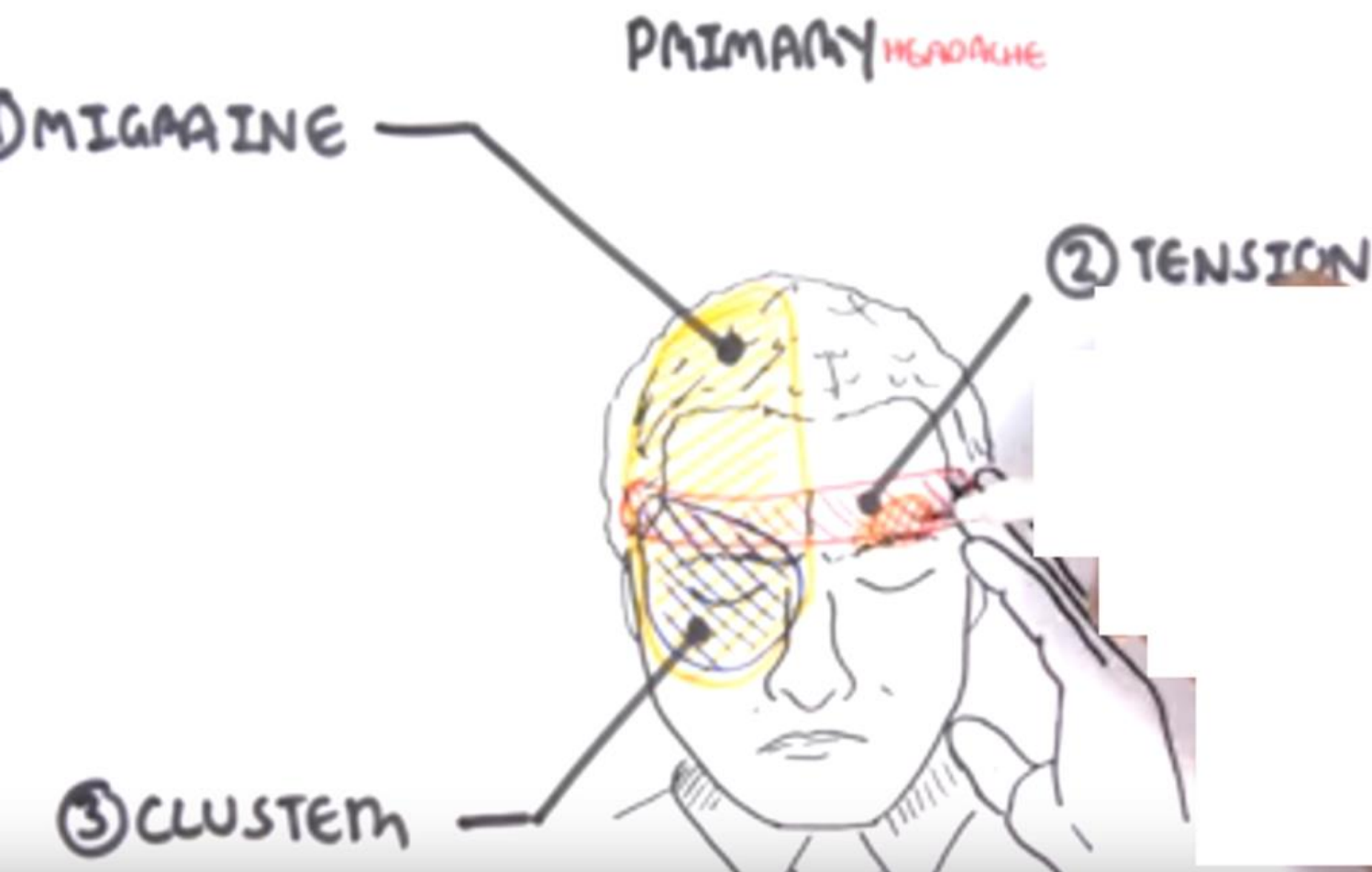




Headache



Abdulsalam Halboup

M.Pharm(Clinical)



