In the name of ALLAH

Headache

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Introduction

- Headache is one of the **most common complaints** encountered by healthcare practitioners and among the top five principal reasons adults 18 to 44 years of age visit US emergency departments.

- **Overall, the prevalence** of headache is highest in adolescence and early adulthood and declines with age through the elderly years.

- **Despite numerous potential causes of headaches**, the vast majority of patients with a chief complaint of continuous or sporadically recurring headaches are eventually diagnosed as having either tension-type or migraine headache.

Classification

- IHS classification provides more precise definitions and standardized nomenclature for both the primary and secondary.
- **For diagnostic and therapeutic purposes**, it is useful to categorize headache into one of two major types (primary and secondary) on the basis of the underlying etiology.
- **Primary headache disorders** are characterized by the lack of an identifiable and treatable underlying cause. Migraine, tension-type, and cluster headaches are examples of primary headache disorders.
- **Secondary headache disorders** are those associated with a variety of organic causes such as trauma, cerebrovascular malformations, and brain tumors.

Classification of Primary Headaches

- **Migraine**
  - Migraine without aura
  - Migraine with aura
- **Tension-Type Headache**
  - Episodic tension-type headache
  - Chronic tension-type headache
- **Cluster Headache**
  - Episodic cluster headache
  - Chronic cluster headache
- **Other Primary Headaches**
  - Cough headache
  - Exertional headache

Secondary Headache Disorders

- **Examples**: **head trauma, vascular disorders, central nervous system (CNS) infection** (including human immunodeficiency virus), or metabolic disorders.
- **The length of time** that a patient has experienced headaches provides highly useful information for assessing the nature and etiology of the headaches.
- **A new severe headache** in a patient without a previous history is the single most useful piece of information for identifying potentially destructive intracranial or extracranial causes of headache.
- Such headaches may develop suddenly, during a period of hours to days (acute headache), or more gradually for days to months (subacute headache).

Migraine Headache

- Young
- high educated
- stress

Pathophysiology

- **The pain and symptoms of migrain**e are a combination of altered perceptions resulting from neural suppression and activation of subcortical structures and trigeminal system .

- **Genetic factors** seem to play an important role in susceptibility to migraine attacks.
- Patients with migraines appear to have a lowered threshold of response to specific environmental circumstances as a result of genetic factors that govern the balance of CNS excitation and inhibition at various levels.
- **The hyperresponsiveness** of the patient's brain may b
- e the result of an inherited abnormality in calcium and/or sodium channels and sodium/potassium pumps that regulate cortical excitability through the release of serotonin (5-hydroxytryptamine [5-HT]) and other neurotransmitters.
- **Increased levels of excitatory amino** acids such as glutamate and alterations in levels of extracellular potassium also can affect the migraine threshold and initiate and propagate the phenomenon of cortical spreading depression

Pathophysiology

- **A)Past theories of pathogenesis** have focused on alterations in cranial vessel diameter and blood flow as the primary cause of migraine.
- **In this "vascular hypothesis,"** it was thought that **focal neurologic** symptoms preceding or accompanying the headache were caused by vasoconstriction and reduction in cerebral blood flow.
- The headache was thought to be caused by a compensatory vasodilation with displacement of pain-sensitive intracranial structures.
- **B) Recent evidence also suggests** that the pain of migraine is generated centrally and involves episodic dysfunction of neural structures that control the cranial circulation (the trigeminovascular system).

Pathophysiology

- **The trigeminovascular system** consists of neurons originating in the trigeminal ganglion, which innervate the cerebral circulation.
- **It projects centrally (photophobia ,…)**

- **Activation of trigeminal sensory** nerves triggers the release of vasoactive neuropeptides, including calcitonin gene-related peptide (CGRP), neurokinin A, and substance P, from perivascular axons.

Pathophysiology

- **Abnormalities in serotonin (5-HT) activity** are also thought to play a role in migraine headache.
- **Plasma 5-HT levels decrease** by nearly half during a migraine attack.

- Acute antimigraine drugs such as the ergot alkaloids and triptan derivatives are agonists of vascular and neuronal 5-HT1 receptors subtypes, resulting in **vasoconstriction of meningeal blood vessels and inhibition of vasoactive neuropeptide release and pain signal transmission**

- **The therapeutic effects of drugs** that stimulate 5-HT1 receptors (e.g., dihydroergotamine, sumatriptan), antagonize 5-HT2 receptors (e.g., methysergide, cyproheptadine), prevent 5-HT reuptake (e.g., amitriptyline) or release (e.g., calcium-channel blockers), or inhibit brainstem serotonergic raphe neurons (e.g., valproate) all lend support to the hypothesis that 5-HT is an important mediator of migraine.

