Migraine

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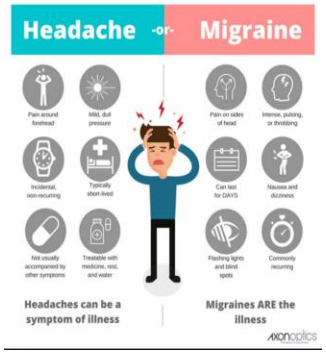
Migraine

- **DEF:** Severe recurrent, throbbing headache affecting only one side of the head.
- Females are 3-fold more affected than males.



TYPES:

1. Migraine without aura (85% of patients)

severe, unilateral, pulsating headache that typically lasts from 2 to 72 hours. These are aggravated by physical activity and are accompanied by nausea, vomiting, photophobia, and phonophobia.

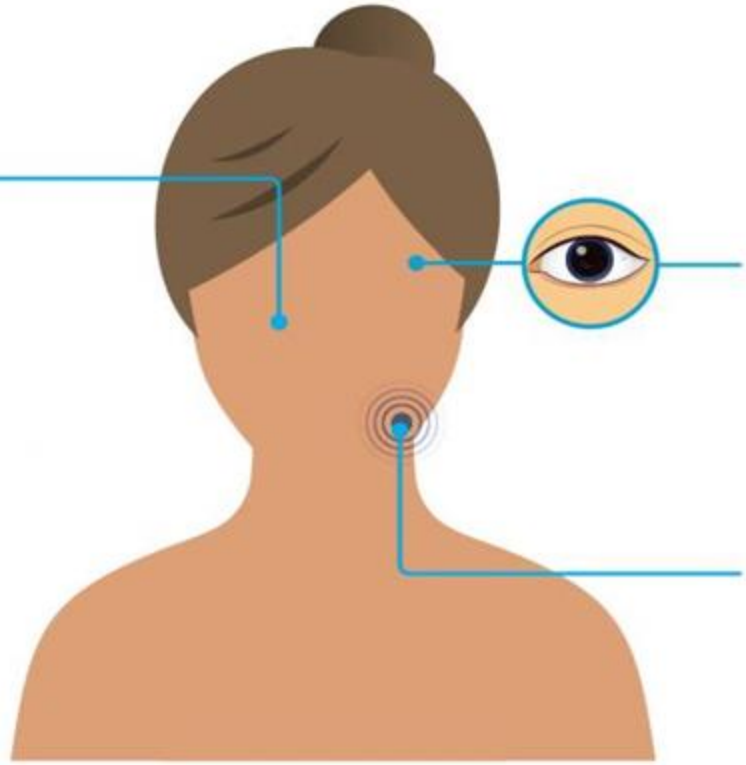
2. Migraine with aura (15% of patients)

neurologic symptoms precede the headache, which can be visual, sensory, and/or cause speech or motor disturbances

MEDICAL NEWS TODAY

Migraine Phases

Aura Phase



Motor auras:
- slurred or jumbled speech
- difficulty understanding what others say
- difficulty writing
- problems thinking clearly

Visual auras:
- flashing lights
- zig-zagging lines
- blurred vision
- blind spots that expand over time

Sensory auras:
- numbness or tingling

Pathophysiology:

1- Vascular Theory: Migraine results from vasoconstriction → aura, followed by vasodilation → throbbing pain.

2- Neurovascular Theory (MOST ACCEPTED): Migraine is caused by abnormal activation in the trigeminal-vascular system (TGVS). Activation of the trigeminal nerve releases neuropeptides: CGRP (Calcitonin Gene-Related Peptide), Substance P, Neurokinin A

3-Cortical Spreading Depression (CSD) theory: A wave of neuronal depolarization spreads across the cortex → causing aura. Steps: A Sudden strong depolarization → followed by suppression.

4- Brainstem Dysfunction Theory: Dysfunction in brainstem nuclei (especially the dorsal raphe nucleus and locus coeruleus) leads to abnormal pain modulation. Outcomes: Abnormal sensory processing, Altered serotonin & norepinephrine pathways.