LEARNING OBJECTIVES

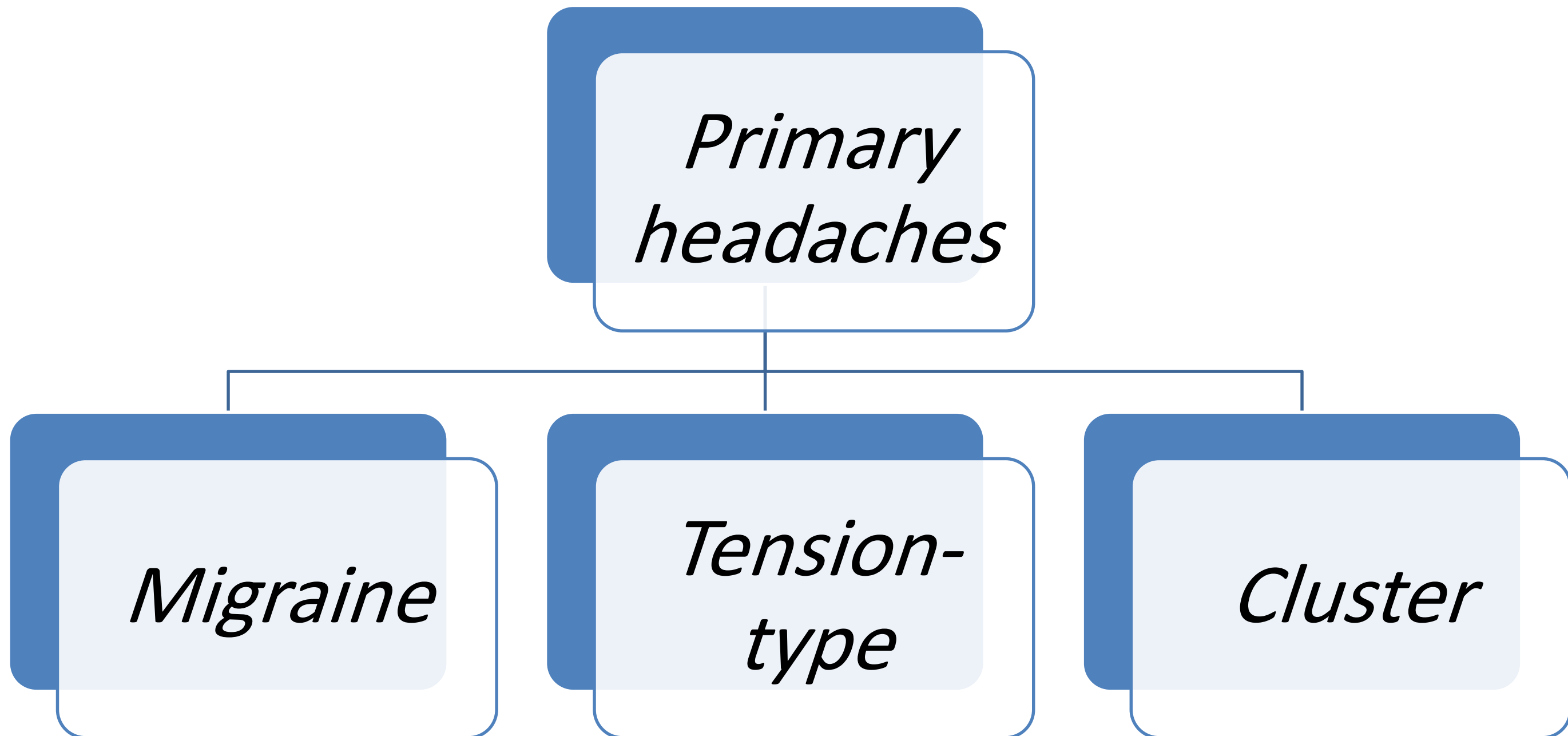
● Upon completion of the chapter, the reader will be able to:

1. Differentiate types of headache syndromes based on clinical features.
2. Recommend nonpharmacologic measures for headache treatment and prevention.
3. Determine when the pharmacologic treatment of headache is indicated.
4. Construct individualized treatment regimens for the acute and chronic management of headache syndromes.
5. Monitor headache treatment to ensure its safety, tolerability, and efficacy.