Summary

- **Low level of serotonin** (ergot, triptan, TCA, venlafaxine)
- **High level of CGRP**:
- CGRP (calcitonin gene-related peptide) is a neuropeptide that plays a crucial role in the pathophysiology of migraine. It is primarily released from trigeminal sensory neurons .

Signs and Symptoms

- Approximately **20.7% of females and 9.7% of males** in the United States experience one or more migraine headaches per year.
- **Sex differences** in migraine prevalence have been linked to menstruation, but these differences persist beyond menopause.
- Prevalence is highest in ages of 18 and 44 years and is inversely related to income and educational attainment
- **After the age of 50**, the onset of new migraine headaches is less common and is **suggestive of a secondary cause.**
- **Symptoms:** Migraine headache pain is usually moderate- severe/ **gradual in onset, peaking in intensity over a period of minutes to hours** and lasting between **4 and 72 hours.**
- Pain can occur anywhere in the face or head but most often involves the frontotemporal region
- In the assessment of headache, the site or location of the pain, the quality of the pain, the duration and time course of the pain, and the conditions that provoke or palliate the pain should be considered.

Migraine Headache

- **The word *migraine* comes from the Greek *hemicrania*** and historically was used to describe unilateral headaches with associated symptoms.
- **More recently, migraine is described as** "paroxysmal attacks of moderate-to-severe, throbbing headache with associated symptoms that may include nausea, vomiting, and photophobia or phonophobia."
- **Migraine headaches are subclassified according** to the presence or absence of *aura* symptoms. Most persons who suffer from migraine do not experience aura symptoms.
- In patients with aura, visual symptoms are most common.

Signs and Symptoms

- ***Aura symptoms*** **are focal neurologic features that precede or accompany the headache in up to 30% of migraine sufferers.**
- When they precede the headache, aura symptoms usually begin 10 minutes to 1 hour before the onset of head pain.
- **Light-headedness and photopsia (unformed flashes of light)** are frequently reported.
- **Visual disturbances, such as *scotoma*** (an isolated area within the visual field where vision is absent), occur in 30% of migraine patients. When scotomata are surrounded by a shiny pattern, they are termed *scintillating scotomata*.
- Other neurologic symptoms of cortical origin (e.g., paresthesias, temporal lobe symptoms) occur commonly in patients who suffer from migraine with aura

photopsia

TABLE 78-2 IHS Diagnostic Criteria for Migraine and Cluster Headache

Migraine without aura

At least five attacks

Headache attack lasts 4-72 hours (untreated or unsuccessfully treated)

Headache has at least two of the following characteristics:

- Unilateral location
- Pulsating quality
- Moderate or severe intensity
- Aggravation by or avoidance of routine physical activity (ie, walking or climbing stairs)

During headache at least one of the following:

- Nausea, vomiting, or both
- Photophobia and phonophobia
- Not attributed to another disorder

Migraine with aura (classic migraine)

At least two attacks

Migraine aura fulfills criteria for typical aura, hemiplegic migraine, retinal migraine or brainstem aura

Not attributed to another disorder

Typical aura

Fully reversible visual, sensory, or speech symptoms (or any combination) but no motor weakness

Homonymous or bilateral visual symptoms including positive features (eg, flickering lights, spot, lines) or negative features (eg, loss of vision) or unilateral sensory symptoms including positive features (eg, pins and needles) or negative features (ie, numbness), or any combination

At least two of the following:

- At least one symptom that develops gradually over a minimum of 5 minutes or different symptoms that occur in succession or both
- Each symptom lasts for at least 5 minutes and for no longer than 60 minutes
- Headache that meets criteria for migraine without aura begins during the aura or follows aura within 60 minutes

IHS, International Headache Society.