5- Serotonin (5-HT) Theory: Migraine involves disturbances in serotonin levels. Mechanisms: During migraine attacks → ↓ serotonin (5-HT). Low 5-HT causes vasodilation & increased CGRP release

6- Genetic Theory: Migraine is associated with familial mutations → neuronal hyperexcitability

7- CGRP Theory : CGRP is a major mediator in migraine.

I- Triptans

These agents rapidly and effectively abort or markedly reduce the severity of migraine headaches in about 70% of patients.

Members: sumatriptan, naratriptan, rizatriptan, eletriptan & zolmitriptan.

Mechanism of action:

-It is a serotonin agonist at ***5-HT$_{1D}$ receptors***.

-This subtype of serotonin receptors is found on small peripheral nerves that innervate the intracranial vasculature.

-Their activation suppresses the release of sensory neuropeptides as substance P.

Uses

Sumatriptan is given orally, S.C. or intranasally.

Side effects:

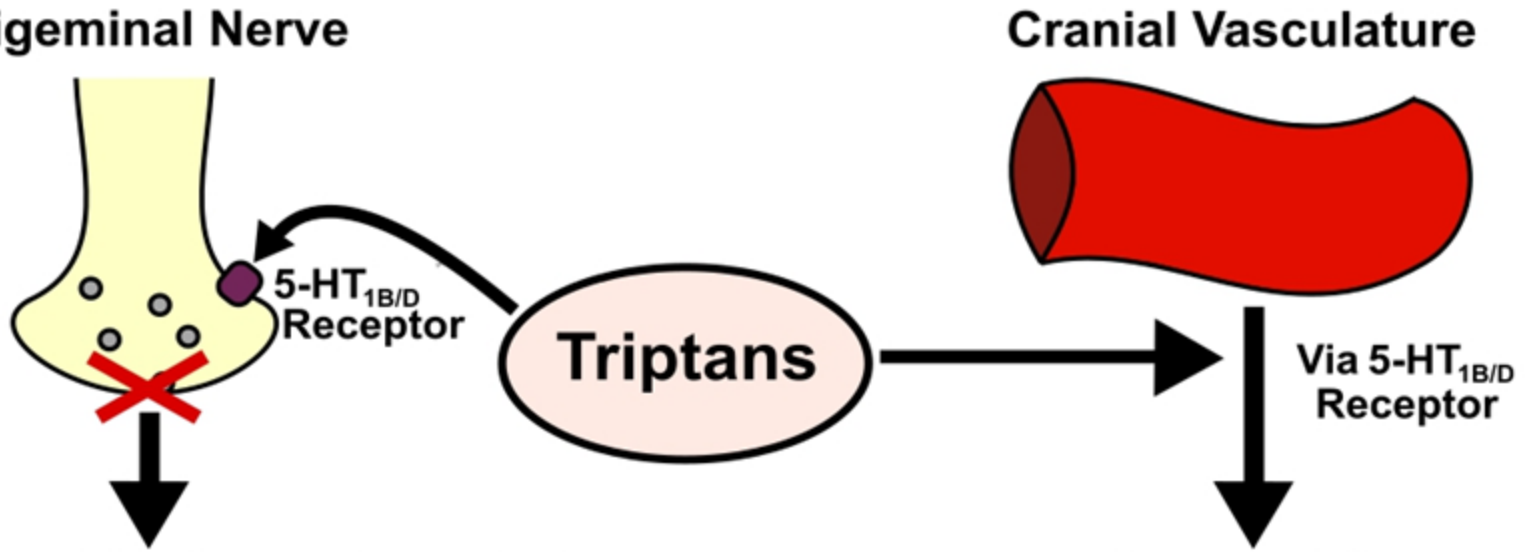
Nausea & vomiting.

Parathesia.

Chest pain.

N.B. It is ***avoided in*** patients with ischemic heart diseases.

Proposed Triptan Mechanism of Action



Prevents peptide release that would lead to:
- Vasodilation
- Neurogenic inflammation
- Pain

Vasoconstriction

Moises Dominguez

II- Ergotamine

Mechanism of action:

Ergotamine is α blocker with vasoconstrictor effect.