INTRODUCTION

- Headache is a common medical complaint with approximately 47% of the adult population experiencing at least one headache per YEAR.
- There are two types of headache
 - ❖ *Primary* headache
 - ❖ *secondary headaches* are caused by an underlying medical disorder and may be medical emergencies.

- *The International Headache Society (IHS) classifies primary headaches to :*



EPIDEMIOLOGY OF HEADACHE DISORDERS

Migraine Headache:

- Prevalence of migraine depends on age, gender, and income.
- In children and adolescents onset typically begins at age 7.9 years for males and 10.9 years for females.
- In adults, prevalence is much higher in women (17.1%) than men (6.1%), and occur most often between 30 and 49 years of age.

□ Tension-Type Headache:

- *Tension-Type Headache (TTH) is the most common primary headache disorder and can be further divided into **episodic** or **chronic**.*
- Overall prevalence of TTH is approximately 86%, and **incidence is more common in women than men.**
- **Episodic TTH is the most common type** followed by frequent episodic TTH, and finally chronic TTH.
- The mean frequency of attacks is **3 days per month** in episodic disorders; chronic TTH is defined as 15 or more attacks in a 1-month period.

Cluster Headache :

- Cluster headache disorders are uncommon and severe primary headache syndromes.
- Unlike migraine and TTH, cluster headaches are more frequently found in men.
- Onset most commonly occurs between 20 and 40 years.

Clinical Presentation and Diagnosis of Migraine without Aura

Patients experiencing “migraine without aura” may display the following headache symptoms and characteristics:

Two or more of the following are present:

1. Pain interrupts or worsens with physical activity
2. Unilateral pain
3. Pulsating pain
4. Moderate to severe pain intensity

One or more of the following are present during headache:

1. Nausea/vomiting
2. Photophobia and phonophobia

Duration: 4 to 72 hours (treated or not treated)

Criteria for diagnosis: Five or more attacks fulfilling above criteria are necessary

Laboratory assessments that may be helpful in excluding medical comorbidities: Complete blood count (CBC), chemistry panel, thyroid function tests (TFTs), erythrocyte sedimentation rate (ESR)

Clinical Presentation and Diagnosis of Migraine with Aura

Patients experiencing “migraine with aura” may display the following headache symptoms and characteristics:

One or more of the following present with no motor weakness:

1. Visual (eg, flashes of light, blind spots)
2. Sensory (eg, sensitivity to light, sound, smell)
3. Speech and/or language (eg, speech or language difficulty)
4. Motor (eg, heaviness of limbs)
5. Brain stem (eg, vertigo, tinnitus)
6. Retinal (eg, change in vision or vision loss)

Two or more of the following:

1. At least one aura symptom that spreads gradually over at least 5 minutes
2. Individual aura symptoms lasting 5 to 60 minutes
3. At least one aura symptom is unilateral
4. The aura is accompanied or followed by a headache within 60 minutes

Criteria for diagnosis: Two or more attacks fulfilling above criteria are necessary

Migraine Aura

- A complex of neurological symptoms that occurs just before or at the onset of migraine headache
 - may include
 - visual disturbances
 - flickering lights, spots or lines, loss of vision
 - dizziness
 - paraesthesiae
 - pins and needles, numbness
 - impaired speech
 - usually develop gradually over 5-20 minutes and last for less than 60 minutes

Clinical Presentation and Diagnosis of Tension-Type Headache

Patients experiencing TTH may display the following headache symptoms and characteristics:

Two or more of the following present and are not aggravated by routine physical activity:

1. Bilateral pain
2. Nonpulsating pain
3. Mild or moderate pain intensity

Both of the following:

1. No nausea or vomiting (anorexia possible)
2. Either photophobia or phonophobia (not both)

Duration: 30 minutes to 7 days

Criteria for diagnosis: 10 or more attacks fulfilling above criteria occurring on average less than 1 day per month are necessary

Clinical Presentation and Diagnosis of Cluster Headache

Patients experiencing "cluster headache" may display the following headache symptoms and characteristics:

At least one or more of the following symptoms:

1. Lacrimation
2. Nasal congestion and/or rhinorrhea
3. Eyelid edema
4. Forehead or facial sweating/flushing
5. Sensation of fullness in the ear
6. Miosis and/or ptosis

Or a sense of restlessness or agitation

Duration of pain: 15–180 minutes (untreated)

Frequency of attacks: One every other day and/or up to 8 per day for more than half the time the disorder is active (may have long periods when headaches are inactive)

Criteria for diagnosis: Five or more attacks fulfilling the above criteria

TREATMENT OF HEADACHE DISORDERS

Desired Outcomes:

- The **most important goal** of acute headache management is **pain relief**.
- The *short-term treatment goal* of migraine is to *achieve rapid pain relief* to allow the patient to resume normal activities.
- The *long-term goal* of therapy is to **prevent headache recurrences** and to diminish headache severity.
- **avoid analgesic overuse** and dependence.