TABLE 78-6 Commonly Reported Triggers of Migraine

Food triggers
Alcohol
Caffeine/caffeine withdrawal
Chocolate
Fermented and pickled foods
Monosodium glutamate (eg, in Chinese food, seasoned salt, and instant foods)
Nitrate-containing foods (eg, processed meats)
Saccharin/aspartame (eg, diet foods or diet sodas)
Tyramine-containing foods
Environmental triggers
Glare or flickering lights
High altitude
Loud noises
Strong smells and fumes
Tobacco smoke
Weather changes
Behavioral–physiologic triggers
Excess or insufficient sleep
Fatigue
Menstruation, menopause
Sexual activity
Skipped meals
Strenuous physical activity (eg, prolonged overexertion)
Stress or poststress

- **Foods containing:**
  - MSG (e.g., Chinese food, canned soups, seasonings)
  - Tyramine (e.g., red wine, ripened cheeses)
  - Nitrites (e.g., cured meat products)
  - Phenylethylamine (e.g., chocolate, cheese)
  - Aspartame (e.g., artificial sweeteners, diet sodas)
- **Drugs**
  - Excess use or withdrawal (ergots, triptans, analgesics)
  - Estrogens (e.g., oral contraceptives)
  - Cocaine
  - Nitroglycerin

A headache diary that records the frequency, severity, and duration of attacks can facilitate identification of migraine triggers.

TABLE 78-3 Goals of Therapy in Migraine Management

Goals of long-term migraine treatment
Reduce migraine frequency, severity, and disability
Reduce reliance on poorly tolerated, ineffective, or unwanted acute pharmacotherapies
Improve quality of life
Prevent headache
Avoid escalation of headache medication use
Educate and enable patients to manage their disease
Reduce headache-related distress and psychological symptoms
Goals for acute migraine treatment
Treat migraine attacks rapidly and consistently without recurrence
Restore the patient's ability to function
Minimize the use of backup and rescue medications[a]
Optimize self-care for overall management
Be cost-effective in overall management
Cause minimal or no adverse effects

Medication is mainstay of treatment:

Abortive vs prophylactic

Abortive or acute therapies can be migraine-specific (eg, ergots, triptans, and CGRP antagonists) or nonspecific (eg, analgesics, antiemetics, NSAIDs, and corticosteroids). Most effective at relieving pain and associated