It has similar actions to triptans but with less selectivity at 5HT receptors.

Contraindications:

Peripheral vascular diseases.

Hypertension.

Angina.

Pregnancy.

Not given with triptans

Dihydroergotamine a derivative of ergotamine. It can be given intravenously

III- Analgesics

NSAIDs are often effective in mild to moderate migraine e.g. aspirin.

Management of migraine

Treatment	Prophylaxis
Mild Attack • Simple analgesics (Non-narcotic analgesics e.g. Aspirin 900 mg or Paracetamol 1g) •Antiemetic (e.g. metoclopramide) • Sedatives (e.g. diazepam)	Indications: 1- If the attack occurs two times or more per month. 2.If the headache is complicated by serious neurologic signs •**Alpha (α2- Agonists) >>> Clonidine** •**Anxiolytic >>>> Diazepam** •**Antidepressants >>> TCA (Amitriptyline)** •**Anti-Serotonin drugs >>> Cyproheptadine Pizotifen** • **Methysergide >>> Strong 5-HT antagonist** •**B- Blocker as Propranolol (1st line of prophylaxis)** •**Calcium channel blockers>>> Verapamil** • **Diuretics & low salt diet: In menstruation-associated migraine**
Severe attack •Ergotamine + metoclopramide + caffeine + simple analgesics •Sumatriptan (5-HT Agonist).	

Anti-CGRP Monoclonal Antibodies("CGRP pathway inhibitors")

These are new migraine-preventive drugs that target Calcitonin Gene-Related Peptide (CGRP) or its receptor.

They are NOT for acute attacks → **ONLY prophylaxis**.

A) Target and neutralize CGRP ligand: Fremanezumab, Galcanezumab

B) Block CGRP receptor: Erenumab

PK

Erenumab, Fremanezumab, Galcanezumab → subcutaneous (SC)

Onset: Start working within 1 week (but full effect in 1–2 months)

Half-life: Long (25–50 days) → supports monthly or quarterly dosing

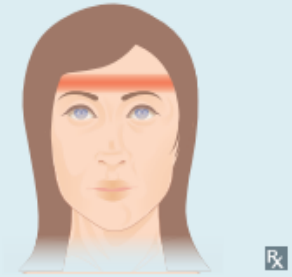
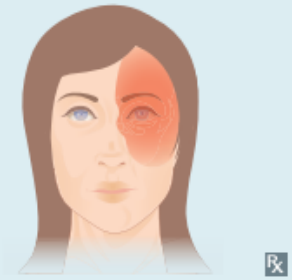
Metabolism: Catabolized by proteolytic enzymes (like all mAbs) NOT metabolized by liver enzymes→ No CYP interactions→ Very few drug–drug interactions

Side Effects:

Generally mild: Common Injection site reactions (pain, redness), Constipation, Muscle cramps