General Approach to Treatment

- **First-line pharmacologic agents** include **nonsteroidal** and **opiate analgesics**, and serotonin-receptor agonists (**triptans**).
- *Pharmacologic treatment of acute headache should be **started early** to abort the intensification of pain and to **improve response to therapy**.*

Pharmacologic Therapy

Migraine:

- Analgesics, such as **nonsteroidal anti-inflammatory drug (NSAIDs)** and **acetaminophen**, with or without an opioid, are the **initial pharmacologic option** for the **acute management of migraine** headache especially when severity is **mild to moderate**.
- If these analgesics prove to be **ineffective**, then **migraine-specific medications**, such as **triptans**, are administered.
- larger doses than otherwise required to produce pain relief may need , why ?
 - due to the **enteric stasis** and **poor drug absorption** accompanying migraine attacks.
- **all triptans are effective treatments to abort or diminish migraine headache.**
- **Relief** is usually experienced within **2 to 4 hours**.

Comparison of Serotonin Receptor Agonists (Triptans)						
Medication (Brand Name)	Dosage Forms	Strength (mg)	Usual Dosage (mg)	May Repeat (hours)	Hepatic and Renal Dosing Considerations (mg)	Potential Drug Interactions
Almotriptan (Axert)	Oral tablets	6.25 12.5	6.25–12.5	2	HI and Severe RI: 6.25 starting dose and ≤ 12.5	Ergot derivatives Substrate: CYP 3A4, CYP 2D6
Eletriptan (Relpax)	Oral tablets	20 40	20–40	2	Severe HI: Not recommended	Ergot derivatives Substrate: CYP 3A4, CYP 2D6
Frovatriptan (Frova)	Oral tablets	2.5	2.5	2	Severe HI: Use caution	Ergot derivatives Substrate: CYP 1A2
Naratriptan (Amerge)	Oral tablets	1 2.5	2.5	4	Mild-mod RI or HI: Do not exceed 2.5; Severe RI (< 15 mL/min [0.25 mL/s]): Do not administer	Ergot derivatives Substrate: CYP (various)
Rizatriptan (Maxalt and Maxalt MLT)	Oral tablets Disintegrating tablets	5 10	5–10	2	None identified	Ergot derivatives MAO-A inhibitors
Sumatriptan (Imitrex)	Oral tablets Subcutaneous injection	25, 50, 100 4,6	50 6	2 1	Mild-mod HI: Oral dose not to exceed 50; Severe HI: contraindicated	Ergot derivatives MAO-A inhibitors
Sumatriptan/ Naproxen sodium (Treximet)	Nasal spray	5, 20/spray	5–20	2	RI (CLcr < 30 mL/min [0.50 mL/s]): Not recommended; Mild to Severe HI: Contraindicated	Ergot derivatives MAO-A inhibitors
	Oral tablets	85/500	85/500	12		
Zolmitriptan (Zomig and Zomig-ZMT)	Nasal spray	5, 20/spray	5–20	2	CLcr 5–25 mL/min (0.08–0.42 mL/s): Clearance reduced by 25%, use caution. Mod-Severe HI: Not	Ergot derivatives MAO-A inhibitors Substrate: CYP 1A2
	Oral tablets	2.5, 5	2.5	2		
	Disintegrating tablets	2.5, 5	1.25–2.5	2		

Table 35–2

Migraine Triggers

Behavioral:

Fatigue
Menstruation or menopause
Sleep excess or deficit
Stress
Vigorous physical activity

Environmental:

Flickering lights
High altitude
Loud noises
Strong smells
Tobacco smoke
Weather changes