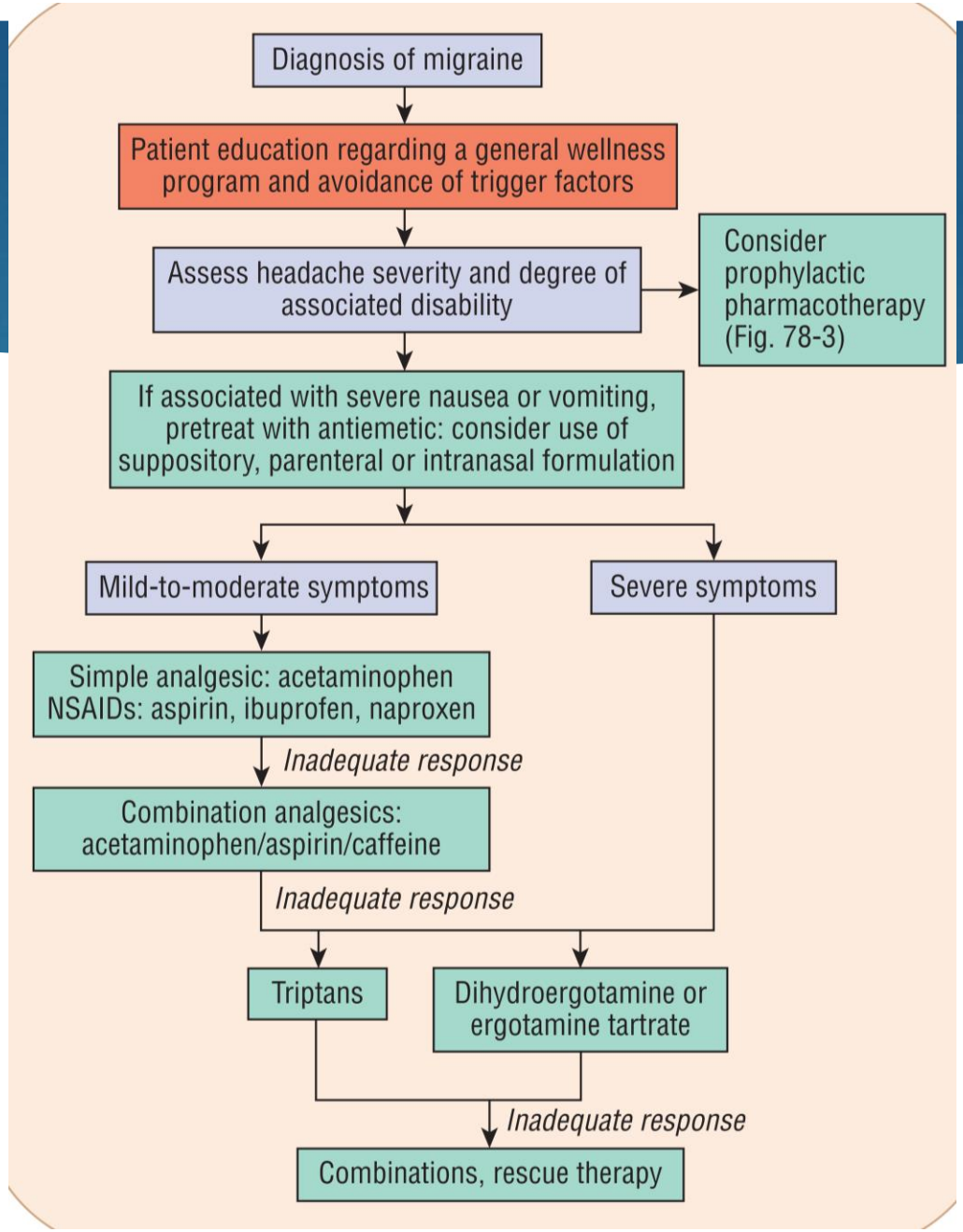
Abortive Therapy

- The general approach to treatment of acute migraine headache attacks is one of pharmacotherapy aimed at relieving migraine headache pain and associated symptoms.

- **Such a treatment plan may include** (a) 5-HT receptor agonists (e.g., triptans or ergot derivatives), (b) analgesics, (c) sedatives, and (d) antiemetic drug therapy, depending on the exact nature of the patient's complaint.

- The selection of a specific treatment should be based on the level of disability and **associated symptoms such as nausea and vomiting.**

- **This "stratified care**" approach is preferred over a "step care" approach that may begin with agents that are likely to be ineffective for the patient's headache.


Diagnosis of migraine
Patient education regarding a general wellness program and avoidance of trigger factors
Assess headache severity and degree of associated disability
Consider prophylactic pharmacotherapy (Fig. 78-3)
If associated with severe nausea or vomiting, pretreat with antiemetic: consider use of suppository, parenteral or intranasal formulation
Mild-to-moderate symptoms
Severe symptoms
Simple analgesic: acetaminophen NSAIDs: aspirin, ibuprofen, naproxen
Inadequate response
Combination analgesics: acetaminophen/aspirin/caffeine
Inadequate response
Triptans
Dihydroergotamine or ergotamine tartrate
Inadequate response
Combinations, rescue therapy

NSAIDs and Combination Analgesics

- In the stratified care approach, NSAIDs and combination analgesics are reasonable treatment options for patients with mild to moderate migraine headaches or those with severe attacks that have responded to these agents in the past.

- Significant clinical benefit has been shown for aspirin, ibuprofen, naproxen sodium, and combination analgesics containing acetaminophen, aspirin, and caffeine.

- If NSAIDs are to be used in the abortive treatment of migraine, the concomitant administration of metoclopramide can enhance their absorption, providing more effective and rapid pain relief.

NSAIDs and Combination Analgesics

- **Nonsteroidal anti-inflammatory** drugs appear to prevent neurogenically mediated inflammation in the trigeminovascular system through the inhibition of prostaglandin synthesis.

- **Suppository analgesic** preparations are an option when nausea and vomiting are severe.

- **NSAIDs should be avoided or used cautiously** in patients with previous ulcer disease, renal disease,cardiac or hypersensitivity to aspirin.

Triptans (5-HT1B/1D Receptor Agonists)

- **First line in moderate- severe/ well tolerated**
- **Agents in the triptan class (sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, frovatriptan, and eletriptan)** are considered **first-line agents** for patients with migraine headaches who do not respond to nonprescription or combination analgesics or **SEVERE ENOUGH**
- **Unlike ergotamine**, which needs to be taken at the earliest sign of a migraine attack for maximal benefit, **the triptans are effective when given 4 hours or longer after the onset of headache**.
- Unlike the ergot alkaloids, which stimulate serotonergic, dopaminergic, and noradrenergic receptors, the triptans have selective agonist activity at 5-HT1B/1D subtype receptors.
- This feature is likely responsible for the **improved tolerability profile** for these agents.

