2}$ (h)
DHE	1	10
Sumatriptan SQ	**0.25**	2
Rizatriptan	1-1.5	2-3
Zolmitriptan	2.5	3
Naratriptan	2-3	**6**
Eletriptan	2.8	**4**
Frovatriptan	2-3	**26**

- **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.
- The **form** of drug preparation could influence the choice, **Injectable Sumatriptan** reaches T_{max} the **fastest** followed by **DHE nasal spray** and **Rizatriptan.**
- 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** (longer $T_{1\backslash 2}$= 26hrs) 2.5 mg twice per day beginning two days before the anticipated onset of menstrual migraine and continuing for six days.

Summary-1

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Summary-2

ACUTE ATTACK (ABORTIVE THERPY) Cont.

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C.I	• 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**, → (5HT increased to toxic level) • Renal or hepatic impairment.		

PREVENT RECURRENCE

Antiepileptics: Block Na^+ channel & augment GABA at GABA-A receptors **Topiramate Valproic**

Antidepressants: TCA; **amitryptylin** and **nortryptyline**

Antihypertensive: B-blockers; **propranolol**, **Ca^{2+} Channel Blockers**
Propranolol is commonly used in prophylaxis of migraine attack.

Antispastic: muscle relaxants **Botulinum toxins**, **Tizanidine**

Patients

- migraines a day or less → **Triptans** (they give rapid relief)
- pregnant women → **paracetamol** or intranasal **sumitriptan** and or **diphenhydramin**, **meclizine** are **safe**.

- Very Helpful!

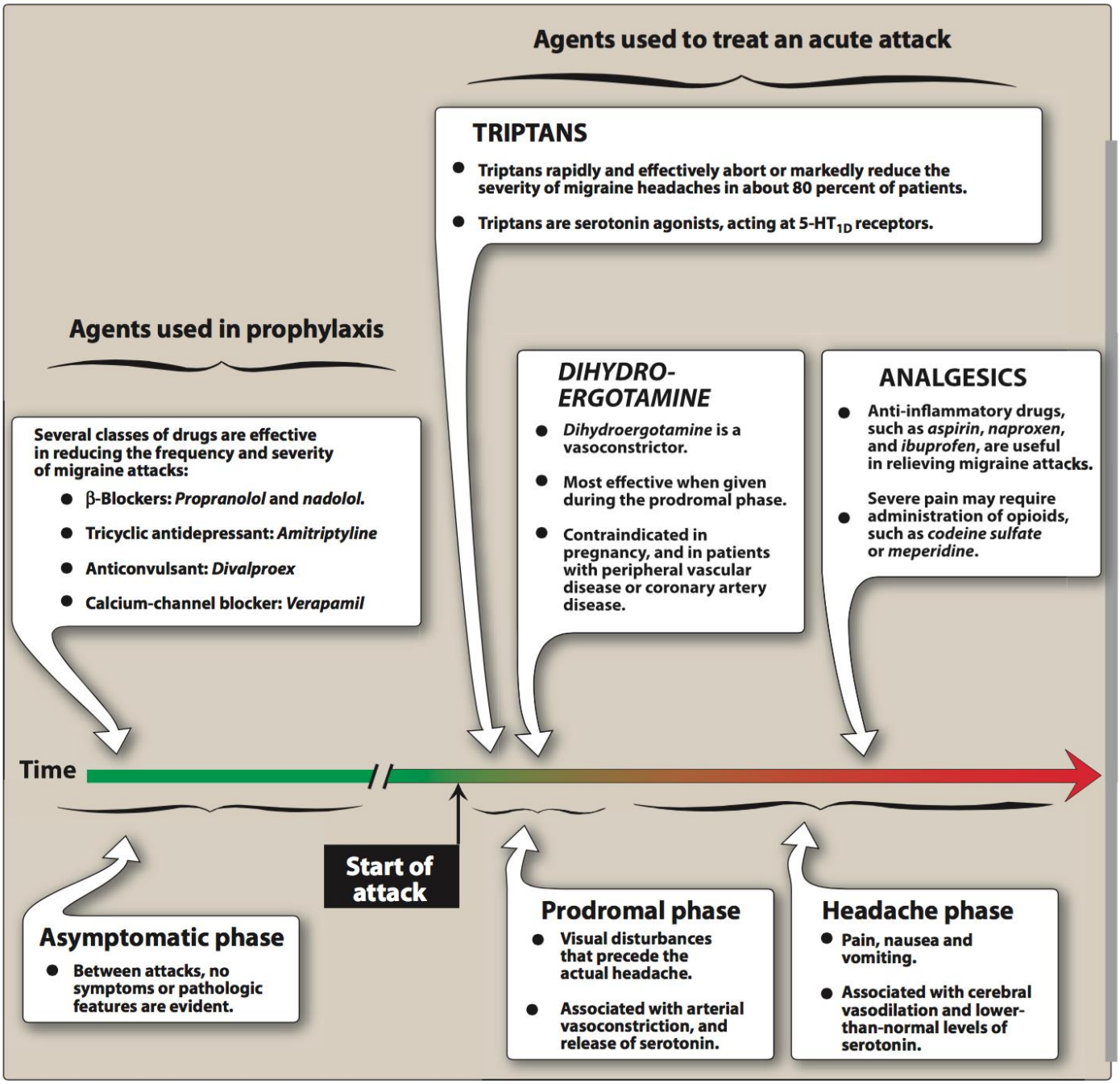

Figure 42.10
Drugs useful in the treatment and prophylaxis of migraine headaches.

Flash Cards | MCQs | Editing File

Thank you for checking our team!

Pharmacology 435

@ pharmacology435

أثير النشوان
أسرار باطرفي
العنود العمير
آية غانم
حصه المزيني
دلال الحزيمي
رغدة قاسم
ريم العقيل
سارا الحسين
ساره الخليفة
لمى الزامل
لولوه الصغيّر
لينا إسماعيل
ملاك اليحيا
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زياد السالم
عبدالعزيز الحماد
فوزان العتيبي
فارس المطيري
قصي عجلان
ماجد العسبلي
محمد ابونيان
محمد السحيباني
يوسف الصامل

Sources:

1- 435's lecture
2- Pharmacology (Lippincotts Illustrated Reviews Series), 5th edition.
3- Basic & Clinical Pharmacology by Katzung. 12th edition

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