Food:

Alcohol
Caffeine intake or withdrawal
Chocolate
Citrus fruits, bananas, figs, raisins
Dairy products
Fermented or pickled products

Food Containing:

Monosodium glutamate (MSG): Asian food, seasoned salt
Nitrites: processed meats
Saccharin/aspartame: diet soda or diet food
Sulfites: shrimp
Tyramine: cheese, wine, organ meats
Yeast: breads

Medications:

Cimetidine
Estrogen or oral contraceptives
Indomethacin
Nifedipine
Nitrates
Reserpine
Theophylline
Withdrawal due to overuse of analgesics, benzodiazepines,
decongestants, or ergotamines

- **Triptans** are well tolerated; **the most common side effects** are **dizziness**, a **sensation of warmth**, and **nausea**.
- Rarely, **ischemic vascular events** may be precipitated by the **potential vasoconstrictive** nature of these drugs.
- Triptans are avoided in patients with migraine associated with :
 - neurologic focality,
 - a history of **previous stroke**,
 - poorly controlled hypertension, or
 - unstable angina.
- Triptans are **relatively contraindicated** for routine use in pregnancy.
- Triptans **should not be** used with **concurrent ergotamine** administration.

- **Ergotamine tartrate** and **dihydroergotamine (DHE)** are the most commonly used agents.
- **Analgesic onset is within 4 hours**, although additional dosing is required if an acceptable response is not achieved.
- **When dosed parenterally**, these drugs are usually provided with an **antiemetic** due to their potential to worsen the nausea associated with migraine.
 - Metoclopramide and chlorpromazine are the drugs of choice in such instances.

- Selection of initial headache treatment is important in reducing the incidence of medication-overuse headache (MOH).
- MOH occurs when patients use ergotamines, triptans, opioids, or other combinations for more than 10 days per month.
- This can also be considered in patients who are using analgesics for more than 15 days per month.
- In patients who present to the hospital with intractable pain, IV metoclopramide supplemented with DHE may be needed.
- Migraine patients with frequent and severe attacks are candidates for prophylactic treatment.

Tension-Type Headache

- Most individuals who experience episodic TTHs will not seek medical attention. Instead, they will find relief with the use of widely available OTC analgesics.
- **Acetaminophen** products and **NSAIDs** are commonly utilized.
- **Relaxation** techniques can often **reduce** headache **frequency** and **severity**.
- When pain is unrelieved, **prescription-strength NSAID** use is required, or the **combination of acetaminophen with an opioid** analgesic may be necessary.
- As described above, **MOH** can occur with **frequent use of analgesics for TTH**.
- For patients experiencing frequent TTH, prophylactic treatment should be considered.

Cluster Headache

- A therapy specific to cluster headaches is the administration of high-flow-rate oxygen: 100% at 12-15 L/min by nonrebreather face mask for approximately 15 minutes.
- Drug therapy is also used when supplemental oxygen is not readily available.
- The triptan class is safe and effective. Intranasal or subcutaneous **sumatriptan** (6mg SC) as well as intranasal **zolmitriptan** has demonstrated efficacy in decreasing cluster headache pain.
- Oral triptans are also effective, but their delayed onset of action may limit their applicability in acute cluster headache treatment.
 - Oral agents may have utility in limiting the recurrence of cluster attacks.
- Intranasal, intramuscular, or IV ergotamine agents are an alternative to triptan use



- For those patients in whom **triptans** and **ergotamine** derivatives are **contraindicated** due to ischemic vascular disease, **octreotide SC** (somatostatin analogue) may be helpful to relieve pain.
- **Glucocorticoids**, **provided IV** and later tapered **orally**, are effective when **cluster headache attacks** are not satisfactorily controlled.
 - prednisolone 50 mg orally, daily (morning) for ~5 days, then taper by ~ 12.5mg every 3 days (alternative)



Pharmacologic Therapy for Headache Prophylaxis

- Prophylaxis for headache disorders is indicated “:
 - ❖ if headaches are frequent or severe,
 - ❖ if significant disability occurs,
 - ❖ if pain-relieving medications are used frequently