Sumatriptan

- All formulations reduce the severity of migraine headache and improve **associated symptoms such as nausea, vomiting, photophobia, and phonophobia**.
- For patients who are **nauseated and prone to vomit during** an acute attack, the subcutaneous and intranasal dosage forms are preferred.
- **Onset :**
- Clinical response to oral sumatriptan usually begins 20 to 60 minutes after administration.
- Reduction in headache intensity is reported within 10 minutes after subcutaneous injection and within 15 minutes after administration of the nasal spray.
- During migraine attacks, the gastrointestinal (GI) absorption of many drugs is delayed.

Sumatriptan

- Response rates for sumatriptan vary from 50% to 82%.
- **Subcutaneous injection** is associated with higher response rates than nonparenteral routes of administration.
- **Side effects** to the triptans are common but usually mild to moderate in nature and of short duration
- After oral administration, the **most common adverse effects** of sumatriptan include nausea and vomiting (which could be related to the migraine itself), malaise, and dizziness.
- The most common adverse events after subcutaneous administration are mild pain or redness at the site of injection.

Sumatriptan

- **Up to 25% of patients receiving** a triptan consistently report "**triptan sensations**," including tightness, pressure, heaviness, or pain in the chest, neck, or throat (vasoconstrictor effects in their arterial receptots)

- These symptoms are **usually mild, resolve within 2 hours**, and are unrelated to cardiac ischemia.

- **The triptans are contraindicated in:**

- Patients with a history of ischemic heart disease (eg, angina pectoris,

- Prinzmetal's angina, or previous myocardial infarction), uncontrolled hypertension, and cerebrovascular disease

- Another complication of sumatriptan use is recurrent migraine headache. This phenomenon may be related to the short half-life of the drug, and the recurrent headache often responds to a repeat dose of sumatriptan.

Sumatriptan

- **The initial dose of subcutaneous sumatriptan is 6 mg**. If there is no relief within 1 hour, the dose can be repeated (Max: 12 mg/day).

- **Initial dose of oral sumatriptan is 25 to 100 mg.** This dose may be repeated if there is no relief within 2 hours (Max: 200 mg/day).

- When migraine headache recurs after an initial positive response, a repeat dose is often effective. However, the maximum doses in a 24-hour period should not be exceeded.

Drug Interactions

- Concomitant use with ergot alkaloids, lithium, selective serotonin reuptake inhibitors (SSRIs), SNRIs, and monoamine oxidase (MAO) inhibitors is not recommended because of the potential for precipitating the serotonin syndrome.

- However, several reports describe the safe use of sumatriptan in conjunction with MAO-B inhibitors, SSRIs, and lithium, and clinical evidence of adverse effects is minimal.

Migraine

- **Triptans:** favorite and common
- The highest likelihood of consistent success was found with rizatriptan (10 mg), **eletriptan** (80 mg), and almotriptan (12.5 mg).
- **Eletriptan**; may be more effective /good agent

- **Lasmiditan**: New/ more selective for $5HT_{1F}$ / good agent
- lacks vasoconstrictor activity and therefore can be used for patients with relative contraindications to triptans due to cardiovascular risk factors
- Dose: tab 50-100 mg
- The most common adverse event associated with lasmiditan is dizziness; other relatively frequent adverse events are paresthesia, somnolence, fatigue, and nausea

Gepant

- **Gepants**: (CGRP antagonist): similar to triptan but less CV side effects
- modulation of **calcitonin-gene related peptide (CGRP**) activity appears to mediate trigeminovascular pain transmission in migraine
- CGRP level increase and causes vasodilation
- (less CV side effects)
- For those with contraindications to or who do not tolerate triptans, a **calcitonin gene-related peptide (CGRP)** antagonist **or lasmiditan** may be effective.

- **Rimegepant (better efficacy) and ubrogepant** in acute migraine /more data is needed

Ergotamine Tartrate

Before the availability of agents in the triptan class, ergotamine was widely considered the drug of choice when analgesics were ineffective.