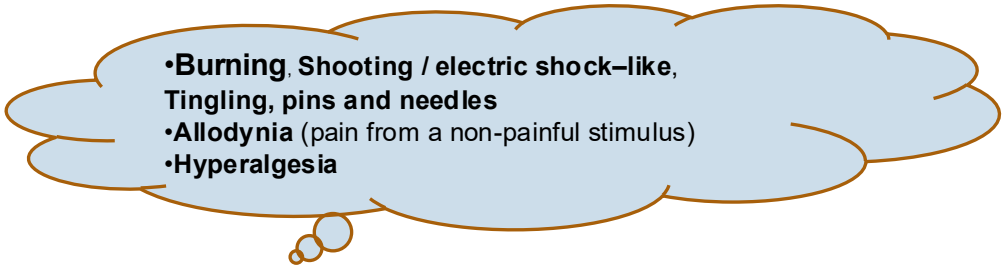
Hypersensitivity/anaphylaxis

Severe constipation with possible obstruction

CLASSIFICATION	LOCALIZATION	DURATION	DESCRIPTION	TREATMENT
Tension-type 	Bilateral	> 30 min (typically 4–6 hr); constant	Steady, "bandlike" pain. No nausea or vomiting. No more than one of photophobia or phonophobia. No aura. Most common primary headache; more common in females.	Acute: analgesics, NSAIDs, acetaminophen. Prophylaxis: TCAs (eg, amitriptyline), behavioral therapy.
Migraine 	Unilateral	4–72 hr	Pulsating pain with nausea, photophobia, and/or phonophobia. May have "aura." Due to irritation of CN V, meninges, or blood vessels (release of vasoactive neuropeptides [eg, substance P, calcitonin gene-related peptide]). More common in females. POUND–Pulsatile, One-day duration, Unilateral, Nausea, Disabling.	Acute: NSAIDs, triptans, dihydroergotamine, antiemetics (eg, prochlorperazine, metoclopramide). Prophylaxis: lifestyle changes (eg, sleep, exercise, diet), β-blockers, amitriptyline, topiramate, valproate, botulinum toxin, anti-CGRP monoclonal antibodies.
Cluster 	Unilateral	15 min–3 hr; repetitive	Excruciating periorbital pain with autonomic symptoms (eg, lacrimation, rhinorrhea, conjunctival injection). May present with Horner syndrome. More common in males.	Acute: sumatriptan, 100% O_2. Prophylaxis: verapamil.

Neuropathic pain

Neuropathic pain is pain caused by damage or disease that affects the nervous system, such as diabetic peripheral neuropathy, postherpetic neuralgia, or spinal cord injury.



Drugs for Neuropathic pain:

Neuropathic pain is a common clinical presentation of many peripheral neuropathies such as painful diabetic neuropathy, HIV-associated neuropathy, chemotherapy-induced neuropathy, post-herpetic neuralgia (herpes zoster virus) and trigeminal neuralgia.

Guidelines offer consistent recommendations for treating neuropathic pain.

There is not much available evidence that supports specific combinations of medications. However, **combination of gabapentin with an opioid were superior to monotherapy.**

Effective therapies

NOT NSAIDs (they don't work). Use medications that target nerve excitability and central sensitization.

1. **Calcium channel α2-delta ligands:** e.g., gabapentin, pregabalin

↓ excitatory neurotransmitter release.

– These medications are recommended as **first-line therapy.**

2. Tricyclic antidepressants (TCAs):e.g., Amitriptyline, Nortriptyline, Desipramine.

– However, TCAs cause possible cardiotoxicity. Therefore, caution should be taken in patients with cardiac disease.

3. Serotonin-norepinephrine reuptake inhibitors (SNRIs):e.g., Duloxetine (best for diabetic neuropathy), venlafaxine.

↑ serotonin & norepinephrine → enhances descending inhibition of pain.

4. Selective serotonin receptor inhibitors (SSRIs):e.g., fluoxetine, citalopram.

5. **Opioid Analgesics:** e.g., Tramadol, oxycodone, and morphine.

– **These medications are recommended as second-line therapy because of concerns about abuse and opioid toxicity**.

6. Antiepileptic drugs: e.g., carbamazepine. **It is one of the first-line therapies for trigeminal neuralgia.**

7. Central skeletal muscle relaxants: e.g., Baclofen.

8. Topical therapies:

-Capsaicin (8% patches): → Excessive stimulation and desensitization of nociceptive fibers ↓ substance P release ↓ pain.

-lidocaine (5% patches or gel), botulinum toxin type A (Subcutaneous injections).

- Topical therapies are recommended in patients with local neuropathy (e.g., postherpetic neuralgia and trigeminal neuralgia) and may be considered first-line therapies for elderly patients.
- The advantages of topical or local therapies include lower systemic drug levels, fewer adverse effects, and fewer drug interactions.

•Capsaicin causes **depolarization of the neuron** → burning/stinging sensation initially

•**Na^+ and Ca^{2+} influx** occur with **Substance P release**

•TRPV1 activation → releases **substance P**, a neuropeptide that **transmits pain signals to the CNS**

- **Repeated or high-concentration application**

•Causes **"defunctionalization"** of the nerve endings

- ↓ TRPV1 receptor sensitivity
- ↓ substance P content
- Nerve fibers become less responsive → **analgesia**

THANK YOU