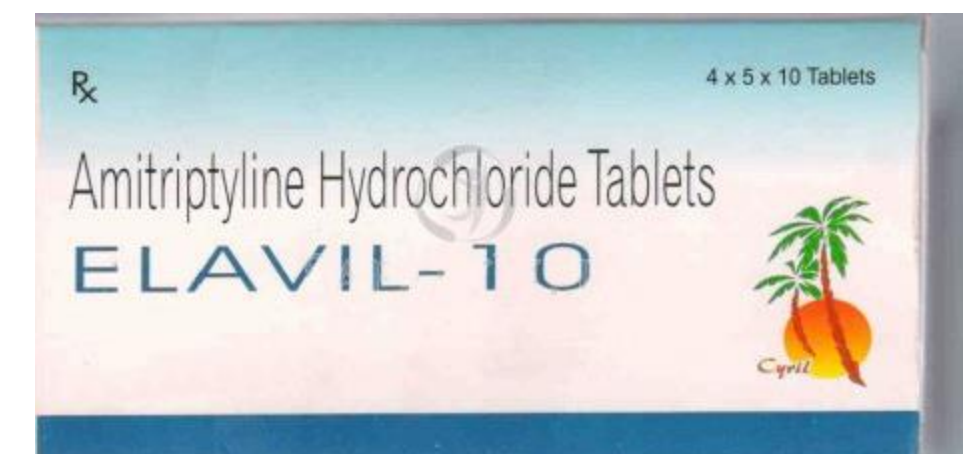
Migraine Prophylaxis

- Caution is advised when using a **serotonergic antidepressant** and a **triptan** concurrently, as the combination may rarely precipitate **serotonin syndrome**:
- **serotonin syndrome**: a serious and potentially **life-threatening drug-drug interaction** that presents clinically with **confusion**, **GI upset**, **symptomatic blood pressure (BP) changes**, and muscle **rigidity**.
- Frovatriptan, naratriptan, and zolmitriptan can be considered and should be started 2 to 3 days prior to the beginning of menstruation.

Table 35–4

Medications for Prophylaxis of Migraines

Medication (Brand Name)	Usual Dosage (mg/day)	Main Adverse Effects
Antiepileptics:		
Topiramate (Topamax) ^a	50–200	Paresthesias, dizziness, fatigue, nausea
Valproic acid (Depakene) ^a	500–1500	
Divalproex sodium (Depakote) ^a	500–1500	
β-Blockers:		
Atenolol (Tenormin) ^b	50–200	Fatigue, exercise intolerance
Metoprolol (Lopressor) ^a	50–200	
Nadolol (Corgard) ^b	20–160	
Propranolol (Inderal) ^a	80–240	
Timolol (Blocadren) ^a	20–30	
Antidepressants:		
Amitriptyline (Elavil) ^a	10–150	Weight gain, dry mouth, sedation
Venlafaxine (Effexor) ^a	37.5–150	



Tension-Type Headache Prophylaxis

- The prevention of chronic TTHs **uses the same pharmacologic strategies as for migraine prophylaxis.**
 - **TCAs are a mainstay of chronic therapy.**
 - **Stress reduction techniques** may be particularly effective in this setting.
 - Although there is little need for muscle relaxants (eg, **methocarbamol**) in the treatment of acute TTH, they are often provided as a preventive intervention.
 - Diclofenac potassium + methocarbamol (50/500 mg tab)