- However, adverse effects of ergotamine are common and potentially serious, particularly when the drug is used in excessive doses or for prolonged periods.
- Ergotamine and other ergot derivatives (e.g., DHE) are agonists at numerous 5-HT1 receptor subtypes (5-HT1A, 5-HT1B, 5-HT1D, 5-HT1F), 5-HT2, adrenergic, and dopaminergic receptors.
- **Ergotamine has both venous and arterial vasoconstrictive effects**. Ergotamine and DHE block inflammation of the trigeminal neurovascular system, presumably by inhibiting the release of the neuropeptides.

Ergotamine Tartrate

- Ergotamine should be in a dosage that is effective and acceptable **given at the first sign of a migraine attack** to the patient.
- If administration is delayed until the headache is firmly established, ergotamine is rarely effective.
- The usual ergotamine dosage is 1 to 4 mg given immediately, followed by 1 to 2 mg at 30-minute intervals to a maximum of 6 mg/attack or 10 mg/week.
- Also, the use of ergotamine should be limited to NO more than twice per week to reduce the risk of **chronic ergot-related adverse effects.**

Ergotamine Tartrate

- **Nausea and vomiting** (resulting from stimulation of the chemoreceptor trigger zone D agonist) are among the most common adverse effects of the ergotamine derivatives.
- **common side effects include** abdominal pain, weakness, fatigue, paresthesias, muscle pain, diarrhea, and chest tightness.
- **Rarely, symptoms of severe peripheral ischemia** (ergotism), including cold, numb, painful extremities, continuous paresthesias, diminished peripheral pulses, and claudication, can result from the vasoconstrictor effects of the ergot alkaloids.
- **Gangrenous extremities**, myocardial infarction, hepatic necrosis, and bowel and brain ischemia have also been reported

- **Pretreatment** with an antiemetic agent should be considered with ergotamine and IV dihydroergotamine therapy.

- **Contraindications to the use of ergot alkaloids include** cardiac, peripheral, and cerebral vascular disease; sepsis; liver and kidney disease; pregnancy; breast-feeding; and concomitant use of erythromycin.

Antiemetics

- **In most patients, triptan agents provide effective relief of migraine-associated nausea**. Therefore, specific antiemetic therapy usually is NOT required.
- However, persistent nausea is more common in patients who use ergotamine for acute migraine therapy. In these patients, and in triptan-treated patients who experience incomplete nausea relief, adjunctive antiemetic therapy should be considered.
- **Metoclopramide** is the antiemetic of choice in migraine. The recommended dose is 10 mg taken orally as soon as possible.
- Metoclopramide provides symptomatic relief from nausea and vomiting while enhancing the oral absorption of medications taken during the migraine attack.
- **Intravenous metoclopramide** is also effective as primary therapy for severe migraine attacks and this therapy is used in some EDs.

Intractable Migraine

- Intractable migraine with associated vomiting usually requires **parenteral therapy with injectable ergot derivatives, sumatriptan, or potent narcotic analgesics.**
- **Dihydroergotamine (DHE)**, 1 mg subcutaneously or intramuscularly or 0.75 mg IV, is particularly effective in the treatment of acute and intractable migraine headaches.
- **An IV antiemetic (metoclopramide 10 mg**) should be administered 15 to 30 minutes before DHE to minimize the GI side effects of this agent.
- **Sumatriptan 6 mg subcutaneously** is also effective for the treatment of established migraine. If the first injection does not provide relief at 1 hour, a second injection may be administered.
- Sumatriptan should NOT be administered within 24 hours of ergot alkaloids because of the potential for prolonged vasospastic reactions.

Intractable Migraine

- **Chlorpromazine given parenterally** has both antimigraine and antiemetic properties and has gained increased acceptance in some EDs.
- The dose of chlorpromazine is 0.1 mg/kg IV or 1 mg/kg by IM route.
- **Parenteral narcotic analgesics** also effectively relieve intractable migraine headache pain, but they should generally be reserved for **second- or third-line** therapy after patients have failed to respond to parenteral sumatriptan, DHE, or chlorpromazine.
- These agents often cause or exacerbate nausea and vomiting. Also, excessive use should be monitored closely because of the risk of addiction and dependence.

Corticosteroids

- **Prednisone 40 to 60 mg PO for 3 to 5 days** or dexamethasone 4 to 24 mg IV or intramuscularly may be considered as alternative treatments for intractable migraine.