Cluster Headache Prophylaxis

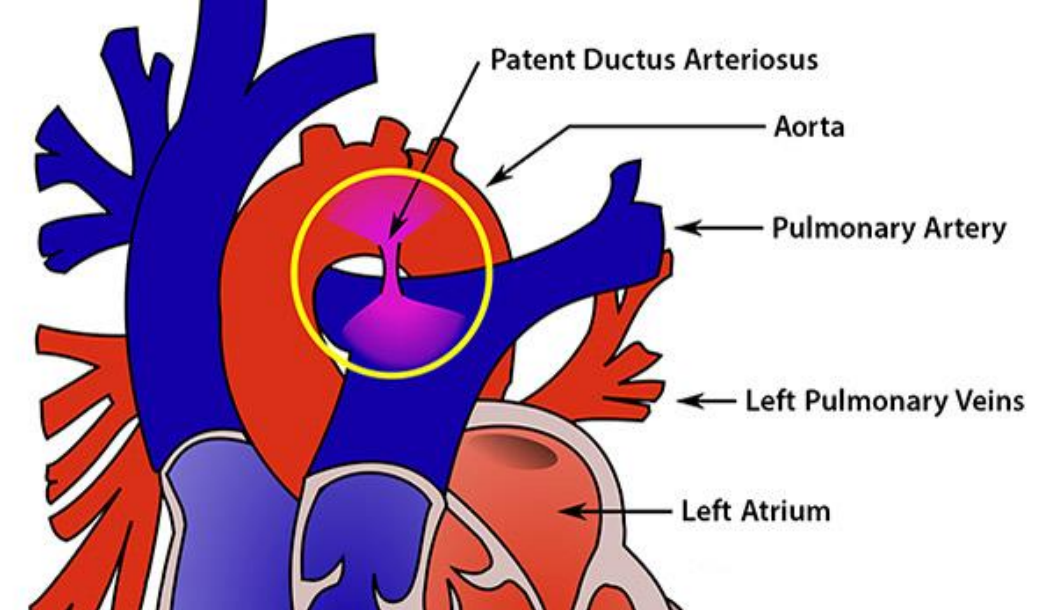
- The calcium channel blocker **verapamil** is the **mainstay of cluster attack prevention** and **chronic prophylaxis**.
- **Beneficial effects** may be appreciated **after 1 week of treatment**, but 4 to 6 weeks is usually needed.
- Adverse effects include smooth muscle relaxation with the subsequent **exacerbation of gastroesophageal reflux** and the development of constipation.
- **Lithium** is another effective therapy to **reduce headache frequency** in a cluster series and to limit recurrences.
- The dose administered should be individualized to achieve a low serum concentration (0.4–0.8 mEq/L).
- **Lithium is contraindicated** in patients concurrently prescribed **thiazide diuretics, NSAIDs, ACEIs, or ARBs**. Why ?

SPECIAL POPULATIONS

❑ Migraine Headache in Children and Adolescents:

- **ibuprofen** as effective and **acetaminophen** as probably effective in the **acute treatment of headache** in patients older than 6 years.
- **Aspirin use is avoided** due to the risk of precipitating **Reye syndrome**.
- **adolescents older than 12, triptans** are effective.
- Only **rizatriptan** is FDA approved for children over 6 and **almotriptan** for children over 12. The rest are approved for greater than 18 years of age.

Pregnancy



Acetaminophen is **safe** for the **pregnant woman and her fetus**.

NSAIDs are avoided late in the **third trimester** to prevent ductus arteriosus closure.

- **Opioids** are second-line agents and **should not to be used chronically** (**dependence** in mother , and **withdrawal** in the infant after birth)
 - Centrally acting antiemetic agents are safe and may be useful as adjunctive agents.
- if **triptans** are considered for acute migraine treatment, **sumatriptan**, **naratriptan**, and **rizatriptan** have the **greatest evidence of safe use during pregnancy**.
- **Migraine prophylaxis** is considered cautiously because β -blockers and calcium channel antagonists may lead to maternal hypotension and diminished placental blood flow or fetal bradycardia. **What about ergot in pregnancy ???!!**

Patient Encounter, Part 1

A 34-year-old woman complains of “almost monthly” headaches around the time of menstruation. She states that the pain is so severe that she has to stay home from work and lie down in a darkened room. She describes her pain as sharp, unilateral, and pulsating. She reports that she can tell when it is about to begin because she can see “floaters” then her peripheral vision begins to fade. She reports using OTC pain relievers to help ease the pain, but she has not had any success thus far.

What type of headache is the patient most likely experiencing?

What characteristics of the headache support this diagnosis?

What are possible causes or triggers of headache in this patient?

What additional information is needed to formulate a treatment plan?

R.M. is a 19-year-old woman with newly diagnosed migraine headaches. She takes an oral contraceptive and has tried nonprescription analgesics, with little relief of her headache. She admits to having trouble sleeping.

9. Which drug is best for R.M. to use for her migraine headaches?
 - A. Naproxen.
 - B. Sumatriptan.
 - C. Dihydroergotamine.
 - D. Isometheptene, acetaminophen, dichloralphenazone.
10. If R.M. needs a drug for migraine prophylaxis, which agent is best to recommend?
 - A. Amitriptyline.
 - B. Valproate.
 - C. Topiramate.
 - D. Frovatriptan.

21. M.R., a 34-year-old woman, has throbbing right-sided headaches. She has nausea, sonophobia, and photophobia with these headaches but no aura. She usually has headaches twice a month. She has hypertension and morbid obesity. She takes an ethinyl estradiol/progestin combination oral contraceptive daily and hydrochlorothiazide 25 mg/day orally. She has a diagnosis of migraine headaches. Which drug is best for prophylaxis of her headaches?
- A. Propranolol.
 - B. Valproate.
 - C. Topiramate.
 - D. Sumatriptan.
22. S.R. is a 54-year-old businessman with squeezing, band-like headaches that occur three or four times weekly. He rates the pain of these headaches as 7/10 and finds acetaminophen, aspirin, ibuprofen, naproxen, ketoprofen, and piroxicam only partly effective. He wants to take a prophylactic drug to prevent these tension headaches. Which drug is best for prophylaxis of his headaches?
- A. Propranolol.
 - B. Valproate.
 - C. Amitriptyline.
 - D. Lithium.

23. D.S. is a 49-year-old male computer programmer who describes lancinating right-eye pain and tearing several times a day for 2–3 days in a row. He will have no episodes for 2–3 weeks but then will have recurrent episodes. In the office, he receives oxygen by nasal cannula during an episode, and his pain is relieved. He has a diagnosis of cluster headaches. Which drug is best for prophylaxis of his headaches?

- A. Atenolol.
- B. Valproate.
- C. Nortriptyline.
- D. Lithium.

T.C. is a 30-year-old woman with migraine headaches. She takes sumatriptan 100 mg, which provides immediate relief. However, about 2 hours later, her headache symptoms return. Which would be best for her?

- A. Eletriptan 20 mg.
- B. Frovatriptan 2.5 mg.
- C. Naproxen 250 mg.
- D. Topiramate 25 mg.

Table 8. Selected Agents for Migraine Headache

	Dosage Forms	T _{max}	Half-Life (hr)	Dose	Maximal Dose/24 Hr (mg)
Triptans					
Almotriptan (Axert)	Tablets 6.25 mg, 12.5 mg	1–3 hr	2–4	1 tablet, may repeat in 2 hr	25
Eletriptan (Relpax)	Tablets 20 mg, 40 mg	1 hr	4–5	1 tablet, may repeat in 2 hr	80
Frovatriptan (Frova)	Tablets 2.5 mg	2–4 hr	26	1 tablet, may repeat in 2 hr	7.5
Naratriptan (Amerge)	Tablets 1 mg, 2.5 mg	2–3 hr	6	1 tablet, may repeat in 4 hr	5
Rizatriptan (Maxalt)	Tablets 5 mg, 10 mg	1–1.5 hr	1.8	1 tablet, may repeat in 2 hr	30
	Orally disintegrating tablets 5 mg, 10 mg	1.6–2.5 hr	1.8	1 tablet, may repeat in 2 hr	30
Sumatriptan (Alsuma, Imitrex, Sumavel, Zecuity)	SC injection 4 mg, 6 mg	12 min	1.9	1 injection, may repeat in 1 hr	12
	Intranasal 5 mg, 20 mg	30 min	2	1 spray in one nostril, may repeat in 2 hr	40
	Tablets 25 mg, 50 mg, 100 mg	2 hr	2.5	1 tablet, may repeat in 2 hr	200
	Iontophoretic transdermal system 6.5 mg/4 hr	1.1 hr	3.1	1 patch, may repeat in 2 hr	13
Zolmitriptan (Zomig)	Tablets 2.5 mg, 5 mg	1.5 hr	3.75	1 tablet, may repeat in 2 hr	10
	Orally disintegrating tablets 2.5 mg, 5 mg	3 hr	3.75	1 tablet, may repeat in 2 hr	10
	Intranasal 2.5 mg, 5 mg	3 hr	3	1 spray in one nostril, may repeat in 2 hr	10

IM = intramuscular(ly); IV = intravenous(ly); SC = subcutaneous(ly).