Prophylactic Therapy

- Effective prophylactic migraine treatment not only reduces the frequency of migraine attacks but also may reduce the severity of ensuing headaches, render them more responsive to abortive measures, or reduce the duration of headaches.

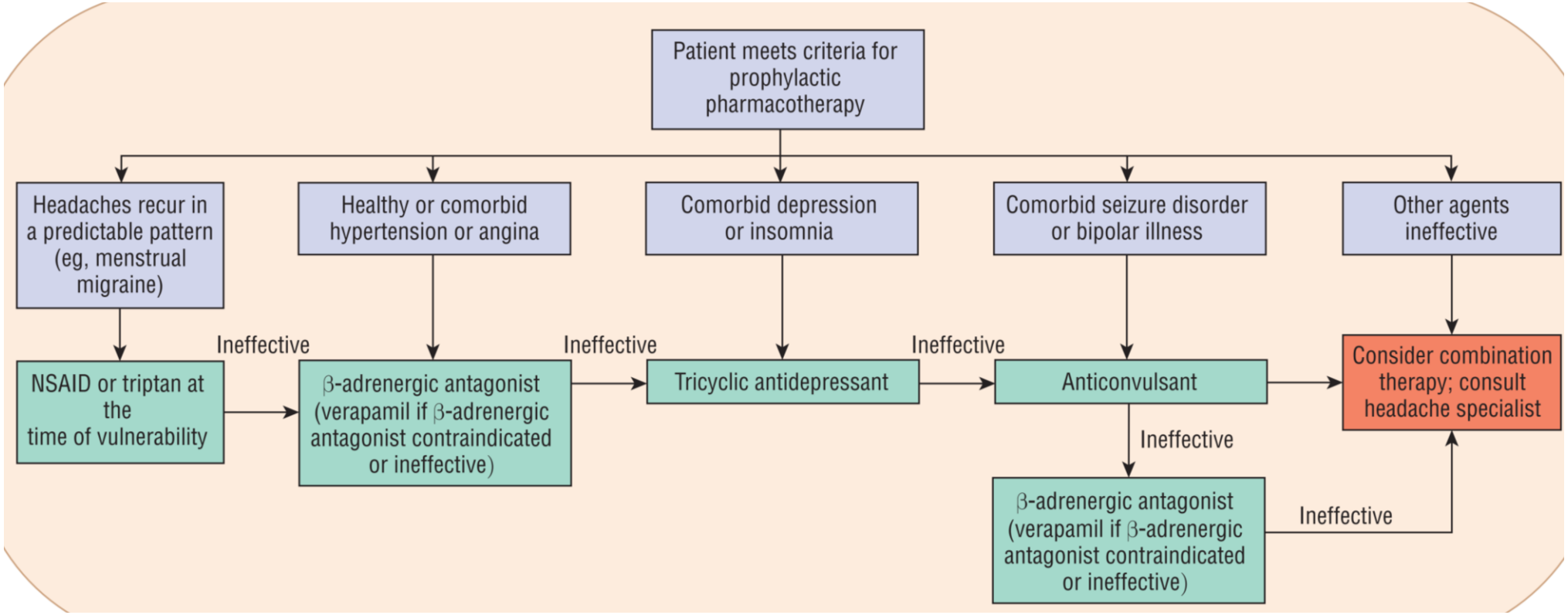
- **The American Academy of Neurology (AAN) and European Federation of Neurological Sciences (EFNS) guidelines for initiating prophylactic treatment for migraine are:**

  (a) headaches that impact a patient's life despite the use of abortive treatments

  (b) headaches occurring twice monthly or more

  (c) disabling headaches that are unresponsive to abortive treatments

  (d) frequent, prolonged, or bothersome auras



Only propranolol, timolol, divalproex sodium, topiramate, erenumab-aooe, fremanezumab-vfrm, galcanezumab-gnlm, eptinezumab-jjmr, atogepant, and rimegepant are currently FDA approved, although other

Prophylactic Therapy

- Generally, the preferred agents for prophylaxis of migraine headache are propranolol, amitriptyline, topiramate, and valproate (including divalproex sodium).

- **Botulinumtoxin A (onabotulinumtoxin A [Botox])** is now approved for treatment of chronic migraine (headaches occurring≥15 days per month and lasting 4 hours a day or longer).

- Prophylactic therapy for migraine should be continued for 6- 12 months.
- If a satisfactory response is achieved, the prophylactic agent should be gradually discontinued for several weeks to assess the continued need for this mode of therapy.

Propranolol

- **Propranolol is a first-line agent** for migraine prophylaxis because of its safety, efficacy, favorable adverse effect profile, and the strength of evidence from randomized, controlled trials.
- When propranolol is used, approximately 50% to 80% of patients obtain complete or partial relief from migraine attacks; most patients who initially respond to propranolol continue to benefit without any evidence of drug tolerance.
- Other β-adrenergic blocking drugs such as **metoprolol and atenolol**, appear to be as efficacious as propranolol.
- **Propranolol 80 to 160 mg/day in two to four divided doses** is effective in the prophylaxis of migraine headaches.
- Most propranolol responders will experience relief **within 4 to 6 weeks** of beginning therapy.

Antidepressants

- It may be the drug of choice for patients whose symptoms suggest features of both headache types **(i.e., mixed tension-type and migraine headaches)** and for those with **coexisting depression**.
- **The initial dose of amitriptyline is 10 to 25 mg at bedtime**. This nightly dose can be increased at weekly intervals by 10 to 25 mg until the maximal dose of 150 mg/day is reached.
- Two-thirds of patients note a **decrease in the number of headaches within 7 days** of starting amitriptyline therapy, but a 6-week trial is warranted before the drug should be considered ineffective.
- ADRs: Evening doses are preferred because of associated sedation and increased appetite and weight gain can occur.
- **Anticholinergic side effects** are common with the TCAs and limit use of these agents in patients with benign prostatic hyperplasia and glaucoma.
- Orthostatic hypotension
- **Venlafaxine (an SNRI)** has been shown to effectively prevent migraine headache compared with placebo.

Antiepiletic drugs

- The beneficial effects of these agents are likely caused by multiple mechanisms of action, including **enhancement of γ-aminobutyric acid (GABA)- mediated inhibition, modulation of the excitatory neurotransmitter** glutamate, and inhibition of sodium and calcium ion channel activity.
- Antiepileptic drugs are particularly useful in patients with migraines and comorbid **seizures, anxiety disorder, or bipolar illness.**

Topiramate

The optimal dose is 100mg/day, which is less than the doses commonly used to treat epilepsy.

- **The most common reason** for topiramate discontinuation is paresthesias.
- Cognitive and word-finding problems are more common with topiramate doses greater than 100 to 200 mg/day.
- **Weight loss** can also occur during topiramate use.
- A history of renal stones is a relative contraindication to the use of topiramate.

Valproate

- The antiepileptic drug valproate (and divalproex sodium) is approved for the prevention of migraine headaches and is useful as a first-line agent in this regard.
- **The initial dose of valproate is 250 mg PO twice daily**. The dose can be increased in 250- to 500-mg/day increments at weekly intervals. The usual range of effective doses is 500 to 1,500 mg/day.
- The most common adverse effects of valproate include nausea, alopecia, tremor, and weight gain.
- Alopecia,Acne / PCOS
- Valproate must be used with caution in women of childbearing potential owing to the detrimental effects the drug can have on the newborn.

NSAIDs

- In addition to being effective as symptomatic therapy for migraine, selected NSAIDs are also effective as prophylactic agents.
- However, their effectiveness as preventive therapy is considered to be modest compared with the first-line agents, propranolol, amitriptyline, topiramate, and valproate.
- The rationale for their use is that inhibition of prostaglandin and leukotriene synthesis might inhibit the neurogenic inflammation of migraine.
- Placebo-controlled trials have documented the effectiveness of naproxen, naproxen sodium, ketoprofen, and mefenamic acid.
- These NSAIDs may be effective as short-term therapy for menstruation-associated migraine.

Calcitonin Gene-Related Peptide Antagonists

- Inhibition of the CGRP receptor is the newest target in the prophylaxis of migraines.
- **Growing data**.
- Initial concerns regarding the potential for cardiovascular, pulmonary, and psychiatric adverse effects due to theoretical vasodilatory actions were not substantiated in clinical trials

- **Aimovig** (erenumab-aooe): Approved May 17, 2018
- **Ajovy** (fremanezumab): Approved Sept 14, 2018
- **Emgality** (galcanezumab-gnlm): Approved Sept 27, 2018
- **Vyepti** (eptinezumab-jjmr): Approved Feb 21, 2020.